I strongly believe that achieving equity for patients across the spectrum of diagnosis, care, and survivorship begins with connecting the oncology community worldwide.

Everett E. Vokes, MD, FASCO
professor of radiation and cellular oncology, University of Chicago Medicine
president, American Society of Clinical Oncology

These results established [that patients with] HER2-low metastatic breast cancer is a targetable population of breast cancer, with trastuzumab deruxtecan as a new standard of care.

Shanu Modi, MD
medical oncologist, Memorial Sloan Kettering Cancer Center
lead investigator, DESTINY-Breast04

I do believe that appropriate representation of population genomics is a key to the success of precision medicine....Without appropriate representation of minorities in clinical trials, we cannot know if a drug works best in every population.

Kashyap Patel, MD
CEO, Carolinas Blood and Cancer Care Associates; president, Community Oncology Alliance; featured in ASCO's Narratives in Oncology
Ensure patients with PSMA-positive mCRPC have access to PLUVICTO.

To learn more, visit hcp.novartis.com/products/pluvicto.

In the phase 3 VISION trial, PLUVICTO + BSOC vs BSOC alone demonstrated:

**Key Secondary End Point**

- **Alternate Primary End Points**
  - Overall response rate
    - **b** 30% (n=319) vs 2% (n=120)
    - **P** <.001
  - Improved overall response rate
  - Significantly improved survival
    - Median OS 15.3 months (n=551) vs 11.3 months (n=280)
    - **HR=0.62 (95% CI, 0.52-0.74); P** <.001
  - Significantly improved rPFS
    - Median rPFS 8.7 months (n=385) vs 3.4 months (n=196)
    - **HR=0.40 (95% CI, 0.31-0.52); P** <.001

Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early dropout in the control arm.

**INDICATION**

PLUVICTO™ (lutetium Lu 177 vipivotide tetraxetan) is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

**IMPORTANT SAFETY INFORMATION**

**Risk From Radiation Exposure**

PLUVICTO contributes to a patient’s long-term cumulative radiation exposure, which is associated with an increased risk for cancer.

Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with PLUVICTO consistent with institutional practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection.
In the phase 3 VISION trial, PLUVICTO + BSOC vs BSOC alone demonstrated\textsuperscript{1-3,a}:

<table>
<thead>
<tr>
<th>Alternate Primary End Point</th>
<th>Key Secondary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Significantly improved survival</strong></td>
<td><strong>Improved overall response rate</strong></td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td><strong>Overall response rate\textsuperscript{b}</strong></td>
</tr>
<tr>
<td>15.3 months (n=551) vs 11.3 months (n=280)</td>
<td>30% (n=319) vs 2% (n=120)</td>
</tr>
<tr>
<td>HR=0.62 (95% CI, 0.52-0.74); \textit{P}&lt;.001</td>
<td>HR=0.40 (95% CI, 0.31-0.52); \textit{P}&lt;.001</td>
</tr>
</tbody>
</table>

Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early dropout in the control arm.

Ensure patients increase oral fluid intake and advise them to void as often as possible to reduce bladder radiation.

To minimize radiation exposure to others, advise patients to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days, to refrain from sexual activity for 7 days, and to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

\textsuperscript{a}VISION was an international, prospective, open-label, randomized, multicenter phase 3 clinical trial evaluating PLUVICTO in 831 adult patients with progressive PSMA-positive mCRPC previously treated with at least 1 AR pathway inhibitor and 1 or 2 taxane regimens. Participants were randomized in a 2:1 ratio to receive PLUVICTO (7.4 GBq every 6 weeks for up to 6 cycles) plus BSOC or BSOC alone.\textsuperscript{1,2}

\textsuperscript{b}ORR is reported as a measure of response in soft tissue disease, lymph node, or visceral lesions.

\textsuperscript{c}Patients with evaluable disease at baseline.

\textsuperscript{d}Stratified Wald’s Chi-square test 2-sided \textit{P} value.

---

Please see additional Important Safety Information and Brief Summary on the following pages.
IMPORTANT SAFETY INFORMATION (continued)

Myelosuppression
PLUVICTO can cause severe and life-threatening myelosuppression. In the VISION study, grade 3 or 4 decreased hemoglobin (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with PLUVICTO. Grade ≥3 pancytopenia occurred in 1.1% of patients (including 2 fatal events). Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia were observed. One death due to sepsis and concurrent neutropenia was observed. Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO based on severity of myelosuppression.

Renal Toxicity
PLUVICTO can cause severe renal toxicity. In the VISION study, grade 3 or 4 acute kidney injury (3%) and increased creatinine (0.9%) occurred in patients treated with PLUVICTO. Advise patients to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Perform kidney function laboratory tests, including serum creatinine and calculated creatinine clearance (CrCl), before and during treatment. Withhold, reduce dose, or permanently discontinue PLUVICTO based on severity of renal toxicity.

Embryo-Fetal Toxicity
The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose.

Infertility
The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation-absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility.

Adverse Reactions
The most common adverse reactions (≥20%) occurring at a higher incidence in patients who received PLUVICTO plus best standard of care (BSoC) were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. Clinically relevant adverse reactions in <5% of patients included dry eye, vertigo, and pancytopenia (including bicytopenia).

Laboratory Abnormalities
The most common laboratory abnormalities that worsened from baseline in ≥30% of patients who received PLUVICTO plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

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

PLUVICTO™ (lutetium Lu 177 vipivotide tetraxetan) injection, for intravenous use

Initial U.S. Approval: 2022

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE
PLUVICTO is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

2 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS
5.1 Risk From Radiation Exposure
PLUVICTO contributes to a patient’s overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with PLUVICTO consistent with institutional good radiation safety practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home.

Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation.

Before the patient is released, the healthcare provider should explain the necessary radioprotection precautions that the patient should follow to minimize radiation exposure to others [see Patient Counseling Information (17) in the full prescribing information]. Following administration of PLUVICTO, advise patients to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days. Following administration of PLUVICTO, advise patients to refrain from sexual activity for 7 days. Following administration of PLUVICTO, advise patients to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

5.2 Myelosuppression
PLUVICTO can cause severe and life-threatening myelosuppression, including anemia, thrombocytopenia, leukopenia, and neutropenia. In the VISION study, Grade 3 or 4 neutropenia (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with PLUVICTO. Grade ≥ 3 pancytopenia occurred in 1.1% (which includes two fatal events) in patients treated with PLUVICTO. Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia and subdural hematoma were observed in patients who received PLUVICTO. One death due to sepsis and concurrent neutropenia was observed in patients who received PLUVICTO.

Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO and clinically treat patients based on the severity of myelosuppression [see Dosage and Administration (2.4) in the full prescribing information].

5.3 Renal Toxicity
PLUVICTO can cause severe renal toxicity. In the VISION study, Grade 3 or 4 acute kidney injury (3%) and increased creatinine (0.9%) occurred in patients treated with PLUVICTO. Decreased renal function was observed in patients who received PLUVICTO. One death due to sepsis and concurrent neutropenia was observed in patients who received PLUVICTO.

Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO based on the severity of renal toxicity [see Dosage and Administration (2.4) in the full prescribing information].

5.4 Embryo-Fetal Toxicity
The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO may cause fetal harm [see Clinical Pharmacology (12.1) in the full prescribing information]. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [see Use in Specific Populations (8.1, 8.3)].

5.5 Infertility
PLUVICTO may cause infertility in males. The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility [see Use in Specific Populations (8.3)].

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Myelosuppression [see Warnings and Precautions (5.2)]
- Renal Toxicity [see Warnings and Precautions (5.3)]

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

The safety of PLUVICTO was evaluated in the VISION study in patients with progressive, PSMA-positive mCRPC [see Clinical Studies (14) in the full prescribing information]. Of the 831 patients randomized, 754 patients received at least one dose of randomized treatment. Patients received at least one dose of either PLUVICTO 7.4 GBq (200 mCi) administered every 6 to 10 weeks plus BSoC (N = 529) or BSoC alone (N = 205). The median duration of exposure to randomized treatment was 7.8 months (range, 0.3 to 24.9) for patients who received PLUVICTO plus BSoC. Among patients who received PLUVICTO plus BSoC, the median number of doses of PLUVICTO received was 5 (range, 1 to 6). The median cumulative dose of PLUVICTO was 37.5 GBq (range, 7.0 to 48.3). The median duration of follow-up was 14.8 months for patients receiving PLUVICTO plus BSoC.

Serious adverse reactions occurred in 36% of patients who received PLUVICTO plus BSoC. The most frequent (≥ 3%) adverse reactions leading to a dose interruption of PLUVICTO in patients who received PLUVICTO plus BSoC were anemia (2.8%), thrombocytopenia (2.8%), and leukopenia (including neutropenia) (1.7%).

Adverse reactions leading to a dose interruption of PLUVICTO occurred in 16% of patients. The most frequent (≥ 3%) adverse reactions leading to a dose interruption of PLUVICTO in patients who received PLUVICTO plus BSoC were anemia (5%) and thrombocytopenia (3.6%).

Adverse reactions leading to a dose reduction of PLUVICTO occurred in 6% of patients. The most frequent (≥ 1%) adverse reactions leading to a dose reduction of PLUVICTO in patients who received PLUVICTO plus BSoC were thrombocytopenia (1.9%) and anemia (1.3%).

The most common laboratory abnormalities that worsened from baseline in ≥ 30% of patients who received PLUVICTO plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

Table 3: Adverse Reactions (≥ 5%) in Patients with PSMA-positive mCRPC Who Received PLUVICTO Plus BSoC in VISION

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PLUVICTO Plus BSoC (N = 529)</th>
<th>BSoC (N = 205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 to 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>43</td>
<td>6</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21</td>
<td>1.9</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>10</td>
<td>0.4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>0.4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>1.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>20</td>
<td>1.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>0.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19</td>
<td>0.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11</td>
<td>1.1</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>3.8</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>9</td>
<td>3.2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>0.9</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>0.8</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: BSoC, best standard of care.
a Peripheral edema includes peripheral edema, fluid retention, and fluid overload.
b Dry mouth includes dry mouth, aphagia, and dry throat.
c Vomiting includes vomiting and retching.
d Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.
e Urinary tract infection includes urinary tract infection, cystitis, and cystitis bacterial.
f Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.

 Clinically relevant adverse reactions in < 5% of patients who received PLUVICTO plus BSoC included dry eye, vertigo, and pancytopenia (including bicytopenia).

Table 4: Select Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Patients with PSMA-positive mCRPC Who Received PLUVICTO Plus BSoC (Between Arm Difference at ≥ 5% All Grades) in VISION

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>PLUVICTO Plus BSoC (%)</th>
<th>BSoC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 to 4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>39</td>
<td>2.5</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>33</td>
<td>0.6</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>28</td>
<td>1.1</td>
</tr>
</tbody>
</table>

(continued)
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Risk Summary**

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm [see Clinical Pharmacology (12.1) in the full prescribing information]. There are no available data on PLUVICTO use in pregnant females. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm.

8.2 Lactation

**Risk Summary**

The safety and efficacy of PLUVICTO have not been established in females. There are no data on the presence of lutetium Lu 177 vipivotide tetraxetan in human milk or its effects on the breastfed child or on milk production.

8.3 Females and Males of Reproductive Potential

**Contraception**

Males

Based on its mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information].

Infertility

The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 529 patients who received at least one dose of PLUVICTO plus BSoC in the VISION study, 387 patients (73%) were 65 years or older and 143 patients (27%) were 75 years or older. No overall differences in effectiveness were observed between patients ≥ 75 years of age and younger patients. Serious adverse reactions occurred in 11% of patients ≥ 75 years of age and in 11% of younger patients. Grade ≥ 3 adverse reactions occurred in 40% of patients ≥ 75 years of age and in 31% of younger patients.

8.6 Renal Impairment

Exposure of lutetium Lu 177 vipivotide tetraxetan is expected to increase with the degree of renal impairment [see Clinical Pharmacology (12.3) in the full prescribing information]. No dose adjustment is recommended for patients with mild (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault) to moderate (CLcr 30 to 59 mL/min) renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Frequently monitor renal function and adverse reactions in patients with mild to moderate renal impairment [see Dosage and Administration (2.4) in the full prescribing information]. The pharmacokinetics and safety of PLUVICTO have not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment or end-stage renal disease.

10 OVERDOSAGE

In the event of administration of a radiation overdosage with PLUVICTO, reduce the radiation absorbed dose to the patient by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. Estimate the effective radiation dose that was applied and treat with additional supportive care measures as clinically indicated.

Distributed by:
Advanced Accelerator Applications USA, Inc.
Millburn, NJ 07041

©2022 Advanced Accelerator Applications USA, Inc.
PLUVICTO is a trademark of Novartis AG and/or its affiliates
U.S. Patents 10398791; 10406240
T2022-17
SP228 FROM THE PUBLISHER

Innovation brings the Crowd to Its Feet

SP230-SP236 ADVANCING HEALTH EQUITY

ASCO Highlights Pallet for Career With “Many Roles”

From Research to Health Care Delivery, Put's Versatility Is Cited by ASCO

ASCO, WHO to Launch Global Quality Initiative

Pierce Looks to the Future of Trial Diversity by Reflecting on Current and Historical Barriers

ASCOS SPOTLIGHT: Randall A. Oyer, MD: Clinical Trials Must Be Accessible to Everyone

SP238-SP243 BREAST CANCER

Trastuzumab Deruxtecan Cuts Risk of Disease Progression or Death by 50% in HER2-Low Metastatic Breast Cancer

Sacituzumab Govitecan Improves PFS for Patients With a Common Breast Cancer and Limited Options—but Is It Enough?

Investigators Evaluate MBC Survival in Studies Addressing Race, Ethnicity, Socioeconomic Disparities

ASCOS SPOTLIGHT: Hope S. Rugo, MD, FASCO, Discusses Clinical Trial Minority Recruitment, PALOMA-2 Findings

SP251-SP261 SOLID TUMORS

Inovio's DNA Vaccine Combo Plus Cemiplimab Shows Promise in Glioblastoma

FOENIX Update: A New Era in Cholangiocarcinoma Precision Medicine

ASCOS SPOTLIGHT: Kim A. Reiss, MD, on CAR Macrophages and Other Developments in Pancreatic Cancer

KEYNOTE-716: First Data on DMFS in Pancreatic Cancer

CAR Macrophages and Other Developments

ASCO SPOTLIGHT: Thanos Zomas, MD, Says Hodgkin Lymphoma Outcomes Improve With Targeted Treatment

CHINE: Adding Ibrutinib to Treatment Improves PFS by 50% for Older Patients

With Mantle Cell Lymphoma

Challenging the “One-Size-Fits-All” Approach in Early MCL Treatment

ROSEWOOD: Zanubrutinib Combo Provides Superior Efficacy in FL

Early ASCT for Multiple Myeloma Improves PFS, but OS Remains the Same

ASCOS SPOTLIGHT: Enrique Ocio, MD, PhD, Discusses the Advantages of Sub-Q Isatuximab for RRMM

SP263-SP276 BLOOD CANCERS

Over 6 Years, First-line Brentuximab Vedeotin Cuts Risk of Death in Hodgkin Lymphoma by 41%

ASCOS SPOTLIGHT: Thanos Zomas, MD, Says Hodgkin Lymphoma Outcomes Improve With Targeted Treatment

SHINE: Adding Ibrutinib to Treatment Improves PFS by 50% for Older Patients

With Mantle Cell Lymphoma

Challenging the “One-Size-Fits-All” Approach in Early MCL Treatment

ROSEWOOD: Zanubrutinib Combo Provides Superior Efficacy in FL

Early ASCT for Multiple Myeloma Improves PFS, but OS Remains the Same

ASCOS SPOTLIGHT: Enrique Ocio, MD, PhD, Discusses the Advantages of Sub-Q Isatuximab for RRMM

SP280-SP286 HEALTH CARE POLICY & DELIVERY

Cultural Humility Elicits the Link Between Patient Spirituality, EOL Care Decisions

Communication Disparities Contribute to Care Disparities

Patients With Cancer Face Major Financial Roadblocks, Not All Concerning Out-of-Pocket Costs

ASCOS SPOTLIGHT: Can Nudges Increase the Number of Serious Illness Conversations in Community Oncology?

SP288-SP290 FROM OUR PARTNERS

Data Indicate Lower Response Rates to Axi-cel Among Black Patients

In KRYSTAL-1, Adagrasib for NSCLC Has 43% Response Rate

Lucitanib With Nivolumab Sees Responses In Gynecological Cancer Treatment

Dosing Study of Modakafusp Alfa Shows Promise In Solid Tumors; Tests Planned With Checkpoint Inhibitors

ASCOS SPOTLIGHT: David R. Penberthy, MD, MBA: Knowledge Gained at ASCO Can Transform Cancer Care
**WHEN NAVIGATING THE DIFFICULTIES OF MULTIPLE MYELOMA IN THE REAL WORLD, YOU NEED DURABLE STRENGTH**

**THE NINLARO® (ixazomib) REGIMEN* OFFERS EXTENDED EFFICACY AND MANAGEABLE TOLERABILITY FOR THE TYPES OF PATIENTS YOU SEE EVERY DAY**

The NINLARO regimen extended median PFS by ~6 months vs the Rd regimen.* Median PFS: 20.6 vs 14.7 months for the NINLARO and Rd regimens, respectively; HR=0.74 (95% CI, 0.59-0.94); P=0.012.4†

- At the final analysis, with a median follow-up of ~85 months, median OS in the ITT population was 53.6 months for patients receiving the NINLARO regimen* and 51.6 months for patients receiving the Rd regimen* (HR=0.94 [95% CI, 0.78-1.13])

*The NINLARO regimen included NINLARO+lenalidomide+dexamethasone. The Rd regimen included placebo+lenalidomide+dexamethasone.

**TOURMALINE-MM1: a global, phase 3, randomized (1:1), double-blind, placebo-controlled study that evaluated the safety and efficacy of NINLARO (an oral PI) vs placebo, both in combination with lenalidomide and dexamethasone, until disease progression or unacceptable toxicity in 722 patients with relapsed and/or refractory multiple myeloma who received 1-3 prior therapies.1,4**

**INDICATION AND USAGE**

**Indication:** NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

**Limitations of Use:** NINLARO is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

- **Thrombocytopenia** has been reported with NINLARO. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

- **Gastrointestinal Toxicities**, including diarrhea, constipation, nausea and vomiting were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive therapies.

Please see additional Important Safety Information on the next page and accompanying Brief Summary.

All trademarks are the property of their respective owners. ©2022 Takeda Pharmaceuticals U.S.A., Inc. All rights reserved.

06/22 USO-IXA-0384
PROTEASOME INHIBITOR-BASED TRIPLET REGIMENS REMAIN A CORNERSTONE OF TREATMENT WITH OPTIMAL OUTCOMES.1,6

How can you help patients on their journey to extended efficacy?

IMPORTANT SAFETY INFORMATION (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)
care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

• Peripheral Neuropathy was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. During treatment, monitor patients for symptoms of neuropathy and consider adjusting dosing for new or worsening peripheral neuropathy.

• Peripheral Edema was reported with NINLARO. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of NINLARO for Grade 3 or 4 symptoms or dexamethasone per its prescribing information.

• Cutaneous Reactions, including a fatal case of Stevens-Johnson syndrome, were reported with NINLARO. If Stevens-Johnson syndrome occurs, discontinue NINLARO and manage as clinically indicated. Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.

• Thrombotic Microangiopathy has been reported with NINLARO. Fatal cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

• Hepatotoxicity has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatic cholestasis and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

• Embryo-fetal Toxicity: NINLARO can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.

• Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting: In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

ADVERSE REACTIONS
The most common adverse reactions (≥ 20%) in the NINLARO regimen compared to placebo in combination with lenalidomide plus dexamethasone, respectively were thrombocytopenia (85%, 67%; pooled from adverse event and laboratory data), neutropenia (74%, 70%; pooled from adverse event and laboratory data), diarrhea (52%, 43%), constipation (35%, 28%), peripheral neuropathy (32%, 24%), nausea (32%, 23%), edema peripheral (27%, 21%), rash (27%, 16%), vomiting (26%, 13%), and bronchitis (22%, 17%). Serious adverse reactions reported in ≥ 2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%), and bronchitis (2%).

DRUG INTERACTIONS: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

USE IN SPECIFIC POPULATIONS
• Lactation: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.
• Hepatic Impairment: Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
• Renal Impairment: Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.

Please see additional Important Safety Information on the previous page and accompanying Brief Summary.

5.5 Cutaneous Reactions: The most common type of rash reported in both regimens included maculo-papular and purpuric rash. Other skin-related adverse reactions were Grade 1 (18% in the NINLARO regimen and 16% in the placebo regimen) or Grade 2 (9% in the NINLARO regimen and 4% in the placebo regimen). Edema peripheral resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Monitor platelet counts at least monthly during treatment with NINLARO and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.6 Thrombotic Microangiopathy: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 in 2% of patients in the NINLARO regimen. The rate of platelet transfusions was 10% in the NINLARO regimen and 7% in the placebo regimen. Monitor platelet counts at least monthly during treatment with NINLARO and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

6.1 Clinical Trials Experience

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

The safety population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=361) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=359). The most frequently reported adverse reactions ≥20% with a difference of ≥5% compared to placebo in the NINLARO regimen were thrombocytopenia, neutropenia, diarrhea, constipation, peripheral neuropathy, nausea, peripheral edema, rash, vomiting, and bronchitis. Serious adverse reactions reported in ≤2% of patients in the NINLARO regimen included diastolic hypertension (3%), thrombocytopenia (2%) and bronchitis (2%). One or more of the three drugs was permanently discontinued in 4% of patients reporting peripheral neuropathy, 3% of patients reporting diarrhea and 2% of patients reporting thrombocytopenia. Permanent discontinuation of NINLARO due to an adverse reaction occurred in 10% of patients.

Table 4 summarizes the non-hematologic adverse reactions occurring in at least 5% of patients with at least a 5% difference between the NINLARO regimen and the placebo regimen.

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥5% of Patients with a ≥5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

<table>
<thead>
<tr>
<th>System Organ Class / Preferred Term</th>
<th>NINLARO + Lenalidomide and Dexamethasone N=361 (%)</th>
<th>Placebo + Lenalidomide and Dexamethasone N=359 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52/10</td>
<td>43/3</td>
</tr>
<tr>
<td>Constipation</td>
<td>35/1</td>
<td>28/1</td>
</tr>
<tr>
<td>Nausea</td>
<td>32/2</td>
<td>23/0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26/1</td>
<td>13/1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy1</td>
<td>32/2</td>
<td>24/2</td>
</tr>
<tr>
<td>Maculopapular and connective tissue disorders</td>
<td>27/1</td>
<td>23/1</td>
</tr>
<tr>
<td>Back pain2</td>
<td>27/1 &lt;1</td>
<td>24/3</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection3</td>
<td>22/2</td>
<td>17/2 &lt;1</td>
</tr>
<tr>
<td>Sinus and subcutaneous tissue disorders</td>
<td>27/3</td>
<td>16/2</td>
</tr>
<tr>
<td>Nausea3</td>
<td>27/3</td>
<td>16/2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>27/2</td>
<td>21/1</td>
</tr>
</tbody>
</table>

Note: Adverse reactions included as preferred terms are based on MedDRA version 23.0.

1 At the time of the final analysis, these adverse reactions no longer met the criterion for a ≥5% difference between the NINLARO regimen and the placebo regimen.
2 Represents a pooling of preferred terms

(Continued on next page)
Brief Summary (cont’d)

Table 5 represents pooled information from adverse event and laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>NINLARO + Dexamethasone (N=361)</th>
<th>Placebo + Dexamethasone (N=309)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Any Grade: 85</td>
<td>Grade 3-4: 30</td>
</tr>
<tr>
<td></td>
<td>Grade 0: 30</td>
<td>Grade 0: 67</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Any Grade: 74</td>
<td>Grade 3-4: 34</td>
</tr>
<tr>
<td></td>
<td>Grade 0: 34</td>
<td>Grade 0: 70</td>
</tr>
</tbody>
</table>

Herpes Zoster

Herpes zoster was reported in 6% of patients in the NINLARO regimen and 3% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the healthcare provider’s discretion. Patients treated in the NINLARO regimen who received antiviral prophylaxis had a lower incidence (1%) of herpes zoster infection compared to patients who did not receive prophylaxis (10%).

5.6 Thrombotic Microangiopathy:

In <1% of patients in both regimens. Manage rash with supportive care or with placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 2% in the placebo regimen. Grade 2 (9% in the NINLARO regimen and 4% in the placebo regimen) or Grade 1 (15% in the NINLARO regimen and 9% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 17% in the placebo regimen) and Grade 3 (6% in the NINLARO regimen and 10% in the placebo regimen) and Grade 4 (2% in the NINLARO regimen and 3% in the placebo regimen). Other Clinical Trials Experience

Peripheral edema was reported in 27% and 21% of patients in the NINLARO regimen and 23% and 17% in the placebo regimen. NINLARO is contraindicated in patients with uncontrolled peripheral edema. Patients experiencing new or worsening peripheral neuropathy may require dose reduction. Grade 3 adverse reactions of peripheral neuropathy were reported at a rate of 10% in the NINLARO regimen and 7% in the placebo regimen. Consider more frequent monitoring during the first three cycles.

5.8 Renal Impairment:

In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

6.1 Clinical Trials Experience

The most common adverse reactions of the eyes were cataract (15%), conjunctivitis (9%), blurred vision (7%), and dry eye (6%).

6.2 Lactation:

Breastfeeding: advise women not to breastfeed if they experience unusual swelling of their extremities or weight gain due to swelling [see Warnings and Precautions (5.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Risk Summary:

Because clinical trials are conducted under widely varying conditions, adverse reactions and laboratory data are not the same time for the first three weeks of a four week cycle. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Advise patients to take the recommended dosage as directed, because overdose has led to death [see Overdosage (10)].

17 PONTEN COUNSELING INFORMATION

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

Dosage Instructions

• Instruct patients to take NINLARO exactly as prescribed.
• Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Advise patients to take the recommended dosage as directed, because overdose has led to death [see Overdosage (10)].
• Advise patients to take NINLARO at least one hour before or at least two hours after food.
• Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
• Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
• Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
• If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is >72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
• If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
• Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO. [see Dosage and Administration (2.1)].

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising. [see Warnings and Precautions (5.1)].

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their healthcare providers if these adverse reactions persist. [see Warnings and Precautions (5.2)].

Peripheral Neuropathy: Advise patients to contact their healthcare providers if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs. [see Warnings and Precautions (5.3)].

Peripheral Edema: Advise patients to contact their healthcare providers immediately if they experience new or worsening rash [see Warnings and Precautions (5.3)].

Thrombotic Microangiopathy: Advise patients to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur [see Warnings and Precautions (5.6)].

Hepatitis: Advise patients to contact their healthcare providers if they experience jaundice or right upper quadrant abdominal pain [see Warnings and Precautions (5.7)].

Other Adverse Reactions: Advise patients to contact their healthcare providers if they experience any new or different symptoms or side effects not mentioned above.

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose. Advise women using hormonal contraceptives to also use a barrier method of contraception [see Use in Specific Populations (8.1)]. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose [see Use in Specific Populations (8.1)].

Lactation: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose [see Use in Specific Populations (8.1)].

Concomitant Medications: Advise patients to speak with their healthcare providers about any other medication they are currently taking and before starting any new medications.

