Lung Cancer Pioneer Paves Path for Future Innovation

PEER EXCHANGE®
Frontline Treatments for RCC March Forward

OnePathways®
Uncommon EGFR Mutations Come Into Focus in NSCLC

20TH ANNUAL INTERNATIONAL CONGRESS ON THE FUTURE OF BREAST CANCER® EAST
Hope S. Rugo, MD, FASCO, Reviews Treatment Strategies for TNBC
Leisha A. Emens, MD, PhD, Discusses Novel Vaccine Combinations for BREAST CANCER

THE TALK
Dose-Reduction Strategy Maintains Efficacy, Averts Serious Events in CML

CLINICAL TRIAL IN FOCUS
Alexander M. Lesokhin, MD, Unpacks the Pivotal MagnetisMM-3 Trial in MULTIPLE MYELOMA

Montefiore Einstein Center for Cancer Care
Now Is the Time to Improve Diversity in Cancer Clinical Trials
By Bruce D. Rapkin, PhD

Roman Perez-Soler, MD
IN ER+/HER2- METASTATIC BREAST CANCER (mBC)

CAN IMPROVING ER ANTAGONISM AND DEGRADATION UNLOCK A BRIGHTER FUTURE?

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

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

\textit{HER2=human epidermal growth factor receptor 2.}

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 64.
After decades of research and dozens of approved agents, investigators have only just begun to make waves in the targeted approaches for the treatment of lung cancer. Roman Perez-Soler, MD, has been at the forefront of several of these efforts and will lead discussions on their impact for the field as part of the 16th Annual New York Lung Cancers Symposium® in November.
Breakthroughs Flip the Script on Untargetable Mutations in NSCLC

The pace of discovery in medical oncology for targeted therapies in non-small cell lung cancer (NSCLC) has been remarkable. Approvals for novel agents, specifically those for patients with KRAS mutations or EGFR-positive disease have opened the playing field for advances in areas previously deemed “untargetable.”

The May approvals of sotorasib (Lumakras) and amivantamab-vmjw (Rybrevant) represented 2 milestones of interest in the treatment landscape.

Sotorasib was approved for the treatment of adult patients with locally advanced or metastatic KRAS G12C–mutant NSCLC who have received at least 1 prior systemic therapy.1 Patients with KRAS mutations are the most frequently identified driver mutations for patients with NSCLC, with G12C mutations representing one of the most common subtypes, appearing in 25% and 13% of patients, respectively.2

“KRAS is driving the interest and the excitement,” Roman Perez-Soler, MD, said in an interview. “It was very frustrating that we were able to develop compounds that could block a number of targets, but this one was a very elusive target. It was very hard to find something that would block that mutated protein. Finally, now we have compounds that are very active, or at least significantly active, against patients that have this mutation. It’s the most exciting thing I have seen lately.”

In addition to generating excitement, the approval of agents such as sotorasib present several clinical questions including where and how to use incorporate these agents into practice, as well as the incorporation of standard testing methods for identifying these targets for patients with NSCLC.

Perez-Soler is a cochair of the upcoming 16th Annual New York Lung Cancers Symposium® hosted by Physicians’ Education Resource® (PER®), a hybrid, interactive event in November. He will be joined by cochair Mark G. Kris, MD, and other experts in lung cancer to discuss the effect of these novel agents on treatment standards. For more information and to register for this and other events, visit gotoper.com.

We hope you enjoy reading about these new therapies. Please let our editorial director, Gina Mauro (gmauro@onclive.com), know what questions you would like us to explore in our publications and on OncLive.com.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder

References
DARZALEX FASPRO™ (daratumumab and hyaluronidase-fihj): subcutaneous administration in ~3 to 5 minutes¹

SAME POWERFUL EFFICACY. FASTER ADMINISTRATION.¹ ²*

Approved across 5 indications spanning a wide range of multiple myeloma patients¹

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

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

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

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

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

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

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO™. Monitor for local reactions and consider symptomatic management.
Neutropenia
Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment, according to the manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO™ until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO™, higher rates of Grade 3-4 neutropenia were observed.

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

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX FASPRO™ can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO™ may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Interference with Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). DARZALEX FASPRO™ demonstrated a non-inferior overall response rate (ORR) vs intravenous daratumumab in an open-label, randomized study assessing monotherapy in 522 patients:
- ORR was 41% (95% CI: 35%, 47%) for DARZALEX FASPRO™ (n=263) and 37% (95% CI: 31%, 43%) for intravenous daratumumab (n=259)†.
- Eligible patients were required to have relapsed or refractory multiple myeloma who had received 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent.

Efficacy consistent with intravenous daratumumab
- In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with lenalidomide and dexamethasone (DRd) was evaluated in 65 patients with multiple myeloma, who received ≥1 prior multiple myeloma therapy. The ORR was 91% (95% CI: 81%, 97%)†.
- In a single arm of a multicohort, open-label trial, DARZALEX FASPRO™ with bortezomib, melphalan, and prednisone (DVMP) was evaluated in 67 patients with newly diagnosed multiple myeloma who were ineligible for a transplant. The ORR was 88% (95% CI: 78%, 95%)†.

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

For intravenous daratumumab, median durations of 16 mg/kg infusions for the first, second, and subsequent infusions were approximately 7, 4, and 3 hours, respectively.† In clinical trials of DARZALEX FASPRO™, DARZALEX® (daratumumab), and the Prescribing Information for DARZALEX®, the term “infusion reactions” was used instead of “systemic administration-related reactions.”
Daratumumab may increase neutropenia induced by background therapy of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) administration-related reactions risk of delayed (defined as occurring the day after administration) systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 94 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients. Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids [see Dosage and Administration (2.3) in Full Prescribing Information]. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions [see Dosage and Administration (2.3) in Full Prescribing Information].

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 9 minutes to 4.7 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

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

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

Embryo-Fetal Toxicity
Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 5 months after the last dose [see Use in Specific Populations]. The combination of DARZALEX FASPRO with lenalidomide is contraindicated in pregnant women, because lenalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide prescribing information on use during pregnancy.

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

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

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

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

• Hypersensitivity and Other Administration Reactions [see Warning and Precautions].
• Neutropenia [see Warning and Precautions].
• Thrombocytopenia [see Warning and Precautions].

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

Newly Diagnosed Multiple Myeloma
In Combination with Bortezomib, Melphanal and Prednison
The safety of DARZALEX FASPRO with bortezomib, melphanal and prednison (D-VMP) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.1) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphanal and prednison. Among these patients, 93% were exposed for 6 months or longer and 19% were exposed for greater than one year. Serious adverse reactions occurred in 38% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fatal adverse reactions occurred in 0.8% of patients. Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia. The most common adverse reactions (>20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

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

<table>
<thead>
<tr>
<th>Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphanal and Prednison (D-VMP) in PLEIADES</th>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pneumonia</td>
<td>15</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES (continued)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>96 (52)</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>93 (42)</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>93 (42)</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88 (49)</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48 (19)</td>
</tr>
</tbody>
</table>

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

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>78 (47)</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>91 (45)</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>92 (45)</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>76 (42)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>69 (52)</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>80 (61)</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>80 (61)</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>64 (49)</td>
</tr>
</tbody>
</table>

Denominator is based on the safety population treated with D-Rd (N=65).
Table 5 summarizes the adverse reactions in COLUMBA.

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

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

### Monotherapy

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA (see Clinical Trials [14.2] in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously daily or daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than one patient were general physical health deterioration, septic shock, and respiratory failure.

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

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

The most common adverse reaction (≥20%) was upper respiratory tract infection.

Table 5 summarizes the adverse reactions in COLUMBA.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO (N=260)</th>
<th>Intravenous Daratumumab (N=258)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>24</td>
<td>1*</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1*</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0.4*</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>15</td>
<td>1*</td>
</tr>
<tr>
<td>Infusion reactionsd</td>
<td>13</td>
<td>2*</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0.4*</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2*</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cougha</td>
<td>9</td>
<td>1*</td>
</tr>
<tr>
<td>Dyspneaa</td>
<td>6</td>
<td>1*</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with D-Rd (N=65).

**Immunogenicity**

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

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

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

**Postmarketing Experience**

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

**Imune System:** Anaphylactic reaction

**Gastrointestinal:** Pancreatitis
Drug Interactions

Interference with Indirect Antiglobulin Tests

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units of blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion (see Warnings and Precautions).

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

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

Lactation

Risk Summary

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

Data

Animal Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, refer to the lenalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

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

Pediatric Use

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

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness were observed based on age. Adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

Clinical studies of DARZALEX FASPRO as part of a combination therapy did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

REFERENCES


PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity and Other Administration Reactions

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

Neutropenia

Advise patients to contact their healthcare provider if they have a fever (see Warnings and Precautions).

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding (see Warnings and Precautions).

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions, Use in Specific Populations).

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for at least 3 months after the last dose (see Use in Specific Populations).

Advise patients that lenalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide is only available through a REMS program (see Use in Specific Populations).

Advises patients to inform their healthcare provider if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again (see Adverse Reactions).

Product of Switzerland

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From the Editor

Untangling Fact From Bias in the Age of Social Media and Mistrust

by MAURIE MARKMAN, MD

It is difficult to overstate the confusion—one might even use the term chaos—associated with our nation’s messaging regarding a well-considered, rational, and scientifically based public health-focused approach to the current and future ramifications of the COVID-19 pandemic.

Concerns range from the effect of the delta variant on schools safely reopening for critical in-person learning,\(^1,^{2}\) to the risk of infection and serious illness among fully vaccinated individuals, to the need for COVID-19 vaccine booster shots.\(^3\) There also is great concern about continued negative economic effects on small businesses, which have been seriously affected by the pandemic and the possibility of a new round of partial or complete lockdowns. Results of a recent survey of small business owners emphasized the magnitude of the issues confronting these establishments.\(^4\)

Many pandemic-related issues have yet to be resolved, such as determining the potential role of vaccination for children younger than 12 years and examining the economic effect of deferred rental payments and possible evictions.\(^5\) Others may become topics of controversy—for example, the potential for multiple legal challenges regarding vaccine mandates,\(^6,^{7}\) the determination of what is an acceptable COVID-19 vaccine (ie, Chinese or Russian vaccine products) for future travel into the United States, and how to address the increasing availability of fake COVID-19 vaccination certificates.

We must add to this list ongoing governmental public health agency “missteps” or seriously inadequate communication regarding their decision-making processes related to the pandemic. These include the apparently unclear (and perhaps even bewildering) lack of urgency related to the FDA providing full approval, not solely emergency use authorizations, to all of the several remarkably safe and effective COVID-19 vaccines. Do the problems stem from inadequate numbers of personnel to complete the required review in a timely manner, or are we dealing with a seriously out-of-date and out-of-touch governmental bureaucracy? In the opinion of this commentator, whatever the explanation, the current state of affairs does little to instill any level of confidence among our citizens in the critically essential federal efforts to protect our health and welfare.

The situation has not been helped by the open debate among the scientific community, governmental public health authorities, and COVID-19 vaccine manufacturers about the potential need for booster vaccination and which individuals should receive a booster shot.\(^8,^{9}\) One must add to this controversy the World Health Organization’s rather strident pronouncements that vaccine booster shots—beyond the initial 2 doses of the several approved products—should not be offered at the present time so that priority can be given to countries with current limited vaccine availability.\(^10\) In addition, confusion regarding governmental public health agency recommendations, particularly by the CDC, about wearing masks—well-considered and appropriately vetted strategies to prevent the spread of the virus—has further added to the lack of trust in these agencies.

Unfortunately, the often disturbingly ineffective and clearly ongoing messaging difficulties experienced by the scientific and public health communities have permitted individuals, small groups, and rogue governments to spread inaccurate statements largely uncontested through almost completely unregulated social media platforms.

“What should be of serious concern for the entire cancer community...is the median number of engagements for articles that contained either misinformation or harmful information.”

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control efforts.10 Space does not permit a formal discussion of remarkably outlandish claims made regarding the origin of the pandemic and falsehoods regarding the potential adverse effects of lifesaving vaccines.10

The concern being expressed in this commentary is for the diminishing ability of governmental agencies to provide an authoritative voice related to the documented effectiveness and safety of critical cancer-associated public health measures vs the destructive effect of current and future posts created by individuals and groups who either unintentionally11 or intentionally spread misinformation.

Unfortunately, this concern is not simply theoretical. A recent peer-reviewed report specifically examined the presence of misinformation or harmful information on Facebook and other social media platforms.12 Two individuals with extensive knowledge of cancer examined popular articles pertaining to 4 common cancers that appeared on social media. They found that 32.5% of posts contained misinformation and 30.5% contained what the investigators considered to be harmful information. In addition, 76.9% of articles that included misinformation also contained harmful information.

Finally, and what should be of serious concern for the entire cancer community, investigators found that the median number of engagements for articles that contained either misinformation or harmful information was greater than for factual articles.12

The final point is a simple question: What are the cancer community, public health authorities, and governmental regulators going to do about this disturbing situation, now and in the future? The public is waiting for an answer.

REFERENCES

Pembrolizumab/Lenvatinib Gets Green Light for Frontline Advanced RCC

The FDA has approved pembrolizumab (Keytruda) plus lenvatinib (Lenvima) for the frontline treatment of patients with advanced renal cell carcinoma (RCC).

The efficacy was investigated in the phase 3 CLEAR/KEYNOTE-581 trial (NCT02811861), in which the combination exhibited statistically significant improvements compared with sunitinib (Sutent). Specifically, pembrolizumab plus lenvatinib resulted in a 61% reduction in the risk of disease progression or death vs sunitinib (HR, 0.39; 95% CI, 0.32-0.49; P < .0001). The median progression-free survival in the investigative arm was 23.9 months (95% CI, 20.8-27.7) vs 9.2 months (95% CI, 6.8-11.0) in the control arm. The combination elicited a 34% reduction in the risk of death over sunitinib (HR, 0.66; 95% CI, 0.49-0.88; P = .0049).

Additionally, the doublet showed an objective response rate of 71% (95% CI, 66%-76%) vs 36% (95% CI, 31%-41%) with the single agent; this included a 16% complete response rate vs 4% and a 55% partial response rate vs 32%, respectively.

FDA Places Pause on Trials for Myeloid Malignancies

A partial clinical hold has been placed on clinical trials examining the combination of eprenetapopt plus azacitidine in patients with myeloid malignancies, according to an announcement from Aprea Therapeutics Inc.

The hold on the investigational combination does not apply to the company’s ongoing clinical trials examining eprenetapopt in patients with lymphoid malignancies and solid tumors. It also does not affect the phase 1 trial of Aprea’s TP53 reactivator, APR-548, which is under investigation in a phase 1 trial (NCT04638309) in combination with azacitidine for the treatment of patients with TP53-mutant myelodysplastic syndrome (MDS).

The combination has recently demonstrated promising clinical activity in results from a phase 2 trial (NCT03588078) patients with TP53-mutated MDS (n = 34) or acute myeloid leukemia (n = 18), eliciting response rates of 62% and 33%, respectively.

Approximately 20 patients are receiving the combination, including the MDS, acute myeloid leukemia, and posttransplant maintenance trials, all of which have completed enrollment, according to the company. Participants who are benefiting from the doublet can continue to receive study treatment. Aprea plans to work with the FDA to review data that led to the hold and no additional patients will be enrolled until the 2 parties reach a resolution.

Finalized Guidance Is Issued for MFS as End Point in CRPC Clinical Trials

Recommendations for sponsors considering the use of metastasis-free survival (MFS)—typically defined as the time from randomization to distant radiographic progression—as an end point in clinical trials for nonmetastatic castration-resistant prostate cancer (CRPC) have been issued by the FDA. The rationale for using MFS stems from the ability to be measured earlier in the course of disease compared with overall survival.

Since patients with nonmetastatic CRPC can have a prolonged disease course, the assessment period—during which patients may have multiple therapies—with low death rates may make the use of overall survival impractical as a primary end point to support approval of products in this disease setting, the FDA wrote in the guidance.

In addition, the FDA wrote considerations for sponsors related to general trial design, imaging, interpretation of trial results, and analyses of MFS. Of note, the agency recommends that sponsors consider additional progression-free survival to support primary MFS analysis, define acceptable imaging modalities and assessment frequencies, and avoid interim efficacy analyses of MFS as they may result in over or underestimation of MFS improvement.

Study Findings Link Melphalan Flufenamide With Increased Risk of Death

The FDA has issued an alert and stopped enrollment for the phase 3 OCEAN trial (NCT03151811) following data that demonstrated treatment with melphalan flufenamide (melflufen; Pepaxto) resulted in an increased risk of death in patients with relapsed or refractory multiple myeloma.

Investigators examined melphalan flufenamide plus dexamethasone vs pomalidomide (Pomalyst) plus dexamethasone in patients with relapsed or refractory multiple myeloma who had received 2 to 4 prior lines of therapy and were resistant to lenalidomide (Revlimid) in the last line of therapy. Results indicated that the median overall survival in patients who received melphalan flufenamide/dexamethasone was 19.7 months (95% CI, 15.1-25.6) vs 25.0 months (95% CI, 18.1-31.9) in those given pomalidomide/dexamethasone (HR, 1.104; 95% CI, 0.846-1.441).

In the alert, the regulatory agency encouraged assessing the progress of patients who are receiving melphalan flufenamide and discussing the risks of continued administration with each recipient in the context of other options.

In February 2021, the agent received an approval in combination with dexamethasone in the fifth-line setting for this patient population based on data from the phase 2 HORIZON study (NCT02963493). The FDA will continue to assess findings from the trial and shared potential plans to hold a public meeting to further discuss these safety data and explore the continued marketing of the drug.

FDA Sets Decision Date for Adjuvant Atezolizumab for PD-L1+ Early-Stage NSCLC

The FDA has granted priority review to a supplemental biologics license application for atezolizumab (Tecentriq). The application is specifically looking for approval for the agent as an adjuvant treatment after surgery and platinum-based chemotherapy for patients with stage II to IIA non–small cell lung cancer (NSCLC) whose tumors have a PD-L1 expression of at least 1% per an FDA-approved test.

Findings from the phase 3 IMPower010 trial (NCT02486718) showed a 34% reduction in the risk of disease recurrence or death vs best supportive care (BSC; HR, 0.66; 95% CI, 0.50-0.88; P = .004). At a median follow-up of 32.8 months (range, 0.1-57.5), the median disease-free survival had not yet been reached (95% CI, 36.1-not estimable) with atezolizumab vs 35.3 months (95% CI, 29.0-not estimable) with BSC.

Follow-up for IMPower010 will continue with planned analyses of disease-free survival and overall survival in the intention-to-treat population. The regulatory agency is anticipated to decide on the application by December 1, 2021.
Nominate a dedicated and deserving nurse to be an Oncology Nurse Champion!

Do you know a nurse who goes above and beyond to make a measurable difference to improve patient outcomes through exceptional supportive care?

We are now accepting nominations from health care professionals, colleagues, patients, friends, and family of outstanding nurses who demonstrate these admirable qualities:

- Ability to help educate both patients and families about the cancer they face and their treatment path
- Knack for showing kindness, patience, and compassion in the face of difficulties faced by their patients
- Understanding of the science and how treatments are designed to overcome their patient’s cancer
- Aptitude to go above and beyond in supportive care for patients and patient families

Scan the code to nominate a nurse to become an Oncology Nurse Champion!
PHASE 1 UPDATES FROM THE 2021 AMERICAN SOCIETY FOR CLINICAL ONCOLOGY (ASCO) ANNUAL MEETING

ALLO-501A With ALLO-647
Lymphodepletion Shows Early Efficacy in Large B-Cell Lymphoma

ALLO-501A, a chimeric antigen receptor (CAR) T-cell product, showed encouraging signs of clinical activity when used with ALLO-647 lymphodepletion in patients with relapsed/refractory large B-cell lymphoma (LBCL) who did not previously receive autologous CAR T-cell therapy, according to findings from the phase 1/2 ALPHA-2 study (NCT04416984) presented during the 2021 ASCO Annual Meeting.

Results indicated that ALLO-501A elicited an objective response rate (ORR) of 56% (95% CI, 21%-86%) in 9 patients, including a complete response (CR) rate of 44% (95% CI, 14%-79%). Patients who received ALLO-501A at the second dose level of 120 x 10⁶ CAR T cells (n=4) had an ORR of 50% (95% CI, 5%-85%). Both responses were CRs. For 5 patients who received ALLO-501A as a consolidation treatment, the ORR was 60% (95% CI, 15%-95%) with a CR rate of 40% (95% CI, 5%-85%).

The primary end point of the study was safety, tolerability, and cell kinetics of ALLO-501A following lymphodepletion. Secondary end points included investigator-assessed ORR and cell kinetics of ALLO-501A.

To read more, visit bit.ly/3kmMbN3.

Pembrolizumab/Cabozantinib Combo Provides Benefit in mRCC

The combination of pembrolizumab (Keytruda) and cabozantinib (Cabometyx) induced a response in more than half of patients with metastatic renal cell carcinoma (mRCC) at the recommended phase 2 dose (RP2D), according to findings from the phase 1/2 trial (NCT03149822) that were presented during the 2021 ASCO Annual Meeting.

Among the efficacy population of 40 patients, the objective response rate (ORR) was 63.2% (95% CI, 48.5%-100%). There was a partial response rate of 50% among 6 patients with nonclear cell RCC. The clinical benefit rate was 97.4% (95% CI, 88%-100%).

Patients who were eligible for the trial included those with histological or cytological documentation of any histologic subtype of RCC, an ECOG performance status of 0 or 1, and measurable or evaluable disease based on RECIST version 1.1 criteria. In terms of histology, 85% of patients had clear cell, 15% had nonclear cell, and 15% had sarcomatoid. Patients who had previously received pembrolizumab or cabozantinib were excluded, but prior treatment with other checkpoint inhibitors and VEGF inhibitors was allowed. The primary end point of the study was ORR at the RP2D.

To read more, visit bit.ly/36KVJco.

Subcutaneous Teclistamab Demonstrates Encouraging Efficacy, Safety in Relapsed/Refractory Multiple Myeloma

Treatment with teclistamab (JNJ-64007957), administered subcutaneously (SC) at a dose of 1500 µg/kg once weekly, led to a high response rate and favorable safety profile in patients with relapsed/refractory multiple myeloma, according to updated findings from the phase 1 MajesTEC-1 trial (NCT03145181) presented during the 2021 ASCO Annual Meeting.

The data showed that among the 40 patients who received the recommended phase 2 dose (RP2D), the agent elicited an overall response rate of 65%, with 58% of patients achieving a very good partial response or better, and more than 40% experiencing a complete response or better.

Of note, 28 patients (70%) experienced cytokine release syndrome with the RP2D dose, but all events were grade 1/2 and generally confined to the step-up in the first full dose.

Finally, investigators reported durable responses—the 26 responders, 22 (85%) were alive and continued on treatment with teclistamab, after a median follow-up of 7.1 months (range, 3.0-12.2).

To read more, visit bit.ly/2XxPAiu.

Talquetamab RP2D Is Effective in Relapsed/Refractory Multiple Myeloma

Talquetamab (GPRC5D) induced a high clinical response rate with favorable tolerability in patients with relapsed/refractory multiple myeloma when administered at the recommended phase 2 dose (RP2D) of 405 µg/kg weekly, according to updated data from an analysis of the phase 1 MonumentTAL-1 trial (NCT03399799) presented during the 2021 ASCO Annual Meeting. At the RP2D, the off-the-shelf T cell–redirecting agent achieved an overall response rate (ORR) of 70% with a median time to first confirmed response of 1 month (range, 0.2-3.8) in 30 patients.

Among 23 patients with triple-refractory disease, the ORR was 65.2% and was 83.3% in those with penta-refractory disease (n=6).

The trial enrolled 184 patients; 102 were given talquetamab intravenously (IV) and 82 received the agent subcutaneously (SC). Patients were administered talquetamab at dose ranges of 0.5 to 180 µg/kg IV and 5.0 to 800 µg/kg SC. The primary objective of part 1 of the trial was identification of the RP2D and the primary objective of part 2 was safety and tolerability.

To read more, visit bit.ly/3wuECJag.
Indication

VITRAKVI® (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

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

Important Safety Information

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

Please see additional Important Safety Information throughout and accompanying Brief Summary of full Prescribing Information.
**The First-in-Class TRK* Inhibitor for TRK Fusion Cancer Across Solid Tumors**

**Indication**

VITRAKVI is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

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

**Important Safety Information (continued)**

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

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

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

**Embryo-Fetal Toxicity:** VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

**Most Common Adverse Reactions (≥20%):** The most common adverse reactions (≥20%) were: increased ALT (45%), increased AST (45%), anemia (42%), fatigue (37%), nausea (29%), dizziness (28%), cough (26%), vomiting (26%), constipation (23%), and diarrhea (22%).

*TRK, tropomyosin receptor kinase.*

*NTRK, neurotrophic receptor tyrosine kinase; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.*
Across solid tumors

**VITRAKVI IS HIGHLY EFFECTIVE IN TRK FUSION CANCER**

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

- **22% CR**
- **53% PR**
- **75% ORR**

*Includes one pediatric patient with unresectable IFS who underwent resection following partial response and who remained disease-free at data cutoff.

** Median DOR not reached at time of data cutoff (N=41)**

Range: 1.6+ to 33.2+ months

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

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

**Important Safety Information (continued)**

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

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

Please see Brief Summary of full Prescribing Information on the following page.
**VITRAKVI** (larotrectinib) capsules, for oral use

**VITRAKVI** (larotrectinib) oral solution

**Initial U.S. Approval:** 2018

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

1. **INDICATIONS AND USAGE**

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

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

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

2. **CONTRAINdications**

None.

3. **WARNINGS AND PRECAUTIONS**

5.1 Neurotoxicity

In clinical trials, neurologic adverse reactions of any grade occurred in 53% of patients, including Grade 3 and Grade 4 neurologic adverse reactions in 6% and 0.6% of patients, respectively [see Adverse Reactions (6.1)]. The most (65%) of neurologic adverse reactions occurred within the first three months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse reactions occurred delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%).

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

5.2 Hepatotoxicity

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

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

5.3 Embryo-Fetal Toxicity

Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, VITRAKVI can cause fetal harm when administered to a pregnant woman. Larotrectinib resulted in malformations in rats and rabbits at maternally exposures that were approximately 11- and 0.7-times, respectively, the clinical dose of 100 mg twice daily. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI [see Use in Specific Populations (8.1, 8.3)].

