OS Advances Gather Steam in Breast Cancer

ESMO 2022 Research Solidifies Therapies

PEER EXCHANGE
PARP Inhibitors in Metastatic Castration-Resistant PROSTATE CANCER: Whom to Treat?

OnPathways®
CRC Tumor Sidedness Plays an Increasing Role in Clinical Practice

CONFERENCE HIGHLIGHTS
ESMO 2022
OncLive® breaks down the latest data from the Annual Congress with exclusive insights from key opinion leaders in the fields of LUNG, GU, GI, GYNECOLOGIC, and SKIN CANCERS.

Praesh C. Shad, MD, provides a surgeon’s insight on ESCC on an episode of Medical World News Deep Dive™ and Suresh G. Nair, MD, takes you Inside the Practice® for an overview of clinical trials at Lehigh Valley Topper Cancer Center.

CLEVELAND CLINIC TAUSSIG CANCER INSTITUTE
Cracking the “MGUS” Code Reveals MONOCLONAL GAMMOPATHY of Clinical Significance
By Sandra Mazzoni, DO

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**STUDY DESIGN**

PAOLA-1 was a phase 3 trial of women with advanced ovarian cancer that enrolled patients regardless of surgical outcome or BRCA mutation status following response to first-line platinum-based chemotherapy with bevacizumab. Patients were randomized 2:1 (N=806) to receive LYNPARZA tablets 300 mg BID in combination with bevacizumab 15 mg/kg (n=537) or bevacizumab 15 mg/kg in combination with placebo BID (n=269).

Bevacizumab was administered every 3 weeks for a total duration of up to 15 months, and LYNPARZA or placebo treatment was administered for up to 24 months or until disease progression or unacceptable toxicity.

The primary endpoint was the investigator-assessed PFS. Prespecified exploratory analyses included PFS in predefined subgroups, including HRD status and BRCA mutation status, which were not controlled for Type 1 error. HRD status was not a stratification factor in PAOLA-1.

Secondary endpoints were the time from randomization until second disease progression or death, overall survival, the time until the first subsequent radiological abnormality occurs, interrupt LYNPARZA treatment and initiate effective contraception during treatment and for 6 months following the last dose.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

**INDICATION**

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

First-Line Maintenance HRD-Positive Advanced Ovarian Cancer in Combination with Bevacizumab

In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

- a deleterious or suspected deleterious BRCA mutation, and/or
- genomic instability

Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

**NEW PFS DATA**

Prespecified exploratory analysis in HRD-positive* patients: Median PFS

<table>
<thead>
<tr>
<th>LYNPARZA + bevacizumab</th>
<th>bevacizumab + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=255)</td>
<td>(n=132)</td>
</tr>
<tr>
<td>37.2 months (3.1 years)</td>
<td>17.7 months (~1.5 years)</td>
</tr>
</tbody>
</table>

HR=0.33 (95% CI: 0.25–0.45)

Prespecified 5-year follow-up analysis in HRD-positive* patients: Median PFS

<table>
<thead>
<tr>
<th>LYNPARZA + bevacizumab</th>
<th>bevacizumab + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=255)</td>
<td>(n=132)</td>
</tr>
<tr>
<td>46.8 months (3.9 years)</td>
<td>17.6 months (~1.5 years)</td>
</tr>
</tbody>
</table>

HR=0.41 (95% CI: 0.32–0.54)

136 (53%) events in the LYNPARZA + bevacizumab arm and 104 (79%) events in the bevacizumab + placebo arm.

The analyses at 5 years are descriptive only; the PAOLA-1 trial was not designed to assess a statistical difference between treatment groups at these time points.

**ADVERSE REACTIONS—First-Line Maintenance Advanced Ovarian Cancer in Combination with Bevacizumab**

Most common adverse reactions [Grades 1-4] in ≥10% of patients treated with LYNPARZA/bevacizumab compared to a ≥25% frequency for placebo/bevacizumab in the first-line maintenance setting for PAOLA-1 were: nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%), and leukopenia (18%). In addition, the most common adverse reactions (≥10%) for patients receiving LYNPARZA/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were: diarrhea (18%), neutropenia (18%), urinary tract infection (15%), and headache (14%). In addition, venous thromboembolic events occurred more commonly in patients receiving LYNPARZA/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).
LYNPARZA + bevacizumab reduced risk of death by 38% \(^2\)

93 (37%) events in the LYNPARZA + bevacizumab arm and 69 (52%) events in the bevacizumab + placebo arm\(^1\)

**IMPORTANT SAFETY INFORMATION (Cont’d)**

**ADVERSE REACTIONS—First-Line Maintenance Advanced Ovarian Cancer in Combination with Bevacizumab (Cont’d)**

Most common laboratory abnormalities (Grades 1–4) in ≥25% of patients for LYNPARZA in combination with bevacizumab in the first-line maintenance setting for PAOLA-1 were: decrease in hemoglobin (79%), decrease in lymphocytes (63%), increase in serum creatinine (61%), decrease in leukocytes (59%), decrease in absolute neutrophil count (35%), and decrease in platelets (35%).

**DRUG INTERACTIONS**

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

**USE IN SPECIFIC POPULATIONS**

**Lactation:** No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

**PEDIATRIC USE:** The safety and efficacy of LYNPARZA have not been established in pediatric patients.

**Hepatic Impairment:** No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

**Renal Impairment:** No dosage modification is recommended in patients with mild renal impairment (CLcr 51–80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31–50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

**You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.**

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

**BID=twice daily; BRCAm=BRCA mutation; CDx=companion diagnostic; CI=confidence interval; DCO=data cutoff; HR=hazard ratio; HRD=homozygous recombination deficiency; OS=overall survival; PFS=progression-free survival; tBRCA=tumor BRCA.**

Combination with Bevacizumab

First-line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Lynparza is indicated in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on a FDA-approved companion diagnostic for Lynparza [see Dosage and Administration (2.1) in the full Prescribing Information].

Maintenance Treatment

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

DOSE AND ADMINISTRATION

Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at the following website: https://www.fda.gov/medical-devices/companion-tests.

Select patients for therapy with Lynparza based on the presence of deleterious or suspected deleterious HRG gene mutations, including BRCA mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Biomarker</th>
<th>Sample type</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCAm, BRCAm X X</td>
<td>BRCAm, BRCAm X X</td>
<td>Blood Plasma (cDNA)</td>
</tr>
<tr>
<td>BRCAm, BRCAm X X</td>
<td>BRCAm, BRCAm X X</td>
<td>Blood Plasma (cDNA)</td>
</tr>
<tr>
<td>Maintenance treatment of recurrent ovarian cancer</td>
<td>Maintenance treatment of recurrent ovarian cancer</td>
<td>No requirement for biomarker testing</td>
</tr>
</tbody>
</table>

*When testing fails or tissue sample is unavailable/treatment, or when genetic testing is not possible/consider using an alternative test, if available.

Recommended Dose

The recommended dose of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at their scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

Duration of Treatment

Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer

Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should undergo additional assessments with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years.

First-Line Maintenance Treatment of HRD-positive Advanced Ovarian Cancer in Combination with Bevacizumab

Continue Lynparza treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should undergo additional assessments with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous Lynparza treatment, can be treated beyond 2 years.

When used with Lynparza, the recommended dose of bevacizumab is 15 mg/kg every three weeks. Bevacizumab should be given for a total of 15 months including the period given with chemotherapy and given as maintenance. Refer to the Prescribing Information for information on bevacizumab when used in combination with Lynparza for more information.

Recurrent Ovarian Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- Maintenance treatment of recurrent ovarian cancer

Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 25% (n=50 mg BID). If a further dose reduction is required, then reduce to 200 mg taken twice daily.

Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A4 Inhibitors

Avoid coadministration of strong or moderate CYP3A4 inhibitors with Lynparza. If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when coadministered with a strong CYP3A4 inhibitor.
- 150 mg twice daily when coadministered with a moderate CYP3A4 inhibitor.

After the inhibitor has been discontinued for 2 days (3 half-lives), resume the Lynparza dosage taken prior to initiating the CYP3A4 inhibitor [see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full Prescribing Information].

Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information].

CONTRAINDICATIONS

None.
The most common adverse reactions (≥ 10%) for patients receiving Lynparza/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were nausea (53%), fatigue (including asthenia) (53%), anemia (41%), dyspepsia (24%), vomiting (22%), diarrhea (20%), thrombocytopenia (18%), neutropenia (18%), leukopenia (15%), and urinary tract infection (14%), and headache (14%). The adverse reactions that occurred in ≥ 10% of patients receiving Lynparza/bevacizumab were dyspnea (8%), pain in bone (8%), stomatitis (5%), dysgeusia (4%), rhinitis (3%), diarrhea (2.6%), hypersensitivity (1.7%) and MDS/AML (0.7%). In addition, venous thromboembolic events occurred more commonly in patients receiving Lynparza/bevacizumab (5%) than in those receiving placebo (1.5%).

Table 5 Laboratory Abnormalities Reported in ≥ 25% of Patients in PACIFIC.*

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Lynparza/bevacizumab n=430</th>
<th>Placebo/bevacizumab n=267</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in hemoglobin</td>
<td>79</td>
<td>13</td>
</tr>
<tr>
<td>Decrease in lymphocytes</td>
<td>83</td>
<td>10</td>
</tr>
<tr>
<td>Increase in serum creatinine</td>
<td>81</td>
<td>4</td>
</tr>
<tr>
<td>Decrease in leukocytes</td>
<td>58</td>
<td>3</td>
</tr>
<tr>
<td>Increase in neutrophil count</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>Decrease in patients</td>
<td>52</td>
<td>25</td>
</tr>
</tbody>
</table>

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1. This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Maintenance Treatment of Recurrent Ovarian Cancer

SOLO-2

The safety of Lynparza for the maintenance treatment of patients with platinum sensitive (BRCAmut or BRCAwt ovarian cancer was investigated in SOLO-2 (*see Clinical Studies (14.3) in the full Prescribing Information*). Patients received Lynparza tablets 300 mg orally once daily (n=243) or placebo (n=124) for a maximum 24 months of disease progression or unacceptable toxicity. The median duration of study treatment was 19.4 months for patients who received Lynparza and 5.6 months for patients who received placebo.

Adverse reactions observed in SOLO-2 that occurred in ≤ 20% of patients receiving Lynparza were nausea (53%), fatigue (including asthenia) (53%), anemia (41%), dyspepsia (11%), increased creatinine (11%), MDS/AML (8%), edema (8%), rash (8%), decreased appetite (7%), constipation (7%), and stomatitis† (2%).

Table 6 Adverse Reactions* in Study 19 (≥ 10% of Patients Who Received Lynparza).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lynparza n=136</th>
<th>Placebo n=128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Decrease in absolute neutrophil count</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Decrease in patients</td>
<td>25</td>
<td>24</td>
</tr>
</tbody>
</table>

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.*

Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in Study 19.

Table 7 Laboratory Abnormalities Reported in ≥ 25% of Patients in SOL0-2.

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Lynparza tablets n=195</th>
<th>Placebo tablets n=98</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in mean corpuscular volume*</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>Decrease in hematocrit</td>
<td>64</td>
<td>23</td>
</tr>
<tr>
<td>Decrease in hemoglobin</td>
<td>25</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter†</th>
<th>Lynparza/bevacizumab</th>
<th>Placebo/bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in platelets</td>
<td>38</td>
<td>2.4</td>
</tr>
<tr>
<td>Decrease in neutrophil count</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Decrease in patients</td>
<td>22</td>
<td>9</td>
</tr>
</tbody>
</table>

† Represents grouped terms of related terms that reflect the medical concept of the adverse reaction.

The safety of Lynparza for the maintenance treatment of patients with platinum sensitive ovarian cancer who had received 2 or more previous platinum containing regimens was evaluated in Study 19 (*see Clinical Studies (14.3) in the full Prescribing Information*). Patients received Lynparza capsules 400 mg orally twice daily (n=136) or placebo (n=128). At the time of final analysis, the median duration of exposure was 8.7 months in patients who received Lynparza and 4.5 months in patients who received placebo.

Adverse reactions led to dose interruptions in 25% of patients receiving Lynparza; dose reductions in 26% and discontinuation in 6% of patients receiving Lynparza. Tables 8 and 9 summarize adverse reactions and laboratory abnormalities in Study 19.

Lynparza can cause fetal harm when administered to a pregnant woman (see Nonclinical/Pharmacology (12.3) in the full Prescribing Information). Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

Pregnancy Testing

Recommend pregnancy testing for females of reproductive potential prior to initiating treatment with Lynparza.

Use with Anticoagulant Agents

Clinical studies of Lynparza with other myelosuppressive anticoagulant agents, including warfarin, have not been conducted. No data are available in patients with severe hepatic impairment (Child-Pugh classification C) or moderate hepatic impairment (Child-Pugh classification B). CYP3A inhibitors in moderate hepatic impairment (Child-Pugh classification B) may increase exposure to Lynparza and CYP3A substrates. Lynparza can cause fetal harm when administered to a pregnant woman (see Nonclinical/Pharmacology (12.3) in the full Prescribing Information). Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

Pregnancy Risk Summary

There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤ 30 mL/min) (see Clinical Pharmacology (12.5) in the full Prescribing Information). There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤ 30 mL/min) (see Clinical Pharmacology (12.3) in the full Prescribing Information). Distributed by: AstraZeneca Pharmaceuticals LP Wilmington, DE ©AstraZeneca 2022

B2/22-US-8673 B22
Your Link to *Everything* Oncology

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The treatment of patients with breast cancer is making noteworthy strides in several clinical settings, with recent trial results showing overall survival improvements for advanced and metastatic disease. Findings presented during the European Society for Medical Oncology Congress 2022 underscored these gains for several novel therapies with different mechanisms of action.
Next Steps on the Road to Curative Therapy

THE BREAST CANCER FIELD has been awash in good news lately. Positive clinical trial findings have been piling up for a range of therapies, starting with the development of fam-trastuzumab deruxtecan-nxki (Enhertu) for patients with previously treated unresectable or metastatic HER2-low breast cancer. The FDA’s approval of the antibody-drug conjugate in this setting in August 2022 is paving the way for new strategies for treating patients with HER2-low tumors—a group that comprises 50% to 60% of all breast cancers.1 Notably, trastuzumab deruxtecan demonstrated a significant improvement in overall survival (OS) in the pivotal DESTINY-Breast04 trial (NCT03734029).2 Similarly, data for several other therapies have shown OS improvements over standard regimens, according to results presented at the European Society for Medical Oncology Congress 2022 in September. These findings, recapped in the cover story of this issue of OncologyLive®, involve CDK4/6 inhibitors in hormone receptor-positive, HER2-negative advanced breast cancer and immune checkpoint inhibitors in metastatic triple-negative breast cancer.

Even in an era of surrogate end points, OS is still the gold standard in oncology studies. By that measure, the recent spate of clinical trial findings that have reached this benchmark in several breast cancer subtypes adds up to an impressive body of work.

However, translating such findings into improved outcomes for patients in real-world settings is another matter. For perspective on the impact that these results might make, we talked with George W. Sledge Jr, MD, a 2018 Giants of Cancer Care® award winner in the breast cancer category. Sledge, a longtime professor of medicine at Stanford University in California and former chief of its Division of Oncology, joined Caris Life Sciences in mid-October 2022 as executive vice president and chief medical officer.

The best opportunity for achieving cures for patients with breast cancer means moving therapies that are effective in advanced disease into earlier settings, Sledge said. “One of the questions is going to be how far will they go in the adjuvant setting,” he said in an interview. “In general terms, women who die of breast cancer die because they have a triple-negative breast cancer that relapses quickly and then goes through a series of increasingly toxic and less effective therapeutics before they go on to die. For women with ER [estrogen receptor]-positive breast cancer, we increasingly see patients who are relapsing 5 or more years out. To what extent can we move these drugs earlier and earlier for a broader and broader population of patients to improve the adjuvant benefit and prevent micrometastases from turning into 900-pound gorillas?”

The answer to that question, Sledge believes, lies not only in the efficacy of these therapies but also in their toxicity. Patients treated in the adjuvant setting are less willing to tolerate adverse effects of treatment than those with metastatic disease, particularly because they may already be cured and biomarkers to predict the benefit of adjuvant therapy have not been identified.

Financial toxicity also looms over these questions, Sledge noted. “We all see patients who cease therapy because they can no longer afford to pay for a drug,” he said. “…A few cycles of therapy are more than the average family of 4 makes in a year.”

Importantly, clinical and financial toxicities are issues that may affect any patient with cancer, not just those diagnosed with breast cancer. Our editorial team is seeking to incorporate coverage of these challenges facing cancer care into the articles we report in OncologyLive® and OncLive.com. We hope that drawing attention to these matters through expert insights will contribute to solutions.

As always, thank you for reading.

Mike Hennessy Jr
President and CEO
MJH Life Sciences®

REFERENCES
**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 care, as necessary. Adjust dosing of NINLARO for peripheral neuropathy.

- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or hepatic impairment.

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

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06/22 USO-IXA-0384
**INDICATION AND USAGE**

The NINLARO regimen included NINLARO+lenalidomide+dexamethasone. The Rd regimen included placebo+lenalidomide+dexamethasone.4 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 that were included in the intent-to-treat analysis. *The study duration was 12 months for patients in the NINLARO regimen* and 51.6 months for patients receiving the Rd regimen* (HR=0.94 [95% CI, 0.78-1.13]).

**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.

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

**REFERENCES:**

4. NINLARO. Prescribing Information. Takeda Pharmaceuticals America, Inc.; 04/2022.
1 INDICATIONS AND USAGE
NINLARO (ixazomib) 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.

2 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Thrombocytopenia: 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 thrombocytopenia was reported in 13% 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. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting have been reported with NINLARO, occasionally requiring use of antiemetics and antidiarrheal medications, and supportive care. Diarrhea was reported in 52% of patients in the NINLARO regimen and 43% in the placebo regimen, constipation in 35% and 26%, respectively, nausea in 52% and 23%, respectively, and vomiting in 26% and 13%, respectively. Diarrhea resulted in 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.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 16% in the placebo regimen) and Grade 2 (11% in the NINLARO regimen and 6% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported in 2% in both regimens. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimen, 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. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 27% and 21% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (17% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 6% in the placebo regimen). Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. Peripheral edema resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 27% of patients in the NINLARO regimen and 16% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (15% in the NINLARO regimen and 9% in the placebo regimen) or Grade 2 (9% in the NINLARO regimen and 4% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Serious adverse reactions of rash were reported in <1% of patients in the NINLARO regimen. The most common type of rash reported in both regimens included maculo-papular and macular rash. 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. Stevens-Johnson syndrome, including a fatal case, has been reported with NINLARO. If Stevens-Johnson syndrome occurs, discontinue NINLARO and manage as clinically indicated.

5.6 The Cabić Microangiopathy: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic urmic 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 relisting NINLARO therapy in patients previously experiencing TTP/HUS is not known.

5.7 Hepatotoxicity: Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic 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.

5.8 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animal studies. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. 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.

5.9 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.

6 ADVERSE REACTIONS
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 (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 diarrhea (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>All Grades</td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>52 10</td>
<td>0 43</td>
</tr>
<tr>
<td>Constipation</td>
<td>35 &lt;1</td>
<td>0 28</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 2</td>
<td>0 23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 1</td>
<td>0 13</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathies</td>
<td>32 2</td>
<td>0 24</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>27 &lt;1</td>
<td>0 24</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>27 1</td>
<td>0 23</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>22 2</td>
<td>0 17</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>27 3</td>
<td>0 16</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>27 2</td>
<td>0 21</td>
</tr>
</tbody>
</table>

Note: Adverse reactions included as preferred terms are based on MedDRA version 23.0. The duration at the time of the final analysis. These adverse reactions met the criteria for a ≥5% difference between the NINLARO regimen and the placebo regimen.

*Represents a pooling of preferred terms (Continued on next page)
Table 5: Thrombocytopenia and Neutropenia

<table>
<thead>
<tr>
<th></th>
<th>NINLARO + Lenalidomide and</th>
<th>Placebo + Lenalidomide and</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexamethasone N=3061</td>
<td>Dexamethasone N=3059</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>74</td>
<td>74</td>
</tr>
</tbody>
</table>

**Hepatitis Zoster**

Hepatitis 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%).

**Eye Disorders**

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 38% in patients in the NINLARO regimen. The most common adverse reactions of the eyes were cataract (15%), conjunctivitis (9%), blurred vision (7%), and dry eye (6%).

The following serious adverse reactions have each been reported at a frequency of <1% in patients treated with NINLARO: acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

**7 DRUG INTERACTIONS**

**7.1 Strong CYP3A4 Inducers:** Avoid concomitant administration of NINLARO with strong CYP3A4 inducers (such as rifampin, phenytoin, carbamazepine, and St. John’s Wort).

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy:** Risk Summary: Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no available data on NINLARO use in pregnant women to evaluate drug-associated risk. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. The U.S. general population; the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**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 renal function. Reduce the starting dose of NINLARO in patients with moderate or severe renal impairment.

**Thrombotic Microangiopathy:** Adverse events of thrombotic microangiopathy (e.g., acute renal failure, acute tubular necrosis, thrombocytopenia) have been reported with NINLARO. Patients should be monitored closely for evidence of thrombotic microangiopathy. If thrombotic microangiopathy is suspected, discontinue NINLARO immediately.

**8.7 Renal Impairment:** Reduce the starting dose of NINLARO in patients with moderate or severe renal impairment.

**8.8 Pregnancy:** Only one case of congenital abnormality has been reported in the cases of treatment with NINLARO. There are no data on the presence of ixazomib or its metabolites in human milk. The effects of the drug on milk production, the potential to use effective contraception during treatment with NINLARO and for 90 days after the last dose.

**9.7 Breastfeeding:** The safety and effectiveness of NINLARO in breastfeeding infants has not been established. The potential for harm to the breastfed infant is unknown. Consider the potential benefits and risks of NINLARO before breastfeeding.

**9.8 Fertility:** There are no data concerning the effects of NINLARO on male or female fertility. Advise patients of reproductive potential about the potential effects of NINLARO on their ability to conceive or maintain a pregnancy if they are pregnant or plan to become pregnant.

**10 OVERDOSAGE:** Overdose, including fatal overdose, has been reported in patients taking NINLARO. Manifestations of overdose include adverse reactions reported at the recommended dosage. Serious adverse reactions reported with overdose include severe nausea, vomiting, diarrhea, aspiration pneumonia, multiple organ failure and death. In the event of an overdose, monitor for adverse reactions and provide appropriate supportive care. NINLARO is not dialyzable.

**17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information). Dosing 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 overdose has led to death [see Overdosage (10)].
- 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 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 Toxities:** 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 if they experience unusual swelling of their extremities or weight gain due to swelling [see Warnings and Precautions (5.4)].

**Cutaneous Reactions:** Advise patients to contact their healthcare providers immediately if they experience new or worsening rash [see Warnings and Precautions (5.5)].

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

**Hepatotoxicity:** 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 signs and symptoms of acute febrile neutrophilic dermatosis (Sweet’s syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, herpes zoster, cataracts, dry eyes, blurred vision, conjunctivitis and thrombotic thrombocytopenic purpura [see Adverse Reactions (6.1)].

**Embryo-Fetal Toxicity:** Adverse 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)].

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

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Time Required to Address Scientific Questions Generates an Information Dilemma

by MAURIE MARKMAN, MD

ONE OF THE MORE perplexing issues surrounding scientific questions is the extended time required to provide an answer. Even once a well-considered and vetted conclusion is obtained, an additional interval of time may be required to modify or reverse the answer because of new, relevant data.