Please see full Prescribing Information for NINLARO at NINLAROhcp.com. All trademarks are the property of their respective owners. ©2022 Takeda Pharmaceuticals U.S.A., Inc. All rights reserved.
Innovation Brings the Crowd to Its Feet

THE FIRST IN-PERSON MEETING of the American Society of Clinical Oncology (ASCO) since 2019 was memorable for many reasons—old friends reconnected and new ones met in person for the first time. For some at The American Journal of Managed Care®, ASCO 2022 marked the first full scientific meeting and trade show experience—and if you haven’t been in person, there’s nothing quite like the crowd at McCormick Place in Chicago.

For their commitment to bringing the best in cancer care to every patient, Kashyap Patel, MD, and Debra Patt, MD, PhD, MBA, were featured in ASCO’s annual Narratives in Oncology during the 2022 annual meeting in Chicago.

Beyond networking and celebrations, the first order of business was the science, and we were not disappointed. The high point came during ASCO’s plenary June 5, when results for the DESTINY-Breast04 trial drew a standing ovation. Shamu Modi, MD, of Memorial Sloan Kettering Cancer Center, shared data showing that when compared with chemotherapy, trastuzumab deruxtecan reduced the risk of disease progression or death by 50% for those with HER2-low metastatic breast cancer. This is the kind of game-changing result doctors will immediately bring back into the clinic, and the need to refine who is “HER2-low” will drive more innovation in pathology to understand who benefits from this breakthrough. One of our board members for Evidence-Based Oncology™ (EBO), Texas Oncology’s Debra Patt, MD, PhD, MBA, said that up to 55% of patients with advanced breast cancer could be candidates for this regimen.

The specter of COVID-19 remained part of the picture during ASCO, as attendees were required to show proof of vaccination and most still wore masks. This was the also first annual meeting featuring trials that were carried out from start to finish during the pandemic. Alexander I. Spira, MD, PhD, of Virginia Cancer Specialists Specialists Research Institute, expressly thanked all the site directors of the KRYSAL-1 study, which produced a 43% response rate for adagrasib, a KRAS G12C inhibitor, in non–small cell lung cancer; Spira said they had endured one of “the most challenging times” he had ever seen in clinical research.

Finally, ASCO’s commitment to achieve greater equity in cancer screening, diagnosis, treatment, and survivorship care was evident across the meeting. Health equity is no longer a topic limited to a single session; it’s a principle of every presentation. This is the approach that EBO’s associate editor, Kashyap Patel, MD, of Carolina Blood and Cancer Care Associates and the current president of Community Oncology Alliance, urged us to take as we plan our 2022 Patient-Centered Oncology Care® meeting for November 9 to 10 in Nashville. For their commitment to bringing the best in cancer care to every patient, both Patel and Patt were featured in ASCO’s annual Narratives in Oncology during the Chicago meeting. We congratulate Patel and Patt on this honor, and we encourage you to read our coverage of their work to improve patient access and health equity.

Sincerely,
Mike Hennessy Jr
PRESIDENT & CEO

Subscribe to our newsletters for breaking news and valuable resources
Scan the code with your smartphone camera or sign up at: ajmc.com/subscribe
BeiGene is committed to a thoughtful approach to drug pricing and is looking to partner with access stakeholders across the US healthcare ecosystem

- We engage customers in meaningful partnerships that drive access and affordability
- We focus on bringing important new medicines to areas of high unmet need
- We believe in demonstrating and proving value through HEOR and real-world customer data

How can BeiGene help bring value to you? Learn more about BeiGene at BeiGene.com and the treatment areas we are focused on at BeiGeneVirtualExperience.com.

BeiGene is a registered trademark owned by BeiGene, Ltd. © BeiGene, Ltd. 2022 All Rights Reserved. 0222-BRU-PRC-027 03/22
ASCO Highlights Patel for Career With “Many Roles”

MAGGIE L. SHAW

“I WAS JUST SO EXCITED and quite pleasantly surprised,” replied Kashyap Patel, MD, CEO of Carolina Blood and Cancer Care Associates (CBCCA) and president of the Community Oncology Alliance (COA), when asked about being included in the 2022 Narratives in Oncology, a special issue introduced by the American Society of Clinical Oncology’s (ASCO) The ASCO Post.1

Each year since 2012,1 from among ASCO’s approximately 45,000-strong global membership,10 leaders have been nominated by their peers to be recognized in Narratives, which is published during the ASCO annual meeting. Besides Patel, who is associate editor of Evidence-Based Oncology2 (EBO), this year’s class includes EBO board member Debra Patt, MD, PhD, MBA, executive vice president of health care policy and strategic initiatives at Texas Oncology and a clinical professor at Dell Medical School at The University of Texas at Austin. Patt is the current secretary of COA (See SP231).

Patel elaborated on this year’s ASCO honor in an interview with EBO.3 “I think I was given this award because of my contribution to community oncologists and how we are trying to survive and play many roles—policy, science, disparities, access to care, all of that.”

Patel launched his career in medicine with a neurology fellowship before opening a private hematology/oncology practice and spending several years as an academic oncologist. He has now been with CBCCA for more than 20 years, fulfilling his self-proclaimed role as a people person and continually stoking his interest in health care policy. Speaking of his time in academia as a hematology/oncology fellow, he has said that although the work was interesting and he was very involved in research and publishing, “I was concerned I’d be unfilled in academic oncology, so I began looking for a position in a community practice.”11

From his start at CBCCA, Patel has been on the go. Not only is he a practicing oncologist, he also works for better outcomes in the community setting by improving the care experience for patients and physicians alike through his efforts to eliminate community oncology-related health care disparities, elevating value-based care and enable access to care through practice-level changes.

“I do believe that appropriate representation of population genomics is a key to the success of precision medicine,” Patel told EBO. “As well for clinical trials, without appropriate representation of minorities in clinical trials, we cannot know if a drug works best in every population.” This is particularly important in this era of precision oncology and personalized medicine and ensuring patients who are candidates for targeted treatment receive optimally effective treatment.

To that end, Patel and CBCCA have partnered with Sema4, a health intelligence company that uses artificial intelligence and machine learning “to build dynamic models of human health and define optimal individualized health trajectories,” and LabCorp, the global life sciences behemoth using technology to improve care delivery, to investigate genomic testing disparities in the community oncology setting. Data from this ongoing study, the primary goal of which is to achieve a clearer understanding of how social determinants of health (SDOH) influence the receipt of and outcomes in oncologic care in underserved communities, were presented at ASCO 2022.8,9

Results from the first abstract show that 43.2% of patients reported an annual household income below $25,000 and the remaining 57.8% reported an annual household income below $50,000. This lack of adequate income as an SDOH was found to be associated with both financial and food insecurity, with patients in these households stressed about their potential inability to pay for food or medical care; 15.1% also reported they had run out of food in the past year. “This ongoing observational study will integrate SDOH, genomic characteristics, and clinical outcomes from a diverse cohort of patients seen in community oncology practices,” Patel and his coauthors wrote.9

Findings from the second abstract show that whole-exome sequencing (WES) and next-generation sequencing (NGS)—offered via liquid biopsy or tissue-based testing—can be scaled up when necessary to help identify potential candidates for targeted therapies, “providing better outcomes and reduced toxicity” and improving cancer-related health disparities (CDHs). These may contribute to almost 34% of deaths among adult cancer patients and additional spending of $230 billion, the analysis noted. Part of the study in the first abstract, this analysis utilized the Sema4/LabCorp partnership to create a real-world evidence registry of biomarker-based testing results (ie, germline implications and actionable variants); 31% of the patients who underwent NGS were reported to be members of ethnic minority groups.11

These ongoing efforts aimed at overcoming CDHs are being made in conjunction with No One Left Alone, CBCCA’s comprehensive program that hopes to improve access to cancer care by addressing financial toxicity: Phase 1 of this program tracked the socioeconomic aspects of cancer care that often adversely affect that care, including transportation and insurance coverage (or lack thereof). Among the major findings, $1.63 million alone in free drug coverage was provided to patients between January and December 2021.9 But addressing financial toxicity was just the first step in designing a road map of sorts that the team hopes to eventually share with other practices around the country.4 Phases 2a and 2b of the program comprise the partnerships with Sema4 and LabCorp, through which close to 85% of eligible patients with cancer have so far received NGS testing,4 a finding in stark contrast to the 25% to 45% reported in precision medicine literature, Patel and his team reported.11 Phase 3 will encompass additional data collection, for lung, breast, cervical, colorectal, and prostate cancers, and phase 4 will address clinical trial access.11

“I’ve narrowed down the disparities causes to: access to care for financial reasons; access to cancer screening; access to NGS testing, molecular testing; SDOH; and access to clinical trials. We have to try one or all of these together in multiple settings to see what works best,” Patel said.

Patel remains rooted in his role as a community oncologist whose first priority has always been his patients and ensuring they get the care they need when they need it. “I’ve spent over 1500 hours now, in the last 2 years, studying about the equity impact of disparities in cancer care. I’ve written about it. I’ve published about it. I’ve walked the talk. I feel that this problem will not be solved by policy makers in Washington, DC—there’s been too much fragmentation and partisanship in DC about the smallest issue. I think we have to start different models and pilots in different regions,” Patel stated. “It’s going to be a learning experience. But until then, that 34% of preventable cancer that’s happened in America haunts me every night before I go to bed, so we just do our best.”10,11

EBO_07_2022_01HealthEquity.indd   230
EBO_07_2022_01HealthEquity.indd   230
7/8/23   1:34 PM
7/8/23   1:34 PM
care management platform than other demographic groups, but non-Hispanic female patients were more likely to be engaged in a oncology practice,” was presented as part of ASCO’s Care Delivery quality and reduce disparities in a large multisite community mass implementation of digital health solutions to improve panel discussion, “Stronger Together: Women/uni00A0Supporting Women.”

Patt has been an important voice during the COVID-19 pandemic, with a focus on public health when few were doing so. Patt’s love of data—and her use of it to drive policy change—was cited by ASCO during the COVID-19 pandemic. Patt sees patients from a variety of ethnic and socioeconomic backgrounds, many of whom lack health coverage. She discussed the disparities in outcomes among these patients in an interview last year: “Between the ages 19 to 65, [there’s] about 25% of adults in Texas who don’t have access to insurance. We know in that patient population, that they’re 6 times more likely to present with advanced breast cancer and they die more rapidly of their disease because they present with advanced cancer,” Patt said. “I think the access issue is a real hurdle that has to be overcome.”

REFERENCES
ASCO, WHO to Launch Global Quality Initiative in Cancer Care

MARY CAFFREY

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) and the World Health Organization (WHO) will join forces to measure and improve the quality of cancer care worldwide. Their aim is to close equity gaps between high- and low-income countries and increase survival in low-income ones, which are being left behind as wealthy nations see the fruits of innovation.

News of the collaboration, established through a memorandum of understanding, was presented on June 4 by surgical oncologist and WHO Cancer Control Officer André Ilbawi, MD, in a keynote address during the presidential symposium at the 2022 ASCO Annual Meeting in Chicago. ASCO President Everett E. Vokes, MD, FASCO, also highlighted the agreement during his talk, “Advancing Equitable Cancer Care Through Innovation.”

Since the start of the COVID-19 pandemic, the focus on health equity in the United States has underscored differences in outcomes between high-income and low-income individuals, between patients who are White and patients of color, and between those living near academic centers vs those in rural settings.

ASCO’s Saturday session pointed out cancer care disparities of a different order of magnitude—those between high-income countries and the rest of the world.

The data Ilbawi presented were stark: 5-year cancer survival rates in the United States are 90%, but 3-year rates in Africa are just 30%. Over a 2-year period, cancer kills twice as many people in low- and middle-income countries as it does in high-income countries. And this does not go unnoticed within the US health system, where more than a third of medical trainees are from other countries.

"Despite advances in cancer care in the last 2 decades, inequalities between and within countries are staggering and progressively increasing," Ilbawi said. "The experience of someone affected by cancer is profoundly determined by where they live and their socioeconomic status." In his address, Everett spoke of the incredible innovation that has occurred over his career—from the work by Janet D. Rowley, MD, on the Philadelphia chromosome and its relationship to leukemia and lymphoma to the discoveries that have revolutionized treatment for lung cancer. Everett also highlighted recent efforts by ASCO to ensure that all patients have access to care, such as setting up programs for rural patients. Yet much remains to be done.

Implementing the ASCO-WHO agreement

"In seeking quality cancer care worldwide, the goals of ASCO and the WHO are fully aligned," Vokes said in a statement released early Saturday. "Building on years of informal collaboration with the WHO, we now look forward to working with our WHO colleagues and stakeholders to advance international quality programs for cancer care—one of ASCO's strategic focus areas."

Through its Department for Noncommunicable Diseases, the WHO is working to strengthen cancer control programs in breast, cervical, and childhood cancers. The organization, which works in 194 countries from 149 offices, is taking the following steps:

- Distributing information, best practices, and innovative strategies on cancer control among developing countries
- Working to ensure that an additional 3 billion people worldwide get universal health coverage, are protected from health emergencies, or have access to evidence-based policies and programs

Ilbawi noted that one-third of ASCO’s 45,000 members practice outside the United States; thus, the collaboration involves 2 groups whose members are already distributed worldwide. ASCO members can work to improve care quality "by providing direct support to governments and hospitals—particularly those in low- and middle-income countries—and incentivizing organizational and social innovations," he explained.

"We are bound in this together," Ilbawi said, "but who will take responsibility?"

Innovation—but Only for Some

To be sure, treatment innovation has spurred the identification of more than 50 molecular targets, setting the era of precision oncology in motion. "But we have not taken innovation to scale," Ilbawi said. "Twenty-five years after the FDA approved trastuzumab, only about one-third of the world has access to this life-saving therapy."

Gaps also exist regarding financial toxicity and social distress, with 70% of patients with cancer in low- and middle-income countries and 20% in high-income countries selling assets to pay for treatment. Both loss of spending power and loss of life have economic consequences, according to a 2018 article published by ASCO, which indicated that less than 30% of low- and middle-income countries had adequate cancer care facilities and that data resources needed for modern care were woefully inadequate in most areas.

What is the path forward? According to Ilbawi, global equity in cancer care requires attention in 3 areas, which will demand collaboration from government, industry, and professional societies:

- Technology innovation: from new products to new digital tools
- Operations innovation: helping low-income countries gain access to new facilities and new business models for delivering care
- Social innovation: low-income countries need more community support for things such as patient navigation

"We should change how we measure success," he pointed out. "Only 1% of early-phase clinical trials measure quality of life, which Ilbawi said must change.

"As we move through these times of instability with our patients, we are urging them to face the greatest disruption in the world systems in almost 70 years," he said. And yet, both Ilbawi and Vokes pointed to examples of how COVID-19-fueled creativity, which will lead to new cancer vaccines or care delivery models. Hard times breed innovation, Ilbawi noted. "We must use this opportunity."

REFERENCES


At Takeda Oncology, we aspire to cure cancer, with inspiration from patients and innovation from everywhere.
LORI J. PIERCE, MD, FASTRO, FASCO, started her session with “the obvious.” The chair of the American Society of Clinical Oncology (ASCO) Board of Directors said, “We know the participation of adult cancer patients on clinical trials in this country is woefully low.” We also know the rate of participation of patients of racial and ethnic minorities is even lower than that.

“No matter which trials you look at, the message is the same.” Pierce, who is professor of radiation oncology at the University of Michigan, painted this stark picture to open her presentation, "Overview of Barriers to Ensuring Racial and Ethnic Diversity in Clinical Trials" at the 2022 ASCO Annual Meeting in a session that focused on strategies to advance equity in cancer clinical trials. She is also co-lead of the ASCO/Association of Community Cancer Centers (ACCC) clinical trials initiative, whose research statement, recently published in the Journal of Clinical Oncology, contains 6 overarching recommendations designed to guide investigators “to improve participation rates among people from racial and ethnic minority populations historically underrepresented in cancer clinical trials.”

Citing 3 important papers, Pierce highlighted their findings on disparities:

- Using 2013 Surveillance, Epidemiology, and End Results data on cancer therapy trials, a 2018 paper showed that although Black and Hispanic patients accounted for 10% and 7%, respectively, of cancer cases that year, only 6% and 2.6% of patients were enrolled in clinical trials listed on the ClinicalTrials.gov website.
- In trials that took place between 2008 and 2018 that led to FDA oncology drug approvals, according to a 2019 paper, upward of 80% of enrollees were White compared with between 10% and 35% Asian and 0% and 10% Black and Hispanic patients.
- For precision oncology studies, a paper from 2021 showed that the ratio of observed/expected trial enrollees remained high for Asian and non-Hispanic White patients but low for American Indian/Alaska Native, Black, and Hispanic patients.

“Noting the obvious,” she emphasized, “we have a very, very low number of minorities going on clinical trials.” Pierce echoed the themes put forth by the ASCO/ACCC clinical trial guidance just released—communication, education, and understanding of intrinsic and extrinsic factors affecting clinical trial participation—by noting 5 fundamental barriers that affect diversity in trials and delving deeper into each one: clinician, trial, patient, institutional, and financial barriers.

Clinician Barriers
Pierce explained that there are several clinician-related barriers to ensuring racial and ethnic diversity in clinical trials. These include the following:

- Physicians do not discuss trial enrollment with their patients; thus, patients do not know they could be a trial candidate or do not understand clinical trials.
- Physicians may be biased; for example, not taking the time to discuss a trial with patients of certain ethnicities because of the assumption these patients won’t enroll anyway.
- Physicians have limited time and resources; a lack of teams to drum up clinical trial enrollment makes it extremely difficult to communicate about trials with patients.
- Physicians may lack knowledge on the trials available to their patients.
- Physicians’ institutions do not have diverse workforces.

In particular, communication and encouragement are of utmost importance, Pierce continued. Citing a 2021 meta-analysis of trials that took place between 2000 and 2020, which focused on patient agreement to participate in cancer clinical trials, she noted that race and ethnicity do not affect trial participation.

“If you look at the patients who go on a trial, if you ask them to go on a study, it makes no difference what race or ethnicity they are. They will go on at the same percentage.” Pierce stated about the results. “The thought that certain populations don’t go on a trial could not be further from the truth. If you ask patients to go on a trial, they will go on a trial at similar rates. That is a key principle.”

Having the workforce better mirror the patient population is also important, “although I don’t believe that every patient of color has to have a provider of color,” Pierce underscored. “But there is no reason that, as a workforce, we should not mirror the population that we care for in diversity of thought and diversity of efforts. We need to mirror that population.”

For example, she said, although Black individuals represent 13.4% of the US population, they account for just 6.2% of recent medical school graduates, 3.9% of oncology fellows, and 3% of oncologists, according to a 2021 paper. In addition, just 4.7% of oncologists are Hispanic or Latino and 0.1% are American Indian or Alaska Native.

Trial Barriers
First and foremost among trial-related barriers is their narrow trial eligibility, which Pierce cited as clearly limiting to patients of color. In particular, these patients frequently have comorbidities that preclude their participation in trials.

To open up trial eligibility, ASCO and Friends of Cancer Research published a joint recommendation statement in 2021 that focused on revisions to criteria for washout periods, concomitant medications, prior therapies, laboratory ranges, and performance status. Unless a scientific basis exists for excluding a patient from a trial, such as potential toxicities from drug-drug interactions, “we need to go from the principle that we need to find the perfect patient to go on a clinical trial to reality, where we broaden the criteria and more patients, especially patients of color, can go in a study,” Pierce said.

The COVID-19 pandemic has had a particular influence on trial eligibility by teaching oncologists several lessons about expanding eligibility. Trials need to be more easily integrated into routine clinical care, treatment should be allowed to be administered remotely, and technology must be leveraged for access and efficiency improvements, as noted in a 2020 Journal of Clinical Oncology paper. “Trials need to not be so boutiquey,” Pierce said. “We need to go where the patients are.”

The adverse impact of trial location also should be considered. How do we provide maximal access to clinical trials, she posed, when location can be a barrier whether the trial is taking place...
at an academic center or a community practice or through telemedicine. Patients living in rural locations may have difficulty traveling to a trial site, so patient location must also be considered.

**Patient Barriers**
Among the patient barriers preventing racial and ethnic diversity in clinical trials, Pierce again listed 5, paying particular attention to the last 2:

- Lack of information regarding trials
- No trial available at patient’s care site
- Available trials do not match patient disease type and stage
- Social determinants of health (SDOH)
- Distrust

Not only do SDOH adversely affect patient care and access to care and clinical trials, she pointed out, but these are intertwined with patient distrust in the medical system. Economic stability (eg, expenses, debt, medical bills), neighborhood and physical environment (eg, housing, safety, walkability), and community and social context (eg, support systems, discrimination, stress)—among others—all affect the patient’s trust level.

To illustrate this point, Pierce cited a study jointly conducted by the Kaiser Family Foundation and The Undefeated (now Andscape), which asked respondents, “Can you trust these institutions to do what is right for you or your community all or almost all of the time?” Regarding trust in doctors, local hospitals, and schools, the health care system, the police, and the courts, Black individuals overwhelmingly had the least amount of trust and White individuals had the most; Hispanic individuals fell in the middle. For example, 59% of Black respondents trusted the courts, Black individuals overwhelmingly had the least amount of trust and White individuals had the most; Hispanic individuals fell in the middle.

**Institutional and Financial Barriers**
Here Pierce concentrated on finances and gaps in coverage as areas to focus on. As SDOH are intertwined with patient distrust, so are patient financial barriers ensured by insurance coverage decisions. Nowhere is this more apparent than when comparing routine cost coverage decisions between patients with private insurance or Medicare and those using Medicaid, as well as when patients incur nonmedical costs.

“We [have known] that for many, many years, patients who are on clinical trials...incur costs when they see their doctor, when they get laboratory studies, when they get x-rays—[all] routine costs within a clinical trial,” Pierce stated.

However, whereas these costs are typically covered by Medicare and private insurers, they are not covered by Medicaid. It was because of this note-worthy gap in payer coverage decisions that ASCO was the driving force behind the Clinical Treatment Act, which guarantees that patients with Medicaid coverage will have qualifying clinical trial-related routine care costs covered. This is regardless of whether the trial is a cancer trial or focused on other life-threatening injuries. Beyond medical costs, too, are those that are nonmedical, such as food, lodging, dependent care, transportation—and now gas. Patients, and their families, are responsible for all of these. And although trial sponsors may often be willing to assist, ethical and compliance concerns can complicate that process, Pierce noted. Thus, ASCO is putting its might behind the Diverse Trials Act, which is aiming to clarify “what sponsors can ethically cover.” The ultimate goal, she emphasized, is to even the playing field in terms of cost of going on a clinical trial.

“To increase the enrollment of racial and ethnic minorities in clinical trials.” Pierce concluded, “interventions must address the multiple barriers from different perspectives.”

**REFERENCES**
Randall A. Oyer, MD: Clinical Trials Must Be Accessible to Everyone

Produced by Mary Caffrey and Maggie L. Shaw

RANDALL A. OYER, MD, medical director of the Ann B. Barshinger Cancer Institute, medical director of oncology, and medical director of the Cancer Risk Evaluation Program at Lancaster General Health in Pennsylvania, talked to Evidence-Based Oncology about the recent ASCO/Association of Community Cancer Centers (ACCC) recommendations for improving diversity in clinical trials, which also were discussed at the meeting.

Oyer is lead author on a paper in increasing racial and ethnic diversity in cancer clinical trials, recently published in the Journal of Clinical Oncology. He is also a clinical professor of cancer biology at Penn Medicine in Philadelphia, Pennsylvania, and past president of ACCC.

The theme of the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting was “Advancing Equitable Cancer Care Through Innovation.” Randall A. Oyer, MD, medical director of the Ann B. Barshinger Cancer Institute, medical director of oncology, and medical director of the Cancer Risk Evaluation Program at Lancaster General Health in Pennsylvania, talked to Evidence-Based Oncology about the recent ASCO/Association of Community Cancer Centers (ACCC) recommendations for improving diversity in clinical trials, which also were discussed at the meeting.

Oyer is lead author on a paper in increasing racial and ethnic diversity in cancer clinical trials, recently published in the Journal of Clinical Oncology. He is also a clinical professor of cancer biology at Penn Medicine in Philadelphia, Pennsylvania, and past president of ACCC.

"CMS can make clinical trial participation...one of the quality metrics that they follow, measure, report on, and value through an advanced payment model. It has been a quality component of the Oncology Care Model, the now 6-year pilot project that's just coming to a close." —Randall A. Oyer, MD, medical director, Ann B. Barshinger Cancer Institute, medical director of oncology, medical director of the Cancer Risk Evaluation Program, Lancaster General Health

EBO: What is the role of community oncology practices in promoting greater diversity in clinical trials?

OYER: In the United States, most cancer patients receive their care in the community setting rather than in the academic medical center, which means that clinical trials need to be brought directly to the communities where patients are receiving their care. Yet 75% of the problem with patients not being offered clinical trials is because a matching clinical trial is not available where a patient is being treated.

Community practices now understand that cancer treatment trials are a component of high-quality care, and we see community practices investing in people, systems, and training to work with an academic partner, to work with industry, or to be part of a cooperative group that can make relevant trials accessible to patients in their communities. ACCC and ASCO are also recommending forming solid partnerships in every community, with patients, patient advisory groups, and with community organizations and leaders.

EBO: What is the role of CMS in this process?

OYER: Well, payers can and must allow their customers and beneficiaries to participate in clinical trials. They must cover trial expenses to the same extent that they cover standard of care. No policy should exclude clinical trials.

EBO: CMS can make clinical trial participation, I believe, one of the quality metrics that they follow, measure, report on, and value through an advanced payment model. It has been a quality component of the Oncology Care Model, the now 6-year pilot project that's just coming to a close.

REFERENCES

EBO: Have you noticed changes even ahead of these recommendations?

OYER: In April, the FDA issued draft guidance for industry that a race and ethnicity diversity plan is recommended for all medical products for which an IND [investigational new drug] submission is required and for clinical studies that support a marketing submission. Sponsors are given guidance to discuss a race and ethnicity diversity plan with the FDA as soon as practical in the process and at any interval along the way. Sponsors are also asked to define enrollment goals and methods that they will use as part of a trial to make sure that the diversity goals are met. Additionally, the American Cancer Society, NCCN [National Comprehensive Cancer Network], and the National Minority Quality Forum recently joined forces to create an institutional and practice equity report card that calls out the need to offer clinical trials to all cancer patients and calls out that staff training is needed to reduce barriers. And ASCO and Friends of Cancer Research have also issued a joint statement to broaden clinical trials eligibility. It's already happening; the awareness is here. And it is really a top agenda item for every cancer organization to increase diversity and make equity a cornerstone of what we do in cancer medicine.

We're not going to be where we want to be in cancer care, nor where we know we can be in cancer care, without improving on clinical trials, and improving on clinical trials means that they're accessible to everyone.
Data like you’ve never seen before.

Only KISQALI.

What could this mean for your patients?
Find out at KISQALI-hcp.com
Trastuzumab Deruxtecan Cuts Risk of Disease Progression or Death by 50% in HER2-Low Metastatic Breast Cancer

MARY CAFFREY

CLASSIFYING BREAST CANCER along the familiar lines of human epidermal growth factor receptor 2 (HER2)-positive or HER2-negative may be a thing of the past, following the June 5 release of landmark findings. These show that trastuzumab deruxtecan (Enhertu) offered significant benefits in both progression-free survival (PFS) and overall survival (OS) compared with chemotherapy in a group of patients with HER2-low metastatic breast cancer.1

Data from the DESTINY-Breast04 study (NCT03734029), published in the New England Journal of Medicine,2 drew a standing ovation during the plenary session of the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago. The findings show that trastuzumab deruxtecan, already approved in certain unresectable or metastatic HER2-positive breast cancers or gastric cancers, reduced the risk of disease progression or death by 50% compared with chemotherapy for HER2-low patients with both hormone receptor (HR)-positive and HR-negative disease.