6. **ADVERSE REACTIONS**

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

- **Neurotoxicity** [see Warnings and Precautions (5.1)]
- **Hepatotoxicity** [see Warnings and Precautions (5.2)]

6.1 Clinical Trial Experience

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

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

Across these 176 patients, the median age was 51 years (range: 28 days to 82 years); 25% were 18 years or younger; 52% were male, and 72% were White, 11% were Hispanic/Latino, 8% were Black, and 3% were Asian. The most common tumors in order of decreasing frequency were soft tissue sarcoma (16%), salivary gland (11%), lung (10%), thyroid (9%), colon (8%), infantile fibrosarcoma (8%), primary central nervous system (CNS) (7%), and melanoma (5%). NTRK gene fusions were present in 60% of VITRAKVI-treated patients. Most (60%) received VITRAKVI 100 mg orally twice daily and 68% of (18 years or younger) received VITRAKVI 100 mg/m² twice daily up to a maximum dose of 100 mg twice daily. The dose ranged from 50 mg daily to 200 mg twice daily in adults and 8.6 mg/m² twice daily to 12.0 mg/m² twice daily in pediatrics [see Pediatric Use (8.4)].

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades* (%)</th>
<th>Grade 3-4** (%)</th>
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<tbody>
<tr>
<td>General</td>
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<tr>
<td>Investigations</td>
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<tr>
<td>Increased weight</td>
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<td>4</td>
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<tr>
<td>Musculoskeletal and Connective Tissue</td>
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<td></td>
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<tr>
<td>Arthralgia</td>
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<tr>
<td>Myalgia</td>
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<td>Muscle weakness</td>
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<tr>
<td>Metabolism and Nutrition</td>
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<td>Decreased appetite</td>
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<td>Hypertension</td>
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</tr>
</tbody>
</table>

**National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.

** One Grade 4 adverse reaction of pyrexia.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades* (%)</th>
<th>Grade 3-4** (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>45</td>
<td>3</td>
</tr>
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<td>Hypophosphatemia</td>
<td>35</td>
<td>0</td>
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<tr>
<td>Increased alkaline phosphatase</td>
<td>30</td>
<td>3</td>
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<tr>
<td>Hematology</td>
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<td></td>
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<tr>
<td>Anemia</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23</td>
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</tr>
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</table>

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

** NCI-CTCAE v4.0.
The efficacy of VITRAKVI was evaluated in 12 pediatric patients and is described in the Clinical Studies section [see Clinical Studies (14)]. The safety of VITRAKVI was evaluated in 44 pediatric patients who received VITRAKVI. Of these 44 patients, 27% were 1 month to < 2 years (n = 12), 43% were 2 years to < 12 years (n = 19), and 30% were 12 years to < 18 years (n = 13). 43% had metastatic disease and 57% had locally advanced disease; and 91% had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common prior cancers were infantile fibrosarcoma (25%), soft tissue sarcoma (23%), primary CNS tumors (20%), and thyroid cancer (9%).

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

7.1 Effects of Other Drugs on VITRAKVI

Strong CYP3A4 Inducers

Coadministration of VITRAKVI with a strong CYP3A4 inducer may increase larotrectinib plasma concentrations, which may result in a higher incidence of adverse reactions [see Clinical Pharmacology (12.3)]. Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice. If coadministration of strong CYP3A4 inhibitors cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

Strong CYP3A4 Inducers

Coadministration of VITRAKVI with a strong CYP3A4 inducer may decrease larotrectinib plasma concentrations, which may decrease the efficacy of VITRAKVI [see Clinical Pharmacology (12.3)]. Avoid coadministration of VITRAKVI with strong CYP3A4 inducers, including St. John’s wort. If coadministration of strong CYP3A4 inducers cannot be avoided, modify VITRAKVI dose as recommended [see Dosage and Administration (2.4)].

7.2 Effects of VITRAKVI on Other Drugs

Sensitive CYP3A4 Substrates

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

Based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action [see Clinical Pharmacology (12.1)], VITRAKVI can cause embryofetal harm when administered to a pregnant woman. There are no available data on VITRAKVI use in pregnant women. Administration of larotrectinib to pregnant rats during the period of organogenesis resulted in malformations at the clinical dose of 100 mg twice daily. Decreased organogenesis resulted in malformations at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily (see Data). Adverse reproductive outcomes 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

Human Data

Published reports of individuals with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action [see Clinical Pharmacology (12.1)], VITRAKVI can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on VITRAKVI use in pregnant women. Administration of larotrectinib to pregnant rats during the period of organogenesis resulted in malformations at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily (see Data). Adverse reproductive outcomes 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.

8.2 Lactation

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

Males

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

Infertility

Female

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

Males

Contraception as recommended [see Dosage and Administration (2.1)].

8.4 Pediatric Use

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

The efficacy of VITRAKVI was evaluated in 12 pediatric patients and is described in the Clinical Studies section [see Clinical Studies (14)]. The safety of VITRAKVI was evaluated in 44 pediatric patients who received VITRAKVI. Of these 44 patients, 27% were 1 month to < 2 years (n = 12), 43% were 2 years to < 12 years (n = 19), and 30% were 12 years to < 18 years (n = 13). 43% had metastatic disease and 57% had locally advanced disease; and 91% had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common prior cancers were infantile fibrosarcoma (25%), soft tissue sarcoma (23%), primary CNS tumors (20%), and thyroid cancer (9%).

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

The pharmacokinetics of VITRAKVI in the pediatric population were similar to those seen in adults [see Clinical Pharmacology (12.3)].

8.5 Geriatric Use

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

8.6 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment [see Clinical Pharmacology (12.3)]. Reduce VITRAKVI dose as recommended [see Dosage and Administration (2.6)].

8.7 Renal Impairment

No dose adjustment is recommended for patients with renal impairment of any severity [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use), Neurotoxicity

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

Hepatotoxicity

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

Embryo-Fetal Toxicity

Advise males and females of reproductive potential of the potential risk to a fetus [see Warnings and Precautions (5.3)]. Use in Specific Populations (8.1). Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective contraception during the treatment with VITRAKVI and for at least 1 week after the final dose [see Use in Specific Populations (8.3)].

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

Lactation

Advise women not to breastfeed during treatment with VITRAKVI and for 1 week following the final dose [see Use in Specific Populations (8.2)].

Infertility

Female

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

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, grapefruit or grapefruit juice while taking VITRAKVI [see Drug Interactions (7.1, 7.2)].
Promising Results Push Nivolumab/Chemotherapy Forward in Gastric Cancer

by KYLE DOHERTY

The combination of Nivolumab (Opdivo) and chemotherapy has shown a significant benefit across outcomes for patients with gastric cancer. On April 16, 2021, the FDA approved the PD-1–blocking antibody in combination with fluoropyrimidine- and platinum-containing chemotherapy for advanced or metastatic gastric cancer, gastroesophageal junction cancer (GE/JC), and esophageal adenocarcinoma.

The approval was based on results from the phase 3 CheckMate 649 trial (NCT02372116), which showed that patients treated with the combination of nivolumab and either FOLFOX (folinic acid, fluorouracil and oxaliplatin) or CapeOX (capecitabine plus oxaliplatin) chemotherapy achieved a median overall survival (OS) of 13.8 months (95% CI, 12.6-14.6; P = .0002) in 789 patients, compared with 11.6 months (95% CI, 10.9-12.5) in 792 patients treated with chemotherapy alone. The overall response rates were 47% (95% CI, 43%-50%) vs 37% (95% CI, 34%-40%), respectively.

In an interview with OncologyLive®, Jaffer A. Ajani, MD, a professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, unpacked the performance of the combination regimen in some subgroups of interest.

The primary end point of the CheckMate 649 study was benefit in patients with a combined positive score (CPS) of 5 or higher. What was the rationale for selecting that end point?

The rationale came from previous studies, particularly KEYNOTE-059 [NCT02335411]. There were a series of prior studies before this which already demonstrated that PD-L1 expression makes a difference. If [a patient is] PD-L1 positive, irrespective of the number, it makes a difference.

Incidentally, this was not the primary end point of this study when it was initially designed; this was [adjusted] during the study as more data came in. The primary end point is PFS and OS for CPS 5 or higher. There were 2 other groups: CPS 1 to 4 and all patients. Looking at the survival curves, there is benefit [seen across groups] and the maximum benefit was for those with CPS of 5 or higher for PFS and OS; this was a considerable benefit. The median survival difference was more than 3 months. You don’t get that with gastric cancer very often, and PFS is about 1.6 months. The P values are very strong.

In the microsatellite instability–high (MSI-H) subset, median OS was not reached. What does the future look like for these patients?

In colon cancer, the MSI-H was crystallized [as a marker] in the clinic. A lot of credit goes to investigators at Johns Hopkins [Medicine] who did the initial study in the second-line setting, demonstrating dramatic responses with single-agent immunotherapy. There was a trial in colon cancer in first line that compared pembrolizumab [Keytruda] with chemotherapy [and with] biological therapy, which has been the standard of care for 15 years. Pembrolizumab was better than chemotherapy and biotreatment and has moved into first line for patients with MSI-H colon cancer.

We’ve been looking at all these data and clearly MSI-H is not uncommon. There have been data in KEYNOTE-061 (NCT02370498), KEYNOTE-590 (NCT03189719), and more; it was clear that these patients can benefit.

In this CheckMate 649, the benefit is dramatically better, although both groups did receive chemotherapy. Now, we must wonder, do we even need chemotherapy in this group of patients?

What is the best way to manage treatment-related adverse events with immunologic etiology?

The addition of nivolumab did not produce any alarming new signals. That’s reassuring. There were a bit more than with chemotherapy alone [because you’re adding another drug]. Most of us, at least in the Western world, are very familiar with nivolumab because it’s been around for a while and we know how to handle it.

The bottom line is familiarity. The entire team needs to [be aware]. Even in private practices, a group of people are helping the patients. There are certain tasks done by certain people. If you are not aware [of what to expect], then you you’re not going to identify it.

Second is the knowledge of what to do once you became aware of a toxicity that is because of immunotherapy. You must know how to grade it. Third, you must know how to manage it and determine whether it’s getting better or not. Finally, you need to know when to refer. There are a lot of subspecialties that have popped up in the past 5 years. For example, if my patient has pneumonitis, I don’t try to manage it; I send them to my pulmonologist who has become expert because they are seeing not only patients with gastric cancer, but with melanoma, lung cancer, you name it. They know what to do. Same thing for a gastroenterologist for a patient with colitis and hepatitis. You have to understand that there may be other people who are better than you in managing organ-specific toxicities.

Are there treatment options that may benefit patients with GE/JC or esophageal adenocarcinoma?

Not that we know. For those with CPS of 5 or higher for gastric, GE/JC, and esophageal, there is sufficient benefit. Pembrolizumab and chemotherapy is approved for esophageal adenocarcinoma, and GE/JC based on data from KEYNOTE-590.

In that study, the number of patients with adenocarcinoma was approximately 200. In CheckMate 649 we are talking about 1500 patients. The KEYNOTE data were quite reasonable, but not robust like CheckMate 649. You can trust these data more than KEYNOTE for adenocarcinoma.

Many of my colleagues have been asking major sponsors to launch the next generation of studies, which should add another immunotherapy or targeted therapy to nivolumab plus chemotherapy. This is a good advance, but it’s still not enough. You will see some data coming out with longer follow-up. I don’t know if you can cure some patients with metastatic disease [with the addition of] nivolumab, that we will [find out]. I can tell you it’s not going to be many patients.

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REFERENCE

PIVOTAL CLINICAL TRIAL
CheckMate 649 (NCT02872116) was a phase 3 randomized, multicenter, open-label trial evaluating nivolumab in combination with chemotherapy vs chemotherapy alone in 1581 adult patients with previously untreated advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

BASELINE PATIENT CHARACTERISTICS
Median age (years, range)
61 (18-90)
N = 1581
Chemotherapy regimen
mFOLFOX: 53.5%
mCapeOx: 46.5%

Tumor location
70%
16.5%
13.5%

Disease characteristics
17.5%
39%
95.5%
 Metastatic disease
Liver metastases
Signet ring cell carcinoma

Efficacy in the CheckMate 649 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab plus mFOLFOX6 or CapeOX (n = 789)</th>
<th>mFOLFOX6 or CapeOX (n = 792)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>13.8 (12.6-14.6)</td>
<td>11.6 (10.9-12.5)</td>
</tr>
<tr>
<td>HR, 95% CI</td>
<td>0.80; 0.71-0.90; P = .0002</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>7.7 (7.1-8.5)</td>
<td>6.9 (6.6-7.1)</td>
</tr>
<tr>
<td>HR, 95% CI</td>
<td>0.77; 0.68-0.87</td>
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<tr>
<td>ORR (95% CI)</td>
<td>47% (43%-50%)</td>
<td>37% (34%-40%)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>8.5 (7.2-9.9)</td>
<td>6.9 (5.8-7.2)</td>
</tr>
</tbody>
</table>

PD-L1 CPS ≥ 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab plus mFOLFOX6 or CapeOX (n = 641)</th>
<th>mFOLFOX6 or CapeOX (n = 655)</th>
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</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>14.0 (12.6-15.0)</td>
<td>11.3 (10.6-12.3)</td>
</tr>
<tr>
<td>HR, 95% CI</td>
<td>0.77; 0.68-0.88; P &lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>7.5 (7.0-8.4)</td>
<td>6.9 (6.1-7.0)</td>
</tr>
<tr>
<td>HR, 95% CI</td>
<td>0.74; 0.65-0.85</td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>49% (45%-53%)</td>
<td>38% (34%-42%)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>8.5 (7.7-10.3)</td>
<td>6.9 (5.8-7.6)</td>
</tr>
</tbody>
</table>

PD-L1 CPS ≥ 5

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivolumab plus mFOLFOX6 or CapeOX (n = 473)</th>
<th>mFOLFOX6 or CapeOX (n = 482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>14.4 (13.1-16.2)</td>
<td>11.1 (10.0-12.1)</td>
</tr>
<tr>
<td>HR, 95% CI</td>
<td>0.71; 0.61-0.83; P &lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>7.7 (7.0-9.2)</td>
<td>6.0 (5.6-6.9)</td>
</tr>
<tr>
<td>HR, 95% CI</td>
<td>0.68; 0.58-0.79; P &lt;.0001</td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>50% (46%-55%)</td>
<td>38% (34%-43%)</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>9.5 (8.1-11.9)</td>
<td>6.9 (5.6-7.9)</td>
</tr>
</tbody>
</table>

CapeOX, capcitabine and oxaliplatin; CPS, combined positive score; DOR, duration of response; mFOLFOX6, modified leucovorin, fluorouracil, and oxaliplatin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Warnings and Precautions
- Immune-mediated adverse reactions
- Infusion-related reactions
- Complications of allogeic hematopoietic stem cell transplantation
- Embryo-fetal toxicity

FDA approval—April 16, 2021
FDA grants approval for nivolumab (Opdivo) in combination with fluoropyrimidine- and platinum-containing chemotherapy for patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma.

Mechanism of action:
- Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

Dose:
- 360 mg every 3 weeks in combination with fluoropyrimidine- and platinum-containing chemotherapy
- 240 mg every 2 weeks in combination with fluoropyrimidine- and platinum-containing chemotherapy

Company: Bristol Myers Squibb

References
Belumosudil Expands Treatment Options for Patients With Chronic GVHD

by ONCOLOGYLIVE® STAFF

DATA FROM THE PHASE 2 ROCKstar trial (NCT03640481) demonstrated that belumosudil (Rezurock) induced clinically meaningful, durable responses in patients with chronic graft-vs-host disease (GVHD), irrespective of previous treatment received, severity of disease, and number of organs involved. Moreover, these findings supported the FDA approval of the agent for use in adult and pediatric patients 12 years and older with chronic GVHD following failure of at least 2 prior lines of systemic therapy. 1

The approval of the ROCK2 inhibitor affords investigators another option to fill the treatment void that exists for patients with disease progression following treatment with other available therapies including ibrutinib (Imbruvica) and ruxolitinib (Jakafi).“Ibrutinib [was] the first approved therapy [for] this disease and was a great step forward for us; [however] it’s not effective in all patients,” said study investigator Corey S. Cutler, MD, MPH, FRCPC, in an interview with OncologyLive®. Cutler is an associate professor of medicine at Harvard Medical School and medical director of the Adult Stem Cell Transplantation Program at Dana-Farber Cancer Institute in Boston, Massachusetts.

“Many patients who initially respond to ibrutinib eventually progress and require later [lines of therapy]. Having more than one option for these patients is really something that our patients need,” he said.

TARGETING ROCK ELICITS RESPONSE

ROCK2 inhibition rebalances immune response to treat at the level of the germinal center by downregulating Th17 cells and upregulating regulatory T cells. 2 Data from the ROCKstar study showed that patients who received belumosudil achieved a clinically meaningful response across all key subgroups. Investigators for ROCKstar examined the agent in 2 cohorts of patients—200 mg of belumosudil once daily and 200 mg of belumosudil twice daily.

In previously reported data, the response rates between the 2 arms were similar, and the FDA approved the 200-mg once-daily dose. Specifically, 65 patients received belumosudil 200 mg once daily, and overall response rate (ORR) was assessed through day 1 of cycle 7 per ROCKstar protocol. The ORR was 75% (95% CI, 63%-85%), with 6% being complete responses and 69% being partial responses. 1 The median time to first response was 1.8 months (95% CI, 1.0-1.9), with a median duration of response of 1.9 months (95% CI, 1.2-2.9), which was determined as time of first response to progression, death, or new systemic therapies for chronic GVHD. In patients who achieved response (n = 49), 62% did not initiate a new systemic therapy or die for at least 12 months since response.

ORRs stratified by organ involvement, a subgroup analysis of interest, were recently published in Blood. 3 The analysis included combined data from the 2 arms of the study (N = 132). In total 75% had involvement in joint/fascia, 10% lower gastrointestinal (GI), 17% upper GI, 55% mouth, 24% esophagus, 74% eyes, 83% skin, 10% liver, and 38% lungs. The ORR was greatest for those with joint/fascia involvement at 71%, with 51% complete responses and 20% partial responses. For patients with lower and upper GI involvement, the ORRs were 69% and 51%, respectively. Further, the ORRs were reported for mouth (55%), esophagus (45%), eyes (42%), skin (37%), liver (39%), and lungs (26%). 2,3

Across all study participants, failure-free survival rates at 6 and 12 months were 75% and 56%, respectively.

FUTURE DIRECTIONS

“[Similar to] any drug in GVHD that we have tested in the past, we tend to use these agents in patients who have very few options left for their therapy,” Cutler said. “The natural thing to think about for the compound—and really any other compound following development—is to look at its activity in earlier stages of chronic GVHD. [This includes] either frontline steroid failures or front line [in combination with] steroids, potentially even frontline [use] instead of steroids. There is always the idea of whether this is an appropriate agent to use for prophylaxis of chronic GVHD or not.”

Cutler noted that investigators are interested in examining the efficacy of the agent in subtypes of GVHD, including patients with fibrosis as one of their prominent features, because ROCK regulates multiple profibrotic processes including myofibroblast activation. 2 “There stands to be at least a reasonable chance that this drug can reverse established fibrosis,” he said. “We would also like to see it tested in larger groups of patients with chronic GVHD-induced fibrosis to determine how effective it can be in reversing established fibrosis.”

The updated analysis demonstrated that the efficacy of belumosudil was maintained, regardless of previous treatment with ibrutinib (n = 46) or ruxolitinib (n = 38). The ORRs in the ruxolitinib and ibrutinib subsets were 68% (95% CI, 51%-83%) and 74% (95% CI, 59%-86%), respectively. Although belumosudil represents a treatment option for patients who experience failure of these agents, future head-to-head studies may provide insights to where this agent best fits into the treatment paradigm.

“We would like to see this agent tested earlier in the treatment of patients with chronic GVHD, perhaps in direct comparison to other commonly used agents,” Cutler said. “There still will be a need for other agents in this space. Some patients will not respond to this drug, and others may require a combination of therapies to maximize the likelihood of successful chronic GVHD outcomes.”

REFERENCES

**PIVOTAL CLINICAL TRIAL**

KD025-213 (NCT03640481) was a phase 2, multicenter, randomized, open-label, dose-ranging trial evaluating belumosudil in patients with chronic GVHD who received 2 to 5 prior lines of systemic therapy and required additional treatment.

**BASELINE PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median global severity rating</td>
<td>7 (range, 2-9)</td>
</tr>
<tr>
<td>Median Lee Symptom Scale score</td>
<td>27 (range, 7-56)</td>
</tr>
<tr>
<td>Median corticosteroid dose (PE/kg)</td>
<td>0.19 (range, 0.03-0.95)</td>
</tr>
</tbody>
</table>

PE, prednisone equivalent.

**EFFICACY IN THE KD025-213 TRIAL**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Belumosudil (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR* (95% CI)</td>
<td>75% (63%-85%)</td>
</tr>
<tr>
<td>CR</td>
<td>6%</td>
</tr>
<tr>
<td>PR</td>
<td>6%</td>
</tr>
</tbody>
</table>

**Response**

| Median DOR, months (95% CI)         | 1.9 (1.2-2.9)        |
| Median time to first response, months (95% CI) | 1.8 (1.0-1.9) |
| No death or new systemic therapy for ≥ 12 months (95% CI) | 62% (46%-74%) |

CR, complete response; DOR, duration of response; ORR, overall response rate; PR, partial response.

*ORR was evaluated through day 1 of cycle 7 and comprised CR or PR according to the 2014 National Institute of Health response criteria.

**WARNINGS AND PRECAUTIONS**

- Embryo-fetal toxicity

**COMMONLY REPORTED ADVERSE EFFECTS IN KD025-213 TRIAL**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>All grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection (pathogen not specified)</td>
<td>53%</td>
<td>16%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>46%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>42%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35%</td>
<td>5%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>Cough</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Edema</td>
<td>27%</td>
<td>1%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>23%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**REFERENCE**

Overall survival with LIBTAYO vs platinum-based chemotherapy in EMPOWER-Lung 1-3,\textsuperscript{1} \\ ITT patient population (N=710)\textsuperscript{1} \\

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Event</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT patient population (N=710)</td>
<td>Median OS: 22.1 months</td>
<td>0.68</td>
<td>0.0022</td>
</tr>
<tr>
<td></td>
<td>Number of deaths: 30% of patients (212 out of 710 patients) with LIBTAYO and 40% of patients (284 out of 710 patients) with chemotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The EMPOWER-Lung 1 study was designed to enroll patients with PD-L1 ≥50%.\textsuperscript{2} 
- A total of 710 patients were enrolled and randomized. For some patients, it was later determined that PD-L1 biomarker testing was not conducted according to the instructions for use, and required retesting.\textsuperscript{2} 
- An analysis was conducted in a subset of patients with known PD-L1 ≥50% (n=563). The analysis excluded 91 patients from the overall population whose PD-L1 status was known because their tumors could not be retested, and 56 patients from the overall population who had <50% PD-L1 expression (LIBTAYO is not indicated in patients with <50% PD-L1 expression).\textsuperscript{2} 

Known PD-L1 ≥50% patient population (n=563)\textsuperscript{2,3} 

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Event</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known PD-L1 ≥50% patient population (n=563)</td>
<td>Median OS: 15.3 months</td>
<td>0.57</td>
<td>0.00022</td>
</tr>
<tr>
<td></td>
<td>Number of deaths: 25% of patients (141 out of 563 patients) with LIBTAYO and 38% of patients (214 out of 563 patients) with chemotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PD-L1 expression was determined using the PD-L1 IHC 22C3 pharmDx assay.\textsuperscript{4} 

*Investigator’s choice: Paclitaxel + cisplatin or carboplatin; gemcitabine + cisplatin or carboplatin; or pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance in patients with non-squamous histology.\textsuperscript{1,3} 
\textsuperscript{1} Platinum-based.\textsuperscript{1,3} 
\textsuperscript{2} ALK=anaplastic lymphoma kinase; EGFR=epidermal growth factor receptor; HR=hazard ratio; IHC=immunohistochemistry; ITT=intention-to-treat; NE=not evaluable; NR=not reached; NSCLC=non–small cell lung cancer; OS=overall survival; PD-L1=programmed death ligand 1; ROS1=ROS proto-oncogene 1, receptor tyrosine kinase.

Clinical safety data\textsuperscript{1} 
- LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients.
- Adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke, and increased aspartate aminotransferase.
- Serious adverse reactions occurred in 28% of patients receiving LIBTAYO.
- The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

**Important Safety Information**

**Warnings and Precautions**

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

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1–blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. No dose reduction for LIBTAYO is recommended. In general, withdraw LIBTAYO for severe (Grade 3) immune-mediated adverse reactions.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.
LIBTAYO safety profile in EMPOWER-Lung 1
Adverse reactions in ≥10% of patients1

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>LIBTAYO monotherapy (n=353)</th>
<th>Chemotherapy (n=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash†</td>
<td>15</td>
<td>1.4</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>3.4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue†</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia†</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough‡</td>
<td>11</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, neck pain, spinal pain, and musculoskeletal stiffness.
††Rash is a composite term that includes rash, dermatitis, articular, rash maculopapular, erythema, rash erythematous, rash pruritic, psoriasis, autoimmune dermatitis, dermatitis acrodermatitis, dermatitis allergic, dermatitis atopic, dermatitis bullosa, drug eruption, dysidrotic eczema, lichen planus, and skin reaction.
†Fatigue is a composite term that includes fatigue, asthenia, and malaise.

In patients who had no EGFR, ALK, or ROS1 aberrations:

EMPOWER-Lung 1 was designed to enroll advanced NSCLC patients with PD-L1 ≥50%1

In the LIBTAYO arm (ITT patient population) at baseline, 12% of patients had pretreated and stable brain metastases, 18% had locally advanced disease, and 2% had controlled hepatitis B or hepatitis C. Patients with HIV were eligible to enroll, but none were recruited.1,2,4

Important Safety Information (continued)

Warnings and Precautions (continued)

Severe and Fatal Immune-Mediated Adverse Reactions (continued)

Permanently discontinue LIBTAYO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated adverse reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

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

Warnings and Precautions (continued)

Severe and Fatal Immune-Mediated Adverse Reactions (continued)

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

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.5%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

Immune-mediated hepatitis: LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%). Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 19% (3/16) of these patients. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence.