A partial explanation for increasingly distressing difficulties with communication between public health officials and the public may be explained by the timelines associated with rigorous scientific investigation, including the conduct and analysis of clinical trials. This was seen especially during the COVID-19 pandemic. Definitive answers to questions relevant to governmental policy to optimize societal health and economic welfare, employer guidance, or individual safety are needed but often what is available in response are no more than reasonable suggestions based on limited and frequently changing data.

The role and benefits of mask mandates or the need for school closures to help ensure public safety in the early days of the pandemic are excellent examples of the dilemma faced by the scientific, medical, and public health communities. In an era of immediate access to information (or in some cases misinformation) provided to society through a variety of social media outlets, the sometimes less than adequate or scientifically supported recommendations/mandates from national or regional scientific and public health officials have not inspired societal confidence.

Further, when questions were raised regarding the safety and effectiveness of the several COVID-19 vaccines, early reassurance had to be based on limited clinical trial data and, admittedly, short follow-up. Critical safety and efficacy features of the products have now been unequivocally documented including observations that specific vaccines appear to possess unique adverse effects. These features would not have been known or available for discussion when the products were initially provided to the public because clinical trials of the agents had not been completed.

A recent report from France has provided data regarding the risk of stroke, pulmonary embolism, or myocardial infarction following review of 46.5 million adults aged 18 to 74 years who received a COVID-19 vaccine between December 27, 2020, and July 20, 2021. Although no association was found between these events with mRNA-based vaccination, a potential risk was observed with the administration of an adenoviral-based vaccine product. Again, this information was available only through examination of this large, population-based database after more than 1 year of follow-up.

Similarly, the question of if the risk of developing myocarditis after COVID-19 vaccination vs COVID-19 infection has required time to document in large patient populations. In a recently published report from England, investigators examined individuals who developed myocarditis following adenoviral-based or mRNA-based vaccination or following a positive SARS-CoV-2 test from December 1, 2020, and December 15, 2021. The findings revealed that, overall, COVID-19 infection was associated with a greater risk of experiencing this potentially serious cardiac event compared with vaccination.

Another large population-based study from England and Wales examined electronic health records from January to December 2020 to understand the risk of the development of arterial or venous thrombotic disease following the diagnosis of a COVID-19 infection. Individuals with confirmed COVID-19

“Definitive answers to questions relevant to governmental policy to optimize societal health and economic welfare, employer guidance, or individual safety are needed but often what is available in response are no more than reasonable suggestions based on limited and frequently changing data.”
infection had a relatively high risk for experiencing a major arterial or venous thrombotic event that persisted for almost 1 year after diagnosis compared with a noninfected control population.

Other studies that followed the effect of COVID-19 infection or vaccination over time have addressed the risk of psychiatric and neurological complications, the potential for the development of chronic fatigue syndrome or myalgic encephalomyelitis in infected children, and the benefits of a booster dose.

In each of the studies patient populations were required to be followed over an extended period to reach clinically meaningful and scientifically (statistically) valid conclusions, including the relative risk of serious adverse effects associated with vaccination. It is also relevant to note that decisions to restrict use of a COVID-19 vaccine product following initial approval have been made based on evolving data. This emphasizes how the nature of rigorous regulatory science holds the potential for unanticipated negative outcomes, which can arise despite proper conduct and interpretation of results of clinical trials that led to drug licensing.

Of course, the cancer arena is not immune to the late effects of clinical research efforts that may substantially alter our understanding of both the science and implications for patient treatment. There is no better example of this phenomenon than the recent decision by the FDA and pharmaceutical manufacturers to withdraw prior approval for the use of several commercially available PARP inhibitors as later-line therapy in recurrent epithelial ovarian cancer.

These decisions were based on data generated from several randomized phase 3 trials that suggested a potential negative effect of the drugs on overall survival compared with a cytotoxic drug treatment study control arm. It is interesting to note that until these outcomes were seen, the major concern among clinicians had been for the possible late development of myelodysplastic syndrome or acute leukemia in heavily pretreated patients with ovarian cancer. However, the effects noted in this analysis do not appear to be related to a secondary malignant hematologic process.

These disquieting results were not anticipated and only observed with extended follow-up of the trial population, which again emphasizes how, over time, conclusions of scientifically valid investigative efforts may substantially change.

REFERENCES
**AFTER HOURS®**

**Passions Enrich Life Outside the Clinic**

Eleonora Teplinsky, MD, head of breast medical oncology at the Icahn School of Medicine at Mount Sinai, embraces her hobbies of running and social media. In this interview with After Hours®, Teplinsky discusses the freedom running gives her to clear her mind and explore new areas of fitness. She also highlights how she developed a social media presence on Instagram, @drteplinsky, where she shares workouts and connects with patients through her posts, which include breast cancer insights. Teplinsky also started a podcast, INTERLUDE, to create a space to talk with patients about their experiences.

› TO WATCH, VISIT bit.ly/3CbqQgy.

**MEDICAL WORLD NEWS DEEP DIVE™**

**A Surgeon’s Insight on Esophageal Cancer**

Treatment of esophageal cancer varies based on the stage of cancer, Paresh C. Shah, MD, a surgical oncologist at NYU Langone Health explains in an episode of Medical World News Deep Dive™. Shah notes that although the goal is to pursue a curative route, it can be challenging for the surgeon and patient. He adds that stage 0 esophageal cancer can be removed endoscopically, surgery occurs for stages 1 to 2 immediately, and chemotherapy plus radiation is an initial option for patients with stage 3 to shrink the tumor, with surgery following.

› TO WATCH, VISIT bit.ly/3EfeOFK.

**INSIDE THE PRACTICE®**

**Trials Propel Oncology Treatment Advances**

Suresh G. Nair, MD, discusses the importance of precision oncology clinical trials at the Lehigh Valley Topper Cancer Institute in this episode of Inside the Practice®. As part of the Memorial Sloan Kettering Cancer Alliance, Topper Cancer Institute is privy to a “wonderful community academic partnership that elevated the level of care.” Nair highlights how Topper Cancer Institute leverages a real-time tumor tracking system, multidisciplinary care teams, and drives research in target genes as they begin the process of developing the facility to start offering chimeric antigen receptor T-cell therapy and autologous stem cell transplants.

› TO WATCH, VISIT bit.ly/3fDmnvD.
Clinical Research Study: KN-4802

Now enrolling adult patients with FGFR2 and/or FGFR3 alterations with solid tumors

Study Synopsis

KN-4802 is a multi-center, open-label, two-part clinical trial sponsored by Kinnate Biopharma Inc. to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of KIN-3248, an irreversible, covalent, small molecule pan-FGFR inhibitor, in adults (18+) with advanced tumors harboring FGFR2 and/or FGFR3 gene alterations and known secondary FGFR resistance mutations.

The dose escalation portion (Part A) of the trial will determine the recommended dose and schedule of KIN-3248 for further evaluation in the expansion portion in participants with solid tumors harboring FGFR2 and/or FGFR3 alterations.

The dose expansion portion (Part B) will evaluate the safety and efficacy of KIN-3248 at the recommended dose and schedule in participants with tumors harboring FGFR2 and/or FGFR3 gene alterations, including intrahepatic cholangiocarcinoma (ICC), urothelial cancer (UC), and other solid tumors.

The U.S. Food and Drug Administration (FDA) cleared the Investigational New Drug application for KIN-3248 in January 2022 and the trial was initiated in the first quarter of 2022. More information can be found at: ClinicalTrials.gov/ct2/show/NCT05242822
Futibatinib Gets Go-Ahead in FGFR2+ Cholangiocarcinoma

The FDA has granted accelerated approval to futibatinib (Lytgobi) for adult patients with previously treated unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene fusions or other rearrangements.

Data from the phase 2 FOENIX*-CCA2 trial (NCT02052778), which evaluated futibatinib in 103 patients with unresectable, locally advanced or metastatic iCCA harboring FGFR2 rearrangements, supported the decision. Futibatinib elicited an overall response rate of 42% (95% CI, 32%-52%) and the median duration of response (DOR) was 9.7 months. Most patients (72%) had a median DOR of at least 6 months and 14% of patients had a DOR that lasted for at least 12 months. The median time to response with the agent was 2.5 months (range, 0.7-7.4).

Futibatinib was given orally at 20 mg once daily and 78% of patients had in-frame FGFR2 gene fusions. Dose reductions were required for 58% of patients because of toxicities with 39% of patients having serious toxicities. The most common adverse reactions were nail toxicity, musculoskeletal pain, constipation, diarrhea, fatigue, dry mouth, alopecia, stomatitis, abdominal pain, and dry skin.

TO READ MORE, VISIT bit.ly/3SJsIV1.

Bevacizumab Biosimilar Receives Indication for 6 Solid Tumors

The FDA has approved bevacizumab-adcd (Vegezela), a bevacizumab (Avastin) biosimilar, for 6 types of cancer: metastatic colorectal cancer; recurrent or metastatic nonsquamous non–small cell lung cancer (NSCLC); recurrent glioblastoma; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer; and epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The approval was supported by totality of evidence, which included findings from a pivotal phase 3 trial (NCT03676192), where bevacizumab-adcd demonstrated similar safety, efficacy, and pharmacokinetic results compared with its reference drug for the frontline treatment of patients with metastatic or recurrent nonsquamous NSCLC. Patients aged 18 years or older with at least 1 measurable lesion by RECIST 1.1 criteria were enrolled, with a primary end point of objective response rate.

With the approval, bevacizumab-adcd becomes manufacturer Celltrion’s third oncology biosimilar approved in the United States, joining rituximab-abbs (Truxima) and trastuzumab-pkrb (Herzuma).

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

Eflapegrastim Gains Approval in Chemotherapy-Induced Neutropenia

The FDA has approved eflapegrastim-xnst (Rolvedon) injection to decrease occurrences of infection manifested by febrile neutropenia in adult patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer drugs.

Data from the phase 3 ADVANCE (NCT02643420) and RECOVER trials (NCT02953340) supported the decision after eflapegrastim demonstrated a similar safety profile compared with pegfilgrastim (Neulasta). The agent also displayed the prespecified hypothesis of noninferiority vs pegfilgrastim in mean duration of severe neutropenia.

The novel, long-acting recombinant human granulocyte colony-stimulating factor was compared with pegfilgrastim in patients with breast cancer receiving docetaxel and cyclophosphamide, which are associated with clinically significant incidences of febrile neutropenia. Patients in the ADVANCE trial treated with eflapegrastim (n = 196) had an incidence rate of 15.8% of severe neutropenia in cycle 1 vs 24.3% in the pegfilgrastim arm (n = 210), resulting in an 8.5% absolute risk reduction and 34.9% relative risk reduction (P = .034). In RECOVER, difference in mean duration of severe neutropenia was −0.073 days (95% CI, −0.292 to −0.129), and incidence of severe neutropenia in cycle 1 was 20.3% in the eflapegrastim arm (n = 118) compared with 23.5% in the pegfilgrastim arm (n = 119).

TO READ MORE, VISIT bit.ly/3M5QNTD.

Selpercatinib Gets Green Light in RET+ NSCLC, Thyroid Cancers

Selpercatinib (Retevmo) was granted an accelerated approval in May 2020 based on data from the phase 1/2 LIBRETTO-001 trial (NCT03157128). This approval was converted to regular approval on September 21, 2022, for patients with locally advanced or metastatic NSCLC harboring a RET gene fusion after confirmatory findings examined durability of response from 172 additional patients and 18 more months of follow-up.

Overall response rates in patients who previously received platinum-based chemotherapy (n = 247) did not receive prior treatment (n = 69), and had RET fusion–positive tumors other than NSCLC and thyroid cancer (n = 41), were 61% (95% CI, 55%-67%), 84% (95% CI, 73%-92%), and 44% (95% CI, 28%-60%), respectively.

The FDA approved the Oncomine Dx Target Test as a companion diagnostic for the selection of patients with RET fusion–positive locally advanced or metastatic non–small cell lung cancer (NSCLC), advanced or metastatic thyroid cancer, and advanced or metastatic medullary thyroid cancer who may be candidates for treatment with selpercatinib.

TO READ MORE, VISIT bit.ly/3C7WpII.
The Giants of Cancer Care® recognition program celebrates individuals who have achieved landmark success within the global field of oncology.

Help us identify oncology specialists whose dedication has helped save, prolong, or improve the lives of patients who have received a diagnosis of cancer.

To nominate, please visit: giantsofcancercare.com/nominate

PROGRAM OVERVIEW

- Nominations are open through January 31, 2023.
- The Giants of Cancer Care® Steering Committee will vet all nominations to determine finalists in each category.
- A selection committee of more than 120 oncologists will vote to determine the 2023 inductees.
- The 2023 Giants of Cancer Care® class will be announced in Spring 2023.
THE TREATMENT OF PATIENTS with breast cancer is making noteworthy strides in several clinical settings, with recent trial results showing overall survival (OS) improvements for advanced and metastatic disease. Findings presented during the European Society for Medical Oncology Congress 2022 (ESMO 2022) underscored these gains for several novel therapies with different mechanisms of action.

Altogether, the research results represent incremental but significant advancements for patients, according to George W. Sledge Jr, MD, a 2018 Giants of Cancer Care® award winner in the breast cancer category. Sledge, a long-time professor of medicine at Stanford University in California and former chief of its Division of Oncology, joined Caris Life Sciences in mid-October 2022 as executive vice president and chief medical officer.

“Whenever you have an improvement in overall survival, that’s certainly something worth offering to patients. Even allowing for toxicities, most patients are going to accept the therapy because most of us want to live longer,” he said in an interview with OncologyLive®.

The most striking results have been seen with ADCs, whose efficacy is expanding into new patient populations.

ADCs LEAD THE WAY
The first milestone was reached with fam-trastuzumab deruxtecan-nxki (Enhertu), a HER2-targeting ADC that the FDA approved in August 2022 for patients with unresectable or metastatic HER2-low breast cancer after prior therapy. The decision was based on findings from the DESTINY-Breast04 trial (NCT03734029), which showed that trastuzumab deruxtecan significantly improved median progression-free survival (PFS; HR, 0.50; 95% CI, 0.40-0.63; P < .0001) and median OS (HR, 0.64; 95% CI, 0.49-0.84; P = .001) over physician’s choice of chemotherapy.1,2

Those results, presented amid much fanfare at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting in June, paved the way for expanding the indications for trastuzumab deruxtecan beyond its initial approval for metastatic HER2-positive disease and carved out a new definition for breast cancers with the potential to respond to HER2-directed therapy. HER2-low expression is defined as immunohistochemistry (IHC) 1+ or IHC 2+/in situ hybridization negative.3 Trastuzumab deruxtecan therapy also results in an improvement in quality-of-life (QOL) outcomes compared with chemotherapy, according to an analysis of patient-reported outcomes (PROs) from DESTINY-Breast04 presented at ESMO 2022 (TABLE 1).4

Also at ESMO 2022, investigators reported that sacituzumab govitecan-hziy (Trodelvy), an ADC that targets TROP-2, demonstrated an OS advantage for patients with previously treated hormone receptor-positive, HER2-negative metastatic breast cancer in the TROPICS-02 trial (NCT03901339). In the second interim analysis, sacituzumab govitecan demonstrated a statistically significant 3.2-month improvement in median OS over treatment of physician’s choice (HR, 0.79; 95% CI, 0.65-0.96; P = .02) (TABLE 2).5

Sacluzumab govitecan initially was approved in April 2020 for patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC). Gilead Sciences, Inc, the company developing the drug, has submitted a supplemental biologics license application for a new indication for the agent based on the TROPICS-02 results.6

These data indicate the growing influence of ADCs in breast cancer, Sledge said. The first ADC for the treatment of patients with breast cancer was ado-trastuzumab emtansine (T-DM1; Kadcyla), a HER2-targeting agent that the FDA initially approved in 2013 in the metastatic setting, which was later expanded to adjuvant therapy for HER2-positive, early-stage disease.

OS Advances Gather Steam in Breast Cancer
ESMO 2022 Research Solidifies Therapies

by ANITA T. SHAFFER
In addition to the subsequent approvals of trastuzumab deruxtecan and sacituzumab govitecan, many other ADCs are in clinical development. “We’re living in the era of antibody-drug conjugates, where you pick out the cell-surface target, and you attach an antibody to some poison via a linker, then that linker is broken down to the cancer cell, releasing the poison,” Sledge said. “You get a lot of cancer cell kill because you’re able to maximize the amount of payload that’s getting to the cancer.”

Hope S. Rugo, MD, FASCO, who presented the TROPICS-02 data at ESMO 2022, also stressed the impact of ADCs in the breast cancer treatment paradigm in an interview with OneLive News Network. “Antibody-drug conjugates have already completely changed the way we’re thinking about delivering toxins and essentially chemotherapy to patients with advanced breast cancer and are rapidly being tested, now the second-generation antibody-drug conjugates, in a variety of settings, in the early-stage settings as well,” said Rugo. “They’ve performed better than we really could have imagined.”

Rugo, a 2020 Giants of Cancer Care award winner in the education category, is a professor in the Department of Medicine and director of breast oncology and clinical trials education at the University of California San Francisco Helen Diller Family Comprehensive Cancer Center.

As oncologists become more experienced with using ADCs in clinical practice, they also are learning about how best to handle adverse effects. “Optimizing management of toxicities is a critical aspect and very important for practitioners,” Rugo said.

PROs are an important piece of the equation, Rugo said, noting that findings were favorable for trastuzumab deruxtecan and sacituzumab govitecan, according to analyses of DESTINY-Breast04 and TROPICS-02 data. “Often survival trumps pretty much everything if it’s a big enough difference, but you’re always going to balance even those survival gains against the toxicities,” she said.

Sledge said the toxicity profiles of approved and emerging ADCs would be an important factor in whether they eventually will move from the metastatic to the adjuvant setting, where they would have curative potential. “There are real toxicities that are greater toxicities than we see with a naked antibody alone [that targets HER2],” Sledge said. “The real question is, how many of these drugs are exportable to the adjuvant setting…[where they are] administered to a basically healthy population of women?”

<table>
<thead>
<tr>
<th>CDK4/6 FINDINGS VARY</th>
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</table>
| For CDK4/6 inhibitors, the latest data present a more nuanced picture. Two agents in this class, ribociclib (Kisqali) and abemaciclib (Verzenio), have demonstrated OS improvements in different patient populations. Palbociclib (Ibrance), the first drug in this class to gain FDA approval in 2015, has not registered OS gains in several late-stage clinical trials. 9,10 At ESMO 2022, investigators bolstered findings for ribociclib. The combination of ribociclib plus endocrine therapy (ET) improved PFS and OS compared with ET alone in patients with hormone receptor-positive, HER2-negative advanced breast cancer with visceral metastases, according to a pooled analysis of data from the phase 3 MONALEESA-2 (NCT01958021), MONALEESA-3 (NCT02422615), and MONALEESA-7 (NCT02778120) trials. 11 Previously reported findings from the trials have shown statistically significant PFS and OS benefits of adding ribociclib to ET for the overall population. The new analysis focused on the impact of this strategy in clinical trial participants with visceral metastases, which indicate more aggressive disease with a worse prognosis. In this population, the use of ribociclib resulted in improvements in median PFS and OS compared with ET, with a worse prognosis. In this population, the use of ribociclib resulted in improvements in median PFS (HR, 0.66; 95% CI, 0.53-0.70) and median OS (HR, 0.81; 95% CI, 0.69-0.94). 11 The analysis confirms the benefit of ribociclib in the first- and second-line settings, Denise A. Yardley, MD, and colleagues said. Ribociclib is approved in combination with an aromatase inhibitor (AI) as initial ET and with fulvestrant (Faslodex) as initial and TROPiCS-02 data. “Often survival trumps anything that is greater toxicities than we see with a nonsteroidal AI (NSAI) as first-line therapy for patients with hormone receptor-positive, HER2-negative advanced breast cancer, according to results from the phase 3 MONARCH 3 study (NCT02246621) presented at ESMO 2022.

Abemaciclib is FDA approved for this population with advanced or metastatic disease in combination with an AI as initial ET and in the second-line setting as monotherapy and in combination with fulvestrant. Additionally, abemaciclib is indicated as adjuvant therapy for patients with hormone receptor-positive, HER2-negative node-positive early breast cancer at high risk of recurrence and a Ki-67 score of 20% or higher based on results from the phase 3 monarchE trial (NCT03155997). 12,13 In MONARCH 3, investigators evaluated the combination of abemaciclib or placebo plus either anastrozole or letrozole, both NSAI, with investigator-assessed PFS as the primary end point. A “robust” PFS benefit led the FDA and regulatory bodies in other countries to approve abemaciclib plus an AI, Matthew P. Goetz, MD, and colleagues said in presenting OS data at ESMO 2022 (TABLE 3). 14 After a median follow-up of 5.8 years, findings from a preplanned second interim analysis showed a 12.6-month improvement in median OS favoring the abemaciclib arm (67.1 vs 54.5 months, respectively; P = .0301). The outcome did not reach the threshold for statistical significance, but investigators noted that abemaciclib therapy improved
OS across key subgroups, including for visceral disease. A final OS analysis is expected after a planned number of events is reached in 2023. “These data are encouraging and support what we saw with monarchE in the very important adjuvant setting where we’re seeing improvements in invasive disease-free survival,” Joyce A. O’Shaughnessy, MD, said in an interview with OncLive® News Network.16 O’Shaughnessy, a 2016 Giants of Cancer Care® award winner in the community outreach/education category, is cochair of breast cancer research, chair of breast cancer prevention research, and the Celebrating Women Chair in Breast Cancer at Baylor-Sammons Cancer Center, Texas Oncology, in Dallas, Texas.

In June 2022, investigators reported further data from monarchE involving a subset of participants (2056 of 5637 patients) who received neoadjuvant chemotherapy followed by ET with or without abemaciclib in JAMA Oncology. Among these patients, treatment with abemaciclib resulted in a 39% reduction in the risk of developing invasive disease compared with ET alone (HR, 0.61; 95% CI, 0.47-0.80; P < .001) and a 6.7% improvement in 2-year distant relapse-free survival (89.5% vs 82.8%, respectively).17 The OS data reported at ESMO 2022 build on the body of knowledge that has been accumulating about an important class of agents, Sledge said. Ribociclib and abemaciclib “have significantly improved overall survival in both the frontline and the second-line setting in an area where, literally for decades, we basically saw no improvement in terms of overall survival. These are real advances.”

In the adjuvant setting, Sledge said, future findings would show whether the disease-free survival benefit shown with abemaciclib translates into an OS improvement. “There’s still a lot to learn, but certainly there’s enough data from the metastatic setting and from the early data in the adjuvant setting to suggest that these [agents] may have a long-lasting impact in terms of improving ultimate outcomes for patients with the disease.”

Other important questions involving CDK4/6 inhibitors involve strategies for patients whose tumors are resistant to initial therapy with these agents or progress after treatment. “The CDK4/6 inhibitors have been transformative in the lives of patients with hormone receptor–positive, HER2-negative breast cancer in the first-line setting but there still are patients who don’t get that median 2-year progression-free-survival,” O’Shaughnessy said.

