A Changing Tide for Patients With Myelofibrosis

Precision Medicine Efforts Pay Off in Hormone Receptor–Positive Breast Cancer

Novel Drug Sparks Hopes for Targeting HER3 in NSCLC and Beyond

Enriqueta Felip, MD, Reviews Immunotherapeutic Strategies for NSCLC
Sukhmani K. Padda, MD, Discusses Overcoming EGFR Resistance in NSCLC

Robert J. Motzer, MD, Unpacks Lenvatinib’s Role in RCC

Onvansertib Combination Aims to Improve Outcomes in Pancreatic Ductal Adenocarcinoma

Cellular Therapy Strategies Offer the Prospect of Deep Remissions for Multiple Myeloma
By Philip McCarthy, MD, and Jens Hillengass, MD, PhD
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CIN CAN STRIKE AT ANY MOMENT

It's time to take a crucial new look at CIN, the dire consequences of leaving patients unprotected, and how the COVID-19 pandemic is changing guidelines as well as your approach to providing the best standard of care.

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With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer. Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.1

When your patients are left unprotected, particularly in Cycle 1,2 CIN may lead to life-threatening events, such as fever, infection, and hospitalization3–severely disrupting the predictability of your treatment plan. These chemotherapy delays and decreases can ultimately impact outcomes and decrease overall survival.4-6

References:
With the ongoing threat of chemotherapy-induced neutropenia (CIN), the COVID-19 pandemic is making oncologists and their care teams revisit their approach as they use aggressive regimens to treat their patients with cancer. Along with this, current treatment guidelines are now recommending the expanded prophylactic use of granulocyte-colony stimulating factors (G-CSFs) to intermediate-risk cancer patients as well.¹

When your patients are left unprotected, particularly in Cycle 1,² CIN may lead to life-threatening events, such as fever, infection, and hospitalization³—severely disrupting the predictability of your treatment plan. These chemotherapy delays and decreases can ultimately impact outcomes and decrease overall survival.⁴-⁶


It’s time to take a crucial new look at CIN, the dire consequences of leaving patients unprotected, and how the COVID-19 pandemic is changing guidelines as well as your approach to providing the best standard of care.

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Strategic Alliance Partnership

Our editors collaborate with renowned cancer centers across the country to bring you reports on cutting-edge developments in oncology research and treatment. For this month’s Partner Perspectives, go to page 56.
A Changing Tide for Patients With Myelofibrosis

by BRITTANY LOVELY

Marked progress has been observed with JAK2 inhibitors for patients with intermediate- or high-risk myelofibrosis. However, efforts are needed to address lingering symptoms, as well as progression on or resistance to stand-of-care therapy. Novel combinations and sequencing strategies may provide a path forward.

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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®)2

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 (IRRs) 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 included 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\(^1\)

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 m\(^2\)), 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.\(^1\)

**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 m\(^2\)) 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.\(^1\)

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, H\(_2\) 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

The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd.\textsuperscript{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.\textsuperscript{1}

SARCLISA + Pd showed a significant increase in ORR\textsuperscript{1*}

\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Patients at risk} & SARCLISA + Pd & \textbf{Pd} & \textbf{SARCLISA + Pd} & \textbf{Pd} & \textbf{SARCLISA + Pd} & \textbf{Pd} & \textbf{SARCLISA + Pd} & \textbf{Pd} & \textbf{SARCLISA + Pd} & \textbf{Pd} \\
\hline
\textbf{Patients} & 154 & 129 & 106 & 89 & 81 & 52 & 30 & 14 & 1 \\
\hline
\textbf{Pd} & 153 & 105 & 80 & 63 & 51 & 33 & 17 & 10 & 0 \\
\hline
\end{tabular}

\textbf{Probability of PFS (%)}

\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Time (months)} & 0 & 2 & 4 & 6 & 8 & 10 & 12 & 14 & 16 & 20 & 22 & 24 \\
\hline
\textbf{SARCLISA + Pd} & 100 & 80 & 60 & 40 & 20 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\textbf{Pd} & 100 & 80 & 60 & 40 & 20 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\hline
\end{tabular}

\begin{itemize}
\item \textbf{HR=0.596} (95% CI: 0.44, 0.81)
\item \textbf{P<0.0001}
\end{itemize}

\begin{tabular}{|c|c|c|c|}
\hline
\textbf{SARCLISA + Pd (n=154)} & \textbf{Pd (n=153)} & \textbf{Pd extended results at interim analysis did not reach statistical significance.}\textsuperscript{1}

\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{ORR} & \textbf{P<0.0001} & \textbf{35.3% ORR} & \textbf{35.3% ORR} & \textbf{35.3% ORR} & \textbf{35.3% ORR} & \textbf{35.3% ORR} & \textbf{35.3% ORR} & \textbf{35.3% ORR} & \textbf{35.3% ORR} & \textbf{35.3% ORR} & \textbf{35.3% ORR} \\
\hline
\textbf{60.4%} & \textbf{P<0.0001} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} \\
\hline
\textbf{31.8%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} & \textbf{35.3%} \\
\hline
\textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} & \textbf{≥VGPR} \\
\hline
\textbf{35 days} & \textbf{Median time to first response among responders} & \textbf{58 days} & \textbf{58 days} & \textbf{58 days} & \textbf{58 days} & \textbf{58 days} & \textbf{58 days} & \textbf{58 days} & \textbf{58 days} & \textbf{58 days} & \textbf{58 days} \\
\hline
\end{tabular}

\textsuperscript{1*} 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.

Finishing:

Prepare the solution for infusion using aseptic technique as follows:

• Gently homogenize the diluted solution by inverting the bag.

• Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever suspected or container permit.

• 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 polycarbonate (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).

• Gently homogenize the diluted solution by inverting the bag.

2.5 Administration

• Administer the infusion solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadene [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 the completion of the infusion (see Table 2).

Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°C–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.

Infusion Rates

Following infusion, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incremental escalation of the infusion rate should be considered only in patients who experience infusion-related reactions (see Warnings and Precautions (5.1) and Adverse Reactions (6.1)).

Table 2: Infusion Rates of SARCLISA Administration

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Initial Rate</th>
<th>Rate Increment</th>
<th>Maximum Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For 30 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 60 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 120 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>For 180 minutes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.4 Laboratory Test Interference

Interference with Serologic Testing (Indirect Antiglobulin Test)

SARCLISA binds to C3bD 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. 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 the patient to be 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 diethilthreitol-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RHD-complementary units may be given as per local blood bank practices (see Drug Interactions (7.1)).

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.

6.2 Postmarketing Experience

The most frequent adverse reactions requiring discontinuation in patients who received Isa-Pd were infections (28%). Infections (28%) were the most frequent adverse reactions requiring discontinuation in patients who received Isa-Pd were infections (28%). Infections (28%) were the most frequent adverse reactions requiring discontinuation in patients who received Isa-Pd were infections (28%). Infections (28%) were the most frequent adverse reactions requiring discontinuation in patients who received Isa-Pd were infections (28%). Infections (28%) were the most frequent adverse reactions requiring discontinuation in patients who received Isa-Pd were infections (28%). Infections (28%) were the most frequent adverse reactions requiring discontinuation in patients who received Isa-Pd were infections (28%). Infections (28%) were the most frequent adverse reactions requiring discontinuation in patients who received Isa-Pd were infections (28%). 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The most common adverse reactions (≥20%) were neutropenia, infusion-related reactions, pneumonia, upper respiratory tract infection, and diarrhea.

### 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)</th>
<th>Pomalidomide + Dexamethasone (Pd)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>38</td>
<td>1.3</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>57</td>
<td>9</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>1.3</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17</td>
<td>5.0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection includes bronchiolitis, bronchitis, bronchitis viral, chronic sinusitis, fungal pharyngitis, influenza-like illness, laryngitis, macropharyngeal fever, pneumonia, pneumonia viral, candida pneumonia, pneumonia bacterial, haemorrhagic infection, lung infection, pneumonia fungal, and pneumocystis pneumonia.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.

### Table 4: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment versus Pd Treatment — ICARIA-MM

<table>
<thead>
<tr>
<th>Laboratory Parameter (%)</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd)</th>
<th>Pomalidomide + Dexamethasone (Pd)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>151</td>
<td>99</td>
</tr>
<tr>
<td>Neutropenia</td>
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<td>99</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>142</td>
<td>99</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>127</td>
<td>99</td>
</tr>
</tbody>
</table>

### 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), photo-maternal immune tolerance (mice), and early embryonic development (turtles).

**8.2 Lactation**

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.

**8.4 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 and over, while 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 OVERDOSE

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

Manufactured by: sanofi-aventis U.S. LLC

Bridgewater, NJ 08807

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ISA-BPLR-SA-MAR20

Revised: March 2020
Welcoming Change in Clinical Practice

THE ARRIVAL OF AUTUMN marks the beginning of the busiest meeting season for oncology professionals. As investigators prepare data for presentation at some of the world’s largest clinical meetings, including the 2021 European Society for Medical Oncology Annual Congress, community oncologists prepare to digest the rapid influx of practice-changing updates.

Rapid changes in optimized testing approaches, locoregional and systemic therapies, including the use of chemotherapies, targeted therapies, immunotherapies, alone and in combination, along with multimodal strategies, continue to drive improved outcomes across multiple lines of care. Additionally, an increased focus has been applied to addressing disparities in care, as well as practicing in the age of COVID-19.

As these diagnostic, therapeutic, and supportive care strategies continually reshape clinical practice, their application requires distillation. Critical knowledge, competence, and performance gaps among practitioners must be addressed to ensure that these approaches are effectively and safely integrated into professional practice.

Each year, the Chemotherapy Foundation Symposium® (CFS®), hosted by Physicians’ Education Resource®, LLC (PER®), brings together more than 2000 health care professionals for 3 days, with the aim of promoting the delivery of evidence-based, state-of-the-art cancer care for both routine and the most challenging clinical scenarios.

At the 39th Annual CFS®—which will be held as a hybrid event November 3-5—internationally renowned faculty will provide you with expert insights on the latest developments in cancer therapeutics across 25 tumor types, offering an unparalleled opportunity to learn how innovative approaches fit into existing treatment paradigms to optimize care and outcomes for patients with cancer.

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

We hope you enjoy reading about these new therapies. For timely insights, expert perspectives, and opportunities to attend educational events, be sure to subscribe the OncLive® e-newsletter. Visit onclive.com/view/enews to register.

As always, thank you for reading.

Mike Hennessy Sr
Chairman and Founder
From the Editor

Questions Loom for the Adequacy of Peer Review in Oncology

by MAURIE MARKMAN, MD

Clinical research published in peer-reviewed general medical and oncology literature is a core component of the process during which advances in care are developed and ultimately instituted as standard of care. Although it is doubtful that many would challenge this statement, there has been limited discussion in the cancer literature for how peer review among the multiple oncology journals and international cancer conferences is conducted.

In the opinion of this commentator, it is not inappropriate to inquire as to just how effective this process is in ensuring both the objectivity and lack of bias of published manuscripts or in the selection of the top abstracts chosen for presentation at national or international oncology meetings. There is no intent in this short commentary to present a formal critique of the current state-of-oncology peer review; however, concerns with the relatively recent publication of 2 articles in high-impact medical journals and 1 widely discussed abstract presented at a major oncology meeting serve to highlight the need for greater attention paid by the academic oncology community to this essential component of the scientific review process.

To be clear, there is no intent in focusing on these manuscripts to negate the hypotheses underlying these papers or the likely considerable efforts undertaken by the authors in the conduct of their research projects. Rather, it was the peer review or editorial decision-making processes that should have challenged the methodologies and conclusions and either suggested additional explanations/discussion within the manuscript, alternative approaches to examine the questions posed, or perhaps even to reject the submissions.

The first paper attempted to examine the “impact of facility surgical volume on survival of patients with cancer.” Although this is a relevant question for multiple audiences, including patients, families, and payers, the methodology employed in this paper is quite concerning. Investigators conducted a retrospective analysis of patients with multiple tumor types in the National Cancer Database over a 10-year period. Patients were included “if they received surgery as treatment of their cancer and had valid survival information available from 2004 [to] 2013.” Multiple prognostic factors were included in the analysis.

The investigators found that “patients who received surgery from low-volume facilities vs very high-volume had the worst survival probability.” The major problem here is that this analysis does not take into consideration what happened to patients over the months or years during which they may have received other treatments, including from centers with treatment volumes vastly different from where the original surgery was performed. This invites questions such as: Is it appropriate to assign the ultimate survival outcome to the initial surgery for a patient who may have lived many years (> 4 years), experiencing 1 or more recurrences and receiving multiple treatment regimens during her/his cancer journey?

Authors of the second manuscript attempted to explore whether patients with cancer who receive complementary medicine are interested in continuing with or adhering to conventional cancer therapies and to compare survival outcomes with those who did not receive complementary medicine. The authors also used data from the National Cancer Database in their analysis. Rather remarkably, the investigators defined complementary medicine as “other unproven cancer treatments administered by nonmedical personnel” that was administered in addition to any conventional cancer therapy as noted in the patient record.

A total of 258 individuals (0.01% of the total population;
From the Editor

N = 1,901,815) were grouped into the complementary medicine cohort. The authors compared outcomes of this extremely small—and certainly underrepresentative—population of individuals who participated in some form of complementary medicine with those who did not receive complementary treatments to conclude that such patients “were more likely to refuse additional conventional cancer treatment.” Finally, they wrote, “The greater risk of death associated with [complementary medicine] is therefore linked to its association with treatment refusal.” This conclusion is based on an analysis of 0.01% of the entire patient population. Somehow this paper was accepted by peer review, a decision supported by the journal’s editors.

Finally, we come to a recently reported abstract at a major oncology meeting addressing a difficult but important subject: sexual harassment. For anyone reading this commentary, I need to make very clear my sole concern with this abstract relates to the methodology employed, rather than the subject matter.

This abstract, which intended to “investigate the incidence and impact of workplace sexual harassment experienced by physicians” through a “targeted social media outreach to examine the prevalence and types of sexual harassment,” included a total of “271 respondents, 250 physicians in practice, and 21 residents/fellows.” The authors reported that in the past year, incidences of sexual harassment by institutional insiders (peers/superiors) was reported by 70% of oncologists; of the individuals surveyed, 80% of women respondents reported sexual harassment and 56% of men reported at least 1 incident. If an accurate observation, this is a remarkable and most distressing finding; however, it must be noted that this sample size of 271 oncologists represents approximately 2% of oncologists practicing in the United States.

The point to be made in criticizing this abstract is directed at the reported methodology and not the fundamental message being delivered. The authors provide no documentation to demonstrate that this is an objectively representative sample of the oncology physician population, and it is reasonable to suggest that those responding to the survey may have been more likely to have experienced sexual harassment or, alternatively, may have for their own reasons failed to be truthful in their responses.

In scientific communication, the underlying message must be linked to the soundness of the methodology employed. In the opinion of this commentator, the message of the 3 highlighted manuscripts is muddled by the failure to pay necessary attention to the procedures employed in the clinical research being presented by the authors, peer reviewers, and editorial leadership.

REFERENCES

Watch Alex Spira, MD, PhD, FACP present data and share insights on Alunbrig® (brigatinib), a treatment option for adult patients with ALK+ mNSCLC.

**Program Objectives**

**Share** the latest clinical efficacy and quality of life data on ALUNBRIG for ALK+ metastatic NSCLC

**Present** a case study detailing treatment of a patient with ALUNBRIG

**Review** important safety and dosing information

**Enhance** your understanding of how ALUNBRIG can improve patient outcomes

**INDICATION**

ALUNBRIG® (brigatinib) is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)/Pneumonitis: Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG. In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), ILD/pneumonitis occurred in 5.1% of patients receiving ALUNBRIG. ILD/pneumonitis occurred within 8 days of initiation of ALUNBRIG in 2.9% of patients, with Grade 3 to 4 reactions occurring in 2.2% of patients. In Trial ALTA, ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred within 9 days of initiation of ALUNBRIG (median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%. Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

Hypertension: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), hypertension was reported in 32% of patients receiving ALUNBRIG; Grade 3 hypertension occurred in 13% of patients. In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1, resume ALUNBRIG at the same dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

Bradydardia: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), heart rates less than 50 beats per minute (bpm) occurred in 8.1% of patients receiving ALUNBRIG. Grade 3 bradycardia occurred in 1 patient (0.7%). In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

Visual Disturbance: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), Grade 1 or 2 adverse reactions leading to visual disturbance including blurred vision, photophobia, photopsia, and reduced visual acuity were reported in 7.4% of patients receiving ALUNBRIG. In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group. Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

Creatine Phosphokinase (CPK) Elevation: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), creatine phosphokinase (CPK) elevation occurred in 81% of patients who received ALUNBRIG. The incidence of Grade 3 or 4 CPK elevation was 24%. Dose reduction for CPK elevation occurred in 15% of patients. In ALTA, CPK elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation with Grade 2 or higher muscle pain or weakness. Upon resolution or recovery to Grade 1 CPK elevation or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), amylase elevation occurred in 52% of patients and Grade 3 or 4 amylase elevation occurred in 6.8% of patients. Lipase elevations occurred in 59% of patients and Grade 3 or 4 lipase elevation occurred in 17% of patients. In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 27% of patients in the 90 mg group and 2.7% in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Hyperglycemia: In the ALUNBRIG arm of trial ALTA 1L (180 mg once daily), 56% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia,
based on laboratory assessment of serum fasting glucose levels, occurred in 7.5% of patients. In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective non-hormonal contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

ADVERSE REACTIONS

In ALTA 1L, serious adverse reactions occurred in 33% of patients receiving ALUNBRIG. The most common serious adverse reactions were pneumonia (4.4%), ILD/pneumonitis (3.7%), pyrexia (2.9%), dyspnea (2.2%), pulmonary embolism (2.2%), and asthenia (2.2%). Fatal adverse reactions occurred in 2.9% of patients and included pneumonia (1.5%), cerebrovascular accident (0.7%), and multiple organ dysfunction syndrome (0.7%).

In ALTA, serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

The most common adverse reactions (≥25%) with ALUNBRIG were diarrhea (49%), fatigue (39%), nausea (39%), rash (38%), cough (37%), myalgia (34%), headache (31%), hypertension (31%), vomiting (27%), and dyspnea (26%).

DRUG INTERACTIONS

CYP3A Inhibitors: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If coadministration of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG.

CYP3A Inducers: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, increase the dose of ALUNBRIG.
**FDA DIGEST**

**Adjuvant Nivolumab Is New Treatment Option for High-Risk Urothelial Carcinoma**

The FDA has approved nivolumab (Opdivo) for the adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical cystectomy, irrespective of prior neoadjuvant chemotherapy, nodal involvement, or PD-L1 status.

Investigators assessed the efficacy of adjuvant nivolumab in the phase 3 CheckMate 274 trial (NCT02632409). Patients who received nivolumab exhibited a median disease-free survival (DFS) that was nearly double that of those who received placebo, at 20.8 months (95% CI, 16.5-27.6) vs 10.8 months (95% CI, 8.3-13.9), respectively. The immunotherapy elicited a 30% reduction in the risk of disease recurrence or death (HR, 0.55; 95% CI, 0.57-0.86; P = .0008).

In patients whose tumors had a PD-L1 expression of 1% or higher, the median DFS had not yet been reached (95% CI, 21.2-not evaluable) with nivolumab and was 8.4 months (95% CI, 5.6-21.2) with placebo. In this subgroup, the immunotherapy showed a 45% reduction in the risk of disease recurrence or death vs placebo (HR, 0.55; 95% CI, 0.39-0.77; P = .0005).

Findings from CheckMate 274 also served as confirmatory evidence for the February 2017 accelerated approval granted to nivolumab. As such, the FDA converted the status to a regular approval for patients with locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or who have disease progression within 1 year of neoadjuvant treatment with a platinum-containing chemotherapy.

**TO READ MORE, VISIT bit.ly/2WcCpDA.**

**Dostarlimab, Companion Diagnostic Move Forward for dMMR Solid Tumors**

The FDA has granted an accelerated approval to dostarlimab-gxly (Jemperli) for the treatment of adult patients with mismatch repair-deficient (dMMR) recurrent or advanced solid tumors who have progressed on or following previous treatment and who have no satisfactory alternative options. The agency simultaneously approved the Ventana MMR RxDx Panel, a qualitative immunohistochemistry test intended for use in the assessment of mismatch repair proteins.

The approval of dostarlimab was supported by collective findings from a prede-termined efficacy cohort of the phase 1 GARNET trial (NCT02715284). This included patients with recurrent or advanced solid tumors whose disease had progressed following systemic therapy and for whom no satisfactory alternative treatment options were available.

The agent elicited an overall response rate (ORR) of 41.6% (95% CI, 34.9-48.6%) for patients with dMMR solid tumors, including those with endometrial cancer (n = 209); this comprised a complete response rate of 9.1% and a partial response rate of 32.5%. The median duration of response was 34.7 months (range, 2.6-35.8+), with 95.4% of patients experiencing a response that persisted for 6 months or longer.

**TO READ MORE, VISIT bit.ly/3kk7xJi.**

**Bezlutifan Gets Go-Ahead for VHL-Associated Cancers**

The FDA has approved bezlutifan (Welireg), a HIF-2α inhibitor, for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNETs) that do not require immediate surgery.

The approval was based on findings from the ongoing, open-label, single-arm phase 2 study 6482-004 (NCT03401788), which demonstrated that bezlutifan elicited an objective response rate (ORR) of 49% (95% CI, 36%-62%) in patients with VHL-associated RCC (n = 61). All responses were partial responses (PRs) and the median duration of response was not reached; 56% of patients maintained a response lasting at least 12 months (n = 17/30).

Data from a subgroup analysis showed that patients with pNETs (n = 12) had an ORR of 83% (95% CI, 52%-98%) comprising a complete response rate of 17% and a PR rate of 67%. For those with CNS hemangioblastoma (n = 24) the ORR was 63% (95% CI, 41%-81%), with a 4% complete response rate and a 58% PR rate. The median duration of response was not reached in either subgroup. Among responders, 50% (n = 5/10) of patients with pNETs and 73% (n = 11/15) of those with CNS hemangioblastoma had a response lasting at least 12 months.

**Complete Response Letter Delays Approval of Oportuzumab Monatox for NMIBC**

The FDA has issued a complete response letter to Sesen Bio stating that more data are needed to demonstrate the clinical/statistical benefit and product quality of oportuzumab monatox-qqrs (Vicineum). The manufacturer was seeking approval of the recombinant fusion protein for the treatment of patients with bacillus Calmette-Guérin (BCG)-unresponsive nonmuscle–invasive bladder cancer (NMIBC).