Trastuzumab deruxtecan, jointly developed by Daiichi Sankyo and AstraZeneca, is among a group of therapies known as antibody-drug conjugates (ADCs), which connect monoclonal antibodies to tumor cells with a “linker,” causing a more targeted and potent effect on cancer. In this case, the well-known trastuzumab, which binds to HER2 receptors, works with deruxtecan to become embedded in the cancer cell, disrupting the cell’s DNA and leading to cell death.3

DESTINY-Breast04 was a phase 3 trial of previously treated patients with metastatic HER2-low disease. It had a primary end point of PFS in patients with HR-positive disease. Secondary end points included PFS based on blinded independent central review of all randomly assigned patients, including those with HR-positive and -negative disease, and OS in HR-positive patients and OS in all patients.4

Results from the trial showed the following:

• Of the 557 randomly assigned patients, 494 (88.7%) had HR-positive disease and 63 (11.3%) had HR-negative disease.

• In the HR-positive group, median PFS was 10.1 months in the trastuzumab deruxtecan group vs 5.4 months for those receiving chemotherapy (physician’s choice), for a hazard ratio (HR) of 0.51 (P < .001). OS in this group was 23.9 months for the study drug vs 17.5 months for chemotherapy (HR, 0.64; P = .003).

• Among all patients, median PFS was 9.9 months for trastuzumab deruxtecan and 5.1 months for chemotherapy (HR, 0.50; P < .001).

• Adverse events of grade 3 or higher were lower in the study drug group at 52% vs 67.4% in the chemotherapy group.

• Of concern in patients receiving ADCs, interstitial lung disease or pneumonitis was seen in 12.1% of the study drug group; 0.8% of patients died.

• Another concern raised was the small number of Black and Hispanic patients enrolled in the trial, and several commenters called for ongoing studies to determine how these patients fared with the therapy.

During a press briefing and the plenary session, Shana Modi, MD, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, New York, and the trial's principal investigator, and experts from ASCO pronounced the results as game changing in breast cancer. As Modi explained, “We currently define the HER2 status of breast cancers in a binary model, where HER2-positive breast cancers driven by the oncogene are treatable with currently available HER2-positive targeted therapies and HER2-negative breast cancers are not.”

In reality, it’s not that clear cut. Within the HER2 group some patients have low levels of HER2 expression that may still be targetable, but thus far therapies have proved ineffective. For this reason these patients have been classified as HER2-negative for treatment.

“These results established [that patients with] HER2-low metastatic breast cancer is a targetable population of breast cancer, with trastuzumab deruxtecan as a new standard of care in this setting.” —Shana Modi, MD, medical oncologist, Memorial Sloan Kettering Cancer Center

ADCs, which Modi called next-generation targeted therapies, offer a delivery system that creates a “bystander” effect, which also targets cells in the immediate vicinity of the tumor. Thus, patients with HER2-low disease see responses unlike any seen previously, said Modi and ASCO commenter Jane L. Meisel, MD, of Winship Cancer Institute at Emory University in Atlanta, Georgia.

The experience with trastuzumab deruxtecan has been remarkable, Meisel said. “Everyone who’s used it in our clinic undoubtedly has seen some patients—even with significant burdens of disease—have their cancer melt away with this agent,” she said. “What this trial does is really extend the benefits of this agent to a whole new group of patients.”

Modi concluded, “These results established [that patients with] HER2-low metastatic breast cancer is a targetable population of breast cancer, with trastuzumab deruxtecan as a new standard of care in this setting.”

Asked by The American Journal of Managed Care to highlight what she found compelling about the results, Debra Patt, MD, PhD, MBA, executive vice president for health care policy and strategic initiatives at Texas Oncology and an expert in breast cancer treatment, cited 3 things:

• Among patients with HER2-low disease, there is a survival benefit of receiving trastuzumab deruxtecan vs physician’s choice chemotherapy.

• The population that stands to benefit is large. “As we understand it, about 55% of patients with advanced breast cancer may benefit from this therapeutic intervention,” Patt said.

• The toxicity profile of patients who received trastuzumab deruxtecan was lower than that of patients who received standard chemotherapy.
“What this tells us, in summary, is that among patients who have HER2-low breast cancer and have been treated previously with a chemotherapy, if they receive trastuzumab deruxtecan, they are likely to have an overall survival benefit and lower toxicity as opposed to if they receive chemotherapy,” said Patt, who is also a member of the Evidence-Based Oncology editorial board.

ASCO Chief Medical Officer and Executive Vice President Julie R. Gralow, MD, FACP, FASCO, added that the pathology of breast cancer would have to be redefined, based on the findings in DESTINY-Breast04.

Patt agreed. “No longer can we simply say that someone is HER2-positive or HER2-negative, but the appreciation of HER2 low becomes really important as these patients clearly benefit from therapeutic intervention,” she said. “As we rethink this, we need to understand better and work with our pathologists [regarding] how we can make sure that we represent [patients who are] IHC [immunohistochemistry] 1 positive or IHC 2 positive, or this HER2-low population, in a systematic way to make sure patients can benefit from particular treatments.”

During the plenary session, Patricia LoRusso, DO, professor, Yale School of Medicine in New Haven, Connecticut, called for better tools to evaluate HER2 status during remarks after Modi’s presentation. Patt concurred with this as well. “We need to understand different limitations of assessment; for example, when the bone is biopsied, can there be false-negative results from the decalcification process? These are specifics that we need to understand as we try to ensure that each patient might benefit from particular therapeutic innovations in clinic,” Patt said.

REFERENCES

Sacituzumab Govitecan Improved PFS for Patients With a Common Breast Cancer and Limited Options—but Is It Enough?

FOR PATIENTS WITH ADVANCED hormone receptor (HR)-positive or human epidermal growth factor receptor 2 (HER2)-negative breast cancer who have gone through available treatment options, anything that offers hope might be worth a try. But how many weeks of keeping the cancer at bay are worth the risk of more adverse effects or higher costs? Are 6 weeks enough?

Those were the unanswered questions after the presentation of data from TROPiCS-02 (NCT03901339), a phase 3 study whose results were presented on June 4 during a session on breast cancer at the 2022 annual meeting of the American Society of Clinical Oncology (ASCO).

TROPiCS-02 was designed to evaluate sacituzumab govitecan (Sacituzumab), an antibody-drug conjugate (ADC), against physician’s choice of chemotherapy in patients who have received multiple prior therapies—including a CDK4/6 inhibitor and endocrine therapy. Sacituzumab, sold by Gilead as Trodelvy, is already approved in advanced triple-negative breast cancer; no ADC is approved in HR-positive or HER2-negative breast cancer, the most common subtype, which comprises about 70% of all breast cancer cases.

The trial results were presented by Hope S. Rugo, MD, FASCO, a professor of medicine and director of Breast Oncology and Clinical Trials Education at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center. Rugo outlined the parameters of the study, which involved 543 patients at 113 international sites; more than half the patients had received 3 or more regimens. According to the study design, overall survival (OS) would be tested if progression-free survival (PFS) was statistically significant, followed by overall response rate and quality of life. The data Rugo presented is the first primary PFS analysis and the first of 3 planned OS interim analyses. Data included the following:

- Sacituzumab showed improved median PFS over chemotherapy by 34%, but the actual time difference was 5.5 months vs 4.0 months (stratified HR, 0.66; 95% CI, 0.53-0.83; P = .003).
- PFS rates favored sacituzumab over chemotherapy at 6, 9, and 12 months; comparisons were 46% vs 30%, 33% vs 17%, and 21% vs 7%, respectively.
- There was a nonsignificant trend in OS in favor of sacituzumab at 13.9 vs 12.3 months (stratified HR, 0.84; 95% CI, 0.67-1.06; P = .14). Rugo said the data are not yet mature and more time is needed to evaluate OS.
- Sacituzumab had a better median duration of response (DOR), which means the tumor responded to treatment for a longer period without spreading. The median DOR for sacituzumab was 7.4 months compared with 5.6 months for chemotherapy.
- Benefits were generally consistent across subgroups.

The safety profile was consistent with previous studies of sacituzumab; 6% of patients discontinued sacituzumab due to treatment-emergent adverse events vs 4% for chemotherapy. Adverse events were reported in 74% of patients receiving sacituzumab vs 60% receiving chemotherapy, the most

Mary Caffrey

Hope S. Rugo, MD, FASCO, professor of medicine, director of Breast Oncology and Clinical Trials Education, University of California, San Francisco.

Veronique Dieras, MD, medical oncologist, Rennes, France.

Yvernique Dieras, MD, medical oncologist, Rennes, France.

JULY 2022 | AJMC.COM SP239
common being neutropenia (51% vs 39%) and diarrhea (10% vs 1%).

During the session, Rugo was asked whether 1.5 months represented a clinically meaningful benefit, and she said she had expected that question. “I think we suffer a little bit from our statistics in patients who are heavily pretreated for metastatic disease,” she noted. In this population, she explained, a large number of patients often progress early on, so it is not unusual to see a “fairly modest absolute difference” in PFS alongside a “very robust hazard ratio.”

Given the lack of choices for these patients, who are both heavily pretreated and endocrine resistant, Rugo said sacituzumab “should be considered a potential treatment option in this patient population.”

ASCO breast cancer expert June Lowe Meisel, MD, agreed. “[The findings from] this trial show that sacituzumab govitecan, which is already approved for the treatment of metastatic triple-negative breast cancer, may represent an important new option for patients with endocrine-resistant HR-positive/HER2-negative metastatic breast cancer,” she said in a statement. “This would address a critical unmet medical need, given the limited number of effective treatment options currently available for these patients.”

But Véronique C. Dieras, MD, of Eugène Marquis Center in Rennes, France, who discussed the first group of abstracts on metastatic breast cancer, said more data are clearly needed. “When we look to the result of a phase 3 study, we have to ask about the magnitude of benefit and if it’s clinically meaningful. We see in these studies that we have only 1.5 months of difference….The data are not mature.”

**REFERENCE**

---

**Investigators Evaluate MBC Survival in Studies Addressing Race, Ethnicity, Socioeconomic Disparities**

**MAGGIE L. SHAW**

**DATA ON DISPARITIES IN OUTCOMES** by race, ethnicity, and socioeconomic status (SES) in patients with metastatic breast cancer (MBC) were presented on June 6 during a poster session at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting. The session addressed such subjects as patient quality of life following treatment with tricobilirin, overall survival (OS) and progression-free survival following treatment for hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative disease and triple-negative disease.

Rachel A. Freedman, MD, MPH, led the first discussion, which was on disparities in MBC and focused on promoting equity to improve outcomes in the disease. Freedman is medical director of the Dana-Farber Cancer Institute (DFCI) Collaborative and Strategic Alliances, senior physician in medical oncology, associate professor, Harvard Medical School. She highlighted the interrelationship between SES and survival in MBC and increasing participation among Black patients in MBC clinical trials.

**MBC Survival Disparities by SES/Neighborhood Deprivation Index**

Patients living in neighborhoods or areas classified as having a lower SES, especially Black patients, are more likely to have worse survival outcomes following a diagnosis of MBC: Lower SES was shown to be an independent predictor of OS in MBC and was associated with a 19% greater risk of poor survival (HR, 1.19; 95% CI, 1.04–1.37; P = .01).

“Poorer outcomes in African American patients are likely due to the association between lower SES and African American race,” the authors wrote.

A team of investigators from the University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center and the Women’s Cancer Research Center used comprehensive data from their Metastatic Breast Cancer Database for 1246 patients who received an MBC diagnosis and were treated for it between 2000 and 2017. They used Neighborhood Deprivation Index (NDI), also known as the Area Deprivation Index, scores to evaluate MBC survival as influenced by SES and race. These scores were derived from the Neighborhood Atlas via zip code.

“The NDI is a novel approach to looking at area level SES. It really is a measurement for neighborhood disadvantage,” Freedman stated. “There are multiple factors that are pulled into this index that measure education, income, and household composition.”

Patients were divided into 2 groups. Those in the low-deprivation/upper SES group (n = 414) had NDI scores in the bottom tertile, and those in the high-deprivation/lower SES group (n = 832) had NDI scores in the middle or top tertile. The median study follow-up was 2.27 years; mean ages were similar at 56.1 (12.8) and 57.6 (13.0) years in the low- and high-SES groups, respectively; mean tumor sizes were identical, at 3.5 cm each; and most patients in each group (55.2% and 52.6%) had estrogen receptor (ER)-positive/HER2-negative disease. More patients in the high-deprivation/lower SES group were African American than those in the low-deprivation/higher SES cohort, at 10.5% vs 3.7%.

“Race was the only baseline characteristic that was significantly different between the SES groups,” the study authors wrote.

For the primary OS outcome, the Kaplan-Meier survival analysis shows consistent higher and longer survival rates among patients with MBC living in an upper-SES area and who are Caucasian vs those who live in a lower-SES area and are African American. Over the 16 years in this analysis, more than twice as many patients living in a lower-SES area died (756 vs 373 in a higher-SES area), with corresponding median survivals of 2.3 vs 2.7 years. In addition, African American patients survived at a lower rate than Caucasian patients: 93% died following a median survival of 1.8 years compared with 91% following a median survival of 2.5 years.

However, using a Cox proportional hazard model, race was shown to factor less in MBC OS when SES was accounted for.
Freedman concluded that although these findings add more evidence that SES mediates much of what we see when it comes to racial disparities, “we don’t really understand how NDI specifically impacts outcomes.”

Overall, the authors posited that future research needs to investigate health care investments in low-SES neighborhoods, assess MBC treatment disparities, and attempt to understand how the stress and inflammatory pathways that adversely influence poor health outcomes are themselves influenced by neighborhood. And Freedman reiterated that investigators and clinicians need to have a standardized method of collecting information on social determinants of health.

**MBC Clinical Trial Participation Disparities**

Having lived with de novo MBC since July of 2015, Stephanie Walker, BSN, first navigated her advanced diagnosis as part of Athena Oncology’s Facing MBC Together campaign. Now she is a member of the Metastatic Breast Cancer Alliance and lead author on an abstract that discusses findings from the patient-led initiative, The BECOME (Black Experience of Clinical Trials and Opportunities for Meaningful Engagement) Research Project. The authors noted goal of BECOME is “to better represent Black people in cancer research by increasing access to clinical trials for MBC.”

“It is vital to have diverse patient enrollment in research. Research informs everything we do in clinic,” Freedman emphasized. “It’s how we understand short-term, long-term, and late effects; efficacy; toxicity; quality of life; the patient experience; genomic and biomarker profiles; and cancer prevention and risk assessment.” She added that if clinical trials fail to represent the population affected by a disease, clinicians are unable to sufficiently inform their patients.

Rich information is needed to understand what is going on, due to the limited depth of current data available, she continued, data that are often not self-reported. This includes not combining race and ethnicity categories, which studies often do, despite “dramatically different” genetics, cultures, and geographies, for example.

To overcome these barriers, BECOME conducted both a literature review (34 articles) and a patient-led web-based survey, with sponsorship from the MBCA. Recruitment took place through social media posts and MBCA emails. Of the 424 survey respondents (from 31 virtual interviews), 24% self-identified as Black. Among this Black patient population, 37% had a postgraduate degree or had taken postgraduate courses, most were aged 25 to 44 years (28%) or 45 to 54 years (33%), private insurance was the most common coverage (42%), and 59% of their oncologists were affiliated with an academic or university medical system.

Although approximately 15% of patients with cancer in the United States are Black, only 4% to 6% of clinical trial participants are Black, the study authors pointed out. Led by Walker, their primary study objectives were to understand trial participation barriers among Black patients with MBC and identify actions to increase that participation. “Only when trial participants reflect the diversity of the general population can oncologists understand how a drug works across subpopulations,” Walker and her coauthors wrote.

Data show that 80% of Black patients with MBC would consider participating in clinical trials, 83% are somewhat likely to consider participating, and 92% have an interest in learning about clinical trials. But only 36% have received as much information as they wanted from their oncologist and care team, and just over half, 54%, are aware there are MBC trials. The top barriers these patients identified as preventing their clinical trial participation were total necessary appointments and tests (40%), travel time (47%), potential extra medical costs (51%), overall financial burden (56%), difficulty finding trials (64%), and insurance not taken at centers running trials (73%). Forty percent also reported that no one on their team had told them about trials.

Black patients wanting to learn more about MBC clinical trials, compared with non-Black patients, felt that the most effective ways to inspire their trust were to learn about the trials from someone of their race/ethnicity (67% vs 10%), from someone who has had breast cancer (73% vs 44%), from someone who has had MBC (73% vs 51%), and from a fellow trial participant (72% vs 48%). In fact, the BECOME study authors noted, “Black patients were more likely than non-Black patients to want to learn about clinical trials from someone with shared experience.”

Addressing patient concerns was another top issue identified in the BECOME study. Compared with non-Black patients, Black patients were more worried about potential adverse effects (73% vs 66%) and drug effectiveness (63% vs 62%), were more likely to believe unstudied treatments were harmful (57% vs 31%), were less likely to believe all patients would be treated fairly and equally during a trial (32% vs 56%), and were principally motivated to participate “to ensure people with my racial or ethnic identity will benefit” (83% vs 51%). In addition, 73% of Black respondents to the BECOME survey vs 91% of non-Black respondents indicated they trust trials overall.

“These findings are consistent with past cited barriers,” Freedman noted, “and highlight the importance of trust, education, logistics, and expense—all of which are actionable.”

For dynamic and positive change to take place, efforts must be made at every step in the clinical trial process—planning, enrollment, and post-trial, she emphasized. Freedman echoed the study authors, who highlighted the need to share results and develop diversity strategies, expand the survey respondent base, step up patient education efforts, expand patient assistance efforts in finding trials, and even train health care providers to communicate with patients more effectively.

More specifically, the BECOME study authors came up with these 4 overarching action steps:

- Enhance awareness about trials
- Build trust through clear communication
- Address concerns
- Help patients find and access trials

All stakeholders have a role to play in increasing Black patient participation, the BECOME authors concluded.

**REFERENCES**


IBRANCE has been helping to change the story since initial US approval in 2015. See how it has all unfolded at IBRANCEhcp.com
Hope S. Rugo, MD, FASCO, Discusses Clinical Trial Minority Recruitment, PALOMA-2 Findings

Produced by Hayley Virgil and Maggie L. Shaw

Hope S. Rugo, MD, FASCO, is a professor of medicine and director of Breast Oncology and Clinical Trials Education at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center. In an interview with Evidence-Based Oncology (EBO), Rugo discussed overall survival (OS) results for PALOMA-2 (NCT01740427) that were presented during the 2022 annual meeting of the American Society of Clinical Oncology (ASCO). Many at the meeting were surprised that PALOMA-2 did not show improved OS for palbociclib and letrozole in advanced breast cancer; investigators said missing data may have been a factor in the results.

EBO: How do PALOMA-2 OS results compare with your experience in clinical practice?

RUGO: You know, it’s hard to know. It just doesn’t align with what we’ve seen in clinical practice at all. And we have a real-world data study that, again, suggests that there is a survival benefit—it’s real-world data—but it just was so surprising to not see this survival benefit in PALOMA-2, with all of the hazard ratios the same across the different trials. And then, the first 4 patients I put in PALOMA-2 are still in at 7 and 8 years—and lots of my other patients in practice—so it just doesn’t make sense to me that somehow there would be some magic with that drug where there wasn’t survival.

The bottom line is, the trial is what it is and was reported the way it’s reported, and maybe some additional analyses will help us understand this better. I think that looking at the combination of PALOMA-1 and -2, and taking out those patients who had the disease-free interval of less than 12 months was really helpful because it shows that those patients probably had the biggest contribution to the lack of OS difference.

EBO: Can you offer guidance on how ASCO can implement its recommendations to improve clinical trial diversity?

RUGO: This is just such an important area. And actually, it was a question asked at the plenary session for DESTINY-Breast04 (NCT03734029), where the question was, how come there’s so [few] minority patients enrolled? How come they’re all Caucasian? Why was that? That’s a big question with clinical trials. We really have to work hard to try and improve that minority enrollment in clinical trials and then access to care outside of the setting of trials.

What can we do to improve the enrollment and trials? We know there are some countries where reporting ethnicity and race is not allowed, because there’s concern about bias. It may be that ASCO as an organization has the power to have people reported in the setting of trials, but not regularly, and maybe that would answer some of the questions of countries like France that don’t allow reporting. But then how do we improve the accrual?

I think it has to do with, as a community, really working with our pharma partners to improve the funding for minority patients to go on to trials, because what happens is patients generally who are of lower socioeconomic status—not all minorities, by any means—live farther away, they have children to take care of, and they’re doing jobs that are not forgiving. And gas prices in California are $7 a gallon. People can’t go anywhere. So I think what we need to do is to provide support for people to have an opinion, to see whether or not we benefit them, to then come in and participate in the trial and to get compensation for the amount of money and time that they have to put into participating in the trial.

“The trial is what it is and was reported the way it’s reported….I think that looking at the combination of PALOMA-1 and -2, and taking out those patients who had the disease-free interval of less than 12 months was really helpful because it shows that those patients probably had the biggest contribution to the lack of [overall survival] difference.”

—Hope S. Rugo, MD, FASCO, professor of medicine and director, Breast Oncology and Clinical Trials Education, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center

I think that’s the only way we’re going to fix this, because right now, it’s all—in my mind—more lip service, because they’re saying, “Well…we just have to have alliances and tell people the trials are there and they’ll come.” But that’s not actually the case. I think we really have to provide some support mechanism, too.

ASCO has, in all fairness, made a lot of collaborations with different groups, including the World Health Organization and UICC [Union for International Cancer Control], and within this affiliation with the World Health Organization they’ve created a lot of different ASCO presence, education, and support in different countries. So that’s great. But I think we also need to have this other part of it where, [because] the drugs are expensive and trials are difficult, there has to be some way to get around that.

References


Important Safety Information

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1–blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

• The first-line treatment of patients with non–small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (tumor proportion score [TPS] ≥50%) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation OR metastatic

• The treatment of patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate

• For the treatment of patients with metastatic BCC (mBCC) previously treated with an HHI or for whom an HHI is not appropriate. The mBCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for mBCC may be contingent upon verification and description of clinical benefit

• The treatment of patients with metastatic cutaneous squamous cell carcinoma (mSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation

Visit LIBTAYOhcp.com for more information.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

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

No dose reduction for LIBTAYO is recommended. In general, withhold LIBTAYO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue LIBTAYO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated adverse reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

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

Immune-mediated colitis: LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/ PD-L1–blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

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

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

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

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

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

• Adrenal insufficiency: LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

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

Immune-mediated endocrinopathies: (cont’d)

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

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

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

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

- **Hypothyroidism:** Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

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

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

Immune-mediated dermatologic adverse reactions: LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

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

- **Cardiac/vascular:** Myocarditis, pericarditis, and vasculitis. Permanently discontinue for Grades 2, 3, or 4 myocarditis

- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.
Important Safety Information (cont’d)

Warnings and Precautions (cont’d)

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

Other immune-mediated adverse reactions: (cont’d)

- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis
- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- **Endocrine:** Hypoparathyroidism
- **Other (hematologic/immune):** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

Infusion-related reactions

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

Complications of allogeneic HSCT

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

Embryo-fetal toxicity

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

Adverse Reactions

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

Use in Specific Populations

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

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


ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; PD-L1, programmed death ligand-1; ROS1, c-ros oncogene 1 receptor tyrosine kinase.
LIBTAYO® (cemiplimab-rxk) injection, for intravenous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Cutaneous squamous cell Carcinoma

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mSCC) or locally advanced cutaneous squamous cell carcinoma (mCSCC) who have failed prior systemic therapy, including radiation therapy, or for whom surgical resection is not appropriate. The mSCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for the mSCC indication may be contingent upon verification and description of clinical benefit.

1.2 Basal Cell Carcinoma

LIBTAYO is indicated for the treatment of patients 18 years of age and older with metastatic basal cell carcinoma (mBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. The mBCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for the mBCC indication may be contingent upon verification and description of clinical benefit.

1.3 Non-Small Cell Lung Cancer

LIBTAYO is indicated for the first-line treatment of patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (Tumor Proportion Score (TPS) ≥50%) as determined by an FDA-approved test (see Dosage and Administration (2.3) in the full prescribing information) with no EGFR, ALK or ROS1 aberrations, and:
- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or metastatic.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor (PD-1) or PD-1 ligand (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed above, Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time during LIBTAYO treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions may develop at any time during LIBTAYO treatment or shortly after discontinuation of LIBTAYO. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

5.1.1 Severe or Fatal Immune-Mediated Pneumonitis

Immune-mediated pneumonitis can occur in any lung or extrapulmonary tissue. Immediate medical consultation should be sought with consideration of underlying immune-mediated adverse reactions. Evaluate lung enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

5.1.2 Severe or Fatal Immune-Mediated Nephritis with Renal Dysfunction

Immune-mediated nephritis with renal dysfunction can occur in any organ system or tissue. Immediate medical consultation should be sought with consideration of underlying immune-mediated adverse reactions. Evaluate kidney enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

5.1.3 Severe or Fatal Immune-Mediated Dermatologic Adverse Reactions

Immune-mediated dermatologic adverse reactions may involve any organ system, tissue, or normal body covering. They may be severe or fatal and may occur at any time during LIBTAYO treatment. Immune-mediated dermatologic adverse reactions affecting more than one body system can occur simultaneously.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Immune-mediated dermatologic adverse reactions may develop at any time during LIBTAYO treatment or shortly after discontinuation of LIBTAYO. Immune-mediated dermatologic adverse reactions affecting more than one body system can occur simultaneously.

5.1.4 Severe or Fatal Immune-Mediated Endocrine Adverse Reactions

Immune-mediated endocrine adverse reactions may involve any organ system or tissue. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Immune-mediated endocrine adverse reactions may develop at any time during LIBTAYO treatment or shortly after discontinuation of LIBTAYO. Immune-mediated endocrine adverse reactions affecting more than one body system can occur simultaneously.

5.1.5 Severe or Fatal Immune-Mediated Hypothyroidism

Immune-mediated hypothyroidism can occur in any organ system or tissue. Immediate medical consultation should be sought with consideration of underlying immune-mediated adverse reactions. Evaluate thyroid stimulating hormone and creatinine at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

5.1.6 Severe or Fatal Immune-Mediated Thyroiditis

Immune-mediated thyroiditis can occur in any organ system or tissue. Immediate medical consultation should be sought with consideration of underlying immune-mediated adverse reactions. Evaluate thyroid stimulating hormone and creatinine at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

5.1.7 Severe or Fatal Immune-Mediated Hypophysitis

Immune-mediated hypophysitis can occur in any organ system or tissue. Immediate medical consultation should be sought with consideration of underlying immune-mediated adverse reactions. Evaluate thyroid stimulating hormone and creatinine at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

5.1.8 Severe or Fatal Immune-Mediated Diabetic Dermatitis Adverse Reactions

Immune-mediated diabetic dermatitis adverse reactions may involve any organ system or tissue. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Immune-mediated diabetic dermatitis adverse reactions may develop at any time during LIBTAYO treatment or shortly after discontinuation of LIBTAYO. Immune-mediated diabetic dermatitis adverse reactions affecting more than one body system can occur simultaneously.