For hepatitis with no tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or if total bilirubin increases to more than 3 times the ULN.

For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

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

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

- Adrenal insufficiency: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 6.7% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

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

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

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

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

- Hypothyroidism: Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 11.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 83.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 3 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement, 1 required ongoing hormone replacement therapy.

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

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

Warnings and Precautions (continued)

**Severe and Fatal Immune-Mediated Adverse Reactions (continued)**

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

**Immune-mediated dermatologic adverse reactions:** LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinstituted LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

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

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

**Infusion-related reactions**

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

**Complications of allogeneic HSCT**

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

**Embryo-fetal toxicity**

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

**Adverse Reactions**

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

**Use in Specific Populations**

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

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

Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in LIBTAYO in 1.4% of patients and withholding of LIBTAYO in 2.1% of the patients received prior thoracic radiation. Antibodies the incidence of pneumonitis is higher in patients who have alternate etiology. In patients treated with other PD-1/PD-L1 blocking immune-mediated pneumonitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated pneumonitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%) adverse reactions. Pneumonitis led to permanent discontinuation of LIBTAYO in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withhold for colitis, 4 reintitated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence of colitis.

Immune-Mediated Hepatitis

LIBTAYO can cause immune-mediated hepatitis. The definition of immune-mediated hepatitits included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Nineteen percent (19%) of these patients (3/16) required additional immunosuppression with mycophenolate. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld for hepatitis, 3 patients reintitated LIBTAYO after symptom improvement; of these, none had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff. Hypophysitis

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

Thyroid Disorders

LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hyperthyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information]. Thyroiditis: Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.
Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Other Immune-Mediated Adverse Reactions

Systemic corticosteroids were required in all patients with immune-mediated adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.5% of patients.

Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

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

Hyperthyroidism: Hyperthyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hyperthyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hyperthyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hyperthyroidism. Hyperthyroidism resolved in 83.0% of the 60 patients. The majority of patients with hyperthyroidism required long-term thyroid hormone replacement.

Of the 9 patients in whom LIBTAYO was withheld for hyperthyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis.

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

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

Immune-Mediated Nephritis with Renal Dysfunction

LIBTAYO can cause immune-mediated nephritis. The definition of immune-mediated nephritis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Immune-mediated nephritis occurred in 0.6% (5/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients.

Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld for nephritis, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), 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. Withhold or permanently discontinue LIBTAYO depending on severity [see Dosage and Administration (2.3) in the full prescribing information].

Immune-mediated dermatologic adverse reactions occurred in 1.6% (12/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients.

Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 7 reinitiated LIBTAYO after symptom improvement; of these 43% (3/7) had recurrence of the dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions

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

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

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

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

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

Musculoskeletal and Connective Tissue: Myositis/polymyositis, myositis, arthritis, polymyalgia rheumatica

Endocrine: Hypoparathyroidism

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

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent in practice. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea.

Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction [see Dosage and Administration (2.3) in the full prescribing information].

5.3 Complications of Allogeneic HSCT

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

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

5.4 Embryo-Fetal Toxicity

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

6 ADVERSE REACTIONS

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

- Severe and Fatal Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.1)]
- Infusion-Related Reactions [see Warnings and Precautions (5.2)]
- Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced cSCC (Studies 1540 and 1423), and 369 patients with NSCLC (Study 1540, and 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=235), 350 mg every 3 weeks (n=543), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 57% were exposed for ≥ 6 months and 25% were exposed for ≥ 12 months. In this pooled safety population, the most common adverse reactions (≥ 15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥ 2%) were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.
Non-Small Cell Lung Cancer (NSCLC)
The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 [see Clinical Studies (14.3) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus cisplatin or carboplatin; gemcitabine plus cisplatin or carboplatin; or pemetrexed plus cisplatin or carboplatin followed by optional pemetrexed maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥ 6 months and 22% were exposed for ≥ 12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

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

### Table 6: Adverse Reactions in ≥ 10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal paina</td>
<td>26</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>1.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rashb</td>
<td>15</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>15</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>16</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.3</td>
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<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughb</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03.
a. Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, neck pain, spinal pain, and musculoskeletal stiffness.
b. Rash is a composite term that includes rash, dermatitis, urticaria, rash maculopapular, erythema, rash erythematous, rash pruritic, psoriasis, autoimmune dermatitis, dermatitis acral, dermatitis allergic, dermatitis toxic, dermatitis bullous, drug eruption, discoid/linear eczema, lichen planus, and skin reaction.
c. Fatigue is a composite term that includes fatigue, asthenia, and malaise.
d. Pneumonia is a composite term that includes atypical pneumonia, embolic pneumonia, lower respiratory tract infection, lung abscess, paracavitary pneumonia, pneumonia, pneumonia bacterial, and pneumonia klebsiella.
e. Cough is a composite term that includes cough and productive cough.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LIBTAYO N=355</th>
<th>Chemotherapy N=342</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 3-4 %</td>
<td>%</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>aminotransferase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alanine</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>aminotransferase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased alkaline</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>phosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased blood</td>
<td>2.1</td>
<td>0.3</td>
</tr>
<tr>
<td>bilirubin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>2.7</td>
<td>16</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>4.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>hypercalcemia</td>
<td>1.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE v. 4.03.
a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

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

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary
Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death [see Data]. Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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

Data
Animal Data
Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth.

As reported in the literature, there were no malformations related to the
8.2 Lactation
Risk Summary
There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO [see Use in Specific Populations (8.1)].

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

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

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

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

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

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

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LIB.21.03.0027 03/21
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Treatment Patterns Differ by Nonbiologic Factors in Undifferentiated Pleomorphic Sarcoma @Creighton @ASCO #ASCO21 #scmsm

The results of #COVID19 studies provide a powerful testimony to support well-designed & conducted trials, & highlight the importance of interpreting investigative studies in optimizing the health of our society @DrMaurieMarkman @CancerCenter #oncology

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Zev A. Wainberg, MD, discusses how he approaches treatment selection for patients with HER2-positive gastrointestinal (GI) malignancies, including factors that help steer treatment selection and advances on the horizon.

LISTEN: bit.ly/3rSsj5Z

ONCLIVE ON AIR™
PATHOGENIC VARIANTS GUIDE TREATMENT DECISIONS FOR CARIBBEAN PATIENTS
Sophia George, PhD; and Judith D. Hurley, MD, discussed the data from their study evaluating whether deleterious variants in genes that characterize hereditary breast and ovarian syndrome are linked with the development of these cancers in populations throughout the Caribbean.

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ANALYZING THE ADVANCING APPLICATIONS FOR NGS IN LUNG CANCER
Shari Brown, MD, of NeoGenomics, a cancer diagnostics and pharma services company in Fort Myers, Florida, and Hatim Husain, MD, discuss potential future applications of next-generation sequencing (NGS) in lung cancer and the emerging technologies that may overcome barriers to biomarker testing.

LISTEN: bit.ly/3sL7ycV

RESEARCH REFLECTIONS
O’MALLEY RELAYS KEY UPDATES IN OVARIAN AND ENDOMETRIAL CANCERS
David M. O’Malley, MD, discusses key findings from 6 trials presented at the virtual 2021 Society of Gynecologic Oncology Annual Meeting on Women’s Cancer. The trials included the phase 3 KEYNOTE-775 (NCT03517449) and SORAYA (NCT04296890) trials and the phase 2 NRG-GY012 trial (NCT03660826).

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TISAGENCLEUCEL DEMONSTRATES HIGH RATES OF DURABLE RESPONSES IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA
Tisagenlecleucel (Kymriah) has been shown to elicit durable responses in adult patients with relapsed/refractory follicular lymphoma with a safety profile that compares favorably with other available products, according to Stephen J. Schuster, MD.

In an interview with OncLive®, Schuster discussed the clinical implications of the phase 2 ELARA trial (NCT03568461) evaluating tisagenlecleucel in patients with relapsed/refractory follicular lymphoma.

“When we are backed into a corner, meaning our existing therapies do not work, guess what? This [agent] works in those patients,” Schuster said. “The response rates are very high, but what is more important, is the durable responses [that we saw] in the pilot study was 60% at 5 years, and this looks like it will be the same.”

READ MORE: bit.ly/3ifJKue

SPOTLIGHT

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In an interview with OncLive®, Schuster discussed the clinical implications of the phase 2 ELARA trial (NCT03568461) evaluating tisagenlecleucel in patients with relapsed/refractory follicular lymphoma.

“When we are backed into a corner, meaning our existing therapies do not work, guess what? This [agent] works in those patients,” Schuster said. “The response rates are very high, but what is more important, is the durable responses [that we saw] in the pilot study was 60% at 5 years, and this looks like it will be the same.”

READ MORE: bit.ly/3ifJKue
LIAO ON OUTCOMES WITH IVOSIDENIB IN ADVANCED CHOLANGIOCARCINOMA
Chih-Yi Liao, MD, unpacks the latest data for ivosidenib (Tibsovo) in patients with advanced cholangiocarcinoma. Ivosidenib was compared with placebo in the phase 3 ClarIDHy trial (NCT02989857) in patients with IDH1-mutant disease. The primary end point of the trial was progression-free survival and was met (2.7 months vs 1.4 months with placebo). Although the data may not seem numerically significant, it translates to a 63% reduction in the risk of progression or death, Liao noted.

WATCH: bit.ly/3j9NU6d

COSTA DISCUSSES ONGOING RESEARCH EFFORTS IN TNBC
Ricardo Costa, MD, MSc, takes stock of the ongoing research efforts in triple-negative breast cancer (TNBC). Immunotherapy remains an area of research to improve anticancer activity without compromising safety in this patient population, Costa explains. Moreover, immunotherapy could minimize the use of chemotherapy in TNBC. Investigational antibody-drug conjugates are in clinical development and PARP inhibitors could play a significant role in the adjuvant treatment of patients with TNBC who harbor germline BRCA mutations.

WATCH: bit.ly/3rVUtxf

REAL-WORLD EVIDENCE IS KEY TO ACCELERATING ONCOLOGY APPROVALS
by Jennifer B. Christian, PharmD, MPH, PhD
Real-world evidence (RWE) has become a significant enabler in research to measure the benefits and risks associated with oncology treatments in development. With the growing number of rare and aggressive cancers stratified by molecular subtypes, it becomes especially important to find alternative solutions for clinical development pathways when clinical trials are not possible. In response, RWE has emerged as a valuable complementary resource to provide information beyond what is learned from randomized clinical trials.

READ MORE: bit.ly/2WDhYiV

RAPID READOUTS
ALPINE DATA SUPPORT ROLE FOR ZANUBRUTINIB IN CLL/SLL
Jennifer R. Brown, MD, PhD, presents an interim analysis of the phase 3 ALPINE study (NCT03734016) of zanubrutinib (Brukinsa) vs ibrutinib (Imbruvica) in patients with relapsed/refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) presented at the 2021 European Hematology Association Virtual Congress. Data suggest that the sustained Bruton tyrosine kinase occupancy of zanubrutinib may result in better efficacy and safety outcomes compared with those seen with ibrutinib.

WATCH: bit.ly/3xiWp3I

VAN TINE ON THE RATIONALE TO EVALUATE CATQUENTINIB IN SYNOVIAL SARCOMA
Brian Van Tine, MD, PhD, discusses the reasoning behind evaluating the novel, multitargeted, oral RTK inhibitor catquequentinib (formerly anlotinib) in synovial sarcoma. Investigators are evaluating catquequentinib compared with dacarbazine in the ongoing phase 3 APROMISS trial (NCT03016819) in patients with advanced or metastatic synovial sarcoma, leiomyosarcoma, and alveolar soft-part sarcoma.

WATCH: bit.ly/3rHnTPg

NOTABLE QUOTABLES
“The role of co-mutations that can occur with KRAS should be explored; this is important. We should be able to identify subpopulations that either absolutely do not benefit, or conversely, derive more benefit from [sotorasib (Lumakras)].”
—Hossein Borghaei, DO, MS
Fox Chase Cancer Center at Temple Health

“The approval of [pevonedistat] would have a very significant effect on the landscape...for patients [with higher-risk myelodysplastic syndromes]. Having anything on the market that we can use will be very welcome.”
—Daniel Pollyea, MD, MS
University of Colorado (UC)
UCHealth Blood Disorders and Cell Therapies Center
WHEN HAIYING CHENG, MD, PhD, was testing a plastic tent for the first-in-human trial of inhaled azacitidine to treat patients with advanced non-small cell lung cancer (NSCLC), she had an unusual subject zero: Roman Perez-Soler, MD, the highly accomplished thoracic oncologist who is her division chief at Montefiore Einstein Cancer Center as well as the deputy director of the Albert Einstein Cancer Center in Bronx, New York.¹

“Dr Perez-Soler was like, ‘No, no, let me try this,’” Cheng recalled with a laugh. He gowned up, ducked under the tent, and put a nebulizer between his lips. “He tried everything himself to make sure the setup was safe for the patients and was doing what it was supposed to do.”

She noted that Perez-Soler had championed the unconventional study from the start, overcoming organizational hurdles and securing funding. “In the beginning, everyone thought it was a little bit crazy,” she said. “Without Dr Perez-Soler, I don’t think we could have done the clinical trial.”

Findings from the study (NCT02009436), published earlier this year in *Lung Cancer*, are among the many hallmarks of Perez-Soler’s long and productive career. For this study in particular, he zeroed in on an experimental and little-known therapy, circumvented doubters, navigated bureaucratic challenges, supported his junior colleagues, and helped produce intriguing results. Specifically, disease control in 3 of 8 patients and a decrease in global DNA methylation in the bronchial epithelium of 2 out of 3 patients who underwent bronchoscopy.¹

In an interview with *OncologyLive*, Perez-Soler said he envisions that inhaled agents such as azacitidine (Vidaza), currently available as an injectable therapy for patients with certain myelodysplastic syndrome subtypes,² may be used some day to reverse lung damage in smokers before they are diagnosed with cancer. He described the trial as the first step in a years-long project to develop such a treatment, but if it eventually succeeds, it will be the latest of several seminal contributions he has made to the field. These achievements include studies of anti-EGFR therapies and topoisomerase inhibitors, extensive research on liposomal delivery systems, and early work on patient-derived xenografts in mice.

“He’s been involved in a lot of really interesting, pioneering efforts both translationally and in clinical research. But more importantly, he’s been a real leader [and] a real adviser and guide for so many thoracic oncologists across the country and the world. I do view him as one of the giants of the field and definitely look at him as a role model,” said Balazs Halmos, MD, MS, associate director of clinical science at Albert Einstein Cancer Center, director of the Multidisciplinary Thoracic Oncology Program at Montefiore, and professor of medicine at Albert Einstein College of Medicine.

Perez-Soler has 17 patents, founded 2 biotechnology companies, and served on
many National Cancer Institute committees, including the Board of Scientific Counselors for Clinical Research and Epidemiology. He also created and cochaired the Annual New York Lung Cancers Symposium®, which provides an environment for a wide range of practitioners to feel comfortable asking questions and sharing their clinical experiences, said meeting cochair Mark G. Kris, MD, the William and Joy Ruane Chair in Thoracic Oncology at Memorial Sloan Kettering Cancer Center in New York, New York.

Kris noted that Perez-Soler worked in various roles at The University of Texas MD Anderson Cancer Center in Houston and at New York University before joining Montefiore and Einstein, where he is chairman of the Department of Oncology, chief of the Division of Medical Oncology, and professor of medicine and molecular pharmacology.

“He has worked very hard to bring together the physicians, nurse practitioners, physicians assistants, nurses, trainees, and others caring for people with lung cancer in the tristate area,” Kris said of the symposium. “His expertise at major institutions, his work in the laboratory, his work in the clinic, his work as an educator—he brings all that to the meeting that he has run for 15 years.”

**HITTING CHALLENGING TARGETS**

Perez-Soler and Kris will cochair the 16th Annual New York Lung Cancers Symposium® on November 6. The conference, hosted by Physicians’ Education Resource®, will be held as a hybrid interactive conference. It will include case presentations and reviews of treatment options for NSCLC, small cell lung cancer (SCLC), and mesothelioma. Presenters will discuss strategies for stopping immunotherapy, management of immune-related adverse events (AEs), practices’ technology needs, and approaches to treating patients with KRAS mutations, EGFR exon 20 mutations, and EGFR-positive NSCLC, among other topics.

Perez-Soler said he expects symposium attendees will be particularly interested in discussing the recent approval of sotorasib (Lumakras), the first treatment targeting KRAS G12C-mutated NSCLC. The RAS GTPase inhibitor demonstrated a median overall survival of 12.5 months among 124 evaluable patients (95% CI, 10.0–not evaluable [NE]), according to updated results from the phase 2 CodeBreaK 100 trial (NCT03600883) presented at the 2021 American Society of Clinical Oncology Annual Meeting and simultaneously published in the *New England Journal of Medicine* (TABLE 1). The trial enrolled patients with locally advanced or metastatic KRAS G12C-mutated NSCLC that had progressed after receiving immune checkpoint inhibitors and/or platinum-based chemotherapy.

An objective response was observed in 46 patients (37.1%; 95% CI, 28.6%-46.2%), including in 4 (3.2%) who had a complete response (CR) and 42 (33.9%) who had a partial response (PR). The median duration of response (DOR) was 11.1 months (95% CI, 6.9-NE). Disease control occurred in 100 patients (80.6%; 95% CI, 72.6%-87.2%). The median progression-free survival (PFS) was 6.8 months (95% CI, 5.1-8.2). Treatment-related AEs (TRAEs) occurred in 88 of 126 patients (69.8%), including grade 3 events in 25 patients (19.8%) and 2 grade 4 events, dyspnea and pneumonitis, for 1 patient each (0.8%). Responses were observed in subgroups defined according to PD-L1 expression, tumor mutational burden, and co-occurring mutations in STK11, KEAP1, or TP53. 3

“KRAS is driving the interest and the excitement,” Perez-Soler said. “It was very frustrating that we were able to develop compounds that could block a number of targets, but this one was a very elusive target. It was very hard to find something that would block that mutated protein. Finally, now we have compounds that are very active, or at least significantly active, against patients that have this mutation. It’s the most exciting thing I have seen lately.”

Kris said another new drug for a previously untargetable mutation will also be a hot topic at the symposium. Amivantamab-vnjw (Rybrevant), a bispecific antibody directed against EGF and MET receptors, was approved in May for adult patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations, as detected by an FDA-approved test, who have progressed on or after platinum-based chemotherapy (TABLE 2). Guardant360 CDx was approved as a companion diagnostic for the drug.

In the phase 1 multicohort CHRYsalis trial (NCT02609776) among 81 patients the overall response rate (ORR) was 40% (95% CI, 29%-51%), including a CR rate of 3.7% and a PR rate of 36%. 6 The median DOR was 11.1 months (95% CI, 6.9-NE), and 63% of patients had a response lasting 6 months or longer. All-grade AEs occurring in 10% or more of patients in the safety population (n = 129) included rash (84%), infusion-related reactions (64%), and paronychia (50%). Grade 3 or 4 AEs included rash (3.9%) and infusion-related reactions, paronychia, and diarrhea, each at 3.1%.

Kris noted that several other agents are being tested in patients with exon 20 mutations. Thirty active studies of potential therapies are listed on ClinicalTrials.gov.

### TABLE 1. NEW DRUG SNAPSHOT: KRAS-mutant NSCLC Approval

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sotorasib (N = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>37.1% (28.6%-46.2%)</td>
</tr>
<tr>
<td>CR</td>
<td>3.2%</td>
</tr>
<tr>
<td>PR</td>
<td>33.9%</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>11.1 (6.9-NE)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>6.8 (5.1-8.2)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>12.5 (10-NE)</td>
</tr>
</tbody>
</table>

### Adverse effects

The most common adverse effects (≥5%) are diarrhea, nausea, fatigue, vomiting, and maculopapular rash.

1. CR, complete response; DOR, duration of response; NSCLC, non-small cell lung cancer; NE, not estimable; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
2. Updated data following approval.
EXPANDING IMMUNOTHERAPY
For Perez-Soler, some of the major outstanding questions in lung cancer research concern the limits of immunotherapies and avenues for expanding their benefits. Although the population of patients eligible for treatment with immune checkpoint inhibitors has soared over the past decade, the current response rate does not exceed 15% for most cancer subtypes.8

“We must try to find better biomarkers to predict the people who are going to respond the best to these drugs. PD-L1 [expression] has been useful, but it’s not perfect. There must be more factors that determine whether you’re going to respond,” he said.

Tumor mutational burden (TMB) has proven useful for predicting response to checkpoint inhibitors in some cancer types, and last year the FDA approved a new indication for pembrolizumab (Keytruda) for patients with advanced and refractory cancers with high TMB as indicated by a defined threshold level of mutations determined by an approved test (≥ 10 mut/Mb). However, studies have found that although TMB status can predict response in lung, melanoma, bladder, and some other cancers, it is not associated with improved outcomes in common malignancies such as breast, prostate, and brain tumors.9

Several other potential predictors of response to immunotherapy have been identified, including the degree of mismatch repair deficiency and microsatellite instability, altered interferon-γ signaling, the extent/density of tumor-infiltrating immune cells, epigenetic modifications, intestinal microbiota, and peripheral blood biomarkers such as lactate dehydrogenase and angiotensin-2. None of these have been confirmed to broadly predict response, although a recent review of biomarkers published in the British Journal of Cancer from Pilard et al8 suggests that successively measuring several of them over time could create a picture of a tumor and its microenvironment that would illuminate response to immunotherapy.

Perez-Soler said if he were a young lung cancer researcher starting out his career today that he might join those investigating the biology of immunotherapy resistance. “These tumors must have other mechanisms of defending themselves against these attacks. If you find the mechanisms, you can neutralize those. I’m pretty sure that it’s going to be less complicated than it looks when we find it,” he said.

Mechanisms of resistance to immunotherapy have been extensively researched and catalogued, with investigators finding they involve multiple aspects of biology such as genes, metabolism, inflammation, and abnormal neovascularization.10 Studies aimed at overcoming resistance are using numerous agents that target novel pathways.

For example, in January, the FDA granted breakthrough therapy designation to the anti-TIGIT immunotherapy tiragolumab in combination with atezolizumab (Tecentriq) for first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression with no EGFR or ALK alterations.11 The designation was based on findings from the phase 2 CITYSCAPE trial (NCT03563716), in which 135 patients were randomized to receive atezolizumab plus placebo (n = 68) or atezolizumab plus tiragolumab (n = 67).12

At a median follow-up of 10.9 months, improvement in ORR and median PFS was maintained in the intention-to-treat population (ORR, 37.3% [95% CI, 25.0%-49.6%]; PFS, 5.6 months [95% CI, 4.2-10.4]) vs those who received placebo (ORR, 20.6% [95% CI, 10.2%-30.9%]; PFS, 3.9 months [95% CI, 2.7-4.5]). In an earlier safety analysis, TRAEs occurred in 80.6% and 72.0% of patients, respectively. Incidence of grade
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Mark G. Kris, MD
Attending Physician, Thoracic Oncology Service
William and Joy Ruane Chair in Thoracic Oncology
Memorial Sloan Kettering Cancer Center
New York, NY

Roman Perez-Soler, MD
Chairman, Department of Oncology
Montefiore Medical Center
Professor of Medicine and Molecular Pharmacology
Deputy Director, Cancer Center
Albert Einstein College of Medicine
Bronx, NY

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Physicians’ Education Resource®’s (“PER®’s”) top priority is the safety and security of our attendees, faculty, staff, and operational personnel. As we develop the programming for the 16th Annual New York Lung Cancers Symposium®, PER® is working diligently to implement health and safety protocols based on the advice of health experts and the latest guidelines and local regulations to mitigate the risk of exposure to COVID-19 and to optimize health and safety conditions for attendees during the event. Despite the protocols we have put in place, no precautions can completely eliminate the risk of exposure to COVID-19 or other airborne illness. Attendance at any public event increases the risk of contracting COVID-19 or other airborne illness. Attendees assume all risk associated with attendance. Any attendees who test positive for COVID-19 within 14 days of the event, or feel ill, regardless of their symptoms, should not attend this event. Personal Accountability Commitment: By attending this PER® program, you agree to abide by and engage in certain health- and safety- beneficial conduct while attending the event.

ACKNOWLEDGMENT OF COMMERCIAL SUPPORT

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3 or more TRAEs was higher in those treated with placebo (19.1%) vs tiragolumab (14.9%). AEs leading to treatment withdrawal occurred in 10.3% for those who received atezolizumab plus placebo and 7.5% for those who received tiragolumab plus atezolizumab.13

Other therapies being investigated as strategies for overcoming resistance, as monotherapies or in combination with immunotherapy, include antiangiogenic drugs in nonsquamous NSCLC; radiotherapy as consolidation therapy in patients with stage III unresectable NSCLC; PARP inhibitors in multiple subsets of patients with NSCLC; STING antagonists in advanced solid tumors or lymphomas; and IDO inhibitors, arginase inhibitors, epigenetic modulators, anti-CD73 antibodies targeting the adenosine A2A receptor, CCR4 and CXCR2 inhibitors, and several others.

**PIONEERING STUDIES**

The rewards from illuminating previously unknown mechanisms of cancer biology have motivated Perez-Soler throughout his career, prompting him to switch from internal medicine to oncology after he finished medical school in his native Spain in the early 1980s.

“I realized that the tools to study cancer were being developed and becoming a reality. What attracted me was not what we knew then of cancer, but the lot we would learn in the next 30 years. I identified, and I guess I was right, that oncology was going to be one of the areas in which there would be tremendous progress,” he said. “I’m more of an adventurer. I like to take risks. I saw that this is tough disease, people die of this, and we know nothing. Then let’s jump on the unknown.”

At MD Anderson he spent several years working on liposomal delivery systems, which offered a potential new alternative to anatomical targeting of tumors. Liposomes promised to boost drug efficacy without increasing toxicity, but in the 1970s and 1980s, investigators struggled to make the technology work.14 In collaboration with chemists who provided him with platinum drugs, adriamycin analogs, early attempts at antibody-drug conjugates, and other agents, Perez-Soler packaged the substances in liposomes and tested them on tumors in mice in dozens of studies.

Among other products, he developed L-NDP (Aroplatin), the first liposomal platinum formulation to enter into clinical trials, and he led a phase 1 study that identified its maximum tolerable dose and found no liposome-related AEs.14 Perez-Soler was awarded several patents related to liposomes and helped pave the way for numerous therapies that were approved beginning in the mid-1990s.