The biologics license application included data from the phase 3 VISTA trial (NCT02449239) and was granted a priority review in February. Investigators assessed the efficacy of oportuzumab monatox in patients with NMIBC whose disease was refractory or had relapsed following adequate BCG treatment.

In preliminary findings, pooled data from 2 cohorts showed that among 89 eval-uable patients the agent induced complete responses in 40% (95% CI, 33%-51%) of patients at 3 months. At 6, 9, and 12 months, the complete response rates were 28% (95% CI, 19%-39%), 21% (95% CI, 13%-31%), and 17% (95% CI, 10%-26%), respectively. These were patients whose disease was determined to be refractory or had recurred less than 11 months after BCG treatment.

In a subgroup analysis of a cohort of patients whose disease was refractory or recurred within 6 months of their last course of BCG (n = 82), the median duration of response was 273 days (95% CI, 122-not available).

The company shared plans to request a type A meeting as soon as possible with the FDA to review the next steps required prior to approval of the application. The agent is currently under investigation at the National Cancer Institute in combina-tion with durvalumab (Imfinzi) for the same patient population.

**TO READ MORE, VISIT bit.ly/2WkVFOD.**
Drug Spotlight | LENVATINIB (LENVIMA)

LENVATINIB Plus Pembrolizumab Makes an Impression in Advanced RCC

by KYLE DOHERTY

THE COMBINATION OF LEVFATINIB (Lenvima), a kinase inhibitor, and pembrolizumab (Keytruda), a PD-1–blocking monoclonal antibody, has demonstrated strong efficacy results with a manageable safety profile in patients with advanced renal cell carcinoma (RCC). On August 10, 2021, the FDA approved the doublet for the first-line treatment of adult patients with RCC.1

The approval was based on data from the phase 3 CLEAR; KEYNOTE-581 trial (NCT02811861), which compared lenvatinib plus pembrolizumab with single-agent sunitinib (Sutent). Results showed that patients treated with the combination (n = 355) achieved a median progression-free survival (PFS) of 23.9 months (95% CI, 20.8-27.7) compared with 9.2 months (95% CI, 6.0-11.0) in patients receiving sunitinib (n = 357; HR, 0.39; 95% CI, 0.32-0.49; P < .0001). Median overall survival (OS) was not reached in either cohort (HR, 0.66; 95% CI, 0.49-0.88; P = .0049) and the objective response rate (ORR) in the lenvatinib plus pembrolizumab arm was 71% (95% CI, 66%-76%) vs 36% (95% CI, 31%-41%) in the sunitinib arm.2 Further, the complete response rates were 16% plus pembrolizumab arm was 71% (95% CI, 66%-76%) vs 36% (95% CI, 31%-41%) in the sunitinib arm.2 Further, the complete response rates were 16% and 4% in the combination and sunitinib arms, respectively.

In an interview with OncologyLive®, Robert J. Motzer, MD, the head of the Kidney Cancer Section of the Genitourinary Oncology Service, and Jack and Dorothy Byrne Chair in Clinical Oncology at Memorial Sloan Kettering Cancer Center in New York, New York, and a Giants of Cancer Care® award winner in the genitourinary cancer category, spoke about the “exceptional” efficacy of the combination and how it fits into the evolving RCC treatment landscape.

Q Please describe the rationale for combining these agents for patients with RCC.

Lenvatinib is a tyrosine kinase inhibitor [TKI] that mainly targets the VEGF receptor. It’s a very potent oral TKI. It also targets other kinases, including fibroblast growth factor and platelet-derived growth factor receptors. It’s considered to be an oral antiangiogenesis drug, meaning clinically it has an effect on the vasculature that surrounds and feeds tumors with a blood supply. Pembrolizumab is a PD-1 inhibitor that is widely used in many malignancies. It’s an intravenous checkpoint inhibitor that augments immune activity directed toward tumors. The combination of the 2 [agents] was largely fostered by [their] mechanisms of action. There were preclinical studies done [the results of which] suggested the 2 together had a high level of activity. Additionally, there has been a history of other TKI and IO [immuno-oncology] combinations that clinically have shown positive outcomes in phase 3 trials.

Q Was there any aspect of the trial results that you found surprising?

The activity of lenvatinib plus pembrolizumab was exceptional. The ORR was over 70%, with 16% [of patients experiencing] complete responses. In addition, the PFS was exceptional. The median PFS was 23.9 months by independent review compared with only 9.2 months with sunitinib. [The trial] met the primary end point of PFS and had a very high response rate, and there was a benefit in OS as well. The high response rate, median PFS, and the OS were really exceptional gains for that regimen. In fact, the response rate and the median PFS are really the longest we’ve seen in any of the first-line trials for RCC.

Q How does this approval potentially alter the treatment paradigm for patients with advanced RCC?

I’ve been in the field for over 30 years. When I was first an attending [physician] at Memorial Sloan Kettering the median PFS for the cytokines that we had at that time was only 4 months. The response rate was approximately 12%. The median OS was only between 9 to 12 months. You can see there’s been one benefit over another with TKI monotherapy, with IO therapy. Now with these TKI and IO combinations you can see [that with] the degree of response rates, [including] the complete responses and a median PFS of almost 24 months, how much of a therapeutic gain it is for our patients.

Q What are some strategies clinicians can employ to manage the immune-mediated adverse effects (AEs) that can arise from this combination?

The immune-related AEs are relatively modest in frequency with lenvatinib plus pembrolizumab. Usually they are managed by either delaying the pembrolizumab, or if they’re moderately severe or highly severe, then we use steroids for management. But for the most part with TKI/IO therapy there are a relatively modest number of immune-related AEs. A majority of the AEs that we see with levantinib plus pembrolizumab are more directed toward levantinib as a TKI, and include diarrhea, hypertension, some fatigue, and some skin toxicity, [among others]. Those largely make up the predominant AEs of the regimen and are mostly managed by local symptomatic management. For example, with diarrhea [we use] Imodium [loperamide], dose reduction, or dose delay. With this program, there are a high number of [individuals who] wound up having a dose reduction of the levantinib on the program, approximately 60%, [because of] AEs over the course of their therapy.

Q What does the future hold for levantinib plus pembrolizumab?

There are 2 ongoing studies that are industry sponsored that have levantinib plus pembrolizumab as the backbone of the regimen. These studies are combining levantinib plus pembrolizumab with other immunotherapies or with the new busulfan inhibitor. For levantinib plus pembrolizumab the efficacy with this particular [combination] would be tough to beat, but there are some trials that are adding additional agents to the combination.

REFERENCES
PIVOTAL CLINICAL TRIAL
The CLEAR; KEYNOTE-581 trial (NCT02811861) was a phase 3, multicenter, open-label, study evaluating the efficacy of lenvatinib plus pembrolizumab vs single-agent sunitinib (Sutent) in patients with advanced RCC in the first-line setting.

BASELINE PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lenvatinib Plus Pembrolizumab (n = 355)</th>
<th>Sunitinib (n = 357)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>23.9 (20.8-27.7)</td>
<td>9.2 (6-11)</td>
</tr>
<tr>
<td>HR, 95% CI</td>
<td>0.39; 95% CI, 0.32-0.49; P &lt; .0001</td>
<td></td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (33.6-NE)</td>
<td>NR (NE-NE)</td>
</tr>
<tr>
<td>HR, 95% CI</td>
<td>0.66; 95% CI, 0.49-0.88; P = .0049</td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>71% (66%-76%)</td>
<td>36% (31%-41%)</td>
</tr>
<tr>
<td>CR</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>PR</td>
<td>55%</td>
<td>32%</td>
</tr>
</tbody>
</table>

CR, complete response; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

WARNINGS AND PRECAUTIONS

Lenvatinib
- Cardiac dysfunction
- Hypertension
- Arterial thromboembolic events
- Hepatotoxicity
- Renal failure or impairment
- Proteinuria
- Diarrhea
- Fistula formation and gastrointestinal perforation
- QT interval prolongation
- Hypocalcemia

Pembrolizumab
- Immune-mediated adverse reaction
- Infusion-related reactions

Reversible posterior leukoencephalopathy syndrome
- Hemorrhagic events
- Impairment of thyroid stimulating hormone suppression/thyroid dysfunction
- Impaired wound healing
- Osteonecrosis of the jaw
- Embryo-fetal toxicity

Efficacy in the CLEAR; KEYNOTE-581 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lenvatinib Plus Pembrolizumab (n = 355)</th>
<th>Sunitinib (n = 357)</th>
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</tbody>
</table>

FDA Approval—August 10, 2021
FDA grants approval to the kinase inhibitor lenvatinib (Lenvima) in combination with pembrolizumab (Keytruda) for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

Mechanism of action:
- Lenvatinib inhibits the kinase activities of the VEGF receptors VEGFR1, VEGFR2, and VEGFR3. Pembrolizumab is a 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. In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti–PD-1 monoclonal antibody compared with either treatment alone.

How supplied:
- Lenvatinib: 4-mg and 10-mg capsules
- Pembrolizumab: 25 mg/mL solution in a single-dose vial

Dose:
- Lenvatinib: 20 mg orally once daily
- Pembrolizumab: 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks for up to 2 years or until disease progression or unacceptable toxicity
- After completing 2 years of combination therapy, patients may receive lenvatinib as a single agent until disease progression or unacceptable toxicity

Company: Eisai, Merck

Efficacy in the CLEAR; KEYNOTE-581 Trial

<table>
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<tr>
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CR, complete response; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

References


Warnings and Precautions

Lenvatinib
- Cardiac dysfunction
- Hypertension
- Arterial thromboembolic events
- Hepatotoxicity
- Renal failure or impairment
- Proteinuria
- Diarrhea
- Fistula formation and gastrointestinal perforation
- QT interval prolongation
- Hypocalcemia

Pembrolizumab
- Immune-mediated adverse reaction
- Infusion-related reactions

Commonly reported adverse effects in the CLEAR; KEYNOTE-581 Trial

<table>
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<th>Adverse effect</th>
<th>Lenvatinib Plus Pembrolizumab (n = 352)</th>
<th>Sunitinib (n = 340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>All grades</td>
<td>All grades</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>62% 10%</td>
<td>50% 6%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>58% 4%</td>
<td>41% 3%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>57% 1%</td>
<td>32% 0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56% 29%</td>
<td>43% 20%</td>
</tr>
</tbody>
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Commonly reported adverse effects in the CLEAR; KEYNOTE-581 Trial

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</table>
THE EVIDENCE TO FIGHT ON with ONIVYDE®

The first and only FDA-approved treatment, in combination with 5-FU/LV, for metastatic pancreatic cancer after gemcitabine-based therapy, proven to extend overall survival (OS)†

INDICATION
ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

CONTRAINDICATION
ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

WARNINGS AND PRECAUTIONS

Severe Neutropenia
ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE + 5-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE + 5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE + 5-FU/LV, and did not occur in patients receiving 5-FU/LV. In patients receiving ONIVYDE + 5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

Severe Diarrhea
ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset ≥24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE + 5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE + 5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE + 5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

Interstitial Lung Disease (ILD)
Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

Severe Hypersensitivity Reactions
Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

Embryo-Fetal Toxicity
Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment.

ADVERSE REACTIONS

• The most common (>20%) adverse reactions in which patients receiving ONIVYDE + 5-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea (any 59%, 26%; severe 13%, 4%) (early diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%; severe 9%, 4%]), fatigue/asthenia (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%,

Please see additional Important Safety Information throughout and Brief Summary of Full Prescribing Information, including Boxed Warning, on adjacent pages.
ONIVYDE®: RECOMMENDED & FDA-APPROVED BASED ON EVIDENCE

THE ONLY CATEGORY 1 NCCN® CHEMOTHERAPY RECOMMENDATION IN POST-GEMCITABINE METASTATIC PANCREATIC CANCER**

FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE1

- Proven in combination with 5-FU/LV in NAPOLI-1— the largest phase 3 trial1 in patients with metastatic pancreatic cancer with disease progression after gemcitabine-based therapy1,4

References: 1. NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE® (100 mg/m² every 3 weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE® (70 mg/m² every 2 weeks) + 5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional efficacy endpoints were progression-free survival and objective response rate.1,4

2. FDA-APPROVED FOR METASTATIC PANCREATIC CANCER AFTER GEMCITABINE1

3. ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE + 5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea reaction) were observed. An individual patient may experience both early- and ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients receiving ONIVYDE + 5-FU/LV, and did not occur in patients receiving 5-FU/LV. In patients receiving ONIVYDE + 5-FU/LV, the incidence of Grade 3/4 neutropenia was 32%, 19%; severe 3%, 1%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%), increased creatinine (any 18%, 13%; severe 0%, 0%).

4. Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration were reported in 3% of patients receiving ONIVYDE or ONIVYDE + 5-FU/LV.

The most common serious adverse reactions (≥2% of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

References: 1. ONIVYDE® [package insert]. Basking Ridge, N.J. Ipsen Biopharmaceuticals, Inc.; 2017. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma V.3.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed November 2, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE Network. 2017. All rights reserved. Accessed November 2, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE
ONIVYDE® (irinotecan liposome injection) for intravenous use
Initial U.S. Approval: 1996

BRIEF SUMMARY: refer to full Prescribing Information for complete product information.

1. INDICATIONS AND USAGE
ONIVYDE® is indicated, in combination with 5-FU/LV, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas (see Clinical Studies, 14).

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE®. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE® in combination with fluorouracil (5-FU) and leucovorin (LV). Withhold ONIVYDE® for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment. (see Dosing and Administration 2.2, 5.1)

Severe diarrhea occurred in 13% of patients receiving ONIVYDE®/5-FU/LV. Do not administer ONIVYDE® to patients with bowel obstruction. Withhold ONIVYDE® for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. (see Dosing and Administration 2.2, see Warnings and Precautions 5.2).

4 CONTRAINDICATIONS
ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE® or irinotecan HCl.

5 WARNINGS AND PRECAUTIONS
5.1 Severe Neutropenia: ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving single-agent ONIVYDE®. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian patients (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients vs 1% of White patients (see Clinical Pharmacology, 12.3).

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE® if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE® when the ANC is 1500/mm³ or above. Reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever following recovery in subsequent cycles (see Dosing and Administration, 2.2).

5.2 Severe Diarrhea: ONIVYDE® can cause severe and life-threatening diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late-onset diarrhea (onset ≥24 hours following chemotherapy) and early-onset diarrhea (onset ≤24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) (see Cholinergic Reactions, 6.1). An individual patient may experience both early- and late-onset diarrhea. In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE®/5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 9% in patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE®/5-FU/LV vs none in patients receiving 5-FU/LV. Of patients receiving ONIVYDE®/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE® for Grade 2–4 diarrhea. Initiate loperamide for late-onset diarrhea of any severity. Administer IV or subcutaneous atropine 0.25–1 mg (unless clinically contraindicated) for early-onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE® at a reduced dose (see Dosage and Administration, 2.2).

5.3 Interstitial Lung Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE® in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE® in patients with a confirmed diagnosis of ILD.

5.4 Severe Hypersensitivity Reaction: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction.

5.5 Embryo-Fetal Toxicity: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month following the final dose (see Use in Specific Populations, 8.1, 8.3; Clinical Pharmacology, 12.1).

6 ADVERSE REACTIONS
The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Severe Neutropenia (see Warnings and Precautions, 5.1: Boxed Warning)
- Severe Diarrhea (see Warnings and Precautions, 5.2: Boxed Warning)
- Interstitial Lung Disease (see Warnings and Precautions, 5.3)
- Severe Hypersensitivity Reactions (see Warnings and Precautions, 5.4)

6.1 Clinical Trials Experience
The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE® 70 mg/m² with LV 400 mg/m² and 5-FU 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE®/5-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks (n=147), or LV 200 mg/m² and 5-FU 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 week rest (5-FU/LV; n=134) (see Clinical Studies, 14). Serum bilirubin within the institutional normal range, albumin ≥3 g/dL, and Karnofsky Performance Status (KPS) ≥70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE®/5-FU/LV arm, 9 weeks in the ONIVYDE® monotherapy arm and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE® were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥10%, Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE® were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE® in 11% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE® were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE® for adverse reactions occurred in 33% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE® was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE®/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
ONIVYDE® when the ANC is 1500/mm³ or above. Reduce Administration contraindicated, for early diarrhea of any severity. (loperamide for late diarrhea of any severity. Administer atropine, if not Withhold ONIVYDE® for diarrhea of Grade 2–4 severity. Administer

5.1 Severe Neutropenia: hypersensitivity reaction to ONIVYDE® or irinotecan HCl. 20% of patients receiving ONIVYDE® in combination with fluorouracil (5-FU/LV vs 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late-onset occurs in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early-onset compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV; n=117), ONIVYDE® 100 mg/m² every 3 weeks 4 weeks followed by 2 week rest (5-FU/LV; n=134). Withhold ONIVYDE® if the absolute

Risk Summary: Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE® 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE® and for 1 month after the final dose.

8.4 Pediatric Use: Safety and effectiveness of ONIVYDE® have not been established in pediatric patients.

8.5 Geriatric Use: Of the 264 patients who received single-agent ONIVYDE® or ONIVYDE®/S-FU/LV in Study 1, 49% were 65 years old and 13% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE®.

Distributed by Ipsen Biopharmaceuticals, Inc. Basking Ridge, NJ 07920 ONIVYDE is a registered trademark of Ipsen Biopharm Limited ©2017 Ipsen Biopharmaceuticals, Inc. August 2017 ONV-US-000700 v2.0

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ONIVYDE®/S-FU/LV n=117</th>
<th>5-FU/LV n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Early diarrhea†</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Late diarrhea†</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>52</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>51</td>
<td>34</td>
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<tr>
<td>Stomatitis§</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>Infections and infestations</td>
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<td></td>
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<tr>
<td>Sepsis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic fever/neutropenic sepsis♠</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Gastroenteritis</td>
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<tr>
<td>Intravenous catheter-related infection</td>
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<td>0</td>
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<tr>
<td>General disorders and administration site conditions</td>
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<tr>
<td>Fatigue/asthenia</td>
<td>56</td>
<td>21</td>
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<tr>
<td>Pyrexia</td>
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<td>2</td>
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<td>Metabolism and nutrition disorders</td>
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<tr>
<td>Decreased appetite</td>
<td>44</td>
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<td>Weight loss</td>
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<td>Skin and subcutaneous tissue disorders</td>
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</tr>
<tr>
<td>Alopecia</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

†Early diarrhea: onset ≤24 hours of ONIVYDE® administration. †Late diarrhea: onset >1 day after ONIVYDE® administration. §Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.

The following laboratory abnormalities were reported (NCI CTCAE v4.0, worst grade shown) with higher incidence (≥5% difference Grades 1–4 [any] or ≥2% difference Grades 3–4 [severe] according to NCI CTCAE v4.0) for patients receiving ONIVYDE®/S-FU/LV (n=117) vs 5-FU/LV (n=134). Percentages were based on the number of patients with a baseline and at least 1 post-baseline measurement. Hematologic: anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%). Hepatic: increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%). Metabolic: hypermagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hypomagnesemia (any 27%, 12%; severe 5%, 3%). Renal: increased creatinine (any 18%, 13%; severe 0%, 0%).
Drug Spotlight | ENFORTUMAB VEDOTIN-EJFV (PADCEV)

Enfortumab Vedotin Challenges Standard of Care in Urothelial Carcinoma

by ONCOLOGYLIVE® STAFF

TWO INDICATIONS HAVE BEEN granted by the FDA to the Nectin-4–directed antibody, enfortumab vedotin-ejfv (Padcev), marking a shift in the treatment landscape for patients with advanced urothelial carcinoma. The first, a conversion of an accelerated approval granted in 2019, is for patients with locally advanced or metastatic urothelial cancer previously treated with a PD-1/PD-L1 inhibitor as well as with platinum-based chemotherapy. The second indication is for those who are ineligible for cisplatin-containing chemotherapy and have previously received 1 or more prior lines of therapy.1,2

“After progression occurs [following chemotherapy sequenced with immunotherapy], there’s a lot of uncertainty around treatment options, so we tend to rechallenge with chemotherapy then test some patients for FGF alterations,” said Thomas Powles, MD, MBBS, MRCP, in an interview with OncologyLive®. “The data are limited for this patient group, and so it’s an area where we need to develop new drugs,” added Powles, who is a professor of genitourinary oncology, director of the Bart Cancer Centre, and lead for Solid Tumour Research at Cancer Research UK in London, England.

“For me, the standard of care is platinum-based chemotherapy and maintenance avelumab [Bavencio], and [should patients] progress, enfortumab vedotin is what we’ll use in the second line,” Powles said.

EV-301 RESULTS USHER IN NEW TREATMENT OPTIONS

The converted approval was based on data from the EV-301 trial (NCT03474107), designed to confirm the benefit of enfortumab vedotin observed in phase 1 and 2 trials. Investigators administered enfortumab vedotin at a dose of 1.25 mg/kg vs investigator’s choice chemotherapy of docetaxel at a dose of 75 mg/m²; paclitaxel at a dose of 175 mg/m²; or vinflunine, where it is approved for treatment of patients with urothelial carcinoma, at a dose of 320 mg/m².3

Among the 608 patients treated in the EV-301 study, patients who received enfortumab vedotin (n = 301) had a median overall survival of 12.9 months (95% CI, 10.6-15.2), compared with 9.0 months (95% CI, 8.1-10.7) for those randomized to investigator’s choice chemotherapy (n = 308; HR, 0.70; 95% CI, 0.56-0.89; P = .0014). The median progression-free survival was 5.6 months (95% CI, 5.3-5.8) for those who received enfortumab vedotin vs 3.7 months (95% CI, 3.5-3.9) for those who received chemotherapy (HR, 0.62; 95% CI, 0.51-0.75; P < .0001). Additionally, the ORRs were 40.6% (95% CI, 34.9%-46.5%) vs 17.9% (95% CI, 13.7%-22.8%), respectively.1,2

“The response rate was 40% vs 18%, [respectively]. The percent and the hazard ratio for [progression-free survival] also favored enfortumab vedotin significantly; the efficacy signal was consistent, which is really important,” Powles said. “When we give this drug to my patients, we see great responses and we see [a reduction in] patients’ pain with therapy. It’s a very active therapy in urothelial cancer.”

EV-201: CISPlATIN-INELIGIBLE

Limited treatment options exist for patients who are ineligible for treatment with cisplatin-based chemotherapy—approximately 50% of all patients with advanced urothelial carcinoma—and even more so for those who progress following treatment with first-line PD-1/PD-L1 inhibitors.

Investigators of EV-201 (NCT03219333) assessed efficacy of enfortumab vedotin in a cohort of 89 patients, which supported the approval for patients who were ineligible for cisplatin-containing chemotherapy. These patients had received prior treatment with a PD-1 or PD-L1 inhibitor and the median number of prior therapies was 1 (range, 1-4).