5.1.9 Severe or Fatal Immune-Mediated Thyroid Disorders

Immune-mediated thyroid disorders can occur in any organ system or tissue. Immediate medical consultation should be sought with consideration of underlying immune-mediated adverse reactions. Evaluate thyroid stimulating hormone and creatinine at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue LIBTAYO depending on severity (see Dosage and Administration (2.3) in the full prescribing information).

5.2 Infusion-Related Reactions

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Mortality for patients with severe or life-threatening infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea. Intermittent or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction (see Dosage and Administration (2.3) in the full prescribing information).

5.3 Contraindications of Allogeneic HSCRT

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

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

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

6. ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1634). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 132 patients with advanced BCC (Study 1620), 555 patients with NSCLC (Study 1624), and 194 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=225), 350 mg every 3 weeks (n=543), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 57% were exposed for ≥ 6 months and 25% were exposed for ≥ 12 months. In this pooled safety population, the most common adverse reactions (≥15%) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥2%) were lymphopenia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

Cerebral Symptomatic Cell Carcinoma (CSCC)

The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 [see Clinical Studies (14.1) in the full prescribing information]. Of these 219 patients, 131 had mCSCC (nodal or distant) and 88 had laCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=162) or 350 mg every 3 weeks (n=56) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 27 weeks (2 weeks to 110 weeks). The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 90% White, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (62%) and 1 (38%).

Serious adverse reactions occurred in 32% of patients. Serious adverse reactions that occurred in ≥ 1% of patients included: pneumonitis (n=1), colitis (n=4), thrombocytopenia (n=3), rash (n=2), and nephrosis (n=2). The composite term includes rash, rash maculo-papular, rash, dermatitis, dermatitis acneiform, rash pruritic, dermatitis, and urticaria. The most common Grade 4-5 laboratory abnormalities (≥2%) were lymphopenia, hypophosphatemia, increased aspartate aminotransferase, and hyperkalemia.

Table 2: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LIBTAYO n=219</td>
<td>LIBTAYO n=132</td>
</tr>
<tr>
<td>General and Administration Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Arthritis</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity was graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 4.03

a. Composite term includes fatigue, anemia, and malaise
b. Composite term includes rash, musculoskeletal pain, cough, myalgia, diarrhea, and pneumonia
c. Composite term includes rash maculo-papular, rash, dermatitis, and eczema

Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>2</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI-CTCAE v. 4.03

a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter

Table 4: Adverse Reactions in ≥ 10% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>49</td>
<td>3.8</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>33</td>
<td>1.5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>0.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>1.5</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12</td>
<td>2.3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>1.5</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>1.5</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 4.03

a. Composite term includes fatigue, anemia, and malaise
b. Composite term includes rash, musculoskeletal pain, cough, diarrhea, and pneumonia
c. Composite term includes rash maculo-papular, rash, dermatitis, and eczema

d. Composite term includes upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, respiratory tract infection, and viral upper respiratory tract infection

The most common Grade 3 or 4 adverse reactions (>2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure, hyperkalemia and visual impairment. The most common (≥3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hyperkalemia.
The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 (see Clinical Studies (14.3) in the full prescribing information). Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator’s choice of chemotherapy (n=342), consisting of paclitaxel plus cisplatin or carboplatin; gemcitabine plus cisplatin or carboplatin; or pemetrexed plus cisplatin or carboplatin followed by optional pemtrexed maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥ 6 months and 22% were exposed for ≥12 months.

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

88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke and increased alanine aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonitis, pneumonia, hypothyroidism, muscle spasms, and musculoskeletal pain.

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

Data
Animal Data
Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to cemiplimab-rwlc may increase the risk of developing immune-mediated disorders or altering the normal immune response.

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

8.3 Females and Males of Reproductive Potential

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

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

Pediatric Use

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

8.5 Geriatric Use

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

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

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

Lib. 21.0610.013 07/21

REGENERON | SANOFI GENZYME © 2021 Regeneron Pharmaceuticals, Inc., and sanofi-aventis U.S. LLC. All rights reserved.

Table 5: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in n = 1% of Patients with Advanced BCC Receiving LIBTAYO in Study 1624

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LIBTAYO n=355</th>
<th>Chemotherapy n=342</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6</td>
<td>1.8</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LIBTAYO n=355</th>
<th>Chemotherapy n=342</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td>Bone and lymphoid system disorders</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>12</td>
<td>3.4</td>
</tr>
<tr>
<td>Decrease glucose</td>
<td>12, 3.4</td>
<td>18, 0.3</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>12, 3.4</td>
<td>18, 0.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12, 3.4</td>
<td>18, 0.3</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>12, 3.4</td>
<td>18, 0.3</td>
</tr>
<tr>
<td>Cough</td>
<td>12, 3.4</td>
<td>18, 0.3</td>
</tr>
</tbody>
</table>

Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03
a. Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, pain, spinal pain, and musculoskeletal stiffness.

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) in the full prescribing information). There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see Data). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>LIBTAYO n=355</th>
<th>Chemotherapy n=342</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>2.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>2.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>2.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>4.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Toxicity graded per NCI CTCAE = 4.03
a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.
Inovio’s DNA Vaccine Combo Plus Cemiplimab Shows Promise in Glioblastoma

MARY CAFFREY

AMID THE PROGRESS SEEN with checkpoint inhibitors in other cancers, glioblastoma stands out as the last frontier—immunotherapies as a group have not worked well in this disease.

But a new method for delivering the treatment offers promising overall survival (OS) results and merits further study, according to a leading glioblastoma investigator who presented findings on June 6, during the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting.

The results involve a pair of DNA medicines combined with the checkpoint inhibitor cemiplimab, which is approved as Libtayo to treat other solid tumors. The regimen is designed to prime a T-cell response before a patient receives radiation.

David A. Reardon, MD, clinical director, Center for Neuro-Oncology, Dana-Farber Cancer Institute in Boston, Massachusetts, offered the first look at median survival findings involving Inovio’s DNA medicines, INO-5401 and INO-9012, which were administered with cemiplimab. Reardon explained the concept of the combination and its mechanism of action: “We rationalized that utilizing a robust vaccine platform with checkpoint blockade may be able to generate antitumor immune responses that could migrate the T cells into the immunologically cold tumor microenvironment, which could translate into a survival benefit.”

This is no simple regimen. INO-5401 contains plasmids that encode the tumor-associated antigens human telomerase, Wilms tumor 1, and prostate-specific membrane antigen. INO-9012 is a synthetic DNA plasmid, which encodes interleukin 12 and works to stimulate the T cells locally.

The primary objective of the study presented at ASCO was to demonstrate safety and tolerability, with secondary end points of activity in terms of links with biomarkers.

There were several exploratory objectives, including examining the FGFR1-4 inhibitor futibatinib (TAS-120) administered with cemiplimab. Reardon explained the concept of the combination and its mechanism of action: “We rationalized that utilizing a robust vaccine platform with checkpoint blockade may be able to generate antitumor immune responses that could migrate the T cells into the immunologically cold tumor microenvironment, which could translate into a survival benefit.”

The study broke the patients down by their MGMT status, methylated or unmethylated, as this marker is known to dictate the effectiveness of therapies in glioblastoma. As expected, the patients with methylated MGMT status fared better. Median OS for patients with unmethylated MGMT status was 17.9 months, which Reardon compared with historical averages of 14.6 to 16 months. For those with unmethylated status, the median OS was 32.5 months, compared with historical averages of 23.2 to 25 months; 3 patients were still alive and on the study at the time of data cutoff in April 2022.

STUDY METHOD. Following tumor resection and enrollment in the study, all patients received the dual DNA regimen with cemiplimab 2 weeks prior to treatment with radiation, to trigger a T-cell response. Radiation was given with temozolomide for 3 weeks in all patients.

There were 2 cohorts of patients: cohort A had unmethylated MGMT (32 patients) and cohort B had methylated MGMT (20 patients). In addition, temozolomide was given to cohort B for 6 adjuvant cycles. All the while, cemiplimab was given every 3 weeks until disease progression.

The median time on study for cohort A was 17.9 (3.7-42.3) months, with a median of 10 (1-60) doses of cemiplimab. For cohort B, the median time on study was 30.7 (1.3-41.9) months, with a median of 17 (1-53) doses of cemiplimab. Most patients discontinued the study due to disease progression.

“We saw a good safety profile and some encouraging survival benefit, but this clearly needs to be definitively evaluated in a randomized clinical trial,” Reardon said.

REFERENCE


FOENIX Update: A New Era in Cholangiocarcinoma Precision Medicine

MAGGIE L. SHAW

DATA FROM THE FINAL ANALYSIS of a trial examining the FGFR1-4 inhibitor futibatinib (TAS-120) bear out its durability, efficacy, and tolerability among patients with the rare cancer intrahepatic cholangiocarcinoma (iCCA). The findings confirm results seen in the primary analysis and show outcomes that exceed historical standards.

Patients with iCCA, particularly those whose disease progresses following first-line chemotherapy, have limited overall treatment options1 and a notoriously poor survival rate.2 Data presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting put the 5-year survival rate at 24%.3 However, data presented at the 2022 ASCO Annual Meeting show that patients may soon have a new agent to fight this rare cancer in futibatinib (Taiho Oncology), an FGFR inhibitor.

Lipika Goyal, MD, an assistant professor of medicine at Harvard Medical School and a medical oncologist at Mass General Cancer Center in Boston, Massachusetts, presented the final data analysis of the phase 2 FOENIX-CCA2 trial (NCT02052778) on futibatinib at the meeting.4 Goyal explained that median overall survival (OS) for iCCA also is short, at just over 6 months with second-line chemotherapy with a FOLFOX (folinic acid, fluorouracil, »
and oxaliplatin) regimen and close to 1 year with first-line gemcitabine and cisplatin, or gemcitabine, cisplatin, and durvalumab.

Approximately 8000 patients receive a CCA diagnosis each year, but patients with FGFR2 gene rearrangements, including fusions, especially stand to benefit from futibatinib, as this genetic mutation is seen more often in those living with iCCA. The mutation occurs at a rate of 9% to 14% in the 40% to 50% of patients with iCCA and actionable targets, said Goyal.

The FDA accepted futibatinib for priority review on March 30, 2022. At that time, Volker Wacheck, MD, vice president of clinical development at Taiho Oncology, Inc, noted: “Given the lack of an accepted standard chemotherapy following the failure of first-line treatment, futibatinib could represent a significant opportunity for a targeted therapy in this subset of patients with CCA, which has driven our pursuit with this investigational compound.”

Futibatinib received a breakthrough therapy designation from the FDA on April 1, 2021, and the Prescription Drug User Fee Act date is set for September 30, 2022.

The final analysis from FOENIX-CCA2, which investigated the use of futibatinib among 103 patients with unresectable or metastatic iCCA and an FGFR2 fusion or rearrangement, confirms the efficacy, safety, and durability of the highly selective, irreversible FGFR1-4 inhibitor, echoing data presented at the 2020 and 2021 meetings. The primary data cutoff was October 1, 2020, and final data cutoff was May 29, 2021, with these newest data including 8 months of efficacy and safety information, including mature OS data.

All patients in the open-label single-arm study had progressive disease (PD) after at least 1 systemic treatment—with 53% having received 2 or more prior lines—consisting of gemcitabine and platinum-based chemotherapy. The investigators evaluated outcomes from a 20-mg once-daily oral dosage of futibatinib given continuously until PD or intolerability in 21-day cycles. Prior therapy with FGFR inhibitors was not allowed. The primary end point was objective response rate (ORR), with a target ORR of 20%; secondary end points were duration of response (DOR), disease control rate, progression-free survival (PFS), OS, safety, and patient-reported outcomes. The median follow-up was 25 months, and patients underwent a median of 13 cycles of treatment.

“A unique aspect of this agent is that it binds covalently and therefore irreversibly to a cysteine residue in the P loop of the FGFR kinase domain,” Goyal noted. “By contrast, most other FGFR inhibitors approved or being investigated are reversible and ATP competitive.”

In an interview with Evidence-Based Oncology, Wacheck, who is also an oncologist and clinical pharmacologist, and head of the global development program for futibatinib, elaborated on the drug’s mechanism of action.

“It is also less sensitive with respect to any mutation in the kinase that might emerge after prolonged treatment with an FGFR inhibitor because that cysteine residue is very rarely subject to any of those acquired mutations,” he said. “We have some preclinical data suggesting that this might be a mechanism [for] how we can delay with this molecule the resistance, or the emergence of resistance, due to kinase domain mutations.”

The final analysis shows the following results compared with those of the primary analysis:

- 93% of patients discontinued treatment vs 70% from the primary analysis
- ORR and DCR remained unchanged, at 41.7% and 82.5%, respectively
- Median DOR was 9.5 vs 9.7 months
- Median time to response was 2.6 months
- 74% vs 72% of responses lasted 6 months or longer
- Median PFS was 8.9 vs 9.0 months
- 12-month PFS rate was 35.4%
- 6-month PFS rate was 65%
- Mature OS rate was 20 months
- 12-month OS rate was 73%
- 6-month OS rate was 88%
- 19% of responses lasted at least 12 months

These objective responses were seen independent of age, sex, region of residence, and number of prior treatment lines. In addition, Goyal highlighted the fact that 42 patients had a confirmed partial response and 1 had a confirmed complete response, as well as that 95% of those with stable disease “had some degree of target lesion shrinkage.”

Much of futibatinib’s success lies in its ability to delay the resistance often seen with other FGFR2 inhibitors, Wacheck emphasized, resistance that stems from the constant onslaught of mutations.

“Some of those mutations in the kinase domain can lead to resistance, particularly to ATP-competitive inhibitors,” he noted. “What we also see in the literature is that also so-called bypass mechanism. Pathways that initially might not be the driver of disease more and more become important for the progression of the disease.”

FOENIX-CCA2 was also among the first FGFR inhibitor studies to report on patient quality of life. EuroQol-5D findings showed that the 89% of patients who provided data were able to maintain their quality of life during treatment.

Adverse effects from futibatinib remained consistent from the primary to the secondary analysis, with the most common being hyperphosphatemia, alopecia, and dry mouth, at 85%, 33%, and 30% in both analyses, respectively, of grade 1/2. No new safety signals were identified, and there were no treatment-related deaths.

Hyperphosphatemia, which leads to an imbalance between phosphorus and calcium homeostasis in a patient, is one of the exclusion criteria for clinical trials of FGFR inhibitors, Wacheck noted. This is because this drug class is increasing phosphate levels in patients, which is a known on-target effect.

Also reported during the session, for the first time, were the results of the exploratory biomarker analysis on circulating tumor DNA (ctDNA) for FGFR2. Ninety-two percent of patients provided these data, Goyal said, with 83% having FGFR2 fusions and rearrangements. This equated to an 87% positive percentage agreement from baseline to ctDNA analysis for the tissue samples collected at both time points.

Wacheck also noted that more data are needed before the day-to-day use of ctDNA to optimize the use of futibatinib in patients. He added that there is great potential for its use “as an interesting alternative for patients” in instances of a lack of available tissue or when rebiopsy is not an option.

“Overall, these results represent another example of the promise of precision medicine in iCCA and establish futibatinib as effective for and well tolerated by patients with advanced FGFR2 fusion- or rearrangement–positive disease,” Goyal concluded.

At present, the phase 3 FOENIX-CCA3 trial (NCT04093362) is evaluating futibatinib vs gemcitabine and cisplatin in the first line in patients with CCA and FGFR2 rearrangements.

Two other FGFR inhibitors are approved for use in a second-line setting for patients with CCA and FGFR2 fusion/rearrangement. However, according to data presented during the ASCO meeting by Marina Baretti, MD, an assistant professor of oncology at Johns Hopkins Medicine in Baltimore, Maryland, the use of futibatinib vs pemigatinib (approved in 2020) and inifatinib (approved in 2021) leads to superior outcomes in overall response rate, median DOR, and median PFS.
Kim A. Reiss, MD, on CAR Macrophages and Other Developments in Pancreatic Cancer

Produced by Hayley Virgil and Maggie L. Shaw

Kim A. Reiss, MD, assistant program director, Hematology/Oncology Fellowship Program, assistant professor of medicine, Hospital of the University of Pennsylvania, Philadelphia, discusses 2 abstracts presented during ASCO.

 referencing a study presented at ASCO's 2022 Annual Meeting. Among the highlights:

- **Evidence-Based Oncology (EBO)** discussed a study involving patients with advanced pancreatic cancer taking a PARP inhibitor with ipilimumab (Yervoy).

- **REISS**: One of the things that we worried about when we opened the study is whether [patients] would agree to do it. So we’re looking at an all-comer population, not a DDR [DNA damage repair]-specific population, and these were patients who were stable on the chemotherapy they were receiving. One of the questions was: Would these patients and their physicians be willing to discontinue effective chemotherapy in the face of a very lethal disease and jump into a noncytotoxic maintenance treatment? And the answer was an overwhelming “Yes.”

Oncologists recommended patients try the study, and patients were very, very enthusiastic and interested. In fact, we enrolled all 84 patients at only the University of Pennsylvania in less than 3 years. There was a huge amount of interest in trying to get away from cytotoxic therapies.

“Most universally patients shared that their life was better, that their quality of life was better, that they could do things that they weren’t able to do while on chemotherapy. That is one of the reasons that this strategy is so important for patients with pancreatic cancer.”

—Kim A. Reiss, MD, assistant program director, Hematology/Oncology Fellowship Program, assistant professor of medicine, Hospital of the University of Pennsylvania

My own experience on this, aside from the couple of patients who had toxicity with IPI (ipilimumab) that was grade 3 or 4 and some [who had toxicity] with niraparib (Zejula), almost universally patients shared that their life was better, that their quality of life was better, that they could do things that they weren’t able to do while on chemotherapy. That is one of the reasons that this strategy is so important for patients with pancreatic cancer. Perpetual chemotherapy is not a reasonable thing to ask of a patient to do. And for those who do well and are on therapy for a long time, the [adverse] effects accumulate. They’re more fatigued, they’re more suppressed, they get more neuropathy, and so we really need to do better. What this study hopefully will open the door to explore maintenance for a broader population than for just the small number of patients with BRCA and PALB2 variants.”

Kim A. Reiss, MD, assistant professor of medicine, Hospital of the University of Pennsylvania

**REFERENCES**


**KEYNOTE-716: First Data on DMFS Show Additional Pembrolizumab Benefit in Patients With Melanoma**

**MAGGIE L. SHAW**

**THE DOUBLE-BLEND KEYNOTE-716 study (NCT03553836) is investigating the use of adjuvant pembrolizumab vs placebo among individuals with cutaneous stage Iib and Iic newly diagnosed, surgically resected (negative sentinel lymph node biopsy) high-risk melanoma. A third interim analysis of data from the ongoing 2-part study bears out the survival benefits of the monoclonal antibody (mAB) in the form of longer-term recurrence-free survival (RFS) and the first analysis of distant metastasis-free survival (DMFS).**

“We know from retrospective studies that patients with resected stage Iib and Iic melanoma have a high risk of melanoma recurrence after 24 months, and these patients have very poor outcomes,” stated lead investigator Georgina V. Long, MBBS, PhD, co-medical director of the Melanoma Institute Australia (MIA) and chair of melanoma medical oncology and translational research at MIA and Royal North Shore Hospital, The University of Sydney. “We also know from KEYNOTE-716 that pembrolizumab significantly improves RFS vs placebo in resected stage Iib and Iic melanoma.”

Long presented the late-breaker abstract of this third interim analysis of the 2022 annual meeting of the American Society for Clinical Oncology (ASCO).

These newest findings—with a data cutoff of January 4, 2022—echo results from the first and second interim analyses, which demonstrate that pembrolizumab reduces the risk of disease recurrence compared with placebo and has a favorable benefit-risk profile in this disease setting. End points of the KEYNOTE-716 trial are RFS vs investigator assessment (primary); DMFS, overall survival (OS), and safety (secondary); and quality of life (exploratory).

In KEYNOTE-716, participants were randomly assigned 1:1 to 200 mg of intravenous pembrolizumab (n = 487) every 3 weeks.
(adult dose) or 2 mg/kg (pediatric dose) or placebo (n = 489) every 3 weeks for 17 cycles. This is part 1 of the trial. Patient characteristics were balanced between the groups: the median (SD) age in the treatment group was 60 years (range, 16-84) and in the placebo group, 61 years (range, 17-87). The most common T subcategories were T3b or T4b, at 41% and 35%, respectively, in both groups; most had stage Iib disease, at 63% and 65%, respectively.

Part 2 of the trial occurred subsequent to a part 1 follow-up period and is a crossover/rechallenge of patients in both groups with disease recurrence. Part 2 data were not presented, but Long did note that patients in part 2 were unblinded and crossed over from placebo or continued treatment with the mAb if more than 6 months had passed since their last dose; treatment continued to disease progression or 2 years.

For the third interim analysis, the median follow-up was 27.4 months (range, 14.0-39.4). At the 12-month and 24-month marks for DMFS, pembrolizumab had produced superior outcomes to placebo, and the median was not reached in either group:

- 12 months: 94.7% vs 90.2%
- 24 months: 88.1% vs 82.2%

In addition, there were 63 distant metastases in the pembrolizumab group and 95 in the placebo group, translating to 24-month DMFS rates of 87.1% and 80.6%, respectively. Overall, this represents a 36% reduction in the risk of distant metastasis (HR, 0.64; 95% CI, 0.47-0.88), favoring pembrolizumab, Long noted.

The trend of pembrolizumab’s superiority continued when comparing DMFS rate results among the T subcategories based on cancer stage, as shown by the following:

- T3b: at 12 months, 95.3% vs 93.9%; at 24 months, 90.4% vs 85.1%
- T4a: at 12 months, 96.2% vs 91.3%; at 24 months, 92.7% vs 85.4%
- T4b: at 12 months, 94.0% vs 86.6%; at 24 months, 83.0% vs 77.9%

Again, the median DMFS was not reached in any of these T subcategories, and the risk of distant metastasis was lower in the pembrolizumab group than in the placebo group:

- For patients classified into the T3b subgroup, there were 23 vs 31 distant metastases, respectively, for an overall 29% reduced risk of distant metastasis (HR, 0.71; 95% CI, 0.41-1.22) and 24-month DMFS rates of 88.5% and 84.5%, respectively
- For those classified into the T4a subgroup, there were 8 vs 20 distant metastases, respectively, for an overall 58% reduced risk of distant metastasis (HR, 0.42; 95% CI, 0.19-0.96) and 24-month DMFS rates of 92.7% and 82.8%
- For those classified into the T4b subgroup, there were 30 vs 41 distant metastases, respectively, for an overall 30% reduced risk of distant metastasis (HR, 0.70; 95% CI, 0.44-1.13) and 24-month DMFS rates of 82.5% and 75.7%

The most common site of first distant metastasis was the lung in both study groups (49% in the pembrolizumab group vs 73% in the placebo group). This was followed by the brain (16%), lymph nodes (14%), and other soft tissue (13%) in the pembrolizumab group, and other soft tissue (13%), lymph nodes (12%), and brain (9%) in the placebo group. Regarding the higher percentages in the pembrolizumab group, Long clarified the fact that some patients had multiple sites of distant metastasis.

“In terms of patterns of distant metastases, we can see that for the pembrolizumab arm, there is a marked reduction in the number of patients who had distant metastasis as first event,” she stated. “A similar number of patients had distant metastases after locoregional recurrence.”

Among those with disease recurrence, fewer patients in the pembrolizumab group had distant recurrence or local, regional, and locoregional recurrence as their pattern of first recurrence, at 9% each, compared with 16% and 11%, respectively, among the placebo group. One percent of participants from each group whose disease recurred died. Overall, there were 93 instances of disease recurrence in the pembrolizumab group vs 139 in the placebo group.

For those in the pembrolizumab group, the top 3 most common treatment-related adverse events (TRAEs) were pruritus (25%), fatigue (21%), and diarrhea (19%). TRAEs of grade 3 or higher most commonly reported were pruritus, rash, and diarrhea (1% each). For the placebo group, fatigue (19%), diarrhea (12%), and pruritus (11%) were the top 3 TRAEs reported overall, and few grade 3 or higher TRAEs were reported; rash, diarrhea, and fatigue were reported at less than 1% each.

“Adjuvant pembrolizumab vs placebo for resected stage Iib and stage Iic melanoma significantly improved DMFS,” Long concluded. “There were fewer distant metastases as instances of RFS, sustained and continued reduction in recurrence risk, and a benefit-risk profile that is consistent with the first and second interim analyses.”

The estimated study completion date of KEYNOTE-716 is October 12, 2023.

REFERENCES


FORGE AHEAD WITH A BOLD APPROACH

For appropriate patients faced with relapsed/refractory multiple myeloma

Target BCMA for RRMM

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

INDICATION

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY

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

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

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

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

**WARNINGS AND PRECAUTIONS**

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

Keratopathy: Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy, 87% recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow-up. For patients in whom events resolved, the median time to resolution was 2 months (range: 11 days to 8.3 months).

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

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

**Thrombocytopenia:** Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17%. The median time to onset of the first thrombocytopenic event was 76.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

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

**Embryo-Fetal Toxicity:** Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

**ADVERSE REACTIONS**

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

Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (7%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

**USE IN SPECIFIC POPULATIONS**

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

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

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

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

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

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

WARNING: OCULAR TOXICITY

BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms, such as blurred vision and dry eyes [see Warnings and Precautions (5.1)].

Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].

Because of the risk of ocular toxicity, BLENREP is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BLENREP REMS [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

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

Keratopathy

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

Visual Acuity Changes

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

Monitoring and Patient Instruction

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

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

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

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

5.2 BLENREP REMS

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

Notable requirements of the BLENREP REMS include the following:

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

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

5.3 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.6%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients.

Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3) of full Prescribing Information]

5.4 Infusion-Related Reactions

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)]. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3) of full Prescribing Information]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

5.5 Embryo-Fetal Toxicity

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

Relapsed or Refractory Multiple Myeloma

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

Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in >3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 5.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

(continued on next page)
Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP. Keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation. Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dosage interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%).

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

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

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

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

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

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

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

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

6.2 Immunogenicity

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Risk Summary**

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

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

**Data**

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

(continued on next page)
8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Contraception

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

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

17 PATIENT COUNSELING INFORMATION

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

Ocular Toxicity

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

• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.2) of full Prescribing Information, Warnings and Precautions (5.1)].

• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
Role of Real-World Evidence in the Evolving Treatment Landscape of Multiple Myeloma
Read more at: https://bit.ly/3bCuU00

FDA Approves Liso-cel for Second-line Relapsed Refractory Large B-cell Lymphoma
Read more at: https://bit.ly/3nAKFy

For patients with non–small cell lung cancer (NSCLC) and no option of a targeted treatment due to genetic alteration, cabozantinib plus atezolizumab could become a second-line treatment beyond chemotherapy, noted Joel Neal, MD, PhD, an associate professor in the Division of Oncology at Stanford Cancer Institute in California.

Neal, lead investigator on the COSMIC-021 trial (NCT03170960), spoke with Evidence-Based Oncology™ (EBO) about the updated analyses presented at the 2022 annual meeting of the American Society of Clinical Oncology (ASCO).