He also conducted early studies with EGFR inhibitors that led to a 1994 study of the monoclonal antibody RG 83852 in patients with NSCLC and head-and-neck cancer that found no toxic effects at doses that resulted in high tumor EGFR saturation.15 His most cited article is a phase 2 trial of erlotinib (Tarceva) in patients with HER1/EGFR-expressing NSCLC previously treated with platinum-based chemotherapy.16 Published in 2004, the study indicated erlotinib was an active and well-tolerated agent for treatment of relapsing NSCLC and supported continuing development of the drug, which was approved later that year.

Among the many other agents that he has studied are topoisomerase inhibitors. He served as principal investigator for trials of topotecan in both NSCLC and SCLC. The study of patients with SCLC refractory to the topoisomerase II poison etoposide showed that topotecan, a topoisomerase I poison, had modest antitumor activity, indicating that clinical resistance to the former did not confer cross-sensitivity to the latter.17 Topotecan subsequently became the only approved second-line therapy for SCLC until lurbinectedin (Zepzelca) was approved last year.18

Perez-Soler said he was also proud of a 2000 paper he described as one of the first reports on patient-derived xenografts (PDXs) in mice.19 The study found that NSCLC tumors implanted in mice had an overall take rate of 46% (95% CI, 36%-56%), were morphologically very similar to the original tumors, and had a response rate to paclitaxel of 21% (95% CI, 9%-38%), which was equivalent to the response in human patients with advanced NSCLC.

“We demonstrated, I think for the first time, that this actually is a clinically relevant model, in the mouse, of human tumors. If that tumor in the mouse—which is your tumor—responds to the drug, your tumor will respond when they give you the drug,” he said. “And then 10 or 15 years after that, the whole thing exploded, and PDXs are now the new standard for in vivo tumor model.”

In recent years, Perez-Soler has remained involved in a broad spectrum of thoracic cancer research while also continuing his professional, administrative, and mentoring work. His projects include leadership of the Paul Calabresi Career Development Award for Clinical Oncology, a National Cancer Institute grant that has allowed approximately 25 young investigators at Einstein to dedicate the bulk of their time to research. He also plans on supporting his colleagues’ work, such as Halmos’ studies of MET mutations and Cheng’s inhaled azacitidine trial as well as her study of RICTOR, a component of the mTOR complex 2 (mTORC2) that is amplified in 8% to 13% of lung cancers.20

Cheng discovered RICTOR amplification in an 18-year-old never-smoker with lung adenocarcinoma, treated the patient with mTORC1/2 inhibitors, and together with her fellow investigators analyzed the protein and its oncogenic effects. They found that in 11% of lung cancers, RICTOR occurs as the sole potentially actionable gene target and launched a drug-screening effort to identify specific RICTOR inhibitors.

“It’s the youngest patient I’ve ever seen with lung cancer,” said Perez-Soler, who is the study’s corresponding author. “Is RICTOR going to be important? We don’t know. It could be important. It might lead to some treatments that would target that. It’s intriguing. It’s novel. The work needs to be done.”

For more on the latest innovations in lung cancer, scan the QR code, or visit: bit.ly/3B6wA9g
IN HER2+ EARLY BREAST CANCER (EBC),
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HER2 = human epidermal growth factor receptor 2.
The CTNeoBC pooled-analysis assessed the risk of recurrence following neoadjuvant treatment among patients with breast cancer, including HER2+ EBC, based on historic data.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.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)**

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

Chemoimmunotherapy Shakes Up Metastatic and Early-Stage TNBC

by JESSICA HERGERT

MODEST RESPONSES TO SINGLE-AGENT checkpoint inhibitors prompted investigators to evaluate immune-based combinations in the first-line setting for patients with metastatic triple-negative breast cancer (TNBC), as well as in the early-stage setting to optimize treatment.

Although chemoimmunotherapy combinations have transformed the treatment of TNBC, balancing potential efficacy with the risk of toxicity with these regimens is critical in both the metastatic and early-stage settings, said Hope S. Rugo, MD, FASCO, during the Giants of Cancer Care® lecture at the 20th Annual International Congress on the Future of Breast Cancer® East and West meetings, programs hosted by the Physicians’ Education Resource® (PER®), LLC.1

TNBC, which has a higher tumor mutational burden vs HER2-positive and hormone receptor-positive breast cancer, was the first breast cancer subtype in which immunotherapy was evaluated, explained Rugo, a professor of medicine in the Department of Medicine (Hematology/Oncology) and the director of Breast Oncology and Clinical Trials Education at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center.

Treatment with chemotherapy induces changes in the immune microenvironment, said Rugo, who is also the 2020 Giants of Cancer Care® award winner in Education. This concept provided the clinical rationale to evaluate checkpoint inhibitors in combination with chemotherapy in TNBC, Rugo said.

Findings from the phase 3 IMpassion130 trial (NCT02425891) led to the first FDA approval of a checkpoint inhibitor in combination with chemotherapy—atezolizumab (Tecentriq) and nab-paclitaxel (Abraxane), respectively—for the treatment of patients with unresectable locally advanced or metastatic TNBC whose tumors are PD-L1 positive.2 However, on August 27, 2021, Roche, the developer of the PD-L1 inhibitor, announced that the company has made the decision to voluntarily withdraw the United States accelerated approval for atezolizumab plus nab-paclitaxel in this indication.

The data from the final analysis of IMpassion130 demonstrated that, at a median follow-up of 18.8 months the median overall survival (OS) was 25.4 months with atezolizumab/nab-paclitaxel (n = 185) vs 17.9 months with placebo/nab-paclitaxel (n = 184) for patients with PD-L1-positive TNBC (HR, 0.67; 95% CI, 0.53-0.86).3 The 3-year OS rates were 36% vs 22%, respectively.

“Sometimes we worry that over time we are going to see a narrowing of OS, but the OS difference [demonstrated in the final analysis of IMpassion130] is 7.5 months, so it broadened over time and was very confirmatory,” Rugo said.

In April, the approval underwent review after data from the confirmatory IMpassion131 trial (NCT03125902) failed to verify clinical benefit of the combination vs nab-paclitaxel alone. The FDA’s Oncologic Drugs Advisory Committee (ODAC) voted 7 to 2 to maintain the indication, with voting members citing that data from IMpassion132 (NCT03371017) may confirm benefit.4

Another checkpoint inhibitor, pembrolizumab (Keytruda), demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) when combined with chemotherapy in patients with previously untreated, locally recurrent, inoperable or metastatic TNBC whose tumors expressed PD-L1 (combined positive score [CPS] ≥ 10)
in the phase 3 KEYNOTE-355 trial (NCT02819518). In this PD-L1–enriched population, the median PFS was 9.7 months with pembrolizumab/chemotherapy vs 5.6 months with placebo/chemotherapy (HR, 0.65; \( P = .0014 \)). No statistically significant difference in PFS was observed with the addition of pembrolizumab in patients with a PD-L1 CPS of 1 or higher (HR, 0.74; \( P = .0012 \)).

On November 13, 2020, the FDA granted an accelerated approval to pembrolizumab plus chemotherapy for patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS \( \geq 10 \)).

Although responses with immunotherapy are good in TNBC, safety remains a consideration, Rugo said. Immune-related adverse events (irAEs), including rash, thyroid changes, hepatitis, and adrenal insufficiencies, remain in need of careful management.

“We have absolutely no idea why this trial was negative, but it leads us to conclude that nab-paclitaxel [should] be our chosen chemotherapy partner rather than paclitaxel. The balance of evidence [with IMpassion130, KEYNOTE-355, and IMpassion131] suggests that checkpoint inhibitors [provide] benefit to [patients with] PD-L1-positive metastatic TNBC,” Rugo said. Notably, trials are ongoing in the metastatic setting to try to improve upon responses demonstrated with chemotherapy (TABLE).

As part of the ongoing, phase 2 I-SPY2 trial (NCT01042379), pembrolizumab in combination with neoadjuvant chemotherapy led to a more than doubling in estimated pathologic complete response (pCR) rates vs neoadjuvant chemotherapy alone in patients with early-stage, high-risk HER2-negative breast cancers, including TNBC.

Also in the neoadjuvant setting, the phase 3 IMpassion031 trial (NCT03197935) demonstrated that atezolizumab plus nab-paclitaxel and anthracycline-based treatment significantly improved pCR rates in patients with early-stage TNBC. The pCR rates were 58% with the atezolizumab-containing regimen (n = 165) vs 41% with the placebo-containing regimen (n = 168; rate difference, 17%; 95% CI, 6%-27%; one-sided \( P = .0044 \)).

Rugo also highlighted the phase 3 KEYNOTE-522 trial (NCT03036488). Initial findings from the study demonstrated a 64.8% pCR rate with neoadjuvant pembrolizumab plus paclitaxel and carboplatin followed by adjuvant pembrolizumab (n = 784) vs 51.2% with placebo plus paclitaxel and carboplatin followed by placebo (n = 390; estimated treatment difference, 13.6%; 95% CI, 5.4%-21.8%; \( P < .001 \)).

Notably, unlike in the metastatic setting, responses in both IMpassion031 and KEYNOTE-522 were observed irrespective of PD-L1 status. However, the irAEs observed in the metastatic setting were present in the early-stage setting, Rugo explained.

In a briefing document that was released ahead of a hearing from the FDA’s ODAC, the study investigators attributed 1 death from pneumonitis that occurred on the KEYNOTE-522 trial to neoadjuvant pembrolizumab treatment. In the adjuvant setting, the investigators noted 2 pembrolizumab-related deaths from a pulmonary embolism and autoimmune encephalitis.

The committee indicated that event-free survival (EFS) results from KEYNOTE-522 were needed, Rugo explained. Therefore, on February 9, 2021, ODAC unanimously voted 10 to 0 against the approval of

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**TABLE.** Efforts to Improve Efficacy of Chemotherapy in Metastatic TNBC

<table>
<thead>
<tr>
<th>Trial name (ClinicalTrials.gov identifier)</th>
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<td>BEGONIA (NCT03742102)</td>
<td>1b/2</td>
<td>Durableumab + paclitaxel with or without a novel agent (ie, capivasertib, oleclumab, trastuzumab deruxtecan, or datotopab deruxtecan)</td>
<td>Primary: ( \text{PART 1: Incidence of AEs} ) ( \text{PART 2: ORR} ) &lt;br&gt;Secondary: ORR, PFS, DOR, OS</td>
<td>200 &lt;br&gt;February 13, 2023</td>
</tr>
<tr>
<td>InCITe (NCT03971409)</td>
<td>2</td>
<td>Arm 1: binimetinib + avelumab &lt;br&gt;Arm 2: anti-0X410 antibody PF-04518600 + avelumab &lt;br&gt;Arm 3: utomilumab + avelumab &lt;br&gt;Arm A: avelumab + binimetinib + liposomal doxorubicin &lt;br&gt;Arm B: avelumab + sacituzumab govitecan &lt;br&gt;Arm C: avelumab + liposomal doxorubicin</td>
<td>Primary: Best ORR &lt;br&gt;Secondary: ORR, CBR, PFS, OS, AEs, QOL</td>
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<td>KEYLynK-009 (NCT04191135)</td>
<td>2/3</td>
<td>Arm 1: pembrolizumab + chemotherapy  &lt;br&gt;Arm 2: pembrolizumab + olaparib</td>
<td>Primary: PFS, OS &lt;br&gt;Secondary: OS and PFS in patients with BRCA-mutant tumors, QOL, AEs</td>
<td>1225 &lt;br&gt;January 26, 2026</td>
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AEs, adverse events; CBR, clinical benefit rate; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QOL, quality of life; TNBC, triple-negative breast cancer.
pembrolizumab in combination with chemotherapy as neoadjuvant treatment for patients with high-risk, early-stage TNBC.13 The vote deferred regulatory action on the submitted biologics license application for the regimen.

Results of the EFS analysis, which were presented during a European Society for Clinical Oncology Virtual Plenary session on July 15, 2021, demonstrated an EFS rate of 84.5% with the pembrolizumab-containing regimen vs 76.8% with the placebo-containing regimen (HR, 0.63; 95% CI, 0.48-0.82; P = .00031).14 This translated to a 7.7% improvement in EFS with the addition of pembrolizumab. Notably, all patient subgroups favored the addition of pembrolizumab.

The FDA approved pembrolizumab in combination with chemotherapy as neoadjuvant treatment, followed by single agent pembrolizumab following surgery for patients with high-risk, early-stage TNBC on July 26.15

Additional findings showed that the EFS rates in patients who achieved a pCR were 94.4% with pembrolizumab (n = 494) vs 92.5% with placebo (n = 217). In patients who did not achieve a pCR, the EFS rates were 67.4% vs 56.8%, respectively. Additionally, the rates of distant recurrence-free survival were 87.0% vs 80.7%, respectively (HR, 0.61; 95% CI, 0.46-0.82). The OS rates were 89.7% vs 86.9%, respectively (HR, 0.72; 95% CI, 0.51-1.02; P = .03214).

Ongoing research efforts are fleshing out whether treatment de-escalation with neoadjuvant chemoinmunotherapy regimens is feasible, Rugo said. “This represents a new standard of care for early-stage TNBC, but we need to balance cost and toxicity in high-risk disease. Since these data are new, we have to start on [this] approach now,” Rugo said. ■

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

Novel Vaccine Combos Represent a Promising Treatment Approach in Breast Cancer

by CAROLINE SEYMOUR

THE FUTURE OF THERAPEUTIC VACCINES in breast cancer will be dependent on their use in combination with standard anticancer drugs, checkpoint antagonists, and distinct checkpoint inhibitors, Leisha A. Emens, MD, PhD, said in a presentation during the 20th Annual International Congress on the Future of Breast Cancer® East.1

Vaccine trials have historically not had much success in breast cancer, and research had been slowed by the advent of checkpoint inhibitors, said Emens, during the meeting, hosted by the Physicians’ Education Resource® (PER®), LLC. Emens is a professor of medicine in hematology/oncology, coleader of the Hillman Cancer Immunology and Immunotherapy Program, and director of Translational Immunotherapy for the Women’s Cancer Research Center at the University of Pittsburgh Medical Center Hillman Cancer Center in Pennsylvania.

Translational research has provided valuable insights into why that is, Emens explained. “Breast cancer is largely a cold tumor. [Additionally,] multiple layers of regulation within the tumor microenvironment can shut down tumor immunity, and beyond the tumor microenvironment, immune tolerance matters,” she said.

Moreover, a minority of tumors have innate T-cell responses that respond to checkpoint inhibitors. This makes vaccines—which can under optimal circumstances induce T cells that can reach the tumor microenvironment—a necessity for the success of immunotherapy in most cancers.

“If there are no T cells, there’s no way for checkpoint inhibitors to work, and that’s where cancer vaccines come in,” Emens said. “Cancer vaccines are developed as a variety of different platforms that deliver exogenous tumor antigens that translocate to the lymph nodes and prime and activate T cells.”

LEVERAGING NEGATIVE TRIAL INSIGHTS

In the phase 3 PRESENT trial (NCT01479244), investigators compared the HER2-peptide vaccine, nelipepimut-S (NP-S), plus granulocyte-macrophage CSF (GM-CSF; n = 376) with placebo plus GM-CSF (n = 382) as adjuvant therapy in patients with HER2-low breast cancer.

However, no significant difference in disease-free survival was reported between arms at a median follow-up of 16.8 months. In the NP-S arm, imaging detected 54.1% of recurrence events in asymptomatic patients vs 29.2% of recurrence events in the placebo arm (P = .069).2

In the phase 2 ABCSG-34 trial, investigators evaluated the MUC1-specific vaccine, tecemotide, as neoadjuvant therapy in patients with early-stage, HER2-negative breast cancer. The primary end point was residual cancer burden (RCB) 0/I vs II/III at surgery.

However, no significant difference in RCB 0/I rates between patients who did (36.4%) or did not receive (31.9%) tecemotide was reported in the overall study population (P = .40) nor in endocrine- and chemotherapy-treated subgroups (25.0% vs 13.3%, respectively, P = .17; 39.6% vs 37.8%, respectively, P = .75).3

At face value, results of these trials indicate the lack of benefit of vaccines and point to clinical trial design issues, Emens said (TABLE).4

In addition, immune tolerance and suppression with regulatory T cells, myeloid-derived suppressor T cells, and tumor-associated macrophages represent additional barriers to tumor immunity, Emens said.

For example, findings from 2 preclinical studies similarly demonstrated that...
activity and subsequent tumor regression. Derived HER2-specific, CD8-positive T-cell responses appeared to be unaffected by the vaccine that the mice with immune tolerance who received 4 immunizations. No dose-limiting toxicities were observed. HER2-specific delayed-type hypersensitivity developed in most patients who received the vaccine alone or with 200 mg/m² of cyclophosphamide.

Notably, HER2-specific antibody responses were enhanced by 200 mg/m² of cyclophosphamide and 35 mg/m² of doxorubicin, but higher doses of cyclophosphamide suppressed immunity. The combination of 200 mg/m² of cyclophosphamide and 35 mg/m² of doxorubicin induced the highest antibody responses.

“We translated this to the clinic and tested this approach using a human GM-CSF-secreting breast cancer vaccine composed of allogeneic breast tumor cells, SKBR3, and T47D,” Emens said. The vaccine was given in sequence with cyclophosphamide and doxorubicin the same way as in the mice in patients with estrogen receptor-positive metastatic breast cancer. Twenty-eight patients received at least 1 immunization, and 10 patients received 4 immunizations. No dose-limiting toxicities were observed. HER2-specific delayed-type hypersensitivity developed in most patients who received the vaccine alone or with 200 mg/m² of cyclophosphamide.

Patient-specific interventions

- Optimal biologic dose and maximum tolerated dose may not be equivalent.
- ORR, PFS, OS considerations are complex.
- RECIST vs immune-related RECIST

Baseline patient selection considerations

- Minimal tumor burden
- Secondary prevention measures
- Indolent disease

Combination with standard therapies

- Surgery
- Radiation therapy
- Chemotherapy
- Targeted therapies

End point considerations

- Objective response rate
- PFS, OS, overall survival
- Safety and immune activation

Experimental intervention considerations

- Combination with immunomodulation and other immunotherapies
- Low-dose cyclophosphamide
- Cytokines
- Immune checkpoint antagonists
- Prime-boost strategies

Safety considerations

- Delivery method
- Schedule
- Timing
- Targeted therapies

Clinical Trial Design Issues for Breast Cancer Vaccine Success

Baseline patient selection considerations

- Minimal tumor burden
- Secondary prevention measures
- Indolent disease

Experimental intervention considerations

- Combination with standard therapies
- Surgery
- Radiation therapy
- Chemotherapy
- Targeted therapies

End point considerations

- Objective response rate
- PFS, OS, overall survival
- Safety and immune activation

TABLE. Clinical Trial Design Issues for Breast Cancer Vaccine Success

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<td>• Minimal tumor burden</td>
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<td>• Secondary prevention measures</td>
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<th>Experimental intervention considerations</th>
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<td>• Combination with standard therapies</td>
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<td>• Surgery</td>
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<td>• Chemotherapy</td>
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<td>• PFS, OS, overall survival</td>
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<td>• Safety and immune activation</td>
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With the addition of PD-L1 blockade plus OX40 receptor activation and delayed tumor growth with the addition of cyclophosphamide, paclitaxel, and doxorubicin. 

“We translated this to the clinic and tested this approach using a human GM-CSF-secreting breast cancer vaccine composed of allogeneic breast tumor cells, SKBR3, and T47D,” Emens said. The vaccine was given in sequence with cyclophosphamide and doxorubicin the same way as in the mice in patients with estrogen receptor-positive metastatic breast cancer. Twenty-eight patients received at least 1 immunization, and 10 patients received 4 immunizations. No dose-limiting toxicities were observed. HER2-specific delayed-type hypersensitivity developed in most patients who received the vaccine alone or with 200 mg/m² of cyclophosphamide.

Notably, HER2-specific antibody responses were enhanced by 200 mg/m² of cyclophosphamide and 35 mg/m² of doxorubicin, but higher doses of cyclophosphamide suppressed immunity. The combination of 200 mg/m² of cyclophosphamide and 35 mg/m² of doxorubicin induced the highest antibody responses.

 “[We learned that] the dose is really important; [in this case], only the low dose [of cyclophosphamide] helped. In contrast, with doxorubicin, it was the high dose that amplified the antibody responses,” Emens said. Additionally, cyclophosphamide preferentially affected regulatory T cells relative to effector T cells, Emens added. The working theory is that the approach decreases the suppressive regulatory T cells and sustains the effector T-cell population, creating a window for the vaccine to be effective.

Similar synergistic activity has been seen with the addition of a vaccine to cyclophosphamide and trastuzumab (Herceptin) in HER2-transgenic mice and patients with metastatic breast cancer, Emens said.

In conclusion, Emens noted that STING agonists represent another potential strategy to induce inflamed tumors and that “these agents are actively in the clinic now, primarily in combination with agents that target the PD-1 pathway.”

REFERENCES


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Pivotal MagnetisMM-3 Trial Aims to Add Elranatamab to Multiple Myeloma Treatment Portfolio

by KYLE DOHERTY

**PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA**

Multiple myeloma, particularly those who have failed a prior BCMA-targeted therapy, represent a population with an unmet need for effective treatment options. Investigators are hoping to help fill this void with the initiation of the phase 2 MagnetisMM-3 study (NCT04649359).

The MagnetisMM-3 study will evaluate the efficacy of single-agent elranatamab (PF-06863135) in adult patients with relapsed/refractory multiple myeloma. Elranatamab is a bispecific, humanized, monoclonal antibody comprising BCMA- and CD3-targeting arms paired on an IgG2a backbone by hinge-mutation technology. The agent has been granted fast track designation by the FDA.

“Elranatamab is in a class of agents called specific engagers,” said Alexander M. Lesokhin, MD, a hematologic oncologist at Memorial Sloan Kettering Cancer Center, in New York, New York, in an interview with OncologyLive. “There are a group of these molecules of various formats, but the concept is that they bind in 2 specific moieties: 1 on the tumor cell and 1 on an immune cell. Elranatamab binds [to] BCMA on myeloma cells and [to] CD3 on T cells, and thereby brings together T cells and activates them in the vicinity of the myeloma cell, resulting in cell kill.”

The agent’s manufacturer, Pfizer, temporarily halted enrollment to the MagnetisMM-3 trial on May 4, 2021, after 3 cases of peripheral neuropathy were observed in the ongoing phase 1 MagnetisMM-1 trial (NCT03269136). New enrollment to the trial was paused as the company provided additional information to the FDA. Patients who were deriving clinical benefit from elranatamab were allowed to continue with treatment.

“Two of those [cases] were patients treated in combination with pomalidomide,” Lesokhin noted. “All patients had prior peripheral neuropathy and all of them improved once the therapy was stopped. The hold has now been lifted and all the [updated] data has been presented to the FDA. There are some mitigation strategies. The main one is to exclude patients with significant prior peripheral neuropathy from participation at this time.”

**INITIAL SAFETY AND EFFICACY DATA OF ELRANATAMAB**

Investigators of MagnetisMM-1 are examining elranatamab both as a single agent and in combination with dexamethasone, lenalidomide (Revlimid), or pomalidomide (Pomalyst) in adult patients with relapsed/refractory multiple myeloma. The primary objectives of the study are to assess safety and tolerability, determine the maximum-tolerated dose, and select the recommended phase 2 dose (RP2D) of elranatamab. Secondary objectives include evaluating the antimyeloma activity, pharmacokinetics, and immunogenicity of elranatamab.

In November 2019, investigators reported data from the administration of intravenous, once-weekly, noncontinuous, elranatamab monotherapy in 17 adult patients with relapsed/refractory multiple myeloma, in 6 dose-escalation groups. Most patients were men (71%), with a median age of 61 years (range, 47-82) and the median disease duration since onset was 7 years (range, 1.1-13.3). Patients had a median of 11 prior antimyeloma therapies and 5 patients had previously received BCMA-targeted therapy.

At the April 9, 2019, data cutoff, 16 patients were evaluable for response. Among the evaluable patients, 1 achieved a minimal response, 6 had stable disease, and 9 experienced disease progression. The clinical benefit rate was determined to be 41% (95% CI, 18.4%-67.1%).

Concerning safety, 50% of patients experienced treatment-related adverse effects.

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**FIGURE.** Elranatamab for Patients With Relapsed/Refractory Multiple Myeloma

**PHASE 2, OPEN LABEL**

<table>
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<tr>
<th>Eligibility criteria</th>
<th>Cohort A (Patients who have not received prior BCMA-directed therapy)</th>
<th>Cohort B (Patients who have received prior BCMA-directed therapy, either an ADC or CAR T-cell therapy)</th>
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<td>Refractory to ≥ 1 anti-CD38 antibody</td>
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<td>MRD negativity rate</td>
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<td>Patients with stem cell transplant within 12 weeks of study entry</td>
<td>TRAEs</td>
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</table>

ADC, antibody-drug conjugate; CAR, chimeric antigen receptor; DOR, duration of response; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; TRAEs, treatment-related adverse effects.