The agent elicited an overall response rate (ORR) of 51% (95% CI, 39.8%-61.3%); this included a complete response rate of 22% and a partial response rate of 28%. The median duration of response was 13.8 months (95% CI, 6.4-not estimable).

Cited reasons for cisplatin ineligibility included baseline creatinine clearance of 30 to 59 mL/min (66%), grade 2 or greater hearing loss (15%), ECOG performance status of 2 (7%), and 12% reported more than 1 cisplatin-ineligibility parameter.1

A SAFE AND EFFECTIVE OPTION

“The toxicity profile is manageable [with enfortumab vedotin]. In fact, the adverse effect profile showed that the percentage of grade 3 or 4 adverse effects were approximately 50% in both groups [of EV-301],” Powles said, noting that “the antibody-drug conjugate had different adverse event profiles to standard chemotherapy.”

Specifically, the most common adverse effects observed with enfortumab vedotin in EV-301 were rash (all grade, 54%; grade 3/4, 14%), fatigue (50%; 9%), and peripheral neuropathy (50%; 5%). For those who received chemotherapy, the most common AEs were fatigue (40%; 7%), alopecia (38%; 0%), and peripheral neuropathy (34%; 3%).

“We looked out for neuropathy, skin toxicity, and hyperglycemia, particularly, which require attention. And we need to look at those while we’re treating our patients. Some patients [required] dose reductions or dose delays because of that,” Powles added.

Of note, the label comes with a box warning for serious skin reactions, as enfortumab vedotin may cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Prescribers are advised to immediately withhold enfortumab vedotin and consider referral for specialized care for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. If grade 3 or 4 skin reactions occur, permanently discontinue treatment.

As the first therapy to receive approval following marked improvements in survival vs the standard of care for patients with urothelial carcinoma, Powles noted that the agent will leave an effect on the landscape. “Overall, when you look at [these data], this is a new class of drug opening a new chapter in urothelial cancer,” Powles said. “We’re showing a drug with a very consistent [safety profile] with a high efficacy signal. I think this is going to be a big change for patients with bladder cancer over the next 10 years.”

“This research is practice-changing,” Powles concluded. “I think this is going to make a massive difference [for these patients] and I think it’s going to be a standard of care.”

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

EV-301 (NCT03474107) was a phase 3 trial that evaluated enfortumab vedotin vs chemotherapy in patients with previously treated locally advanced or metastatic urothelial cancer. EV-201 (NCT03219333) was a phase 2, multicohort study, that assessed the efficacy of enfortumab vedotin in 89 patients (cohort 2) with locally advanced or metastatic urothelial cancer who had received prior treatment with a PD-1 or PD-L1 inhibitor, and did not receive platinum-based chemotherapy.

BASELINE PATIENT CHARACTERISTICS:

<table>
<thead>
<tr>
<th></th>
<th>EV-301</th>
<th>EV-201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>68 (30-88)</td>
<td>75 (49-90)</td>
</tr>
<tr>
<td>n = 608</td>
<td>n = 89</td>
<td></td>
</tr>
</tbody>
</table>

Number of prior lines of therapy

- EV-301: 63%, 11%, 26%
- EV-201: 8%, 26%, 66% (Cisplatin-based therapy), 11%, 26% (Carboplatin-based therapy), 63% (Both cisplatin and carboplatin)

Efficacy in the EV-301 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Enfortumab vedotin (n = 301)</th>
<th>Chemotherapy (n = 307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>12.9 (10.6-15.2)</td>
<td>9.0 (8.1-10.7)</td>
</tr>
<tr>
<td>HR, 0.70; 95% CI, 0.56-0.89; P = .0014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>5.6 (5.3-5.8)</td>
<td>3.7 (3.5-3.9)</td>
</tr>
<tr>
<td>HR, 0.62; 95% CI, 0.51-0.75; P &lt; .0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| ORR (95% CI) | 40.6% (34.9%-46.5%) | 17.9% (13.7%-22.8%) |
| CR | 4.9% | 2.7% |
| PR | 35.8% | 15.2% |

Efficacy in Cohort 2 of the EV-201 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Enfortumab vedotin (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>51% (39.8%-61.3%)</td>
</tr>
<tr>
<td>CR</td>
<td>22%</td>
</tr>
<tr>
<td>PR</td>
<td>28%</td>
</tr>
</tbody>
</table>

Patients with response by BICR (n = 55)

| Median DOR, months (95% CI) | 713.8 (6.4-NE) |

BICR, blinded independent central review; CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

Boxed Warning

Serious skin reactions: enfortumab vedotin may cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Immediately withhold enfortumab vedotin and consider referral for specialized care for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis; permanently discontinue if confirmed or grade 3 or 4 skin reactions occur.

Warnings and Precautions

- Hyperglycemia
- Pneumonitis
- Peripheral neuropathy
- Ocular disorders
- Infusion side extravasation
- Embryo-fetal toxicity

Reference


FDA Approval—July 9, 2021

The FDA grants approval to enfortumab vedotin-ejfv (Padcev) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy following at least 1 line of prior therapy. The approval also converts the prior accelerated approval to a full approval for patients who have previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy.

How supplied:

- 20-mg and 30-mg of single-dose vials as a lyophilized powder for reconstitution

Dose:

- 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on days 1, 8, and 15 of a 28-day cycle.

Company: Astellas Pharma US Inc

Mechanism of action:

- Enfortumab vedotin is an antibody-drug conjugate, constructed with a human IgG1 antibody directed against Nectin-4, and adhesion protein located on the surface of cells, with the microtubule-disrupting agent, MMAE, attached via a protease-cleavable linker. The release of the small molecule disrupts the microtubule network within the cell, inducing cell arrest and apoptotic cell death.

Efficacy in the EV-301 Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Enfortumab vedotin (n = 301)</th>
<th>Chemotherapy (n = 307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (95% CI)</td>
<td>51% (39.8%-61.3%)</td>
<td>34.5% (26.8%-42.7%)</td>
</tr>
<tr>
<td>CR</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td>PR</td>
<td>29%</td>
<td>27%</td>
</tr>
</tbody>
</table>

TCC, transitional cell carcinoma.
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, and only those patients with CD19-directed ADC1,2

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

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Effusion and Edema** Serious effusion and edema occurred. Grade 3 edema: 3% (primarily peripheral edema or ascites); Grade 3 pleural effusion: 3%; Grade 3/4 pericardial effusion: 1%.  

Monitor patients for new/worsening edema or effusions. Withhold ZYNLONTA for Grade >2 until toxicity resolves. Consider diagnostic imaging in patients with symptoms of pleural or pericardial effusion, such as new/worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management.  

**Myelosuppression** Serious or severe myelosuppression—including neutropenia, thrombocytopenia, and anemia—occurred. Grade 3/4 neutropenia: 32%; thrombocytopenia: 20%; anemia: 12%. Grade 4 neutropenia: 21%; thrombocytopenia: 7%. Febrile neutropenia occurred: 3%.  

Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA.  

Consider prophylactic granulocyte colony-stimulating factor administration as applicable.  

**Infections** Fatal and serious infections, including opportunistic infections, occurred. Grade ≥3: 10%; fatal infections: 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia.  

Monitor for any new/worsening signs or symptoms consistent with infection. For Grade 3/4 infection, withhold ZYNLONTA until infection has resolved.  

**Cutaneous Reactions** Serious cutaneous reactions occurred. Grade 3: 4%, including photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.  

Monitor patients for new/worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for Grade 3 until resolution.  

Advise patients to: minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows; protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, consider dermatologic consultation.  

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch.  

You may also report side effects to ADC Therapeutics at 1-855-690-0340.  

**AR = adverse reaction; CI = confidence interval; CR = complete response; DOR = duration of response; ORR = overall response rate; NE = not estimable; PR = partial response; r/r = relapsed or refractory**
more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Challenge expectations in 3L DLBCL

Take the next step...

...on the path to response with the first and only single-agent, CD19-directed ADC\(^1,2\)

<table>
<thead>
<tr>
<th>ORR(^a)(^+)(^+)(^+)</th>
<th>1.3 Months</th>
<th>Single-Agent IV(^1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48.3% (95% CI: 39.9, 56.7)(^1)</td>
<td>median time to response (range: 1.1–8.1)(^1)</td>
<td>30-minute infusion Once every 3 weeks</td>
</tr>
<tr>
<td>24.1% CR; 24.1% PR(^2) (95% CI for each: 17.4, 31.9)(^1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

\(^d\) ORR: n=70. CR: n=35. PR: n=35.\(^1\)

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

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

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

Fatal ARs: 1%, due to infection.

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

www.zynlontahcp.com

DOSE DELAYS AND MODIFICATIONS Permanent treatment discontinuation due to an AR of ZYNLONTA: 19%. Of these, ≥2% were increased GGT, edema, and effusion.

Dose reductions due to an AR of ZYNLONTA: 8%. Of these, ≥4% was increased GGT.

Dosage interruptions due to an AR of ZYNLONTA: 49%. Of these, ≥5% were increased GGT, neutropenia, thrombocytopenia, and edema.

For Grade ≥3 nonhematologic toxicity, hold ZYNLONTA until toxicity ≤Grade 1. For neutropenia: if ANC <1 x 10⁹/L, hold ZYNLONTA until ANC ≥1 x 10⁹/L. For thrombocytopenia: if platelet count <50,000/mcL, hold ZYNLONTA until ≥50,000/mcL. For Grade ≥2 edema or effusion, hold ZYNLONTA until ≤Grade 1. If dosing is delayed >3 weeks due to toxicity related to ZYNLONTA, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation. Note: If toxicity requires dose reduction following second dose of 0.15 mg/kg (C2D1), patient should receive 0.075 mg/kg for Cycle 3.
ZYNLONTA® (loncastuximab tesirine [pvl]) for injection, for intravenous use

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

INDICATIONS AND USAGE
ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS

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

Myelosuppression. Treatment with ZYNLONTA can cause severe or serious myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%. Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable. Infections. Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥ 3 infections included sepsis and pneumonia. Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved.

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

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

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

- Effusion and Edema
- Myelosuppression
- Infections
- Cutaneous Reactions
- Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 213 patients with DLBCL in studies ADC-402-201 (LOTIS-2) and ADC-402-202, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles. In this pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

Relapsed or Refractory Diffuse Large B-Cell Lymphoma
LOTIS-2. The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies [see Clinical Studies (14.1)]. The trial required hepatic transaminases, including gamma-glutamyltransferase (GGT), <2.5 times upper limit of normal (ULN), total bilirubin <1.5 times ULN, and creatinine clearance ≥60 mL/min. Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease or unacceptable toxicity. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles. The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.

Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection.

Permanent treatment discontinuation due to an adverse reaction of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.

Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

Table 1 summarizes the adverse reactions in LOTIS-2.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZYNLONTA (N=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>38</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>30</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
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<tr>
<td>Photosensitivity reaction</td>
<td>10</td>
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<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
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<tr>
<td>Nausea</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
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<tr>
<td>Musculoskeletal pain</td>
<td>23</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
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<tr>
<td>Pleural effusion</td>
<td>10</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10</td>
</tr>
</tbody>
</table>


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

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

Selected Other Adverse Reactions

- Inflammatory-related conditions were reported in <3% of patients in LOTIS-2, including pericarditis, pneumonitis, pleuritis, and dermatitis.

Table 2 summarizes the laboratory abnormalities in LOTIS-2.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYNLONTA* All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
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<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>58</td>
<td>17</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>51</td>
<td>10b</td>
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<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT increased</td>
<td>57</td>
<td>21</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>AST increased</td>
<td>41</td>
<td>&lt;1b</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>37</td>
<td>&lt;1b</td>
</tr>
<tr>
<td>ALT increased</td>
<td>34</td>
<td>3</td>
</tr>
</tbody>
</table>

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

No Grade 4 adverse reactions occurred.

Immunogenicity

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

In LOTIS-2, 0 of 134 patients tested positive for antibodies against loncastuximab tesirine-ipil after treatment. The potential effect of anti-drug antibodies to ZYNLONTA on pharmacokinetics, efficacy, or safety is unknown.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells. There are no available data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

ZYNLONTA can cause fetal harm when administered to pregnant women.

Contraception

Pregnancy testing

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

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

Males Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during the treatment with ZYNLONTA and for 6 months after the last dose.

Infertility

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

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin > 1 to 1.5 × ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions. ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST).

PATIENTS WITH MYELOFIBROSIS, A subclassification of Philadelphia chromosome-negative myeloproliferative neoplasms (MPN), often present with symptom burden that excludes them from curative options, specifically transplant. The hallmarks of myelofibrosis—including clonal myeloproliferation, bone marrow fibrosis, anemia, splenomegaly, and constitutional symptoms—are associated with risk of morbidity and mortality; however, the recent advent of novel combinations and sequencing strategies have built on the foundation of care established with JAK2 inhibitors.1

Although investigators have observed progress in achieving clinical benefit for patients, efforts are needed to address lingering symptoms as well as progression on or resistance to standard-of-care therapy with ruxolitinib (Jakafi) for patients with intermediate- or high-risk disease and who are ineligible for transplant.

“In the field of myelofibrosis, there are several unmet needs, one being the improvement of overall survival in a setting of prior JAK2 inhibitor use and failure to it,” said Pankit Vachhani, MD, an assistant professor at the University of Alabama at Birmingham School of Medicine. “In the second-line space in myelofibrosis, we don’t have good options, and several clinical trials are ongoing to assess various new drugs [TABLE].”

The management of anemia and thrombocytopenia represent 2 other areas of unmet need, according to Vachhani. “Thrombocytopenia, as one knows, is a risk factor for worse outcomes. But in the case of patients with myelofibrosis, and especially those with a platelet count of less than 50 x 10^9/L, for example, there aren’t any good treatment options,” he said. “[Additionally,] anemia can sometimes prevent physicians from using the most optimal dose of JAK inhibitor that they would like. It is a burden on the patients because of the transfusion requirement and symptoms such as fatigue, dyspnea, headaches, and tiredness generally. Improving anemia therapeutically, [with or without] transfusion, would help improve the field and optimize the treatment options in the form of better dosing of JAK inhibitors or other treatment options.”

BUILDING ON SUCCESS WITH RUXOLITINIB

Ruxolitinib was approved by the FDA for the treatment of patients with intermediate- or high-risk myelofibrosis based on data from the phase 3 COMFORT-I (NCT00952289) and COMFORT-II (NCT00934544) trials.2 Investigators of COMFORT-I compared ruxolitinib vs placebo in JAK inhibitor-naïve patients with myelofibrosis. Investigators of COMFORT-II compared ruxolitinib vs best alternative therapy in JAK inhibitor-naïve patients. Both trials met the primary end point of patients achieving greater than or equal to a 35% reduction from baseline in spleen volume vs placebo at 42% with ruxolitinib (n = 155) vs less than 1% with placebo (n = 154) in COMFORT-I (P < .0001) and 29% with ruxolitinib (n = 146) vs 0% with placebo (n = 73) in COMFORT-II (P < .0001).

In 2019, the FDA approved the JAK-2/FLT-3 inhibitor fedratinib (Inrebic) patients with intermediate- or high-risk myelofibrosis based on data from the JAKARTA trial (NCT01437787), in which 37% (n = 35/96)
of patients treated with the recommended 400-mg dose achieved at least a 35% reduction in spleen volume vs 1 patient who experienced a response following treatment with placebo (n = 96; P < .0001).3

Investigators are exploring the long-term efficacy and safety of fedratinib in the phase 3, single-arm FREEDOM trial (NCT03755518) and the phase 3 FREEDOM2 trial (NCT03952039) vs best available care.

The clinical utility of ruxolitinib and fedratinib are challenged by compounding symptom burden and the development of JAK inhibitor–induced adverse effects, such as anemia. Further, patients who initially demonstrate a response to treatment will develop resistance to therapy after 2 to 3 years.1 For example, in the COMFORT-I and COMFORT-II trials approximately 50% of patients discontinued therapy by year 3 and 75% of patients discontinued by year 5. Indicators of suboptimal response to ruxolitinib may include failure to achieve minimum clinical improvement, or an increase in the severity of anemia, thrombocytopenia, or neutropenia within the first 4 months of therapy.

THE “ADD ON” EFFECT
The JAK/STAT pathway has long been recognized as the central therapeutic target for myelofibrosis; however, investigators are looking to other viable options as a better understanding of escape mechanisms comes into focus. This includes “add-on” approaches, in which investigators are rechallenging patients whose disease exhibits resistance or failure to ruxolitinib, with the addition of new agents plus ruxolitinib to reignite response.

Pelabresib
BET and JAK inhibitors in combination have shown efficacy in preclinical humanized mouse models and may be a therapeutic strategy for myelofibrosis.4 Investigators hypothesize that the novel BET inhibitor pelabresib (formerly known as CPI-0610) in combination with ruxolitinib may circumvent treatment-related anemia, enhance splenic response, and address symptoms.

Results of the phase 2 MANIFEST trial (NCT02158858) showed that pelabresib was an effective treatment for patients with myelofibrosis in different clinical settings including as monotherapy for patients who are refractory, intolerant, ineligible, or are no longer receiving ruxolitinib (arm 1); as an additional therapy for patients being treated with ruxolitinib who are not adequately controlled (arm 2); and as a first-line treatment in combination with ruxolitinib for patients who have not received prior treatment with a JAK inhibitor (arm 3).5

In arm 1, seven of 23 (30%) evaluable patients who were not transfusion dependent at baseline achieved reduction in spleen volume at 24 weeks. Of the patients from arm 2 who received pelabresib as addition to ruxolitinib, 6 of 21 (29%) evaluable non-transfusion-dependent patients achieved reduction in spleen volume at 24 weeks. Findings from arm 3 included 63 evaluable patients and response was 67% (95% CI, 54%-78%) at 24 weeks.

The agent is under investigation in the phase 3 MANIFEST-2 trial (NCT04603495) in combination with ruxolitinib compared with ruxolitinib alone.

Navitoclax
Early efficacy has also been demonstrated with the addition of navitoclax to ruxolitinib in findings from the phase 2 REFINE trial (NCT03222609). Navitoclax, a small molecule targeting the BCL2 family of apoptotic receptors, including BCL-XL, may help overcome resistance to JAK2-targeted therapy based on results of preclinical models. Specifically, the inhibition of BCL-XL may result in cell death for JAK2-mutated cells and may prevent fibrosis in the bone marrow.6

Investigators of the REFINE trial enrolled patients who did not respond to ruxolitinib after at least 12 weeks of treatment were enrolled to receive the combination and were assessed for splenic volume reduction of at least 35%.7 At week 24, investigators observed splenic volume reduction in 27% of patients (n = 9/34) who had received at least 1 dose of the combination. Further, a reduction of 50% or greater in total symptom score through week 24 was reported for 6 of 20 patients (30%) and elicited bone marrow fibrosis improvements of at least 1 grade at any time in 29% of 34 patients.8

Investigators had a dual objective in the evaluation of findings from the study in that they sought to evaluate whether the presence of mutations in the high-molecular risk (HMR) category (ASXL1, EZH2, SRSF2...
and IDH1/2) affected clinical outcomes. Mutational analysis was conducted at baseline and week 24, including next-generation sequencing with a 54-gene assay of variant allele frequency (VAF) in peripheral blood samples. Nineteen patients (58%) had mutations in HMR genes and, notably, 5 of the 9 patients (56%) who achieved splenic volume reduction at week 24 had HMR mutations.7

Investigators are exploring the efficacy of navitoclax and ruxolitinib as a potential first-line option for the treatment of myelofibrosis. The combination is being assessed vs ruxolitinib plus placebo in adults with primary or secondary MF who have not previously received a JAK2 inhibitor in the phase 3 TRANSFORM-1 trial (NCT04472598).8 The TRANSFORM-2 study (NCT04468984) is evaluating the combination vs best available therapy for patients with relapsed or refractory myelofibrosis.

**SYMPTOM MANAGEMENT BEYOND THE FIRST LINE**

In later stages of development, investigators are setting their sights on 2 JAK2 inhibitors—momelotinib and pacritinib—that may provide more options for patients who experience treatment-related anemia and thrombocytopenia. “There are some important potential differentiators with the JAK inhibitors that are still in development,” said Ruben A. Mesa, MD, director of the Mays Cancer Center at UT Health San Antonio MD Anderson Cancer Center in Texas.

**Momelotinib**

Momelotinib, a JAK1/2 and ACVR1 inhibitor, may represent an option for patients with disease-related anemia. In long-term survival data, the agent conveyed a treatment benefit for patients with myelofibrosis regardless of prior JAK inhibitor therapy treated in the SIMPLIFY-1 (NCT01969838) and SIMPLIFY-2 (NCT02101268) trials. In addition to prolonging overall survival (OS), the agent had similar splenic response compared with ruxolitinib and reduced the transfusion burden and improved anemia.

“Data suggest that activity with momelotinib inhibits hepcidin, which may create a state of anemia, chronic disease, and inflammation,” Mesa said.

In SIMPLIFY-1, patients who had no prior JAK inhibitor were randomized to momelotinib monotherapy or ruxolitinib. At 4.5 years follow-up, the median OS was not reached for patients who started on momelotinib therapy and was 53.1 months for those who were assigned to ruxolitinib but crossed over to momelotinib. Patients enrolled in SIMPLIFY-2 had prior ruxolitinib treatment and were randomized to momelotinib monotherapy or best available care. The median OS was 34.3 months for those in the momelotinib arm vs 37.5 months in the crossover arm, which investigators reported as the “best OS in the previously ruxolitinib-treated setting.”

Investigators are evaluating the agent in the MOMENTUM trial (NCT04173494) to determine if the agent, when administered after primary treatment with a JAK inhibitor, can continue to exhibit efficacy in reducing disease-related symptoms, the need for blood transfusions, and reverse splenomegaly.9

**Pacritinib**

Thrombocytopenia is a dose-limiting toxicity associated with JAK inhibitors, such as ruxolitinib and fedratinib. The available JAK inhibitors are not approved for individuals with a platelet count of less than 50,000.

To address this treatment gap, investigators are evaluating pacritinib, a JAK1/2 inhibitor, in this patient population. The agent, which has demonstrated efficacy in patients with severe thrombocytopenia across trials, is currently under priority review for FDA approval. The application was based on findings from the phase 3 PERSIST-1 (NCT01773187) and PERSIST-2 (NCT02055781) trials, as well as data from the phase 2 PAC203 trial (NCT03165734).10

Patients enrolled to the PERSIST-2 trial received pacritinib at a twice-daily dose of 200 mg (n = 74), and 29% experienced a reduction in spleen volume of at least 30% vs 3% of those who were given best available therapy (n = 72), which included ruxolitinib. Moreover, 23% of patients experienced a reduction in total symptom scores of at least 50% vs 13% of those given best available therapy.11

Data from the PERSIST-1 study showed that at 24 weeks, 19.1% of patients in the pacritinib arm (n = 220) experienced a 35% or greater reduction in spleen volume vs 4.7% of those in the best available therapy arm (n = 107; P = .0003). Of note, there was platelet count threshold was included for enrollment; however, 32% of patients had levels under 100,000 μL and 16% had levels under 50,000 μL.12

The phase 3 PACIFICA study (NCT03165734), which has opened as an amendment to the PAC203 trial, is recruiting patients with myelofibrosis and severe thrombocytopenia to evaluate pacritinib as first- or second-line treatment following JAK inhibition.