She noted that results of a mutational signature analysis presented at ESMO 2022 helps to advance the understanding of resistance to CDK4/6 inhibition plus ET. Investigators used the MSK-IMPACT targeted gene panel to sequence approximately 4500 breast cancer samples. They found that estrogen receptor–positive, HER2-negative tumors with higher signatures for the APOBEC family of cytidine deaminases and for homologous recombination deficiency are associated with shorter PFS on first-line ET plus a CDK4/6 inhibitor.18

For patients whose tumors progress after treatment with a CDK4/6 inhibitor, findings from the phase 2 MAINTAIN trial (NCT02632045) that explored switching therapy might prove helpful, Sledge noted. The study randomly assigned 119 patients with hormone receptor–positive, HER2-negative metastatic breast cancer who developed resistance to ET plus a CDK4/6 inhibitor to subsequent therapy with a different ET with or without ribociclib. Fulvestrant was used as ET in patients who had progressed on a prior AI whereas exemestane was permitted for those who had progressed on prior fulvestrant. Approximately 87% of the participants had received palbociclib as prior therapy.19

After a median follow-up of 18.2 months, the median PFS was 5.29 months (95% CI, 3.02-8.12) with ribociclib plus ET compared with 2.76 months (95% CI, 2.66-3.25) with placebo plus ET (HR, 0.57; 95% CI, 0.39-0.95; P = .006). The PFS rates with ribociclib were 41.2% at 6 months and 24.6% at 12 months vs 23.9% and 7.4%, respectively, with placebo.20

Sledge said the study “points to an important question that we all have to deal with: Once we’ve had a major success, but we don’t cure the patient, what do we do next? That’s another broad challenge for the field as a whole.”

ICIs MAKE MARK IN EARLY-STAGE TNBC
Recent clinical trial findings also point to advancements in the use of immunotherapy. In July 2022, investigators reported findings from the phase 3 KEYNOTE-355 study (NCT02819518) evaluating pembrolizumab (Keytruda), a PD-1 inhibitor, in patients with triple-negative breast cancer (TNBC), in the New England Journal of Medicine (NEJM).21

The addition of pembrolizumab to chemotherapy demonstrated significantly longer OS compared with chemotherapy alone in patients with previously untreated locally recurrent inoperable or metastatic TNBC whose tumors express PD-L1 with a combined positive score (CPS) of 10 or more (CPS-10). (The CPS reflects the number of PD-L1-staining tumor cells, lymphocytes, and macrophages divided by the total number of tumor cells multiplied by 100.)

In November 2020, the FDA granted an accelerated approval for pembrolizumab for this patient population based on OS findings from KEYNOTE-355.21 The study involved 847 patients who were randomly assigned 2:1 to receive chemotherapy with or without pembrolizumab, including 323 participants (38.1%) in the CPS-10 subgroup.20

After a median follow-up of 44.1 months, the median OS among patients in the CPS-10 cohort was 23.0 months (95% CI, 19.0-26.3) for those who treated with pembrolizumab and 16.1 months (95% CI, 12.6-18.8) for those who received placebo, according to results of the final analysis. Pembrolizumab reduced the risk of death by 27% (HR, 0.73; 95% CI, 0.55-0.95) with a 2-sided P value of .0185, which crossed the prespecified threshold for statistical significance.20

Pembrolizumab also is approved in combination with chemotherapy as neoadjuvant treatment for patients with high-risk, early-stage TNBC, followed by surgery and pembrolizumab monotherapy. The FDA granted the approval based on findings from the phase 3 KEYNOTE-522 study (NCT03036488), in which 1174 patients were randomly assigned 2:1 to receive neoadjuvant chemotherapy with or without pembrolizumab. The trial recruited patients with tumors greater than 1 cm and a maximum of 2 cm or smaller in diameter with nodal involvement or tumor size greater than 2 cm in diameter regardless of nodal involvement.22

At the time, the pathological complete response (pCR) rate was 63% (95% CI, 59.5%-66.4%) with the pembrolizumab-containing regimen compared with 56% (95% CI, 50.6%-60.6%) with chemotherapy alone. In February 2022, investigators reported event-free survival (EFS) data from KEYNOTE-522 in

### TABLE 3. Interim OS Data in MONARCH 3 Trial

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Abemaciclib + NSAI</th>
<th>Placebo + NSAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>n = 328</td>
<td>n = 166</td>
</tr>
<tr>
<td>Median OS</td>
<td>67.1 months</td>
<td>54.5 months</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.754 (0.584-0.974); P = .0301*</td>
<td></td>
</tr>
<tr>
<td>Visceral disease subgroup</td>
<td>n = 173</td>
<td>n = 90</td>
</tr>
<tr>
<td>Median OS</td>
<td>65.1 months</td>
<td>48.8 months</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.708 (0.508-0.985); P = .0392*</td>
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</table>
At 36 months, the EFS rate was 84.5% (95% CI, 81.7%-86.9%) in the pembrolizumab plus chemotherapy arm vs 76.8% (95% CI, 72.2%-80.7%) for those who received chemotherapy alone (HR, 0.63; 95% CI, 0.48-0.82; P < .001). The efficacy of pembrolizumab in the neoadjuvant setting was supported by results of a network meta-analysis presented at ESMO 2022. Investigators compared pCR and EFS rates reported in clinical trials of pembrolizumab plus chemotherapy vs chemotherapy alone as neoadjuvant therapy followed by adjuvant treatment. For pCR, the analysis showed that the pembrolizumab-containing regimen had a statistically favorable pCR rate compared with 3 of 7 chemotherapy-alone regimens (ORs for pembrolizumab ranging from 1.36, 1.89, and 3.12). For EFS rates, the use of pembrolizumab was statistically favorable to 3 of 5 regimens (HRs favoring pembrolizumab of 0.36, 0.57, and 0.63). Investigators concluded that neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab “is an effective treatment relative to most competing interventions” in the neoadjuvant setting.

Although defining a role for ICI therapy in metastatic TNBC has been problematic, Sledge said, findings for earlier stages of disease have been encouraging so far. “There is clear and compelling evidence of benefit and, as a result, excitement about these agents for their potential to improve the outcomes for patients with triple-negative breast cancer.”

Looking forward, Sledge said unsettled questions include whether there is an OS benefit with neoadjuvant ICI therapy in patients with TNBC and which biomarkers might predict responses to therapy. He also noted that so far investigators have focused on testing ICIs in TNBC but that future research might show a role in other breast cancer subtypes.

“The reason we do the trials is the same reason that you play basketball games,” Sledge said. “Even when you have 2 teams on the [court], and you think 1 is better than another, at the end of the game the score may tell you that you were wrong. We need to actually play the contest and see what the final score is.”

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

ON LOCATION: Advances in Breast Cancer at ESMO 2022

Host Caroline Seymour sits down with Hope S. Rugo, MD, FASCO; and Joyce A. O’Shaughnessy, MD, to discuss the top highlights from the breast cancer news presented during the European Society for Medical Oncology Annual Congress 2022.

Data from the phase 3 TROPiCS-02 trial (NCT03901339) in hormone-receptor-positive, HER2-negative metastatic breast cancer, showed that treatment with sacituzumab govitecan-hziy (Trodelvy) improved median overall survival at 14.4 months vs 11.2 months with treatment of physician’s choice. Moreover, the objective response rate, global health status and quality of life, and fatigue were improved vs treatment of physician’s choice.

In the phase 3 MONARCH 3 trial (NCT02246621), a numerical improvement was reported with abemaciclib (Verzenio) plus a nonsteroidal aromatase inhibitor placebo vs a nonsteroidal aromatase inhibitor alone in patients with hormone receptor-positive, HER2-negative advanced breast cancer.

In the AMEERA-3 trial (NCT04059484), amcenestrant, an oral selective estrogen receptor degrader, failed to demonstrate a statistically significant improvement in progression-free survival vs treatment of physician’s choice in patients with estrogen receptor-positive, HER2-negative advanced breast cancer who progressed after endocrine-based therapy.

WATCH THE FULL EPISODES HERE: bit.ly/3g81Z5Z and bit.ly/3FQQLTO
duration of therapy in patients who developed secondary MDS/cancer including some fatal cases, was reported in 15 patients (0.8%) out of Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), ZEJULA is indicated for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.

Important Safety Information

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

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

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

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

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

**More than 2X PFS vs placebo in HRd PATIENTS**

**MEDIAN PFS IN THE HRd POPULATION**

(n=373), 51% of overall study population

21.9 months ZEJULA

VS

10.4 months placebo

Reduction in Risk
of progression or death
with ZEJULA vs placebo
HR, 0.43 (95% CI, 0.31-0.59) P<0.0001

57 %

**MEDIAN PFS IN THE OVERALL POPULATION**

(N=733)

13.8 months ZEJULA

VS

8.2 months placebo

Reduction in Risk
of progression or death
with ZEJULA vs placebo
HR, 0.62 (95% CI, 0.50-0.76) P<0.0001

38 %

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

**Important Safety Information (continued)**

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

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

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

Please see Brief Summary on the following pages.

References:
4. Rubraca (rucaparib), Prescribing Information. Clovis Oncology, Inc; 2022.

CI = confidence interval; CR = complete response; HR = hazard ratio; PR = partial response.

Visit ZEJULAHCP.COM to explore the PRIMA data

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NRFJRNA220002 September 2022
Produced in USA.
Monitor all patients treated with ZEJULA for signs and symptoms of PRES. If PRES is suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of restarting ZEJULA in patients previously treated with PRES is not known.

5.5 Embryo-Fetal Toxicity
Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman (see Clinical Pharmacology (12.1) of full Prescribing Information). ZEJULA has the potential to cause teratogenicity and/or embryofetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) (see Warnings and Precautions (5.2), Nonclinical Toxicology (13.1) of full Prescribing Information). Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.
Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months following the last dose of ZEJULA (see Use in Specific Populations (8.1, 8.3)).

5.6 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)
ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including anaphylaxis) in patients who have shown a reaction to FD&C Yellow No. 5 (tartrazine) or other components of ZEJULA capsules.

6. ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- MDS/AML (see Warnings and Precautions (5.1))
- Bone marrow suppression (see Warnings and Precautions (5.2))
- Hypertension and cardiovascular effects (see Warnings and Precautions (5.3))
- Posterior reversible encephalopathy syndrome (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.
In a pooled safety population of patients (n = 1,314) with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with ZEJULA monotherapy including PRIMA (n = 484), NOVA (n = 367), and another clinical trial (n = 463), the most common adverse reactions >10% were nausea (62%), thrombocytopenia (59%), anemia (56%), fatigue (55%), constipation (39%), musculoskeletal pain (36%), abdominal pain (35%), vomiting (33%), neutropenia (31%), decreased appetite (24%), leukopenia (24%), insomnia (23%), headache (23%), diaphoresis (22%), rash (21%), diarrhea (18%), hypertension (17%), cough (16%), dizziness (14%), acute kidney injury (13%), urinary tract infection (12%), and hypomagnesemia (11%).

First-Line Maintenance Treatment of Advanced Ovarian Cancer
The safety of ZEJULA for the treatment of patients with advanced ovarian cancer following first-line treatment with platinum-based chemotherapy was studied in the PRIMA trial, a placebo-controlled, double-blind study in which 728 patients received niraparib or placebo. Among patients who received ZEJULA, the median duration of treatment was 11.1 months (range: 0.03 to 29 months).

All Patients Receiving ZEJULA in PRIMA: Serious adverse reactions occurred in 32% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were thrombocytopenia (16%), anemia (6%), and small intestinal obstruction (2.9%). Fatal adverse reactions occurred in 0.4% of patients, including intestinal perforation and pleural effusion (1 patient each).
Permanent discontinuation due to adverse reactions occurred in 12% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >1% of patients who received ZEJULA included thrombocytopenia (3.7%), anemia (1.9%), and nausea and neutropenia (1.2%) each.
Adverse reactions led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%).

Table 1: Adverse Reactions Reported in >10% of All Patients Receiving ZEJULA in PRIMA

<table>
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<tr>
<th>Adverse Reaction</th>
<th>Grades 1–4</th>
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<th>Placebo (n=244)</th>
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<tbody>
<tr>
<td>ZEJULA (n=884) %</td>
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<td>Placebo (n=244)</td>
<td>Placebo (n=244)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>66</td>
<td>5</td>
<td>39</td>
</tr>
</tbody>
</table>

Blood and lymphatic system disorders

Patients Receiving ZEJULA with Dose Based on Baseline Weight or Platelet Count in PRIMA: Among patients who received ZEJULA with the dose based on weight and platelet count, the median duration of treatment was 11 months (range: 1 day to 16 months).
6 ADVERSE REACTIONS (cont’d)

Serious adverse reactions occurred in 27% of patients receiving ZEJULA. Serious adverse reactions in >2% of patients were anemia (8%) and thrombocytopenia (7%). No fatal adverse reactions occurred.

Permanent discontinuation due to adverse reactions occurred in 14% of patients who received ZEJULA. Adverse reactions resulting in permanent discontinuation in >2% of patients who received ZEJULA included thrombocytopenia and anemia (5% each) and nausea (2.4%).

Adverse reactions led to dose reduction or interruption in 72% of patients, most frequently from thrombocytopenia (40%), anemia (23%), and neutropenia (13%). Table 3 and Table 4 summarize adverse reactions and abnormal laboratory findings in the groups of patients who received ZEJULA.

### 6.2 Postmarketing Experience

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

- **Blood and lymphatic system disorders**
- **Neurological disorders**
- **Gastrointestinal disorders**
- **Respiratory, thoracic, and mediastinal disorders**
- **Renal and urinary disorders**
- **Skin and subcutaneous tissue disorders**
- **Vascular disorders**

### 8.2 Lactation

**Risk Summary**

No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed child. This child should not be breastfed during treatment with ZEJULA and for 1 month after receiving the final dose.

### 8.3 Females and Males of Reproductive Potential

**ZEJULA** can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1) of full Prescribing Information]. There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see Warnings and Precautions (5.2), Nonclinical Toxicology (13.1) of full Prescribing Information]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. 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.

**Contraception**

Females: Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months following the last dose.

**Infertility**

Males: Based on animal studies, ZEJULA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) of full Prescribing Information].

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

In PRIMA, 39% of patients were aged 65 years or older and 10% were aged 75 years or older. No overall differences in safety and effectiveness of ZEJULA were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

**Renal Impairment**

No dose adjustment is necessary for patients with mild (Clcr: 60 to 89 mL/min) to moderate (Clcr: 30 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end-stage renal disease undergoing hemodialysis is unknown.

### 8.7 Hepatic Impairment

For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily [see Dosage and Administration (2.3) of full Prescribing Information]. Niraparib exposure increased in patients with moderate hepatic impairment (total bilirubin ≤1.5 x upper limit of normal (ULN) to 3.0 x ULN and any aspartate transaminase (AST) level). Monitor patients for hematoxicity and reduce the dose further, if needed [see Dosage and Administration (2.3) of full Prescribing Information].

For patients with mild hepatic impairment (total bilirubin <1.5 x ULN and any AST level or bilirubin ≤ULN and AST>ULN), no dose adjustment is needed.

The recommended dose of ZEJULA has not been established for patients with severe hepatic impairment (total bilirubin ≥3.0 x ULN and any AST level) [see Clinical Pharmacology (12.2) of full Prescribing Information].

### 17 PATIENT COUNSELING INFORMATION

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

### 8.6 Lactation

Bedtime administration may be a potential method for managing adverse effects, such as nausea, vomiting, decreased appetite, headache, and insomnia.

### 13.1 Nonclinical Toxicology

The safety and effectiveness of ZEJULA have not been established in pregnant women or in nursing mothers. Because of the potential for serious adverse effects in nursing infants, advise women not to breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

### 13.3 Antiproliferative Activity

Serious adverse reactions

### 13.4 Human and Animal Studies

Bone Marrow Suppression

Advises patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood counts or a need for blood transfusions. This may be a sign of hematological toxicity or MDS or AML, which has been reported in patients treated with ZEJULA [see Warnings and Precautions (5.1)].

### 13.5 Lactation

Advises patients to take their oral suspension with food as a potential method for managing nausea.

### 13.7 Embryo-Fetal Toxicity

Advises patients to contact their healthcare provider if they develop any of these signs or symptoms [see Warnings and Precautions (5.4)].

### 13.8 Dosing Instructions

Advice patients on how to take ZEJULA [see Dosage and Administration (2.1) of full Prescribing Information]. ZEJULA should be taken once daily. Instruct patients that if they miss a dose of ZEJULA not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZEJULA may be taken with or without food.

### 13.9 Breastfeeding

Bedtime administration may be a potential method for managing nausea.

### 13.10 Pregnancy

Advice to women who are pregnant or who may become pregnant that they should not breastfeed.

### 13.118.1 Pregnancy

Also includes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, and blood creatine increased.

**Includes neutropenia, neutropenic infection, neutropenic sepsis, and neutropenic sepsis.**

**Includes leukopenia, lymphocyte count decreased, lymphopenia, and white blood cell count decreased.**

**Includes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, and blood creatine increased.**

### 13.118.2 Lactation

Advice to women who are pregnant or who may become pregnant that they should not breastfeed.

### 13.12 Contraception

Advice to women who are pregnant or who may become pregnant that they should not breastfeed.

### 13.13 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

Advice to patients that ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons or in patients who also have aspirin hypersensitivity [see Warnings and Precautions (5.6)].

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GSK

GlaxoSmithKline

Durham, NC 27701

ZMC-MRS

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BPNNPAT2019 September 2022

Produced in USA.
SODIUM THIOSULFATE (PEDMARK) demonstrated efficacy as an ototoxicity-mediating agent in pediatric patients with solid tumors treated with cisplatin. This agent was also approved by the FDA in September 2022 based on data from the randomized, open-label, multicenter phase 3 SIOPEL6 (NCT00652132) and phase 3 COG-ACCL0431 (NCT00716976) trials.

SIOPEL6 evaluated cisplatin-based chemotherapy with or without sodium thioulsulfate in patients between the ages of 1 month and 18 years with standard-risk hepatoblastoma. Incidence of hearing loss was lower in patients who received the combination compared with those who received cisplatin alone (39% vs 68%, respectively).

The combination in this trial, at 44% vs 58%, respectively, in those who received cisplatin, the risk of significant ototoxicity is dramatic. Some recent reviews and retrospective research have shown that rates can be as high as 65% in those patients. The ability to obtain a drug that has good evidence and shows a reduction in the primary toxicity of sodium thiosulfate is related to the bolus of the actual sodium. 

The SIOPEL6 study had 2 cohorts; this was more of a basket study. Any patients who were receiving a platinum agent, typically cisplatin, were eligible. Patients had hepatoblastoma, medulloblastoma, neuroblastoma, and osteosarcoma, to the same treatments. Incidence of hearing loss was also lower in patients who received the combination in this trial, at 44% vs 58%, respectively, in those who received cisplatin alone.

There are patients in whom the use of sodium thiosulfate as a standard of care should be considered, based on those most recent retrospective studies, including patients with localized tumors, particularly those who are young—under 6 years of age—and those who seem to be at the highest risk," Nilay Shah, MD, said in an interview with OncologyLive®.

In the interview, Shah, a physician scientist in the Center for Childhood Cancer and Blood Diseases at Nationwide Children’s Hospital and an assistant professor in the Department of Pediatrics at The Ohio State University College of Medicine in Columbus, discussed the importance of this approval for pediatric patients with solid tumors, the favorable toxicity profile of the agent, and how these trial findings may inform future care in this population.

Please discuss the significance of the approval. Many pediatric patients [with solid tumors] are receiving cisplatin as part of their curative therapy and, in some cases, in later lines of therapy as well. With the advances that we’ve made across many solid tumors, the improvements in survival have been quite significant and dramatic, [in the range of] 30 to 40 years, but [these often come] at the cost of treatment-related morbidity.

For many of our patients—especially those with tumors such as hepatoblastoma, medulloblastoma, and neuroblastoma—who are particularly young and receiving cisplatin, the risk of significant ototoxicity is dramatic. Some recent reviews and retrospective research have shown that rates can be as high as 65% in those patients. The ability to obtain a drug that has good evidence and shows a reduction in the risk of ototoxicity can have a dramatic effect on the quality of life for these patients. Just because we’ve worked to cure them of their disease doesn’t mean they should have to suffer the stigma of it for the rest of their lives.

What is the mechanism of action of sodium thiosulfate? Sodium thiosulfate works by acting as a scavenger for free radicals. Platinum agents, particularly cisplatin, work as an adduct to DNA and a cross-link to DNA, but this results in a significant release of inflammatory molecules, including reactive oxidative species. In the inner ear, that leads to direct damage to the cilia, and in humans, that damage is irreversible.

Sodium thiosulfate, when it’s infused, can enter that space in the inner ear and scavenge those free radicals, mitigating the degree of direct toxicity to the cilia and preventing premature damage. The timing of the sodium thiosulfate [administration] is important. When administered too close to either a preceding or subsequent dose of cisplatin, there’s potential for reduction of efficacy. There is a clear window of administration, which allows for otoprotection without reducing the efficacy of the chemotherapy.

What key efficacy data were found with the SIOPEL6 and COG-ACCL0431 trials? SIOPEL6 looked more at tumors [such as] hepatoblastoma. [In that disease], tumors tend to be restricted in their metastatic potential, although they can have widespread involvement of the liver and occasionally some distant metastases. It was a cleaner study in that sense.

There was evidence that administration of sodium thiosulfate 6 hours after the completion of cisplatin infusion, and at least 10 hours before the subsequent dose, [caused] significant improvements in the rates of cisplatin-associated ototoxicity without any direct effect on disease-free survival [DFS] or overall survival [OS]. Those data were quite impactful, and the analyses were robust.

The COG-ACCL0431 study had 2 cohorts; this was more of a basket study. Any patients who were receiving a platinum agent, typically cisplatin, were eligible. Patients had hepatoblastoma, medulloblastoma, neuroblastoma, and osteosarcoma, predominantly, and some germ cell tumors were also included in those cohorts. [This study did not have] a preplanned analysis based on the metastatic burden of the disease. The analyses were done post-hoc.

For patients with localized disease, there was excellent evidence showing reduction in ototoxicity over time with the use of sodium thiosulfate without a significant effect on DFS or OS.

What adverse effects should clinicians be aware of with this agent? The primary toxicity of sodium thiosulfate is related to the bolus of the actual sodium that’s part of the compounding. Usually, at the time of the infusion, [patients have] a sudden degree of nausea and/or vomiting. The patients can literally feel that sensation. [This is] interesting, in which patients will feel that sensation and have significant nausea and vomiting is somewhat hard to predict. [This toxicity does seem to arise in more] older patients, those school-aged and adolescent patients, compared with infants, toddlers, and preschool or early school-aged children. Regardless, this is certainly a toxicity that can be directly managed. We recommend the administration of an antiemetic as a premedication. There are some questions regarding in which patients with neuroblastoma this will be most appropriate.

[However, in general, sodium thiosulfate is] worth discussing with patients who are potentially going to be receiving cisplatin, as well as other ototoxic agents, such as high-dose carboplatin. The indication for sodium thiosulfate is with the use of cisplatin. It should not necessarily be used in patients who are receiving high-dose carboplatin, but [it should be considered in patients] who will later be receiving high-dose carboplatin, because there’s an increased risk [of hearing loss with carboplatin, and the] use of sodium thiosulfate with cisplatin [earlier on] may reduce the overall risk of hearing loss.

Dr Shah would like to disclose that he has served on advisory panels for, and received a consulting remuneration from, Fennec Pharmaceuticals Inc.

**Drug Spotlight**

**Baseline Patient Characteristics**

**Vol. 23 | No. 21 | NOVEMBER 2022**

**BASELINE PATIENT CHARACTERISTICS**

**Median age (years, range)**

<table>
<thead>
<tr>
<th></th>
<th>SIOPEL 6</th>
<th>COG ACCL0431</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1.2 months to 8.2 years)</td>
<td>(1-18)</td>
</tr>
<tr>
<td>N =</td>
<td>114</td>
<td>125</td>
</tr>
</tbody>
</table>

**Tumor histology**

- **Hepatoblastoma**
- **Medulloblastoma**
- **Osteosarcoma**
- **Germ cell tumor**
- **Neuroblastoma**
- **Anaplastic astrocytoma**
- **Atypical teratoid/rhabdoid tumor**
- **Choroid plexus carcinoma**

**FDA Approval—September 20, 2022**

The FDA grants approval to sodium thiosulfate (Pedmark) to reduce the risk of ototoxicity because of cisplatin chemotherapy in pediatric patients aged 1 month and older with localized, nonmetastatic solid tumors.