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(TRAEs) of any grade. Grade 1/2 TRAEs were most common and included cytokine release syndrome (CRS; 24%), thrombocytopenia (24%), and anemia (18%). Grade 3 TRAEs were observed in 18% of patients and no patients experienced grade 4/5 TRAEs or discontinued treatment because of a TRAE.3

Updated data from MagnetisMM-1, presented at the European Hematology Association 2021 Virtual Congress, reported results of the subcutaneous administration of elranatamab as a single agent. As of the February 4, 2021, data cutoff, 30 patients had received elranatamab subcutaneously at doses of 80 μg/kg (n = 6), 130 μg/kg (n = 4), 215 μg/kg (n = 4), 360 μg/kg (n = 4), 600 μg/kg (n = 6), or 1000 μg/kg (n = 6) weekly.4

The population was heavily pretreated, with a median of 8 (range, 3-15) prior antimyeloma treatments; all patients were treated with an immunomodulatory agent and a proteasome inhibitor in the past. Patients were mostly female (56.7%) and the median age was 63 years (range, 46-80). A large majority of patients were triple-class refractory (86.7%).4

Responses to treatment were observed beginning at the 215 μg/kg dose, with an overall response rate (ORR) of 70% in 20 patients who received at least 215 μg/kg of elranatamab. Patients who received elranatamab 1000 μg/kg had an ORR of 83.3%, with 1 patient experiencing a complete response. For the 14 patients who responded, the median time to response was 22 days (range, 21-50) and the median duration of response has not yet been reached.4

The most common TEAEs of any grade were lymphopenia (83.3%), CRS (73.3%), and anemia (60%). Grade 3/4 TEAEs included lymphopenia (83.3%), neutropenia (53.3%), and anemia (50%). No dose-limiting toxicities were observed across all subcutaneous dose levels.4

Based on data from this analysis, investigators stated that elranatamab had a manageable safety profile and the RP2D was 1000 μg/kg. Investigators concluded that results from the updated analysis supported further development of elranatamab both as a monotherapy and in combination with other agents for the treatment of patients with relapsed/refractory multiple myeloma.4

**DETAILS OF THE MAGNETISMM-3 TRIAL**

MagnetisMM-3 is an open-label, multicenter, nonrandomized study and investigators plan to enroll approximately 150 adult patients with relapsed/refractory multiple myeloma in the United States and Australia (FIGURE 1). Patients must be refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 anti-CD38 monoclonal antibody. Participants must also have a maximum ECOG performance status of 2.5

Patients who are not eligible for the study include those with smoldering multiple myeloma, active plasma cell leukemia, or amyloidosis. Study participants must also be without any other active malignancy within 3 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ. Stem cell transplant within 12 weeks prior to enrollment is not permitted.5

The trial will be divided into 2 cohorts: Cohort A (n = 60) will include patients who have not received prior BCMA-directed therapy and cohort B (n = 90) will include those who have received a prior BCMA-directed therapy. Elranatamab monotherapy will be administered via subcutaneous injection at a dose of 76 mg weekly after a priming dose of 44 mg.1

“There’s a variety of step-up dose administrations that are being explored with this agent,” Lesokhin said. “It remains to be seen precisely which 1 will be used, but I suspect that there will be a step-up that will ultimately be utilized with the administration of this agent. I should say that this is a strategy that is being used across the board with similar agents in with this type of mechanism of action. This is not unique to elranatamab.”

The primary end point of the trial is to evaluate the efficacy of elranatamab as a single agent by ORR, which will be assessed approximately every 4 weeks for about 2 years by blinded independent central review. Secondary end points include duration of response, cumulative complete response rate, progression-free survival, and overall survival. The expected completion date of the trial is June 2022.5

“In the triple-refractory space, this and therapies of this type are very likely to become highly utilized,” Lesokhin concluded. “I say that because they are off the shelf, immediately available treatments. In this space, we [currently] have belantamab mafodotin-blmf [Blenrep] and CAR T-cell therapy. Different treatments will be appropriate for different patients. The location of patients, meaning relative proximity to a treatment center that can deliver CAR T-cell therapy, will determine the utilization of 1 therapy or another in the future. For treatments like CAR T-cell therapy and elranatamab, bispecific engagers, it’s likely that these will move into earlier-line therapies as time goes on to evaluate their impact on longevity and improvement of overall quality of life for patients.”

**REFERENCES**


Nab-paclitaxel Plus Gemcitabine Boosts Survival for Pancreatic Cancer in 5-Year Follow-Up

by BRITTANY LOVELY

Table 1. Updated Survival Outcomes in the APACT Trial

<table>
<thead>
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<th>Outcome</th>
<th>Interim analysis</th>
<th>5-year updated analysis</th>
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<tr>
<td></td>
<td>Nab-paclitaxel</td>
<td>Gemcitabine</td>
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<tr>
<td></td>
<td>plus gemcitabine</td>
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</tr>
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<td></td>
<td>(n=432)</td>
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<td>Median OS, months</td>
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<td>36.2</td>
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<tr>
<td>HR, 95% CI</td>
<td>0.82; 0.680-0.996;</td>
<td>.045</td>
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</table>

**updated overall survival (OS) data** from the APACT trial (NCT01964430) suggest improved outcomes for patients with resected pancreatic cancer who receive adjuvant nab-paclitaxel (Abraxane) plus gemcitabine, despite missing the primary endpoint in an earlier analysis.1

Investigators selected disease-free survival (DFS) as the primary objective of the study, making it the first adjuvant pancreatic cancer trial to use the independently assessed marker.2 The interim analysis of OS was reported in 2019 and demonstrated early signs of efficacy for the combination regimen compared with gemcitabine alone. In a presentation of the data at the 2019 American Society of Clinical Oncology Annual Meeting, lead investigator Margaret A. Tempero, MD, said, “The overall survival [data are] encouraging and longer follow-up will clarify the role for this combination as adjuvant therapy for [patients with] pancreatic adenocarcinoma.” Tempero added that based on the early data, investigators should consider exploring the regimen in patients with lymph node-positive disease, R1 resection, or an inability to tolerate modified FOLFIRINOX.1

Tempero presented the updated OS analysis as part of the 2021 European Society for Medical Oncology Virtual World Congress on Gastrointestinal Cancer. At the 5-year data cutoff, the OS outcomes were consistent with those observed in the primary analysis and a prior post hoc update analysis. At a median follow-up of 63.2 months, the median OS for patients in the nab-paclitaxel plus gemcitabine cohort was 41.8 months compared with 37.7 months in the gemcitabine cohort (HR, 0.80; 95% CI, 0.678-0.947; P = .0091).1 Further, the 5-year OS rates were 38% and 31%, respectively.

Investigators noted that a survival benefit was observed across all subgroups and was consistent with observations in the intention-to-treat population. When stratified by resection status, OS favored the nab-paclitaxel plus gemcitabine combination compared with gemcitabine monotherapy for patients with R1 disease (HR, 0.73; 95% CI, 0.534-1.003). Additionally, a greater benefit was observed for those with lymph node–positive status (HR, 0.77; 95% CI, 0.636-0.922) compared with those with lymph node–negative status (HR, 0.97; 95% CI, 0.667-1.415).

“Although APACT did not meet its primary end point of independently assessed DFS in the primary analysis, these OS data suggest improved outcomes with nab-paclitaxel plus gemcitabine,” Tempero said of the updated data. Tempero is a 2020 Giants of Cancer Care® award winner in the gastrointestinal cancers category and, at the University of California, San Francisco (UCSF), holds the Rombauer Family Distinguished Professorship in Pancreas Cancer Clinical and Translational Science; is director of the UCSF Pancreas Center and leader of the Pancreas Cancer Program; and is a professor of medicine at the UCSF Helen Diller Family Comprehensive Cancer Center.

Rationale and study design

Results of the phase 3 MPACT trial (NCT00844649) demonstrated significantly longer OS with nab-paclitaxel plus gemcitabine compared with gemcitabine alone for patients with metastatic pancreatic cancer, which led to the approval of the combination in 2013. Investigators determined that a similar benefit may be observed with the combination over gemcitabine alone, anticipating a DFS of 18.5 months vs 13.5 months.1

The 2019 analysis demonstrated a median independently assessed DFS of 19.4 months with the addition of nab-paclitaxel vs 18.8 months with gemcitabine alone (HR, 0.88; 95% CI, 0.729-1.063; P = .1824). Investigator-assessed analysis aligned more closely with the reported OS analysis and the hypothesized outcomes (Table 1).2 Specifically, investigator-assessed DFS results were 16.6 months with the combination vs 13.7 months with gemcitabine (HR, 0.82; 95% CI, 0.694-0.965; P = .0168). At the time of presentation, Tempero noted that the concordance rate between disease recurrence by independent radiological review and by investigator review was 77%.1

Per APACT trial protocol, patients with surgically resected pancreatic adenocarcinoma were randomized to receive either nab-paclitaxel plus gemcitabine (n = 432) or gemcitabine alone (n = 434) and radiographic evaluation took place for 5 years of follow-up following the last dose of treatment or until recurrence, commencement of new cancer therapy, or death. Data cutoff for OS analysis was April 9, 2021, at which time all patients had been followed up for at least 5 years or had discontinued from the study.2

Nab-paclitaxel was administered intravenously (IV) at 125 mg/m² on days 1, 8, and 15 of a 28-day cycle, and IV gemcitabine was given at 1000 mg/m² on days 1, 8, and 15 of a 28-day cycle for a total of 6 cycles. Gemcitabine was administered at the same dose and same schedule in the monotherapy arm. Overall, 69% of patients completed
6 treatment cycles; 287 patients (66%) completed treatment with the combination and 310 (71%) completed treatment with gemcitabine alone.

To be eligible for enrollment, patients had to have histologically confirmed resected ductal pancreatic adenocarcinoma with macroscopic complete resection and pancreatic cancer surgical staging of T1 to T3, N0 to N1, M0 disease. Patients must have been able to start treatment no later than 12 weeks following surgery. Further, patients must have had a CT scan without evidence of disease and have CA19-9 levels of less than 100 U/mL assessed within 14 days of randomization.

Those who received prior neoadjuvant treatment or radiation therapy, had metastatic disease, had any other malignancy within 5 years of randomization, had an active infection requiring systemic therapy, and/or had known hepatitis B or C infection or HIV infection were excluded.

Baseline characteristics were well balanced between the arms. The median age was 64 years (range, 34-86); many patients had a resection status of R0 (76%), indicating a reported tumor-free margin; and most patients had positive lymph nodes (72%). Median baseline CA19-9 levels were reported as 13.65 U/mL.

REFERENCES

Urologic Care Rates Decline Across US Demographics During Height of COVID-19 Pandemic

by JESSICA HERGERT

THE PROVISION OF UROLOGIC CARE
underwent a significant decline during the height of the COVID-19 pandemic across all demographic groups and practice settings in the United States, regardless of the timing of stay-at-home order mandates, according to findings from a study that were presented during the 36th Annual European Association of Urology Congress.1

Notably, declines of more than 40% were observed among outpatient visits from March 2020 to April 2020. Although outpatient visits recovered in May 2020 and early June 2020, they began to fall again in July 2020 in the overall population.

Nonurgent visits, including visits for microscopic hematuria, overactive bladder, elevated prostate-specific antigen, erectile dysfunction, and benign prostatic hyperplasia, also declined, as did procedure visits compared with the respective weeks in 2019 (FIGURE).

Specifically, nonurgent visits declined by 39% to 47% from March 2020 to April 2020, whereas visits for urgent diagnoses declined by 29% to 43%. Surgical procedures for nonurgent conditions declined by 37% to 53% compared with surgical procedures for potentially urgent matters, which declined by 13% to 21% during the evaluated time period.

“This study provides timely, real-world evidence on the magnitude of decline in the provision of urological care across demographic groups and practice settings and demonstrates a differential impact on the utilization of urologic health services by sociodemographic strata and specific diagnoses,” Daniel J. Lee, MD, MS, an assistant professor of urologic oncology in the Department of Surgery at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, and coauthors wrote.

The COVID-19 pandemic affected facets of health care access and delivery, including
Elective Surgery and COVID-19 Are Associated With Higher Mortality Risk for Patients With Urologic Cancers

by KRISTI ROSA

AN ANALYSIS OF THE COVIDSurg-Cancer study (NCT04384926) demonstrated that patients who underwent elective surgery for urological cancer and later reported SARS-CoV-2 positivity were found to have a significantly higher likelihood of experiencing postoperative respiratory complications and mortality than those without the virus.\(^1\) Results of the study were presented during the 36th Annual European Association of Urology Congress.

Prospective data from 436 consecutive patients with urological cancer were collected from several centers between March 11, 2020, and April 19, 2020. Of those patients, 39.7% had kidney and upper tract urothelial cancer (UTUC); 28.9% had bladder cancer (n = 126), and 31.4% had prostate cancer (n = 137).

Investigators of the observational study set out to examine the impact of the COVID-19 pandemic on the 30-day outcomes of patients with urological cancers such as kidney cancer, bladder cancer, and prostate cancer who had undergone elective cancer surgery.

In terms of postoperative respiratory complications, patients were more likely to experience adult respiratory distress syndrome (n = 3; \(P < .01\)), pneumonia (n = 4; 28.6%; \(P < .01\)), oxygen therapy (n = 10; 71.4%; \(P < .01\)), and pulmonary embolism (n = 1; 7.1%; \(P < .01\)) within 30 days of their operation.

“\(^{2}\)To continue elective cancer surgery throughout future waves of the pandemic, it would be sensible to take precautions to minimize the risk of patients developing COVID-19 perioperatively,” lead study author Chuanyu Gao, MD, of the British Urology Researchers in Surgical Training, and colleagues, concluded.

Two of 412 patients (0.5%) who did not have the virus died within 30 days following their surgical procedure vs 3 of 14 patients (21.4%) with COVID-19 \((P < .01)\). The rates of postoperative Clavien-Dindo Grade III+ complications were 1.7% \((n = 2/119)\), 7.6% \((n = 4/53)\), and 3.3% \((n = 2/61)\) for nephrectomy, cystectomy, and prostatectomy, respectively.

To be included, patients must have been planned for curative cancer surgery and underwent the procedure during the pandemic or they had their procedure delayed or canceled during the pandemic.\(^2\)

Patients needed to be at least 18 years of age and have a confirmed diagnosis of an included cancer type. They could not have surgery planned with non-curative intent. Moreover, patients could not have planned neoadjuvant therapy without a set date for surgery, nor could they be awaiting restaging.

The primary outcome measure for the trial was mortality within 30 days, and key secondary outcomes were COVID-19 infections, respiratory complications, and postoperative complications within 30 days.

Of the 173 patients with kidney cancer and UTUC, 172 underwent elective cancer surgery. The majority, or 98.8% \((n = 170)\) of these patients were alive at 30 days after the procedure; 2 patients died. One of the patients who died (50.0%) was positive for COVID-19.

Among the 126 patients with bladder cancer, 120 underwent surgery; 115 patients were alive at 30 days and 3 had died at that time point.

Two of the 3 patients (66.6%) who died had COVID-19. Of the 137 patients with prostate cancer, all patients received elective cancer surgery and no patients died at 30 days.\(^1\)

REFERENCE


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

hospital admissions and outpatient care for certain conditions, throughout the United States, Lee and coauthors wrote. However, the significance of the pandemic with regard to specialty care had not been fully realized, which provided the clinical rationale to conduct the analysis.

The specialty-wide, community-based cohort study evaluated trends in outpatient urologic care visits, as well as procedural volume from February 2020 to July 2020. The study utilized the American Urological Association Quality (AQUA) Registry, which automatically extracts patient data from electronic health records.

AQUA collects data from 157 urology practices, which comprise 3165 providers. Notably, these providers account for approximately one-fourth of all urologists in the United States. The practices are spread across 48 states and territories in the United States.

The trends were evaluated based on patient, practice, and local or regional demographic and pandemic response features. Primary outcomes included mean visit volume and procedure volume-per-week.

Overall, 2,750,001 patients were included in the cohort, which comprised 8,953,832 outpatient visits and 1,570,161 procedures.

The decrease in visits was smaller among African American and Hispanic patients compared with Asian and Caucasian patients; however, African American and Hispanic patients experienced a slower recovery in visits to baseline.

Patients insured by Medicare, most of whom were over the age of 65, observed the steepest reduction in visits at 50%. Additionally, 84.4% of patients insured by Medicaid, most of whom were low-income patients, did not recover to the baseline number of weekly visits before the COVID-19 pandemic.

Finally, among practices located in areas with lower median incomes, higher poverty levels, and lower urologist-to-population ratios experienced smaller decreases in outpatient visits.
IN THE TREATMENT OF RELAPSED REFRACTORY MULTIPLE MYELOMA IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE (Pd)

ACHIEVE GREATER OUTCOMES FOR YOUR PATIENTS

SARCLISA is an anti-CD38 therapy proven to deliver superior PFS (median PFS of 11.53 months with SARCLISA + Pd vs 6.47 months with Pd alone, HR=0.596, 95% CI: 0.44, 0.81, P=0.0010). SARCLISA also demonstrated a significant increase in ORR (60.4% with SARCLISA + Pd [95% CI: 52.2%, 68.2%] vs 35.3% with Pd alone [95% CI: 27.8%, 43.4%], P<0.0001)*

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Preferred Category 1 recommendation for isatuximab-irfc (SARCLISA)

Isatuximab-irfc (SARCLISA), in combination with pomalidomide and dexamethasone, is a Preferred Category 1 option for previously treated multiple myeloma by the National Comprehensive Cancer Network® (NCCN®)

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.

*ORR included sCR, CR, VGPR, and PR. sCR, CR, VGPR, and PR were evaluated by an IRC using the IMWG response criteria.1

CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; mAb=monoclonal antibody; NCCN=National Comprehensive Cancer Network; ORR=overall response rate; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

Indication

SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Important Safety Information

CONTRAINDICATIONS
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions
Infusion-related reactions (IRR) have been observed in 39% of patients treated with SARCLISA. All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases. The most common symptoms of an IRR include dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension and dyspnea.

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Choose SARCLISA + Pd to Offer Improved Outcomes to More Patients vs Pd Alone

Studied in the phase 3 ICARIA-MM trial, which included patients with poor prognostic factors

Based on the ICARIA-MM trial, SARCLISA + Pd is a treatment choice for patients with relapsed refractory multiple myeloma

- Who have received at least 2 prior therapies, including lenalidomide and a PI
- Who may have renal impairment (creatinine clearance <60 mL/min/1.73 m²), high cytogenetic risk, or a history of COPD or asthma
- Who may have poor performance status or are ≥75 years of age
- Who are refractory to lenalidomide, a PI, or both

STUDY DESIGN: ICARIA-MM (NCT02990338), a multicenter, open-label, randomized, phase 3 study, evaluated the efficacy and safety of SARCLISA in 307 patients with relapsed refractory multiple myeloma who had received at least 2 prior therapies, including lenalidomide and a PI. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA was given weekly in the first cycle and every 2 weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. PFS was the primary endpoint; ORR and OS were key secondary endpoints. PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. Median follow-up was 11.6 months.

PATIENT CHARACTERISTICS: The median patient age was 67 years (range, 36 to 86), and 20% of patients were ≥75 years of age. Ten percent of patients entered the study with a history of COPD or asthma. The proportion of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) was 34%. The ISS stage at study entry was I in 37%, II in 36%, and III in 25% of patients. Overall, 20% of patients had high-risk chromosomal abnormalities at study entry: del(17p), t(4;14), and t(14;16) were present in 12%, 8%, and 2% of patients, respectively. The median number of prior lines of therapy was 3 (range, 2 to 11). All patients received a prior PI, all patients received prior lenalidomide, and 56% of patients received prior stem cell transplantation; the majority of patients (93%) were refractory to lenalidomide, 76% to a PI, and 73% to both an immunomodulator and a PI.

COPD=chronic obstructive pulmonary disease; ISS=International Staging System; IV=intravenous; OS=overall survival; PI=proteasome inhibitor.

Important Safety Information (cont’d)

Infusion-Related Reactions (cont’d)
To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H₂ antagonists, diphenhydramine or equivalent, and dexamethasone. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if a grade 3 or higher IRR occurs and institute appropriate emergency medical management.
SARCLISA + Pd Extended Median PFS to ~1 Year

Superior PFS with SARCLISA + Pd vs Pd alone\(^1\)

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The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd.\(^1\)

At a median follow-up time of 11.6 months, 43 patients (27.9%) receiving SARCLISA + Pd and 56 patients (36.6%) receiving Pd had died. Median OS was not reached for either treatment group at interim analysis. The OS results at interim analysis did not reach statistical significance.\(^1\)

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SARCLISA + Pd showed a significant increase in ORR\(^1*\)

<table>
<thead>
<tr>
<th>SARCLISA + Pd (n=154)</th>
<th>Pd (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60.4%</strong> ORR</td>
<td><strong>35.3%</strong> ORR</td>
</tr>
<tr>
<td>(P&lt;0.0001)</td>
<td></td>
</tr>
<tr>
<td><strong>31.8%</strong> ≥VGPR</td>
<td><strong>8.5%</strong> ≥VGPR</td>
</tr>
<tr>
<td>~4× increase</td>
<td></td>
</tr>
<tr>
<td><strong>35</strong> days</td>
<td><strong>58</strong> days</td>
</tr>
</tbody>
</table>

Median time to first response among responders

*ORR included sCR, CR, VGPR, and PR. ORR: SARCLISA + Pd (95% CI: 52.2%, 68.2%), Pd (95% CI: 27.8%, 43.4%).

Important Safety Information (cont’d)

**Neutropenia**

SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Febrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥3 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
Important Safety Information (cont’d)

Neutropenia (cont’d)
Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Second Primary Malignancies
Second primary malignancies were reported in 3.9% of patients in the SARCLISA, pomalidomide, and dexamethasone (Isa-Pd) arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm, and consisted of skin squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm), breast angiosarcoma (0.7% of patients in the Isa-Pd arm), and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of second primary malignancies.

Laboratory Test Interference

Interference with Serological Testing (Indirect Antiglobulin Test)
SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA--multiple myeloma (MM), the indirect antiglobulin test was positive during SARCLISA treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment. Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity
Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS
The most common adverse reactions (≥20%) were neutropenia (laboratory abnormality, 96% Isa-Pd vs 92% Pd), infusion-related reactions (38% Isa-Pd vs 0% Pd), pneumonia (31% Isa-Pd vs 23% Pd), upper respiratory tract infection (57% Isa-Pd vs 42% Pd), and diarrhea (26% with Isa-Pd vs 19% Pd). Serious adverse reactions occurred in 62% of patients receiving SARCLISA. Serious adverse reactions in >5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

USE IN SPECIAL POPULATIONS
Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see accompanying brief summary of full Prescribing Information.

Prepare the solution for infusion using aseptic technique as follows:

- Dilute 10 mg/kg actual body weight as an intravenous infusion in combination with pomalidomide and dexamethasone, according to the schedule in Table 1 (see Clinical Studies (14) in the full prescribing information).

**Table 1: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Days 1, 8, 15, and 22 (weekly)</td>
</tr>
<tr>
<td>Cycle 2 and beyond</td>
<td>Days 1, 15 (every 2 weeks)</td>
</tr>
</tbody>
</table>

Each administration cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. SARCLISA is used in combination with pomalidomide and dexamethasone.

**Missed SARCLISA Doses**

If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

**2.2 Recommended Premedications**

Administer the following premedications prior to SARCLISA infusion to reduce the risk and severity of infusion-related reactions:

- Dexamethasone 40 mg orally or intravenously (or 20 mg orally or intravenously for patients ≥75 years of age).
- Acetaminophen 650 mg to 1000 mg orally (or equivalent).
- H2 antagonists.
- Diphénylméthane 25 mg to 50 mg orally or intravenously (or equivalent). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (orally or intravenously) corresponds to the total dose to be administered only once before infusion as part of the premedication and of the background treatment, before SARCLISA and pomalidomide administration.

Administer the following premedications 15 to 60 minutes prior to starting a SARCLISA infusion.

**2.3 Dose Modifications**

No dose reduction of SARCLISA is recommended. Dose delay may be required for recovery of blood counts in the event of hematological toxicity (see Warnings and Precautions (5.1)).

For information concerning drugs given in combination with SARCLISA, see manufacturer's prescribing information. For other medical products that are administered with SARCLISA, refer to the respective current prescribing information.

**2.4 Preparation**

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg) of required SARCLISA based on actual patient weight (measured prior to each cycle to have the administered dose adjusted accordingly) (see Dosage and Administration (2.1)). More than one SARCLISA vial may be necessary to obtain the required dose for the patient.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever such inspection is feasible.
- Remove the volume of diluent from the 250 mL Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP diluent bag that is equal to the required volume of SARCLISA injection.
- Withdraw the necessary volume of SARCLISA injection and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to achieve the appropriate SARCLISA concentration for infusion.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or vinyl octyl acetate (VOA).
- Gently homogenize the diluted solution by inverting the bag. Do not shake.

**2.5 Administration**

- Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene (PBD), or polyurethane (PU)) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).
- The infusion solution should be administered for a period of time that will allow for the infusion (see Table 2).
- Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°–8°C, followed by 8 hours (including the infusion time) at room temperature.
- Do not administer SARCLISA infusion solution concomitantly in the same intravenous line with other agents.

**Table 2: Infusion Rates of SARCLISA Administration**

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Initial Rate</th>
<th>Absence of Infusion-Related Reaction</th>
<th>Rate Increment</th>
<th>Maximum Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First infusion</td>
<td>250 mL 25 mL/hour for 60 minutes</td>
<td>50 mL/hour every 30 minutes</td>
<td>100 mL/hour every 30 minutes</td>
<td>200 mL/hour</td>
</tr>
<tr>
<td>Second infusion</td>
<td>250 mL 50 mL/hour for 30 minutes</td>
<td>75 mL/hour every 30 minutes</td>
<td>100 mL/hour every 30 minutes</td>
<td>200 mL/hour</td>
</tr>
</tbody>
</table>

**4 CONTRAINDICATIONS**

- SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients (see Warnings and Precautions (5.1)).

**5 WARNINGS AND PRECAUTIONS**

**5.1 Infusion-Related Reactions**

Infusion-related reactions have been observed in 39% of patients treated with SARCLISA (see Adverse Reactions (6.1)). All infusion-related reactions started during the first SARCLISA infusion and resolved on the same day in 98% of cases. The most common symptoms of an infusion-related reaction included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hyperension and dyspnea (see Adverse Reactions (6.1)).

- To decrease the risk and severity of infusion-related reactions, premedicate patients prior to SARCLISA infusion with acetaminophen, H2 antagonists, diphenhydramine, or equivalent, dexamethasone (see Dosage and Administration (2.2)). Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2 (see Dosage and Administration (2.5)). In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA therapy if a grade 3 or higher infusion-related reaction occurs and institute appropriate medical management.

**5.2 Neutropenia**

SARCLISA may cause neutropenia. Neutropenia (reported in ≥1% of patients) occurred in 12% of patients receiving SARCLISA, pomalidomide, and dexamethasone ( Isa-Pd). Neutropenia was also observed in patients with neuroendocrine tumors who were treated with SARCLISA alone (see Adverse Reactions (6.1)).

- Monitor complete blood cell counts periodically during treatment. If grade 3-4 neutropenia occurred in 85% of patients treated with SARCLISA and pomalidomide, and dexamethasone ( Isa-Pd), the treatment should be interrupted, and closely monitor patients. If symptoms do not recur after interruption, permanently discontinue SARCLISA and institute appropriate management.