“Having application in this patient population sets pacritinib apart from other available treatments,” Mesa said.

**Luspatercept**

Another strategy to combat anemia is with luspatercept-aamt (Reblozyl). The agent was approved in 2020 for the treatment of adult patients with very low- to intermediate-risk MDS with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis of anemia failing an erythropoiesis stimulating agent who require 2 or more red blood cell units over 8 weeks. The decision was based on data from the MEDALIST trial (NCT02631070).13

“The biggest change, compared with the [National Comprehensive Cancer Network] guidelines [for MPNs] from 2020, is the addition of the luspatercept,” Vachhani said.14 The agent is under investigation for patients with myelofibrosis on concomitant JAK2-inhibitor therapy who require red blood cell transfusions vs placebo in the phase 3 INDEPENDENCE trial (NCT04717414).

“It has been gratifying to see these updates to the guidelines,” Mesa said. “The [NCCN] guidelines provide some framework for a practice that had been quite heterogeneous, particularly in the United States, where some utilized the last review article they read or the last board review they heard or an outdated chapter of the [Ronald] Hoffman textbook [Hematology: Basic Principles and Practice] to guide how they were treating patients with MDS,” Mesa said, adding that the guidelines have “helped to bring [treatment strategies] into greater alignment.”
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Utility of Immunotherapy Keeps Evolving in Unresectable Stage III NSCLC

by HAYLEY VIRGIL

ALTHOUGH CONCURRENT CHEMORADIOOTHERAPY (CRT) has historically been the standard of care for patients with unresectable stage IIIA and stage IIIB non-small cell lung cancer (NSCLC), the addition of immunotherapies to this setting, such as durvalumab (Imfinzi), have been linked with improvements in survival. Now, other checkpoint inhibitors are under investigation in combination with concurrent radiotherapy, and experts propose they could have practice-changing implications.

CRT: A HISTORICAL STANDARD

Concurrent CRT has been identified as the treatment of choice for patients with unresectable stage IIIA and IIIB NSCLC, although sequential chemotherapy followed by radiotherapy stands as a valid alternative treatment option, according to Enriqueta Felip, MD, head of the Lung Cancer Unit in the Oncology Department at Vall d’Hebron University Hospital and an associate professor of medical oncology at the Autonomous University of Barcelona in Spain. Felip walked through the shifts taking place in the treatment landscape for this patient population as part of a presentation during the 22nd Annual International Lung Cancer Congress®.

She highlighted several studies that examined the optimal use of concurrent and sequential CRT strategies in this setting.

Results of a meta-analysis by the NSCLC Collaborative Group, which compared outcomes of concomitant vs sequential chemotherapy for patients with locally advanced NSCLC, identified that treatment with sequential chemotherapy plus radiation was linked with a 5-year overall survival (OS) rate of 10.6% compared with 15.1% with concurrent therapy.²

Investigators of the randomized phase 3 PROCLAIM trial (NCT00686959) examined the use of concurrent pemetrexed/cisplatin plus thoracic radiation therapy (TRT), followed by pemetrexed consolidation or standard etoposide/cisplatin plus TRT, followed by consolidation platinum-based doublet chemotherapy in those with stage IIIA/B unresectable nonsquamous NSCLC. However, data showed that the median OS with concurrent therapy was 25.0 months vs 26.8 months in the etoposide/cisplatin arm (HR, 0.98; 95% CI, 0.79-1.20; P = .831).³

Additionally, investigators of the phase 3 RTOG 0617 trial (NCT00533949) examined standard-dose vs high-dose conformal radiotherapy with concurrent chemotherapy with or without cetuximab (Erbitux) in patients with unresectable stage IIIA or IIIB NSCLC. Here, data revealed that radiotherapy at the standard dose elicited a median OS of 28.7 months vs 20.3 months for the high-dose arm (HR, 1.38; 95% CI, 1.09-1.76; P = .004).⁴

Felip noted past efforts to try and build upon these treatment approaches—including the addition of induction chemotherapy, consolidation chemotherapy, or targeted therapies in non-biomarker-driven patients, twice-daily irradiation, and increased radiotherapy dosage—have not yielded positive results.

BREAKTHROUGH WITH DURVALUMAB IN STAGE III NSCLC

The addition of durvalumab has notably improved the benefit of CRT, as documented in results of the phase 3 PACIFIC study (NCT02125461). The trial enrolled 713 patients with unresectable stage III
NSCLC that had not progressed following concurrent platinum-based CRT who were randomized 2:1 to receive either durvalumab (n = 476) or placebo (n = 237) for up to 1 year.

In a 3-year survival data update, findings indicated that the addition of durvalumab led to a significant improvement in progression-free survival (PFS) vs placebo (HR, 0.52; 95% CI, 0.42-0.65; P < .0001). The updated OS data remained consistent with previously reported results (stratified HR, 0.69; 95% CI, 0.55-0.86); the median OS was not reached with durvalumab vs 29.1 months with placebo. Moreover the 12-, 24-, and 36-month OS rates for the durvalumab cohort vs placebo were 83.1% vs 74.6%, 66.3% vs 55.3%, and 57.0% vs 43.5%, respectively.

Pneumonitis was a notable concern associated with the consolidation immunotherapy, Felip explained; all-grade and grade 3/4 pneumonitis occurred in 33.9% and 3.6% of patients treated with durvalumab, respectively.

Findings from the study led to the February 2018 FDA approval of durvalumab as a treatment for patients with locally advanced, unresectable stage III NSCLC who have not progressed following CRT. A

Five-year survival findings of the PACIFIC study were recently presented at the 2021 American Society of Clinical Oncology Annual Meeting. At a median follow-up of 34.2 months, the updated median OS was 47.5 months with durvalumab vs 29.1 months with placebo (HR, 0.72; 95% CI, 0.59-0.89). The median PFS in the durvalumab arm was 16.9 months vs 5.6 months with placebo (HR, 0.55; 95% CI, 0.45-0.68).

Additionally, the 60-month OS rate was 42.9% with durvalumab vs 33.4% with placebo. The 60-month PFS rates were 33.1% and 19.0%, respectively.

ASSESSING OTHER IMMUNOTHERAPY AGENTS PLUS CONCURRENT CRT

Investigators have explored other approaches with checkpoint inhibitor beyond durvalumab.

In the phase 2 KEYNOTE-799 study (NCT03631784), pembrolizumab (Keytruda) plus concurrent CRT was found to induce antitumor effects in patients with unresectable locally advanced, stage III NSCLC irrespective of PD-L1 expression or tumor histology. In cohort A, which comprised both patients of nonsquamous and squamous histology (n = 112), the overall response rate (ORR) was 70.5% (95% CI, 61.2%-78.8%). Results were similar in the nonsquamous cohort (n = 102), with a reported ORR of 70.6% (95% CI, 60.7%-79.2%); however, more patients in the mixed cohort had a response lasting at least 12 months (79.7% vs 75.6%, respectively).

The phase 2 NICOLAS trial (NCT02434081)–which assessed concurrent radiotherapy along with nivolumab (Opdivo) and followed by consolidation nivolumab for up to 1 year–identified the regimen’s feasibility with no unexpected adverse effects or increased risk of severe pneumonitis.

Additionally, the phase 2 DETERRED study (NCT02525757) was a 2-part trial assessing concurrent radiotherapy plus atezolizumab (Tecentriq) in patients with unresectable NSCLC. Findings from part 1, which examined conventionally fractionated CRT followed by consolidation atezolizumab, showed that the median PFS was 18.6 months and the median OS was 22.8 months at a median follow-up of 22.5 months. In part 2, which had a median follow up of 15.3 months and involved concurrent CRT with atezolizumab and the same consolidation and maintenance therapies as in part 1, the median PFS was 13.2 months and the median OS was not reached.

Ongoing clinical trials are examining the efficacy of immunotherapy agents within this patient population. For example, the phase 2 COAST study (NCT03822351) is examining durvalumab, durvalumab/olectumab, and durvalumab/monalizumab; the phase 2 LUN14-179 (NCT02343952) trial is assessing pembrolizumab; and the phase 2 BTCRC-LUN16-081 trial (NCT03285321) is evaluating nivolumab vs nivolumab/ipilimumab (Yervoy) following concurrent radiotherapy (TABLE).

<table>
<thead>
<tr>
<th>ClinicalTrials.gov identifier (trial name)</th>
<th>Phase</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03822351 (COAST)</td>
<td>2</td>
<td>Durvalumab + olectumab; or durvalumab + monalizumab vs durvalumab alone</td>
<td>Primary: ORR&lt;br&gt;Secondary: AEs, DOR, disease control, PFS</td>
</tr>
<tr>
<td>NCT02343952 (LUN14-179)</td>
<td>2</td>
<td>Pembrolizumab</td>
<td>Primary: time to death or distant metastases&lt;br&gt;Secondary: PFS, OS, AEs</td>
</tr>
<tr>
<td>NCT03285321 (BTCRC-LUN16-081)</td>
<td>2</td>
<td>Nivolumab vs nivolumab + ipilimumab</td>
<td>Primary: PFS&lt;br&gt;Secondary: OS, time to metastatic disease, AEs</td>
</tr>
<tr>
<td>NCT03519971 (PACIFIC2)</td>
<td>3</td>
<td>Durvalumab + platinum-based chemotherapy and radiation vs placebo vs platinum-based chemotherapy and radiation</td>
<td>Primary: PFS&lt;br&gt;Secondary: OS, ORR, DOR, AEs</td>
</tr>
<tr>
<td>NCT04026412 (CheckMate73L)</td>
<td>3</td>
<td>Nivolumab + CCRT + ipilimumab vs nivolumab + CCRT vs durvalumab + CCRT</td>
<td>Primary: PFS&lt;br&gt;Secondary: ORR, DOR, AEs, time to response</td>
</tr>
</tbody>
</table>

AEs, adverse effects; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

*Investigator choice of cisplatin/etoposide, carboplatin/paclitaxel, pemetrexed/cisplatin, or pemetrexed/carboplatin.
Other ongoing studies include the randomized phase 3 PACIFIC trial (NCT03519971), which is assessing concurrent radiotherapy plus durvalumab in locally advanced, unresectable stage III NSCLC, and the phase 3 CheckMate73L trial (NCT04026412), which will evaluate the use of nivolumab plus concurrent CRT followed by nivolumab with or without ipilimumab in previously untreated, locally advanced stage III NSCLC; another arm is looking at durvalumab plus concurrent CRT.

**REMAINING QUESTIONS AND OTHER POTENTIAL AVENUES UP AHEAD**

“One important question now is [whether] we should give chemoradiotherapy first… or if it is better to start up front with chemotherapy, radiotherapy, and immunotherapy,” Felipe noted.

In hopes of answering this question, investigators are enrolling patients on the phase 3 EA5181 trial (NCT04092283), which is assessing the value of durvalumab as concurrent and consolidative therapy alone for patients with unresectable stage III disease.

Some patients are ineligible to receive radiation or may not be able to have chemotherapy-free regimens. A radiotherapy-free treatment with durvalumab is currently being assessed through the phase 3 BRIDGE trial (NCT04765709), which will determine whether chemoimmunotherapy can enhance tumor shrinkage in a population of patients who are not eligible for radiotherapy or surgery. The goal is to achieve radiotherapy eligibility within this population and possibly move on to an immunotherapy combination and consolidation immunotherapy, Felipe said. Patients will receive durvalumab and chemotherapy induction followed by durvalumab and radiotherapy, followed by 1 year of consolidation durvalumab.

Other chemotherapy-free options are being tested in the phase 1 ARCHON-1 trial (NCT03801902) of durvalumab plus radiotherapy in patients with stage II to III NSCLC with a PD-L1 status of 50% or more, a single-center phase 1 pilot trial (NCT04013542) examining ipilimumab plus nivolumab and radiotherapy in patients with stage II to III NSCLC, and the phase 2 SPRINT trial (NCT03523702) of pembrolizumab and radiotherapy in patients with a PD-L1 status of 50% or more.

**REFERENCES**

Research Study

Do you have a patient with myelofibrosis?

We are conducting three research studies to evaluate an investigational medication (called navitoclax) in patients with myelofibrosis. The primary objective of this program is to evaluate the effect of navitoclax (in some cases, in combination with ruxolitinib) on reducing spleen volume in patients with myelofibrosis. Patients may continue on study as long as they are receiving benefit. We need help from the local medical community to help us identify qualified study participants.

Locations Worldwide

If you would like to speak with a Principal Investigator conducting one of the AbbVie myelofibrosis studies in your area, please contact us today.

AbbvieResearchStudies.com

Navitoclax, an investigational medication, is under clinical development and is not approved by regulatory health agencies. Safety and efficacy have not been established.
Strategies to Overcome EGFR Resistance Mechanisms in NSCLC

by RYAN SCOTT

RESEARCH EFFORTS TO OVERCOME resistance to EGFR-directed therapies continue to build on the demonstrated success of agents such as osimertinib (Tagrisso) for patients with advanced non-small cell lung cancer (NSCLC), according to Sukhmani K. Padda, MD.

“There may be strategies after a certain resistance that are going to be helpful across a diversity of mechanisms of resistance,” said Padda, director of thoracic medical oncology at Cedars-Sinai Medical Center in Los Angeles, California. “There are other strategies that are going to be much more specific to the resistance profile in that patient’s particular tumor.”

In an interview with OncologyLive® during the 22nd Annual International Lung Cancer Congress®, a program hosted by Physicians’ Education Resource®, LLC (PER®), Padda discussed strategies to overcome EGFR resistance in patients with NSCLC.

What are the key considerations to keep in mind when determining EGFR resistance mechanisms in clinical practice?

One of the first things I focus on is [to identify the type of EGFR resistance. Is it EGFR-dependent? Has there been a second-site EGFR mutation that prevents binding of the drug? Is it an EGFR-independent mechanism of resistance? That means looking to see if a bypass track has been activated downstream of activation of pathways, such as MAPK or PI3K. Or has there been histologic transformation, where the tumor can transform from adenocarcinoma to high-grade neuroendocrine or small cell lung cancer [SCLC]?

Unfortunately, it’s not always so simple [to identify], and sometimes these mechanisms of resistance co-occur with one another, and as each generation of targeted therapy gets better, the mechanisms of resistance also get much more diverse.

As an example, with earlier-generation TKIs [tyrosine kinase inhibitors] such as erlotinib [Tarceva] and gefitinib [Iressa], there was a dominant mechanism of resistance—EGFR-dependent resistance with development of T790M in 60% of tumors. However, with the third-generation drug osimertinib, you see much more complexity and do not see a dominant mechanism resistance. When osimertinib is given in the second-line setting in the context of a T790M mutation, you can see evidence of an on-site EGFR mutation called C797S in approximately 20% [of these cases].

However, if we move osimertinib into the first-line setting, [the development of acquired mutations] become even less frequent, only occurring in the single digits; some literature quotes around 7%.

Then there are a diversity of resistance mechanisms, [including] MET amplification—the second most common to activation of the MAP kinase pathway—with acquired BRAF mutations, KRAS mutations, and PIK3CA mutations. Histologic transformation to SCLC seems to be potentially a more prominent mechanism of resistance to third-generation drugs.

There have been some data showing that combining a third-generation TKI with [a] MET inhibitor for those patients has some probability of shrinking and controlling the tumor. An example of that was the combination of the third-generation drug lazertinib and a bispecific monoclonal antibody that hits EGFR and MET. Activity was seen in this group of patients who had been [previously] treated with EGFR-directed drugs. Moreover, activity [was] most prominent in patients who had EGFR- or MET-based resistance, [with an] objective response rate of 47%.

There may be a role for precision oncology at the time of resistance. [One therapeutic is a small-molecule inhibitor known as savolitinib, [which was studied in combination] with osimertinib at the time of resistance with evidence of MET amplification. Again, there was a modest objective response rate of approximately 30%. You may be able to use your combination strategies at the time of resistance.

For EGFR-dependent resistance, one of the most challenging to treat is what is called the triple mutation. This is where the tumor has an EGFR-activating mutation as well as acquired T790M resistance and C797S resistance. Fourth-generation EGFR Inhibitors are being developed—these are not TKIs—their allosteric inhibitors. There is some hope, and now clinical trials are ongoing in that specific population.

What is your current approach to treating a patient who develops resistance to EGFR inhibition?

How do you determine their next line of treatment?

One of the first things is to reassess the molecular profile of the tumor when it has progressed on osimertinib. With liquid biopsy, you can get an assessment of what’s going on at all tumor sites throughout the body that are shedding their DNA into circulation. That’s the first step, but the other step to consider is to reassess the molecular profile with tissue biopsy. This is even more important after osimertinib because the rates of histologic transformation seem to be reported at slightly higher rates and first- and second-generation drugs. You don’t want to miss a transformation to SCLC, squamous cell carcinoma, or pleomorphic undifferentiated cancers. Tumor biopsy is often a part of that.

Secondly, we need to assess how the disease progression is occurring. Is it relatively limited, with only 1 or 2 sites progressing, and the rest of the body is stable? In that case, one could consider continuing osimertinib. You could still...
interrogate the molecular profile, but you could continue osimertinib and consider a local approach of stereotactic radiation to take care of the misbehaving tumors. Some data suggest that you can get increased time on therapy with that approach.

However, if the disease is more disseminated, there is progression on multiple sites, or there is development of new lesion sites, you’re generally thinking about switching therapies. In that scenario, that molecular profile testing could help to either guide a patient to a clinical trial or consider off-label combination strategies that have been published in the literature.

Finally, the other thing to look at is the status of the brain. We know one of the best qualities of osimertinib is how well it controls central nervous system [CNS] disease because of its pharmacokinetic profile. In the case of a patient with systemic disease that is progressing, but CNS disease is controlled, you would typically combine osimertinib and start new chemotherapy to control the disease in the body. Some data have been published showing that the combination seems relatively tolerable, and in my own experience, that’s also what I’ve seen.

**What molecular markers do you envision will play a bigger role in future investigative efforts?**

The diversity of resistance after osimertinib is complicated, and it seems to be even more complex after being used in the frontline setting. It’s going to be a tailored approach. If you’ve seen an acquired fusion, such as RET or ALK, go after that. If you see acquired MET amplification, go after that. If you see C797S and if it’s in the context of T790M, depending on how those 2 mutations are sitting on the DNA strands, you can even potentially combine osimertinib with an older-generation TKI such as erlotinib and gefitinib.

There are also fourth-generation allosteric EGFR inhibitors that are emerging for [those patients with] triple-mutant EGFR-positive lung cancers. One of the things to consider as this area evolves is how to best inform oncologists who are treating these patients around the country.

At the 2021 [American Society of Clinical Oncology] Annual Meeting, we saw that the rates of testing in the frontline setting for metastatic lung adenocarcinoma [were] lower than what we want; they’re around 50%. There is a proportion of patients we’re missing who have actionable mutations and are not necessarily getting matched with targeted therapies.

However, something that is underestimated is when you do get genomic testing, [you need to interpret] the report. The reports are extremely complex. Education around performing testing is one thing, but the next step is to also think about what tools or resources we can provide oncologists around the country with, in terms of how to interpret these reports. That is challenging because of how quickly drug development is happening and all this technology that is allowing us to interrogate the tumors in these ways. It’s great, but then there is a lag in terms of how to keep up with that information.

**What combinations are under investigation in EGFR-positive lung cancer that you’re looking forward seeing results from?**

Patritumab deruxtecan is a HER3 body-drug conjugate, and HER3 is not necessarily a resistance mechanism, but for patients with EGFR TKI resistance it’s widely expressed; approximately 80% of patients will have evidence of HER3 expression by immunohistochemistry. It’s an interesting target for these patients. [Investigators] saw a good response rate in patients who had received prior osimertinib and platinum doublet chemotherapy, at around 40%. It really seemed to have an effect across the diversity of resistance mutations. That is an interesting and early observation for that therapy, and it will be notable if that plays out as more patients enroll.

**You mentioned that fourth-generation EGFR inhibitors are emerging. How do you see that potentially affecting the treatment of patients who develop resistance?**

The fourth-generation EGFR allosteric inhibitors are very exciting. They are a new class of EGFR drugs, and they’re not TKIs, monoclonal antibodies, or bispecific antibodies. These are really going to address that subset of patients with the problematic triple mutations. Fourth-generation drugs may be an avenue to really help those patients. There are EGFR-dependent mechanisms of resistance, but there are also other independent mechanisms of resistance and I’m curious what we’ll see in terms of that.
Serious adverse reactions occurred in ≥ 1 % of patients who received NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions whether on NUBEQA + ADT or ADT alone were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs. 11%), pain in extremity (6% vs. 3%) and rash (3% vs. 1%).

Clinically significant adverse reactions occurring in ≥ 2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs. 3.4% on placebo) and heart failure (2.1% vs. 0.9% on placebo).

**Drug Interactions**

**Effect of Other Drugs on NUBEQA** – Concomitant use of NUBEQA decreases darolutamide exposure, which may decrease NUBEQA concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates wherever possible. If used together, consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when dose reduction is not possible. Patients on BCRP substrates should be monitored more frequently for adverse reactions, and the dose of the BCRP substrate may need to be adjusted.

**INDICATION**

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

**IMPORTANT SAFETY INFORMATION**

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

**Adverse Reactions**

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

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NUBEQA®—Focus on both MFS and tolerability

40 MONTHS

PROVEN TOLERABILITY

SAME RATE OF PERMANENT DISCONTINUATION

NUBEQA®—proven to extend MFS, now with statistically significant OS

31% reduction in the risk of death with NUBEQA + ADT compared to ADT alone

Metastasis-free survival (MFS) was the primary endpoint. Overall survival (OS) was a key secondary endpoint. OS data were not mature at time of first analysis (57% of the required number of events). At final analysis, OS was statistically significant but median not reached. HR: 0.69 (95% CI: 0.53-0.88); P=0.003.1,3

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, or bone scan by BICR, unacceptable toxicity, or withdrawal.1,2

The most frequent reasons for permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%). The most frequent reasons for dose interruptions included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%). The most frequent reasons for dose reductions included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).1

3.3 with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure, which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed.