EBO: What do the phase 1b results from COSMIC-021 show in NSCLC?

NEAL: The COSMIC-021 phase 1b study included a number of different cohorts across a number of different types of tumors, as well as a number of different patients with NSCLC. One of the most interesting cohorts in my opinion was cohort 7, in which patients who had had prior immune checkpoint inhibitor therapy, plus or minus optional platinum chemotherapy, then went on at time of tumor progression to get second-line treatment with cabozantinib plus atezolizumab.

We reported at ASCO a couple of years ago that the first 10 patients had a significant response rate, higher than we would have seen otherwise, in the 20% range. We would have expected cabozantinib or chemotherapy alone to have less than 10% response rates. So based on that, in this phase 1b we expanded that cabozantinib cohort to include 81 patients and started randomly assigning them in the middle between the cabozantinib-plus-atezolizumab cohort and a cabozantinib-alone cohort to try and get a sense of how cabozantinib was performing alone after prior immunotherapy in the frontline setting, as well as together with continued immunotherapy.

EBO: What unmet need in NSCLC is potentially addressed through treatment with cabozantinib plus atezolizumab?

NEAL: From here, we’re excited that cabozantinib plus atezolizumab might have a role in the second-line treatment of NSCLC. Docetaxel alone is the approved therapy, but often providers use other single-agent chemotherapies relatively interchangeably—of course with the exception of patients with tumors harboring targeted alterations like EGFR, ALK, and all the other molecular alterations we have.

So for those patients without a targetable therapy, [we are] encouraged that the second-line treatment using this VEGF small molecule inhibitor plus immunotherapy, a strategy that’s been successful in renal cell cancer and is emerging in other cancers, may meet this unmet need.

“For those patients without a targetable therapy, [we are] encouraged that the second-line treatment using this VEGF small molecule inhibitor plus immunotherapy, a strategy that’s been successful in renal cell cancer and is emerging in other cancers, may meet this unmet need.”

—Joel Neal, MD, PhD, associate professor, Division of Oncology, Stanford Cancer Institute

ONE PROVEN PORTFOLIO. TWO FDA-APPROVED OPTIONS. THAT'S OUR FOUNDATION.

Only Foundation Medicine has an FDA-approved portfolio of tissue- and blood-based comprehensive genomic profiling tests. Our tests help identify treatment options across all solid tumors. FoundationOne® Liquid CDx and FoundationOne® CDx both analyze 300+ cancer related genes, report additional relevant biomarkers and genomic signatures, and offer high quality insights. Our proven portfolio allows providers to choose the most appropriate sample option, between a blood draw and a tissue biopsy, to help guide treatment strategies for advanced cancer patients.

Learn more about Foundation Medicine's proven portfolio at foundationmedicine.com/portfolio

FoundationOne® CDx and FoundationOne® Liquid CDx are next-generation sequencing based in vitro diagnostic tests for advanced cancer patients with solid tumors and are for prescription use only. FoundationOne CDx utilizes FFPE tissue and analyzes 324 genes as well as genomic signatures. FoundationOne Liquid CDx analyzes 324 genes utilizing circulating cell-free DNA and is FDA-approved to report short variants in 311 genes. The tests are companion diagnostics to identify patients who may benefit from treatment with specific therapies in accordance with the therapeutic product labeling. Additional genomic findings may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the tests does not guarantee a patient will be matched to a treatment. A negative result does not rule out the presence of an alteration.

Some patients may require a biopsy for testing with FoundationOne CDx when archival tissue is not available which may pose a risk. Patients who are tested with FoundationOne Liquid CDx and are negative for companion diagnostic mutations should be reflexed to tumor tissue testing and mutation status confirmed using an FDA-approved tumor tissue test, if feasible.

For the complete label, including companion diagnostic indications and important risk information, please visit www.F1CDxLabel.com and www.F1LCDxLabel.com.
**Over 6 Years, First-line Brentuximab Vedotin Cuts Risk of Death in Hodgkin Lymphoma by 41%**

MARY CAFFREY

WHEN FIRST PRESENTED in 2017, results for ECHELON-1 (NCT01712490) showed a modest modified progression-free survival (PFS) benefit for brentuximab vedotin when given with chemotherapy in patients with previously untreated stage III or IV classic Hodgkin lymphoma.1

The trial compared the classic combination of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) with brentuximab vedotin (Adcetris), doxorubicin, vinblastine, and dacarbazine (A + AVD) in patients with advanced Hodgkin lymphoma. Some taking the new regimen would experience peripheral neuropathy, and some would need growth factors. Early on, the question was whether it was worth it, given the adverse effects and the cost.

Six years later, the answer at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting was a resounding yes, according to Stephen M. Ansell, MD, PhD, professor of medicine, Mayo Clinic College of Medicine, Rochester, Minnesota. On June 3, Ansell presented a prespecified update for ECHELON-1, which showed that over the long haul, the new combination with brentuximab vedotin cut the risk of death by 41% and the risk of secondary cancers for patients whose Hodgkin lymphoma was already advanced when they received their diagnosis.2 The results demonstrated that:

- After a median follow-up of 73 months, OS significantly favored A + AVD vs ABVD (HR, 0.598; 95% CI, 0.396-0.879; P = .009).
- 39 OS events occurred in the A + AVD arm vs 64 in the ABVD arm. Estimated 6-year OS rates were 93.3% for A + AVD compared with 89.4% for ABVD.
- The PFS benefit for A + AVD widened over time; at 6 years it was estimated to be 82.3% vs 74.5% for ABVD (HR, 0.678; 95% CI, 0.532-0.863).
- Fewer second malignancies were reported in the A + AVD arm than in the ABVD arm (23 vs 32).
- Although it was an imperfect measure of fertility, said study authors, more female patients in the A + AVD arm than in the ABVD arm reported pregnancy (49 vs 28) or live births (42 vs 19). No stillbirths were reported.

No new safety signals were seen, and investigators reported that treatment-emergent peripheral neuropathy continued to resolve or improve in both arms over time; 86% and 87% of cases in the A + AVD and ABVD arms were reported to have resolved or improved by the last follow-up.

Ansell reviewed the design of ECHELON-1 and reminded the audience of several key elements: patients were randomly assigned 1:1 to receive up to 6 cycles of A + AVD (n = 664) or ABVD (n = 670) on days 1 and 15 every 28 days. He noted that 15% of patients were over age 60 years, and one-fourth had poor prognostic factors. Given this starting point, Ansell said the 6-year OS results are remarkable.

“This really shows that brentuximab vedotin plus chemotherapy significantly improved the overall survival, with a 41% reduction in the risk of death compared with the standard ABVD chemotherapy.”

—Stephen M. Ansell, MD, PhD, professor of medicine, Mayo Clinic College of Medicine, Rochester, Minnesota

The ABVD regimen has been the standard since the mid-1970s, she said, with other regimens used as salvage therapies when ABVD failed. Moskowitz reviewed the criticism of ECHELON-1 and noted the seemingly small PFS benefit in the early results.

“This was met with not that much enthusiasm initially,” she said. “One of the criticisms was the use of the modified progression-free survival, which can be associated with some bias, particularly in a nonblinded study.”

But the other issue was whether the observed benefit mattered. "Many people questioned whether this difference was big enough to justify the higher rates of peripheral neuropathy—as well as the [therapy’s] cost—and also the requirement for growth factors and for getting the highest rates of neutropenic fever.”

But with longer follow-up, "We saw the 3-year progression-free survival was starting to widen a bit. We also saw that this benefit was observed in patients with both stage III and stage IV disease.”

With more follow-up, the PFS was maintained, she said, and transferred to OS. “I agree with the prior speakers that this is now a preferred treatment for stage III and stage IV Hodgkin lymphoma.”

REFERENCES


Thanos Zomas, MD, Says Hodgkin Lymphoma Outcomes Improve With Targeted Treatment

Produced by Ryan Scott and Maggie L. Shaw

Updated results from the ECHELON-1 trial showed a significantly improved mortality risk and overall survival rate at 6 years when brentuximab vedotin was added to first-line chemotherapy, Thanos Zomas, MD, said during the 2022 American Society of Clinical Oncology Annual Meeting in June. Zomas, who is global medical lead for lymphoma and leukemia and for the Adcetris program at Takeda Oncology, discussed the new data with Evidence-Based Oncology (EBO).

EBO: Can you discuss the unmet need for patients with newly diagnosed classical Hodgkin lymphoma?

ZOMAS: Hodgkin lymphoma is a relatively rare form of lymphoma. There are more than 100 different types of lymphoma, and Hodgkin lymphoma is one of them. It’s been considered, thankfully, a very curable disease, but despite this, there is a percentage—perhaps in the region of 20% to 30%—of patients who unfortunately relapse after their initial therapy, and so they require additional treatment. Most of the time this treatment is more intensive and repetitive. There is an unmet medical need there that requires better treatments in the beginning.

EBO: Why is finding optimal first-line treatment so important for these patients?

ZOMAS: The majority of these patients are relatively young. The average age of Hodgkin lymphoma patients is between 35 and 40 years—although we’ve seen patients at a much earlier age and at very [later] age. They are in the most productive phase of their life, so it’s very important to cure as many as possible with the first round of chemotherapy in order to avoid additional treatment, which is associated with a very negative impact on their quality of life, as well as some very unpleasant secondary [adverse] effects, including secondary malignancies, fertility problems, and cardiovascular [adverse] effects.

EBO: Can you discuss the design and end points of ECHELON-1?

ZOMAS: The ECHELON-1 study (NCT01712490) was an international study that included many countries across the world. It was a phase 3 fully randomized study that compared the standard of care of therapy in frontline treatment, which is called ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine), with a new regimen called A+AVD [brentuximab vedotin [Adcetris], doxorubicin, vinblastine, and dacarbazine]. It basically substituted one of the weakest drugs of the ABVD regimen, bleomycin, with the anti-CD30-targeted agent brentuximab vedotin.

This trial started enrolling patients in 2012 and completed its enrollment in 2016. It created a lot of excitement because the disease is relatively rare. The fact that ECHELON-1 included a very large number of patients, [approximately] 1400 patients, created a lot of expectations and hopes.

EBO: What do the 6-year results of ECHELON-1 show?

ZOMAS: In this Congress for the first time, we report the first official overall survival analysis of the ECHELON-1 study, which showed a fairly significant survival advantage in favor of Adcetris arm, the A+AVD regimen, vs the standard of care. This regimen has shown very clearly, and for the first time in the past 20 years, that the addition of targeted agents in the regimen in frontline Hodgkin lymphoma treatment can reduce the risk of death by 41%. This corresponds to a very high survival rate.

“...This regimen has shown very clearly, and for the first time in the past 20 years, that the addition of targeted agents in the regimen in frontline Hodgkin lymphoma treatment can reduce the risk of death by 41%. This corresponds to a very high survival rate.”

—Thanos Zomas, MD, global medical lead for lymphoma and leukemia, and for the Adcetris program, Takeda Oncology

REFERENCE

SHINE: Adding Ibrutinib to Treatment Improves PFS by 50% for Older Patients With Mantle Cell Lymphoma

MARY CAFFREY

During a press conference ahead of his presentation, Wang said the difference of 2.3 years in PFS between patients whose regimen included ibrutinib and those who with standard of care was "significant."

“This is truly meaningful, and really a remarkable achievement in the field for these patients,” he said.

He noted that the OS results needed to be viewed in context of the age of the patients. When patients were enrolled in the study 7 years ago, their median age was 76; today, the median age is 78, and half the patients are over 80 years. “So, they are going to die from other causes,” he said.

Wang has conducted multiple studies to treat MCL using newer therapies that have fewer toxic effects than traditional chemotherapy, which can be particularly hard for older patients to tolerate. Besides currently approved BTK inhibitors, Wang has noted the potential for venetoclax or investigational therapies such as pirtobrutinib.

Adverse events (AEs) of grade 3 or 4 were 81.5% and 77.3% in the ibrutinib vs. placebo groups, respectively. The safety profile was consistent with the known effects of ibrutinib and bendamustine-rituximab, according to investigators.

Asked whether this treatment regimen would be optimal for younger patients, Wang said for most, a more aggressive approach would still be preferred. In response to a question from The American Journal of Managed Care®, both Wang and Gralow acknowledged that some clinicians have had difficulty gaining insurer approval for ibrutinib in this setting, despite the availability of Wang’s abstract. However, both said after today, the data should put that question to rest.

Wang said that publication in NEJM should lead to inclusion in clinical guidelines, and that if clinicians attach the article with prior authorization requests, they should be approved. “That has been my experience,” he said.

REFERENCES


Challenging the “One-Size-Fits-All” Approach in Early MCL Treatment

MARY CAFFREY

IN THE UNITED STATES, about 4000 people per year are diagnosed with mantle cell lymphoma (MCL), a cancer that develops from malignant B-lymphocytes in an area of the lymph node known as the mantle zone.

Leading off a session at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting, Anita Kumar, MD, a medical oncologist with Memorial Sloan Kettering (MSK) Cancer Center in New York, New York, explained that MCL is associated with chronic activation of the B-cell receptor complex. Kumar, who is regional care network medical site director, Basking Ridge, New Jersey, said, “This has allowed for the development of Bruton tyrosine kinase [BTK] inhibitors, such as ibrutinib, as well as PI3 kinase inhibitors.”

Many factors guide decisions on initial treatment after diagnosis, such as the patient’s age, fitness, and especially transplant eligibility. In recent years, the chemoimmunotherapy combination of bendamustine and rituximab has become the standard of care for patients who are not eligible for autologous stem cell transplant (ASCT).

“However, mantle cell lymphoma is both clinically and biologically heterogeneous,” Kumar said. “And this really challenges the one-size-fits-all approach using chemoimmunotherapy across the board. We know this from our clinical practice.”

Kumar’s talk on approaches for treatment-naïve MCL anchored the ASCO session she chaired, “New Directions for Mantle Cell Lymphoma in 2022.” The June 6 session also featured talks by Toby A. Eyre, MBChB (Hons), MD, DipMedEd, FRCP, a consultant hematologist in the Department of Hematology at the University of Oxford in England, who discussed prognostic markers in MCL, and Chan Cheah, MBBS(Hons), DMSc, FRACP, FRCPA, a clinical professor of medicine at the University of Western Australia in Perth. Cheah focused on novel therapies in relapsed/refractory settings, including the use of chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies to treat MCL.

Eyre offered an overview of current risk stratification of patients with MCL, which highlighted the importance of the TP53 mutation as an extremely strong predictor of inferior overall survival (OS) in trials across several new therapeutic classes. Clinical factors can be useful, but not at the expense of testing for TP53 mutations, he said.

The use of the Mantle Cell Lymphoma International Prognostic Index (MIPI), combined with a measure of proliferation of the Ki-67 protein, allows clinicians to group patients into one of 4 risk categories for diagnostic, treatment, and clinical trial purposes, Eyre said.

Kumar followed with a case for stratification, as she discussed the range of conditions among patients with a new diagnosis of MCL. There are patients with non-nodal leukemia MCL, whose disease is indolent; often, these patients can be monitored for years. “And on the other end of the spectrum, we see blastoid mantle cell lymphoma that’s highly aggressive with high proliferation, oftentimes with evidence of chemoresistance and inferior survival,” she said.

Investigators are learning more about the biology of these different presentations, Kumar said. More conventional MCL is associated with greater genomic instability and TP53 mutation, along with inferior OS. “In addition, minimal residual disease assessment has allowed for novel treatment paradigms to be explored in mantle cell lymphoma,” she said, as she reviewed studies that linked minimal residual disease (MRD) status to remission duration. MRD has the potential as a surrogate end point, as a marker to predict relapse during surveillance or therapeutic resistance, and to potentially help doctors decide when treatment can cease or less treatment is needed, she noted.

A case in point: in the ECOG-ACRIN Cancer Research Group study EA4151 (NCT03267433), patients newly diagnosed as transplant eligible are randomly assigned after induction therapy to ASCT with rituximab maintenance or rituximab alone. This is an exciting clinical trial design, because it leverages MRD assessment as a prognostic biomarker, and potentially in patients who achieve a deep molecular remission investigates whether we can omit upfront autologous stem cell transplant,” Kumar said.

As with other types of lymphoma, there is discussion on whether to move newer targeted therapies and other nonchemotherapy treatments into earlier lines of treatment, where they might be more effective with fewer toxic effects. Kumar outlined this discussion in light of results from the SHINE trial (NCT017768440), presented earlier at ASCO, which showed that adding ibrutinib to bendamustine and rituximab offered a progression-free survival (PFS) benefit but no OS benefit.

Kumar further noted that the TRIANGLE trial (NCT02858258) will examine 870 younger, fitter patients in 3 arms: 1 with alternating regimens of well-known chemotherapy combinations followed by ASCT, 1 with ibrutinib added to one of the chemotherapy combinations followed by ASCT, and 1 with the chemotherapy combinations and ibrutinib only. Again, she said, the trial may demonstrate an ability to achieve better outcomes without ASCT.

Chemotherapy-free combinations, including those that include BTK inhibitors, are a major area of study. Kumar reviewed these findings:

• A study of lenalidomide with rituximab in 38 patients (median age, 65 years), with 78% having low-to-intermediate disease and 21% having Ki-67 levels of 30% or greater, showed a 5-year PFS rate of 64% and 5-year OS rate of 77%.

• Ibrutinib and rituximab in 50 patients at least 65 years of age (36% with low-to-intermediate disease and 24% with Ki-67 levels of ≥30%; no patients with blastoid MCL) showed a 3-year PFS rate of 87%; however, 34% of patients developed atrial fibrillation and 10 had to stop taking ibrutinib.

Concern about the cardiovascular effects of ibrutinib has led to trials with zanubrutinib, a second-generation BTK inhibitor. A 500-patient, phase 3 clinical trial of 2 different regimens of zanubrutinib with bendamustine vs zanubrutinib alone is underway.

Triplet combinations are now being studied in MCL. Kumar reviewed the results for the OAsis trial (NCT02538816), which studied ibrutinib, obinutuzumab, and venetoclax in 15 patients with mostly low to intermediate disease, of whom 2 had a TP53 mutation. The idea here is to leverage dual BTK and BCL2 inhibition, which is known to be synergistic in MCL, Kumar said. The positron emission tomography (PET) complete response rate at 6 months was 86.6%; after a median follow-up of 14 months, the 1-year PFS rate was 93%.
“This establishes this triplet combination as a highly active treatment program in mantle cell lymphoma, and it was also demonstrated that this was well tolerated,” she said. “Of great interest, we see that this combination was active in patients who had a TP53 mutation as well as blastoid disease.”

Kumar concluded by noting 2 other trials of interest to payers:

- For low-risk patients, a study involving ibritinib and rituximab for indolent MCL, called IMCL-2015 (NCT02682641), could shed light on the use of MRD to indicate when ibritinib can be stopped. After 12 treatment cycles, the overall response rate was 84% and the 36-month PFS rate was 93%. Ibrutinib was stopped in 24 of 35 patients after cycle 24.6

- For high-risk patients—who have no current standard of care—the BOVEN regimen study (NCT03824483) offers a variation on the OAs regimen, using zanubrutinib instead of ibritinib. This is a higher-risk group of patients; preliminary findings presented at the American Society of Hematology 2021 meeting.9 100% of patients had the TP53 mutation, patient median age was 68 years, and only 35% had low-to-intermediate disease as per MIPI. But so far, the results are encouraging: 17 patients were evaluated for toxicity and 14 for efficacy. Of the 14, 12 had a response and 9 had a complete response. One responding patient was lost to follow-up and died of an unknown cause.

“We really recommend enrollment in a clinical trial for patients who have a TP53 mutation,” Kumar said. “Insights into mantle cell lymphoma disease biology have improved our biologic risk stratification, and certainly identification of a TP53 mutation at time of initial diagnosis is of great importance.”

REFERENCES


ROSEWOOD: Zanubrutinib Combo Provides Superior Efficacy in FL

CHRISTINA MATTINA

A PRIMARY ANALYSIS of the phase 2 ROSEWOOD trial finds that a combination of zanubrutinib and obinutuzumab (ZO) is superior to obinutuzumab (O) alone in relapsed/refractory (R/R) follicular lymphoma (FL). Results were presented first at the American Society of Clinical Oncology, held June 2-7, in Chicago, and then at the 2022 European Hematology Association Congress, held June 9-12 in Vienna, Austria.1,2

Lead investigator Pier Luigi Zinzani, MD, PhD, of the University of Bologna, noted in his presentation in Vienna that FL is the most common subtype of non-Hodgkin lymphoma, but treatment options are limited and, particularly in the third line or later, associated with low rates of long-term disease control. Phase 1b trials showed early signals of efficacy with ZO, leading the investigators to continue with the ROSEWOOD phase 2 trial presented here. A total of 217 patients who had received at least 2 lines of therapy (including an anti-CD20 antibody and an alkylating agent) were randomized to receive ZO (n = 145) or O (n = 72). The primary end point was overall response rate (ORR) as assessed by independent central review; secondary end points included complete response rate (CRR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. After a median study follow-up of 12.5 months, ORR was 68.3% with ZO vs 45.8% with O (P = .0017), signifying that the study met its primary end point. The secondary outcomes also favored ZO vs O: CRR, 37.2% vs 19.4%, respectively; 18-month DOR rate, 70.9% vs 54.6%; and median PFS, 27.4 months vs 11.2 months. ZO was associated with a 49% reduction in risk of progression or death compared with O. The 18-month probability of OS was 85.4% for the ZO arm and 72.6% for the O arm, although Zinzani noted that the study was not powered to detect significance for this outcome.

Zinzani added that patients’ time to their next antilymphoma treatment was significantly prolonged in the ZO arm. Together, he said, these findings indicate a “deep and durable response” associated with ZO. An “important point,” according to Zinzani, was that patients receiving O were allowed to cross over to ZO if their disease progressed or if they experienced no response in 12 months. Among the 29 patients who did so, the ORR was 24.1%.

Safety analyses revealed no unexpected findings. The most common adverse events (AEs) in the ZO arm were thrombocytopenia (34.3%) and neutropenia (27.3%); these were also the most common AEs of grade 3 or higher (14.0% and 22.4%, respectively). The rate of treatment-emergent AEs leading to death was lower in the ZO arm than in the O arm (5.6% and 9.9%, respectively).

“ZO demonstrated superior efficacy to O in treatment of [patients] with R/R FL,” the abstract concluded. “ZO had a favorable benefit-risk profile and represents a potential combination therapy for [patients] with R/R FL.”

REFERENCES

2. Zinzani PL, Mayer J, Auer R, et al. Zanubrutinib plus obinutuzumab (ZO) vs obinutuzumab (O) monotherapy in patients (pts) with relapsed or refractory (R/R) follicular lymphoma (FL): primary analysis of the phase 2 randomized ROSEWOOD trial. Hematol Oncol 2022;Suppl 3;S205.
She needs a treatment shown to reduce risk of recurrence in high-risk early breast cancer (EBC)\(^1\)

The first FDA-approved addition to adjuvant ET in nearly 2 decades\(^{1-9}\)

ET=endocrine therapy; HER2=human epidermal growth factor receptor 2-negative; HR+=hormone receptor-positive.
INDICATION

VERZENIO® (abemaciclib) is indicated in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA-approved test.1

SELECT IMPORTANT SAFETY INFORMATION

Severe diarrhea associated with dehydration and infection occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, diarrhea occurred in 81 to 90% of patients who received Verzenio. Grade 3 diarrhea occurred in 8 to 20% of patients receiving Verzenio. Most patients experienced diarrhea during the first month of Verzenio treatment. The median time to onset of the first diarrhea event ranged from 6 to 8 days; and the median duration of Grade 2 and Grade 3 diarrhea ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19 to 26% of patients with diarrhea required a Verzenio dose interruption and 13 to 23% required a dose reduction.

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

Neutropenia, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with Verzenio. Across four clinical trials in 3691 patients, neutropenia occurred in 37 to 46% of patients receiving Verzenio. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19 to 32% of patients receiving Verzenio. Across trials, the median time to first episode of Grade ≥3 neutropenia ranged from 29 to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 to 16 days. Febrile neutropenia has been reported in <1% of patients exposed to Verzenio across trials. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

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

Severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis can occur in patients treated with Verzenio and other CDK4/6 inhibitors. In Verzenio-treated patients in EBC (monarchE), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 3 or 4 and there was one fatality (0.1%). In Verzenio-treated patients in MBC (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD or pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD or pneumonitis. Permanently discontinue Verzenio in all patients with Grade 3 or 4 ILD or pneumonitis. 

TAKE HOPE FURTHER

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
Verzenio: FDA-APPROVED for patients with HR+, HER2-, node-positive EBC at high risk of recurrence and a Ki-67 score ≥20%\textsuperscript{1-3}

APPROVAL BASED ON RESULTS IN PATIENTS WITH THE INDICATED CLINICAL AND PATHOLOGICAL RISK FACTORS (n=2,003)\textsuperscript{1}

Consider Verzenio for your patients with

\begin{itemize}
\item \textbf{NODE-POSITIVE DISEASE}
\item \textbf{AND}
\item \textbf{Ki-67 \geq 20%}
\end{itemize}

\[4+ \text{ nodes OR } 1-3 \text{ nodes with}
\begin{itemize}
\item Grade 3 disease or tumor size \geq 5 \text{ cm}
\end{itemize}\]

monarchE was a phase III clinical trial that enrolled 5,637 peri- and postmenopausal adult women and men with HR+, HER2-, node-positive EBC at high risk of recurrence. High risk was defined as 4+ positive nodes, or 1-3 positive nodes with Grade 3 disease or tumor size \geq 5 cm (central Ki-67 testing was conducted retrospectively for patients with untreated breast tissue samples), or 1-3 positive nodes with Ki-67 \geq 20%. All patients completed primary treatment prior to 1:1 randomization to receive either 150-mg, twice-daily Verzenio plus SoC ET or SoC ET alone for 2 years. ET continued through 5-10 years as clinically indicated. The primary endpoint was IDFS.\textsuperscript{1,2}

IDFS=invade disease-free survival; SoC=standard of care.

\textbf{SELECT IMPORTANT SAFETY INFORMATION (cont’d)}

Grade \geq 3 increases in alanine aminotransferase (ALT) (2 to 6%) and aspartate aminotransferase (AST) (2 to 3%) were reported in patients receiving Verzenio. Across three clinical trials in 3559 patients (monarchE, MONARCH 2, MONARCH 3), the median time to onset of Grade \geq 3 ALT increases ranged from 57 to 87 days and the median time to resolution to Grade <3 was 13 to 14 days. The median time to onset of Grade \geq 3 AST increases ranged from 71 to 185 days and the median time to resolution to Grade <3 ranged from 11 to 15 days.

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

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.
In patients with HR+, HER2−, node-positive EBC at high risk of recurrence and a Ki-67 score ≥20% (n=2,003)

Verzenio: The only CDK4 & 6 inhibitor to reduce risk of recurrence in combination with ET 1,7-9

At 3 years, Verzenio reduced the risk of recurrence by more than a third

86.1% of patients remained recurrence-free with Verzenio plus ET vs 79.0% with ET alone.1
The number of events at the time of analysis was 104 with Verzenio plus ET vs 158 with ET alone.1

OS was immature. A total of 95 (4.7%) patients had died. Long-term follow-up is planned.1,2
This post hoc efficacy analysis was performed at a median follow-up of 27.1 months. Additional exploratory analyses were performed at this time; efficacy results for the subpopulation with high-risk clinicopathological features and Ki-67 ≥20% are provided.3*

*Statistical significance was achieved for this subpopulation earlier at the final IDFS analysis. The result in this post hoc analysis cannot be interpreted as statistically significant.1

SELECT IMPORTANT SAFETY INFORMATION (cont’d)

Venous thromboembolic events (VTE) were reported in 2 to 5% of patients across three clinical trials in 3559 patients treated with Verzenio (monarchE, MONARCH 2, MONARCH 3). VTE included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. In clinical trials, deaths due to VTE have been reported in patients treated with Verzenio.