**5.3 Second Primary Malignancies**

Second primary malignancies were reported in 3.9% of patients in the Isa-Pd arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pom-D) arm, and consisted of skin squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Pom-D arm), breast angiosarcoma (0.7% of patients in the Isa-Pd arm) and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of second primary malignancies, as per International Myeloma Working Group (IMWG) guidelines.

**5.4 Laboratory Test Interference**

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA-multiple myeloma (MM), the indirect antiglobulin test was positive during SARCLISA treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, patients were administered without evidence of hemolysis.

**5.5 Embryo-Fetal Toxicity**

Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose (see Use in Specific Populations (8.1, 8.3)). The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

**6 ADVERSE REACTIONS**

The following clinically significant adverse reactions from SARCLISA are also described in other sections of the labeling:

- Infusion-Related Reactions [see Warnings and Precautions (5.1)].
- Neutropenia [see Warnings and Precautions (5.2)].
- Second Primary Malignancies [see Warnings and Precautions (5.3)]

**6.1 Clinical Trials Experience**

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

**Multiple Myeloma**

The safety of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients were eligible for inclusion if they had ECOG status of 0–2, platelets ≥75,000 cells/mm3, absolute neutrophil count ≥1.5x10^9/L, creatinine clearance ≥30 mL/min (MDRD formula), and AST and ALT ≤3 ULN. Patients received SARCLISA 10 mg/kg intravenously, weekly in the first cycle and every two weeks thereafter, in combination with pomalidomide and low dose dexamethasone (Isa-Pd) (n=152) or pomalidomide and low dose dexamethasone (Pom-Pd) (n=135) (see Clinical Studies (14) in the full prescribing information). Adverse reactions during Isa-Pd, 66% were exposed to SARCLISA for 6 months or longer and 24% were exposed for greater than 12 months or longer. The median age of patients was 66 years (range 36–83); 58% male, 76% white, and 14% Asian. Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. Serious adverse reactions occurred in 5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% were pneumonia and other infections [3%]).

Permanently discontinue due to an adverse reaction (grades 4–5) occurred in 7% of patients who received Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2%). In addition, SARCLISA and pomalidomide and dexamethasone (Pom-D) arm may be required to allow recovery of blood counts in the event of hematological toxicity.
Table 3: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Pomalidomide, and Dexamethasone with a Difference Between Arms of ≤5% Compared to Control Arm in ICARIA-MM Trial

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related reaction</td>
<td>38 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>31 (20%)</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>57 (38%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinous peritonitis</td>
<td>12 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (8%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

CTCAE version 4.03

*Pneumonia includes atypical pneumonia, bronchopulmonary, pneumonia bacterial, haemophilus infection, pneumonia streptococcal, pneumonia viral, candida fungal pharyngitis, influenza-like illness, laryngitis, bronchitis, bronchitis viral, chronic sinusitis, respiratory tract infection, and diarrhea.

Table 4 summarizes the hematologic laboratory abnormalities in ICARIA-MM.

Table 4: Treatment Emergent Hematologic Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment versus Pd Treatment – ICARIA-MM

<table>
<thead>
<tr>
<th>Laboratory Parameter (N=152)</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd)</th>
<th>Pomalidomide + Dexamethasone (Pd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades Grade 3 Grade 4</td>
<td>All Grades Grade 3 Grade 4</td>
<td>Grade 3 Grade 4</td>
</tr>
<tr>
<td>Anemia</td>
<td>951 (68)</td>
<td>49 (32)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>745 (49)</td>
<td>37 (24)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>130 (86)</td>
<td>64 (42)</td>
</tr>
<tr>
<td>Cholesterolopenia</td>
<td>127 (84)</td>
<td>22 (14)</td>
</tr>
</tbody>
</table>

Description of Selected Adverse Reactions

Infusion-related reactions

In ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusion, with an onset typically within 24 hours from the start of the infusion) were reported in 50 patients (36%) treated with SARCLISA. All patients who experienced infusion-related reactions, experienced them during the 1st infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 3.3%, Grade 2 in 32%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypertension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 29.6%. The median time to infusion interruption was 55 minutes.

In a separate study (TCD 14079 Part B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

Infections

In ICARIA-MM, the incidence of Grade 3 or higher infections was 43% in Isa-Pd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 22% of patients in Isa-Pd group compared to 16% in Pd group, and Grade 4 in 3.3% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in Isa-Pd group compared to 5.4% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and in 4% in Pd group.

6.2 Immunogenicity

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

In ICARIA-MM, no patients tested positive for antidrug antibodies (ADA). Therefore, the neutralizing ADA status was not determined. Overall, across 6 clinical studies in multiple myeloma (MM) with SARCLISA single-agent and combination therapies including ICARIA-MM (N=544), the incidence of treatment emergent ADAs was 2.3%. No clinically significant differences in the pharmacokinetics, safety, or efficacy of isatuximab-irfc were observed in patients with ADAs.

7 DRUG INTERACTIONS

7.1 Laboratory Test Interference

Interference with Serological Testing

SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with SARCLISA (see Warnings and Precautions (5.4)). Interference with Serum Protein Electrophoresis and Immunofixation Tests

SARCLISA may be incidentally detected by serum protein electrophoresis and immunofixation assays used for the monitoring of M-protein and may interfere with accurate electrophoresis and immunofixation assays used for the detection of monoclonal gammopathies of undetermined significance (MGUS).

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

Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.

Males

Refer to the pomalidomide prescribing information.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of SARCLISA, 53% (306 patients) were 65 or over, and 14% (82 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years of age and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

There is no known specific antidote for SARCLISA overdose. In the event of overdose of SARCLISA, contact the patients for signs or symptoms of adverse effects and take all appropriate measures immediately.

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A SANOFI COMPANY
U.S. License No. 1752

SARCLISA® (isatuximab-irfc) injection, for intravenous use

Data

Animal data
Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density which recovered 5 months after birth. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), fetal-maternal immune tolerance (mice), and early embryonic development (turtles).

8.2 Lactation

Risk Summary

There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

With the combination of SARCLISA with pomalidomide, refer to the pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Females

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

Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.

Males

Refer to the pomalidomide prescribing information.

8.6 Drug Interactions

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

Advise female patients of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of SARCLISA. Additionally, refer to the pomalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential.

Males

Refer to the pomalidomide prescribing information.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of SARCLISA, 53% (306 patients) were 65 or over, and 14% (82 patients) were 75 and over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years of age and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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ISA-PLBR-SA-MAR20
Revised: March 2020
No-Cost Counseling Can Address Psychosocial Needs of Patients With Cancer

by DENISE MYSHKO

DEPRESSION, ANXIETY, AND OTHER mental health disorders are not uncommon among patients diagnosed with cancer. Counseling, psychotherapy, and mental health services provide the opportunity for patients to develop coping skills and inspire hope; however, patients often experience hurdles to accessing such care. Among these obstacles are cost, unawareness that programs exist, the COVID-19 pandemic, and other external factors.

Many cancer institutions offer free services that include support groups, programs and seminars on stress management, and yoga for patients with cancer. Few practices offer comprehensive, individual counseling and psychotherapy at no cost. If counseling services are offered, they are typically billed to insurance companies, leaving patients to cover the costs of deductibles and copays. Incurring additional costs may not be an option for patients already struggling with the costs of cancer treatments. According to results of a study published in 2018 in the Journal of Oncology Practice, 26% of adults with cancer reported financial toxicity, which was associated with an increased risk for medical noncompliance. ¹ Specifically, patients were less likely to fill their medications, attend office visits, and undergo recommended medical tests.

Further, an analysis presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program showed that patients with recurrent ovarian cancer at high risk of struggling financially because of ongoing treatment costs or potential loss of income scored higher on measures for depression and anxiety and lower on quality of life.²

High costs and insurance coverage are significant barriers to seeking counseling, but providing accessible mental health services to patients is important for their healing, said Barry Russo, MBA, CEO of The center for Cancer & Blood Disorders in Fort Worth, Texas.

“We knew from our original approach of referring people out to psychologists and psychiatrists that many didn’t go,” Russo said in an interview with OncologyLive®. “Removing financial hurdles opens the door for people to seek psychological support who otherwise wouldn’t.”

This understanding led the center to launch a different type of counseling and psychotherapy program in 2016. Funded in part by the Careity Foundation in Fort Worth, the program is operated on-site at the center and is of no cost for patients. “We knew that if we were going to start a program, we did not want any financial hurdles,” Russo said. “We wanted them to access this without a concern about the costs involved.”

A SNAPSHOT OF MENTAL HEALTH

Estimates of the prevalence of depression and anxiety among patients with cancer varies, but several studies generally show approximately one-third of patients with cancer have some type of mental health issue. Investigators reported in 2014, for example, that approximately 32% of patients with cancer were diagnosed with at least 1 mental disorder; anxiety disorders (11.5%) and mood disorders (6.5%) were the most common.³

In a subsequent study from 2018, investigators found that depression and anxiety affects up to 20% and 10% of patients with cancer, respectively, compared with 5% and 7% for the general population.⁴ The prevalence is highest at diagnosis and at the beginning of treatment. Investigators found that poor recognition of depression and...
anxiety is associated with reduced quality of life and survival.

The COVID-19 pandemic has added to the mental health struggles patients with cancer experience. For example, 53% of surveyed patients with cancer (n = 606) reported experiencing loneliness in recent months and higher symptom severity scores for all the symptoms evaluated, according to a new survey published online in May in Cancer (FIGURE).3

From the early analysis, investigators found patients in the lonely group reported higher levels of social isolation, as well as more severe symptoms of anxiety, depression, fatigue, sleep disturbance, cognitive dysfunction, and pain.

“There is a really robust literature about the impact of loneliness and social isolation on morbidity and mortality in cardiovascular disease, but it hasn’t been studied in cancer,” lead author Christine Miaskowski, PhD, RN, FAAN, said. Miaskowski is the Sharon A. Lamb Endowed Chair in Physiological Nursing and a professor in the Department of Physiological Nursing at the University of California, San Francisco.

“It is clear that if you take out all the other risk factors for mortality in cardiovascular disease, loneliness and social isolation make independent, significant contributions to morbidity and mortality,” she said. “If the association holds with what we see with cardiac disease, the stress from loneliness can impact patients with cancer and their disease progression.”

Miaskowski noted that respondents were mostly women, White, and wealthy. The survey is continuing, and approximately 1100 patients have completed the questionnaire so far. “I want to know about what is happening with the people who are less well served,” she said.

CARING FOR THE WHOLE PATIENT

The association between cancer survival and mental health is just beginning to be understood, and early studies have demonstrated that investment in mental health and social needs has a strong correlation with improved health outcomes. “There is a growing consensus that mental health plays a significant role in oncology care,” Chris Murray, PhD, a psychotherapist who helped launch the center’s program, said.

A study of veterans with non-small cell lung cancer who had preexisting mental health disorders found that mental health treatment programs, housing programs, and employment support programs were associated with improved lung cancer-related outcomes.4 Participation in a mental health program was associated with a significant decrease in all-cause mortality and lung cancer-specific mortality across every mental health diagnosis evaluated. Investigators suggested that seeing mental providers enabled patients to engage more with their non-mental health medical treatment.

The need for counseling and psychotherapy is much greater than anyone would expect, said Beverly Branch, cofounder of Careity Foundation. “People can’t heal physically if they aren’t healed psychologically,” she said.

Providing mental health services to patients with cancer is critical, especially now because of COVID-19, said Lyn Walsh, cofounder of Careity Foundation. “There are patients who are just so overwhelmed,” she said. “Psychotherapy was something that we used to offer patients. Now we get calls requesting someone to talk to.”

For patients with cancer, chemotherapy, radiation, and financial burdens can cause depression and hopelessness, said Vernesa Perry, PhD, who conducted the research for her dissertation at the center. “People who
have had full lives may now find getting out of bed is an accomplishment,” she said. “They struggle to accept their new normal. It is so complex, and there really is a need for therapy services in the oncology setting because research shows it really has a big impact.”

Perry’s dissertation looked at whether a solution-focused narrative model of therapy could provide a more hopeful outlook for patients with cancer. This model counseling looks toward solutions instead of discussing problems at length. In her analysis, Perry noted that patients in the traditional therapy group did not return after one session, with one patient saying that there was too much negativity in the group in a follow-up call. Those in the solution-focused group, however, highlighted the importance of such a group.

“A solution-focused narrative therapy is a short-term model that has been shown to work in 1 to 3 sessions,” Perry said. “This becomes more helpful in the cancer setting because we don’t know if that patient is going to come back.

“Traditional therapy models are designed to be long term. They can be effective, but my experience at the cancer hospital showed that for patients with cancer, you may not have that luxury of time. At the center we were also flexible with scheduling. If I have a patient that is supposed to come after chemotherapy or radiation, there is a high chance they won’t be able to make it because they don’t feel well.”

AID AT THE COMMUNITY LEVEL

Services such as group therapy or private counseling can provide patients with needed support, but patients may not know where to get help or they may not have insurance coverage. There are no national data around how many community oncology practices offer counseling or mental health services, according to the Community Oncology Alliance. Anecdotally, services vary by geographic area, and many are billable services.

Murray said that in the Dallas–Fort Worth metroplex, few institutions or direct providers of mental health services specifically for patients with cancer offer services at no cost to the patient. “The big hospital providers also provide mental health services but those are not grant funded or no cost to patients,” he said. “Typically, they are insurance-covered services that are subject to copays and deductibles.”

Branch said it’s important to make the counseling accessible to all patients regardless of insurance status. “If it isn’t, people won’t take advantage of it because of all the other expenses they have and because of complication of their treatments,” she said. “We’ve had patients say the counseling was the greatest gift they had received from us.”

SPOTLIGHT ON THE CENTER’S PSYCHOTHERAPY PROGRAM MODEL

The center’s program is staffed by Murray and graduate-level behavioral health providers. Murray was brought on in 2016 to develop the psychotherapy program and provide oversight of providers.

The team of behavioral health providers includes graduate-program clinical training students, licensed providers, doctoral research candidates, and volunteers. “The program helps to provide training to future psychologists on how to help patients [with cancer],” Russo said. “We wanted to provide services for the patients, but we also wanted to provide a training ground for psychologists to have experience with the challenges that patients with cancer face. We want to be able to have an educated force of psychologists that can help patients all over Dallas–Fort Worth.”

Behavioral health services are provided to patients at all of the center’s 9 locations. In the 5 years the program has been operational, the center has provided services to approximately 800 patients, offering more than 5000 hours of session time.

“W e believe this approach is targeted for those in need of behavior health intervention,” Murray said. It’s in-house, and it’s there when and where patients need it.”

The services provided have been developed specifically for patients with cancer because most programs and outside counseling services, although beneficial, may not be specific to this population’s specific needs. “A typical provider would be able to provide services that cover a lot of the things we see, such as depression, anxiety, high stress levels, and some PTSD [posttraumatic stress disorder],” Murray said. “There is this whole other dimension of patients’ mental health needs that is specific to what has happened after they got that cancer diagnosis that we tend to be more equipped to help them process and address those needs.”

The center has continued to offer services virtually during the COVID-19 pandemic. “Like other clinical and mental health providers, we were forced to rethink how to effectively deliver services that were needed, sometimes desperately,” Murray said. “We moved to virtual sessions quickly and found patient satisfaction and outcomes on the whole seemed to be at least that of in-person, although about half have since chosen to resume in-person [services] as restrictions have eased. Research now coming out seems to validate this was the case in other settings as well with mental health providers. As a result, I anticipate virtual psychotherapy on a significant level is here to stay.”

For a full list of references, see the article at OncLive.com.
Now Is the Time to Improve Diversity in Cancer Clinical Trials

by BRUCE D. RAPKIN, PhD

PARTICIPATING IN A CLINICAL TRIAL is the most effective way to gain access to new and potentially better ways to treat cancer, yet we’ve seen a decrease in the number of African American and Hispanic patients participating in oncology trials in 2003 to 2016, compared with 1996 to 2002.1

Moreover, according to the 2020 Drug Trials Snapshot Summary Report, the 18 new oncology drugs approved by the FDA last year included a mere 5% Black and 6% Hispanic participants out of 4922 patients whose data supported the approval of these treatments.

WHY THE LOW PERCENTAGES?
Achieving equal representation in clinical trials is a major challenge. Historically, there have been many reports of abuses of patients of color in medical research. We’re all familiar with the infamous syphilis studies carried out at Tuskegee2 in the 20th century. It was not until 2020 that the family of Henrietta Lacks, a young Black woman whose cell line has supported a multibillion-dollar biotechnology industry, started to receive financial compensation. As a reminder, Lacks was never consulted about the research taking place.

These abuses, combined with language barriers among other hurdles, often result in the question from patients in minority populations: What is the benefit of participating in a clinical trial for me and my family?

In January 2020, Montefiore Health System and Albert Einstein Cancer Center were awarded a $5.9 million grant from the National Cancer Institute (NCI) to build on our success recruiting minority and underserved patients to cancer clinical trials. This new grant is part of the NCI Community Oncology Research Program (NCORP) and is a continuation of funding that was first awarded in 2014.

Our cancer center, based in the Bronx, New York, is one of only 14 NCORP Minority/Underserved Community Clinical Sites. The designation means that investigators of clinical trials must enroll at least 30% racial/ethnic minorities or rural residents. We take great pride that at our institution, 80% of clinical trial participants are minorities, compared with the nationwide figure of only 8%.

Part of our success in recruiting diverse populations is our ongoing research into community attitudes regarding clinical trial recruitment. In 2018, we conducted a Bronx community health survey, which sampled more than 1350 nonpatient residents of our catchment area. Results showed that 88% of Bronx residents trust their doctors and hospitals “a lot” or “a fair amount”; however, when it comes to cancer care, only 56% of both non-Hispanic Black and Hispanic respondents agreed with the statement that “cancer care in your community is excellent” compared with 74% of non-Hispanic White respondents.

FIGURE 1. Complex Combinations of Research Attitudes Held by Bronx Residents

Mean Cluster Differences in Research Attitudes

Strongly agree

Strongly disagree

Cluster key

1 Trusts safeguards, has low suspicions, sees research as needed

2 Wants more research, has no suspicions but has safety concerns

3 Highly suspicious, concerned about safeguards, but sees research as important

4 Medical research is low priority, has some suspicions

5 Does not think that more research is needed in the community

More research is needed  Safeguards are sufficient  Suspicious about intentions
Perception that cancer care in the Bronx is excellent was notably higher among 110 cancer survivors in our sample (74% for non-Hispanic Blacks, 80% for all Hispanics, and 79% for non-Hispanic Whites), but not among 903 family members of current or past patients with cancer (55% for non-Hispanic Blacks, 58% for all Hispanics, and 76% for non-Hispanic Whites).

There was also a wide variation in attitudes about clinical research (FIGURE 1). Although most Bronx residents see the importance of medical research, many have safety concerns and suspicions regarding researchers’ intentions despite seeing the need for research (Figure 1, cluster 3).

Despite community concerns, it is important to stress that in past studies, the main reason patients gave for not participating in research is that nobody asked them. These findings reinforce why we need to always be refining our strategies for clinical trial enrollment.

THREE KEYS TO SUCCESS
Similar to any relationship, successful accrual is all about putting in the work. As FIGURE 2 summarizes, our NCORP team has identified 3 fundamental aspects:

1. **Maintaining effective working relationships with providers and clinical staff**
   For those of us involved in clinical research, logistics must be a labor of love. Finding ways to shift research tasks from providers and staff is a priority. Support for screening patients for eligibility criteria is only the beginning. Orientation of clinic staff to study procedures and materials, figuring out space for research staff, and timing of approaches to clinicians and patients are also imperative. Ongoing communication and problem-solving are important to accommodate missed appointments, late arrivals, and unexpected patient care issues that arise. Throughout each study, our team monitors accrual and provides feedback to clinics about what worked and opportunities for improvement.

2. **Engaging clinicians as study champions**
   Even at an academic cancer center, it can be difficult for practicing clinicians to carve out time for research. Involvement in NCORP is invaluable for clinicians early in their academic careers as it affords them the opportunity to contribute to research in a substantive way and to expand their professional and academic networks. NCORP

<table>
<thead>
<tr>
<th>Racial/ethnic group</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic Black (N = 428)</td>
<td>18%</td>
<td>33%</td>
<td>26%</td>
<td>20%</td>
<td>3%</td>
</tr>
<tr>
<td>Hispanic (N = 581)</td>
<td>23%</td>
<td>32%</td>
<td>21%</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hispanic White (N = 282)</td>
<td>29%</td>
<td>37%</td>
<td>11%</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>Other (N = 57)</td>
<td>16%</td>
<td>28%</td>
<td>26%</td>
<td>28%</td>
<td>2%</td>
</tr>
<tr>
<td>Overall (N = 1350)</td>
<td>22%</td>
<td>33%</td>
<td>20%</td>
<td>21%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Partner Perspectives

research bases offer funding opportunities for pilot studies with a focus on cancer health equity to assist early-stage faculty in launching work that addresses the needs of underserved and underrepresented patients.

At our center, this approach has led investigators to find practical ways to address disparities. Examples include a screening program to preempt emergency department diagnoses of stomach cancer, fitness trackers to support patients undergoing radiation for lung cancer, and developing prostate cancer treatment aids tailored to men of ethnic minorities.1,2

3. Building rapport with patients and families

The accrual process must meet patients where they are at. Many patients in our system are not comfortable with written documents, and we’ve found a significant amount of people are reluctant to disclose reading difficulties. For that reason, our research staff default to reading consents, surveys, and other materials aloud, unless the patient expresses a preference for proceeding independently. Providing a signature on a consent from can also constitute a barrier for some patients, especially when the document they are signing is not clear.

Patients in low-income communities, such as the Bronx, are often affected by significant negative social determinants of health. This speaks to the essential role of clinic navigators. These skilled individuals proactively identify challenges such as transportation barriers, lack of caregiver support, or financial concerns, and are experts in finding resources available to help.

As is evident in Figure 1, members of our community hold preconceived attitudes about medical research. Patients’ decisions regarding trial participation can be greatly influenced by their social network. We’re partnering with area hospitals and schools along with the Stand Up to Cancer Foundation to address knowledge gaps and attitudes surrounding clinical trials in the community. Education on the importance of representation in trials and the safeguards in place is essential. Equally important are the opportunities for community members to meet investigators outside the clinic to get a sense for the cancer research that is happening in their own backyard.

A TEACHABLE MOMENT

Any diagnosis of cancer is daunting and can leave the most prepared and equipped individuals feeling lost. Now, put yourself in the shoes of an individual with cancer who is all too familiar with historical abuses, or for whom English may not be their first language.

To ensure that the newest options for cancer prevention, screening, and treatment benefit all, we must do everything possible to make clinical trials accessible. We must share information about our findings with communities so people who have traditionally been excluded can begin to see the benefits of participation—for themselves and future generations.

The COVID-19 pandemic shined a bright light on health disparities. Now, we have a once-in-a-lifetime opportunity to open dialogue with the communities we serve about how best to further science and medicine. Physicians, patient representatives, and advocates must act to achieve representation in clinical trials and ensure the latest cancer therapies are both tailored and accessible to all. We hope the lessons we have learned through our experiences help others in this endeavor.

REFERENCES

For women with HR+, HER2- MBC* who have visceral disease† or primary ET resistance‡

Survival doesn’t have to be at higher risk

Visceral disease† and primary ET resistance‡ are associated with higher risk.¹,²

*With disease progression following ET.
†Visceral disease was defined as at least 1 lesion on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement.²
‡Primary resistance was defined as relapse within the first 2 years of adjuvant ET or progressive disease within the first 6 months of first-line ET for MBC.³,⁴
§Patients with higher-risk disease, defined as the presence of visceral disease or primary ET resistance, were included in the MONARCH 2 clinical trial.⁸

ET=endocrine therapy; HER2=human epidermal growth factor receptor 2–negative; HR+=hormone receptor–positive; MBC=metastatic breast cancer.

Indication
Verzenio® (abemaciclib) is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) advanced or metastatic breast cancer (MBC)⁶:

• In combination with fulvestrant for women with disease progression following endocrine therapy

Important Safety Information
Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
**Verzenio is the only CDK4 & 6 inhibitor to achieve significant overall survival improvement in combination with fulvestrant regardless of menopausal status**

**OS in ITT Population**

- Results are based on a prespecified interim analysis and are considered definitive.\(^{10}\)
- The percentage of deaths at the time of analysis was 47.3% (n=211) and 57.0% (n=127) in the Verzenio plus fulvestrant and fulvestrant alone arms, respectively.\(^{10}\)
- Primary endpoint of median PFS was met: 16.4 months (95% CI: 14.4-19.3) median PFS with Verzenio plus fulvestrant vs 9.3 months (95% CI: 7.4-12.7) with fulvestrant alone (HR=0.553; 95% CI: 0.449-0.681; \(P<0.0001\)).\(^{6}\)
- The percentage of PFS events at the time of analysis was 49.8% (n=222) and 70.4% (n=157) in the Verzenio plus fulvestrant and fulvestrant alone arms, respectively.\(^{6}\)

**Study Design**

MONARCH 2 was a phase III, randomized, double-blind, placebo-controlled trial that enrolled 669 patients with HR+, HER2- MBC who progressed on or after ET. Pre/perimenopausal women (17%) were rendered postmenopausal prior to the study. Patients had received no chemotherapy and no more than 1 prior ET in the metastatic setting. Patients were randomized 2:1 to Verzenio plus fulvestrant (n=446) or placebo plus fulvestrant (n=223). Verzenio and placebo were dosed PO BID on a continuous dosing schedule until disease progression or unacceptable toxicity. 500 mg fulvestrant was administered by IM injection on days 1, 15, and 29 of the first month and once monthly thereafter. The primary endpoint was PFS. Key secondary endpoints were ORR, OS, and DoR.\(^{6,8}\)

**Important Safety Information (cont’d)**

**Neutropenia** occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with Verzenio and other CDK4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.
In HR⁺, HER2- MBC*  

Even women with worse prognoses achieved survival outcomes consistent with the overall study population¹

**WOMEN WITH VISCERAL DISEASE† HAD**  

8.1 months longer mOS¹  

40.3 months mOS with Verzenio plus fulvestrant (n=245) vs 32.2 months mOS with fulvestrant alone (n=128).  

HR=0.675 (95% CI: 0.511-0.891)

**WOMEN WITH PRIMARY ET RESISTANCE‡ HAD**  

7.2 months longer mOS¹  

38.7 months mOS with Verzenio plus fulvestrant (n=112) vs 31.5 months mOS with fulvestrant alone (n=60).  