Effects of NUBEQA on Other Drugs – NUBEQA is an inhibitor of breast cancer resistance protein (BCRP) transporter. Concomitant use of NUBEQA increases the exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

NUBEQA®—proven to extend MFS, now with statistically significant OS

with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

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3.3 with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure, which may decrease NUBEQA activity. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

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NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

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

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

4 CONTRAINDICATIONS
None.

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

5.2 Lactation
There are no human data on the use of NUBEQA in pregnant females.

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

ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC). In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

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

Permanently discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%). Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%). Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA.

The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

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

Table 1: Adverse Reactions in ARAMIS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades ≥ 3 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>Rash</td>
<td>0.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia
2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

Table 2: Laboratory Test Abnormalities in ARAMIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades 3-4 %</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>20.0</td>
<td>4.0</td>
</tr>
<tr>
<td>AST</td>
<td>23.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16.0</td>
<td>0.7</td>
</tr>
</tbody>
</table>

1 The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.
2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on NUBEQA

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see Clinical Pharmacology (12.3)] which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see Dosage and Administration (2.2)].

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) Substrates
NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C_{max} of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug. Consult the approved product labeling of the BCRP substrate when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1)]. Animal embryo-fetal developmental toxicity studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

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

8.3 Females and Males of Reproductive Potential

Contraception
Males
Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1)].

Infertility
Males
Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 mL/min/1.73 m²). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

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

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the in vivo combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hyposeremia, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

17 PATIENT COUNSELING INFORMATION
Dosage and Administration
Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

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

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see Dosage and Administration (2.1)].

Embryo-Fetal Toxicity
Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see Use in Specific Populations (8.1)].

Advise male patients with female partners of reproductive potential to utilize effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].

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

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Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA
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6711000BS

Onvansertib Combination Aims to Improve Poor Prognosis in PDAC

**by KYLE DOHERTY**

**PATIENTS WITH PANCREATIC DUCTAL adenocarcinoma (PDAC) experience limited benefit with available first- and second-line second line of therapy. Investigators aim to greatly improve upon this standard of care with the initiation of a phase 2 trial (NCT04752696) on June 8, 2021.**

The study is designed to evaluate the safety and efficacy of the highly selective polo-like kinase 1 (PLK1) inhibitor onvansertib (PCM-075) in combination with nanoliposomal irinotecan (Onivyde), leucovorin, and 5-fluorouracil (5-FU) in adult patients with metastatic PDAC.

"PLK1 is a serine/threonine unique protein kinase that strongly promotes progression of cells through mitosis," explained Daniel H. Ahn, DO, in an interview with OncologyLive. "PLK1 is often overexpressed in solid tumors and has been associated with a poor prognosis. PLK1 inhibition results in the arrest of cell division and subsequent cell death. It has also been shown to impair the viability of KRAS-mutated cell lines in tumor cells with mutations in TP53 as well as KRAS. These findings suggest that PLK1 may be a potential target, specifically in those with KRAS-mutated solid tumors."

Ahn is the principal investigator for the trial and a consultant in the Division of Hematology/Oncology, Department of Internal Medicine at Mayo Clinic in Phoenix, Arizona.

**INITIAL SAFETY AND EFFICACY DATA**

Investigators are examining onvansertib in a phase Ib/2 trial (NCT03829410) in combination with FOLFIRI (leucovorin calcium, 5-FU, and irinotecan hydrochloride) and bevacizumab (Avastin) for the second-line treatment of adult patients with metastatic colorectal cancer (mCRC) harboring a KRAS mutation. The primary end point is the overall response rate (ORR) in patients who receive at least 1 cycle of treatment. Secondary end points include PFS and a reduction in KRAS allelic burden assessed by liquid biopsies.

In phase Ib, successive cohorts of 3 patients received onvansertib orally in escalating doses of 12 mg/m², 15 mg/m², and 18 mg/m² on days 1 to 5 every 2 weeks over 2 treatment courses (1 cycle). They received the agent in combination with FOLFIRI, plus 2400 mg/m² of 5-FU via intravenous (IV) infusion and 5 mg/kg of bevacizumab. In phase 2, patients will receive the recommended phase 2 dose (RP2D) of onvansertib orally in combination with FOLFIRI, 2400 mg/m² of 5-FU via IV infusion, and 5 mg/kg of bevacizumab, with treatment modifications or delays based on unresolved toxicity experienced during a previous cycle.

As of November 1, 2020, 6 patients have been treated with 12 mg/m² of onvansertib, 3 with 15 mg/m², and 6 with 18 mg/m². All patients dosed at 12 mg/m² and 15 mg/m² completed their first cycle, as well as 4 patients receiving the 18 mg/m² dose. Those currently on treatment included 1 at

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**FIGURE. Combination Therapy for Pancreatic Ductal Adenocarcinoma**

**Eligibility criteria**

- Histologically or cytologically confirmed metastatic pancreatic ductal adenocarcinoma
- Prior gemcitabine-based chemotherapy as first-line therapy for metastatic disease
- Progression after completion of neoadjuvant or adjuvant therapy of < 6 months in duration is considered 1 line of therapy for metastatic disease
- Has measurable disease according to RECIST 1.1, defined as at least 1 lesion that can be accurately measured in at least 1 dimension as > 20 mm with conventional techniques or as > 10 mm with spiral computed tomography scan
- ECOG performance status 0 to 1

**Trial design and treatment schedule**

<table>
<thead>
<tr>
<th>N = 40</th>
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<tr>
<td>1 cycle = 28 days</td>
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</table>

**End points**

**Primary**

- Overall response rate

**Select secondary**

- Adverse events
- Duration of response
- Overall response for patients who receive ≥ 2 treatment cycles
- Overall survival
- Disease control rate
the lowest dose and 2 at the highest dose. No patients who received 15 mg/m² of onvansertib are currently still on treatment.3

Of the 12 patients from phase 1b evaluable for efficacy, 5 achieved a partial response (PR). Confirmed PRs were seen in 4 patients and 1 went on to have curative surgery. Additionally, 8 patients experienced durable responses of at least 6 months (6.1-13.7 as of the data cutoff date).3

Investigators measured KRAS-mutant allelic frequency (MAF) by droplet digital polymerase chain reaction at baseline (cycle 1, day 1, predose) and on treatment (day 1 of cycles 2 to 9). Most evaluable patients (n = 10) had a KRAS variant detected at baseline, and clinical responses were observed across multiple KRAS variants, including the 3 most seen in CRC. The greatest decrease in KRAS MAF after the first cycle of treatment (~78% to ~100%) was observed in the patients who experienced PRs; the 2 patients who progressed showed a KRAS MAF of ~55% and ~26%.3

In terms of safety, the most common adverse effects (AEs) of any grade were neutropenia (n = 11), fatigue (n = 11), and nausea (n = 9). Only 9% of AEs were grade 3 or 4, and 4 patients experienced dose-limiting toxicities attributed to the 5-FU bolus. No major or unexpected toxicities were attributed to onvansertib and investigators determined that the 18-mg/m² dose exceeded the maximum-tolerated dose.3

Based on the updated data, the study investigators concluded that the combination of onvansertib and FOLRIRI is well tolerated and that 15 mg/m² would be further explored as the RP2D.3

“There’s been a lot of interest in targeting KRAS,” said Ahn. “KRAS is the most common oncogene that’s mutated in PDAC; it’s mutated in nearly all the tumors. We know that mutations in KRAS are central for growth. Activation of the RAS proteins contribute to tumorigenesis, treatment resistance, and metastasis. We’ve been working with Cardiff Oncology [who have] developed onvansertib, which has demonstrated activity against KRAS through the inhibition of PLK1.”

### DETAILS OF THE PHASE 2 TRIAL IN PATIENTS WITH PDAC

The phase 2, open-label, multicenter trial will enroll approximately 40 adult patients with histologically or cytologically confirmed metastatic PDAC across 6 sites in the United States. Eligible patients will have previously received 1 gemcitabine-based chemotherapy as a first-line therapy for metastatic disease and a maximum ECOG performance status of 1. Patients must also have adequate organ and bone marrow function and must be able to undergo a tissue biopsy at screening (FIGURE).4

Patients with prior irinotecan, nanoliposomal irinotecan, or investigational PLK1 inhibitor treatment will be excluded from the study. Additional ineligible patients include those with a history of interstitial pneumonitis or interstitial lung disease and those with uncontrolled intercurrent illness within 3 months of therapy. Patients with major bleeding within 4 weeks, have been treated with more than 1 prior chemotherapy regimen administered in the metastatic setting, or have undergone major surgical resection within 4 weeks prior to enrollment will also be excluded.4

In the safety lead-in portion of the study, the first 3 patients will receive onvansertib orally once a day at a dosing schedule of 12 mg/m² on day 1 to day 10 for 2 cycles, 2 weeks in length. Subsequent participants may be assigned alternate dosing schedules depending on the number of dose-limiting toxicities observed in the first 3 patients. Onvansertib will be combined with 70 mg/m² of nanoliposomal irinotecan, 400 mg/m² of leucovorin, and 2400 mg/m² of 5-FU.4

“Based on what we’ve observed in our study of patients with CRC, this treatment is well tolerated without any significant AEs,” Ahn noted. “Any [adverse] effects that were observed were reversed upon treatment discontinuation. The combination with chemotherapy appears to be safe and well tolerated.”

In the experimental treatment portion of the trial, patients will receive onvansertib orally at the dosing schedule selected based on the results of the safety lead-in, in cycles of 2 weeks. Nanoliposomal irinotecan, leucovorin, and 5-FU will again be administered at doses of 70 mg/m², 400 mg/m², and 2400 mg/m², respectively.4

The primary end point of the study is ORR by RECIST v1.1. Secondary and exploratory end points include DOR, median OS, ORR in patients receiving at least 2 treatment cycles, disease control rate, and assessment of KRAS allelic burden in liquid biopsies as measured by circulating tumor DNA. The estimated completion date of the trial is March 11, 2024.4

“If the combination does appear to be effective for patients with KRAS-mutant PDAC, which is more than 90% of patients, it would potentially represent another treatment strategy in the second-line setting,” Ahn concluded. “If [this regimen] is deemed to be effective in the second-line setting, the natural progression would be to examine this combination in the frontline setting. So far we’ve seen very encouraging results, at least in CRC, with several updates being presented at ASCO [American Society of Clinical Oncology] and ASCO GI [Gastrointestinal Cancers Symposium]. Hopefully, we should have the final results of this study in patients with CRC [soon. Although] these results can’t necessarily be extrapolated and compared to a different disease, the findings are very encouraging. We hope to see the same results in our PDAC study.”

### REFERENCES


3. Ahn DH, Ridinger M, Erlander M, et al. A phase Ib/II study of onvansertib orally at the dosing schedule selected based on the results of the safety lead-in, in cycles of 2 weeks. Nanoliposomal irinotecan, leucovorin, and 5-FU will again be administered at doses of 70 mg/m², 400 mg/m², and 2400 mg/m², respectively.4

Immunogenicity of COVID-19 Vaccines Boosts Seropositivity in Patients With Cancer

by KRISTI ROSA

HIGH RATES OF SEROCONVERSION have been observed with COVID-19 vaccination in patients with cancer, according to data from a study published in Cancer Cell. When utilizing a validated antibody assay against the SARS-CoV-2 spike protein, investigators reported a high seroconversion rate of 94% among 200 patients with cancer in New York City who had received a full dose of 1 of the FDA-authorized COVID-19 vaccines. Patients with solid tumors experienced an impressive seroconversion rate of 98% compared with a rate of 85% in those with hematologic malignancies, 70% in those who had received highly immunosuppressive therapies such as anti-CD20 agents, and 73% in those who had previously undergone stem cell transplantation. Notably, patients who received treatment with immune checkpoint inhibitors or hormonal therapies experienced seroconversion rates of 97% and 100%, respectively, following vaccination. Patients with hematologic malignancies have demonstrated lower immunogenicity and those who previously received immunosuppressive therapies appear to be less responsive (FIGURE).

“Our study, along with other emerging data, strongly highlights the continued need to vaccinate patients with a cancer diagnosis urgently and broadly, as vaccinations are likely to be highly effective,” the study authors wrote. “[Results also] highlight at-risk cohorts of patients, in particular patients with hematologic malignancies following receipt of immunosuppressive therapies such as stem cell transplantation, anti-CD20 therapies, and CAR [chimeric antigen receptor] T-cell treatments. These cohorts of patients could potentially benefit from passive immunization with anti-COVID-19 antibodies in the face of the ongoing pandemic.”

METHODOLOGY AND PATIENT CHARACTERISTICS
Investigators launched this study to develop a better understanding with regard to the immunogenicity of vaccines in a group of patients with a cancer diagnosis in New York City by examining the rates of antispike immunoglobulin G (IgG) antibody positivity after receiving 1 of the 3 authorized COVID-19 vaccines.

A total of 213 patients were enrolled to the study through an informed-consent process. Twenty-nine additional patients with cancer who received the SARS-CoV-2 spike IgG testing were identified through retrospective chart review. Eighteen patients did not have this test conducted following consent, and thus, they were excluded from the analysis. Twenty additional patients were excluded because they had their test done before having received full vaccination in accordance with FDA guidance; 4 patients were excluded for other reasons.

As such, 233 patients with cancer were noted to have received all required doses of their COVID-19 vaccine and were included in the safety analysis. A subset of 200 patients received the IgG test and were included in the immunogenicity analysis. Serological information from these patients were utilized in association studies between cancer subtypes and therapies.

Investigators also examined the link between the quantitative titer of SARS-CoV-2 spike IgG and cancer subtypes and therapies. Of the 200 patients, 185 had available IgG titers that were at least 2 days following the last vaccine dose. A total of 15 patients were excluded from the vaccination cohort with titers; these patients had received the vaccine, but titers were checked less than 1 week from their last dose.

Among those included in the efficacy analysis (n = 200), the median age was 67 years (range, 27-90), 58% were female, and 42% were male. The study population was noted to be representative of the diverse population that resides in the Bronx, New York, with 32% of patients identifying...
as African American, 39% as Hispanic, 22% as Caucasian, 5% as Asian, and 3% as other ethnicities.

Additionally, 67% of patients had a solid tumor diagnosis and 33% had a hematologic malignancy. Among those with solid tumors, 26% had breast cancer, 14% had gastrointestinal cancer, 9% had genitourinary cancer, 5% had gynecologic cancer, 13% had thoracic or head and neck cancer, 1% had skin or musculoskeletal cancer, and 1% had carcinoma of an unknown primary. Among those with hematologic malignancies, 13% had lymphoid disease, 9% had myeloid disease, and 11% had plasma cell disease.

Seventy-five percent of patients had an active malignancy and 67% were receiving active treatment at the time that they received the COVID-19 vaccine. Fifty-six percent of patients were on active chemotherapy. Moreover, 19% of patients were on active chemotherapy within 48 hours of receiving at least 1 of their COVID-19 vaccine doses.

Fifty-four percent of patients completed vaccination with the Pfizer vaccine, 31% with the Moderna vaccine, and 10% with the Johnson & Johnson vaccine. A total of 3 patients had received a complete mRNA vaccination series but the information regarding the type of vaccine (Pfizer vs Moderna) are not yet available.

**STRATIFIED EFFICACY RESULTS**

Additional findings from the study showed that significantly higher titer values were observed in solid tumors vs hematologic malignancies among a subgroup of 185 patients with available IgG titers longer than 7 days post vaccination, at a median of 7858 AU/mL vs a median of 2528 AU/mL, respectively ($P = .013$).

When comparing patients who were receiving active cancer treatment vs those who were not, no significant differences in seroconversion were reported, at 96% and 93%, respectively. However, investigators did report lower seropositivity rates in those who were on active cytotoxic chemotherapy vs other treatments, at 92% vs 99%, respectively ($P = .04$). Moreover, significantly lower seroconversion rates were also noted in those who received immunosuppressive therapies like stem cell transplant (73%; $P = .0002$), CD20 antibody therapy (70%; $P = .0001$), or CAR T-cell therapy (all seronegative; $P = .0002$).

Significantly lower titer levels were observed in patients who received CD20 antibody therapy vs the overall patient population, which underscored the susceptibility of patients receiving these treatments during the pandemic. No statistically significant associations between age, ethnicity, time since immunosuppressive therapy, steroid use, or treatment within 48 hours of a vaccine dose, and seropositivity were reported.

Although all patients who were receiving CDK4/6 inhibitor treatment demonstrated positive antispoke IgG test results, antibody titers were noted to be very low in this subset ($n = 5$), at a median of 1242 AU/mL vs a median of 6887 AU/mL in the overall cohort. “Given the known involvement of the CDK4/6 pathway in immune activation, this might be biologically plausible and warrants further studies into the impact of CDK4/6 inhibitors on vaccine efficacy,” the study authors wrote.

A trend to lower titers were also reported among subsets of patients who received BCL2 or Bruton tyrosine kinase inhibitors.

Among a subset of 22 patients with cancer who had previously been infected with COVID-19, the seroconversion rate was 95%. Notably, antibody titers in those who had prior infection with the virus were found to be significantly higher than those who did not have a known prior infection at a median of 46,737 AU/mL and a median of 5296 AU/mL, respectively ($P < .001$).

**REFERENCE**


**FIGURE.** Antibody Response in Patients With Cancer Following COVID-19 Vaccination

- **Low antibody response**
  - Hematologic malignancies
  - Anti-CD20 treatment
  - Stem cell transplantation
  - Chimeric antigen receptor
- **High antibody response**
  - Solid tumors
  - Prior COVID-19 infection

94% of individuals with cancer demonstrated seropositivity to COVID-19 vaccines.

- **Completed vaccination**
  - N = 200
  - 54%
  - 31%
  - 10%

- **Pfizer**
- **Moderna**
- **Johnson & Johnson**
"We have some unfinished business!"

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

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

Please see Important Safety Information and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
CYRAMZA as a single agent, or in combination with paclitaxel, is indicated for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

**Adding CYRAMZA to paclitaxel nearly doubles the response vs paclitaxel alone**

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel</th>
<th>Placebo + paclitaxel</th>
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<tbody>
<tr>
<td><strong>ORR (Complete and Partial Response):</strong></td>
<td><strong>Supportive Outcome Measure</strong></td>
</tr>
<tr>
<td>RAINBOW ORR: percent of patients (95% CI)</td>
<td>CYRAMZA + paclitaxel (n=330)</td>
</tr>
<tr>
<td><strong>28%</strong> (23.33)</td>
<td><strong>16%</strong> (13, 20)</td>
</tr>
</tbody>
</table>

Disease progression and tumor response were assessed by investigators in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

- 2 complete response in CYRAMZA-treated patients and 1 complete response in the placebo-treated patients

**CYRAMZA plus paclitaxel significantly extended OS and PFS**

<table>
<thead>
<tr>
<th>CYRAMZA + paclitaxel</th>
<th>Placebo + paclitaxel</th>
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<tbody>
<tr>
<td><strong>Overall Survival:</strong></td>
<td><strong>Major Outcome Measure Median-Months (95% CI)</strong></td>
</tr>
<tr>
<td>CYRAMZA + paclitaxel (n=330)</td>
<td>Placebo + paclitaxel (n=335)</td>
</tr>
<tr>
<td><strong>9.6 MONTHS</strong> (8.5, 10.8)</td>
<td><strong>7.4 MONTHS</strong> (6.3, 8.4)</td>
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</tbody>
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Hazard ratio=0.81 (0.68, 0.96); *P=0.017*

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

<table>
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<tr>
<th>CYRAMZA + paclitaxel</th>
<th>Placebo + paclitaxel</th>
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<tbody>
<tr>
<td><strong>4.4 MONTHS</strong> (4.2, 5.3)</td>
<td><strong>2.9 MONTHS</strong> (2.8, 3.0)</td>
</tr>
</tbody>
</table>

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

*median
CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; GEJ=gastroesophageal junction; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

**SELECT IMPORTANT SAFETY INFORMATION**

**GASTROINTESTINAL PERFORATIONS**

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

**IMPAIRED WOUND HEALING**

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

Please see Important Safety Information on next page and Brief Summary of Prescribing Information for CYRAMZA on subsequent pages.
Warnings and Precautions

Hemorrhage

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

Gastrointestinal Perforations

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

Impaired Wound Healing

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

Arterial Thromboembolic Events (ATEs)

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

Hypertension

- An increased incidence of severe hypertension occurred in patients receiving CYRAMZA. In 1161 patients with various cancers treated with CYRAMZA, the incidence of all Grade hypertension ranged from 11-26%. Grade 3-5 hypertension incidence ranged from 6-19%.
- Control hypertension prior to initiating treatment with CYRAMZA. Monitor blood pressure every two weeks or more frequently as indicated during treatment. Withhold CYRAMZA for severe hypertension until medically controlled. Permanently discontinue CYRAMZA for medically significant hypertension that cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

Infusion-Related Reactions (IRR)

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

Worsening of Pre-existing Hepatic Impairment

- Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatoportal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration.
- Based on safety data from REACH-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of hepatic encephalopathy and hepatoportal syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

Posterior Reversible Encephalopathy Syndrome (PRES)

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

Proteinuria Including Nephrotic Syndrome

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

Thyroid Dysfunction

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

Embryo-Fetal Toxicity

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

Lactation

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

Adverse Reactions

REGARD:

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

RAINBOW:

- The most common adverse reactions (All Grades) observed in patients treated with CYRAMZA with paclitaxel at a rate of ≥5% and ≥2% higher than placebo with paclitaxel were fatigue/asthenia (57% vs 44%), neutropenia (54% vs 31%), diarrhea (32% vs 23%), epistaxis (31% vs 7%), hypertension (25% vs 6%), peripheral edema (25% vs 14%), stomatitis (20% vs 7%), proteinuria (17% vs 6%), thrombocytopenia (13% vs 6%), hypercalcemia (11% vs 5%), and gastrointestinal hemorrhage events (10% vs 6%).
- The most common serious adverse reactions with CYRAMZA with paclitaxel were neutropenia (3.7%) and febrile neutropenia (2.4%), 19% of patients who received CYRAMZA with paclitaxel received granulocyte colony-stimulating factors.
- Adverse reactions resulting in discontinuation of any component of the CYRAMZA with paclitaxel combination in ≥2% of patients in RAINBOW were neutropenia (4%) and thrombocytopenia (3%).
- Clinically relevant adverse reactions reported in ≥1% and <5% of patients receiving CYRAMZA with paclitaxel were sepsis (3.1%), including 5 fatal events, and gastrointestinal perforations (1.2%), including 1 fatal event.

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

References:

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

Worsening of Pre-existing Hepatic Impairment
Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatic encephalopathy, was reported in patients with Child-Pugh B or C cirrhosis who received single agent CYRAMZA. Use CYRAMZA in patients with Child-Pugh B or C cirrhosis only if the potential benefits of treatment are judged to outweigh the risks of clinical deterioration. Based on safety data from REGARD and REGARD-2, in patients with Child-Pugh A liver cirrhosis, the pooled incidence of worsening of hepatic encephalopathy and hepatic encephalopathy syndrome was higher for patients who received CYRAMZA (6%) compared to patients who received placebo (0%).