**Mechanism of action**

- Sodium thiosulfate is an inorganic salt compound that interacts directly with cisplatin to produce an inactive platinum species, and it enters cells through the sodium sulfate cotransporter 2 to cause intracellular effects.

**How supplied**

- 12.5 g/100 mL in a single-dose vial

**Dose**

- Body weight of less than 5 kg: 10g/m²
- Body weight of 5-10 kg: 15g/m²
- Body weight of greater than 10 kg: 20 g/m²

**Dosing considerations**

- Administer as an intravenous infusion over 15 minutes starting 6 hours after completion of cisplatin infusion.

**Limitations of use**

- Sodium and efficacy of sodium thiosulfate have not been established when administered following cisplatin infusions longer than 6 hours.
- Sodium thiosulfate may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.

**Company:**

Fennec Pharmaceuticals Inc

**Pivotal Clinical Trials**

- **SIOPEL 6 (NCT00652132)** was multicenter, randomized, controlled, open-label study of pediatric patients who were receiving cisplatin-based chemotherapy for standard-risk hepatoblastoma.
- **COG-ACCL0431 (NCT00716976)** was a multicenter, randomized, controlled, open-label study of pediatric patients who were receiving a chemotherapy regimen that included a cumulative cisplatin dose of 200 mg/m² or higher, with individual cisplatin doses infused over 6 hours or less.

**Efficacy in SIOPEL 6**

<table>
<thead>
<tr>
<th>Experienced hearing loss</th>
<th>Cisplatin plus sodium thiosulfate (n = 61)</th>
<th>Cisplatin (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>39%</td>
<td>68%</td>
</tr>
<tr>
<td>No</td>
<td>61%</td>
<td>32%</td>
</tr>
<tr>
<td>Unadjusted relative risk (95% CI)</td>
<td>0.58 (0.40-0.83)</td>
<td></td>
</tr>
<tr>
<td>Adjusted relative risk  (95% CI)</td>
<td>0.58 (0.41-0.81)</td>
<td></td>
</tr>
</tbody>
</table>

**Efficacy in COG-ACCL0431**

<table>
<thead>
<tr>
<th>Experienced hearing loss</th>
<th>Cisplatin plus sodium thiosulfate (n = 39)</th>
<th>Cisplatin (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>44%</td>
<td>58%</td>
</tr>
<tr>
<td>No</td>
<td>56%</td>
<td>42%</td>
</tr>
<tr>
<td>Unadjusted relative risk (95% CI)</td>
<td>0.75 (0.48-1.18)</td>
<td></td>
</tr>
<tr>
<td>Adjusted relative risk  (95% CI)</td>
<td>0.84 (0.53-1.35)</td>
<td></td>
</tr>
</tbody>
</table>

**Warnings and Precautions**

- Hypersensitivity
- Hypertension and hypokalemia
- Nausea and vomiting

**FDA Approval**

- September 20, 2022

- The FDA grants approval to sodium thiosulfate (Pedmark) to reduce the risk of ototoxicity because of cisplatin chemotherapy in pediatric patients aged 1 month and older with localized, nonmetastatic solid tumors.

**Mechanism of action**

- Sodium thiosulfate is an inorganic salt compound that interacts directly with cisplatin to produce an inactive platinum species, and it enters cells through the sodium sulfate cotransporter 2 to cause intracellular effects.

**Dose**

- Body weight of less than 5 kg: 10g/m²
- Body weight of 5-10 kg: 15g/m²
- Body weight of greater than 10 kg: 20 g/m²

**Dosing considerations**

- Administer as an intravenous infusion over 15 minutes starting 6 hours after completion of cisplatin infusion.

**Limitations of use**

- Sodium and efficacy of sodium thiosulfate have not been established when administered following cisplatin infusions longer than 6 hours.
- Sodium thiosulfate may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.

**Company:**

Fennec Pharmaceuticals Inc

**Commonly Reported Adverse Events in SIOPEL 6**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sodium thiosulfate plus cisplatin (n = 53)</th>
<th>Cisplatin alone (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>85%</td>
<td>8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>40%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>34%</td>
<td>19%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Commonly Reported Adverse Events in COG-ACCL0431**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sodium thiosulfate plus cisplatin (n = 59)</th>
<th>Cisplatin alone (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>14%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Reference**


[bit.ly/3GOG2Pv]
ENGINEERED FOR A CHALLENGING LANDSCAPE

In the world of EGFR+ mNSCLC, few challenges have been tougher to navigate than EGFR exon 20 insertion mutations.1-10

Until RYBREVANT®—the first and only bispecific antibody built for the treatment of adult patients with locally advanced or mNSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.11

INDICATION
RYBREVANT® (amivantamab-vmwj) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Infusion-Related Reactions
RYBREVANT® can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

Interstitial Lung Disease/Pneumonitis
RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

Dermatologic Adverse Reactions
RYBREVANT® can cause rash (including dermatitis acniform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad-spectrum UV-A/UV-B sunscreen. Alcohol-free emollient cream is recommended for dry skin.
Results for tough-to-treat disease

ORR†

40%
95% CI: 29%, 51%
(n=81)

3.7% of patients achieved a CR
36% of patients achieved a PR

- Efficacy was evaluated by ORR† and DOR11

MEDIAN DOR WAS 11.1 MONTHS*11
(95% CI: 6.9, NE)*11

*CHRYSALIS was a multicenter, open-label, multicohort study conducted to assess the safety (n=129) and efficacy (n=81) of RYBREVANT® in adult patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had EGFR exon 20 insertion mutations as determined by prospective local testing, whose disease had progressed on or after platinum-based chemotherapy. RYBREVANT® was administered intravenously at 1050 mg for patients <80 kg or 1400 mg for patients ≥80 kg once weekly for 4 weeks, then every 2 weeks thereafter, starting at Week 5, until disease progression or unacceptable toxicity.11

†According to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR).11

Based on Kaplan-Meier estimates.11

The safety of RYBREVANT® was evaluated in the CHRYSALIS* study (n=129):11
- The warnings and precautions included infusion-related reactions, interstitial lung disease/pneumonitis, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity.
- The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%).11
- The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphorus (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).11
- IRRs occurred in 66% of patients treated with RYBREVANT®, the majority of which may occur with the first infusion.11

Based on the safety population, N=302.

The innovation you've been waiting for. RYBREVANThcp.com

CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; mNSCLC, metastatic non–small cell lung cancer; NE, not estimable; ORR, overall response rate; PR, partial response.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Ocular Toxicity

RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT®.

Adverse Reactions

The most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphorus (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

Please see Brief Summary of full Prescribing Information for RYBREVANT® on subsequent pages.

RYVAMB vulgar (amivantamab-pmp) injection, for intravenous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

RYVAMB vulgar is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations, as determined by an FDA-approved test (see Dosage and Administration (2.1) in Full Prescribing Information), whose disease has progressed on or after platinum-based chemotherapy.

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

CONTRAINDICATIONS

Use in pregnancy and lactation.

WARNINGS AND PRECAUTIONS

Infusion-Reactions

RYVAMB vulgar may cause infusion-related reactions (IR). Signs and symptoms of IR include dyspnea, flushing, lower, chills, nausea, chest discomfort, hypotension, and vomiting. Based on the safety population (see Adverse Reactions), IR occurred in 68% of patients treated with RYVAMB vulgar. An analysis of 61 patients experiencing IR at week 1 and week 4, 61% experiencing IR at week 1, and 36% experiencing IR at week 4. The incidence of IR was 2.4% with the Day 1 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRs, 27% were Grade 1-2, 22% were Grade 3, and 0.4% were Grade 4. The median time to onset of IR was 1 hour (range 0.5 to 4 hours) after start of infusion. The incidence of infusion-related modifications due to IR was 82% and 13% of patients permanently discontinued RYVAMB vulgar due to IR. Premedications with antiemetics and glucocorticoids and use of RYVAMB vulgar as recommended (see Dosage and Administration (2.3) in Full Prescribing Information) may reduce the incidence of infusion-related modifications and discontinuations due to IR.

Dermatologic Adverse Reactions

RYVAMB vulgar can cause cutaneous reactions (see dermatologic adverse reactions) and oropharyngeal adverse reactions. For Grade 3 reactions, oral lesions may occur (see dermatologic adverse reactions). Oropharyngeal adverse reactions may occur during treatment with RYVAMB vulgar. Oropharyngeal adverse reactions may occur once started and may persist throughout treatment with RYVAMB vulgar. Oropharyngeal adverse reactions may include pharyngitis, tonsillitis, oropharyngeal pain, dysphonia, oropharyngeal pain, pharyngitis, oropharyngeal pain.

Diabetes

RYVAMB vulgar may cause hyperglycemia (see diabetes). RYVAMB vulgar may cause hyperglycemia in patients with or without a history of diabetes. For patients with diabetes, monitor glucose levels regularly throughout treatment with RYVAMB vulgar. Monitor glucose levels in patients with a history of diabetes, and maintain strict control of glucose levels during treatment with RYVAMB vulgar. RYVAMB vulgar may be administered to patients with or without a history of diabetes.

Immunohematology

RYVAMB vulgar may cause decreased levels of antithrombin (see decreased levels of antithrombin) and decreased levels of factor X (see decreased levels of factor X).

Clinically Significant Laboratory Abnormalities

For patients with or without a history of diabetes, monitor glucose levels regularly throughout treatment with RYVAMB vulgar. For patients with diabetes, monitor glucose levels regularly throughout treatment with RYVAMB vulgar. Monitor glucose levels in patients with a history of diabetes, and maintain strict control of glucose levels during treatment with RYVAMB vulgar. RYVAMB vulgar may be administered to patients with or without a history of diabetes.

Table 1: Adverse Reactions (≥10%) in Patients with NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-Based Chemotherapy and Received RYVAMB vulgar

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>RYVAMB vulgar (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>84</td>
</tr>
<tr>
<td>Pruritis*</td>
<td>1.0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>14.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>26.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11.0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10.0</td>
</tr>
<tr>
<td>Increased phosphorus*</td>
<td></td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>27.0</td>
</tr>
<tr>
<td>Increased calcium</td>
<td>46.0</td>
</tr>
<tr>
<td>Increased sodium</td>
<td>22.0</td>
</tr>
<tr>
<td>Decreased phosphorus*</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>18.0</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>22.0</td>
</tr>
<tr>
<td>Decreased phosphorus*</td>
<td></td>
</tr>
<tr>
<td>Decreased calcium</td>
<td>18.0</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>22.0</td>
</tr>
<tr>
<td>Reduced potassium *</td>
<td>26.0</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>Reduced hemoglobin</td>
<td>36.0</td>
</tr>
</tbody>
</table>

* The denominator used to calculate the rate was 128 based on the number of patients with a baseline value and at least one post-treatment value.

Table 2: Summary of Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-Based Chemotherapy and Who Received RYVAMB vulgar

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>RYVAMB vulgar (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased albumin</td>
<td>79.0</td>
</tr>
<tr>
<td>Increased glucose</td>
<td>56.0</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>54.0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>46.0</td>
</tr>
<tr>
<td>Increased calcium</td>
<td>18.0</td>
</tr>
<tr>
<td>Increased phosphorus*</td>
<td>33.0</td>
</tr>
<tr>
<td>Increased magnesium</td>
<td>27.0</td>
</tr>
<tr>
<td>Increased calcium</td>
<td>46.0</td>
</tr>
<tr>
<td>Increased sodium</td>
<td>22.0</td>
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<tr>
<td>Decreased phosphorus*</td>
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</tr>
<tr>
<td>Decreased sodium</td>
<td>22.0</td>
</tr>
<tr>
<td>Decreased phosphorus*</td>
<td>26.0</td>
</tr>
</tbody>
</table>

* The denominator used to calculate the rate was 128 based on the number of patients with a baseline value and at least one post-treatment value.
Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the 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 that observed in other studies or to other amivantamab products may be misleading.

In CHRYSTALIS, 3 of the 284 (1.1%) patients who were treated with RYBREVENT and evaluable for the presence of anti-drug antibodies (ADA) tested positive for treatment-emergent anti-amivantamab-umjv antibodies (one at 28 days, one at 58 days, and one at 168 days after the first dose) with titer of 1:40 or less. There are insufficient data to evaluate the effect of ADA on the pharmacokinetics, safety, or efficacy of RYBREVENT.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVENT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVENT in pregnant women or animal data to assess the risk of RYBREVENT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryonic/fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryolethality, malformations, and postnatal death in animals (see Data). Adverse pregnancy outcomes in animals may be due to the mechanism of action of RYBREVENT. 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

No animal studies have been conducted to evaluate the effects of amivantamab-umjv on reproduction and fetal development; however, based on its mechanism of action, RYBREVENT can cause fetal harm or developmental anomalies. In mice, EGRF is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryonic/fetal/postnatal survival and development. Reduction or elimination of embryonic/fetal or maternal EGRF signaling can prevent implantation, cause embryonic/fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/fetuses of mice with disrupted EGRF signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in multiple organs. EGRF is known to cross the placenta; therefore, amivantamab-umjv has the potential to be transmitted from the mother to the developing fetus.

Laboration

Risk Summary

There are no data on the presence of amivantamab-umjv in human milk in milk production, or its effects on the breastfed child. Because of the potential for serious adverse reactions from RYBREVENT in breastfed infants, advise women not to breastfeed during treatment with RYBREVENT and for 3 months after the final dose.

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

Advisse females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVENT.

Pediatric Use

The safety and efficacy of RYBREVENT have not been established in pediatric patients.

Geriatric Use

Of the 129 patients treated with RYBREVENT, 41% were 65 years of age or older, and 9% were 75 years of age or older. No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advisse patients that RYBREVENT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately if any signs or symptoms of infusion-related reactions (see Warnings and Precautions).

Interstitial lung disease/ Pneumonitis

Advisse patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms (see Warnings and Precautions).

Dermatologic Adverse Reactions

Advisse patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVENT (see Warnings and Precautions). Advise patients to apply alcohol-free emollient cream to dry skin.

Ocular toxicity

Advisse patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated (see Warnings and Precautions).

Pneumonia

Advisse patients of the risk of pneumonia. Advise patients to contact their healthcare provider for signs or symptoms of pneumonia (see Adverse Reactions).

Embryo-Fetal Toxicity

Advisse females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVENT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy (see Warnings and Precautions, Use in Specific Populations).

Lactation

Advisse women not to breastfeed during treatment with RYBREVENT and for 3 months after the final dose (see Use in Specific Populations).

Other Information

Product of Ireland

Manufactured by:
Janssen Biotech, Inc., Horsham, PA 19044
U.S. License Number 1884
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ep-213279v1
PARP Inhibitors in Metastatic Castration-Resistant Prostate Cancer: Whom to Treat?

by CHRISTINA T. LOGUIDICE

DESpite the availability of numerous testosterone-suppressing treatments, including second-generation antiandrogens, and a trend toward treatment intensification earlier in the disease course (ie, castration-sensitive disease), an estimated 10% to 50% of prostate cancers progress to metastatic castration-resistant prostate cancer (mCRPC) within 3 years of diagnosis.1,2 Although mCRPC remains a lethal disease, several novel treatments associated with improved oncological outcomes have emerged, including poly PARP inhibitors—targeted agents that have been associated with improved oncological outcomes in certain patient populations, particularly those with BRCA alterations.

During a recent OncLive Peer Exchange®, a panel of genitourinary cancer experts provided an overview of currently available and emerging PARP inhibitors for mCRPC. They shared their insights on the clinical trials evaluating these agents as monotherapy and in combination with second-generation antiandrogen therapies. The combination approach in particular holds promise both for overcoming resistance mechanisms against PARP inhibitors and expanding these treatments to larger patient populations, including men with treatment-naïve mCRPC and those without BRCA or other gene alterations affecting DNA repair, according to the experts.

Over the past decade, PARP has emerged as a new target in cancer, with PARP inhibitors exploiting the deficiency of some cancer cells in repairing DNA double-strand breaks.3 PARP enzymes repair single-strand breaks in DNA, which enables cells to continue with their normal replication process.4 PARP inhibitors prevent repair of single-strand breaks, causing these breaks to evolve into double-strand breaks. Although normal cells can fix double-strand breaks through the process of homologous recombinational repair (HRR), cells deficient in HRR are unable to fix these breaks, causing them to accumulate and result in cell death through apoptosis.4

“

It seems today is relatively consensual that BRCA2 seems to be the strongest marker driving the signal [for PARP inhibitor efficacy],” Pedro C. Barata, MD, MSc, said.

Other relatively frequent alterations in DNA repair genes that have been identified in prostate cancer include ATM and BRCA1.

### Table 1. Overview of Olaparib and Rucaparib6,7

<table>
<thead>
<tr>
<th>Olaparib</th>
<th>Rucaparib</th>
</tr>
</thead>
</table>
| **Indications** | Prostate cancer: Adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone acetate  
Other indications: Ovarian cancer, breast cancer, and pancreatic cancer | Prostate cancer: Adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy  
Other indications: Ovarian cancer |
| **Recommended dosage** | 300 mg orally twice daily with or without food | 600 mg orally twice daily with or without food |
| **Warnings/precautions** | Myelodysplastic syndrome/ acute myeloid leukemia, pneumonitis, embryo-fetal toxicity, and venous thromboembolic events | Myelodysplastic syndrome/ acute myeloid leukemia and embryo-fetal toxicity |
| **Most common AEs in mCRPC** | ≥ 10% in clinical trials: Nausea, fatigue/asthenia, anemia, vomiting, diarrhea, decreased appetite, headache, dysgeusia, cough, neutropenia, dyspepsia, dizziness, leukopenia, and thrombocytopenia | ≥ 20% in clinical trials: Fatigue/asthenia, nausea, anemia, ALT/AST increased, decreased appetite, rash, constipation, thrombocytopenia, vomiting, and diarrhea |

AEs, adverse effects; ALT, alanine transaminase; AST, aspartate aminotransferase; HRR, homologous recombinational repair; mCRPC, metastatic castration-resistant prostate cancer.
"DEVELOPING STRATEGIES FOR THE TREATMENT OF PROSTATE CANCER"

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OLAPARIB CONTINUES TO DISPLAY EFFICACY IN mCRPC

Olaparib was the first PARP inhibitor to be approved by the FDA, with the initial indication granted for patients ovarian cancer in 2014, and the first drug targeting DNA damage response to enter the clinic. It received FDA approval in mCRPC in 2020 based on data from the phase 3 PROfound study (NCT02987543).

In the PROfound study, patients with mCRPC were randomly assigned 2:1 to receive olaparib (n = 256) or physician’s choice of enzalutamide or abiraterone plus prednisone (n = 131). Patients were placed into 1 of 2 cohorts based on the presence of genetic alterations: cohort A, which included those with BRCA1, BRCA2, or ATM alterations (n = 245), and cohort B, which included those with alterations in any of 12 other prespecified genes (n = 142). In cohort A, 162 patients were treated with olaparib and 83 with physician’s choice of antiandrogen. In cohort B, 94 patients were treated with olaparib and 48 with physician’s choice of antiandrogen.

Olaparib was associated with improved imaging-based progression-free survival (PFS) and overall survival (OS). In cohort A, the median imaging-based PFS was 7.4 months in the olaparib arm vs 3.6 months in the control arm (HR, 0.34; 95% CI, 0.25-0.47; P < .001). The median OS in cohort A was 19.1 months with olaparib and 14.7 months with physician’s choice of antiandrogen (HR, 0.69; 95% CI, 0.50-0.97; P = .02). A benefit with olaparib was also observed in cohort B, with a median OS of 14.1 months vs 11.5 months with physician’s choice of antiandrogen. Overall, 86 of 131 patients in the control group (66%) crossed over to receive olaparib, including 56 patients (67%) in cohort A. When adjusting for crossover to olaparib, the HR for death was 0.42 in cohort A (95% CI, 0.19-0.91) and not statistically significant in cohort B. Patients do way better in the context of biomarker disease and this is prechemotherapy," Barata said.

Recently, quality of life (QOL) analyses from PROfound have reported olaparib to be associated with reduced pain burden and better health-related QOL compared with enzalutamide or abiraterone. In cohort A, the median time to pain progression was not reached (NR) in the olaparib arm vs 9.92 months (95% CI 5.39-NR) in the control arm. In patients who had not used opiates at baseline, median time to first opiate use for cancer-related pain was 18 months in the olaparib arm vs 7.5 months in the control arm. Health-related QOL was assessed via Functional Assessment of Cancer Therapy-Prostate (FACT-P), which showed clinically meaningful improvement in FACT-P total score during treatment in the olaparib vs control arm, with 15 of 152 evaluable patients (10%) showing response in the olaparib arm vs 1 of 77 evaluable patients (1%) in the control arm.

Additional data regarding olaparib from the phase 3 PROpel study (NCT03732820) were presented at the 2022 American Society of Clinical Oncology Annual Meeting. PROpel randomly assigned patients with mCRPC 1:1 to receive abiraterone plus prednisone/prednisolone plus olaparib 300 mg twice daily or placebo. A pharmacokinetics analysis found no clinically significant effect on the pharmacokinetic profiles of either olaparib or abiraterone when these agents were combined, with similar steady-state exposures between treatment arms, providing reassurance that these agents can be combined despite both drugs being metabolized by CYP3A4/5.

Thus far, a median radiographic PFS (rPFS) of 24.8 months has been reported for abiraterone plus olaparib compared with 16.6 months for abiraterone plus placebo (HR, 0.66; 95% CI, 0.54-0.81; P < .0001). Safety analyses found the frequency and severity of AEs to be similar with the combination as when given individually. Anemia was the most frequent AE with the combination, which was typically managed by olaparib dose reductions or temporary cessation of treatment.

"[PROpel] did not require the presence of a biomarker ... The results, in my opinion, are very striking because the benefit in terms of our PFS seems to be very good, clinically significant in my opinion, but it is interesting that if you look at the absence of a biomarker, we cannot say it’s a negative study there," Barata said. He noted this finding needs to be validated in subsequent studies since other studies predominantly show benefit in the presence of certain biomarkers.

“We need to settle the question: Do we need the

with less commonly observed alterations including FANCA, RAD51B, RAD51C, MLH1, and MSH2, among others. It remains unclear what effect these other alterations may have on the efficacy of PARP inhibitors. Two PARP inhibitors have received FDA approval for mCRPC: olaparib (Lynparza) and rucaparib (Rubraca). These agents have slightly different indications, dosages, and adverse effect (AE) profiles (TABLE 1). Niraparib (Zejula) has received an FDA breakthrough therapy designation for mCRPC, and talazoparib (Talzenna) is a promising emerging PARP inhibitor for treating mCRPC."
who harbored some less frequently observed alterations in HRR genes, such as PALB2, were found to derive some benefit from PARP inhibition (Table 2).

“We’re waiting for data from the phase 3,” Barata said. “[TRITON2] shows that patients benefit from rucaparib. When we put all these data together again, [it supports] a biomarker-based approach.”