HR=0.686 (95% CI: 0.451-1.043)

- Preplanned subgroup analyses of PFS and OS were performed for stratification factors of disease site (including visceral disease) and endocrine resistance (including primary ET resistance). Analyses were not adjusted for multiplicity, and the study was not powered to test the effect of Verzenio + fulvestrant among subgroups.¹¹

*With disease progression following ET.  
†Visceral disease was defined as at least 1 lesion on an internal organ or in the third space and could have included lung, liver, pleural, or peritoneal metastatic involvement.⁵  
‡Primary resistance was defined as relapse within the first 2 years of adjuvant ET or progressive disease within the first 6 months of first-line ET for MBC.⁶,⁷

**Important Safety Information (cont’d)**

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.  

Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue Verzenio in all patients with grade 3 or 4 ILD/pneumonitis.  

Grade ≥3 increases in alanine aminotransferase (ALT) (6% versus 2%) and aspartate aminotransferase (AST) (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 2.  

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.  

For assessment of potential hepatotoxicity, monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.  

Please see Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents. Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

Verzenio can cause fetal harm when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

The most common adverse reactions (all grades, ≥10%) observed in MONARCH 2 for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The most frequently reported ≥5% Grade 3 or 4 adverse reactions that occurred in the Verzenio arm vs the placebo arm of MONARCH 2 were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%).

Lab abnormalities (all grades; Grade 3 or 4) for MONARCH 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs <1%), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), and increased AST (37% vs 25%; 4% vs 4%).

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of the strong CYP3A inhibitor ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.

Avoid concomitant use of strong or moderate CYP3A inhibitors and consider alternative agents. Coadministration of strong or moderate CYP3A inhibitors decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosage frequency to once daily. The pharmacokinetics of Verzenio in patients with severe renal impairment (CLcr <30 mL/min), end stage renal disease, or in patients on dialysis is unknown. No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr ≥30–89 mL/min).

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

AL HCP ISI_M2 23ОCT2019

*At disease progression following ET.
†Patients with higher-risk disease, defined as the presence of visceral disease or primary ET resistance, were included in the MONARCH 2 clinical trial.

VERZENIO® (abemaciclib) tablets, for oral use

Initial U.S. Approval: 2017

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

INDICATIONS AND USAGE
VERZENIO® (abemaciclib) is indicated:

• in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

CONTRAINDICATIONS:
None

WARNINGS AND PRECAUTIONS
Diarrhea
Diarrhea occurred in 81% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 90% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection. Diarrhea incidence was greatest during the first month of VERZENIO dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 was 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further reductions and appropriate follow up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue VERZENIO until toxicity resolves to < Grade 1, and then resume VERZENIO at the next lower dose.

Neutropenia
Neutropenia occurred in 41% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and 37% of patients receiving VERZENIO alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving VERZENIO plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2, and in 27% of patients receiving VERZENIO in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1 was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Feverle neutropenia has been reported in <1% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

Interstitial Lung Disease (ILD)/Pneumonitis
Severe, life-threatening, or fatal lung disease (ILD) and/or pneumonitis can occur in patients treated with VERZENIO and other CDK 4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, and MONARCH 3), 3.3% of VERZENIO-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended for patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue VERZENIO in all patients with Grade 3 or 4 ILD or pneumonitis.

Hepatotoxicity
In MONARCH 3, Grade ≥3 increases in ALT (6% versus 2%) and AST (3% versus 1%) were reported in the VERZENIO and placebo arms, respectively. Across clinical trials (MONARCH 1, MONARCH 2, and MONARCH 3), 3.3% of VERZENIO-treated patients had ALT/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for laboratory evidence of abnormal liver function tests. If laboratory tests for liver function tests reflect abnormal liver function tests, monitor liver function tests (LFTs) prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

Venous Thromboembolism
In MONARCH 3, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo. In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported.

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Embryo-Fetal Toxicity
Based on findings from animal studies and the mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VERZENIO and for at least 3 weeks after the last dose.

ADVERSE REACTIONS
Clinical Studies 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.

MONARCH 2: VERZENIO in Combination with Fulvestrant
Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving VERZENIO plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 19% of patients receiving VERZENIO plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. VERZENIO dose reductions due to neutropenia of any grade occurred in 10% of patients receiving VERZENIO plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving VERZENIO plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of VERZENIO plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving VERZENIO plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonia, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral hemorrhage.

The most common adverse reactions reported (≥20%) in the VERZENIO arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 3). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, and anemia.
Table 1: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>VERZENIO plus Fulvestrant N=223</th>
<th>Placebo plus Fulvestrant N=441</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>86 13 0 25 &lt;1 0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>45 3 0 23 1 0</td>
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<tr>
<td>Abdominal Paina</td>
<td>35 2 0 16 1 0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 &lt;1 0 10 2 0</td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15 &lt;1 0 10 0 0</td>
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</tr>
<tr>
<td>Infections and Infestations</td>
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<td></td>
</tr>
<tr>
<td>Infections</td>
<td>43 5 &lt;1 25 3 &lt;1</td>
<td></td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
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<td></td>
</tr>
<tr>
<td>Neutropeniaab</td>
<td>46 24 3 4 1 &lt;1</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>29 7 &lt;1 4 1 0</td>
<td></td>
</tr>
<tr>
<td>Leukopeniaab</td>
<td>28 5 &lt;1 4 0 0</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 2 1 3 0 &lt;1</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
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<td></td>
</tr>
<tr>
<td>Fatigue</td>
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<tr>
<td>Edema peripheral</td>
<td>12 0 0 7 0 0</td>
<td></td>
</tr>
<tr>
<td>Pruria</td>
<td>11 &lt;1 1 6 &lt;1 0</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27 1 0 12 &lt;1</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>15 0 0 11 0 0</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
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<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>16 0 0 2 0 0</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 0 0 6 0 0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
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</tr>
<tr>
<td>Nervous System Disorders</td>
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<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20 1 0 15 &lt;1</td>
<td></td>
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<tr>
<td>Dizziness</td>
<td>18 0 0 3 0 0</td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td>12 1 0 6 0 0</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
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<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>13 4 &lt;1 5 2 0</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>12 2 0 7 3 0</td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>12 &lt;1 0 11 0 0</td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>10 &lt;1 0 2 0 0</td>
<td></td>
</tr>
</tbody>
</table>

*Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.

$i$Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.

$g$Includes neutropenia, neutrophil count decreased.

$T$Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

$e$Includes leukopenia, white blood cell count decreased.

$f$Includes platelet count decreased, thrombocytopenia.

$g$Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 2: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>VERZENIO plus Fulvestrant N=223</th>
<th>Placebo plus Fulvestrant N=441</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine increased</td>
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<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>26 1 0 74 0 0</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>87 29 4 30 4 &lt;1</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>84 3 0 33 &lt;1 0</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>63 12 &lt;1 32 2 0</td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>53 &lt;1 1 15 0 0</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>41 4 &lt;1 32 1 0</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>37 4 0 25 4 &lt;1</td>
<td></td>
</tr>
</tbody>
</table>

$\text{Creatinine Increased}$

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.2 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

**DRUG INTERACTIONS**

*Effect of Other Drugs on VERZENIO*

**CYP3A Inhibitors**

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold.

**Other Strong CYP3A Inhibitors**

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. Patients should avoid grapefruit products.

Moderate CYP3A Inhibitors

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements, if necessary.

**Strong and Moderate CYP3A Inducers**

Concomitant use of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose (see Data). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

**Data**

**Animal Data**

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses ≥4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

**Lactation**

**Risk Summary**

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

**Females and Males of Reproductive Potential**

**Pregnancy Testing**

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

**Contraception**

**Females**

VERZENIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for at least 3 weeks after the last dose.

**Infertility**

**Males**

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.
Pediatric Use
The safety and effectiveness of VERZENIO have not been established in pediatric patients.

Geriatric Use
Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Renal Impairment
No dosage adjustment is required for patients with mild or moderate renal impairment (Clcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (Clcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

Hepatic Impairment
No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C).

OVERDOSAGE
There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

Rx only.

Additional information can be found at www.verzenio.com.
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AL HCP BS_M2 28JAN2020
Dose-Reduction Strategy Maintains Efficacy, Averts Serious Events in CML

by BRITTANY LOVELY

DESpite early induced efficacy, first- and second-generation tyrosine kinase inhibitors (TKIs) have limited efficacy for patients with chronic myeloid leukemia (CML). Disease resistance occurs in approximately 40% of patients who receive the standard treatment with imatinib (Gleevec). In the second-line setting, patients who initially respond to treatment with a second-generation TKI, approximately 26% lose response within 2 years and up to 50% experience no response at all.1

Investigators have determined that the development of point mutations in the BCR-ABL pathway is a contributing factor to resistance and is associated with poor prognosis.1,2 A third-generation TKI, ponatinib (Iclusig), has demonstrated activity against T315I, a mutation of BCR-ABL that is present in approximately 20% of patients with CML whose disease develops resistance to other TKIs. Deep and durable responses were observed with the agent in the phase 2 PACE trial (NCT01207440), the data from which supported the 2012 FDA approval.2

However, safety data demonstrating high incidence of arterial occlusion events prompted the agency to include a boxed warning and recommended dose-reduction guidelines on the prescribing information.3 Investigators have revisited the dosing recommendations for ponatinib across histologic subtypes. Investigators of the OPTIC trial (NCT02467270) set out to evaluate the optimal risk-benefit profile of lower doses of ponatinib (FIGURE).4

A primary analysis of OPTIC, presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting, demonstrated benefit in patients with resistant CML in the 3 dosing regimens evaluated.5 The largest benefit was observed in patients who were enrolled in the 45-mg to 15-mg dose-reduction cohort, meeting the primary end point of the study (TABLE 1). For patients enrolled in the 30- and 45-mg cohorts, 73 patients had a dose reduction to 15 mg and 55 (75%) maintained a response to treatment. In the 45-mg cohort specifically, 45 patients (73.3%) had a dose reduction to 15 mg after achieving BCR-ABL transcript level of less than 1%.

Moreover, investigators reported that most patients who had dose re-escalation in the 45-mg (n = 13) and 30-mg (n = 5) cohorts after loss of response regained less than 1% BCR-ABL (61.5% and 80%, respectively). The median time to regain response was 3.9 months for those in the 45-mg cohort and 4.2 months for those in the 30-mg cohort.

The incidence of treatment-emergent arterial occlusion events decreased in correlation with dose reductions in the study (TABLE 2). The rates of these events in patients who achieved a response by 12 months were 9.6%, 5.3%, and 3.2% in the 45-, 30-, and 15-mg starting dose cohorts, respectively.
The analysis demonstrated that in clinical practice, establishing a treatment algorithm that stratifies patients based on comorbidities, mutational status, and response to prior treatment. This method may maximize the efficacy of ponatinib maintenance therapy and avoid increased risk of arterial occlusion events.

Lead investigator Jorge E. Cortes, MD, was joined by a panel of experts in hematologic malignancies including Elias Jabbour, MD; B. Douglas Smith, MD; and Robert Foà, MD, for a discussion of the OPTIC data as part of the OncLive® Leukemia Talk program.

CORTES  I’m going to start by introducing an abstract that I presented at ASCO—the results of the OPTIC trial. We all know that ponatinib has been a very effective drug, and when it came it was very exciting. It inhibited T315I with high rates of response in patients who had received multiple prior therapies. Shortly after that excitement, the recognition of arterial occlusive events arrived.

Different numbers have been thrown around, but incidence was approximately 20% to 30% and the bottom line is that this has limited the use of ponatinib. Something that many investigators first started doing was using lower doses or starting at lower doses of ponatinib to try to minimize the risk.

OPTIC [investigators examined] prospective data for the use of lower starting doses to see whether that would minimize the safety concerns but maintain the efficacy, because you want to keep the efficacy that we like from ponatinib. Patients received either 45-mg, 30-mg, or 15-mg starting dose. One important thing of the trial design here is that patients who responded—response was defined as 1% or less of the transcript levels—were mandated to reduce to 15 mg daily. What these study data showed was that the 45-mg dose was by far the most effective. The response rate was almost 45%, whereas it was 29% at the 30-mg dose and even lower with the 15-mg dose [Table 1].

In a subset analysis, patients with the worst [prognostic] features had the biggest difference—patients with T315I mutations, patients who had received [1 or] more TKIs, all of that. Clearly, from the efficacy point of view, there was a big difference in favor of the standard dose, the 45-mg daily dose. Most patients maintained response after dose reduction; although approximately a quarter lost the response, many of them regained response after re-escalation of the dose.

In terms of arterial occlusive events, there is a difference. The rate of any arterial occlusive event was approximately 10% with 45 mg and is approximately 5% with 30 mg [Table 2]. There is a price to pay for that higher efficacy. Now, the difference between the efficacy and the safety is much larger in favor of the efficacy, meaning you gain a lot more by using the 45 mg than you lose, but you do lose some [with the] higher rate of arterial occlusive events.

The conclusion here is that 45 mg is the [dose] that provides the best ratio of risk and benefit. This efficacy-driven dose reduction has made it into the label of ponatinib, which remains now with a standard dose of 45 mg daily, and it gives some light to how to use ponatinib.

One important thing is that the overall rate of these arterial occlusive events is lower than we had seen [in the data from the] PACE trial [NCT01207440], and you could argue whether this is [a result of] the efficacy-driven dose reduction or whether there are more stringent eligibility criteria. [You must also ask] whether that is enough for us to consider 45 mg daily.

I will say that, for me, I prefer 45 mg for most of my patients. Perhaps for the highest-risk patients in terms of arterial occlusive events, you may want to consider 30 mg, but you must acknowledge that you give up something in terms of efficacy. Again, I find myself using 45 mg more often than 30 mg, and certainly much more than 15 mg, which I hardly ever use. I don’t know if anybody sees this differently.

Dr Jabbour, how do you see this data, and how do you do it in your practice for patients with CML?

JABBOUR  I think dose adjustment is very important, and the fact that once you induce an optimal response reducing the dose of the drug seems to not

---

### TABLE 1. Efficacy in OPTIC Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>45 mg to 15 mg (n = 93)</th>
<th>30 mg to 15 mg (n = 93)</th>
<th>15 mg (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response at 12 months</td>
<td>44.1% (31.7%-57.0%)</td>
<td>29.0% (18.4%-41.6%)</td>
<td>23.1% (13.4%-35.3%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>NR</td>
<td>NR</td>
<td>45.6 months</td>
</tr>
<tr>
<td>Estimated PFS rate at 12 months</td>
<td>91.6%</td>
<td>86.1%</td>
<td>84.9%</td>
</tr>
<tr>
<td>Estimated PFS rate at 24 months</td>
<td>79.9%</td>
<td>76.1%</td>
<td>78.1%</td>
</tr>
<tr>
<td>Estimated PFS rate at 36 months</td>
<td>73.3%</td>
<td>66.3%</td>
<td>69.7%</td>
</tr>
<tr>
<td>(n = 15)</td>
<td>(n = 9)</td>
<td>(n = 23)</td>
<td></td>
</tr>
<tr>
<td>Response by 12 months in patients with T315I mutation at baseline</td>
<td>60%</td>
<td>56%</td>
<td>46%</td>
</tr>
</tbody>
</table>

NR, not reached; PFS, progression-free survival.
*Response defined at ≤ 1% BCR-ABL1.

### TABLE 2. Risk/Benefit in OPTIC Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>45 mg to 15 mg (n = 93)</th>
<th>30 mg to 15 mg (n = 93)</th>
<th>15 mg (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with response by 12 months*</td>
<td>51.6%</td>
<td>35.5%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Δ*</td>
<td>26.3%</td>
<td>10.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Rate of TE-AOE</td>
<td>9.6%</td>
<td>5.3%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Δ*</td>
<td>6.4%</td>
<td>2.1%</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable; TE-AOE, treatment-emergent arterial occlusive event.
*Response defined at ≤ 1% BCR-ABL1.
*As compared with 15-mg starting dose.
Dose reduction to 10 mg daily if AEs may lose. Doug, any thoughts on this?

We know that from experience with patients with Ph-positive ALL [Philadelphia chromosome-positive acute lymphoblastic leukemia]; when we started 45 mg, 30 mg, and 15 mg—we did not compromise on efficacy once [there was] an optimal response and it was maintained, we did see a reduction of the vascular events.

When it comes to the OPTIC trial, [there is] something I am struggling to understand. The data showed that the 45-mg dose reduced to 15 mg is better in inducing CCyR [complete cytogenetic response] than the 2 other arms, and this benefit was mainly seen in patients with a T315I mutation, in those who failed multiple TKIs, or compound mutations, which we know this is the worst group. But when it comes to PFS [progression-free survival] and survival there’s no difference, so why is that? Or did you do a subset analysis by T315I mutation for PFS and survival?

Well, a couple of things. The PFS curves are starting to open up. When we presented this a year ago there was no difference; by now the 3-year PFS probability is 73% vs 66% with 30 mg. Survival [curves are not opening up] yet. I think it is a matter of the follow-up.

Now you mentioned the difference in ALL between the different doses, but of course there we use it in combination with chemotherapy, so that compensates to some extent anything that you may lose. Doug, any thoughts on this?

I loved this study, and I loved it because I think that it’s a very interesting model, and this model needs to be applied to other uses of TKIs. For example, there is probably a way to optimize dosing for each of the different TKIs based on response and based on time to that response, so that we could have patients on less drug and have less long-term toxicities.

Even if those toxicities are not as dramatic as we sometimes see with high-dose ponatinib, they’re still important. So, I love this model that you’ve put out there for people to follow. I think we need more data with the use of all other TKIs. I have to say I was interested in the model that you’ve put out there for people to follow. I think we need more data with the use of all other TKIs. I have to say I was one of the most reluctant individuals to change doses for patients who were doing well. Why take chances? Of course, early on, we didn’t know what was going to happen long term; now we feel more comfortable.

Do we really need to keep the patients at the maximum dose all the time, even if they’re doing well and not having any adverse effects? This [model of] response-adjusted dose reduction may be the way to go for all the TKIs, at least the second-generation [agents]. I would have my doubts for imatinib [Gleevec]. There’s probably not as much potency to spare. But for the second-generation or the third-generation TKIs, I don’t see why not.

I’ve been a very strong proponent of the higher doses of imatinib. You could start with higher doses of imatinib, which give you rates that are not dissimilar to second-generation TKIs, and then drop [the dosage] down to the standard dose when you get the response that you want. Professor Foà, I think you wanted to mention something.

We must keep in mind that here we’re talking about CML, which is obviously a disease which we can manage with any TKI, more or less. We’ve had worries with the adverse effects of ponatinib, and I think it’s extremely important particularly for the frail patients or patients with comorbidities. The key point is that now we’re moving toward offering less or no chemotherapy, so we don’t have the effect of chemotherapy stopping it. [Treatment for these patients is] going to be largely a TKI alone, and then maybe chemotherapy after or maybe not at all.

I think that is a key point as a bridge between CML and ALL. The end point is very different. We can always rescue patients with CML in the second line. Ph-positive ALL is very different, and we must obtain MRD [minimal residual disease] negativity as much as we can with the first-line treatment, so we can’t go wrong. I think that’s a key point that we must address in ALL.

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

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Uncommon EGFR Mutations Come Into Focus With Novel NSCLC Therapies

by JANE DE LARTIGUE, PhD

THE UNDERSTANDING OF EGFR signaling in non–small cell lung cancer (NSCLC) continues to evolve, helping to spark the development of novel therapies for new patient populations with uncommon alterations.

In May, the FDA granted an accelerated approval to amivantamab-vmjw (Rybrevant) for patients with locally advanced or metastatic NSCLC harboring EGFR exon 20 insertion mutations with disease progression on or after platinum-based chemotherapy. The bispecific antibody, which targets EGF and MET receptors, is the first therapy approved for this subset of patients with NSCLC.

Amivantamab is among a growing number of drugs with activity against EGFR exon 20 insertion–mutant disease undergoing clinical testing (TABLE). These include mobocertinib (TAK-788), which the FDA is evaluating under its priority review program for patients with metastatic exon 20 insertion mutation–positive NSCLC who have received platinum-based chemotherapy. The agency is scheduled to decide on a new drug application (NDA) by October 26, 2021, according to Takeda Pharmaceutical Company Limited, the company developing the therapy.

The development of therapies aimed specifically at exon 20 alterations is the latest step in personalizing EGFR-directed therapies in the NSCLC field. Until recently, EGFR inhibitors were available only for patients with the so-called classical EGFR mutations (exon 19 deletions and the L858R substitution in exon 21) and the secondary resistance mutation T790M.

Growing use of next-generation sequencing (NGS) has increased recognition of less common EGFR mutations in NSCLC. In particular, exon 20 insertion mutations have become increasingly therapeutically relevant, with evidence that they confer poorer patient prognosis and insensitivity to first- and second-generation EGFR inhibitors.

REFINING FIRST-GENERATION INHIBITORS

Despite their introduction into clinical practice in the United States nearly 20 years ago, EGFR inhibitors began to truly transform patient outcomes only with the identification of EGFR activating mutations as biomarkers of response. Investigators initially believed that high EGFR expression as opposed to EGFR mutations was needed for efficacy of the inhibitors.

The first generation of EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib (Iressa) and erlotinib (Tarceva), have a complicated history. The recognition of EGFR as a driver of NSCLC prompted their development, but their initial approvals in the early 2000s predated a complete understanding that response to EGFR TKIs was predicted by alterations in the EGFR gene. As a result, both drugs received broad approval to treat patients who had progressed following chemotherapy.

As confirmatory trials failed to translate improved response rates into prolonged

FIGURE 1. The EGFR Mutational Landscape in Non–Small Cell Lung Cancer

Among patients with non–small cell lung cancer whose tumors harbor EGFR aberrations, exon 19 deletions and exon 21 L858R mutations are the most frequently detected types of alterations, as shown in this analysis of adenocarcinomas. The category of rare alterations is multifaceted. The term “complex mutations” refers to co-occurring alterations. Of note, the common T790M and C797S resistance mutations were excluded from this study.

progression-free survival (PFS) or overall survival (OS), these drugs quickly fell out of favor, and gefitinib was withdrawn from the market. Despite the rocky start, the approvals of gefitinib and erlotinib paved the way for the identification of activating mutations in the EGFR kinase domain in patients with NSCLC, which predicted response to these agents.11,16

Clinical development of the first-generation adenosine triphosphate (ATP)–competitive, reversible EGFR TKIs was refocused on patients with EGFR-mutant NSCLC, and these 2 drugs ultimately reemerged as highly effective frontline treatment options in this patient population.9

Despite their clear superiority over chemotherapy, first-generation EGFR TKIs are eventually associated with disease progression in almost all patients, typically after approximately 1 year of therapy. As a result, a second generation of more potent, irreversible EGFR TKIs was developed.8,9

The FDA has approved afatinib (Gilotrif) and dacomitinib (Vizimpro) for the frontline treatment of EGFR-mutant NSCLC. However, their clinical utility is still impeded by the frequent development of resistance, and they are associated with significant dose-limiting toxicities because they nonspecifically target the wild-type EGFR protein and additional members of the HER family.5,6

**TACKLING RESISTANCE**

As the mechanisms underlying resistance to EGFR inhibitors were explored, one particular mutation emerged as a key target for novel drug development. **EGFR T790M**, in which a bulkier methionine is substituted for threonine at amino acid 790, is known as the gatekeeper mutation because it is the most common activating mutation in NSCLC and can be associated with disease progression even in patients who have not been previously treated with TKI therapy.8

The T790M mutation, which is the primary mechanism of resistance to the first- and second-generation EGFR TKIs, is identified as a somatic alteration in more than half of patients previously treated with a TKI but few treatment-naïve patients.8,11,12

The third generation of EGFR TKIs are designed to specifically target this mutation to help overcome resistance. In 2015, osimertinib (Tagrisso) became the first and thus far only third-generation EGFR TKI to receive FDA approval, with an indication for metastatic T790M-positive NSCLC in the relapsed/refractory setting.8,13,14

**TABLE. Select Clinical Trials Targeting Uncommon EGFR Mutations in NSCLC**

<table>
<thead>
<tr>
<th>Drug (brand name if applicable/developers)</th>
<th>Study description (ClinicalTrials.gov identifier/trial name)</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amivantamab-vmjw (Rybrevant; Janssen)*</td>
<td>EGFR ex20ins mutation–positive metastatic disease that has progressed on or after platinum-based chemotherapy (NCT02609776/CHRYSALIS)</td>
<td>1</td>
</tr>
<tr>
<td>Osimertinib (Tagrisso; AstraZeneca)*</td>
<td>In patients with uncommon EGFR mutations: G719X, S768I, or L861Q (NCT03434418) +/- bevacizumab in first line in patients with EGFR ex19del, L858R, E709X, G719X, or ex19ins, L861Q, or S768I (NCT04181060)</td>
<td>2</td>
</tr>
<tr>
<td>Almonertinib (Amelie; Hansoh Pharma)*</td>
<td>In patients with uncommon EGFR mutations in first line: G719X, S768I, or L861Q (NCT04951648) +/- amivantamab in metastatic disease: EGFR ex19del or L858R; ex20Ins; or G719X, S768I, or L861Q (NCT04077463/CHRYSALIS-2)</td>
<td>3</td>
</tr>
<tr>
<td>Lazertinib (Leclaza; Yuhan/Janssen)*</td>
<td>EGF T790M mutation–positive relapsed/refractory disease with ex19del, L858R, G719X, or L861Q must have T790M since progression (NCT03502850)</td>
<td>1/2</td>
</tr>
<tr>
<td>ASK120067 (Jiangsu Aosaikang Pharma)</td>
<td>EGF T790M mutation–positive relapsed/refractory disease with ex19del, L858R, G719X, or L861Q (NCT04820023)</td>
<td>1/2</td>
</tr>
<tr>
<td>BBT-176 (Bridge Biotherapeutics)</td>
<td>Ex20Ins mutation–positive disease in first line: ex20Ins +/- other EGFR or HER2 mutations except EGFR mutations for which there are approved anti-EGFR TKIs (NCT04129502) +/- chemotherapy in ex20Ins mutation–positive advanced/metastatic disease: EGFR ex20Ins; HER2 ex20Ins; EGFR or HER2 point mutations; EGFR ex19del or L858R (+/- T790M) (NCT02717116)</td>
<td>1/2</td>
</tr>
<tr>
<td>Mobocertinib (TAK-788) (Takeda)</td>
<td>EGF ex20Ins mutation–positive relapsed/refractory disease (NCT04036682)</td>
<td>1/2a</td>
</tr>
<tr>
<td>CLN-081 (Cullinan Oncology)</td>
<td>EGF L858R, ex19del, or ex20Ins mutation–positive disease (NCT04209465/MasterKey-01)</td>
<td>1/2</td>
</tr>
<tr>
<td>BDTX-189 (Black Diamond Therapeutics)</td>
<td>EGF mutation–positive relapsed/refractory disease, including EGFR ex20Ins, HER2 ex20Ins, or EGFR G719X, S768I, or L861Q (NCT03974022/WU-KONG1)</td>
<td>1/2</td>
</tr>
<tr>
<td>DZD9008 (Dizal Pharmaceuticals)</td>
<td>EGF/HER2 ex20ins mutation–positive advanced/metastatic disease, including EGFR or HER2 +/- cetuximab in EGFR TKI sensitivity mutation–positive relapsed/refractory disease (NCT0318939/ZENITH20)</td>
<td>2</td>
</tr>
<tr>
<td>Pozotinib ( Spectrum Pharmaceuticals)</td>
<td>EGF/HER2 ex20ins mutation–positive disease that has progressed on or after platinum-based chemotherapy (NCT03805841/RAIN)</td>
<td>2</td>
</tr>
</tbody>
</table>

Del, deletion; EGFR, epidermal growth factor receptor; ex, exon; ins, insertion; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

*Approved in the United States.
*Approved in China.
*Trial is not yet recruiting.
*Approved in South Korea.
Subsequently, investigators demonstrated superior efficacy and improved toxicity for osimertinib compared with erlotinib and gefitinib in patients with classical mutations, most likely because of osimertinib’s minimal inhibition of wild-type EGFR. These findings led to osimertinib’s approval in the frontline setting in 2018, where it has supplanted the other EGFR TKIs as the preferred treatment option for patients with EGFR-mutant NSCLC. Most recently, osimertinib was approved for the adjuvant treatment of patients with early-stage EGFR-mutant (L858R/exon 19 deletion) NSCLC after tumor resection.