Verzenio has not been studied in patients with early breast cancer who had a history of VTE. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate. Dose interruption is recommended for EBC patients with any grade VTE and for MBC patients with a Grade 3 or 4 VTE.

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

Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for 3 weeks after the last dose. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants.

See the breakthrough results at VerzenioData.com/EBC
SELECT IMPORTANT SAFETY INFORMATION (cont’d)

The most common adverse reactions (all grades, ≥10%) observed in monarchE for Verzenio plus tamoxifen or an aromatase inhibitor vs tamoxifen or an aromatase inhibitor, with a difference between arms of ≥2%, were diarrhea (84% vs 9%), infections (51% vs 39%), neutropenia (46% vs 6%), fatigue (41% vs 18%), leukopenia (38% vs 7%), nausea (30% vs 9%), anemia (24% vs 4%), headache (20% vs 15%), vomiting (18% vs 4.6%), stomatitis (14% vs 5%), lymphopenia (14% vs 3%), thrombocytopenia (13% vs 2%), decreased appetite (12% vs 2.4%), ALT increased (12% vs 6%), AST increased (12% vs 5%), dizziness (11% vs 7%), rash (11% vs 4.5%), and alopecia (11% vs 2.7%).

The most frequently reported ≥5% Grade 3 or 4 adverse reaction that occurred in the Verzenio arm vs the tamoxifen or an aromatase inhibitor arm of monarchE were neutropenia (19.6% vs 1%), leukopenia (11% vs <1%), diarrhea (8% vs 0.2%), and lymphopenia (5% vs <1%).

Lab abnormalities (all grades; Grade 3 or 4)

- Monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.
- Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.
- Monitor for adverse reactions and consider reducing the Verzenio dose to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of moderate CYP3A inhibitors.
- In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors.
- In patients taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose to 50 mg decrements. Patients should avoid grapefruit products.

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

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

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

Please see Select Important Safety Information throughout and Brief Summary of full Prescribing Information for Verzenio on the following pages.

AL HCP ISI_mE 12OCT2021

VERZENIO® (abemaciclib) tablets, for oral use

Initial U.S. Approval: 2017

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

VERZENIO® (abemaciclib) is indicated:

- in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA-approved test.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Diabetes

Severe diarrhea associated with dehydration and infection occurred in patients treated with VERZENIO.

Across four clinical trials in 3981 patients, diabetes occurred in 8% to 9% of patients who received VERZENIO.

Grade 3 diabetes occurred in 8% to 20% of patients receiving VERZENIO.

Most patients experienced diabetes during the first month of VERZENIO treatment. The median time to onset of the first diabetes event ranged from 6 to 8 days; and the median duration of Grade 2 and Grade 3 diabetes ranged from 6 to 11 days and 5 to 8 days, respectively. Across trials, 19% to 26% of patients with diabetes required a VERZENIO dose interruption and 13% to 23% required a dose reduction.

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

Hepatotoxicity

Neutropenia, including febrile neutropenia and fatal neutropenic sepsis, occurred in patients treated with VERZENIO.

Across four clinical trials in 3981 patients, neutropenia occurred in a 37% to 46% of patients receiving VERZENIO. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 19% to 32% of patients receiving VERZENIO. Across trials, the median time to the first episode of Grade ≥3 neutropenia ranged from 29 days to 33 days, and the median duration of Grade ≥3 neutropenia ranged from 11 days to 16 days.

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

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

Interstitial Lung Disease (ILD) or Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) or pneumonitis can occur in patients treated with VERZENIO and other CDK4/6 inhibitors. In VERZENIO-treated patients in early breast cancer (monarchE, N=2791), 3% of patients experienced ILD or pneumonitis of any grade: 0.4% were Grade 4 and there was one fatal case (0.1%). In VERZENIO-treated patients in advanced or metastatic breast cancer (N=100: MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of VERZENIO-treated patients had ILD or pneumonitis of any grade: 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD or pneumonitis have been observed in the postmarketing setting, with fatalities reported.

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

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

Hepatotoxicity

Grade ≥3 ALT (2% to 6%) and AST (2% to 3%) were reported in patients receiving VERZENIO. Across 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.

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.

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

Clinical Studies Experience

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

The safety population described in the Warnings and Precautions reflects exposure to VERZENIO in 3691 patients from four clinical trials: monarchE, MONARCH 1, MONARCH 2, and MONARCH 3. The safety population includes exposure to VERZENIO as a single agent at 200 mg twice daily in 132 patients in MONARCH 1 and to VERZENIO at 150 mg twice daily in 3559 patients administered in combination with fulvestrant, tamoxifen, or an aromatase inhibitor in monarchE, MONARCH 2, and MONARCH 3. The median duration of exposure ranged from 4.5 months in MONARCH 1 to 24 months in monarchE. The most common adverse reactions (incidence ≥20%) across clinical trials were: diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.

Early Breast Cancer

monarchE: VERZENIO in Combination with Tamoxifen or an Aromatase Inhibitor as Adjuvant Treatment

Adult patients with HR-positive, HER2-negative, node-positive early breast cancer at a high risk of recurrence

The safety of VERZENIO was evaluated in monarchE, a study of 5591 adult patients receiving VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor) or endocrine therapy (tamoxifen or an aromatase inhibitor) alone. Patients were randomly assigned to receive 150 mg of VERZENIO orally, twice daily, plus tamoxifen or an aromatase inhibitor, or tamoxifen or an aromatase inhibitor, for two years or until discontinuation criteria were met. The median duration of VERZENIO treatment was 24 months.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, leukopenia, diarrhea, and lymphopenia.

Fetal adverse reactions occurred in 0.8% of patients who received VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor), including: cardiac failure (0.1%), cardiac arrest, myocardial infarction, ventricular fibrillation, cerebral hemorrhage, cerebrovascular accident, pneumonitis, hypoxia, diarrhea and mesenteric artery thrombosis (0.03% each).

Permanent VERZENIO treatment discontinuation due to an adverse reaction was reported in 19% of patients receiving VERZENIO, plus tamoxifen or an aromatase inhibitor. Of the patients receiving tamoxifen or an aromatase inhibitor, 1% permanently discontinued due to an adverse reaction. The most common adverse reactions leading to VERZENIO discontinuations were diarrhea (5%), fatigue (2%), and neutropenia (0.9%).

Dose interruption of VERZENIO due to an adverse reaction occurred in 62% of patients receiving VERZENIO plus tamoxifen or aromatase inhibitions. Adverse reactions leading to VERZENIO dose interruptions in ≤5% of patients were diarrhea (20%), neutropenia (16%), leukopenia (7%), and fatigue (5%).

Dose reductions of VERZENIO due to an adverse reaction occurred in 44% of patients receiving VERZENIO plus endocrine therapy (tamoxifen or an aromatase inhibitor). Adverse reactions leading to VERZENIO dose reductions in ≤5% were diarrhea (17%), neutropenia (8%), and fatigue (5%).

The most common adverse reactions reported (≥20%) in the VERZENIO, plus tamoxifen or an aromatase inhibitor, arm and ≥2% higher than the tamoxifen or an aromatase inhibitor arm were: diarrhea, infections, neutropenia, fatigue, leukopenia, nausea, anemia, and headache. Adverse reactions are shown in Table 1 and laboratory abnormalities are shown in Table 2.

Table 1: Adverse Reactions (≥10%) of Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor (with a Difference between Arms of ≥2%) in monarchE

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N=2791</th>
<th>Difference</th>
<th>N=2800</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>84</td>
<td>8</td>
<td>91</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>0.5</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
<td>0.5</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>Stomatitis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14</td>
<td>0.1</td>
<td>14</td>
<td>0.1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51</td>
<td>4.9</td>
<td>51</td>
<td>5.2</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41</td>
<td>2.9</td>
<td>41</td>
<td>2.9</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20</td>
<td>0.3</td>
<td>20</td>
<td>0.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>0.1</td>
<td>11</td>
<td>0.1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.6</td>
<td>12</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Differences are based on comparisons of the difference between arms of ≥2%.

<sup>b</sup> Fatigue may include asthenia.

<sup>c</sup> Headache may include paresthesia.

<sup>d</sup> Dizziness may include vertigo.

<sup>e</sup> Decreased appetite may include anorexia.

VERZENIO® (abemaciclib) tablets, for oral use

AL HCP BS_MonE 12OCT2021

VERZENIO® (abemaciclib) tablets, for oral use

AL HCP BS_More 12OCT2021

VERZENIO® (abemaciclib) tablets, for oral use

AL HCP BS_MonE 12OCT2021
Table 1: Adverse Reactions (≥10%) of Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor (with a Difference Between Arms of ≥2%) in monarchE (Cont.)

<table>
<thead>
<tr>
<th></th>
<th>VERZENIO Plus Tamoxifen or an Aromatase Inhibitor</th>
<th>Tamoxifen or an Aromatase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades%</td>
<td>Grade 3%</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Alopea</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

- Includes the following fatal adverse reactions: diarrea (n=1), and infections (n=6)
- Includes the following fatal adverse reactions: infections (n=5)
- Includes mouth ulceration, mucosal inflammation, esophagitis, stomatitis.
- Includes all reported preferred terms that are part of the Infections and Infestations system organ class.
- Includes common infections (n=5) and common respiratory tract infection, urinary tract infection, and nasopharyngitis.
- Includes hyperglycemia, fatigue.
- Includes exfoliative rash, mucocutaneous rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash maculopapular exanthematous, rash morbilliform, rash papular, rash papulopapular, rash pruritic, rash vesicular, urticarial rash.

Clinically relevant adverse reactions in ≤0.1% of patients who received VERZENIO in combination with tamoxifen or an aromatase inhibitor in monarchE include:
- Pruritus-9%
- Dyspepsia-8%
- Nail disorder-6% (includes nail bed disorder, nail bed inflammation, nail disorder, nail dystrophy, nail pigmentation, nail ridging, nail toxicity, onychia, onychia totalis, onycholyis, onychomadesis)
- Lactation increased-6%
- Dyspepsia-5%
- Intestinal lung disease, (idiopathic) (n=1)
- Cushing syndrome, (idiopathic) (n=1)
- Venous thromboembolic events (n=1)
- Deep vein thrombosis, disease related thrombosis, embolism, hepatic vein thrombosis, jugular vein occlusion, jugular vein thrombosis, ovarian vein thrombosis, portal vein thrombosis, pulmonary embolism, subclavian vein thrombosis, venous thrombosis limit

Table 2: Laboratory Abnormalities (≥10%) in Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor (with a Difference Between Arms of ≥2%) in monarchE

<table>
<thead>
<tr>
<th></th>
<th>VERZENIO Plus Tamoxifen or an Aromatase Inhibitor</th>
<th>Tamoxifen or an Aromatase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades%</td>
<td>Grade 3%</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>99</td>
<td>0.5</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>89</td>
<td>19</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>84</td>
<td>18</td>
</tr>
<tr>
<td>Anemia</td>
<td>68</td>
<td>1.0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>37</td>
<td>0.7</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>37</td>
<td>2.5</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>31</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>11</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Table 3: Laboratory Abnormalities (≥10%) in Patients Receiving VERZENIO Plus Tamoxifen or an Aromatase Inhibitor (with a Difference Between Arms of ≥2%) in monarchE

**DRUG INTERACTIONS**

**Effect of Other Drugs on VERZENIO**

**CYP3A Inhibitors**

Strong and moderate CYP3A4 inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

**Ketconazole**

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

**Other Strong CYP3A Inhibitors**

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

**Moderate CYP3A Inhibitors**

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

**Strong and Moderate CYP3A Inducers**

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

VERZENIO® (abemaciclib) tablets, for oral use

AL HCP BS_MonE 12OCT2021

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

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

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

**Data**

**Animal Data**

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

**Lactation**

**Risk Summary**

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

**Females and Males of Reproductive Potential**

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman.

**Pregnancy Testing**

Verify pregnancy status in females of reproductive potential prior to initiating treatment with VERZENIO.

**Contraception**

**Females**

Advise females of reproductive potential to use effective contraception during VERZENIO treatment and for 3 weeks after the last dose.

**Infertility**

**Males**

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential.

**Pediatric Use**

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

**Geriatric Use**

Of the 2791 VERZENIO-treated patients in monarchE, 15% were 65 years of age or older and 2.7% were 75 years of age or older.

Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were: neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased.

No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

**Renal Impairment**

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

**Hepatic Impairment**

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

Additional information can be found at www.verzenio.com
WHEN IS THE RIGHT TIME for transplant in multiple myeloma (MM) treatment?

Given the advances over the past decade—including the arrival of the first chimeric antigen receptor (CAR) T-cell therapies—the question can be difficult to answer. The use of autologous stem cell transplant (ASCT) is not without risk, and it guides the course of future treatment.

It’s a question investigators explored with the DETERMINATION trial (NCT01208662), which compared long-term outcomes of different initial treatments in MM. Two groups of patients were randomly assigned to receive either an early course of a standard triplet therapy or a treatment centered on ASCT.

Curiously, whereas the ASCT group showed a significant 21.4-month advantage in progression-free survival (PFS), there was no advantage in overall survival (OS).

Results were presented on June 5 during the plenary session at the 2022 annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago and published in the *New England Journal of Medicine* (NEJM).

It would seem that the OS result would catch the eye of payers, given the cost and toxicity of ASCT, but the issue is more complex. The group that did not receive upfront transplant ultimately needed more treatment; one-fourth of those who deferred transplant later needed one.

MM is a highly heterogenous disease; 34,470 cases will be diagnosed in 2022 in the United States with an estimated 12,640 deaths, according to information from ASCO. Of note, 18% of patients diagnosed in 2022 in the United States with an estimated 12,640 deaths, according to information from ASCO. Of note, 18% of those with higher body mass index. Work is underway to examine outcomes “according to cytogenetic risk and specific genetic abnormalities, given preliminary whole genome–sequencing analyses suggesting lower response rates associated with the presence of 17p deletion with impairment of the tumor suppressor p53,” he said.

New developments in MM “inform our decision-making even more, with the value of certain research tools such as MRD, providing us with additional guidance as to what makes the best choices there may be for patients.”

After a median follow-up of 76 months, results showed the following:

- Median PFS was 46.2 months among patients who did not receive ASCT, and 67.6 months among those in the ASCT arm, (HR 1.53; 95% CI, 1.23-1.91; *P* < .0001).
- No OS advantage was seen in either group.
- Among patients who did not receive transplant, 63% needed additional treatment compared with 53% of those in the ASCT group; 28% of those who did not receive the initial transplant later received one.
- 90 deaths occurred in the nontransplant arm vs 88 deaths in the ASCT arm, which translated to 4-year OS rates of 84% vs 85% (HR 1.10; 95% CI, 0.81-1.47; *P* = .274). The 5-year OS estimates did not differ.
- Adverse events (AEs) were less likely in patients who did not receive transplant than in ASCT patients (78% vs 94%, respectively). Quality-of-life scores with ASCT were initially lower than those in the nontransplant arm but later recovered.
- Both groups had roughly the same likelihood of secondary malignancies, with 10% for nontransplant vs 11% for ASCT patients, but the latter group was far more likely to have secondary acute myeloid leukemia or myelodysplastic syndromes. The ASCT group also reported more blood-borne AEs than the nontransplant group, at 90% vs 61%.

Richardson predicted that the results of DETERMINATION would be important in real-world practice, especially for clinicians treating younger patients with a new MM diagnosis. The need for customized approaches was emphasized by both Richardson and plenary commenter Joseph Mikhael, MD, a professor in the Applied Cancer Research and Drug Discovery Division at the Translational Genomics Research Institute, an affiliate of City of Hope Cancer Center, in Phoenix, Arizona.

According to the NEJM paper, the most important findings of the study may be the subgroup analyses still to come: investigators plan to drill down into outcomes among Black patients and among those with higher body mass index. Work is underway to examine outcomes “according to cytogenetic risk and specific genetic abnormalities, given preliminary whole genome–sequencing analyses suggesting lower response rates associated with the presence of 17p deletion and TP53 mutations and the known association of 17p deletion with impairment of the tumor suppressor p53, an impairment that confers resistance to chemotherapy.”

Mikhael said that although he envisioned a time when ASCT would be less common, it remains very much the standard of care for younger patients. But the role of transplant will evolve, as a patient’s age, risk status, and treatment preferences are considered. The ability to store a patient’s stem cells may be a factor in decision-making, along with short-term and long-term toxicities. In addition, the move to quadruple therapy will shift decision-making.

“We may not have this simplistic way of saying that [a patient] is eligible or not eligible” for transplant, Mikhael said.

**REFERENCE**


• 90 deaths occurred in the nontransplant arm vs 88 deaths in the ASCT arm, which translated to 4-year OS rates of 84% vs 85% (HR 1.10; 95% CI, 0.81-1.47; *P* = .274). The 5-year OS estimates did not differ.

• Adverse events (AEs) were less likely in patients who did not receive transplant than in ASCT patients (78% vs 94%, respectively). Quality-of-life scores with ASCT were initially lower than those in the nontransplant arm but later recovered.

• Both groups had roughly the same likelihood of secondary malignancies, with 10% for nontransplant vs 11% for ASCT patients, but the latter group was far more likely to have secondary acute myeloid leukemia or myelodysplastic syndromes. The ASCT group also reported more blood-borne AEs than the nontransplant group, at 90% vs 61%.

Richardson predicted that the results of DETERMINATION would be important in real-world practice, especially for clinicians treating younger patients with a new MM diagnosis. The need for customized approaches was emphasized by both Richardson and plenary commenter Joseph Mikhael, MD, a professor in the Applied Cancer Research and Drug Discovery Division at the Translational Genomics Research Institute, an affiliate of City of Hope Cancer Center, in Phoenix, Arizona.

According to the NEJM paper, the most important findings of the study may be the subgroup analyses still to come: investigators plan to drill down into outcomes among Black patients and among those with higher body mass index. Work is underway to examine outcomes “according to cytogenetic risk and specific genetic abnormalities, given preliminary whole genome–sequencing analyses suggesting lower response rates associated with the presence of 17p deletion and TP53 mutations and the known association of 17p deletion with impairment of the tumor suppressor p53, an impairment that confers resistance to chemotherapy.”

Mikhael said that although he envisioned a time when ASCT would be less common, it remains very much the standard of care for younger patients. But the role of transplant will evolve, as a patient’s age, risk status, and treatment preferences are considered. The ability to store a patient’s stem cells may be a factor in decision-making, along with short-term and long-term toxicities. In addition, the move to quadruple therapy will shift decision-making.

“We may not have this simplistic way of saying that [a patient] is eligible or not eligible” for transplant, Mikhael said.

**REFERENCE**

Enrique Ocio, MD, PhD, Hematology Department head, Marqués de Valdecilla University Hospital, Santander, Spain, spoke with Evidence-Based Oncology™ (EBO) about the phase 1b trial results for subcutaneous (sub-Q) vs intravenous (IV) isatuximab, both formulations of which were administered in combination with pomalidomide and dexamethasone for relapsed/refractory multiple myeloma (RRMM).

OCIO: Isatuximab can be administered by using a on-body delivery system (OBDS), a specific OBDS device.

This was a phase 1b study that evaluated the activity of isatuximab, pomalidomide, and dexamethasone in patients with RR myeloma. In this phase 1b, there were different methods of administration. We started with an IV formulation and then moved to a sub-Q, and the subsequent patients received a sub-Q administration of isatuximab with 2 doses at 100 mg per dose, and then we went to 1000 mg and 1400 mg. Then at the end, more than 20 patients received the sub-Q administration of isatuximab by using an OBDS, a specific OBDS device.

I think the main message of the study is that the combination is active in these patients with RR myeloma, with a response rate around 70% to 80%, and it’s safe and in fact is quite convenient for patients. Also, we can say that higher doses seem to be a bit more active with the 1400 mg in combination with pomalidomide and dexamethasone, as well as with the feasibility of using this OBDS that I think is also an advantage for these patients.

EBO: Can you discuss your study findings that show sub-Q isatuximab is safe and effective for use in RRMM?

OCIO: There are questionnaires for PROs for patients. I don’t have the data of the questionnaires, I don’t know if they are already analyzed, but definitely I have to say that our patients are really comfortable with this system. It is quite convenient for them also; it is very important. Once we have seen that the efficacy is similar or it’s maintained, we need to see the safety; and, of course, there’s the convenience [of having a device or a way of just in 10 minutes [being able to] have the drug administered quite safely without any adverse events, even without infusion-related reactions. So I think this is very convenient for patients.

EBO: Is sub-Q isatuximab also convenient for cancer centers and clinicians?

OCIO: Of course. This is also convenient for us, as we have such a tight schedule. You have so many patients, so having a device that is quick and fast with delivery and administration gives us more time for other patients. And it’s very convenient because it’s also very easy to use. It even can be used by the patients on their own. But of course in our centers, it’s given by the nurses. This is really convenient for all the people involved in the trial.

EBO: What are the next steps for sub-Q administration of isatuximab?

OCIO: For the sub-Q administration of isatuximab, we need to confirm these data—here we have 30 patients treated with the sub-Q formulation. We have to confirm these data in other studies and other combinations. And at the end, sub-Q would be the way to go; it would be the way of administration that would be approved in the future for isatuximab, which is very important. Also, then we will have the OBDS device that has to be approved and confirmed. Again, I think this should be the way to administer isatuximab…. In the future this could be administered in patients at home, not only in the hospital or in the medical centers. But even with that, it could be administered very easily at home to patients in 10 minutes… by nurses or even by the patients; we could think of that [taking place] in the future. We have to change something, but this would also be interesting. I want to add that this is one of the combinations that have demonstrated activity with isatuximab, pomalidomide, and dexamethasone in this RR patient population, with a good schedule of administration. Patients are really responding. From my point of view, and from my patients’, they are responding very well. The ability [to respond] is very good for this combination. It’s good to have it, this isatuximab anti-CD38 monoclonal antibody, to be ready in different combinations for our patients.

REFERENCE
SARCLISA®
(isatuximab-irfc)
Injection for IV use | 500mg/25mL, 100mg/5mL

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 2 prior therapies including lenalidomide and a proteasome inhibitor.

SARCLISA is indicated, in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy.

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 Serious infusion-related reactions (IRRs), including life-threatening anaphylactic reactions, have occurred with SARCLISA treatment. Severe signs and symptoms include cardiac arrest, hypertension, hypotension, bronchospasm, dyspnea, angoedema, and swelling.

Based on ICARIA-MM, IRRs occurred in 38% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases.

In IKEMA, infusion-related reactions occurred in 46% of patients treated with SARCLISA, carfilzomib, and dexamethasone (Isa-Kd). In the Isa-Kd arm, the infusion-related reactions occurred on the infusion day in 59% of episodes. In patients treated with Isa-Kd, 95% of those experiencing an infusion-related reaction experienced it during the first cycle of treatment. All infusion-related reactions resolved: within the same day in 74% of episodes, and the day after in 24% of episodes.

The most common symptoms (≥5%) of an infusion-related reaction in ICARIA-MM and IKEMA (N=329) included dyspnea, cough, nasal congestion, and nausea. Anaphylactic reactions occurred in less than 1% of patients. To decrease the risk and severity of IRRs, begin treatment with ISA-Kd, Isa-Pd, or Isa-Kd.

In combination with pomalidomide and dexamethasone, 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
In combination with pomalidomide and dexamethasone: The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea. The most common hematologic laboratory abnormalities were decreased hemoglobin, decreased lymphocytes, and decreased platelets.

Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. 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%]). SARCLISA treatment continued for 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in <5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients).

The most common (≥1%) second primary malignancies in ICARIA-MM and IKEMA (N=329) included skin cancers (4% with SARCLISA-containing regimens and 1.5% with comparative regimens) and solid tumors other than skin cancer (1.8% with SARCLISA-containing regimens and 1.5% with comparative regimens). All patients with skin cancer continued treatment after resolution of the skin cancer.

Monitor patients for the development of second primary malignancies.

Laboratory Test Interference
Interference with Serological Testing (Indirect Antiglobulin Test)
SARCLISA binds to RBCs on red blood cells (RBCs) and may result in a false-positive indirect antoglobulin test. A positive indirect Coombs test was observed in 63% of patients. In patients with a positive indirect antoglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/Rh typing was not affected by SARCLISA treatment.

Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider photocopying prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and that SARCLISA interferes with blood compatibility testing that can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non-crossmatched ABO/Rh-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 Igκ 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.

The most common reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea. The most common hematologic laboratory abnormalities were decreased hemoglobin, decreased lymphocytes, and decreased platelets.

In combination with carfilzomib and dexamethasone, the most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, pneumonia, and diarrhea. The most common hematologic laboratory abnormalities were decreased hemoglobin, decreased lymphocytes, and decreased platelets.

Serious adverse reactions occurred in 62% of patients receiving Isa-Pd. 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%]).

Serious adverse reactions occurred in 59% of patients receiving Isa-Kd. The most frequent serious adverse reactions in <5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the Isa-kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients).

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 Brief Summary of the Prescribing Information on the following pages.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma v1.2022 © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 24, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding its content, use or application and disclaims any responsibility for their application or use in any way.

To see the data and for full Prescribing Information, visit sarclisahcp.com

© 2021 sanofi-aventis U.S. LLC. All rights reserved. MAT-US-2108767-v1.0-09/2021
2.2 Recommended Premedications
If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule.

2.3 Dose Modifications
If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, taking into account the interval since the last dose.

2.4 Preparation
Preparation (see instructions for use for specific protocols).

3.2 Laboratory Test Interference
With the exception of ADA testing, the addition of SARCLISA to Isa-Pd or Isa-Kd does not significantly interfere with the following tests: serotonin reuptake inhibitors, warfarin, heparin, and neutralizing antibodies.

5.3.2 Primary Malignancies
SARCLISA may cause malignancy.

5.4 Laboratory Test Interference
With the exception of ADA testing, the addition of SARCLISA to Isa-Pd or Isa-Kd does not significantly interfere with the following tests: serotonin reuptake inhibitors, warfarin, heparin, and neutralizing antibodies.

6.1.1 Clinical Trials Experience
The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information for contraception requirements prior to initiating treatment in pregnant women.

6.2 Neutropenia
In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients. In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3–4 neutropenia in 19% of patients.

6.3 Infusion-Related Reactions
SARCLISA should be administered as an intravenous infusion in combination with pomalidomide and dexamethasone or in combination with carboplatin and dexamethasone, according to the schedule in Table 1 (see Clinical Studies [14] in the full prescribing information).

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

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

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

7.1.1 Drug Interactions
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of SARCLISA are not necessarily predictive of adverse reaction frequency in routine medical practice. However, the observed incidence of antibody (including neutralizing antibody) is less than 2% in patients treated with Isa-Kd. The observed incidence of antibody (including neutralizing antibody) is less than 2% in patients treated with Isa-Pd.