Posterior Reversible Encephalopathy Syndrome
Posterior Reversible Encephalopathy Syndrome (PRE) (also known as Posterior Reversible Leukoencephalopathy Syndrome [PReLS]) has been reported in ~0.1% of 2137 patients enrolled in six clinical studies with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension. Confirm the diagnosis of PRES with magnetic resonance imaging and permanently discontinue CYRAMZA in patients who develop PRES. Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Proteinuria Including Nephrotic Syndrome
Across six clinical studies in 2137 patients with various cancers treated with CYRAMZA, the incidence of Grade ≥3 proteinuria ranged from 3-24%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%. Monitor proteinuria by urine dipstick and/or urinary protein creatinine ratio. If the result of the urine dipstick is >2 + or greater, perform a 24-hour urine collection for protein measurement. Withhold CYRAMZA for urine protein levels that are 2 or more grams per 24 hours. Reinitiate CYRAMZA at a reduced dose once the urine protein level returns to less than 2 grams per 24 hours. Permanently discontinue CYRAMZA for urine protein levels greater than 3 grams per 24 hours or in the setting of nephrotic syndrome.

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

Embryo-Fetal Toxicity
Based on its mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGFR to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CYRAMZA and for 3 months after the last dose.

ADVERSE REACTIONS

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the Warnings and Precautions section reflect exposure to CYRAMZA in 2137 patients from six studies: REGARD, RAINBOW, RAISE, RELAY-1, and RELAY-2.

Gastric Cancer
The safety of CYRAMZA was evaluated in REGARD and RAINBOW. Patients in both trials had locally advanced or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy. Patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Both trials excluded patients with uncontrolled hypertension, major surgery within 28 days, or patients receiving chronic anti-platelet therapy other than once daily aspirin. REGARD excluded patients with bilirubin >1.5 mg/dL and RAINBOW excluded patients with bilirubin >1.5 times the upper limit of normal (ULN). CYRAMZA was administered as a Single Agent (REGARD).

Patients receiving CYRAMZA 8 mg/kg or placebo intravenously every two weeks. Patients randomized to CYRAMZA received a median of 4 doses; the median duration of exposure was 8 weeks and 32 (14% of 238) patients received CYRAMZA for at least six months.

The most common serious adverse reactions with CYRAMZA were anemia (3.8%) and intestinal obstruction (2.1%). Red blood cell transfusions were given to 11% of CYRAMZA-treated patients versus 8.7% of patients who received placebo. The most common adverse reactions (all grades) observed in CYRAMZA-treated patients at a rate of ≥10% and ≥2% higher than placebo were hypertension and diarrhea. Table 1 provides the frequency and severity of adverse reactions (CTCAE, version 4.0) in REGARD.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CYRAMZA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 (%)</td>
<td>Grade ≤3 (%)</td>
<td>Grade ≤3 (%)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Metabolism and Nutrition

<table>
<thead>
<tr>
<th>Metabolism and Nutrition</th>
<th>Grade ≤3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>CYRAMZA + Paclitaxel</th>
<th>Placebo + Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 (%)</td>
<td>Grade ≤3 (%)</td>
<td>Grade ≤3 (%)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, Thoracic</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Vascular</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
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<td>Proteinuria</td>
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<tr>
<td>Lactate Dehydrogenase</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, Thoracic</td>
<td>32</td>
<td>4</td>
</tr>
</tbody>
</table>
Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to CYRAMZA with the incidences of antibodies to other products may be misleading.

In clinical trials, 96/2690 (3%) of CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Lactation

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

Females and Males of Reproductive Potential

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

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

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

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

Pediatric Use

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

Juvenile Animal Toxicity Data

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

Geriatric Use

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

Of the 221 patients who received CYRAMZA with erlotinib in RELAY, 119 (54%) were 65 and over, while 29 (13%) were 75 and over. Overall, no clinically meaningful differences in effectiveness were observed between these patients and younger patients. Adverse reactions occurring at a 10% or higher incidence in patients receiving CYRAMZA with erlotinib and with a 10% or greater difference between patients aged 65 or older compared to patients aged less than 65 years were: diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (32% versus 29%), increased AST (39% versus 31%), anemia (10% versus 6%), decreased platelet count (73% versus 65%), and weight loss (26% versus 20%).

Of the 1253 patients in REVEL, 455 (36%) were 65 and over and 84 (7%) were 75 and over. Of the 627 patients who received CYRAMZA with docetaxel in REVEL, 237 (38%) were 65 and over, while 45 (7%) were 75 and over. In an exploratory subgroup analysis of REVEL, the hazard ratios for overall survival in patients less than 65 years old was 0.74 (95% CI: 0.62, 0.87) and in patients 65 years and over was 1.10 (95% CI: 0.89, 1.36).

Of the 529 patients who received CYRAMZA with FOLFIRI in RAISE, 209 (40%) were 65 and over, while 51 (10%) were 75 and over. Overall, no differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

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

Additional information can be found at www.cyramza.com

RB-G HCP BS 03JUN2020

CYRAMZA® (ramucirumab) injection, for intravenous use
Addressing AYA Cancer Requires a Tailored Approach to Practice

by DEBORAH ABRAMS KAPLAN

INVESTIGATORS HAVE EXPANDED THE scientific understanding of cancer in the adolescent young adult (AYA) patient population over the past decade. However, unmet needs remain in establishing treatment standards, addressing unique survivorship challenges, and providing a framework for patients to reference as they navigate their challenges, and providing a framework for standards, addressing unique survivorship needs remain in establishing treatment

The AYA group, defined as patients aged 15 to 39 years, does not fall neatly into either the pediatric or adult cancer category. This population has different psychosocial and fertility needs, and their outcomes are not always tracked with the other populations. Because the health care system is not built to perfectly accommodate this age group, improvements in outcomes have historically lagged.

In terms of AYA care, Damon Reed, MD, a medical oncologist and program leader of the Adolescent Young Adult Program at Moffitt Cancer Center in Tampa, Florida, said, “You don’t think of [patients who are] 20 to 30 years [old] walking through the door.” The reality, however, is that 125 patients younger than 40 years walk into Moffitt Cancer Center every day, according to Reed, and oncologists see, on average, 6 new patients in this population daily.

Reed also serves as the interim chair of the Department of Individualized Cancer Management and the clinical codirector of the Center of Excellence for Evolutionary Therapy at Moffitt.

CANCER IN THE AYA POPULATION
This AYA age was defined by the National Cancer Institute (NCI) nearly 2 decades ago when researchers investigated outcomes data for different age groups. Data have shown that mortality rates changed little with this population from 1975 to 2000, with the least amount of improvement demonstrated in the 20 to 40 age range (< -1.5%).

From 2009 to 2018, mortality rates decreased 0.8% annually, according to the NCI Surveillance, Epidemiology, and End Results Program. Further, the data show that AYAs will account for 4.6% of all new cancer cases in 2021, with 88,260 cases new cases predicted annually.

Common cancer types in this age group are thyroid (16%), breast (15%), melanoma (8%), testicular (8%), and other (53%). In 2021, an estimated 9130 AYA patients will die from cancer, comprising 1.5% of all cancer deaths for any age.

A study of registry data from 1973 to 2015 showed that the diagnosis rate of cancer in AYA patients increased by 29.6% in this period (from 57 to 74 per 100,000). Results showed that among 497,452 patients, the most common cancer types in men were testicular, melanoma, and non-Hodgkin lymphoma, and in women were breast, thyroid, cervical, and uterine cancers. The authors noted that because patients were often grouped together with pediatric or adult patients for research studies, it was important to understand how this population was distinct to develop appropriate care guidelines for the rising case numbers.

HOW ONCOLOGY CENTERS ARE ADDRESSING AYA PATIENTS
Several factors make cancer in the AYA population a different experience than adult or pediatric cancer (TABLE 1–4). Fertility is the easiest difference to explain to others, Reed said. For many AYA patients, the time of their diagnosis is their first experience with the health care system, outside of routine care. Advocating for yourself in a health care system can be difficult, Reed noted, adding that a diagnosis of cancer may also be coupled with anxiety and depression.

The establishment of AYA cancer programs and services are one way in which providers can anticipate and potentially alleviate the avalanche of sudden needs without a patient needing to submit a request.

Cathy Eng, MD, the David H. Johnson Chair in Surgical and Medical Oncology at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee, said that although the average patient with colorectal cancer is 65 years or older and tends to be mostly or semi-retired with an established family and/or career, she also sees patients who are much

### TABLE. Considerations for AYA Cancer Care1,4

<table>
<thead>
<tr>
<th>Area of concern</th>
<th>Issues facing the AYA population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Most common malignancies (&gt;90%) include leukemias, lymphomas, sarcomas, melanoma, breast cancer, testicular cancer, colorectal cancer, thyroid cancer, and brain tumors.</td>
</tr>
<tr>
<td></td>
<td>There is a need for oncologists who can tackle a multidisciplinary role, serving as a bridge between pediatric and adult care.</td>
</tr>
<tr>
<td>Biology</td>
<td>Biologic and clinical behavior may differ for AYA patients, and age-specific molecular features are poorly understood.</td>
</tr>
<tr>
<td>Genetics</td>
<td>Standard-of-care approaches for adult or pediatric care may not apply.</td>
</tr>
<tr>
<td>Early diagnosis</td>
<td>Genetic counseling and testing for cancer prevention should be provided because AYA patients have a high percentage of pathogenic variants.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Pathways to diagnosis should be established, and education about early symptoms is essential.</td>
</tr>
<tr>
<td></td>
<td>Limited participation in clinical trials (range, 5%-34%) has been reported.</td>
</tr>
</tbody>
</table>

AYA, adolescent young adult.
younger and can have complicated cases. “Many of these AYA patients present with stage IV disease, as they may delay seeking care until long after noticing initial symptoms,” Eng said. “AYA patients are often embarking on new chapters in their lives, [such as] graduating college and starting new jobs or families. Job security, health insurance insecurity, and fertility concerns are top of mind in this group.”

Eng, who also serves as professor of medicine, codirector of gastrointestinal oncology, and coleader of the Gastrointestinal Cancer Research Program at Vanderbilt-Ingram Cancer Center, was told by one AYA patient that when he was in the waiting room before treatment, he could feel people staring at him—so he started wearing aviator glasses to deflect the looks. “I always remember that,” she said.

Eng wanted to start an AYA program for patients with cancer and finally got her chance after joining Vanderbilt; she helped establish the Vanderbilt-Ingram Cancer Center Young Adult Program in 2020. “How can I help these young patients from every possible perspective so they can go through their treatment feeling they have additional support, not just from their oncologists, but their community?” Eng asked, adding that her initial plan was to serve patients with colorectal cancer, but it expanded across tumor types after her colleagues wanted their patients to have support too.

This Vanderbilt-Ingram program offers patients consultations with people specializing in fertility, spiritual/religious needs, social work, and exercise and fitness programs. The program leverages both community and institutional support. For example, a former patient with lymphoma creates individual exercise programs and gives 12 weeks of free personal training to AYA patients seeking cancer treatment in Tennessee.

The clinical staff also talks with patients about their treatment objectives, as well as the financial implications of a cancer diagnosis. “Egg preservation is not necessarily covered by insurance companies,” Eng said, and younger patients may not have the resources for that. Patients fear the financial insecurity that can result from receiving a diagnosis because some are underinsured and may have job security issues due to treatment demands.

“All those things need to be discussed,” Eng said.

Reed and other clinicians at Moffitt launched a program for AYA patients in 2011. “When we started the program, our patients felt they were the only ones [in their age group],” Reed said. Despite securing initial funding, the monies were not allocated to help the patients directly because investors wanted to see the funds go toward research. “In my gut, I thought that was important, but the bigger need was for patients to feel less alone,” Reed said.

Moffit leaders decided to ask AYA patients what they wanted. “AYA patients hate support groups,” Reed noted, so they changed the name and organized a meetup. Social workers led guided discussions with patients and discovered that some patients were worried about their family members while others wanted more information about their cancer and treatment.

The mission of Moffitt’s AYA program is to improve the cancer care experience from diagnosis to survivorship. Ways in which the program addresses the long-term effects for this patient population include providing access to resources that will help them manage the emotional toll of cancer, helping them navigate access to cutting-edge clinical trials, hosting social events, and supporting advocacy efforts. Patients also have access to care providers to discuss fertility risks and options, as well as funding options, some of which are provided by Moffitt to offset sperm banking and egg retrieval. The program provides new patients with information and a user-friendly website, an on-site dedicated meeting space, and meetups for patients’ spouses or parents.

The NCI recommends that AYA patients with cancer be treated within an AYA oncology program. However, according to results of a survey in which 53 respondents from NCI-designated cancer centers participated, only half report having a dedicated AYA program.3 Of these, 70% of programs were

![Cathy Eng, MD](image)

**FIGURE.** AYA Cancer Snapshot

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>8%</td>
</tr>
<tr>
<td>Breast</td>
<td>16%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>53%</td>
</tr>
<tr>
<td>Testis</td>
<td>15%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
</tr>
</tbody>
</table>

AYAs, adolescent young adults.
started within the past 5 years. Only 4% of programs offer dedicated in-patient space, and 30% of the centers provide AYA-specific training to their staff members.

Twenty-one respondents were from community practices; of these, approximately 60% noted that they have an AYA program, and nearly 15% reported that they do not currently have one but plan to develop one. Of those surveyed, 62% said they provided good/excellent AYA care overall, but only 19% considered their AYA staff education good/excellent. Fertility, survivorship, and psychological services were all reported at 52%.

These programs, however, cost money, something that smaller practices may not have access to. Larger institutions, such as Moffitt, dedicate approximately 80% of their AYA philanthropy funding to research, which is collecting data on patient-reported outcomes, toxicity, and pain at various treatment and posttreatment points; findings will determine which unmet AYA needs to address going forward. The remaining funding pays for events, dedicated building space, and patient programs. Although Reed said he does not know if the program draws patients to Moffitt, those coming for a second opinion “can’t believe it exists.”

Eng noted that the Vanderbilt-Ingram Young Adult Program funding comes from grants.

MOVING FORWARD WITH AYA CARE
Reed said he is surprised AYA cancer has not had its breakout moment. Although not all cancer centers can have dedicated programs, he encourages small efforts, which will help this population immensely.

“Keep moving toward it,” he said.

An easy step is training. Moffitt trains every new staff member about AYA issues, and if nothing else, these patients get a smile when they walk in the door, Reed noted. Not every patient will want the services offered, but the services make a big difference to those who do. Reed said they used to send an email out to 2000 patients for an event, 8 people wouldn’t leave,” he said, noting how small victories add up. “We realized we changed 8 people’s lives.”

REFERENCES

Undercoding Has Medical Practices Leaving Money on the Table

by ALICE MCKEE, MD; and LOHITH REDDY

AS PHYSICIANS, WE ARE extremely proud of the work we do. Our work includes improving the quality of countless lives and involves maintaining, promoting and restoring health of those who seek our help.

But when it comes to getting paid for our work, we do not always take full advantage.

That often results from undercoding our Evaluation and Management (E/M) codes and sometimes not using current procedure terminology (CPT) codes for all services performed during a patient encounter.

There are a variety of reasons undercoding occurs. Among them:

• Clinicians are distracted by seeing numerous patients in a short period, leading them to forgo charting notes.
• Chart notes are often written in a way that does not take specific codes into account.
• Clinicians may not be aware that a single procedure–such as putting a cast on a patient’s arm–can include multiple codes and modifiers.
• Concern among providers that overly aggressive coding may trigger an audit by an insurer or recovery audit contractors (RACs), prompting them to be overly conservative when coding.

Compounding the issue, there have been significant changes in billing codes. This occurred in January, when the American Medical Association (AMA) substantially revised the guidelines of the E/M codes for outpatient visits, covering CPT codes 99202-99215.

The AMA’s intent in making these changes was to provide better direction and increased patient care through the reporting of services rendered or considered at the time of service. They also want providers to better utilize the time spent managing patient care and the medical decision-making process, rather than counting body systems in the exam.

The importance of the coding changes aside, they came at a particularly difficult time for providers. Medical practices were already struggling with the fallout from the COVID-19 pandemic. The financial risk of having coding rejected by payers increased exponentially.

As the world and the practice of medicine returns to something more closely resembling normal, it’s become increasingly clear that the financial future for medical practices will rely on a clearer focus on coding optimization and proper documentation to move that forward.
**Cellular Therapy Strategies Offer the Prospect of Deep Remissions for Multiple Myeloma**

by PHILIP MCCARTHY, MD; and JENS HILLENGASS, MD, PhD

**FOR MORE THAN A DECADE,** we’ve been able to approach multiple myeloma, in most cases, as a chronic disease treatable through long-term maintenance therapy. However, this disease has long been an outlier among cancer types.

Multiple myeloma is a primarily incurable disease but new treatment options—particularly newly approved cellular therapies—have opened the possibility for extending disease control for patients who would otherwise not have treatment options. As a result of these advances, we now have reason to move our eyes toward heightened goals of treatment.

Despite the availability of multiple treatment options, the majority of patients with multiple myeloma will have recurrent or progressive disease. Patients with newly diagnosed multiple myeloma who require therapy typically receive induction therapy with a combination of drugs to decrease tumor burden.

Multiple myeloma is a spectrum of disease. Monoclonal gammopathy of undetermined significance is an early plasma cell disorder that can progress to multiple myeloma or remain stable for years. Smoldering multiple myeloma is a more advanced form of early disease and may require therapy based on disease burden. Multiple myeloma requires induction therapy for patients who present with bone lesions, high serum calcium levels, renal insufficiency/failure and anemia.1

Standard treatment for newly diagnosed multiple myeloma typically involves a combination of glucocorticoids, immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs) and monoclonal antibodies (mAbs).

To deepen remission, induction therapy can be followed by high-dose therapy—usually with a melphalan-based treatment with autologous hematopoietic cell rescue, also known as autologous stem cell transplant. After transplant, patients typically receive maintenance therapy to prolong response to induction and high-dose therapy. An important consideration for patients who are eligible for transplant and elect to delay transplant is to have hematopoietic cells collected for future use.

Newly diagnosed patients with multiple myeloma who are transplant-ineligible patients—those who are frail or have significant comorbidities—should receive induction therapy and once response is achieved continue treatment with dose-reduced therapy to maintain that favorable response.

**CAR T JOINS THE OPTIONS FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA**

For patients whose disease continues to progress after multiple lines of treatment, it becomes progressively difficult to control multiple myeloma that is resistant or refractory to approved therapies. The FDA approval of the first chimeric antigen receptor (CAR) T-cell therapy in March 2021 for the treatment of relapsed/refractory multiple myeloma represented a significant advance.2,3 (SNAPSHOT)

Idecabtagene vilocilc (ide-cel; Abecma), targets BCMA, which is expressed by malignant as well as normal plasma cells. It is approved for patients with relapsed/refractory multiple myeloma after 4 or more prior lines of therapy, including treatment with an IMiD, a PI, and an anti-CD38 mAb.3

CAR T-cell therapy involves the insertion of a CAR into the T cell, targeting a cell surface molecule that is expressed by the myeloma cells. This form of gene therapy utilizes the T cell cytolytic capacity to target and eradicate the cancer cells.

The process involves using a patient’s own T cells for CAR insertion, which is achieved using a viral vector. The cells are obtained through leukapheresis, altered through insertion of the CAR and then expanded in the laboratory. The patient then undergoes lymphodepletion followed by infusion of these CAR-enhanced T cells. The lymphodepletion is thought to temporarily favor the expansion of the CAR T cells over the patient’s own T cells. The CAR T cells target myeloma cells, reducing tumor cell burden.

The toxicities associated with CAR T-cell products for multiple myeloma are similar to those of the CAR T products for lymphoma and include tumor lysis syndrome, cytokine release syndrome, and immune effector cell associated neurotoxicity syndrome. Other adverse effects include cytopenias as well as B cell aplasia, resulting in hypogammaglobulinemia because of the targeting of B cells. These toxicities can be managed but require early identification and treatment by the clinical team.

**INVESTIGATIONS UNDERWAY IN ROSWELL PARK’S LABS AND CLINICS**

Other CAR T-cell products are being evaluated in clinical trials, including 2 at Roswell Park. The products our
teams are investigating both target BCMA with different approaches to vector design and expansion in the laboratory. It remains to be determined how successful these CAR T-cell products will be for long-term control of relapsed/refractory multiple myeloma; however, this is an exciting new therapy that can be offered to patients for whom may not have many options left for control of the disease.

Our research team is devoted to understanding the biology of multiple myeloma as well as improving therapeutic outcomes. Maximilian Merz, MD, initiated a project using single-cell RNA sequencing on isolated malignant plasma cells as a postdoctoral research fellow at Roswell Park. The team behind that work observed that biopsies from standard bone marrow samples contained multiple myeloma cells that had important differences in molecular behavior when compared with multiple myeloma cells from osteolytic lesions—knowledge that will allow us to better understand the mechanisms of drug resistance that develop during multiple myeloma treatment. This research was presented during the 2020 American Society for Clinical Oncology Virtual Scientific Program and has been submitted for publication.

Hamn Mohammadpour, DVM, PhD, a Roswell Park postdoctoral fellow in the laboratory of Elizabeth Repasky, PhD, is leading a project to characterize the immune cells in bone marrow and osteolytic lesions. This study is ongoing and will allow us to characterize the mechanisms by which local immune suppression occurs during the development and treatment of multiple myeloma.

Investigators at Roswell Park aim to also develop strategies to reverse immune dysfunction to prevent infections as well as control the endogenous immune response to multiple myeloma. Mohammadpour is investigating how myeloma tumors prevent the immune system from recognizing and eradicating the cancer. He has an interest in both allogeneic and endogenous tumor killing—the former during allogeneic hematopoietic cell therapy and the latter during tumor immunotherapy.

Mohammadpour is also pursuing novel strategies for allogeneic CAR T-cell therapy. This approach, which is under investigation, uses an allogeneic T cell, modified to express a CAR, to prevent rejection and to prevent alloreactivity by the T cell against the host.

We’re proud to highlight these clinical, translational, and basic research projects because they all represent exciting opportunities to improve patient outcomes and provide novel therapies for our patients. Cellular therapies, along with promising new agents, will continue to allow us to develop strategies that will lead to long-term disease control and possibly cure.