A swath of other third-generation EGFR inhibitors are in clinical development, with the goal of improving upon the efficacy and safety of osimertinib, and several have been approved for use outside the United States. Lazertinib (Leclaza) is a novel third-generation TKI that targets the classical mutations T790M and C797S mutation–positive NSCLC in the second-line setting. Phase 3 clinical trials of all 3 drugs are ongoing in patients with exon 20 insertion mutations.

Meanwhile, a fourth generation of EGFR TKIs is in development to tackle resistance to third-generation agents such as osimertinib, which typically emerges after 1 to 2 years of treatment. The most common mechanism of such resistance is the EGFR C797S mutation, which affects a cysteine at the edge of the ATP binding pocket to which these drugs covalently bind.

Fourth-generation EGFR TKIs are triple inhibitors, designed to target the classical activating mutations as well as the T790M and C797S resistance mutations. BLU-945 and BBT-176 have recently entered phase 1/2 clinical trials.

**UNCOMMON MUTATIONS**

Much less is known about uncommon EGFR mutations; however, with the increasing availability of NGS, they are more readily identifiable, and there is a growing body of information about the clinicopathologic characteristics and treatment response associated with these mutations. The development of molecularly targeted therapies has become increasingly specific.

Among them, the most prevalent point mutations are G719X (exon 18), S768I (exon 20), and L861Q (exon 21). In 2018, the FDA expanded the afatinib approval to include NSCLC displaying these point mutations, based on data from a subset of 32 patients with metastatic NSCLC bearing these mutations across 3 pivotal clinical trials of afatinib, LUX-Lung 2 (NCT00525148), LUX-Lung 3 (NCT00949650), and LUX-Lung 6 (NCT01121393), in which responses lasting 12 months or more were observed in 52% of the 21 responders. Osimertinib also recently demonstrated efficacy in patients with NSCLC with tumors harboring these and other uncommon mutations in a phase 2 study (NCT03424759).

The pan-HER inhibitor neratinib (Nerlynx) had previously demonstrated a dismal 3% ORR in patients with EGFR-mutant NSCLC in a phase 2 study (NCT00266877). However, the few patients who responded had exon 18 mutations, another type of uncommon EGFR mutation. According to an interim analysis of the phase 2 SUMMIT basket trial (NCT01953926), neratinib produced 4 confirmed PRs among 10 efficacy-evaluable patients with previously treated, exon 18-mutant NSCLC.

The largest group of uncommon mutations are insertion mutations in exon 20. Similarly to the classical EGFR mutations, exon 20 insertions are more common in women, nonsmokers, and those with adenocarcinoma histology. Patients with exon

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**FIGURE 2. EGFR Alterations With Targeted Therapies for NSCLC**

The advent of next-generation sequencing has resulted in the development of therapies directed more specifically at oncogenic activity associated with EGFR molecular alterations.

NSCLC, non-small cell lung cancer.
20 insertions have a worse prognosis compared with those with other types of EGFR mutations, with outcomes similar to patients with wild-type EGFR.\(^6\)

Although exon 20 insertions are located within the kinase domain, they do not affect the ATP-binding pocket, which plays a critical role in the regulation of enzyme activity by undergoing a conformational change. Because exon 20 insertions affect the EGFR protein differently compared with classical mutations, most are insensitive to the first- and second-generation EGFR TKIs and chemotherapy remains standard of care.

The jury is still out on whether third-generation TKIs are effective in patients with exon 20 insertion mutations, with recent clinical trial data suggesting that osimertinib may have significant activity.\(^28\)

**TARGETING EXON 20 INSERTION MUTATIONS**

*Amivantamab*

Given the poor prognosis of patients with exon 20 insertion mutations and the lack of effective treatment options, there has been considerable investment in novel drug development. The FDA approved amivantamab for this patient population based on findings from the phase 1 multicohort CHRYSALIS trial (NCT02609776).

In 81 patients previously treated with platinum-based chemotherapy, the ORR with amivantamab monotherapy was 40% (95% CI, 29%-51%), including 3 complete responses. The median DOR was 11.1 months (95% CI, 6.9-not estimable), and 63% of patients had a response lasting 6 months or more.\(^{29}\)

In the safety population of 129 patients, adverse effects (AEs) were mostly of grade 1 or 2 severity. The most common all-grade AEs included rash (84%), infusion-related reactions (64%), paronychia (50%), and musculoskeletal pain (47%). The grade 3/4 incidence of these AEs was 3.9%, 3.1%, 3.1%, and 0%, respectively.\(^{29}\)

Amivantamab, which is administered intravenously, also has shown promise in other EGFR-mutant populations in combination with lazzertinib. Results from a combination arm of the CHRYSALIS trial were recently presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting for an expansion cohort of patients with exon 19 deletions or L858R mutations who had relapsed after osimertinib therapy.

Among 45 patients treated with the combination, the ORR was 36% (95% CI, 22%-51%) at a median follow-up of 11.0 months (range, 1.0-15.0). The median DOR was 9.6 months (95% CI, 5.3-not reached), and the median PFS was 4.9 months (95% CI, 3.7-9.5). High combined protein expression of EGFR and MET, as evaluated by immunohistochemistry, was identified as a potential biomarker of response to the combination.\(^{30}\)

The amivantamab-lazzertinib combination is being explored in several clinical trials involving classical and/or uncommon EGFR mutations.

In the phase 3 MARIPOSA study (NCT04487080), investigators are seeking to randomize 1000 patients to lazzertinib plus either amivantamab or placebo versus osimertinib plus placebo as first-line therapy for patients with locally advanced or metastatic NSCLC with exon 19 deletions or L858R substitutions. The phase 1/1b CHRYSALIS-2 study (NCT04077463) is testing the amivantamab-lazzertinib combination in several cohorts, including one for previously treated patients with exon 20 insertions and one for patients with other uncommon EGFR alterations such as S768I, L861Q, and G719X who have not yet been treated or have received a first- or second-generation EGFR TKI as their last therapy.\(^{31}\)

Janssen Research & Development, LLC, which helped bring amivantamab to the US market, is sponsoring the studies.

*Mobocertinib*

In terms of TKIs, mobocertinib is the most advanced drug in development that specifically targets exon 20 insertion mutations, and it is hot on the heels of amivantamab. The FDA approved mobocertinib for this patient population based on findings from the phase 1 multicohort ZENITH20 trial (NCT03318939) in patients with locally advanced or metastatic NSCLC with EGFR or HER2 exon 20 mutations.\(^{34}\)

Results from cohort 1 for 115 previously treated patients with EGFR exon 20 insertion mutations in the intent-to-treat population demonstrated an ORR of 14.8% (95% CI, 8.9%-22.6%), with a median DOR of 7.4 months (95% CI, 3.7-9.7). Among 88 evaluable patients, the ORR was 19.3% (95% CI, 11.7%-29.1%), with the same median DOR. However, 65% of patients required dose reductions; grade 3 and higher treatment-related AEs included rash, diarrhea, stomatitis, and paronychia.\(^{34,35}\)

In 79 treatment-naive patients (cohort 3), the ORR was 27.8% (95% CI, 18.4%-39.1%), with a median DOR of 6.5 months. More than 90% of patients experienced a reduction in tumor burden. To reduce toxicity, cohort 5 of this study is exploring different doses and dosing schedules, and preliminary data from 40 patients suggest that the rates of AEs and dose interruptions may be lower with twice-daily dosing.\(^{35,36}\)

Among these patients, mobocertinib demonstrated an ORR of 28% (95% CI, 20%-37%) with a median DOR of 17.5 months (95% CI, 7.4-20.3) by IRC and 35% (95% CI, 26%-45%) with a median DOR of 11.2 months (95% CI, 5.6-not estimable) per investigator review. All responses were partial under both assessments. The median PFS was 7.3 months (95% CI, 5.5-9.2), and the median OS was 24.0 months (95% CI, 14.6-28.8), both by IRC assessment.\(^{31,32}\)

**Pozotinib**

Analogous mutation mutations also are found within exon 20 of the HER2 protein in NSCLC, and the FDA has granted pozotinib, a dual EGFR/HER2 inhibitor, a fast track designation for patients with HER2 exon 20 mutations, according to Spectrum Pharmaceuticals, which is developing the drug.\(^{33}\)

Investigators are exploring pozotinib in the multicohort phase 2 ZENITH20 trial (NCT03318939) in patients with locally advanced or metastatic NSCLC with EGFR or HER2 exon 20 mutations.\(^{34}\)

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Frontline Treatments for Metastatic RCC March Forward

by CHRISTINA T. LOGUIDICE

TREATMENT OF METASTATIC RENAL cell carcinoma (RCC) continues to evolve as new regimens steadily receive FDA approval and are added to the armamentarium. “[Several] pivotal trials have redefined our practice and shaped the path from monotherapy to considering immuno-oncology [IO]-based combinations for most of our patients,” Martin H. Voss, MD, said during a recent OncLive Peer Exchange®.

Voss was joined by a panel of experts in genitourinary cancer who discussed these pivotal IO trials and shared some of the latest data updates that were presented for these trials at recent oncology meetings, including the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting.

A SHIFIT TO IO-BASED COMBINATION REGIMENS

“A lot has changed in the front line in the past many years,” Sandy Srinivas, MBBS, said. She explained that the advent of immunotherapy combinations has resulted in clinicians now using the International Metastatic RCC Database Consortium (IMDC) to classify patients into risk categories to guide treatment selection. “When we had targeted drugs with TKIs [tyrosine kinase inhibitors] and mTOR [inhibitors], we used this IMDC risk classification mostly for prognosis and not really in selecting therapy…. CheckMate 214 [NCT02231749] was the first trial that really changed our practice with integrating risk assessment into treatment groups,” she said.

Srinivas explained that a dual IO treatment and 3 TKI-IO combinations are currently available as first-line treatments for patients with RCC across the different risk groups and have been incorporated into the National Comprehensive Cancer Network (NCCN) Guidelines for kidney cancer (TABLE). “We also have TKI monotherapy. It’s becoming less commonly used, but we certainly have our old friends pazopanib [Votrient] and sunitinib [Sutent] as monotherapy for favorable-risk and cabozantinib [Cabometyx] as a monotherapy for poor-risk [patients],” she said. Srinivas and the panelists proceeded to discuss the pivotal trials that have shifted treatment away from monotherapy and toward the IO-based combinations.

NIVOLUMAB PLUS IPILIMUMAB

On April 16, 2018, the FDA approved nivolumab [Opdivo] plus ipilimumab [Yervoy] for the treatment of treatment-naive patients with intermediate- or poor-risk advanced RCC, making it the first immunotherapy combination approved for metastatic kidney cancer. The approval was based on data from the phase 3 CheckMate 214 trial. “It was the first of these large phase 3 randomized controlled trials where we saw an immune checkpoint combination strategy in the frontline setting that importantly changed our overall survival [OS] landscape,” Amishi Y. Shah, MD, said.

The CheckMate 214 trial randomly assigned 847 patients to receive either nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks (n = 425) or sunitinib 50 mg daily for 4 weeks followed by 2 weeks off every cycle (n = 422). At the time of its approval, with a
minimum follow-up of 17.5 months, the estimated median OS was not estimable in the combination arm compared with 25.9 months in the sunitinib arm (HR, 0.63; 95% CI, 0.44–0.89; P < .001).

At the 2020 Genitourinary Cancer Symposium, investigators presented updated OS data for a minimum follow-up of 42 months. The median OS was 47.0 months in the combination arm vs 26.6 months in the sunitinib arm among the primary efficacy population (HR, 0.66; 95% CI, 0.55–0.80; P < .0001). The overall response rate (ORR) was also found to be superior with the combination, with a complete response (CR) rate of 10% or higher consistently observed regardless of risk category.

“One of the most interesting and gratifying pieces of data from this long-term follow-up is that the vast majority of CRs achieved on this trial are ongoing at this point—over 3.5 years out,” Shah said. “This combination has shown us a true tail on the curve, where patients have maintained this response to therapy. Not all patients get CRs. That’s in the 11% range, but those who do seem to have a very durable response.”

The panelists were especially excited about results from a small phase 1B study (NCT03829111) presented at 2021 ASCO. Investigators reported the first results of the immunotherapy doublet in kidney cancer were randomized 2:1 to receive CBM 588 (80 mg) orally twice daily plus nivolumab plus ipilimumab, which was found to augment the activity of checkpoint inhibitors in non–small cell lung cancer in retrospective studies.

In the study, patients with metastatic kidney cancer were randomized 2:1 to receive CBM 588 (80 mg) orally twice daily plus nivolumab 3 mg/kg and ipilimumab 1 mg/kg intravenously (IV) every 3 weeks for 4 doses followed by nivolumab monotherapy (480 mg IV) monthly (n = 19) or to nivolumab plus ipilimumab alone (n = 10). The primary end point was change in Bifidobacterium species (spp) levels from baseline to week 12, and the secondary end points included progression-free survival (PFS), response rate, and toxicity.

Higher levels of Bifidobacterium spp were found in responders to the triplet, with declines in Bifidobacterium spp observed in responders to the triplet, with reductions in Bifidobacterium spp levels from baseline to week 12, and the secondary end points included progression-free survival (PFS), response rate, and toxicity.

Thomas Powles, MBBS, MD, MRCP, said he was surprised that the CBM 588 study did not constitute more prominent news at 2021 ASCO. “I know it didn’t hit its primary end point and the biological end points weren’t quite there. That may be why we dampened our enthusiasm, but those biological end points are really tough. I thought they were terrific data. We should invest emotionally and intellectually in this target,” he said, noting a need for more diverse treatments for patients with advanced kidney cancer.

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**TABLE 1. NCCN Recommended First-Line Treatments for Metastatic or Relapsed Clear Cell RCC**

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Preferred⁴</th>
<th>Other recommended⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Axitinib + pembrolizumab</td>
<td>Axitinib + avelumab</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib + nivolumab</td>
<td>Cabozantinib (category 2b)</td>
</tr>
<tr>
<td></td>
<td>Lenvatinib + pembrolizumab</td>
<td>Ipilimumab + nivolumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sunitinib</td>
</tr>
<tr>
<td>Intermediate/poor</td>
<td>Axitinib + pembrolizumab</td>
<td>Axitinib + avelumab</td>
</tr>
<tr>
<td></td>
<td>Cabozantinib + nivolumab</td>
<td>Cabozantinib (category 2a)</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab + nivolumab</td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td>Lenvatinib + pembrolizumab</td>
<td>Sunitinib</td>
</tr>
</tbody>
</table>

NCCN, National Comprehensive Cancer Network; RCC, renal cell carcinoma.

*All preferred regimens are category 1 recommendations unless otherwise indicated.
*All other recommended regimens are category 2a unless otherwise indicated.

**TABLE 2. Response Rates and Secondary End Point Outcomes With the Addition of CBM-588 to Nivolumab Plus Ipilimumab⁵**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab + ipilimumab</th>
<th>Nivolumab + ipilimumab + CBM-588 (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (n = 10)</td>
<td>20%</td>
<td>58%</td>
</tr>
<tr>
<td>PR (n = 10)</td>
<td>20%</td>
<td>58%</td>
</tr>
<tr>
<td>SD (n = 10)</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>PD (n = 10)</td>
<td>60%</td>
<td>21%</td>
</tr>
<tr>
<td>Median PFS, weeks (95% CI)</td>
<td>10.7 (7.45–14.55)</td>
<td>55 (NR-NR)</td>
</tr>
<tr>
<td>Median OS</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

**AXITINIB PLUS PEMBROLIZUMAB**

On April 19, 2019, the FDA approved axitinib (Inlyta) plus pembrolizumab (Keytruda) as the first TKI-IO combination for treatment-naive patients with advanced kidney cancer, based on data from the phase 3 KEYNOTE-426 trial (NCT02853331).

The study included 861 patients with previously untreated advanced clear cell RCC who were randomly assigned 1:1 to pembrolizumab 200 mg IV once every 3 weeks plus...
axitinib 5 mg orally twice daily (n = 432) or sunitinib 50 mg orally once daily for the first 4 weeks of each 6-week cycle (n = 429). “[Unlike CheckMate 214], this really was an ITT [intention-to-treat] design rather than focusing on the intermediate- and poor-risk categories,” Powles said.

After a median follow-up of 12.8 months, 89.9% of patients in the pembrolizumab/axitinib arm and 78.3% in the sunitinib arm were estimated to be alive at 12 months (HR for death, 0.53; 95% CI, 0.38-0.74; P < .0001).7 The median PFS was 15.1 months vs 11.1 months in these arms, respectively (HR for disease progression or death, 0.69; 95% CI, 0.57-0.84; P < .001). “It’s important to remember the minimum follow-up [when considering the HR]. That is an important piece of information because you’ll hear a series of [HRs for the various pivotal trials], but they’re all related to the timing of the analysis because all of them drift downward a little as time goes by,” Powles explained.

He noted that the most recent update for the KEYNOTE-426 trial, which was presented at 2021 ASCO, had a median follow-up of 42.8 months. The results showed a median OS of 45.7 months (95% CI, 43.6-NR) in the sunitinib arm, which was in 55.7% and 27.1% in these arms, respectively (HR for death, 0.60; 95% CI, 0.41-0.84; P < .001). The probability of OS at 12 months was 85.7% and 75.6% in these arms, respectively (HR for death, 0.69; 95% CI, 0.57-0.84; P < .001). “The statistic I like most is — the ORR was in 55.7% and 27.1% in these arms, respectively (P < .001). The statistical I like most is that progression of disease at first response was almost 5.5% for the combination arm compared with almost 14% in the sunitinib arm,” Alter said.

Grade 3 or higher AEs occurred in 75.3% of patients in the nivolumab plus cabozantinib arm and 76.6% of the sunitinib arm. “There were dose reductions in both arms: 56% with nivolumab/cabozantinib and around 52% in the sunitinib arm,” Alter said. Overall, 19.7% of the patients in the combination group discontinued at least 1 of the trial drugs because of AEs and 5.6% discontinued both.10 Despite more patients in the combination therapy arm experiencing grade 3 or higher AEs, these patients reported better health-related quality of life (HRQOL) than those receiving sunitinib, Alter said.

At 2021 ASCO, exploratory analyses of key efficacy outcomes in CheckMate 9ER across multiple patient subgroups defined by baseline disease characteristics were presented during a poster session.11 The minimum follow-up was 16.0 months, with a median follow-up of 23.5 months. The findings were consistent with those observed in the ITT patients, with nivolumab plus cabozantinib showing benefit over sunitinib regardless of cycle (n = 328). At a median follow-up of 18.1 months, the median PFS was 16.6 months with nivolumab plus cabozantinib and 8.3 months with sunitinib (HR for disease progression or death, 0.51; 95% CI, 0.41-0.64; P < .001). The probability of OS at 12 months was 85.7% and 75.6% in these arms, respectively (HR for death, 0.69; 95% CI, 0.57-0.84; P < .001). The probability of OS at 12 months was 85.7% and 75.6% in these arms, respectively (HR for death, 0.69; 95% CI, 0.57-0.84; P < .001).

NIVOLUMAB PLUS CABOZANTINIB
On January 22, 2021, nivolumab plus cabozantinib received FDA approval as a first-line treatment for patients with advanced RCC, based on data from the phase 3 CheckMate 9ER trial (NCT03141177).7 “Cabozantinib has been our first-line regimen as an oral TKI for patients with intermediate- and poor-risk disease for several years,” Robert S. Alter, MD, said. “It’s interesting to now take what we’ve considered to be the maintenance drug of nivolumab and add cabozantinib to it as the first-line agent,” he said, noting that this study, like the KEYNOTE-426 trial of axitinib plus pembrolizumab, also had a 2-year maximum of the checkpoint inhibitor, with patients continuing on cabozantinib thereafter.

CheckMate 9ER randomly assigned 651 adults with previously untreated advanced clear cell RCC to either nivolumab 240 mg every 2 weeks plus cabozantinib 40 mg once daily (n = 323) or sunitinib 50 mg once daily for 4 weeks of each 6-week cycle (n = 328). At a median follow-up of 18.1 months, the median PFS was 16.6 months with nivolumab plus cabozantinib and 8.3 months with sunitinib (HR for disease progression or death, 0.51; 95% CI, 0.41-0.64; P < .001). The probability of OS at 12 months was 85.7% and 75.6% in these arms, respectively (HR for death, 0.69; 95% CI, 0.57-0.84; P < .001). The probability of OS at 12 months was 85.7% and 75.6% in these arms, respectively (HR for death, 0.69; 95% CI, 0.57-0.84; P < .001). The probability of OS at 12 months was 85.7% and 75.6% in these arms, respectively (HR for death, 0.69; 95% CI, 0.57-0.84; P < .001).
IDMC risk status (Table 3), site of metastasis, and extent of tumor burden at baseline. "Across all [IDMC] subgroups, this post hoc analysis was quite impressive," Alter said. "This may give a little more credence to how we can now treat our favorable-risk patients with a little more data, as compared with believing this was a population yet to be analyzed."

**LENVATINIB PLUS PEMBROLIZUMAB**

At the time of the Peer Exchange, lenvatinib (Lenvima) plus pembrolizumab had been incorporated into the NCCN guidelines as a preferred treatment for patients with favorable- and intermediate-poor-risk disease (Table 1), but it had not yet received FDA approval as a first-line treatment for adult patients with advanced RCC. On August 10, the FDA approved this indication. The approval was based on data from the CLEAR study (NCT02811861), in which 1069 patients were randomized 1:1:1 to lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg IV once every 3 weeks (n = 355); lenvatinib 18 mg orally once daily plus everolimus (Afinitor) 5 mg orally once daily (n = 357); or sunitinib 50 mg orally once daily, alternating 4 weeks on treatment with 2 weeks off treatment (n = 357).13,14

"Lenvatinib’s first appearance in RCC came as a combination with everolimus in the second line, so [the CLEAR trial] was an opportunity to test lenvatinib and everolimus in the first line as well," Srinivas said. She pointed out that the 20-mg dose of lenvatinib used in the lenvatinib/pembrolizumab arm is "the highest dose we’ve ever seen of lenvatinib in any of our prior trials." She added that the trial had a high proportion of favorable-risk patients. "Approximately a third of patients, 31%, were favorable risk. If you look at the 3 IO-TKI combinations, this one probably had the highest fraction of patients with favorable risk," she said.

Both lenvatinib arms showed a significantly longer median PFS than the sunitinib arm. The median PFS was 9.2 months in the sunitinib arm compared with 23.9 months in the lenvatinib/pembrolizumab arm (HR, 0.39; 95% CI, 0.32-0.49; P < .001) and 14.7 months in the lenvatinib/everolimus arm (HR, 0.65; 95% CI, 0.53-0.80; P < .001). OS was also significantly longer in the lenvatinib/pembrolizumab arm vs the sunitinib arm (HR, 0.66; 95% CI, 0.49-0.88; P = .005) but not in the lenvatinib/everolimus arm vs the sunitinib arm (HR, 1.15; 95% CI, 0.88-1.50; P = .30).13,14

“The response rate [with lenvatinib plus pembrolizumab] was the highest we have seen with any of the IO-TKI combinations, with an ORR of more than 70%. Most impressive was the complete response at 16%,” Srinivas said.

The lenvatinib arms had more frequent worsening or emergence of grade 3 or higher AEs, affecting 82.4% of patients in the lenvatinib/pembrolizumab arm and 83.1% of patients in the lenvatinib/everolimus arm compared with 71.8% of patients in the sunitinib arm.13,14 The most frequent grade 3 or higher AEs (≥ 10% of patients in any group) included hypertension, diarrhea, and elevated lipase levels.

“Some of the things that clearly need to be ironed out include the dosing of lenvatinib. If you dive a little deeper into the trial, you must look at what the discontinuation rates are for lenvatinib and pembrolizumab. The starting dose of lenvatinib and how we adjust the dose are things we must learn and adjust for adverse effects,” Srinivas said.

At ASCO 2021, investigators presented an HRQoL analysis from the CLEAR trial, lending further support to the use of lenvatinib plus pembrolizumab for treatment-naïve patients with advanced RCC. The quality-of-life data get a little complicated and confusing, but the top line is that the quality of life with lenvatinib plus placebo was similar or improved compared with sunitinib. This trial meets all the top-line benchmarks that a trial can,” Srinivas said.

**REFERENCES**

Nearly 5 years

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