In addition to the ongoing phase 3 TRITON3 study assessing rucaparib as a monotherapy (NCT02975934), rucaparib is being studied in combination with enzalutamide as a first-line treatment for mCRPC in the phase 3 CASPAR trial (NCT04455750).20

NIRAPARIB RAPIDLY MOVING AHEAD IN BRCA1/2-MUTATED MCRPC

Niraparib received a breakthrough therapy designation from the FDA in October 2019 as a treatment for patients with BRCA1/2-mutated mCRPC who have been previously treated with taxane chemotherapy and androgen receptor-targeted therapy.4 The designation was based on data from the phase 2 GALAHAD study (NCT02854436), which showed an ORR of 34.2% (95% CI, 23.7%-46.0%) among heavily pretreated men harboring tumors with BRCA alterations.21 Niraparib is currently being studied in the phase 3 MAGNITUDE trial (NCT03748641) as a first-line combination therapy with abiraterone acetate plus prednisone in men with mCRPC with or without HRR gene alterations.22

“Treatment in biomarker-negative [patients in the MAGNITUDE trial] was stopped for fertility, which made sense based on what we learned so far, but when we look in the biomarker-positive [patients], the combination of an NHT with niraparib was promising,” Barata said. In patients with HRR gene alterations, the combination has thus far shown benefit in rPFS, ORR, time to initiation of cytotoxic chemotherapy, time to symptomatic progression, and time to PSA progression.21 Barata said OS data are anticipated.

TABLE 2. Radiologic and PSA Responses in Patients With Non-BRCA HRR Gene Alterations Enrolled in TRITON2

<table>
<thead>
<tr>
<th>Alteration</th>
<th>Radiologic response n/N</th>
<th>PSA response n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>2/19 (10.5%)</td>
<td>2/49 (4.1%)</td>
</tr>
<tr>
<td>CDK12</td>
<td>0/10 (0%)</td>
<td>1/5 (6.7%)</td>
</tr>
<tr>
<td>CHEK2</td>
<td>1/9 (11.1%)</td>
<td>2/12 (16.7%)</td>
</tr>
<tr>
<td>Other*</td>
<td>4/14 (28.6%)</td>
<td>5/14 (35.7%)</td>
</tr>
</tbody>
</table>

*Responses were observed in patients with alterations in PALB2, FANCA, BRIP1, and RAD51B.

REFERENCES

“Developing Strategies for the Treatment of Prostate Cancer” is an 18-episode OncLive Peer Exchange® video series. To watch the full series, visit bit.ly/3SbmsVv, or get started by viewing one of the following episodes:

**EPISODE 4**
**Establishing Eligibility for Frontline AR-Targeted Therapy in mHSPC**

Continuing their discussion on frontline AR-targeted therapy in mHSPC, experts define how accessibility and patient eligibility impact treatment selection.

**EPISODE 5**
**Clinical Trial Data in mHSPC From the 2022 ASCO Annual Meeting**

The panelists briefly share their excitement for trial data readouts in mHSPC from the 2022 American Society of Clinical Oncology Annual Meeting.

**EPISODE 6**
**Improving Patient Monitoring in the Setting of mHSPC**

Closing out their discussion on a clinical scenario of mHSPC, panelists consider optimal patient monitoring strategies and novel imaging.


CRC Tumor Sidedness Plays an Increasing Role in Clinical Practice

by GINA BATTAGLIA

PROGNOSIS, TREATMENT OUTCOMES, AND molecular characteristics have become associated with sidedness in colorectal cancers (CRCs) making the distinction an essential characteristic for consideration in decision-making. Right-sided CRCs (derived from the cecum, ascending colon, or hepatic flexure) have been shown to have a worse prognosis than left-sided CRCs (derived from the splenic flexure, descending colon, or sigmoid colon) in retrospective studies.

Recent studies have aimed to elucidate the underlying molecular mechanisms using single-cell sequencing and transcriptional analyses to explain the differing prognoses and potentially identify targets for treatment.

Retrospective analyses of treatment trials showing that responses and outcomes to systemic treatment regimens differed between left- and right-sided metastatic CRC (mCRC) have prompted development of prospective studies and introduced the idea of using tumor sidedness to guide selection of first-line treatment for mCRC. Additionally, CRCs associated with hereditary cancer syndromes (with the exception of familial adenomatous polyposis) tend to occur more frequently in women and at older ages. However, the overall frequency of left-sided CRC after age 50 is higher than that of right-sided CRC. CRCs associated with hereditary cancer syndromes (with the exception of familial adenomatous polyposis) tend to occur more often on the right side. Common sites of metastases are also different between left- and right-sided CRCs, with liver and lung metastases common in patients with left-sided CRC and peritoneal metastases more common in patients with right-sided CRC.

CLINICAL CHARACTERISTICS

Left-sided CRC accounts for approximately two-thirds of CRCs, and cohort studies show that left-sided CRC occurs more commonly in men and in younger patients, whereas right-sided CRC tends to occur more frequently in women and at older ages. However, the overall frequency of left-sided CRC after age 50 is higher than that of right-sided CRC.

HISTOLOGY, MORPHOLOGY, AND molecular characteristics have become associated with sidedness in colorectal cancers (CRCs) making the distinction an essential characteristic for consideration in decision-making.

The relationship between molecular characteristics and clinical outcomes has also been shown to differ between left- and right-sided CRCs. Mismatch repair deficiency (dMMR) in stage III disease appears to be associated with favorable prognosis in patients with right-sided CRC, whereas patients with dMMR left-sided CRC have poorer disease-free and overall survival than those with dMMR right-sided CRC. OS is also poorer with left-sided KRAS-mutated CRCs than with right-sided KRAS-mutated CRCs.

FIGURE. Clinical Characteristics of Left- vs Right-Sided CRCs

<table>
<thead>
<tr>
<th>Location</th>
<th>Molecular characteristics</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIGHT</td>
<td>Mismatch repair deficiency (dMMR)</td>
<td>Worse prognosis</td>
</tr>
<tr>
<td>Location</td>
<td>Microsatellite instability (MSI)-high</td>
<td>Lack of benefit from anti-EGFR therapy</td>
</tr>
<tr>
<td></td>
<td>CIMP-H</td>
<td>Presents in older populations, women</td>
</tr>
<tr>
<td>LEFT</td>
<td>Microsatellite instability (MSI)-high</td>
<td>Better prognosis</td>
</tr>
<tr>
<td>Location</td>
<td>Consensus molecular subtype (CMS)</td>
<td>Benefit from anti-EGFR therapy</td>
</tr>
<tr>
<td></td>
<td>High TML</td>
<td>Presents in younger populations, men</td>
</tr>
</tbody>
</table>

OSCI-00003048: CIMP-H, CpG island methylator phenotype-high; CMS, consensus molecular subtype; MSI, microsatellite instability; TML, tumor mutation load.
right-sided CRC. By contrast, left-sided CRCs tend to be chromosomal instability (CIN)-high, which is characterized by aneuploidy and loss of heterozygosity, and typically progress via the Wnt pathway, which is characterized by aneuploidy and loss of tumor suppressor genes.

**NEW MOLECULAR PROFILE STUDIES FILL OUT DISTINCTIONS**

Much research has established left- and right-sided CRC as having distinct clinical and molecular features, and new research has aimed to distinguish the molecular mechanisms for tumorigenesis. For example, a study of 411 samples of colon tumors from The Cancer Genome Atlas-COAD cohort found that dysregulation of APC, GSK3B, and several genes in the Wnt/B-catenin pathway was observed in left- and right-sided tumors, with NOTUM, an inhibitor of Wnt activation, associated with CRC progression and OS. However, NOTUM expression levels had a different relationship with OS in right- and left-sided CRC, with high levels associated with shorter OS in right-sided CRC (HR, 0.44; 95% CI, 0.24-0.82; *P* < .01) and longer OS in left-sided CRC (HR, 3.23; 95% CI, 1.27-8.2; *P* < .01). The study also found that right-sided CRCs had lower levels of genes encoding for enzymes involved in breakdown of carcinogens, namely CYP2C8, CYP4F12, GSTA1, and UGT1A, as well as a greater shift toward aerobic glycolysis from oxidative phosphorylation, which may explain the aggressive nature of these tumors. By contrast, left-sided tumors had more predominant suppression of MTA41 (CD20 tumor-infiltrating B cell marker) and BACH2 (transcriptional regulator of B and T follicular helper cells), and a potential connection with calcium homeostasis may contribute to less immune infiltration and may partially explain the less aggressive behavior compared with right-sided tumors.

Post-transcriptional regulation was mediated by different RNA-binding proteins (NKRF and MSI2 for left- and right-sided CRCs, respectively) and micro-RNAs (miRNAs; miR-3607 and miR-29a in left-sided tumors; miR-155, miR-181d, miR-576 and miR-23a in right-sided tumors). Marker methylation also differed, with more hypermethylated CpG sites in right-sided CRCs and more hypomethylated CpG sites in left-sided CRCs. The authors concluded that their findings highlighted the considerable differences in left- and right-sided CRCs at multiple levels of epigenetic, transcriptional, and posttranscriptional regulation, which could help with future identification of biomarkers, prognostic indicators, and targeted therapies.

Another recent study used single-cell RNA sequencing to profile the transcriptomes of 27,927 cells from 3 left- and 3 right-sided human CRCs obtained during curative surgery, with the goal of evaluating a complete spectrum of cell types and their molecular characteristics in left- and right-sided CRC to identify differences in pathogenesis that may contribute to increased tumor aggressiveness and poorer prognosis. The study found that compared with left-sided CRCs, right-sided CRCs had a 9-fold higher number of naive CD4-positive T cells, which are a marker of poor prognosis in breast cancer. Further, molecular characteristics showed that a larger proportion of exhausted CD8-positive T cells were migratory. Left-sided CRC had a 13.8-fold higher ratio of preexhausted to exhausted T cells (a higher ratio is associated with better prognosis in lung adenocarcinoma) compared with right-sided CRC.

Additionally, the T regulatory cells from left-sided CRCs had higher expression of immunotherapy-related genes, suggesting that they may respond better than right-sided CRCs to immunotherapies that act on dysfunctional T regulatory cells. The study also found that cancer cell subgroup 5, which were derived exclusively from left-sided CRC, had upregulated signaling pathways associated with cancer, such as estrogen, HER2, TNF, HIF-1, and AMPK signaling, as well as cell death pathways (eg, apoptosis, necroptosis, autophagy, and mitophagy), the latter of which may explain the better prognosis associated with left-sided CRC. Additionally, the stronger signaling through EGFR, VEGF, and HER2 observed in left-sided CRC cells may reflect a greater sensitivity to monoclonal antibodies against these respective targets.

**RESPONSES TO TREATMENT**

In addition to the recent molecular analysis studies, early retrospective data from clinical trials have suggested that tumor sidedness may have implications for treatment. A retrospective analysis of results from the CRYSTAL trial (NCT00154102), which compared cetuximab plus FOLFIRI (folinic acid, fluorouracil, irinotecan) with FOLFIRI alone, and the FIRE-3 trial (NCT00433927), which compared FOLFIRI plus bevacizumab with FOLFIRI plus cetuximab, found significantly longer PFS, OS, and overall response rate (ORR) with FOLFIRI plus cetuximab in patients with RAS wild-type left-sided tumors but not in patients with RAS wild-type right-sided tumors. Authors cautioned that the small sample sizes of right-sided tumors may limit interpretability of the findings.

Findings from a retrospective subgroup analysis of the CALGB/SWOG 80405 trial (NCT00265850), presented at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting, were pivotal for establishing the poorer prognosis of right-sided CRCs in response to conventional systemic therapy. The study found that the median OS was significantly shorter in right-sided CRC compared with left-sided CRC (19.4 months; *P* < .0001). See Table 37 for a summary of outcomes by tumor sidedness.

**TABLE. Retrospective Analysis of Tumor Sidedness Outcomes in mCRC**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 1137)</th>
<th>Tumor side</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Right (n = 293)</td>
<td>Left (n = 732)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>58.4</td>
<td>61.2</td>
<td>57.3</td>
</tr>
<tr>
<td>Men</td>
<td>62.1%</td>
<td>54.9%</td>
<td>65.0%</td>
</tr>
<tr>
<td>Stage IV disease</td>
<td>79.3%</td>
<td>86.9%</td>
<td>76%</td>
</tr>
<tr>
<td>Prior adjuvant therapy</td>
<td>14.2%</td>
<td>10.6%</td>
<td>15.7%</td>
</tr>
<tr>
<td>FOLFOX/FOLFIRI</td>
<td>73.4%/26.6%</td>
<td>74.4%/25.6%</td>
<td>72.4%/27.6%</td>
</tr>
<tr>
<td>Primary in place</td>
<td>26.6%</td>
<td>19.2%</td>
<td>29.6%</td>
</tr>
<tr>
<td>Liver-only metastases</td>
<td>30.9%</td>
<td>27.5%</td>
<td>32.1%</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>42.8%</td>
<td>40.5%</td>
<td>43.2%</td>
</tr>
<tr>
<td>Extraregional</td>
<td>28.5%</td>
<td>32.0%</td>
<td>24.7%</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>8.9</td>
<td>11.7</td>
<td>HR, 1.03; 95% CI, 1.11-1.54; <em>P</em> &lt; .0006</td>
</tr>
<tr>
<td>Median PFS with cetuximab, months</td>
<td>7.8</td>
<td>12.4</td>
<td>HR, 1.56; 95% CI, 1.26-1.94; <em>P</em> &lt; .0001</td>
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<tr>
<td>Median PFS with bevacizumab, months</td>
<td>9.6</td>
<td>11.2</td>
<td>HR, 1.06; 95% CI, 0.86-1.31; <em>P</em> = .56</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>19.4</td>
<td>33.3</td>
<td>HR, 1.55; 95% CI, 1.32-1.82; <em>P</em> &lt; .0001</td>
</tr>
<tr>
<td>Median OS with cetuximab, months</td>
<td>16.7</td>
<td>36.0</td>
<td>HR, 1.87; 95% CI, 1.48-2.32; <em>P</em> &lt; .0001</td>
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<tr>
<td>Median OS with bevacizumab, months</td>
<td>24.2</td>
<td>31.4</td>
<td>HR, 1.32; 95% CI, 1.05-1.65; <em>P</em> = .01</td>
</tr>
</tbody>
</table>

*FOLFOX, 5-fluorouracil, folinic acid, and irinotecan; FOLFIRI, folinic acid, 5-fluorouracil, and oxaliplatin; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.

*Any liver metastases vs extraregional.
Marshall Discusses the Increasing Role of Molecular Testing in GI Cancers

The field of precision medicine in gastrointestinal (GI) cancer is growing rapidly, according to John L. Marshall, MD. In an interview with OncLive®, he outlines key points from a presentation delivered at the 4th Annual Precision Medicine Symposium® including developments in molecular testing, as well as the unique offerings of tissue and blood tests that may make diagnosis and treatment more effective. READ NOW: bit.ly/3CGP3f1

95% CI, 16.7-23.6) than in those with left-sided CRC (33.3 months; 95% CI, 31.4-35.7). Patients with treatment-naïve, KRAS wild-type (exon 12 and 13), right-sided CRC who received bevacizumab in addition to mFOLFOX6, in patients with unresectable CRC who received cetuximab or panitumumab (Vectibix) or bevacizumab and cetuximab, respectively, to chemotherapy.5

Patients with treatment-naïve, KRAS wild-type, left-sided CRC had a median OS of 31.4 months (95% CI, 28.3-33.6) and 36.0 months (95% CI, 32.6-40.3) with the addition of bevacizumab and cetuximab, respectively, to chemotherapy.5

Similarly, a retrospective analysis of pooled data from the ARCAD trials showed that cetuximab was associated with improved PFS and OS in KRAS wild-type left-sided mCRC and a trend toward poorer outcomes with KRAS wild-type right-sided mCRC.7 The median OS was 22.3 months vs 20.5 months, respectively (HR, 0.985; 95% CI, 0.75-0.97; \( P = .01 \)), and the median PFS was 9.3 months vs 8.5 months, respectively (HR, 0.77; 95% CI, 0.67-0.88; \( P < .001 \)). Although the superiority of 1 drug cannot be established due to the retrospective and post hoc nature of the studies, they suggest that response to EGFR inhibitors may be inferior in right-sided CRCs.5

Accordingly, the National Comprehensive Cancer Network guidelines note that systemic therapy regimens containing an EGFR inhibitor (cetuximab or panitumumab) are only recommended for RAS wild-type and left-sided advanced and metastatic CRCs.31 Based on these findings, investigators aimed to prospectively evaluate whether right- and left-sided mCRCs had different responses to treatment.24 The phase 3 PARADIGM trial (NCT02394795) was a randomized, open-label, multicenter trial that evaluated the superiority of the anti-EGFR therapy panitumumab (Vectibix) or the anti-VEGF therapy bevacizumab (Avastin), in addition to mFOLFOX6, in patients with unresectable RAS wild-type mCRC.7

The first primary end point was OS in the subgroup with left-sided disease which, if significant, would be analyzed as a secondary primary endpoint in the overall population.7 The median OS for left-sided tumors were 37.9 months (95% CI, 34.1-42.6) and 34.3 months (95% CI, 30.9-40.3) in the panitumumab and bevacizumab groups, respectively (HR, 0.84; 95.798% CI, 0.68-0.99; \( P = .031 \)), which met the 2-sided significance level of 0.04202 determined by the alpha spending function approach after 1 interim analysis.7 The median OS in the overall population were 36.2 months (95% CI, 32.0-39.0) and 31.3 months (95% CI, 29.3-34.1) in the panitumumab and bevacizumab groups (HR, 0.84; 95% CI, 0.72-0.98; \( P = .03 \)), which met the P < .05 cutoff for significance for primary endpoint 2.7

Although the median PFS was similar between panitumumab and bevacizumab groups in the left-sided (13.7 vs 13.2 months; HR, 0.98; 95% CI, 0.82-1.17) and overall populations (12.9 vs 12.0 months; HR, 1.01; 95% CI, 0.87-1.18), response rates were higher with panitumumab than with bevacizumab (left-sided population: 80.2% vs 68.6%; overall population: 74.9% vs 67.3%).7 Additionally, rates of R0 resection were numerically higher with panitumumab (left-sided population: 18.3% [95% CI, 14.1%-23.0%] vs 11.6% [95% CI, 8.2%-15.9%]; overall population: 16.5% [95% CI, 13.0%-20.5%] vs 10.9% [95% CI, 8.7%-17.1%]).7

The data support using panitumumab with mFOLFOX6 as first-line therapy for patients with RAS wild-type and left-sided mCRC, according to the authors.7 However, in an interview with OncologyLive®, Tanios S. Bekaii-Saab, MD, FACP, said that although EGFR inhibitors are likely detrimental for right-sided mCRC, the PARADIGM trial findings that panitumumab is preferred as first-line therapy for left-sided disease should be interpreted cautiously because it compared FOLFOX/FOLFIRI plus panitumumab with doublet chemotherapy plus bevacizumab, which was found to be inferior to triplet chemotherapy (FOLFOXIRI; folinic acid, 5-fluorouracil, oxaliplatim, and irinotecan) plus bevacizumab in the phase 3 CAIRO5 trial (NCT02162563).8 Bekaii-Saab the leader of the Gastrointestinal Cancer Program at the Mayo Clinic Comprehensive Cancer Center, medical director of the Cancer Clinical Research Office, and the vice chair and section chief for medical oncology in the Department of Internal Medicine at Mayo Clinic in Phoenix, Arizona.

This trial aimed to identify the optimal regimen for systemic treatment for patients with initially unresectable CRC liver metastases that are potentially resectable after downsizing.8 Patients with initially unresectable-only liver metastases (confirmed prospectively by an expert panel) were enrolled, and those with RAS or BRAF V600E mutations and/or right-sided primary CRC were randomly assigned to receive FOLFOX or FOLFIPII plus bevacizumab or FOLFOnIRI plus bevacizumab, and those with RAS/BRAF V600E wild-type and left-sided primary tumors were randomly assigned to receive FOLFOX/FOLFIPI plus bevacizumab or FOLFOnIRI plus panitumumab.8

Data from the RAS/BRAF V600E-mutated and/or right-sided tumor group presented at the 2022 ASCO Annual Meeting showed that FOLFOnIRI plus bevacizumab led to longer PFS (10.6 months vs 9.0 months; HR, 0.77; 95% CI, 0.60-0.95; \( P = .038 \)) after a median follow-up of 41 months.8 The FOLFOnIRI-bevacizumab group also had higher rates of response (53.5% vs 33.3%; \( P < .001 \)) and R0 or R1 resection (51% vs 37%; \( P = .02 \)) but also had higher rates of grade 3 or higher adverse events (75.7% vs 59.2%; \( P = .003 \)), including neutropenia (38.2% vs 12.9%; \( P < .001 \)) and diarrhea (19.4% vs 3.4%; \( P < .001 \)).8 The authors concluded that triplet chemotherapy plus bevacizumab improves PFS, ORR, and R0/R1 resection rates, although this comes at the cost of greater toxicity.8

Bekaii-Saab said FOLFOnIRI plus bevacizumab is his chemotherapy of choice for patients who are eligible for FOLFOnIRI (typically younger, otherwise healthy patients), regardless of their tumor sidedness. Although the PARADIGM data suggest FOLFOnX plus an EGFR inhibitor may be a good choice for patients with left-sided disease, Bekaii-Saab added that with RAS/BRAF wild-type, non–HER2 amplified CRC, he added that the regimen may be difficult to tolerate, particularly for older patients. Furthermore, he noted that because the OS curves separated late (at approximately 2 years) in the PARADIGM trial, it is unclear whether the difference in OS was directly related to treatment or another factor. “I’m not convinced that this regimen [FOLFOnX-panitumumab] is for every patient,” he said.

Although recent data from the PARADIGM and CAIRO5 trials point toward differential responses between left- and right-sided mCRC to conventional first-line treatment regimens, tumors within a given subsite also show considerable heterogeneity in their molecular characteristics and tumor behavior. Further research is needed to identify relationships between tumor sidedness, molecular pathways, and response to treatment in mCRC.8

For a full list of references, see the article at OncLive.com.
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Investigators Seek to Refocus on FGFR2-altered Cholangiocarcinoma

by KYLE DOHERTY

TREATMENT OPTIONS FOR THE treatment of patients with cholangiocarcinoma are rapidly expanding with multiple approved targeted therapies and immunotherapy. Investigators hope to add RLY-4008, the first highly selective FGFR2 inhibitor, to this list growing arsenal of treatment options with the initiation of the phase 1/2 ReFocus trial (NCT04526106).1

Cholangiocarcinoma is considered a rare disease with a poor prognosis and effective treatment options begin to decline as later lines of therapy are introduced. Frontline treatment with gemcitabine/cisplatin has historically resulted in a median OS of approximately 1 year. Second-line treatment with FOLFOX has historically resulted in a median OS of approximately 6 months. FGFR2 fusions or rearrangements have been shown to drive approximately 10% to 15% of intrahepatic cholangiocarcinoma (ICC) cases.2

“Available agents [in the cholangiocarcinoma space] have historically relied on cytotoxic chemotherapy,” Mitesh J. Borad, MD, an oncologist at the Mayo Clinic in Phoenix, Arizona, said in an interview with OncologyLive®. “With the advent of the TOPAZ-1 [NCT03875235] data, we now have durvalumab also in the tool kit in the first-line setting. [Additionally], there are a whole host of therapies in the targeted therapy setting. These have primarily been used in the beyond first-line setting and have been restricted currently to FGFR2 fusions and IDH1 mutations as disease specific targets.”