Table 2: Incidence Rates of SARCLISA Administration

<table>
<thead>
<tr>
<th>Dilution Volume</th>
<th>Initial Rate</th>
<th>Absence of Infusion-Related Reaction</th>
<th>Rate Increment</th>
<th>Maximum Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First infusion</td>
<td>250 mL</td>
<td>25 mL/hour</td>
<td>For 60 minutes</td>
<td>150 mL/hour</td>
</tr>
<tr>
<td>Second infusion</td>
<td>50 mL</td>
<td>50 mL/hour</td>
<td>For 30 minutes then increase by 100 mL/hour</td>
<td>200 mL/hour</td>
</tr>
</tbody>
</table>

4 CONTRAINDICATIONS
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-riv or to any of its excipients (see Warnings and Precautions [5.1] and Adverse Reactions [6.1]).

5.1 Infusion-Related Reactions
SARCLISA should be infused slowly to avoid life-threatening anaphylactic reactions that have occurred with SARCLISA treatment.

5.2 Interference with Serum Protein Electrophoresis and Immunofixation Tests
The combination of SARCLISA and pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information for contraception requirements prior to initiating treatment in pregnant women.

5.3 Pregnancy
SARCLISA is pregnancy category D. There is no information on the effects of SARCLISA on the fetus in pregnant women. There is no information on the effects of SARCLISA on the fetus in pregnant women. There is no information on the effects of SARCLISA on the fetus in pregnant women.

5.4 Laboratory Test Interference
With the exception of ADA testing, the addition of SARCLISA to Isa-Pd or Isa-Kd does not significantly interfere with the following tests: serotonin reuptake inhibitors, warfarin, heparin, and neutralizing antibodies.

6.2 Neutropenia
In patients treated with Isa-Pd, neutropenia occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients. In patients treated with Isa-Kd, neutropenia occurred in 55% of patients, with grade 3–4 neutropenia in 19% of patients.

6.3 Infusion-Related Reactions
SARCLISA should be administered as an intravenous infusion in combination with pomalidomide and dexamethasone or in combination with carboplatin and dexamethasone, according to the schedule in Table 1 (see Clinical Studies [14] in the full prescribing information).

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

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

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

For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information.

Table: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carboplatin and Dexamethasone

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

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

For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information.

Table: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carboplatin and Dexamethasone

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

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

For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information.

Table: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carboplatin and Dexamethasone

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

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

For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information.

Table: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carboplatin and Dexamethasone

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

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

For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information.

Table: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carboplatin and Dexamethasone

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

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

For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information.

Table: SARCLISA Dosing Schedule in Combination with Pomalidomide and Dexamethasone or in Combination with Carboplatin and Dexamethasone

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

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

For dosing instructions of combination agents administered with SARCLISA, see Clinical Studies [14] in the full prescribing information.
**Table 4** summarizes the hematology laboratory abnormalities in 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>(N=152)</td>
<td>(N=169)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>All Grades (%)</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin decreased</td>
<td>99</td>
<td>32</td>
<td>0</td>
<td>97</td>
<td>28</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>96</td>
<td>24</td>
<td>61</td>
<td>92</td>
<td>38</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>92</td>
<td>42</td>
<td>13</td>
<td>92</td>
<td>35</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>84</td>
<td>14</td>
<td>16</td>
<td>79</td>
<td>9</td>
</tr>
</tbody>
</table>

The denominator used to calculate the percentages was based on the safety population.

Combination treatment with carfilzomib and dexamethasone (Isa-Kd) was safe and effective. The safety of SARCLISA was evaluated in ICARIA, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. Patients received SARCLISA 10 mg/kg intravenously weekly, in combination with carfilzomib and dexamethasone (Isa-Kd) (n=177) (see Clinical Studies (14) in the full prescribing information). Among patients receiving Isa-Kd, 68% were exposed to SARCLISA for 12 months or longer and 51% were exposed for 18 months or longer. SARCLISA was discontinued in 5% of patients due to adverse reactions related to insulin-related reactions. The most frequent serious adverse reactions in ≥5% of patients who received Isa-Kd were pneumonia (25%) and upper respiratory tract infections (9%). Adverse reactions with a fatal outcome occurred in 2.4% of patients in the Isa-Kd group (those occurring in more than 1% of patients were pneumonia occurring in 1.7% and cardiac failure in 1.1% of patients). Permanent treatment discontinuation due to an adverse reaction (grade 4) occurred in 8% of patients who received Isa-Kd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Kd were infections (28%). SARCLISA alone was discontinued in 0.6% of patients due to infusion-related reactions.

Discontinuation of the Isa-Kd regimen due to adverse reactions was 33% of patients who received SARCLISA. The most frequent adverse reaction requiring discontinuation was infusion-related reaction (30%). The most common adverse reactions (≥20%) were upper respiratory tract infection, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, dyspnea, insomnia, bronchitis, cough, and back pain.

Table 5 summarizes the adverse reactions in IKEMA.

### Table 5: Adverse Reactions (% of Patients Receiving SARCLISA, Carfilzomib, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in IKEMA

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Infusion-related reaction*</th>
<th>Infections</th>
<th>Neutropenia†</th>
<th>Lymphopenia‡</th>
<th>Vascular disorders</th>
<th>Hypertension§</th>
<th>Respiratory, thoracic, and mediastinal disorders</th>
<th>Gastrointestinal disorders</th>
<th>Diarrhea</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>84.0</td>
<td>6.0</td>
<td>9.0</td>
<td>3.0</td>
<td>4.0</td>
<td>3.0</td>
<td>8.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Grade 1 (%)</td>
<td>32.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Grade 2 (%)</td>
<td>20.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Grade 3 (%)</td>
<td>4.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Table 6: Hematology Laboratory Abnormalities During the Period of Patients Receiving Isa-Pd versus Pd in ICARIA-MM

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>SARCLISA® + Pomalidomide + Dexamethasone (Isa-Pd) (N=177)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 1 (%)</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>99</td>
<td>22</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>94</td>
<td>52</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>94</td>
<td>19</td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>55</td>
<td>18</td>
</tr>
</tbody>
</table>

The denominator used to calculate the percentage was based on the safety population.

In ICARIA-MM, infusion-related reactions were reported in 81 patients (46%) treated with Isa-Kd. Grade 1 infusion-related reactions were reported in 14%, grade 2 in 32%, and grade 3 in 6.8% of the patients treated with Isa-Kd. Signs and symptoms of grade 3 or 4 infusion-related reactions included dyspnea, hypertension, and bronchospasm. SARCLISA was discontinued in 0.6% of patients due to infusion-related reactions [see Warnings and Precautions (5.1)].

In a separate study (TCT1409 Part B) with SARCLISA vs placebo, SARCLISA was administered by a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all grade 2) were reported in 49% of patients, at the first administration, the day of the infusion. Overall, the incidence of infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion were similar to that of SARCLISA as administered in ICARIA-MM.

In IKEMA, the incidence of grade 3 or higher infections was 43% in the Isa-Pd group. Pneumonia was the most common serious infection with grade 3 reported in 22% of patients in the Isa-Pd group compared to 16% in the Pd group, and grade 4 in 4% of patients in the Isa-Pd group compared to 2% in the Pd group. Discontinuations from treatment due to infection in patients who received Isa-Pd compared to 4.9% in the Pd group. In IKEMA, the incidence of grade 3 or higher infections was 38% in the Isa-Kd group. Pneumonia was the most common serious infection with grade 3 in 19% of patients in the Isa-Kd group compared to 15% in the Kd group, and grade 4 in 4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.6% of patients in the Isa-Pd group and 5.4% in the Pd group. SARCLISA was not administered to 12 patients in the Isa-Pd group and 4% in the Pd group.

In IKEMA, the incidence of grade 3 or higher infections was 38% in the Isa-Kd group. Pneumonia was the most common severe infection with grade 3 in 19% of patients in the Isa-Kd group compared to 15% in the Kd group, and grade 4 in 4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.6% of patients in the Isa-Kd group and 5.4% in the Kd group. SARCLISA was not administered to 12 patients in the Isa-Pd group and 4% in the Pd group.

In IKEMA, the incidence of grade 3 or higher infections was 38% in the Isa-Kd group. Pneumonia was the most common severe infection with grade 3 in 19% of patients in the Isa-Kd group compared to 15% in the Kd group, and grade 4 in 4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.6% of patients in the Isa-Kd group and 5.4% in the Kd group. SARCLISA was not administered to 12 patients in the Isa-Pd group and 4% in the Pd group.

In IKEMA, the incidence of grade 3 or higher infections was 38% in the Isa-Kd group. Pneumonia was the most common severe infection with grade 3 in 19% of patients in the Isa-Kd group compared to 15% in the Kd group, and grade 4 in 4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.6% of patients in the Isa-Kd group and 5.4% in the Kd group. SARCLISA was not administered to 12 patients in the Isa-Pd group and 4% in the Pd group.

In IKEMA, the incidence of grade 3 or higher infections was 38% in the Isa-Kd group. Pneumonia was the most common severe infection with grade 3 in 19% of patients in the Isa-Kd group compared to 15% in the Kd group, and grade 4 in 4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.6% of patients in the Isa-Kd group and 5.4% in the Kd group. SARCLISA was not administered to 12 patients in the Isa-Pd group and 4% in the Pd group.
Cultural Humility Elucidates the Link Between Patient Spirituality, EOL Care Decisions

MAGGIE L. SHAW

A PRESENTATION DURING the 2022 American Society of Clinical Oncology Annual Meeting addressed end-of-life care and how it is influenced by patient spirituality. One education session titled “Knowing What We Don’t Know: The Importance of Cultural Humility in Delivering High-Quality Care” made clear that much remains to be learned if clinicians and care providers are to effectively utilize cultural humility to understand the relationship between their patients’ spirituality and end-of-life and advanced care planning decisions, as well as to optimize patient care.

At the heart of a discussion on these topics is understanding the difference between cultural competence and cultural humility, emphasized Tracy A. Balboni, MD, MPH, senior physician and radiation oncologist at Dana-Farber/Brigham & Women’s Cancer Center and associate professor in radiation oncology at Harvard Medical School in Boston, Massachusetts. Balboni presented “Cultural Humility in Engaging Patient Spirituality in End-Of-Life Care.”

“Cultural competence is built through the clinical encounter, where a clinician is a humble learner, using clinical skills to draw out, listen to, and respect the patient’s culture, identity, and values,” she said. “When you see it this way, this definition of cultural competence, you see cultural humility is that clinical tool and skill that’s required to build cultural competence in our interactions with our patients.”

An important tool that can help shape cultural humility regarding spirituality, and thereby help to better engage with patients, she highlighted, is the HUMBLE model from the Center to Advance Palliative Care:

- Be Humble about your assumptions
- Understand your background and culture
- Motivate yourself to learn about your patients’ backgrounds
- Begin to incorporate this knowledge into your care
- Be a Life-long learner
- Emphasize respect and collaboration when forming patient treatment plans

Balboni illustrated her point of ensuring cultural humility regarding spirituality by using the case of a 43-year-old Haitian woman with cervical squamous cell carcinoma who was referred to both radiation and medical oncology and was accompanied to all her appointments by church friends. When this patient was up front in her faith, stating “God’s with us all the time,” her radiation oncologist quickly pivoted the discussion to treatment.

Cultural humility as a clinical skill is already used on a regular basis when evaluating patients’ clinical records because clinicians want to build their knowledge of and understand each patient’s disease. However, its use should not stop there, Balboni noted. This skill is also needed to understand a patient’s spiritual dimensions, she said.

Although these can translate elsewhere, Balboni suggests asking such questions: Does the patient have spiritual needs related to their diagnosis? What are the patient’s spiritual understandings about their illness and medical care?

She cited previous research highlighting the importance of spirituality to patients during their cancer experience, including through coping, spiritual practices (eg, prayer), and beliefs that frame their understanding of their illness. That spirituality was an independent predictor of better quality of life at end of life compared with those who reported no spiritual care. Additionally, that spirituality influences decisions regarding medical care, particularly that given toward the end of life.

For example, Balboni noted, if they have high spiritual support from their medical team, highly religious–coping patients are almost more likely to receive hospice care, less likely to have aggressive care, and less likely to die in the intensive care unit (ICU). On the other hand, high spiritual support from religious communities frequently translates to fewer decisions to enter hospice care, a greater likelihood to get aggressive care, and a greater chance of dying in the ICU. The research she cited demonstrated a difference of 17 percentage points in patients who receive high spiritual support from their medical team vs their religious community, respectively (26% vs 43%).

“For spirituality in cancer, it’s important to many patients in dynamic ways, but it’s often neglected in cancer care. We need cultural humility to listen and provide the best care [for] our patients, including attending to their spiritual needs. It’s a clinical skill [that requires] humility, inquiry, curiosity, and respect [for] our patients.”

—Tracy A. Balboni, MD, MPH, senior physician and radiation oncologist; Dana-Farber/Brigham & Women’s Cancer Center; associate professor, radiation oncology, Harvard Medical School

“Knowing What We Don’t Know: The Importance of Cultural Humility in Delivering High-Quality Care” made clear that much remains to be learned if clinicians and care providers are to effectively utilize cultural humility to understand the relationship between their patients’ spirituality and end-of-life and advanced care planning decisions, as well as to optimize patient care.

“Cultural competence is built through the clinical encounter, where a clinician is a humble learner, using clinical skills to draw out, listen to, and respect the patient’s culture, identity, and values,” she said. “When you see it this way, this definition of cultural competence, you see cultural humility is that clinical tool and skill that’s required to build cultural competence in our interactions with our patients.”

An important tool that can help shape cultural humility regarding spirituality, and thereby help to better engage with patients, she highlighted, is the HUMBLE model from the Center to Advance Palliative Care:

- Be Humble about your assumptions
- Understand your background and culture
- Motivate yourself to learn about your patients’ backgrounds
- Begin to incorporate this knowledge into your care
- Be a Life-long learner
- Emphasize respect and collaboration when forming patient treatment plans

Balboni illustrated her point of ensuring cultural humility regarding spirituality by using the case of a 43-year-old Haitian woman with cervical squamous cell carcinoma who was referred to both radiation and medical oncology and was accompanied to all her appointments by church friends. When this patient was up front in her faith, stating “God’s with us all the time,” her radiation oncologist quickly pivoted the discussion to treatment.

Cultural humility as a clinical skill is already used on a regular basis when evaluating patients’ clinical records because clinicians want to build their knowledge of and understand each patient’s disease. However, its use should not stop there, Balboni noted. This skill is also needed to understand a patient’s spiritual dimensions, she said.

Although these can translate elsewhere, Balboni suggests asking such questions: Does the patient have spiritual needs related to their diagnosis? What are the patient’s spiritual understandings about their illness and medical care?

She cited previous research highlighting the importance of spirituality to patients during their cancer experience, including through coping, spiritual practices (eg, prayer), and beliefs that frame their understanding of their illness. That spirituality was an independent predictor of better quality of life at end of life compared with those who reported no spiritual care. Additionally, that spirituality influences decisions regarding medical care, particularly that given toward the end of life.

For example, Balboni noted, if they have high spiritual support from their medical team, highly religious–coping patients are almost more likely to receive hospice care, less likely to have aggressive care, and less likely to die in the intensive care unit (ICU). On the other hand, high spiritual support from religious communities frequently translates to fewer decisions to enter hospice care, a greater likelihood to get aggressive care, and a greater chance of dying in the ICU. The research she cited demonstrated a difference of 17 percentage points in patients who receive high spiritual support from their medical team vs their religious community, respectively (26% vs 43%).

“For spirituality in cancer, it’s important to many patients in dynamic ways, but it’s often neglected in cancer care. We need cultural humility to listen and provide the best care [for] our patients, including attending to their spiritual needs,” Balboni said. “It’s a clinical skill [that requires] humility, inquiry, curiosity, and respect [for] our patients. Applying that skill is necessary for building culturally competent care.”

REFERENCE

We’re Heading Back to Nashville!

Join us for our annual Patient-Centered Oncology Care® (PCOC) conference, where you can:

• Learn how the focus on equity can improve care delivery;
• Listen to engaging discussions on key topics in oncology and beyond;
• Meet and network with other experts and key stakeholders.

November 9-10, 2022
Nashville, TN
AC Hotel Nashville Downtown

Join us by registering here
or visit https://bit.ly/3NRwJDU
Communication Disparities Contribute to Care Disparities

MAGGIE L. SHAW

THERE ARE DISPARITIES in end-of-life (EOL) care decisions and serious illness communication between non-Hispanic White patients and minority patients, echoing the need to increase health care equity, according to a speaker at the 2022 Annual Meeting of the American Society of Clinical Oncology in June.

End-of-Life Communication

“We probably have the most data when it comes to satisfaction with care, communication, support, pain management, hospitalization, and other utilization and advance care planning,” noted Cardinale B. Smith, MD, PhD, professor of medicine, Division of Hematology/Medical Oncology and Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai.

Comparing what is known on outcomes among non-Hispanic White patients compared with minority patients, Smith cited research showing that although Black patients were more likely to want aggressive, curative care at EOL, they were less likely to receive the EOL care they wanted and more likely to receive noncurative but intensive EOL treatment. Advance directives are also less common among these patients, and they have less favorable beliefs about hospice care.

Reasons for these disparities between patient wants and provided care fall into 5 categories, Smith noted, which were:
• patient preferences,
• distrust in the medical system,
• implicit bias leading to ineffective communication,
• religious coping, and
• lack of advance care planning (both documentation and discussion).

Black patients are more likely to report problems with physician communication, receiving inadequate information, and lack of familial support vs White patients, respectively: 41.6% vs 27.9%, 63.3% vs 41.0%, and 57.55% vs 37.3%.

“We’re not communicating with these populations in a way that is effective for them and in a way that is leading and contributing to what outcomes happen to them at EOL.”

—Cardinale B. Smith, MD, PhD, professor of medicine, Division of Hematology/Medical Oncology, Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai

“Racial/ethnic disparities in serious illness communication exist between patients with cancer and their oncologists,” the authors wrote. “Our prior work has shown that goals of care discussions are 3 minutes shorter with racial/ethnic minority patients. In this study, we sought to compare oncologist’s use of serious illness communication skills, patient participatory behavior, and overall communication quality.”

Outcomes were compared between solid-tumor oncologists who did and did not receive a coaching intervention. Baseline recordings and postimaging patient encounters were analyzed for coaching intervention effectiveness and use of serious communication skills (for this study, open-ended questions, reflective statements, empathic responses, empathetic statements, “sorry” statements, and elicitation of questions), respectively. Patient participation and global codes of oncologist communication also were evaluated. Fifty-six recordings were included in the final analysis.

Serious Illness Communication

A study by a team of investigators at Albert Einstein College of Medicine, Icahn School of Medicine at Mount Sinai, and the Duke Cancer Institute looked at interactions between oncologists and patients with advanced cancers. The results showed that clinicians were found to spend considerably less time in communication with their non-Hispanic Black patients compared with their non-Hispanic White and Hispanic patients—and these findings echoed previous research from the group.

Findings from a communications study at Icahn School of Medicine, which enrolled both patients and physicians, continued this disparities trend. According to those results, physicians spent 5 fewer minutes with minority patients than they did with White patients when discussing their overall care, as well as during visits that did not focus on disease progression. The largest average difference of 7.5 minutes, favoring more communication time with White patients, was seen when both patient groups rated their general oncology care as low quality.

“I think we’ve been hoping for magic for a while, but magic does not work,” Smith concluded. “Change is necessary for our patients. They are our priority and why we’re here.”

“At the same time, ongoing research at Icahn School of Medicine at Mount Sinai—Cardinale B. Smith, MD, PhD, professor of medicine, Division of Hematology/Medical Oncology, Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai—looking at serious illness communication and other utilization and advance care planning, continues to support the need for ongoing training and development of skills in this area for oncologists and other health care professionals.”

CARDINALE B. SMITH, MD, PHD, Professor of Medicine, Division of Hematology/Medical Oncology, Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai.
20% were Hispanic, and 41% were non-Hispanic White. Forty-nine percent were older than 65 years. Overall, less than 20% of oncologists’ communication was considered to be empathetic, even though encounter quality for flow, concerns addressed, attention, warmth, and respect were consistent among the patient groups. However, downward trends were seen when comparing outcomes among the patient groups.

The fewest reflective statements were used with non-Hispanic Black patients vs non-Hispanic White patients and Hispanic patients: 0.3 statements per encounter vs 1.1 (P = .02). And using a 5-point Likert scale, the lowest ratings for addressing patient concerns and for warmth toward their patients (P = .04 for both) were given to oncologists who met with non-Hispanic Black patients. These clinicians received 3.1 and 2.9 ratings, respectively, compared with 3.4 and 3.3 for oncologists when they met with Hispanic patients and 3.8 for both when meeting with non-Hispanic White patients.

Additional study findings show the following:

- Clinicians took advantage of fewer empathetic opportunities with non-Hispanic Black patients (2.2) and Hispanic patients (2.3) vs non-Hispanic White patients (2.6). They issued fewer “I’m sorry” statements: 0.2 and 0.0 vs 0.3.
- Far fewer questions were asked during encounters with non-Hispanic Black patients (3.9) and Hispanic patients (5.5) vs non-Hispanic White patients (7.8).
- Non-Hispanic Black patients gave the fewest assertive responses to questions (5.6), followed by non-Hispanic White patients (6.0) and Hispanic patients (7.0).

“In this diverse sample of patients with advanced cancer, oncologists used fewer reflective statements, were less attentive to concerns, and expressed less warmth with Black non-Hispanic patients,” the authors concluded. “Interventions are needed to overcome these striking racial/ethnic disparities in serious illness communication for patients with cancer.”

**REFERENCES**


---

**Patients With Cancer Face Major Financial Roadblocks, Not All Concerning Out-of-Pocket Costs**

**MAGGIE L. SHAW**

**TWO PRESENTATIONS AT** the 2022 annual meeting of the American Society of Clinical Oncology (ASCO) addressed different facets of the financial burden imposed on patients with diagnosed cancers. Both were part of a session on health services research and quality improvement.

**Financial Burden From HDHPs**

In his presentation, Nicolas K. Trad, a fourth-year medical student at Harvard Medical School in Boston, Massachusetts, and a research fellow in the Department of Population Medicine, discussed findings on the potential impact of high-deductible health plans (HDHPs) on delaying metastatic cancer diagnoses. In 2006, Deductible Relief Day—the date when most people have met their annual medical deductible and insurance kicks in—typically occurred by the end of February. As recently as 2019, this milestone had been pushed back almost 3 months to mid-May—indicating it took patients 3 additional months of out-of-pocket spending to reach their deductible. Concurrent with this trend, Trad and colleagues’ research on workers enrolled in HDHPs shows a consistent uptick in enrollment between 2006 and 2019, to the point that HDHPs now cover more than half of US workers.

“Due to increased out-of-pocket obligations, patients may postpone presenting for concerning symptoms or diagnostic testing, leading to delayed diagnosis,” lead author Trad and his team wrote. “We therefore assessed the impacts of HDHPs on the timing of metastatic cancer detection,” knowing that previous research already shows use of HDHPs has led to breast cancer—related delays in biopsy, imaging, diagnosis, and chemotherapy initiation. HDHPs were originally intended to control health care costs, when first introduced in 2003. Instead, they have led to a decrease in health care utilization due to patients’ increasing out-of-pocket spend to reach their annual deductibles, even with the plans’ goals of “incentivizing” patients to shop around for lower prices and avoid unnecessary care. As a result, patients may be more likely to delay diagnostic visits and receive a later-stage cancer diagnosis, Trad noted.

The participants in this study were aged from 18 to 64 years and had no cancer history. They were matched 1:5 to a study group (n = 345,401; employers mandated the switch to an HDHP from a low-deductible health plan [LDHP]) and a control group (n = 1,654,775; employers only offered LDHPs), with 2003-2017 data gleaned from a national commercial and Medicare Advantage database. Matching criteria included demographics (age, gender, race/ethnicity, poverty level, region), morbidity as measured by Adjusted Clinical Groups (ACG) score, and baseline medical and pharmacy costs. For this analysis, HDHPs had annual deductibles of at least $1000, whereas those of LDHPs were $500 or less. The baseline period was 1-year LDHP enrollment for all participants, who were followed for 13.5 years. During a mean follow-up period of 38 months, 1668 metastatic cancer diagnoses were made. Whereas no difference in time to metastatic diagnosis was seen in the baseline period (HR, 0.96; P = .67), participants were shown to have a longer time to first metastatic diagnosis if they had to switch from an LDHP to an HDHP (HR, 0.88; P = .01). This was “indicative of delayed detection relative to the control group,” the authors wrote, for a total of 4.6 months compared with the control group with continuous enrollment in LDHPs.

These delayed diagnoses could further translate into delayed palliative care and limited therapeutic options, Trad pointed out, all because of the exposure to high cost-sharing.

“The policy relevance of these findings are that they highlight a great need for innovative insurance models that don’t deter patients from seeking care,” Trad concluded, “as well as plans that...”
align rather than contradict the goal of improving population-level survival from cancer.” Areas of focus for future research include how HDHPs affect quality of life and treatment use among this patient population.

**Medicaid Expansion’s Impact on Clinical Trial Participation**

In the second presentation, Joseph M. Unger, PhD, MS, an associate professor in the Cancer Prevention Program, Public Health Sciences Division at Fred Hutchinson Cancer Center in Seattle, Washington, and a SWOG Cancer Research Network biostatistician, discussed how passage of the Affordable Care Act (ACA) and Medicaid expansion influenced enrollment and participation in cancer clinical trials.1

Unger and colleagues’ study of 51,751 participants, which accounted for peaks and troughs of cancer clinical trial enrollment, compared total patients using Medicaid coverage who enrolled before and after initial implementation of the ACA. Unger and his team found that the ACA improved clinical trial access for patients using Medicaid coverage between 2014 and 2015. Overall, by 2020, following the act’s expansion, the number of patients using Medicaid in clinical trials increased to 17.8% compared with 6.9% before the expansion. When investigators compared states that expanded coverage versus those that did not, the odds of patients using Medicaid in clinical trials was nearly 4 times greater in states with expanded coverage.

Unger and his team used data from the SWOG Cancer Research Network. All patients aged 18 to 64 years who were enrolled in treatment trials between April 1, 1992, and February 28, 2020, were included in the analysis. Data on patients who enrolled in trials starting in March 2020, when the COVID-19 pandemic was just beginning, were excluded because “this period was considered not to be representative of previously demonstrated temporal associations between unemployment and use of Medicaid insurance.” Adjustments were made for the monthly unemployment rate using Bureau of Labor Statistics data.

“Our analysis is premised on the idea that the proportion of patients using Medicaid for their medical insurance generally parallels national economic trends,” Unger stated, “especially the unemployment rate.” He highlighted the fact that trends in Medicaid use among trial participants typically follow unemployment trends—for example, coverage increases as unemployment increases, as it did during the 2007-2009 recession—by about 1 year’s lag time, but that this was reversed following implementation of the ACA.

The study coauthors saw an overall 19% greater annual chance of clinical trial enrollment among patients using Medicaid coverage following the act’s expansion (odds ratio [OR], 1.19; 95% CI, 1.11-1.28; P < .001), as the number of those with Medicaid coverage increased by just over 37% pre- to post-ACA implementation, from 8.6% to 11.8%. However, the number of those actually using the coverage is highly variable over time, Unger pointed out, a finding considered statistically significant. The findings between male and female patients were starkly different: female patients were 26% (OR, 1.26; 95% CI, 1.13-1.38; P < .001) more likely to use Medicaid coverage in clinical trials, whereas male patients were only 8% (HR, 1.08; 95% CI, 0.96-1.22; P = .21) more likely.