**REFERENCES**


**SNAPSHOT. Idecabtagene Vicleucel for Multiple Myeloma**

**Mechanism of action:** The chimeric antigen receptor (CAR) construct includes an anti-BCMA scFv-targeting domain for antigen specificity, a transmembrane domain, a CD3ζ T-cell activation domain, and a 4-1BB costimulatory domain. Antigen-specific activation of idecabtagene vicleucel results in CAR-positive T-cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

**EFFICACY RESULTS IN THE KARMMA TRIAL (NCT03361748)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Idecabtagene vicleucel (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>72% (62%-81%)</td>
</tr>
<tr>
<td>sCR (95% CI)</td>
<td>28% (19%-38%)</td>
</tr>
<tr>
<td>VGPR (95% CI)</td>
<td>25% (17%-35%)</td>
</tr>
<tr>
<td>PR (95% CI)</td>
<td>19% (12%-28%)</td>
</tr>
<tr>
<td>MRD-negativity rate* in all treated patients (95% CI)</td>
<td>21% (13%-30%)</td>
</tr>
<tr>
<td>MRD-negativity rate* in patients achieving CR or sCR status (n=28) (95% CI)</td>
<td>75% (55%-89%)</td>
</tr>
<tr>
<td>Median DOR* for PR or better, months (n = 72) (95% CI)</td>
<td>11.0 (10.3-11.4)</td>
</tr>
<tr>
<td>Median DOR* for sCR, months (n=28) (95% CI)</td>
<td>19.0 (11.4-NE)</td>
</tr>
</tbody>
</table>

- CR, complete response; DOR, duration of response; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
- MRD negativity was defined as the proportion of patients with CR or stringent CR who are MRD negative at any time point within 3 months prior to achieving CR or stringent CR until the time of progression or death.
- Median follow-up for DOR was 10.7 months.

**ADVERSE EFFECTS IN THE KARMMA TRIAL**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Idecabtagene vicleucel (n = 127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>85%</td>
</tr>
<tr>
<td>Infections (pathogen unspecified)</td>
<td>51%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>45%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45%</td>
</tr>
<tr>
<td>Hypogammaglobulinemia</td>
<td>41%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>34%</td>
</tr>
<tr>
<td>Nausea</td>
<td>29%</td>
</tr>
</tbody>
</table>

**BOXED WARNING**

- Cytokine release syndrome
- Neurologic toxicities
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome

**Prior therapy refractory characteristics (%)**

- 85% Triple-class refractory
- 26% Pentarefractory
- 95% Anti-CD38 monoclonal antibody
- 92% Prior autologous stem cell transplantation

*Refractory to a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody.
*Refractory to 2 proteasome inhibitors, 2 immunomodulatory drugs, and an anti-CD38 monoclonal antibody.
The first and only EGFR TKI to help prevent disease recurrence or death

ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients\(^1\)\(^3\)

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

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

83% REDUCTION IN RISK of recurrence or death

**Control arm**: placebo. **TAGRISSO**: 80 mg orally, once daily. **HR**: 0.17 (95% CI: 0.12, 0.23); \(P<0.0001\)

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

- Patients in the ADAURA trial are treated with **ORAL TAGRISSO FOR 3 YEARS** or until disease recurrence or unacceptable toxicity\(^4\)

**INDICATION**

- TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test

**SELECT SAFETY INFORMATION**

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.7% of the 1479 TAGRISSO-treated patients. 0.3% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed

\(\text{TAGRISSO}\) is a registered trademark of the AstraZeneca group of companies. ©2021 AstraZeneca. All rights reserved. US-53002 4/21
† Median DFS was not reached for TAGRISSO (95% CI: 38.8, NE) and was 19.6 months (95% CI: 16.6, 24.5) for control arm.

• There are no contraindications for TAGRISSO.

TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer.

INDICATION

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients. The first and only EGFR TKI to help prevent disease recurrence or death.

The planned treatment duration was 3 years or until disease recurrence/unacceptable toxicity.1,2,4

• Patients in the ADAURA study design: Phase III, double-blind, randomized, placebo-controlled trial in 682 patients with completely resected stage IB, II, and IIA NSCLC with or without adjuvant chemotherapy. NSCLC patients had centrally confirmed EGFR mutations (exon 19 deletion or L858R mutation). Patients were stratified by stage (IB vs II vs IIA), EGFR mutation (exon 19 deletion or L858R), and race (Asian vs non-Asian). Patients were randomized to either TAGRISSO (n=339; 80 mg orally, once daily) or placebo (n=343). The maximum interval between surgery and randomization was 26 weeks with adjuvant chemotherapy and 10 weeks without adjuvant chemotherapy. The primary endpoint of the study was DFS by investigator assessment in stage II/IIIA patients. The secondary endpoints were DFS in the overall population (stage IB/II/IIIA), DFS rate at 2, 3, 4, and 5 years, overall survival (stage II/IIIA and overall population), safety, and health-related QoL. The planned treatment duration was 3 years or until disease recurrence/unacceptable toxicity.1,2,4

1-3

1-year DFS rate
28%
97%
78%
2-year DFS rate

6 12 18 24 30 36 42 48 54

DFS Probability
0
0.2
0.4
0.6
0.8
1
0.0
0.16 (95% CI: 0.10, 0.26) and for patients without adjuvant control arm=placebo.

Control arm † n=237

P <0.0001

83%
97%
78%
30%
5

• Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose.

INDICATIONS AND USAGE
Adjuvant Treatment of EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)
TAGRISSO is indicated as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in the full Prescribing Information].

First-line Treatment of EGFR Mutation-Positive Metastatic NSCLC
TAGRISSO is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test [see Dosage and Administration (2.1) in the full Prescribing Information].

Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC
TAGRISSO is indicated for the treatment of adult patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [see Dosage and Administration (2.1) in the full Prescribing Information].

DOSEAGE AND ADMINISTRATION
Patient Selection
Select patients with resectable tumors for the adjuvant treatment of NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions, or on exon 21 L858R mutations in tumor specimens [see Clinical Studies (14) in the full Prescribing Information]. Testing for the presence of the T790M mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing. Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen
The recommended dosage of TAGRISSO is 80 mg tablet once daily. If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

If treatment is interrupted due to disease recurrence, or unacceptable toxicity, or for up to 3 years.

Treat patients with metastatic lung cancer until disease progression or unacceptable toxicity.

Administration to Patients Who Have Difficulty Swallowing Solids
Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not disperse in 60 mL (2 ounces) of non-carbonated water only. If administration via nasogastric tube is required, disperse the tablet or ultrasonicate during preparation. Rinse the container with 120 mL of non-carbonated water only.

DOSAGE MODIFICATIONS
Cardiac (see Warnings and Precautions (5.3) in the full Prescribing Information)
For patients with heart conditions or baseline QTc interval greater than 500 msec on at least 2 separate ECGs, monitor heart rate-corrected QTc (QTcF) interval at baseline and during treatment, in patients with cardiac risk factors. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors.

Table 1. Recommended Dosage Modifications for TAGRISSO (cont’d)

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Adverse Reaction*</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (see Warnings and Precautions (5.6) in the full Prescribing Information)</td>
<td>Interstitial lung disease (ILD)/Pneumonitis</td>
<td>Permanently discontinue TAGRISSO.</td>
</tr>
</tbody>
</table>

Table 1. Recommended Dosage Modifications for TAGRISSO

* Adverse reactions graded by the National Cancer Institute Common Toxicity Criteria version 4.0 (NC-CTCAE v4.0). QTcF = QT Interval corrected for heart rate.

DRUG INTERACTIONS

Strong CYP3A4 Inducers
If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A4 inducer. Resume TAGRISSO at 80 mg 2 weeks after discontinuation of the strong CYP3A4 inducer [see Drug Interactions (7) and Clinical Pharmacology (12.2) in the full Prescribing Information].

OTHER PATIENT SAFETY INFORMATION

Cardiovascular Diseases

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1479 patients treated with TAGRISSO in clinical trials, 0.6% were found to have a QTcF > 500 msec, and 3.1% of patients had an increase from baseline QTcF > 60 msec [see Clinical Pharmacology (12.2) in the full Prescribing Information]. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTcF > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO if ILD is confirmed [see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information].

QTc Interval Prolongation
Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1479 patients treated with TAGRISSO in clinical trials, 0.6% were found to have a QTcF > 500 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia [see Dosage and Administration (2.4) in the full Prescribing Information].

Cardiovasculopathy
Across clinical trials, cardiovasculopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 3% of the 1479 TAGRISSO-treated patients; 0.1% of cardiovasculopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF) ≤ 10 percentage points from baseline and to less than 50% LVEF occurred in 3.2% of 1233 patients who had baseline and at least one follow-up LVEF assessment. In the ADAURA study, 1.5% (23/1529) of patients treated with TAGRISSO experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50%.

Conduct cardiac monitoring, including assessment of LVEF at during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO [see Dosage and Administration (2.4) in the full Prescribing Information].

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

Erythema Multiforme and Stevens-Johnson Syndrome
Postmarketing cases consistent with Stevens-Johnson syndrome (SJS) and erythema multiforme major (EMM) have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if SJS or EMM is suspected and permanently discontinue if confirmed.

Cutaneous Vasculitis
Postmarketing cases of cutaneous vasculitis including leukocytoclastic vasculitis, urticarial vasculitis, and IgA vasculitis have been reported in patients receiving TAGRISSO. Withhold TAGRISSO if cutaneous vasculitis is suspected, evaluate for systemic involvement, and consider dermatology consultation. If no other etiology can be identified, consider permanent discontinuation of TAGRISSO based on severity.

Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended dose of 80 mg once daily. Various studies in mice and rats did not indicate a risk to females of reproductive potential prior to initiating TAGRISSO.

Advising pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO for 6 weeks prior to the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose [see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information].

ADVERSE REACTIONS

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

Intestinal Lung Disease/Pneumonitis
[see Warnings and Precautions (5.1) in the full Prescribing Information]

QTc Interval Prolongation
[see Warnings and Precautions (5.2) in the full Prescribing Information]

Cardiovasculopathy
[see Warnings and Precautions (5.3) in the full Prescribing Information]

Keratolysis
[see Warnings and Precautions (5.4) in the full Prescribing Information]

Erythema Multiforme and Stevens-Johnson Syndrome
[see Warnings and Precautions (5.5) in the full Prescribing Information]

Cardiovasculopathy
[see Warnings and Precautions (5.6) in the full Prescribing Information]

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 in the Warnings and Precautions section reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in three randomized, controlled trials [ADAURA (n=337), FLAURA (n=293), and AURA2 (n=278)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study [AURA1 (n=173)] [see Warnings and Precautions (5) in the full Prescribing Information]. Among 1479 patients who received TAGRISSO, 81% were exposed for 6 months or longer and 60% were exposed for greater than one year. In this pooled safety population, the most common adverse reactions in ≥ 10 percentage of the 1479 TAGRISSO-treated patients were: diarrhea (47%), rash (45%), stomatitis (26%), fatigue (21%), and cough (20%). The most common laboratory abnormalities in ≥ 20% of 1479 patients who received TAGRISSO were leukopenia (36%), lymphopenia (36%), dry skin (32%), neutropenia (31%), decreased hemoglobin (27%), and increased aspartate transaminase (23%).

The data described below reflect exposure to TAGRISSO (80 mg daily) in 327 patients with EGFR mutation-positive metastatic NSCLC, and 558 patients with EGFR mutation-positive metastatic NSCLC in three randomized, controlled trials [ADAURA (n=337), FLAURA (n=293), and AURA2 (n=278)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.
**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in ADAURA**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=277)</th>
<th>PLACEBO (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Abnormality</strong> ¹</td>
<td>All Grades</td>
<td>Grade 3 or higher</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>44</td>
<td>3.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>25</td>
<td>2.3</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>24</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>20</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>NCI CTCAE v4.0</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or higher</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in ADAURA**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>44</td>
<td>3.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>25</td>
<td>2.3</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>24</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>20</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=279)</th>
<th>EGFR TKI comparator (gefitinib or erlotinib) (N=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Any Grade (%)</td>
<td>Grade 3 or higher (%)</td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>10</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Respiratory and Infection Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td><strong>Laboratory Abnormalities</strong> ¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>59</td>
<td>0.7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>51</td>
<td>0.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>41</td>
<td>10</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>30</td>
<td>0.7</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>26</td>
<td>1.1</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>22</td>
<td>1.1</td>
</tr>
<tr>
<td>Increased AST</td>
<td>21</td>
<td>0.7</td>
</tr>
<tr>
<td>Increased ALAT</td>
<td>16</td>
<td>0.4</td>
</tr>
<tr>
<td>Increased ALAT</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving EGFR TKI comparator (gefitinib or erlotinib) in FLAURA (cont'd)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory and Infection Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinical studies have been conducted to evaluate the safety of TAGRISSO (osimertinib) tablets, for oral use in patients with non-small-cell lung cancer (NSCLC) with EGFR T790M mutation-positive disease. TAGRISSO (osimertinib) tablets were granted accelerated approval by the U.S. Food and Drug Administration (FDA) on October 11, 2016, for the treatment of patients with EGFR T790M mutation-positive NSCLC who have progressed on or are intolerant to an EGFR TKI and have not received previous systemic treatment for advanced disease.

The safety of TAGRISSO was evaluated in ADAURA, a randomized, double-blind, placebo-controlled trial for the treatment of patients with EGFR exon 19 deletions or exon 21 L858R mutation-positive NSCLC who had complete tumor resection, with or without prior adjuvant chemotherapy. At time of DFS analysis, the median duration of exposure to TAGRISSO was 29.3 months.

SERIOUS ADVERSE REACTIONS OCCURRING IN ≥10% OF PATIENTS TREATED WITH TAGRISSO:

- **Abnormalities occurring in >10% of patients treated with TAGRISSO and placebo**:
  - Abdominal discomfort: 24.7%
  - Abdominal pain: 12.0%
  - Abdominal lower pain: 11.8%
  - Rash: 40.6%
  - Rash generalized: 32.1%
  - Rash erythematous: 18.7%
  - Rash macular: 12.2%
  - Rash papular: 12.2%
  - Rash pustular: 12.2%
  - Rash pruritic: 12.2%
  - Rash vesicular: 12.2%
  - Constipation: 15.0%
  - Diarrhea: 14.5%
  - Flatulence: 14.5%
  - Fatigue: 14.5%
  - Headache: 14.5%
  - Rash: 12.2%

**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in ADAURA**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TAGRISSO (N=277)</th>
<th>Placebo (N=343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or higher (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47</td>
<td>2.4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>32</td>
<td>1.8</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>12</td>
<td>0.3</td>
</tr>
<tr>
<td>Skins Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>40</td>
<td>0.6</td>
</tr>
<tr>
<td>Nail toxicity</td>
<td>37</td>
<td>0.9</td>
</tr>
<tr>
<td>Dry skin</td>
<td>29</td>
<td>0.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>18</td>
<td>0.3</td>
</tr>
<tr>
<td>Infection and Infestation Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13</td>
<td>0.6</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>0.6</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Table 3. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in ADAURA**

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>54</td>
<td>0</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>44</td>
<td>3.4</td>
<td>14</td>
<td>0.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>30</td>
<td>12</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26</td>
<td>6</td>
<td>0</td>
<td>10.3</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>25</td>
<td>2.3</td>
<td>30</td>
<td>0.9</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>24</td>
<td>1.3</td>
<td>14</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>20</td>
<td>1.8</td>
<td>16</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>NCI CTCAE v4.0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Grades</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or higher</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>10</td>
<td>2.2</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Respiratory and Infection Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving EGFR TKI comparator (gefitinib or erlotinib) in FLAURA (cont'd)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory and Infection Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4. Adverse Reactions Occurring in ≥10% of Patients Receiving EGFR TKI comparator (gefitinib or erlotinib) in FLAURA (cont'd)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory and Infection Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 7. Laboratory Abnormalities Worsening from Baseline in <20% of Patients in AURA3 (cont’d)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TARGRISSO (N=279)</th>
<th>Chemotheraphy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>43 0.4</td>
<td>79 3.1</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63 8</td>
<td>61 10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46 0.7</td>
<td>48 7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 2.2</td>
<td>49 12</td>
</tr>
</tbody>
</table>

Table 6. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TARGRISSO (N=279)</th>
<th>Chemotheraphy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>All Grades (%)</td>
</tr>
</tbody>
</table>

Gastrointestinal Disorders
- Diarrhea: 41 1.1 - 11 1.5
- Nausea: 16 0.7 - 49 3.7
- Stomatitis*: 19 0 - 15 1.5
- Constipation: 14 0 - 35 0
- Vomiting: 11 0.4 - 20 2.2

Skin Disorders
- Rash: 34 0.7 - 6 0
- Dry skin*: 23 0 - 4 0
- Nail toxicity¶: 22 0 - 1.5
- Pruritus*: 13 0 - 5 0

Respiratory, Thoracic and Mediastinal Disorders
- Cough: 17 0 - 14 0

Musculoskeletal and Connective Tissue Disorders
- Back pain: 10 0.4 - 9 0.7

Laboratory Abnormality
<table>
<thead>
<tr>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>43 0.4</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63 8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46 0.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 2.2</td>
</tr>
</tbody>
</table>
Novel Drug Sparks Hopes for Targeting HER3 in NSCLC and Beyond

by ANITA T. SHAFFER

ALTHOUGH ONCOGENIC ACTIVATION of the HER3 receptor has been identified as a significant source of drug resistance and treatment failure, efforts to develop therapies targeting this mechanism have so far fallen short. Now, patritumab deruxtecan, a novel antibody-drug conjugate (ADC), is emerging as a promising HER3-directed therapy in patients with non–small cell lung cancer (NSCLC) and perhaps other solid malignancies.

Patritumab deruxtecan monotherapy resulted in a 39% objective response rate (ORR) in patients with EGFR-mutated adenocarcinoma previously treated with anti-EGFR tyrosine kinase inhibitor (TKI) therapy and platinum-based chemotherapy, according to interim data from the phase 1 U31402-A-U102 study (NCT03260491) presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting. The median progression-free survival (PFS) was 8.2 months.

Those findings impressed lung cancer experts who participated in “Molecular Targets on the Horizon in Non–Small Cell Lung Cancer OncLive® Scientific Interchange & Workshop,” a panel discussion held on July 15.

“The median progression-free survival and response rate in the fourth line are far exceeding anything else we’ve seen before” in this setting, noted program moderator Paul A. Bunn Jr, MD, a 2014 Giants of Cancer Care® award winner in the lung cancer category.

Bunn is the James Dudley Chair in Cancer Research and a distinguished professor of medicine–medical oncology at the University of Colorado School of Medicine in Aurora.

Patients who participated in the study had a median of 4 prior lines of systemic therapy (range, 1-9), with 86% having received osimertinib (Tagrisso), a third-generation EGFR TKI that is the preferred first-line option for patients with EGFR-mutated NSCLC.

“I think the largest clinical need that we’re thinking about addressing right now in the context of the treatment paradigm in the United States is patients who’ve received prior osimertinib,” said panel member Christine M. Lovly, MD, PhD, who detailed the 2021 ASCO findings during the program.

Patritumab deruxtecan, also known as HER3-DXd and U3-1402, “is a very exciting drug” that generated responses in heavily pretreated patients regardless of HER3 protein expression and genomic resistance alterations, said Lovly, an associate professor of medicine and the Ingram Associate Professor of Cancer Research at Vanderbilt University in Nashville, Tennessee.

### TABLE. Ongoing Clinical Studies of Patritum Deruxtecan

<table>
<thead>
<tr>
<th>Trial description</th>
<th>Estimated enrollment/phase</th>
<th>ClinicalTrials.gov identifier/name if applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non–small cell lung cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER3-DXd monotherapy for patients in 3 cohorts: EGFR-mutated adenocarcinoma after prior EGFR TKI and platinum-based chemotherapy; squamous or nonsquamous without EGFR-activating mutations; EGFR-mutated with any histology other than combined SCLC and NSCLC</td>
<td>216 patients/phase 1</td>
<td>NCT03260491/U31402-A-U102*</td>
</tr>
<tr>
<td>Fixed-dose regimen of 5.6 mg/kg of HER3-DXd vs up-titration regimen from 3.2 mg/kg to 6.4 mg/kg in patients with metastatic or locally advanced EGFR-mutated NSCLC previously treated with osimertinib and platinum-based chemotherapy</td>
<td>420 patients/phase 2</td>
<td>NCT04619004 / HERTHENA-Lung01</td>
</tr>
<tr>
<td>HER3-DXd +/- osimertinib in patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletion or L858R mutation after osimertinib therapy and without prior treatment</td>
<td>252 patients/phase 1</td>
<td>NCT04676477 / U31402-A-U103</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER3-DXd in patients with HER3 high (IHC 3+, 2+) or HER3 low/negative (IHC 1+, 0) advanced or metastatic resistant/refractory CRC</td>
<td>80 patients/phase 2</td>
<td>NCT04479436/U31402-A-U202</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER3-DXd in patients with HER3-high (≥75% of tumor cells express HER3), HER2-negative, unresectable locally advanced or metastatic breast cancer that is HR-positive at time of diagnosis</td>
<td>100 patients/phase 2</td>
<td>NCT04965766 / ICARUS-BREAST</td>
</tr>
<tr>
<td>HER3-DXd in treatment-naive patients with HR-positive/HER2-negative early breast cancer</td>
<td>80 patients/phase 1</td>
<td>NCT04610528 / TOT-HER3</td>
</tr>
<tr>
<td>HER3-DXd in patients with metastatic breast cancer who have not received prior anti-HER2 therapy</td>
<td>120 patients/phase 2</td>
<td>NCT04699630 / BRE 354</td>
</tr>
<tr>
<td>HER3-DXd in patients with HER3-positive, HER2-negative, HR-positive previously treated metastatic breast cancer</td>
<td>184 patients/phase 1/2</td>
<td>NCT02980341/ U31402-A-J101*</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; HER3-DXd, patritumab deruxtecan; HR, hormone receptor; IHC, immunohistochemistry; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.

*Active but no longer recruiting participants.
“I’m really looking forward to future development of this drug as a potential mechanism to fill this unmet need of how we treat patients who develop acquired resistance to osimertinib therapy,” Lovly said. “[Investigators are] trying to fill this niche of how we treat EGFR TKI resistance across multiple potential genomic biomarkers of resistance. And I think they’ve hit the mark so far.”

The ongoing clinical development program for patritumab deruxtecan in EGFR-mutated NSCLC includes the phase 2 HERTHENA-Lung01 study (NCT04619004), which is comparing fixed and up-titration dosing schedules, and a phase 1 study (NCT04676477) that is evaluating the ADC in combination with osimertinib in patients with recurrent and treatment-naïve disease. Patritumab deruxtecan also is being studied in colorectal and breast cancers (TABLE).

In the broader context of anticancer research, Lovly said that much remains to be learned about HER activity. “We have studied the ERBB or HER family of receptors in human tumors for many, many years now, but I would say we are far from exhausting the therapeutic opportunities offered by inhibiting these receptors, either as a single receptor or in receptor pairs,” Lovly said.