RLY-4008 is designed to selectively inhibit FGFR2, specifically via its unique conformational dynamics. The agent has displayed potent in vivo antitumor activity in disease harboring primary FGFR2 alterations, in addition to other common resistance mutations.3

“First-line treatment with gemcitabine and cisplatin chemotherapy has significant toxicity and limited efficacy with a median progression-free survival of 6 to 8 months and an overall survival of less than 7 months,” said Antoine Hollebecque, MD, head of the conventional hospital in the Drug Development Department at Gustave Roussy Cancer Center in Villejuif, France, during the European Society of Medical Oncology Annual Congress 2022.2

In further preclinical study, RLY-4008 led to a biochemical half maximal inhibitory concentration (IC50) of 864.3, 3.1, 274.1, and 17,633 in FGFR1, FGFR2, FGFR3, and FGFR4, respectively. Futibatinib, an irreversibly pan-FGFR inhibitor, has been shown elicit an IC50 of less than 2 in FGFR1, FGFR2, and FGFR3, and an IC50 of approximately 3.7 in FGFR4. Similarly, the reversible pan-FGFR inhibitor infrafibratinib displayed an IC50 between 1 and 2 in FGFR1, FGFR2, and FGFR3, and an IC50 of 61 in FGFR4.2,3

“[RLY-4008] would probably be considered a third-generation [FGFR] inhibitor,” Borad said. “This is an allosteric inhibitor. It binds to a different side of the ATP pocket [compared with first- and second-generation agents] and is very selective for FGFR2. It does not hit FGFR1 or FGFR3 like many of the other agents. Hopefully, we will have a different dosing approach compared with the other drugs [in the space] given some of these unique facets.”

RLY-4008 DISPLAYS EFFICACY IN FGFR2+ CHOLANGIOCARCINOMA ReFocus is an open-label phase 2 study of RLY-4008 for the treatment of patients with ICC and other advanced solid tumors. Patients must have FGFR2 alterations, an ECOG performance status of 1 or less, and disease that is refractory to standard therapy, not responsive to standard therapy, or lacking a standard therapy (FIGURE).1

Patients with central nervous system (CNS) metastases or a primary CNS tumor associated with progressive neurologic symptoms are ineligible for the trial. Patients who lack adequate organ function, have clinically significant FGFR inhibitor-induced retinal detachment or an ongoing clinically significant corneal or retinal disorder, and patients with an active infection are also excluded from the study.

The primary end points of the study are objective response rate (ORR), and safety. Secondary end points include duration of response, disease control rate, and pharmacokinetics.

In the dose escalation portion of the trial, investigators noted that RLY-4008 displayed a predicted median receptor occupancy of at least 85% across all dose levels. The agent exhibited a half-life of approximately 15 hours to 30 hours, which supported daily dosing. The RP2D of oral RLY-4008 was determined to be 70 mg daily and the maximum-tolerated dose was not reached per protocol.1,2

“Together these data indicate that RLY-4008 targets FGFR2 without inducing FGFR1-related hyperphosphatemia,” Hollebecque said. “Early ReFocus data validate this novel mechanism of action and supports expedited development [of the agent]."

FIGURE. ReFocus Phase 1/2 Trial Design

Key inclusion criteria
• Histologically or cytologically confirmed unresectable or metastatic solid tumor
• Documented FGFR2 gene fusion, mutation, or amplification per local testing of blood and/or tumor
• Measurable disease per RECIST v1.1
• ECOG performance status of 0-1
• Disease that is refractory to standard therapy, disease that has not adequately responded to standard therapy, disease for which standard or curative therapy does not exist, or the patient must be intolerant to or have declined standard therapy

N = 440

Dose escalation
Multiple doses of RLY-4008 for oral administration

Dose expansion
Oral dose of RLY-4008 as determined during dose escalation

End points
Primary
- ORR
- MTD and RP2D
- AEs and serious AEs
Secondary
- DOR
- FGFR2 gene status in plasma ctDNA and tumor tissue
- DCR
- Pharmacokinetics
- Pharmacodynamics

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“RLY-4008 is the first highly selective, irreversible inhibitor designed to target oncogenic FGFR2 driver alterations and resistance mutations. These results suggest that RLY-4008 has the potential to transform the cholangiocarcinoma treatment paradigm and strongly support seamless expansion of ReFocus with registrational intent.”

— ANTOINE HOLLEBECQUE, MD

Investigators presented additional preliminary findings from the FGFR2 fusion or rearrangement, FGFR inhibitor-naïve cholangiocarcinoma cohort of the ReFocus trial during the ESMO Congress 2022. They noted that RLY-4008 is showing great promise in the space and has the potential to shift the treatment landscape in patients with cholangiocarcinoma harboring an FGFR2 fusion or rearrangement who have not previously received treatment with an FGFR inhibitor.

“RLY-4008 is the first highly selective, irreversible inhibitor designed to target oncogenic FGFR2 driver alterations and resistance mutations,” Hollebecque said. “These results suggest that RLY-4008 has the potential to transform the cholangiocarcinoma treatment paradigm and strongly support seamless expansion of ReFocus with registrational intent.”

Efficacy-evaluable patients treated at all dose levels (n = 38) achieved an ORR of 63.2% (95% CI, 46%-78.2%). Stable disease was observed in 31.6% of patients and 5.3% experienced disease progression. The disease control rate (DCR) was 94.7% (95% CI, 82.3%-99.4%). At the data cutoff, progression. The disease control rate (DCR) was 94.7% (95% CI, 82.3%-99.4%). At the data cutoff, 11.8% of patients experienced an ongoing response at the time of the data cutoff and 88.2% in this cohort were experiencing an ongoing response at the time of the data cutoff and 88.2%.

In the cohort that received the RP2D, the median age was 57 years (range, 36-81) and most patients were women (59%). A majority of patients in this cohort had an ECOG performance status of 0 (53%). Forty-one percent of patients underwent prior treatment with a single-line of treatment, 47% received 2 prior lines, and 12% were treated with 3 or more prior lines.

In terms of safety, patients in the safety population who received the RP2D (n = 89) experienced a treatment-related adverse event (TRAE) that led to dose interruption or dose reduction at a rate of 42% and 27%, respectively. Only 1 patient discontinued treatment with RLY-4008 because of a TRAE.

Commonly occurring TRAEs of any grade occurring at the RP2D included nail toxicities (43%), stomatitis (42%), and palmar plantar erythrodysesthesia syndrome (35%). Grade 3 TRAEs were less common, consisting only of stomatitis (8%), palmar plantar erythrodysesthesia syndrome (8%), and nail toxicities.

Comparatively, patients in the safety population treated with RLY-4008 at any dose level (n = 195) experienced TRAE-related dose interruptions, reductions, and discontinuations at a rate of 47%, 3%, and 1%, respectively. The most common any-grade TRAEs included stomatitis (48%), nail toxicities (46%), palmar plantar erythrodysesthesia syndrome (46%), and dry mouth (31%). Grade 3 TRAEs were limited to palmar plantar erythrodysesthesia syndrome (15%), stomatitis (8%), and nail toxicities (2%).

Investigators noted that, overall, the adverse effects observed with RLY-4008 were low grade, manageable, and largely reversible. This is indicative of selective FGFR2 inhibition accompanied by sparing of FGFR1 and FGFR4, they wrote.

“The key [next steps] will be a larger cohort of patients compared with what was presented,” Borad said. “I am sure there will be updates over time as more data is accumulated in a larger group of patients. I will eagerly await [seeing] if the initial response rates that have been observed hold up, or if there’s some diminishment, like we typically see when we have larger groups of patients. But given how high [the ORR] is, we will really want to keep an eye out and see where the final numbers end up.”

The trial is open to enrollment.

REFERENCES

Schramp Discusses Phase 2 Data of Different Dose Levels of RLY-4008

Alison Schram, MD, highlights the safety and efficacy data of the FGFR2 inhibitor. RLY-4008 from the phase 1/2 ReFocus trial (NCT04526106) in patients with FGFR2-positive, unresectable, or metastatic cholangiocarcinoma, presented at the European Society for Medical Oncology Congress 2022.

▶ WATCH NOW: bit.ly/3TrSz3H
ADJUVANT TAGRISSO: DELIVERING OVERWHELMING EFFICACY

TAGRISSO demonstrated extraordinary disease-free survival in resected EGFRm NSCLC patients

Consistent results with or without prior adjuvant chemotherapy

- Patients in the ADAURA trial are treated with ORAL TAGRISSO FOR 3 YEARS or until disease recurrence or unacceptable toxicity

INDICATION

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

SELECT SAFETY INFORMATION

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

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

DFS Probability

<table>
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<tr>
<th>Months</th>
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<th>60%</th>
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<td>61%</td>
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<td>90%</td>
<td>97%</td>
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<td>3-year DFS rate</td>
<td>97%</td>
<td>61%</td>
<td>78%</td>
<td>87%</td>
<td>97%</td>
</tr>
</tbody>
</table>

INDICATIONS AND USAGE

For complete prescribing information consult official package insert.

WARNINGS AND PRECAUTIONS

Cardiomyopathy

QTc Interval Prolongation

Baseline

Cardiac monitoring, including assessment of LVEF at baseline and during treatment,
with TAGRISSO in clinical trials.

Contraindications

Withhold TAGRISSO and promptly investigate for ILD in patients who present with
symptoms of life-threatening or symptomatic ILD.

Drug Interactions

Withhold TAGRISSO if baseline QTc is greater than or equal to 480 milliseconds.

Drug Interactions

If baseline QTc is greater than 500 milliseconds on at least two occasions, discontinue
TAGRISSO. Of the 1479 patients treated with TAGRISSO in clinical trials, 0.8% were
exposed to TAGRISSO in clinical trials.

Adverse reactions rated in 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.

All Grades

For complete prescribing information consult official package insert.

Cardiac monitoring, including assessment of LVEF at baseline and during treatment,
with TAGRISSO experienced LVEF decreases greater than or equal to 10 percentage points
with TAGRISSO following progression on or after EGFR TKI therapy based on the presence
of EGFR exon 19 deletions or exon 21 L858R mutations in tumor

Withhold TAGRISSO if baseline QTc is greater than or equal to 500 milliseconds on at least two occasions, discontinue
TAGRISSO. Of the 1479 patients treated with TAGRISSO in clinical trials, 0.8% were
exposed to TAGRISSO in clinical trials.

Table 1. Recommended Dosage Modifications for TAGRISSO

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Grade 1 or Greater Resurgence (%)</th>
<th>Permanent Discontinue (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>≥ 20%</td>
<td>TAGRISSO</td>
</tr>
<tr>
<td>Cardiac</td>
<td>≥ 20%</td>
<td>TAGRISSO</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>≥ 20%</td>
<td>TAGRISSO</td>
</tr>
<tr>
<td>Skin Disorders</td>
<td>≥ 20%</td>
<td>TAGRISSO</td>
</tr>
</tbody>
</table>

Acneiform rash, dry skin, erythema, edema.

Includes aphthous ulcer, cheilitis, gingival ulceration, glossitis, tongue ulceration, stomatitis and
fiagulosa.

Serum Electrolytes

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

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Table 5. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in FLAURA

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Table 7. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

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Table 8. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

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Table 9. Adverse Reactions Occurring in <10% of Patients Receiving TAGRISSO in AURA*

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Table 10. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

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Table 11. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

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Table 12. Laboratory Abnormalities Worsening from Baseline in ≥20% of Patients in AURA3

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Cracking the “MGUS” Code Reveals Monoclonal Gammopathy of Clinical Significance

by SANDRA MAZZONI, DO

When assessing monoclonal gammopathy

It is important to rule out clinically significant associations requiring treatment. On initial patient consultation, gathering a detailed patient history and thorough physical exam can catch clinically significant pearls to guide next diagnostic steps. It is critical to recall that monoclonal proteins can be produced by both plasma cells and B cells, and identifying the source will determine the treatment in many cases. A referral to a center with multidisciplinary care is best practice to ensure appropriate workup in a timely manner. There are recognized monoclonal gammopathies of dermatologic, neurologic, renal, skeletal, and hematologic significance.

Monoclonal gammopathy of dermatologic significance (MGDS)

There are a variety of skin manifestations driven by either clonal B cell or plasma cell protein production and associated alteration of the immune system. Referral to a dermatology department for skin biopsy is essential in most cases.

Cryoglobulin Vasculitis

Cryoglobulins are immunoglobulins in the serum that precipitate at cooler temps leading to organ damage. Referral to a dermatology department for skin biopsy is essential in most cases.

TABLE. Monoclonal Gammopathy of Neurologic Significance Conditions

<table>
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<tr>
<th>Etiology</th>
<th>Typical monoclonal protein</th>
<th>Associated neuropathy</th>
<th>Unique features</th>
<th>Treatment</th>
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<tr>
<td>POEMS</td>
<td>Elevated IL6 and VEGF leading to organ damage</td>
<td>λ</td>
<td>Polyneuropathy demyelinating</td>
<td>Sclerotic bone lesions, endocrinopathy, organomegaly</td>
</tr>
<tr>
<td>Cryoglobulinemia (type I and II)</td>
<td>Proteins that precipitate at cooler temps</td>
<td>Type I: monoclonal IgG or IgM</td>
<td>Peripheral neuropathy</td>
<td>Foot drop/wrist drop, vasculitic rash</td>
</tr>
<tr>
<td>IgM associated neuropathy</td>
<td>Anti-MAG or other ganglioside antibody</td>
<td>IgM</td>
<td>Pure sensory deficit</td>
<td>Symmetrical bilateral, typically ascending</td>
</tr>
<tr>
<td>SLOMN</td>
<td>Nemaline rod deposition in muscle, rare to be sporadic most cases are hereditary</td>
<td>No predominant monoclonal protein</td>
<td>Pure motor deficit</td>
<td>Muscle atrophy of axial and respiratory muscles, requires muscle biopsy for diagnosis</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>Accumulation of misfolded light chain amyloid fibrils</td>
<td>Free light chains: λ &gt; κ</td>
<td>Peripheral neuropathy</td>
<td>Bilateral carpal tunnel, cardiomyopathy, diffuse systemic symptoms (GI, renal, etc)</td>
</tr>
<tr>
<td>CANOMAD</td>
<td>IgM monoclonal antibody that binds to disialosyl epitopes common to gangliosides</td>
<td>IgM</td>
<td>Sensorimotor</td>
<td>Ataxia, ocular motor and bulbar dysfunction resulting in ophthalmoplegia, paresthesia, dysphagia, dysarthria, loss of kinesesthesia</td>
</tr>
</tbody>
</table>

AL, amyloid light chain; ASCIT, autologous stem cell transplant; CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, monoclonal gammopathy—IgM, agglutinin (cold), disialosyl antibodies; CyBORD, cyclophosphamide, bortezomib, and dexamethasone; GI, gastrointestinal; IVIG, intravenous immunoglobulin; MAG, myelin-associated glycoprotein; PLEX, plasma exchange; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; SLOMN, sporadic late-onset nemaline myopathy.
psychosis. It is typically preceded by malaise with fever. Treatment consists of steroids, intravenous immunoglobulin (IVIG), and plasmapheresis (plasma exchange; PLEX).  

**Schnitzler Syndrome**  
This urticarial rash is driven by increased IL1. It is typically seen with IgM monoclonal gammopathy with systemic symptoms that include fever, arthritis, arthralgia, bone pain, lymphadenopathy, and hepatosplenomegaly. The disease has an indolent course with a low-risk of progression to Waldenström or B-cell lymphoma. The rash is treated with IL1 inhibitors.  

**Sweet Syndrome**  
Also known as acute febrile neutrophilic dermatosis, the erythematous annular skin rash can be quite painful and is often associated with fever. Skin punch biopsy reveals neutrophilic infiltrate into the dermis. Treatment of the rash is a combination of steroids and therapy targeted at either the B cell or plasma cell clone producing the monoclonal protein.  

**Pyoderma Gangrenosum**  
Most often associated with inflammatory bowel disease and arthritis, pyoderma gangrenosum has been reported in up to 20% of cases of IgA monoclonal gammopathy. These cases can progress to multiple myeloma, so patients should receive plasma cell–directed therapy. Unfortunately, these patients often prove to be refractory to treatment.  

**MONOCLONAL GAMMOPATHY OF NEUROLOGIC SIGNIFICANCE (MGNS)**  
There exists a wide range of monoclonal protein–driven neurologic conditions. Presenting symptoms may include myopathy, neuropathy (sensory and/or motor), muscle atrophy, and ataxia. These cases should be assessed by both a hematologist and a neurologist. Typical workup includes a thorough neurologic assessment with electromyography and additional studies such as imaging, biopsy, and laboratory tests. A bone marrow biopsy is essential in these cases for both diagnosis and to guide treatment.  

<table>
<thead>
<tr>
<th>MGNS conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes)</td>
<td></td>
</tr>
<tr>
<td>Cryoglobulinemia (type I and II)</td>
<td></td>
</tr>
<tr>
<td>IgM-associated neuropathy</td>
<td></td>
</tr>
<tr>
<td>SLONM (sporadic late-onset nemaline myopathy)</td>
<td></td>
</tr>
<tr>
<td>Amyloid light-chain (AL) amyloidosis</td>
<td></td>
</tr>
<tr>
<td>CANOMAD (chronic, ataxic, neuropathy, ophthalmoplegia, monoclonal gammopathy—IgM, agglutinins [cold], and distialysol antibodies)</td>
<td></td>
</tr>
</tbody>
</table>

**MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE (MGRS)**  
Monoclonal gammopathy in the setting of unexplained proteinuria and/or declining renal function requires renal biopsy for diagnosis. It is important to elicit the source of monoclonal protein production by obtaining a bone marrow biopsy and advanced imaging as these can be either plasma cell or B-cell clones. Treatment is focused on targeting the clonal cells to stop the monoclonal protein production with the goal of preserving renal function. Twenty-four-hour urine studies are helpful to monitor response to treatment. The mechanism of injury determines the site of renal damage. Additional immunofluorescent stains can identify the monoclonal proteins within the renal biopsy. They are as follows:  

- **Gomeruluri only:**  
  - Proliferative glomerulonephritis with monoclonal immunoglobulin deposits  
  - Immunotactoid glomerulonephritis  
  - C3 glomerulopathy  

- **Proximal tubules only:**  
  - Light chain proximal tubulopathy  

- **Gomeruluri plus vessels:**  
  - Cryoglobulinemic glomerulonephritis (type I and II cryoglobulins only)  
  - Atypical hemolytic uremic syndrome  
  - POEMS glomerular microangiopathy–cytokine-induced endothelial injury  
  - Distal tubules  
  - Cast nephropathy  

- **All renal compartments:**  
  - Monoclonal immunoglobulin deposition disease  
  - Light chain and or heavy chain  
  - AL amyloidosis

**MONOCLONAL GAMMOPATHY OF SKELETAL SIGNIFICANCE**  
There is more evidence emerging regarding an association between monoclonal gammopathy and skeletal changes. With POEMS it is common to see sclerotic bone lesions. In acquired Fanconi syndrome osteomalacia can develop because of hypophosphatemia. The International Myeloma Working Group recommends bisphosphonate use in all cases of monoclonal gammopathy with osteopenia or osteoporosis. The purported mechanism driving increased bone turnover is an increase in cytokines CCL3/MIP-1α (osteoclast-activating factor) and DKK1 (osteoblast-suppressive factor).  

**MONOCLONAL GAMMOPATHY OF HEMATOLOGIC SIGNIFICANCE**  
Even small plasma cell or B-cell clones can alter the bone marrow environment and immune response leading to different acquired hematologic disorders. These include acquired pure red cell aplasia, acquired Willebrand syndrome, (AVWS), cold agglutinin disease, and other rare, acquired bleeding disorders. These are complex conditions that warrant involvement of benign hematology experts. The mechanism of acquired pure red cell aplasia associated with monoclonal gammopathy is due to an antibody or effector T lymphocytes targeting an erythroid precursor, leading to arrest of erythropoiesis. Treatment is a combination of plasma cell–directed therapy and immunosuppression. Cyclosporine with or without steroids is the most used immunosuppression regimen. There is evidence for the use of eltrombopag plus immunosuppression in refractory cases.  

Anti-von Willebrand factor (VWF) antibodies lead to a reduction of VWF in monoclonal gammopathy-driven AVWS. These patients can have significant bleeding phenotypes. It is important to treat the underlying clonal disorder, provide replacement VWF with either DDAVP or recombinant VWF and reduce the anti-VWF antibodies with either IVIG or PLEX. An acquired factor X deficiency can be seen with amyloidosis. This occurs because both factor X and pentraxin-2 (PTX-2) bind to amyloid fibrils. PTX-2 binds to factor X to form a complex with scavenger receptor class A member 1, which protects factor X from macrophage clearance. When PTX-2 levels decrease there is increased macrophage clearance of factor X.  

Other reported acquired bleeding conditions seen with monoclonal gammopathy driven by auto-antibody formation include Bernard-Soulier with anti-GPIb/IX/V, Glanzmann thrombasthenia with anti-GPIb/IIa, and antifibrinoid antibodies leading to dysfibrinogenemia and hypofibrinogenemia. IgM Hyper-viscosity is also a known cause of bleeding diathesis.
ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE

In the treatment of newly diagnosed, transplant-ineligible multiple myeloma:

Reach for a treatment that significantly extended progression-free survival vs Rd alone in a clinical trial.¹³

IMPORTANT SAFETY INFORMATION DARZALEX® AND DARZALEX FASPRO®:

CONTRAINDICATIONS

DARZALEX® and DARZALEX FASPRO® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX FASPRO®), or any of the components of the formulations.

DARZALEX®: Infusion-Related Reactions

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, and pulmonary edema.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and anaphylaxis. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate medical management as needed.
Powerful efficacy to start the treatment journey\textsuperscript{1,4}
After a median ~30 months\textsuperscript{*} of follow-up, mPFS was not reached with DARZALEX\textsuperscript{®} + Rd vs 31.9 months with Rd alone.\textsuperscript{1,4}
• 70.6% of patients had not progressed with DRd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0–75.4; Rd: 95% CI, 49.5–61.3)\textsuperscript{1}

Demonstrated safety profile
(median treatment duration of 25.3 months)\textsuperscript{1}
• The most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthma
• Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)\textsuperscript{1}

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was PFS.\textsuperscript{1}

Efficacy results in long-term follow-up\textsuperscript{2,3}
At median ~5 years (56 months)\textsuperscript{j} of follow-up, mPFS was not reached with DRd vs 34.4 months with Rd alone.\textsuperscript{9}
• 53% of patients had not progressed after ~5 years of treatment with DRd vs 29% with Rd alone (DRd: 95% CI, 47–58; Rd: 95% CI, 23–35)\textsuperscript{9}

Safety results in long-term follow-up
(median treatment duration of 47.5 months)\textsuperscript{2}
At median ~5 years of follow-up\textsuperscript{2,4}:
• Most frequent TEAEs\textsuperscript{§} ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms
• Grade 3/4 infections were 41% for DRd vs 29% for Rd
• Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

These ~5-year analyses were not adjusted for multiplicity and are not included in the current Prescribing Information.

With an ~3 to 5 minute subcutaneous injection, DARZALEX\textsuperscript{®} can be administered substantially faster than intravenous daratumumab\textsuperscript{1,5,6}

See the latest data rolling out.
Visit FrontlineMomentum.com

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE
Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO® depending on dosing regimen and medical history to minimize the risk of delayed [defined as occurring the day after administration] systemic administration-related reactions.

Local Reactions
In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 3.5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX FASPRO®: Neutropenia and Thrombocytopenia
DARZALEX® and DARZALEX FASPRO® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX FASPRO® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX FASPRO®: Interference With Serological Testing
Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX® and DARZALEX FASPRO®.