Among their primarily female (67.3%) population, younger than 50 years (40.4), 62.6% were living in the 32 states that expanded Medicaid coverage between 2014 and 2015. Most participants were neither Black (91.6%) nor Hispanic (95.5%).

Among the policy implications of these findings are that improved access to clinical trials for Medicaid patients means that those who are socioeconomically vulnerable have greater access to the newest treatments, Unger emphasized.

“Improved access to clinical trials for more vulnerable patients is critical for improving confidence that trial findings apply to the general cancer population as well,” he concluded. “And one might reasonably assume from these findings that the recently enacted [Clinical] Treatment Act, which mandates that state-level Medicaid programs cover routine care across clinical trials for Medicaid patients may, in fact, improve access to clinical trials for socioeconomically underserved populations.”

**REFERENCES**


---

**ASCO SPOTLIGHT**

Can Nudges Increase the Number of Serious Illness Conversations in Community Oncology?

Mary Caffrey

RAVI B. PARIKH, MD, MPP, assistant professor, Department of Medical Ethics and Health Policy and Medicine, Perelman School of Medicine, University of Pennsylvania, presented long-term results from an experiment with an algorithm designed to prompt oncologists to have serious illness conversations.

Getting oncologists to speak with patients about their care goals at the start of treatment has been a mission of the quality care movement for years. But matching this with the reality of busy clinic schedules has been a challenge, especially among community oncologists, who typically see more patients than their counterparts in academic medicine.

Yet if conversations about serious illness (SI) or end-of-life (EOL) care are to translate into hospice referrals—or fewer costly, toxic late treatments that won’t work—community practice is where they must happen, according to Ravi B. Parikh, MD, MPP, an assistant professor in the Department of Medical Ethics and Health Policy and Medicine at Perelman School of Medicine, University of Pennsylvania in Philadelphia. Parikh spoke with Evidence-Based Oncology™ (EBO) during the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting, just before he presented long-term findings from a clinical trial. The trial tested a protocol that prompted oncologists to have SI conversations with patients who were predicted to have a 6-month mortality risk, based on inputs from their electronic health record (EHR) to an algorithm.1

---

This type of work applies nudge theory, a Nobel Prize–winning concept rooted in behavioral economics that calls for the use of positive reinforcement to influence decision-making. Many health-related applications have involved patient behavior; Parikh’s team applies the concepts to physician behavior.

Parikh’s team at Penn Medicine deployed the protocol, and data first published in JAMA Oncology showed that after oncologists received artificial intelligence–driven prompts at the start of their shift, conversations increased 4-fold, from a rate of 3.4% to 13.5%. As Parikh explained during his ASCO presentation, the protocol was layered with a “kitchen sink” of motivational tools:

- Each week, oncologists were emailed a secure list of how their SI conversations compared with those of their peers.
- Oncologists were sent a secure list each week of high-risk patients on their upcoming schedule who, based on the algorithm, were deemed candidates for SI conversations. The doctors were asked to preselect up to 6 patients per week for conversations.
- Opt-out texts were sent ahead of high-risk patient encounters, on the morning of the clinic visit.
- Long-term results shared at ASCO showed that after the initial 16-week study period, the conversation rate in the intervention group held steady at 12% through 40 weeks. Of interest to payers, there was a decrease in the use of systemic therapy at EOL compared with the control group (6.8% vs 9.3%; adjusted odds ratio, 0.27; 95% CI, 0.12-0.63; P = .002). However, there was no difference in hospice enrollment or length of hospital stay.

Parikh discussed where things stand today with the protocol and what new steps are planned. This interview has been lightly edited for clarity.

EBO: Since you collected your initial data, has this protocol been fully implemented at Penn?

PARIKH: We’ve rolled it out across the entire cancer service line in our 12 medical oncology clinics. It’s been deployed system-wide because of its durable success in the rates of conversations. We’ve also sought to expand upon the intervention, both by refining the algorithm and also by incorporating other elements, including having patients prefill out their own SI conversation at home—by thinking about certain aspects of care goals and trade-offs—and reporting those to clinicians. I think there’s a lot of elements of how machine learning and behavioral nudges can merge together to create long-lasting change in care delivery. And I think our trial is one of the first ones to test those concepts.

EBO: We’ve all become accustomed to “nudge” applications in everyday life—anyone who uses a Peloton or tries Noom has experienced this. Is the nudge experience not as foreign to physicians as it might have been 10 years ago?

PARIKH: Overall, there was receptivity toward the idea, partially because there had been a lot of education before we started the trial on the importance of SI communication. So doctors knew this was important. What the nudge does is create a nonfinancial, nonaggressive mechanism of trying to change the architecture of how doctors make their choices—to make it easier to do the right thing. Prior to the study, we were asking doctors to look at their panel and try to identify those patients who they felt might be at risk for death or symptom worsening. That part requires a lot of mental energy for the doctor; oftentimes, doctors simply don’t have time to do it. And so they just don’t do it, they don’t have the conversation, or they have conversations too late.

What we’re trying to make easier here is not only identifying patients—using an algorithm-based strategy—but also reminding doctors on the morning of the clinic visit that a conversation may be appropriate. That takes away not only the mental energy of having to identify the patients, but also remembering to do it on the day of clinic. We think that’s a replicable strategy to remove some of the cognitive burden of some of these decisions. Of course, having the conversation is not something an algorithm is going to do. That’s the hardest part, and that’s still on them. And that’s why we didn’t achieve close to 100% of patients getting a conversation.

There’s still a lot to overcome here. But I think with regard to the identification, and the reminder process, this type of strategy is a way that doesn’t necessarily infringe on the doctor’s autonomy.

EBO: Which subgroups of doctors did the best?

PARIKH: We actually just put out [findings from] a study on this. [Those who had more conversations were] younger doctors, doctors who tended to practice in academic settings, and doctors who saw a lower number of patients on a given day. And the fourth group were doctors who had higher baseline rates of conversation, so they were bought in. Those folks tended to respond disproportionately and actually accounted for most of our intervention. In fact, busier doctors in general oncology practices or doctors who are not having a lot of conversations at baseline... still had some increases due to intervention, but not nearly as much as the other groups. So those doctors are where the phenotyping work is really important.

EBO: Did those on the lower end of the improvement spectrum get better over time? Will this process be similar to a New Year’s resolution, where you have to periodically review their data, see where they improved, and celebrate the wins, instead of just saying, “You were on the low end.” What is the approach for this group?

PARIKH: This is a great question. We have a graph that’s part of the presentation that exactly speaks to this: the rates of conversations for the average clinician went up by almost 6-fold in the first 4 to 5 months of the intervention. And then in the follow-up period [they] decreased, just as any behavioral intervention does.

Now, the difference here is that when we relied on education alone, the rates went basically back to baseline; they settled at around 4 to 5 times the baseline. So there was a new decrease during the course of the follow-up period, but they still settled at a much higher rate than...
the baseline rate. And in fact, the last 2 months of our trial were during [the] COVID-19 [pandemic]. And rates of conversations actually went up [then], largely because I think doctors were more in tune with wanting to do what their patients wanted to do during COVID-19 and trying to avoid treatment when it was unnecessary.

The algorithm in the intervention helped there because it pointed toward the type of patients that were most likely to potentially do poorly with COVID-19 [infection], and it targeted the intervention there. We were expecting because people weren’t coming into clinic that the intervention rates would just fall off a cliff....

**EBO:** What was the effect of having these conversations via telemedicine?

**PARIKH:** It’s hard to have these conversations via telemedicine. Because of the intervention, the doctors had some experience doing the conversations and may have been a little more receptive toward having [them] over telemedicine, because otherwise, we’re not usually trained to do conversations.... One key aspect I think is important to mention is that normally, doctors and nurse practitioners and physician assistants wait until something goes wrong to have these conversations. So when someone has a bad scan result, or someone’s lab tests are going in the wrong direction, that’s when we usually have the conversations. And that’s not an early conversation; that’s a delayed conversation.

We’re forcing patients to not only process the weight of bad news, but also discuss a lot of really heavy topics. What we’re trying to do with this is say, “Let’s not wait for a bad event. Let’s use some of our predictive algorithm tools to identify the right patients and have these conversations early on, so that patients can be in the right mindset or not necessarily think about a million things.”

**EBO:** What are your next steps?

**PARIKH:** There are 3 key areas that we are focused on. The first is running randomized trials now using algorithm-based strategies in community oncology settings, where most patients receive their cancer care, to try to test the same concept. The second thing that we’re doing, as I mentioned, is trying to refine the behavioral intervention a bit more. Doctors are busy—they have a lot on their plate and we are trying to push doctors to do more and more and more without making their lives easier. So allowing patients to think about some of this at home and allowing high-risk patients to prefile in their own conversation so that doctors can, if it makes sense, jump in on a particular aspect of the conversation is another thing we’re trying.

And the last thing we’re trying involves refining the algorithm to make it more personalized on a cancer-specific level. We’re using other sources of data, particularly patient-reported data, which we’ve started to collect a lot more these days. We feel it’s important to get the algorithm right for situations like this.

**EBO:** Given what you’re saying, you’ll be working more with community oncology physicians. Might one of the algorithm’s cut points be an academic vs community setting?

**PARIKH:** Community oncology practices are busier. So perhaps they’re going to respond less [than other settings]. But the other counterpoint is that in academic settings, when people are getting second opinions and when people are coming in for perhaps 1- or 2-time visits and going back to the community, maybe there’s not as much of an incentive to have a conversation, even with a higher-risk patient.

With the community doctors, these are the doctors that are trusted that patients are seeing oftentimes for years and years. Perhaps there’s more receptivity to bring up the conversation when it’s necessary. So I’m not sure which one of those is going to win out. We’ve seen a lot of enthusiasm about this from community practices, particularly community practices that have embedded palliative care in their own practice because they’re attuned to the idea that these folks need better conversations on EOL care. But doctors need a little bit of a nudge to remind them to do the right thing and have the conversation when necessary. The algorithm can sometimes relieve some of that cognitive burden.

**EBO:** In terms of scaling this, right now you’re in an academic center. If this concept were applied broadly, who would pay for it? How and from where would you be reimbursed?

**PARIKH:** There’s been a lot of work on the entrepreneurial side around partnerships with payers…. There’s a high cost of care near EOL, but it’s more that there’s unwarranted and unwanted care near the end. Even though I think [reimbursement could come] from the payer side, there’s alignment of incentives toward trying to reduce costs and ensure that the patients who are getting chemo[therapy] are truly the ones who would benefit. An intervention like this can be helpful.

Several interventions have tested similar algorithm-based palliative care, or algorithm-based supportive care, to try to do this in concert with payers. I really think there’s going to be an emphasis more on the practices, particularly those practices that are participating in value-based contracts and that may be judged by performance indicators, including care near EOL.... I think there’s going to be a lot more likelihood of success here, first, because practices have more granular and up-to-date data to make the algorithm better, and second, because doctors don’t want to hear from their payer that they need to have a conversation. Doctors don’t want to hear that they need to refer [a patient] to palliative care. It’s better to have doctors make that decision for themselves. When we can embed something like this into practices that are committed to improving EOL, palliative supportive care, I think that’s going to be the biggest alignment.●

**REFERENCES**


can provide your patients with access support throughout their treatment journey
- we are here to help.

To learn more about the program, visit viatrisadvocate.com

NON-2022-2833
VIATRIS ADVOCATE and the Viatris Advocate Logo are registered trademarks of Mylan Inc., a Viatris Company.
VIATRIS and the Viatris Logo are trademarks of Mylan Inc., a Viatris Company.
© 2022 Viatris Inc. All Rights Reserved.
Data Indicate Lower Response Rates to Axi-cel Among Black Patients

**COMPARSED WITH WHITE PATIENTS**, Black patients who received axicabtagene ciloleucel (axi-cel) to treat large B-cell lymphoma had lower response rates to the chimeric antigen receptor (CAR) T-cell therapy. The review of real-world data was presented during the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting.

Frederick L. Locke, MD, vice chair of the Department of Blood and Marrow Transplant and Cellular Immunotherapy and program coleader of immuno-oncology at Moffitt Cancer Center in Tampa, Florida, said the data from 1389 patients help fill in gaps in understanding how patients from different racial and ethnic groups respond to axi-cel (Yescarta). Data were gathered in a postapproval safety study among patients treated between October 2017 and August 2020, with a data cutoff of June 22, 2021. The median follow-up was 12.7 months. Outcomes were overall response rate (ORR), complete response (CR) rate, duration of response (DOR), progression free survival (PFS), and overall survival (OS) at 12 months: grade 3 or greater cytokine release syndrome (CRS); and immune effector cell-associated neurotoxicity syndrome (ICANS).

In this group, 1127 patients were White (81%), 102 were Black (5%), 81 were Asian (6%), and 152 (11%) were Hispanic, which included 104 White Hispanic, 2 Black Hispanic, and 1 Asian Hispanic patients. Black patients were younger than White patients, had a median age of 55.5 years vs 62.8 years, and were more likely to have pulmonary impairment (41% vs 28%). Hispanic patients were younger than non-Hispanic patients (58.5 vs 62.6 years).

Black patients also had a longer time between diagnosis and treatment; 71% had a wait time of at least 12 months compared with 59% of White patients. Response rates were as follows:

- **White patients**: ORR 74%, with CR 57%, PFS 48%, and OS 63%
- **Black patients**: ORR 57%, with CR 45%, PFS 36%, and OS 62%
- **Asian patients**: ORR 67%, with CR 53%, PFS 55%, and OS 65%
- **Hispanic patients**: ORR 73%, with CR 55%, PFS 50%, and OS 65%

In addition, Hispanic patients had lower rates of grade 3 or higher CRS (4%) and ICANS (15%) than non-Hispanic patients (9% and 27%, respectively). The ORR of Black patients was inferior to that of White patients (odds ratio [OR], 0.40; 95% CI, 0.24-0.69), as was the CR (OR, 0.55; 95% CI, 0.32-0.93). However, no statistical differences were found in PFS or OS across races. Locke elaborated further during the session.

“No differences in efficacy outcomes were observed among patients who were Hispanic or Latino and those who were not Hispanic or Latino,” he said. “Asian patients appeared to have a favorable duration of response compared with White and Black or African American patients. Lastly, a lower response rate observed among Black or African American patients compared (with) White patients warrants further investigation into additional factors that may account for this difference, such as high disease burden, different disease biology, and importantly, different access to care.”

**REFERENCE**

In KRYSTAL-1, Adagrasib for NSCLC Has 43% Response Rate

**PHASE 2 RESULTS FOR ADAGRASIB**, a KRAS G12C inhibitor, showed promise for the treatment of patients previously treated for KRAS G12C-mutated non-small cell lung cancer (NSCLC), with no new safety signals seen. Adagrasib selectively binds to KRAS G12C and renders it inactive, making the drug potentially useful across multiple tumor types. The Food and Drug Administration has already accepted a new drug application for adagrasib’s use in NSCLC based on results from this study, called KRYSTAL-1 (NCT03785249).

The findings, presented at the 2022 American Society of Clinical Oncology Annual Meeting, were also published in the New England Journal of Medicine.

Alexander I. Spira, MD, PhD, FACP, director of Virginia Cancer Specialists Research Institute and the Phase 1 Trial Program, presented the results on behalf of the KRYSTAL-1 investigators. He stated that the trial had been carried out during extraordinary circumstances. “I want to acknowledge the patients and their families for making this trial possible (and), most importantly, all the clinical study teams and investigators, especially at all the sites doing this trial during the height of the pandemic and candidly one of the most challenging times I’ve ever been involved in clinical research.”

Among the initial 116 patients in the study, 98.3% had received both chemotherapy and immunotherapy previously. Spira said that 112 patients were evaluable, and they were similar to the population with NSCLC—65% of the patients were female, the median age was 64 years, and 96% were current or former smokers.

Among the evaluable patients, 43% responded to adagrasib, and the disease control rate was 80%. According to Spira the overall response rate (ORR) was 51% when calculated without including those patients who received scans too early or left the study. The duration of response was 8.5 months (95% CI, 6.2 to 13.8). Results also showed the following:

- Median PFS was 6.5 months (95% CI, 4.7-8.4).
- As of January 15, 2022 (median follow-up, 15.6 months), median OS was 12.6 months (95% CI, 9.2-19.2).
- Among those with previously treated central nervous system metastases, intracranial ORR was 33.3% (95% CI, 18.0-51.8).

Spira said most patients were able to tolerate the drug, although 52% had dose reductions; 7% discontinued treatment. Treatment-related adverse events were seen in 97.4% of patients; 52% of patients had grade 1 or 2.

A phase 3 study, KRYSTAL-12 (NCT04685135), is already underway that will compare the effectiveness of adagrasib vs docetaxel. Spira noted. The primary completion date is set for August 2023.

**REFERENCES**


Lucitanib With Nivolumab Sees Responses in Gynecological Cancer Treatment

Lucitanib is a novel dual inhibitor that targets human vascular endothelial growth factor receptors (VEGFRs) and fibroblast growth factor receptors (FGFRs) and restricts the blood supply feeding the tumors. In this case, lucitanib blocks VEGFR 1-3 and FGFR1/2 kinases, leading to tumor cell death.

The LIO-1 study (NCT04042116) is examining the combination of lucitanib with the PD-1 inhibitor nivolumab across a range of solid tumor cancers. During the 2022 annual meeting of the American Society of Clinical Oncology, Manish R. Patel, MD, director of drug development at Florida Cancer Specialists/Sarah Cannon Research Institute in Sarasota, Florida, presented findings from the phase 1/2 dose escalation study evaluating lucitanib with nivolumab in advanced gynecological cancers, including cervical cancer (CC), endometrial cancer (EC), and ovarian cancer (OC).

The following patients were enrolled: those with EC who had received at least 1 prior platinum-based chemotherapy; patients with CC who had received chemotherapy with or without bevacizumab; patients with high-grade OC who had received at least 2 prior chemotherapy lines; and those with EC or OC with clear-cell histology who had received at least 1 prior platinum-based chemotherapy plus taxane. Patients with prior PD-1 or PD-L1 therapy were excluded, except for 10 patients in the EC group.

**DOsing.** Patients started with 6 mg of lucitanib daily, escalating to 8 mg per day and then 10 mg per day if safety criteria were met, along with intravenous nivolumab 480 mg every 28 days. At the time of data cutoff, 31 of 124 patients were continuing in the study. Across cohorts, 32 (26%) patients escalated to the 8-mg dose and 20 (16%) escalated to the 10-mg dose. More patients continued in the CC cohort in phase 2 of the trial.

**RESULTS.** Updated data presented in a poster showed responses as follows:

- A confirmed overall response rate (ORR) was seen in 5 of 22 patients with EC (22.7%); 5 partial responses (PRs).
- 12 of 46 responses were reported in patients with CC (26.1%); 2 complete responses (CRs), 10 PRs.
- 4 of 33 responses were reported in patients with OC (12.1%); 4 partial responses.
- 6 of 23 responses were reported in patients with EC/OC clear cell (21.7%); 1 CR, 5 PRs.
- Response duration ranged from 1.9 to 13.1+ months in the CC cohort, 5.6 to 14.8+ months in the EC cohort, 3.7 to 14.9+ months in the OC cohort, and 3.5 to 10.4+ in the EC/OC clear cell cohort.
- Of 5 patients with EC with prior PD-1 inhibitor treatment, 2 had PRs and 1 had stable disease of more than 7 months.

Across the cohorts, the median duration of lucitanib and/or nivolumab treatment was 3.7 months (range, <0.1-17.3). At cutoff, 37 patients (30%) had remained on 1 or both therapies for at least 6 months. Of the 124 patients, 50 (40%) met the bar for dose escalation at cycle 2, 63 (51%) were ineligible, and 11 (9%) did not reach cycle 2.

Of the 124 total patients, 115 had treatment-emergent adverse events (TEAEs) related to the study; 44% were grade 3 or higher. The most common TEAE was hypertension. Of the group, 21 patients had a dose reduction in lucitanib and 14 patients had TEAEs related to lucitanib that led to discontinuation.

Safety results were similar across tumor types. Investigators concluded that the combination of lucitanib and nivolumab in advanced gynecological malignancies “has a manageable safety profile through effective dose titration.”

**REFERENCE**


Dosing Study of Modakafusp Alfa Shows Promise in Solid Tumors; Tests Planned With Checkpoint Inhibitors

Modakafusp alfa is a first-in-class immune-targeting attenuated cytokine, which was tested in patients with a variety of solid tumors.

Melissa L. Johnson, MD, who is program director of lung cancer research at Sarah Cannon and a medical oncologist with Tennessee Oncology, explained how modakafusp alfa consists of 2 interferon alpha 2b (IFNα2b) molecules that are genetically fused to the to the Fc portion of a humanized anti-CD38 IgG4 monoclonal antibody. Modakafusp alfa, which is being developed by Takeda Oncology, had previously demonstrated antitumor activity in mouse models.

Because of the way IFNα2b behaves, dosing is extremely important: the attenuated molecules seek out the CD38+ cells, triggering immune responses. “Upregulation of CD38 in the tumor microenvironment has been shown to be a mechanism of acquired resistance to treatment with anti-PD-1 or anti-PD-L1 inhibitors in solid tumors,” Johnson said.

“Thus, this increased CD38 target expression could enable increased modakafusp binding and therefore, increased interferon pathway activation in the tumor microenvironment, where it could be most beneficial for eliciting antitumor responses,” she said.

The study’s primary objective was determining safety and tolerability for modakafusp alfa. Secondary objectives included (1) defining a maximally tolerated dose and (2) evaluating pharmacokinetics and immunogenicity.

**RESULTS.** Adult patients with advanced or metastatic solid tumors received modakafusp alfa intravenously on day 1 of a 21-day cycle. Dose escalation started at 0.1 mg/kg. A total of 21 patients were dosed in the escalation phase at 0.1 (n = 3), 0.2 (n = 3), 0.4 (n = 3), 0.75 (n = 3), 1.0 (n = 3), and 1.5 mg/kg (n = 6) once every 3 weeks. Two patients experienced dose-limiting toxicities during cycle 1 at 1.5 mg/kg; 1 patient with baseline bone infiltration had grade 4 thrombocytopenia and 1 patient had grade 3 confusion.

Across all dose levels, patients had received a median of 2 treatment cycles (range, 1-11) as of November 2021. Modakafusp alfa treatment-related adverse events (TRAEs) were reported in 81% of patients; these included infusion-related reactions (52.4%), chills (47.6%), and nausea (33.3%); TRAEs of grade 3 or higher were reported in 42.9% of patients and included neutropenia (14.3%) and hypertension (9.5%).

There was an increase in greater than dose-proportional exposure in the 0.1-1.5 mg/kg dose range, with no exposure accumulation after each dose every
3 weeks. Pharmacodynamic data suggested saturation of the IFN pathway modulation at greater than 0.2 mg/kg in the peripheral blood, with duration of modulation increasing with each dose.

Among the 14 response-evaluable patients, 7 had a best response of stable disease, including 1 with cutaneous melanoma who had 21% target lesion shrinkage. "Modakafusp alfa had a manageable safety profile in the dose range 0.1 to 1.5 mg/kg in patients with solid tumors. Proof of mechanism was validated," the investigators concluded. They recommended the phase 2 dose at 1.0 mg/kg every 3 weeks. The next round of studies will test modakafusp alfa with a checkpoint inhibitor in selected tumor types.

REFERENCE

David R. Penberthy, MD, MBA: Knowledge Gained at ASCO Can Transform Cancer Care

The way I look at ACCC, it’s more of a how-to organization [that says,] “So, this is what we need to do.” And ACCC has such a wide breadth. Approximately two-thirds of the oncology care in America is delivered by a member of ACCC. And within that large group of organizations, somebody has oftentimes solved the issue that’s facing another facility. So we can tap into shared experience, into what I like to call the hive mind. If somebody has figured this out, in some small area in Arizona, we can apply that same technology or that same method in Virginia. This is how we can leverage the resources that we have to improve patient care or at least deliver the most optimal patient care in their backyard.

“The underserved are enrolling in clinical trials at a lower rate than other populations are, and we want to change that. And technologies, artificial intelligence, and decision support tools can help us match patients with clinical trials.”

—David R. Penberthy, MD, MBA, medical director of radiation oncology, Bon Secours–Southside Medical Center, Petersburg, Virginia; president, Association of Community Cancer Centers

The information shared during the annual meeting of the American Society of Clinical Oncology (ASCO) can change cancer care, nationally and globally, and providers must direct their resources toward improving patient care, said David R. Penberthy, MD, MBA. Penberthy, medical director of radiation oncology at Bon Secours–Southside Medical Center in Petersburg, Virginia, is the current president of the Association of Community Cancer Centers.

EBO: How can digital tools help achieve equity in clinical trials administration as set forth by the recent ASCO/ACCC recommendations?

PENBERTHY: We’ve recognized for a while now that there are some health disparities. The underserved populations are enrolling in clinical trials at a lower rate than other populations are, and we want to change that. And technologies, artificial intelligence, and decision support tools can help us match patients with clinical trials. But it goes beyond just matching patients with a clinical trial. I’ll give you an example.

In my clinic, we serve a population that has difficulty with some basic needs. Sometimes they don’t have transportation, sometimes they don’t have access. They live in areas that are relative food deserts. So how do you get somebody fed? How do you get somebody motivated to show up to a clinic at their appropriate time? It goes beyond just matching the disease process to a clinical trial. Absolutely, that’s important, but then a real-world issue is, how do you get the patient into the center? How do you get them to pay for that? And how do you get government agencies and payers and all that to recognize the importance of that? ACCC is a wonderful organization for helping to design systems.
JOIN US AT AN IVBM EVENT NEAR YOU!

The American Journal of Managed Care® (AJMC®) is hosting regional Institute for Value-Based Medicine® (IVBM) events, where a diverse panel of health care professionals—including physicians, pharmacists, nurses, practice administrators, and payers—deliver engaging conversations focused on key topics within the oncology or population health landscape.

Register for an IVBM event near you to:

- Join the discussion among health care professionals about timely topics within oncology or population health
- Gain new perspectives from a diverse panel of health care experts
- Collaborate and network with peers

To learn more and view the full list of scheduled events, visit AJMC.com/ivbmevents or scan the QR code.

CHECK OUT WHERE WE’LL BE IN 2022

- August 11
  Minneapolis, MN
- September 13
  New Orleans, LA
- September 22
  New York, NY
- July 28
  Atlanta, GA
- September 29
  Phoenix, AZ

Attendance to IVBM events is complimentary for health care providers, administrators, and allied health professionals. For anyone else who is interested in attending, please contact us at IVBMevents@ajmc.com.
First- and second-generation EGFR TKIs have limited efficacy in patients with EGFR Exon20+ mNSCLC. 4-9

Overall survival for EGFR Exon20 patients is half that of patients with common EGFR mutations when treated with first- and second-generation EGFR TKIs. 4*

Overall response rates when treated with first- and second-generation EGFR TKIs. 4-9

PCR testing identifies only 50% of EGFR Exon20 insertions. NGS is able to detect all EGFR Exon20 variants. 1-3

*These results were not statistically significant (P=0.06). 4

EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer; NGS, next-generation sequencing; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.

References:

All trademarks are the property of their respective owners.
©2021 Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. All rights reserved. 04/21 USO-NON-0214

Learn more at changecourseforexon20.com