**HER3’S ROLE IN CANCER**

HER3 is one of 4 receptor tyrosine kinases (RTKs) that make up the HER family. Found predominantly on the surface of epithelial, mesenchymal, and neuronal cells, these receptors are key players in the transduction of intracellular signals that regulate normal cell growth and differentiation via binding of a wide range of different ligands.4-6

Discovered 30 years ago, HER3 is unique among HER family members because it is a pseudokinase.1 Typically upon ligand binding, RTKs pair up with either another receptor molecule of the same type (homodimerization) or a different kind of RTK (heterodimerization). This causes a conformational change in the second receptor molecule and triggers its tyrosine kinase activity. Because it has limited kinase activity, HER3 cannot signal through homodimers; its activity therefore relies on the formation of heterodimers with other members of the HER family, predominantly HER2.4-4

HER3 is activated by 2 ligands, HRG1 and HRG2, both members of the heregulin protein family (also referred to as neuregulins NGR1 and 2, respectively). Following ligand binding and heterodimerization, HER3’s kinase partner is activated and phosphorylates tyrosines within the intracellular domain of HER3.7,8 These phosphorylated tyrosines form a binding platform for a host of key proteins that subsequently trigger downstream signaling cascades, including in the PI3K/AKT, MAPK, and JAK/STAT pathways.4-4 Preclinical studies also have shown that HER3 promotes drug resistance by upregulating HER3 in cancer cells resistant to EGFR TKIs.9 (FIGURE 1)

HER3 overexpression has been noted in many types of cancer, including breast, gastric, colorectal, bladder, prostate, and ovarian, as well as NSCLC, head and neck squamous cell carcinoma, and melanoma.5,6

However, the precise function of HER3 overexpression across these tumor types is not entirely clear; questions remain regarding whether and exactly how it might operate as a driver of cancer. The most solid evidence has been observed in breast and lung cancers, in which the tumor-promoting role of HER3 overexpression has been shown to be predominantly in its capacity as a partner for HER2 and EGFR, respectively.4-6,10

In NSCLC, HER3 overexpression in primary tumors has been significantly associated with metastatic progression ($P = .006$) and decreased relapse-free survival time ($P = .013$). Investigators detected HER3 expression via immunohistochemistry (IHC) analysis in 82.7% of 148 NSCLC samples, with intensity levels classified as negative, intermediate, or strong. The prevalence of strong HER3 expression was 9.1% in primary tumors vs 35.3% in brain metastases.11

**THE MAKING OF AN ADC**

Despite the rationale for HER3 inhibition, more than a decade of research has not yet produced an FDA-approved drug with this mechanism. Because HER3 has limited intrinsic kinase activity, small-molecule kinase inhibitors are unlikely to be useful, leading investigators to explore development of HER3-targeted monoclonal antibodies (mAbs). However, most HER3 mAbs evaluated in clinical studies demonstrated limited activity, so the focus has shifted to novel designs such as ADCs (FIGURE 2).1,6

The development arc of patritumab deruxtecan illustrates this trend. Daiichi Sankyo Company, Limited initially sought to develop patritumab (U3-1287), a fully human anti-HER3 mAb that forms the antibody component of the ADC.

As a naked mAb, patritumab demonstrated disease stabilization as the best response in a first-in-human phase 1 study (NCT00730470) in 57 patients with advanced...
solid tumors, including 20 participants with NSCLC. Overall, 24.6% of participants had stable disease and 40.4% had progressive disease.12 In breast cancer, the combination of patritumab plus trastuzumab (Herceptin), an anti-HER2 mAb, resulted in an ORR of 38.9% (95% CI, 20.3%-61.4%), including 2 complete responses (CRs), and a median PFS of 274 days among 18 patients with HER2-overexpressing metastatic disease, according to findings from a phase 1b study (JapicCTI-121772) conducted in Japan.13

Patritumab advanced to phase 3 testing in combination with erlotinib (Tarceva) in patients with previously treated locally advanced or metastatic EGFR wild-type NSCLC in the HER3-Lung study (NCT02134015). However, Daiichi Sankyo halted the study in May 2016 after the combination failed to meet the efficacy criteria of superior PFS in participants with high heregulin expression.14 The median PFS was 1.9 months (80% CI, 1.4-3.0) in 47 patients treated with the patritumab-erlotinib combination vs 2.7 months (80% CI, 1.7-2.9) in 48 patients who took erlotinib plus placebo.15

Scientists in Japan subsequently engineered patritumab deruxtecan by joining the mAb with a topoisomerase I inhibitor payload (deruxtecan) via a tetrapeptide-based cleavable linker. In preclinical studies, the novel agent showed promising antitumor activity in mouse models, including patient-derived xenografts, and a tolerable safety profile in tests conducted in rats and monkeys.16 The experiments showed that the ADC inhibited HER3-activated signaling similar to the naked antibody patritumab while the deruxtecan released into HER3-expressing cells promoted cytotoxic activity through DNA damage and apoptosis induction. The investigators concluded that the activity of the drug was “driven by HER3-mediated payload delivery via high internalization into tumor cells.”16

Moreover, the design uses the same linker-payload technology that Daiichi Sankyo developed for fam-trastuzumab deruxtecan-nxki (Enhertu), a HER2-directed ADC.16 The FDA has approved the drug for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting and for patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma previously treated with a trastuzumab-based regimen.17

**PROMISING NSCLC FINDINGS**

In targeting HER3 in NSCLC, investigators are seeking to improve upon current treatment options for patients with disease progression on prior EGFR TKI therapy. Platinum-based chemotherapy for these patients yields a PFS ranging from 2.7 to 6.4 months, and salvage therapies have shown a PFS of 2.8 to 3.2 months, Pasi A. Jänne, MD, PhD, said in presenting the patritumab deruxtecan findings at 2021 ASCO.2 Moreover, there is a wide variation of genomic alterations associated with EGFR TKI resistance, with differing genomic profiles after first-line therapy with erlotinib, gefitinib (Iressa), or afatinib (Gilotrif), second-line therapy with osimertinib, and first-line treatment with osimertinib.

“The resistance mechanisms are diverse. They include on-target mechanism resistance, as well as bypass alterations. And importantly, in many patients, especially those treated with first-line osimertinib, no identifiable resistance mechanism is often found,” said Jänne, director of the Lowe Center for Thoracic Oncology, the Belfer Center for Applied Cancer Science, and the Chen-Huang Center for EGFR Mutant Lung Cancers at Dana-Farber Cancer Institute in Boston, Massachusetts.

In U31402-A-U102, Jänne and colleagues established a recommended dose for patritumab deruxtecan of 5.6 mg/kg every 3 weeks in 21-day cycles during the study’s dose-escalation phase. In the dose-expansion phase, the agent is being evaluated in 3 cohorts of patients: (1) *EGFR*-mutant adenocarcinoma with prior EGFR TKI therapy and platinum-based chemotherapy; (2) squamous or nonsquamous NSCLC without *EGFR*-activating mutations; and (3) *EGFR*-mutated NSCLC of any histology other than combined small cell lung cancer and NSCLC.

After a median follow-up of 10.2 months (range, 5.2-19.9), the ORR was 39% (95% CI, 20.3%-61.4%), including 2 CRs, and a median PFS of 274 days among 18 patients with HER2-overexpressing metastatic disease, according to findings from a phase 1b study (JapicCTI-121772) conducted in Japan.13

**FIGURE 2. Components of an Antibody-Drug Conjugate**

This illustration shows the basic mechanisms of antibody-drug conjugates such as patritumab deruxtecan, which targets HER3. Recreated under a Creative Commons license from Yonesaka K. Cancers (Basel). 2021;13(5):1047. doi:10.3390/cancers13051047
26%-52%), including 1 CR among 57 patients who received the recommended dose in cohort 1 and in the dose-escalation phase. The median PFS was 8.2 months (95% CI, 4.3-8.3), the median time to response was 2.6 months (range, 1.2-5.4), and the median duration of response (DOR) was 6.9 months (95% CI, 3.1-not evaluable [NE]).

In a subgroup of 44 patients in the same cohort who received prior osimertinib and platinum-based chemotherapy at the recommended dose, the findings were similar: an ORR of 39% (95% CI, 24%-55%), including 1 CR; a median PFS of 8.2 months (95% CI, 4.0-NE); a median time to response of 2.7 months (range, 1.2-5.4); and a median DOR of 7.0 months (95% CI, 4.0-NE).

Of note, patritumab deruxtecan generated antitumor responses in patients with varied mechanisms of EGFR TKI resistance such as EGFR-activating mutations and amplification, as well as mutations and fusions involving other genes. Moreover, responses were reported across a wide range of baseline HER3 H-scores, an IHC analysis of membrane HER3 expression in pretreatment biopsy tissue. HER3 was expressed in all evaluable patients, for whom the median H-score was 180 (range, 2-280).

In a safety analysis of patritumab deruxtecan therapy among 81 patients treated across all dosing levels, the incidence of treatment-emergent adverse events (TEAEs) of grade 3 or greater severity was 64%, with the most prevalent TEAEs including a decrease in platelet and neutrophil counts, fatigue, and anemia. There were 4 cases (5%) of interstitial lung disease, none of which were grade 4 or 5 severity. Overall, 7 patients (9%) discontinued treatment due to TEAEs, which included 2 cases of fatigue and 1 each of nausea, decreased appetite, interstitial lung disease, decreased neutrophil count, pneumonitis, and upper respiratory tract infection.

**NEED TO REFINE BIOMARKERS**

During the program, panel members said they were intrigued by the responses seen in patients with low levels of HER3 protein expression.

“Does this reflect on the design of the ADCs, meaning if there are more payloads that are delivered per molecule, could that help promote more of these patients to respond, even with low levels of targets?” Erin Schenk, MD, PhD, an assistant professor of medicine at the University of Colorado School of Medicine in Aurora, asked.

“That’s a great question,” Lovly responded, adding she was not certain of the answer. “We tend to focus on the target of the antibody but also need to think about how the linker is cleaved in the tumor microenvironment and into the tumor cell. We need to think about the totality of these molecules, not just what they’re targeting on the tumor cell itself, but how that target on the tumor cell is then going to be downregulated and trafficked through the cell; how the linker is going to be cleaved within the tumor, because you can imagine a scenario if you don’t get the cleavage, you’re not going to deliver the payload; and then how different tumors metabolize the payload in different ways.”

Ferdinandos Skoulidis, MD, PhD, MRCP, wondered about using the H-score, which factors in intensity of staining and the percentage of positive cells, to assess HER3 expression. The biomarker could be refined if the extent or uniformity of HER3 staining was assessed, suggested Skoulidis, an assistant professor at The University of Texas MD Anderson Cancer Center in Houston.

“We really need something a little bit more sophisticated than immunohistochemistry to look at the biomarker itself and then really need to think about the receptor coupling and how that’s playing into response as well,” Lovly agreed, noting EGFR and HER3 receptor coupling as an example.

“We really need a lot of rigorous correlative science and preclinical studies to understand how exactly these drugs are working,” she added. “We’re so used to thinking about small molecules now in terms of actionable biomarkers and predicting how the small molecules work. I think we need to reshape our paradigms for studying antibodies in terms of oncogenic signaling and how we’re going to understand resistance, and importantly, how we’re really going to understand efficacy.”

*Jane de Lartigue, PhD, a freelance medical writer, contributed information to this article.*

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

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**Molecular Targets on the Horizon in Non–Small Cell Lung Cancer OncLive® Scientific Interchange & Workshop**

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- TROP-2 expression
- SHP2 inhibition
- KEAP1/NRF2 mutations
- HER3 expression
- TGFβ signaling

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  University of Colorado School of Medicine

**Panelists**

- Hossein Borghaei, DO, MS
  Fox Chase Cancer Center
- Gina DeNicola, PhD
  Moffitt Cancer Center
- Christine M. Lovly, MD, PhD
  Vanderbilt University Medical Center
- Joshua E. Reuss, MD
  Georgetown Lombardi Comprehensive Cancer Center
- Erin Schenk, MD, PhD
  University of Colorado Anschutz Medical Center
- Ferdinandos Skoulidis, MD, PhD, MRCP
  The University of Texas MD Anderson Cancer Center
EARLY-STAGE HORMONE RECEPTOR–POSITIVE, HER2-negative breast cancer is generally associated with a good prognosis; however, even with early intervention, some patients recur and have reduced survival. This has led to the development of a variety of molecular profiling tools to determine patients’ risk of recurrence, including distant metastases, and the search for better adjuvant treatments to prevent such events in these patients.

During a recent OncLive Peer Exchange®, a panel of breast cancer experts discussed data surrounding a variety of genomic assays that are being used and investigated toward individualized treatment planning, enabling escalation of treatment in at-risk patients and de-escalation strategies for those unlikely to benefit. They also discussed some of the latest data for CDK4/6 inhibitors in the adjuvant treatment setting. “In the next 5 years, we’re going to see more precision medicine in breast cancer,” Aditya Bardia, MD, MPH, said. “It’ll be about the right drug for the right patient based on understanding tumor biology at the right time,” he added, noting that breast cancer is “the poster child for precision medicine” because treatment is already heavily influenced by molecular markers.

UNRAVELING MOLECULAR MARKERS
The panelists discussed various efforts that are being made to better understand the biology of early-stage breast cancer, focusing on 3 frequently used genomic assays: Oncotype DX, MammaPrint, and the Breast Cancer Index (BCI) (Table 1).1-7

Oncotype DX
Oncotype DX, a genomic test for patients with early-stage invasive breast cancer, measures the expression of 21 genes—including 16 cancer-related genes and 5 reference genes—to determine a patient’s recurrence score (RS). The score is then used to classify the tumor as low, intermediate, or high risk.1 Investigators of the SWOG S1007 RxPONDER trial (NCT01272037) evaluated the benefit of chemotherapy in women with hormone receptor–positive, HER2-negative breast cancer and 1 to 3 positive lymph nodes.2 Results of the study showed that postmenopausal women with a 21-gene recurrence score (RS) no greater than 25 per the Oncotype DX assay derived no benefit from the addition of chemotherapy to endocrine therapy, whereas premenopausal women meeting the same criteria had an approximate 45% relative risk reduction in invasive disease-free survival (iDFS) events when chemotherapy was added to endocrine therapy.

“Recent data that have come out from RxPONDER help us understand that patients who are premenopausal and have node-positive disease, pending further subset analyses of the RxPONDER trial, really everyone who is premenopausal should be considered for chemotherapy at this time,” Nicholas McAndrew, MD, MSCE, said.
Prior to the data from RxPONDER, I tended to use the Oncotype DX assay for my node-negative patients, and I would consider using the MammaPrint for my node-positive patients with 3 or fewer nodes. However, in the setting of RxPONDER, there are good data that are predictive for both node-negative and node-positive disease with the use of Oncotype,” McAndrew said. Although several panelists agreed that the default position based on the RxPONDER data should be to give chemotherapy to all premenopausal women with early-stage hormone receptor-positive, HER2-negative, node-positive disease, Hope S. Rugo, MD, FASCO, cautioned against this one-size-fits-all approach, especially since the data are still in their infancy. “Giving a patient who has 1 positive node and a recurrence score of 2 chemotherapy, including an anthracycline and a taxane, doesn’t really make sense to me,” she said, emphasizing the importance of considering the long-term toxicities of chemotherapy. “With anthracyclines, the long-term serious consequences are low, but even a low risk isn’t worth it if you don’t need it,” she said.

**MammaPrint**

MammaPrint is a genomic test that analyzes the activity of 70 of the most important genes associated with breast cancer recurrence to determine relapse risk for women with early-stage breast cancer, based on their tumor profile. At the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting, data for a relatively recent subclassification, dubbed ultralow risk, were presented.

The analysis included patients who had a score of at least 0.355 on MammaPrint, a cutoff that had been previously identified and found to be associated with an “exceedingly low risk” of death from breast cancer after surgery alone in women who were followed for 2 decades. The results confirmed these findings, showing women with ultralow-risk disease who participated in the randomized phase 3 MINDACT trial (NCT00433589) to have a breast cancer-specific survival greater than 99%, regardless of their clinical risk status. Further, the results also showed an 8-year distant metastasis-free interval of 95% to 98%. Based on the findings, the study investigators concluded that “patients with ultralow-risk tumors could be candidates for further de-escalation of treatment,” which might help prevent overtreatment and reduce the risk of treatment-related adverse events.

**Breast Cancer Index**

BCI analyzes the activity of 11 genes that can indicate how likely the cancer will recur 5 to 10 years after diagnosis. The results of the assay provide a recurrence percentage as well as an answer as to whether the patient is likely to benefit from an additional 5 years of hormone therapy, which is indicated as yes or no. During 2021 ASCO, data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 study (NCT00382070) were presented, which examined the effect of the BCI HOXB13/IL17BR ratio (BCI-H/I) in predicting benefit with extended aromatase inhibitor therapy with letrozole. The BCI-H/I ratio has been previously shown to be predictive of benefit to endocrine and extended endocrine therapy.

“If a patient had a high-risk score and you gave extended-duration aromatase inhibitor therapy, [as you might expect] you saw the benefit later…because you get a carry-over from your first 5 years for the first few years [post treatment],” Rugo said, adding that using the ratio “suggests that you may benefit from additional endocrine therapy.”

### TABLE 1. Genomic Assays for Patients With Early-Stage Breast Cancer

<table>
<thead>
<tr>
<th>Genomic assay</th>
<th>Genes analyzed</th>
<th>Information</th>
<th>Results</th>
<th>Trials with supportive data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td>21 (16 cancer-related genes and 5 reference genes)</td>
<td>Recurrence Benefit from additional chemotherapy</td>
<td>Recurrence score (0-100) Low (0-25) Low (0-25) Low (0-25) Low (0-25)</td>
<td>RxPONDER (NCT01272037)</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>70</td>
<td>Recurrence Benefit from additional chemotherapy</td>
<td>Traditional: low risk or high risk Exploratory: ultralow risk</td>
<td>MINDACT (NCT00433589)</td>
</tr>
<tr>
<td>Breast Cancer Index</td>
<td>11</td>
<td>5-to-10-year recurrence risk Benefit from additional endocrine therapy</td>
<td>Calculated risk percentage Yes or no answer</td>
<td>IDEAL (Netherlands Trial Register, [NTR3077]; Dutch Breast Cancer Research Group [BOOG 2006-05]; and Eudra-CT 2006-003958-16) National Surgical Adjuvant Breast and Bowel Project (NSABP) B-42 study (NCT00382070)</td>
</tr>
</tbody>
</table>
be differentiating the group of patients who benefit from longer-term aromatase inhibitor therapy, but that we’re going to need even longer follow-up of the NSABP trial to really understand that true benefit.”

The panelists agreed that while the genomic tests are important, they provide a static snapshot and more dynamic testing is needed. “Mutation profiling is only a first step…We should aggressively pursue full profiling of tumors at the time of diagnosis, with serial profiling as the patient proceeds through therapy, which hopefully, with incorporation of machine learning approaches, will help us develop decision support systems that can help busy oncologists make these decisions in a more comprehensive way using the totality of data,” Dejan Juric, MD, said.

**CDK4/6 Inhibitors**

Despite early-stage hormone receptor–positive, HER2-negative breast cancer being associated with the best outcomes among all breast cancer subtypes, an estimated one-third of patients will relapse,9 which has led to a search for novel treatment approaches. Because CDK4/6 inhibitors have changed the treatment paradigm for metastatic hormone receptor–positive, HER2-negative breast cancer, with benefit observed in both progression-free survival (PFS) and overall survival (OS), there has been a lot of excitement about using them in the adjuvant setting. However, recent data have been mixed, Andrew D. Seidman, MD, explained. “PALLAS [data] were a bit of a letdown compared with the practice-changing data observed in the metastatic setting, Bardia explained that there are several key differences in these settings that may help account for the disparity. First, he said that the mechanism of action may play a role, as these agents work by blocking cell proliferation. “If a patient has metastatic disease in general, that’s a cell that’s proliferating. But in the adjuvant setting, particularly for ER [estrogen receptor]-positive disease, cells could be dormant…if the cells are dormant, CDK4/6 inhibitors are unlikely to have an impact,” Bardia said.

Another factor may be treatment duration. “In the metastatic setting, we don’t stop the CDK4/6 after 6 months, 1 year, or 1.5 years. We continue until disease progression,” he said. In contrast, the trials in patients with early-stage disease had set durations. “What we saw from PENETOPE was that when you’re using the CDK4/6 inhibitors, it can put the brakes on, but when you stop the CDK4/6 inhibitor, the cells maybe started proliferating again and you start seeing the recurrences,” he said. Subsequently, Bardia explained it will be important to identify biomarkers to guide treatment duration.

Finally, he said adherence is another key challenge in the adjuvant setting. “In the metastatic setting in general, patients continue therapies unless there is severe toxicity, but in the adjuvant setting, we have patients who discontinue aromatase inhibitors and now you’re adding a second agent. We saw in PALLAS that about 50% of patients discontinued an aromatase inhibitor plus palbociclib. If you don’t use the drug, you’re not going to see the benefit,” he said.

**Abemaciclib**

In a subanalysis of the phase 3 monarchE trial (NCT03155997), abemaciclib showed benefit in patients with high-risk, early-stage, hormone receptor–positive, HER2-negative breast cancer previously treated with neoadjuvant chemotherapy.11 Patients were deemed high risk if they had at least 4 positive lymph nodes or 1 to 3 positive lymph nodes and either grade 3 disease, tumor size measuring at least 5 cm, or central Ki-67 at least 20%. Among the 2056 patients who received neoadjuvant chemotherapy in monarchE, 1025 received abemaciclib and endocrine therapy and 1031 received endocrine therapy alone. Abemaciclib plus endocrine therapy showed benefit, with improvements in iDFS vs endocrine therapy alone, with an HR of 0.614 (95% CI, 0.473-0.797) and a 2-year iDFS rate of 87.2% vs 80.6%, respectively. The addition of abemaciclib to endocrine therapy also improved distant relapse-free survival (DRFS), with an HR of 0.609 (95% CI, 0.459-0.809) and a 2-year DRFS rate of 89.5% and 82.8%, respectively.

“What is special about the monarchE trial is that they successfully identified a group of patients who seemed to have higher recurrence risk in the first 5 years,” Rugo said. “If we can identify those patients in practice, we should consider use of abemaciclib.” She explained that a higher lymph node burden is a clearer path to using abemaciclib, but that decision-making remains uncertain in patients with no more than 3 positive lymph nodes. “By Ki-67 alone, an inherently unstable marker, we don’t know. Patients who have a lot of disease have such a high risk. We probably aren’t doing them a big disservice—no long-term toxicities—so we would consider it now while waiting for longer-term data,” she said.
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