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

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

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

DARZALEX®: ADVERSE REACTIONS
The most frequently reported adverse reactions (incidence ≥20%) were: upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are: neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

DARZALEX FASPRO®: ADVERSE REACTIONS
In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, pyrexia, cough, muscle spasms, back pain, vomiting, upper respiratory tract infection, peripheral sensory neuropathy, constipation, and pneumonia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX FASPRO® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS
DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:
- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:
  - In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
  - In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
  - In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
  - In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
  - In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
  - As monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX FASPRO® on adjacent pages.


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N Engl J Med
Adverse reactions described in Table 1 reflect exposure to DARZALEX in a median treatment duration of 23.6 months. Severe reactions have included, but not limited to, cardiovascular reactions, cerebrovascular reactions, central nervous system reactions, and hypersensitivity reactions. Common symptoms were hypotension, headache, chest pain, and dyspnea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension (see Adverse Reactions).

When DARZALEX was dosed in the setting of interrupted ASCST (CASSIOPEIA) for a median of 3.76 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCST. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCST were consistent in terms of symptoms and severity (Grade 3 or <1% vs 30% with subsequent infusions). In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over 3 days in 5.6 hours. In this study, the incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0 to 5.4 hours). The incidence of infusion-related reactions due to infusions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion (see Dosage and Administration (2.3) in Full Prescribing Information). Interrupt DARZALEX infusion for reactions of new severity or institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion (see Dosage and Administration (2.4) in Full Prescribing Information). To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions (see Dosage and Administration (2.3) in Full Prescribing Information). Patients with a history of a prior delayed infusion reaction may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with a history of chronic obstructive pulmonary disease (see Dosage and Administration (2.3) in Full Prescribing Information).

When DARZALEX is administered in the setting of interrupted ASCST (CASSIOPEIA) for a median of 3.76 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCST. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCST were consistent in terms of symptoms and severity (Grade 3 or <1% vs 30% with subsequent infusions). In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over 3 days in 5.6 hours. In this study, the incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0 to 5.4 hours). The incidence of infusion-related reactions due to infusions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.
Table 3: Adverse Reactions Reported in ≥ 10% of Patients and With At Least a 5% Greater Frequency in the DdR Arm in POLYCLL (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DdR (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Hair discoloration</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Transaminase increases</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4: Treatment-Emergent Laboratory Abnormalities in POLYCLL

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DdR (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Combs Test)

Daratumumab does not interfere with Coombs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference methodology includes treating reagent RBCs with diethyldithrotol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the kell blood group phenotype system is also used for compatibility testing, a supply K-negative units (either by using a DTT or cutting out identifying all antibodies using DTT-treated RBCs).

If an emergency transfusion is required, administer non-cross-matched ABO/Rh-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assays may result for patients with IgG kappa myeloma protein mimicking initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial responses, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout mice. There are no data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women due to the risk of fetal harm. Women of reproductive potential should be advised not to become pregnant while taking DARZALEX.

Fetal/Neonatal Adverse Reactions

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

Other Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout models also suggest the involvement of CD38 in regulating humoral immune responses (mice), fetalmaternal immune tolerance (mice), and early embryonic development (frogs).

Lactation

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

Females and Male Reproductive Potential

DARZALEX can cause fetal harm when administered to a pregnant woman.[See Use in Specific Populations].

Pregnancy Testing

When the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

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

Pediatric Use

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

Geriatric Use

Of the 2,630 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years or older. No overall differences in effectiveness were observed between these age groups and patients younger than 75 years. The incidence of adverse reactions in patients aged 75 years and older were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

REFERENCES


PATIENT COUNSELING INFORMATION

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

Infertility/Reproductive-related Information

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: tachy, runny or bloated nose, fever, chills, nausea, vomiting, throat irritation, cough, shortness of breath or difficulty breathing, itching [see Warnings and Precautions].

Neutropenia

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

Thrombocytopenia

Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding [see Warnings and Precautions].

Intensive Care/ICU Information

Advise patients to inform their healthcare providers, including personnel at blood transfusion centers that they are taking DARZALEX, in the event of a planned transfusion [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation

Advise patients to contact their healthcare providers if they have ever had or might have a hepatitis B infection [see Warnings and Precautions].

Embryo-Fetal Toxicity

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

Informed Consent

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX and for 3 months after the last dose of the last treatment cycle. Daratumumab is not available through a REMS program as required for other daratumumab products. One past-reported DARZALEX-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

Janssen Biotech, Inc.

Manufactured by:

Janssen Biotech, Inc.

Horsham, PA 19044

U.S. License Number 1864

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

**INDICATIONS AND USAGE**

DARZALEX FASPRO® is indicated for the treatment of adult patients with multiple myeloma:

- In combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity and Other Administration Reactions**

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO® (see Adverse Reactions).

**Systemic Reactions**

In a pooled safety population of 822 patients with multiple myeloma (N=439) or light chain (AL) amyloidosis (N=183) who received DARZALEX FASPRO® in combination with bortezomib, cyclophosphamide and dexamethasone (bortezomib-cyd) as a combination regimen, 8.8% of patients experienced a systemic administration-related reaction (Grade 3-5). Systemic administration-related reactions occurred in 4% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with all subsequent injections. The median time to onset was 3.2 hours (range: 0 minutes to 3.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 115 (88%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

**Injection-Site Reactions**

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.8%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5.5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.

**Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis**

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO® in combination with bortezomib-cyd. Twenty-nine patients (17%) of 175 patients who received DARZALEX FASPRO® developed serious or fatal cardiac adverse reactions during treatment. Thirteen of these patients (76%) died. Cardiac adverse reactions included atrial flutter, atrial fibrillation, and ventricular fibrillation.

**Neutropenia**

Neutropenia 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 results of other studies or to other daratumumab products or other hyaluronidase products may be misleading.

**Immunogenicity**

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

**ADVERSE REACTIONS**

**General disorders and administration site conditions**

- Fatigue
- Pruritus
- Edema peripheral

**Gastrointestinal disorders**

- Diarrhea

**Infections**

- Upper respiratory tract infection
- Pneumonia
- Bronchitis
- Urinary tract infection

**Musculoskeletal and connective tissue disorders**

- Muscle spasms
- Back pain

**Respiratory, thoracic and mediastinal disorders**

- Dyspnea
- Cough

**Nervous system disorders**

- Peripheral sensory neuropathy

**Psychiatric disorders**

- Insomnia

**Metabolism and nutrition disorders**

- Hyperglycemia

**Musculoskeletal and connective tissue disorders**

- Arthralgia, musculoskeletal chest pain

**Gastrointestinal disorders**

- Dizziness, headache, paresthesia

**Skin and subcutaneous tissue disorders**

- Rash, pruritus

**Gastrointestinal disorders**

- Abdominal pain

**Metabolism and nutrition disorders**

- Decreased appetite

**Cardiac disorders**

- Atrial fibrillation

**Vascular disorders**

- Hypertension, hypotension

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.
In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 756 patients developed treatment-emergent anti-daratumumab antibodies. In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, the estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Animal reproduction studies have not been conducted.

Females and Males of Reproductive Potential

In offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times the maximum human dose based on body surface area, no systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times the maximum human dose based on body surface area). Data from studies using CD38 knockout animal models also suggest the very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient’s serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen (CD38) knockout animal models (see Data). There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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

The combination of DARZALEX FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are all available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 9 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 300,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 99,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

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

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 99,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.
Efforts Are Under Way to Generate Real-World Evidence for Second-line Strategies in SCLC

by ASHLING WAHNER

INVESTIGATORS OF ONGOING STUDIES seek to gain a better understanding of how patients with small cell lung cancer (SCLC) are selected and treated with lurbinectedin (Zepzelca) in clinical practice, according to Nicolas Girard, MD, PhD. He added that these efforts also seek to confirm the agent’s efficacy in this population and to compare real-world data with those reported on clinical trials.1-3

“It will be interesting to analyze the patient characteristics and the outcomes with lurbinectedin, and also to understand the treatment sequences in those patients,” said Girard, who is a professor of respiratory medicine at Versailles Saint Quentin University and a professor and head of the Curie-Montsouris Thorax Institute at Institut Curie in France. “This information is not available from the clinical trials that only focus on 1 specific line of therapy.”

LURBICLIN (NCT05285033) is a real-world study that is ongoing in France in which investigators are evaluating data from patients with SCLC who received lurbinectedin as part of the French Early Access Program.1 The key objectives of this study are to understand patient characteristics, analyze outcomes with the agent, and investigate the treatment sequences they received to best leverage the agent in this population. A similar study, CLINATEZO (NCT04920981), is evaluating the outcomes of patients treated with atezolizumab (TecEntriq).2

“It’s important to generate real-world evidence in patients with SCLC, because we have clinical trials, but we also have many real-world patients who are receiving these agents,” Girard said. In an interview with OncologyLive®, Girard highlighted current treatment practices, the value real-world data would provide for future investigative approaches in SCLC, and the observed benefit of administering available treatment options such as lurbinectedin as early as possible.

Q What limitations may physicians experience when treating SCLC?

Most patients who receive a diagnosis of SCLC [have] metastatic disease. In such situations, their treatment is chemotherapy based, [using] agents such as [platinum and] etoposide. [Historically, we have also] combined chemotherapy with immune checkpoint inhibitors, such as the PD-L1 inhibitors atezolizumab or durvalumab [Imfinzi] for 4 cycles, [with subsequent] maintenance therapy until toxicity or disease progression. [With this approach, we have seen] some long-term efficacy.

[Prior data have shown] progression-free survival and overall survival [OS] benefit with these combinations over chemotherapy alone. [For example,] approximately 17% of patients [were] alive at 3 years with durvalumab [in the phase 3 CASPIAN trial (NCT03043872)].3 This is obviously limited, but in SCLC, which is an aggressive disease, it’s interesting to see that we can increase the survival of patients through [the use of] such combinations.

The main issue is what to do in the second-line setting, as many patients develop disease progression after first-line treatment. In such situations, we are differentiating between 2 groups of patients. The first group is patients who are refractory and who have cisplatin-resistant tumors and disease progression early, less than 3 months after the initiation of first-line therapy. We consider patients progressing after 3 months to be sensitive to platinum.

In the [platinum]-sensitive patients, we can rechallenge with chemotherapy, although we do not know how to do that in combination with immunotherapy, and some patients may discontinue immunotherapy and start chemotherapy alone again. My practice is to continue immunotherapy and reintroduce chemotherapy for these patients.

Still, at some point, patients may develop disease progression. In those patients, the standard of care has been topotecan, with limited efficacy. Response rates have been less than 10% in the historical studies, so it’s better than placebo. However, its efficacy is limited, and this is because of the aggressiveness of the disease.

We need additional options. Lurbinectedin, an original compound, has broad biological efficacy. We have seen data with lurbinectedin as a single agent with high response rates, over 35%.3 [There has been a] significant response rate in the clinic for patients with refractory disease. We have also seen data from the randomized [phase 3 ATLANTIS study (NCT02566993)] investigating lurbinectedin plus the anthracycline doxorubicin vs topotecan, although this was a negative study.4

In France, we have access to lurbinectedin in the second-line setting through an expanded access program. [In partnership with] French Intergroup, we are conducting 2 [real-world] studies.5 One study is a real-world evidence study for patients who received the combination of chemotherapy plus atezolizumab in the first-line setting.5 This study is ongoing, and we will hopefully get the results soon. Another study is looking at real-world data for patients with SCLC who received lurbinectedin.6

It’s important to understand the strategy, the treatment sequencing, and how patients are selected and treated in a real-world setting. [We are also aiming] to confirm the efficacy of these agents, compare [those data] with clinical trials, and understand clinical practices. We are waiting for the results of those real-world evidence cohorts. There will hopefully be an opportunity to present those data at future meetings.

Q What has been your experience with using lurbinectedin, and in which patients will you typically consider this therapy?

Lurbinectedin is a new line of treatment for patients. Besides first-line treatment with chemotherapy plus immunotherapy and topotecan, we need additional options. Overall, in lung cancer and other solid cancers, offering more lines [of therapy] to a patient, with an early assessment to decide quickly whether they’re working, is a way to improve OS.

Lurbinectedin is not replacing the other options that we have, but it adds a new line of treatment for patients. Close monitoring of the patients is a way to assess whether [the agent is] working. Then, we can continue or switch to another line of treatment.

In my practice, I use lurbinectedin as early as possible, and in most of my patients, as second-line treatment. Again, SCLC is an aggressive disease. The [longer] you wait, the higher the risk that the patient has a poorer general condition and more tumor burden, [and it is] more difficult to get disease control.

Q What data are being collected on patients who are receiving lurbinectedin through the France Compassionate Care Act (L’Autorisation d’Accès Compassionnel)?

This will be the topic of the real-world evidence study called LURBICLIN. It’s an expanded access program for patients previously treated for SCLC. It will be interesting to see which lines of treatment [these patients received], as well as their general condition, [as follows]:

• Are these patients sensitive or refractory?

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There are new options coming in SCLC, including many developments regarding the targeting of DLL3, which is one of the antigens expressed on SCLC tumor cells. We have seen data with targeted agents against DLL3, and we also have new compounds such as immunotherapy with antibodies that target DLL3 on one side and attract the T cells near the cancer cells. These treatments are currently in phase 2 studies, and they may transform the outcomes of patients with refractory disease.

We also have a better understanding of the biology of SCLC, with 4 groups of patients defined by their RNA sequencing. This is another way to separate groups of patients based on their biology and maybe implement different strategies. It’s important to try to correlate these molecular clusters with [treatment] efficacy and individual selection of patients from one strategy or another. ■

REFERENCES

LEARNING OBJECTIVES
• Explain diagnostic criteria, prognostic evaluation, best practices, and the use of biomarkers guiding decision-making in FL
• Synthesize safety data with current and emerging therapeutics in the context of sequencing in FL
• Compare guideline recommendations in consideration of practice-changing advances in the management of FL

What are some of the anticipated therapeutic alternatives for this patient population?

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Houston, TX

Acknowledgment of Support
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INDICATION

BESREMi is indicated for the treatment of adults with polycythemia vera.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DISORDERS

Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy.

CONTRAINDICATIONS

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
- History or presence of active serious or untreated autoimmune disease
- Immunosuppressed transplant recipients

WARNINGS AND PRECAUTIONS

Patients exhibiting the following events should be closely monitored and may require dose reduction or discontinuation of therapy:

- Depression and Suicide: Monitor closely for symptoms and need for treatment.
- Endocrine Toxicity: Discontinue if endocrine disorders occur that cannot be medically managed.
- Cardiovascular Toxicity: Avoid use in patients with severe, acute or unstable cardiovascular disease. Monitor patients with history of cardiovascular disorders more frequently.
- Decreased Peripheral Blood Counts: Perform blood counts at baseline, every 2 weeks during titration, and at least every 3-6 months during maintenance treatment.
- Hypersensitivity Reactions: Stop treatment and immediately manage reaction.
- Pancreatitis: Consider discontinuation if confirmed pancreatitis.
- Colitis: Discontinue if signs or symptoms of colitis.
- Pulmonary Toxicity: Discontinue if pulmonary infiltrates or pulmonary function impairment.
- Ophthalmologic Toxicity: Advise patients to have eye examinations before and during treatment. Evaluate eye symptoms promptly and discontinue if new or worsening eye disorders.
- Hyperlipidemia: Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated.

ADVERSE REACTIONS

The most common adverse reactions reported in > 40% of patients in the PEGINVERA study (n=51) were influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis, and musculoskeletal pain. In the pooled safety population (n=178), the most common adverse reactions greater than 10%, were liver enzyme elevations (20%), leukopenia (20%), thrombocytopenia (19%), arthralgia (13%), fatigue (12%), myalgia (11%), and influenza-like illness (11%).

DRUG INTERACTIONS

Patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs. Avoid use with myelosuppressive agents and monitor patients receiving the combination for effects of excessive myelosuppression. Avoid use with narcotics, hypnotics or sedatives and monitor patients receiving the combination for effects of excessive CNS toxicity.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.
- Lactation: Advise women not to breastfeed during treatment and for 8 weeks after the final dose.
- Avoid use in patients with eGFR <30 mL/min.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent pages.

Reference: 1. Besremi. Package insert. PharmaEssentia Corporation; 2021. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.3.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed September 22, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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BESREMi is contraindicated in patients with:

1. INDICATIONS AND USAGE

- Patients with active serious or untreated autoimmune disease
- History or presence of active serious or untreated autoimmune disease
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
- History or presence of active serious or untreated autoimmune disease
- Immunosuppressed transplant recipients

5 WARNINGS AND PRECAUTIONS

5.1 Depression and Suicide

- Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness. Serious neuropsychiatric reactions have been observed in 3% of patients treated with BESREMi during the clinical development program. Among the 178 patients in the clinical development program of BESREMi, 17 cases of depression, depressive symptoms, depressed mood, and litheness occurred. Of these seventeen cases, 3.4% of the patients recovered with temporary drug interruption and 2.8% stopped BESREMi treatment.

- Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products. BESREMi is contraindicated in patients with a history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt [see Contraindications (4)].

5.2 Endocrine Toxicity

- Endocrine toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include worsening hypothyroidism and hyperthyroidism. Autoimmune thyroiditis and hyperglycemia, including new onset type 1 diabetes, have been reported in patients receiving interferon alfa-2b. Excesses or deficits of TSH, T4, and T3 have been observed in patients with BESREMi. Patients should have good oral hygiene and regular dental examinations.

5.3 Cardiovascular Toxicity

- Cardiovascular toxicity has occurred in patients receiving interferon alfa products, including BESREMi. Toxicities may include cardiomyopathy, myocardial infarction, aortic fibration and coronary artery ischemia [see Adverse Reactions (6.1)]. Patients with a history of cardiovascular disorders should be closely monitored for significant cardiovascular toxicity during BESREMi therapy. Avoid use of BESREMi in patients with severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (> NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction.

5.4 Decreased Peripheral Blood Counts

- Decreased peripheral blood counts have occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include thrombocytopenia (increasing the risk of bleeding), anemia, and leukopenia (increase in risk of infection) [see Contraindications (4)]. Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchospasm, anaphylaxis). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.

5.5 Hypersensitivity Reactions

- Hypersensitivity reactions have occurred in patients receiving interferon alfa products, including BESREMi. BESREMi is contraindicated in patients with hypersensitivity reactions to interferon products or any of the inactive ingredients in BESREMi [see Contraindications (4)]. Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchospasm, anaphylaxis). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.

5.6 Pancreatitis

- Pancreatitis has occurred in patients receiving interferon alfa products, including BESREMi. Pancreatitis was reported in 2.2% of patients receiving BESREMi. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever. Patients may experience elevated lipase, amylase, white blood cell count, or altered renal/hepatic function. Interrupt BESREMi treatment in patients with possible pancreatitis and evaluate promptly. Consider discontinuation of BESREMi in patients with confirmed pancreatitis.

5.7 Colitis

- Fecal and serious ulcerative or hemorrhagic/ischecmic colitis has occurred in patients receiving interferon alfa products, some cases occurring as early as 12 weeks after start of treatment. Symptoms may include abdominal pain, bloody diarrhea, and fever. Discontinue BESREMi in patients who develop these signs or symptoms. Colitis may resolve in 1 to 3 weeks of stopping treatment.

5.8 Pulmonary Toxicity

- Pulmonary toxicity has occurred in patients receiving interferon alfa products, including BESREMi. Pulmonary toxicity may manifest as diffuse interstitial pulmonary infiltrates with or without pleural effusion, bronchiolitis obliterans, pulmonary hypertension, and sarcoidosis. Some events have resulted in respiratory failure or death. Discontinue BESREMi in patients who develop pulmonary infiltrates or pulmonary function impairment.

5.9 Ophthalmologic Toxicity

- Ophthalmologic toxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include severe eye disorders such as retinopathy, retinal hemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness. During BESREMi therapy, 23% of patients were identified with an eye disorder. Eye disorders >5% included cataract (6%) and dry eye (5%). Advise patients to have eye examinations before and during BESREMi therapy. Typically in those patients with a retinopathy-associated disease such as diabetes mellitus or hypertension. Evaluate eye symptoms promptly. Discontinue BESREMi in patients who develop new or worsening eye disorders.

5.10 Hyperlipidemia

- Hyperlipidemia has occurred in patients treated with interferon alfa products, including BESREMi. Hyperlipidemia, hypertriglycerideremia, or dyslipidemia occurred in 3% of patients receiving BESREMi. Elevated triglycerides may result in pancreatitis [see Warnings and Precautions (5.6)]. Monitor serum triglycerides during BESREMi treatment and manage when elevated. Consider discontinuation of BESREMi in patients with persistently, markedly elevated triglycerides.

5.11 Hepatotoxicity

- Hepatotoxicity has occurred in patients receiving interferon alfa products, including BESREMi. These toxicities may include increases in serum ALT, AST, GGT and bilirubin. BESREMi is contraindicated in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment [see Contraindications (4)].

- Increases in serum ALT ≥3 times the upper limit of normal (ULN), AST ≥3 times the ULN, GGT ≥3 times the ULN, and bilirubin >2 times the ULN have been observed in patients treated with BESREMi. In the clinical development program of BESREMi, transaminase elevations >3 x ULN were observed in 18% of patients who received BESREMi treatment. In the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the Warnings and Precautions section reflects exposure to BESREMi as of the last treatment of patients with leukaemia vera. The mean dose of BESREMi was 334 mcg SD ± 121 during the treatment period. In this pooled safety population, the most common adverse reactions greater than or equal to 10% were: nausea (49%), fatigue (48%), anemia (38%), leukopenia (36%), diarrhea (35%), vomiting (34%), headache (32%), infections (31%), upper respiratory tract infections (29%), and pyrexia (28%). The most common serious adverse reaction was death (4%).
Adverse reactions requiring permanent discontinuation in >2% of patients who received BESREMi included depression (8%), atrial fibrillation (4%), fatigue (4%), and general physical health deterioration (4%). In the PEGINVERA study, patients were not pre-screened for depression or anxiety disorders.

The most common adverse reactions reported in ≥10% of patients in the PEGINVERA study are listed in Table 2.

Table 2 Adverse Reactions in > 10% of Subjects with Polycythemia Vera in the PEGINVERA Study Over 7.5 Years.

<table>
<thead>
<tr>
<th>Adverse Reactions*</th>
<th>BESREMi N=51</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Influenza-like illness</td>
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<tr>
<td>Arthralgia</td>
<td>47</td>
<td></td>
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<tr>
<td>Fatigue</td>
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<td></td>
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<tr>
<td>Pruritus</td>
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<tr>
<td>Nasopharyngitis</td>
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<td></td>
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<tr>
<td>Musculoskeletal pain</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Upper respiratory tract infection</td>
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<td></td>
</tr>
<tr>
<td>Local administration site reactions</td>
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<td></td>
</tr>
<tr>
<td>Dizziness</td>
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<td></td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Depression</td>
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<td>Sleep disorder</td>
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<td>Leukopenia</td>
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<tr>
<td>Decreased appetite</td>
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<tr>
<td>Edema</td>
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<tr>
<td>Hypertension</td>
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<td>Muscle spams</td>
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<tr>
<td>Neutropenia</td>
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<td>Rash</td>
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<td>Transaminase elevations</td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Thrombocytopenia</td>
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<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>12</td>
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</tr>
</tbody>
</table>

Adverse Reactions defined as all treatment emergent adverse events.

*Includes pyrexia, chills, and influenza-like illness.

†Includes arthralgia, malaise, and fatigue.

‡Includes pharyngitis and nasopharyngitis.

§Includes musculoskeletal pain, back pain, pain in extremity, bone pain, flank pain, and spinal pain.

‖Includes headache, migraine, and head pain.

¶Includes night sweats and hyperhidrosis.

‖Includes upper respiratory tract infection, mumps, bronchitis, and respiratory tract infection.

‡‡Includes abdominal pain upper, abdominal pain lower, and abdominal pain.

‡‡‡Includes insomnia, sleep disorder, and abnormal dreams.

‡‡‡‡Includes peripheral edema and generalized edema.

‡‡‡‡‡Includes hypertension and hypertensive crisis.

‡‡‡‡‡‡Includes rash, maculopapular rash, and pruritic rash.

‡‡‡‡‡‡‡Includes transaminase increase, hepatic enzyme increase, GGT increase, AST increase, and ALT increase.

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

Cardiovascular System: Atrial fibrillation

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 interferon alfa-2b products may be misleading.

The incidence of binding antibodies to ropeminterferon alfa-2b-njft was 1.4% (2/146) and they were observed as early as 8 weeks post-dosing. Among the patients who tested positive for binding antibodies, none developed neutralizing antibodies.

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450

Certain proinflammatory cytokines, including interferons, can suppress CYP450 enzymes resulting in increased exposures of some CYP substrates [see Clinical Pharmacology (12.3) in the full prescribing information]. Therefore, patients on BESREMi who are receiving concomitant drugs that are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs.
Adagrasib With Cetuximab Moves Into Phase 3 for KRAS G12C-Mutated CRC

by MEGAN HOLLASCH

Targeted Treatment with Adagrasib (MRTX849) monotherapy and combination therapy with cetuximab (Erbitux) has shown promise when treating patients with KRAS G12C-mutated colorectal cancer (CRC) according to Rona Yaeger, MD.

Investigators of the phase 3 KRYSAL-10 (NCT04793958) trial seek to build on early efficacy observed with the dual blockade of KRAS G12C and EGFR in patients who have disease progression following standard first-line therapy. Safety data showed that the combination is tolerable with the most frequent treatment-related adverse events including nausea (63%), diarrhea (56%), vomiting (53%), dermatitis acriform (47%), fatigue (47%), and dry skin (41%).

“The rationale for the combination is that in CRC we have a high level of basal RTK activation, particularly EGFR, therefore treatment with adagrasib or any KRAS G12C inhibitor is likely limited by the activation of these receptors. The idea is to administer cetuximab you may inhibit with adagrasib KRAS G12C signaling and then inhibit the reactivation of EGFR and so any rebound in signaling,” Yaeger said.

In an interview with OncologyLive®, Yaeger, an associate attending physician at Memorial Sloan Kettering Cancer Center in New York, New York, discussed the unmet needs for patients with KRAS G12C mutations and the promising combination therapy of adagrasib and cetuximab.

What is the mechanism of action of adagrasib?

Adagrasib is a selective KRAS G12C inhibitor. KRAS is like a switch in that when it is bound to GDP it is active and when it is bound to GDP is inactive. Adagrasib and the other KRAS G12C inhibitors that are now moving through clinical trials or being used in the clinic are designed to take advantage of the cytosine to bind to the G12C. Adagrasib binds covalently and traps KRAS when it is in the inactive state and by doing that it prevents its activation and the reactivation of KRAS.

These drugs take advantage of the natural cycling of KRAS. There is some natural cycling from the active GTP bound state to the GDP bound state and when KRAS G12C is in the GDP bound state if drug is around it, it can trap it in that state. Adagrasib has a longer half-life of approximately 23 hours; it is given twice daily with the idea of providing continuous inhibition of KRAS G12C and to prevent the formation of new, active KRAS molecules. It has central nervous system (CNS) penetration and has been shown to have some activity in tumors with CNS spread such as lung cancer, where we see that more commonly.

What has been observed with adagrasib in combination with cetuximab in this patient population in KRYSAL-1?

KRYSAL-1 (NCT03785249) is a phase 1/2 study that has looked at adagrasib alone and in multiple combinations. More mature data were recently reported at the European Society for Medical Oncology [Annual Congress 2022] for the monotherapy cohort as well as the cohort [examining adagrasib in] combination with cetuximab in CRC. In the [phase 2] monotherapy cohort they treated 44 patients and 43 were valuable for a response with an objective response rate of 19% and median PFS [progression-free survival] of 5.6 months.

The combination was tested in a phase 1b cohort [where] 32 patients were treated; 28 of them were evaluable for response with a response rate of 46%, 100% disease control rate, and a median PFS of 6.9 months. The activity of the combination is very encouraging and that sets the stage for the potential to develop this further.

If you look at targeted therapy in general and in CRC, I think it stacks quite well [with the progress we’ve seen]. We’ve been through this recently for BRAFT600E-mutated CRCs where we see that adding an EGFR antibody improves the activity [of targeted agents] rather than just inhibiting the activated oncogene. When we look at the activity that we’re seeing with KRAS G12C inhibitors, the combination of these drugs with EGFR inhibitors is very encouraging in the context of what we see with targeted therapies for CRC.

What is important to know about patients with CRC who progress on a first-line chemotherapy regimen?

Patients with metastatic CRC are treated with a combination of chemotherapy and if appropriate targeted therapies. Patients who have a KRAS mutation are precluded from receiving targeted therapies right now. In terms of subsequent lines of treatment after progression on chemotherapy, they have fewer options and so the patients with KRAS G12C mutations are in need of another treatment.

What is the biggest unmet need in this patient population?

KRAS G12C mutations occur in approximately 3% to 4% of CRC [cases and] up to approximately 50% of CRCs have an activating mutation in the RAS genes, either KRAS or NRAS. The frequency is higher for right-sided colon tumors and is a lower on the left side, but overall, it’s nearly 50% and a small portion of those are the KRAS G12C mutations. There’s been a lot of data over the years looking at the prognostic significance of having mutations in the RAS genes and the overall thought is that it’s a modest poor prognostic factor.

Now there’s more of an interest on KRAS G12C because of potential to target it with new drugs. There have been studies that have looked at whether the presence of this mutation affects prognosis. Investigators have looked retrospectively at patients with metastatic disease and those who have a tumor KRAS G12C mutation compared with other KRAS mutations appear to have shorter overall survival [OS] and shorter [time to] progression. In that sense, there’s clearly a need for new therapies and there’s a need for ideally something matched, which is what we’re trying to develop.

These patients can get standard chemotherapy, but they have no targeted treatment and, in some sense, they’re missing a potential for therapy. Now that there are new drugs which are selective to develop this further.

If you look at targeted therapy in general and in CRC, I think it stacks quite well [with the progress we’ve seen]. We’ve been through this recently for BRAFT600E-mutated CRCs where we see that adding an EGFR antibody improves the activity [of targeted agents] rather than just inhibiting the activated oncogene. When we look at the activity that we’re seeing with KRAS G12C inhibitors, the combination of these drugs with EGFR inhibitors is very encouraging in the context of what we see with targeted therapies for CRC.

Can you expand on the design of the KRYSAL-10 study and the overall trial objectives?

KRYSAL-10 is a [phase 3] study looking...
Adagrasib/Cetuximab Is Under Exploration in KRAS G12C+ CRC

by DYLANN COHN-EMERY

THE COMBINATION OF ADAGRASIB and cetuximab (Erbitux) is being investigated in patients with previously treated, advanced, KRAS G12C–mutant colorectal cancer (CRC) in the international, phase 3 KRISTAL-10 study (NCT04793958).

Previous findings have shown clinical activity with KRAS G12C inhibitors for pretreated patients with KRAS G12C-mutated CRC. Adagrasib, a covalent inhibitor of this mutation, irreversibly and selectively binds KRAS G12C and locks it in an inactive, GDP-bound state. This drug was made to be highly selective for the mutant KRAS G12C protein versus wild-type KRAS and have favorable pharmacokinetic (PK) properties, such as extensive tissue distribution, oral bioavailability, and a long half-life.

Previously, the phase 1/2 KRISTAL-1 trial (NCT03785249) of adagrasib monotherapy showed preliminary antitumor activity and a tolerable safety profile in multiple tumor types all with KRAS G12C mutation. These data included patients with CRC who were heavily pretreated. Patients were treated with 600 mg of adagrasib twice daily.

There were 3 patients out of 18 (17%) with pretreated CRC in KRISTAL-1 that had a confirmed objective response rate (ORR). Fourteen patients (78%) achieved stable disease and the disease control rate was 94%.

A safety analysis of 110 patients from this early phase trial demonstrated low incidence of grade 3 or 4 treatment-related adverse events (TRAEs) with adagrasib, which was well tolerated. Nausea, diarrhea, vomiting, and fatigue were the most common TRAEs.

Investigations of patient-derived xenograft models using adagrasib plus cetuximab, an EGFR inhibitor, resulted in deep, durable regression. These human xenograft mouse models suggested synergistic activity of adagrasib and cetuximab because it led to increased antitumor activity and more durable tumor regression compared with either drug as a single agent. The investigators wrote that this combination may enhance inhibition of KRAS-dependent signaling or overcome adaptive feedback and improve clinical outcomes.

In KRISTAL-10, about 420 patients with previously treated advanced CRC and KRAS G12C mutations will be randomized 1:1 to oral adagrasib at 600 mg twice daily plus intravenous cetuximab at 500 mg/m² every 2 weeks versus chemotherapy with either FOLFIRI (folinic acid, fluorouracil, irinotecan) or modified FOLFOX6 (folinic acid, fluorouracil, oxaliplatin). Patients will be stratified by region, United States and Canada versus other countries, and time to disease progression after initiation of first-line treatment, less than 6 months versus 6 months or more.

The primary end points are progression-free survival and overall survival. Secondary end points include safety, ORR per RECIST 1.1 criteria, duration of response, 1-year survival rate, plasma PK parameters of adagrasib, and patient-reported outcomes. There are 2 exploratory end points of gene alterations in tumor tissue and circulating tumor DNA and progression-free survival 2.

Patients had to have available primary or metastatic tumor specimen, either archival or newly obtained, for central laboratory testing of KRAS G12C mutation status. They also had to receive first-line treatment with a fluoropyrimidine-based chemotherapy regimen containing either oxaliplatin or irinotecan in the advanced disease setting and radiographically documented disease progression on or after treatment; maintenance therapy was not considered a separate regimen in the metastatic setting and patients who experienced disease relapse in the 6 months following the completion of adjuvant treatment are eligible for the trial. An ECOG performance status of 0 or 1, adequate organ function, and presence of evaluable or measurable disease per RECIST 1.1 were also required.

Those who had received a KRAS G12C–targeted agent, anti-EGFR antibody of cetuximab or panitumumab, or both an oxaliplatin- and irinotecan-based regimen in the advanced disease setting and/or later treatment setting for CRC are not eligible for KRISTAL-10. Patients with active brain metastases were also not eligible. However, those with adequately treated brain metastases, and are neurologically stable, were allowed on the trial.

Every 8 weeks, tumor assessments will be performed starting from randomization until objective disease progression is documented by the investigators or a subsequent anticancer therapy has been initiated. The trial is being carried out across about 300 global sites in 34 countries. Patients are currently being enrolled on KRISTAL-10.

REFERENCE


What main message about KRAS G12C mutations in CRC would you like to impart to colleagues?

This is really exciting; the idea of KRAS being targetable is a whole paradigm shift. It’s a huge deal and in the data we have now, we can see that many patients can benefit from these drugs. Hopefully they will be developed further, and we’ll see [more positive] results in the KRISTAL-10 study.

What I would like clinicians to take from this is to be alert, to look at the sequencing results for patients, and if patients do have a KRAS G12C mutation to consider them for clinical trials and be able to connect them with clinical trials so they have the potential to receive targeted therapies.
Practices Should Refocus Efforts on Helping Patients Address Financial Toxicities

by ONCLIVE® STAFF

OPTIMIZING CLINICAL PATHWAYS to address financial toxicities faced by patients with cancer requires a complex, multifaceted approach. However, even small in-practice changes may ease the financial burdens and improve outcomes.

Validated measures to describe, quantify, and qualify have proven difficult to establish across all levels of care. At an institutional level, assessments from the National Cancer Institute’s Community Oncology Research Program (NCORP) and the National Comprehensive Cancer Network (NCCN) have demonstrated that despite nearly three-fourths of practices having financial screening methodologies in place, effective management protocols are not established. Using a benchmark of 75% of NCCN centers (n = 17) having a financial screening process, reports in the community setting were comparable. Among 221 practices, 72% had a financial screening process, with 50% reporting a cancer-specific financial navigator among their staff.

Despite the high rates of screening, the most common method for financial screening was identified as in-take forms (68%), which investigators noted may only highlight insurance-related burdens. Financial burden of care can influence several aspects of patient quality of life, the most prevalent 3 being material consequences (ie, out-of-pocket expenses, debt, decreased income), psychological effects, and deleterious coping mechanisms (ie, delaying care, nonadherence). Results of a recent survey of individuals with cancer who received treatment at ambulatory infusion centers (Mayo Clinic in Phoenix, Arizona; and Mississippi Medical Center in Jackson) showed that financial hardship has been demonstrated most predominantly in patient-reported findings. Using several measures, the range of financial hardship was reported in 48% to 68% of participants. The authors found that financial literacy may be integral in reducing adverse outcomes and that intervention programs are needed to increase literacy and aid those without it.

"Patient-reported financial hardship from cancer treatment is a growing challenge," Khera et al wrote in the study. "The field of financial hardship is now shifting toward interventions. Understanding the association between health insurance literacy and financial hardship and how financial literacy may change this association is important because these factors are potentially modifiable." One of the crucial tools used to determine financial literacy is the FACT-FUN (Functional Assessment of Chronic Illness Therapy—Functional). This uses a scored assessment (range, 0-44) with lower scores indicative of higher burden.

Topics in the FACT-FUN include the following:

- I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment.
- My out-of-pocket medical expenses are more than I thought they would be.
- I worry about the financial problems I will have in the future as a result of my illness or treatment.
- I feel I have no choice about the amount of money I spend on care.
- My cancer or treatment has reduced my satisfaction with my present financial situation.

Additional tools include the National Health Interview Survey and the Health Insurance Literacy Measure, which captured insights on an individual’s ability to evaluate health plan information and select the best plan to cover their health circumstances.

METHODS OF TACKLING FINANCIAL TOXICITIES

A theme in each financial hardship study is that awareness is a key first step in any process. In the analysis of the NCORP and NCCN studies, ongoing assessments were signified as a vital component for continued awareness. For example, despite 75% of NCCN centers reporting financial assessments, only 56% reported repeating that assessment. Results from an additional study of NCORP sites showed that patients with metastatic colorectal cancer experienced a "major financial hardship" defined as major debt, loans, refinancing, or a loss in income of at least 20% of cases within in 3 months of starting treatment.

The NCORP investigators proposed adapting the 5As approach, which has had success in smoking cessation, to tackling financial toxicity in the community setting: ask, advise, assess, assist, and arrange. Major components of effectiveness rest in the assess and assist steps. Financial navigators, nurses, and clinicians can assess whether altering treatments alleviates the financial burden and reduces nonadherence issues. They then can assist in updating and monitoring outcomes to ensure continued effective care.

Takeaways from several studies presented during the 2022 American Society of Clinical Oncology (ASCO) Quality Care Symposium showed efforts are underway to assess integrative approaches to tackling financial hardships in practice.

Investigators at The Ohio State University in Columbus implemented a study to identify patients with breast, lung, or hematologic malignancies who stated they had financial hardships and to optimize pathways to connect them with appropriate services. At 3 clinics—surgical breast oncology, hematologic, and thoracic medical oncology—no financial screening systems were in place. The screening asked, “How hard is it for you to pay for the very basics such as food, housing, medical care, and heating?” Responses ranged from not hard at all to very hard, with the option to not respond. Among 4732 participants, 10% of respondents noted financial hardships by choosing "somewhat hard," "hard," or "very hard.”

The investigators proposed a workflow that would cycle patients to the appropriate services; however, several hurdles were identified in the areas of accountability for components of the process. For example, if a patient was identified as having financial hardships, who should put the referral in (eg, nurse, advanced practice provider, physician), how should the referral be documented (eg, phone call, email, consult), and who was responsible for follow-up on the referral?

A second workflow tackling these questions demonstrated a more complex, but staggered patient referral system that identified stakeholders. Following the intake nurse asking...
a screening question, patients were categorized as urgent or not if they identified as having financial hardships. From there, individuals categorized as in urgent need were assigned a social worker, whereas those who were not categorized as in urgent need were placed on a weekly list and assigned to a patient navigator who would either address the need or refer the individual to a social worker or financial counselor.7

These workflows rely on practices having appropriate staff in place to accommodate the steps of this process. Other areas of need include optimizing electronic health records to record and provide these data to the appropriate parties.

Another study from the O’Neal Comprehensive Cancer Center at University of Alabama at Birmingham came to the same conclusion when examining the referral process in place for patients treated at the gynecologic oncology clinic. In addition to intake questions about ability to afford medication and distress screening conducted by medical assistants and lay navigators, respectively, an additional financial hardship screening using the FACIT-COST was conducted during cycle.1,6

Referrals to social workers, lay navigators, financial counselors, or other appropriate services were made if difficulties were identified. Overall, among 115 patients who had at least 1 financial need, 38 were assisted by a lay navigator and 98 had referrals placed, most of which were with social workers (86.7%). In addition to assistance, the investigators reported qualitative data from 43 patient interviews with most participants reporting that they “felt positively” about the financial questions and considered them relevant to their care.8

Universal financial screening is feasible and patients are open to participating, the authors noted; however, a dedicated financial hardship tool is needed. Fully integrating the assessment into workflow to ensure continuity of support for financial burdens remains an unmet need.9

Beyond the scope of major cancer centers, practice size, resources, and locations in the community setting have varying factors at play that may set them up at an increase for handling financial hardships.2

For example, in a recent study, investigators sought to identify gaps in care pathways based on responses from stakeholders in 10 cancer care sites (5 rural and 5 nonrural practices).3

Across the sites, the investigators compiled 6 elements that were identified in the financial assistance processes: distress screening, referrals, resource connection points, pharmaceutical resources, insurance, and community. Identified opportunities included more systemic, proactive, and routine distress screening over time; dedicated staff in financial navigation; and the development of infrastructure to track external resource availability. These internal adjustments could take place across practices; however, investigators also noted that system-level reforms also are needed to influence change, including insurance expansion and pharmaceutical cost regulations.9

As with the other studies, facilitators were identified as the key stakeholders in implementing continued change. These must be staff members with institutional knowledge and relationships with external resources who are able to assess, process, and enact solutions for patients facing financial hardships, Biddell et al noted.9

“Financial hardship is most common among populations who have historically experienced challenges with accessing cancer care, including [individuals] who have low incomes, are uninsured/underinsured, or are racial/ethnic minorities, but financial hardship is becoming commonplace across the economic spectrum,” Yabroff et al wrote.9 “Advances in expensive cancer treatments threaten to widen disparities in access to care based on the ability to pay. Thus, understanding how institutions and providers identify patients experiencing financial hardship and the strategies used to mitigate hardship and address patient needs is increasingly important.”

REFERENCES


Now recruiting KRYSYAL-10 (NCT04793958) the randomized Phase 3 study of investigational *adagrasib* in combination with cetuximab vs chemotherapy in patients with previously treated advanced CRC with KRAS\(^{G12C}\) mutation

**Study Synopsis:**
KRYSYAL-10 is a global, open-label, randomized Phase 3 study, comparing the efficacy and safety of *adagrasib* (MRTX849) administered in combination with cetuximab versus chemotherapy in the second-line treatment setting in patients with KRAS\(^{G12C}\) mutation (NCT04793958)

**What is adagrasib?**
The investigational study drug adagrasib is an inhibitor of the KRAS\(^{G12C}\) mutant protein. The KRAS\(^{G12C}\) mutation is found in approximately 3-4% of colorectal cancers. *Adagrasib* is delivered in the form of an oral pill taken twice daily (12 hours apart) on a continuous basis.

**Key eligibility criteria:**
- Histologically confirmed diagnosis of colorectal carcinoma with KRAS\(^{G12C}\) mutation in tumor tissue
- Progression on first-line treatment in advanced CRC with a fluoropyrimidine-based oxaliplatin or irinotecan regimen
- No prior treatment with a KRAS\(^{G12C}\) inhibitor or anti-EGFR antibody

**Primary endpoints:**
- Overall survival (OS)
- Progression free survival (PFS)

**Secondary efficacy endpoints:**
- Objective response rate (ORR)
- Duration of response (DOR)
- Safety and tolerability
- Patient reported outcomes (PROs)
- Quality of life assessment

More information can be found by scanning the QR code below.
**LUNG, HEAD AND NECK CANCERS**

Sotorasib versus docetaxel for previously treated non-small cell lung cancer with KRAS G12C mutation: CodeBreaK 200 phase III study (Abstract LBA 10)

The KRAS G12C inhibitor sotorasib (Lumakras) doubled the rate of progression-free survival (PFS) at 12 months and reduced the risk of progression or death by 34% compared with docetaxel for patients with previously treated non–small cell lung cancer (NSCLC) with KRAS G12C mutations, according to findings from the phase 3 CodeBreaK 200 trial (NCT04303780).

At a median follow-up of 17.7 months, the 12-month PFS rate was 24.8% with sotorasib compared with 10.1% with docetaxel. Median PFS was 5.6 months (95% CI, 4.3-7.8) with sotorasib vs 4.5 months (95% CI, 3.0-5.7) with docetaxel (HR, 0.66; 95% CI, 0.51-0.86; P = .002). There were fewer grade 3 or greater treatment-related adverse effects with the KRAS G12C inhibitor compared with chemotherapy (33.1% vs 40.4%, respectively). Additionally, serious adverse events were less common with sotorasib vs docetaxel (10.7% vs 22.5%).

The median overall survival was 10.6 months (95% CI, 8.9-14.0) with sotorasib compared with 11.3 months (95% CI, 9.0-14.9) with docetaxel (HR, 1.01; 95% CI, 0.77-1.33; P = .53). Thirty-six percent of patients in the sotorasib arm received a subsequent therapy at crossover compared with 42% in the docetaxel arm. A subsequent KRAS G12C inhibitor was received by 34% of patients in the docetaxel arm. The most common treatment at crossover for those in the sotorasib arm was chemotherapy (21%).

For the study, patients were randomly assigned to receive either oral sotorasib at 960 mg per day (n = 171) or intravenous (IV) docetaxel at 75 mg/m² every 3 weeks (n = 174). All patients had received prior platinum-based chemotherapy and a checkpoint inhibitor either concurrently or sequentially.

The objective response rate with sotorasib was 28.1% (95% CI, 21.5%-35.4%) compared with 13.2% (95% CI, 8.6%-19.2%) with docetaxel (P < .001). When also considering patients with stable disease, the overall disease control rate was 82.5% for sotorasib compared with 60.3% with docetaxel. Any degree of tumor shrinkage was seen in 80.4% of patients treated with sotorasib compared with 62.8% of those treated with docetaxel.

"In my opinion, this supports sotorasib as a new second-line standard for patients with KRAS G12C–mutated NSCLC. We look at [CodeBreaK 200] as the first step. There are more studies ongoing adding other drugs to it. It is well tolerated, so it will pair nicely with other drugs inhibiting MAP kinase, EGFR, and even PD-L1."
Pembrolizumab (Keytruda) plus chemoradiation failed to demonstrate a statistically significant improvement in event-free survival (EFS) vs chemoradiation alone in patients with locally advanced head and neck squamous cell carcinoma, according to findings from the phase 3 KEYNOTE-412 trial (NCT03040999). The results showed that median EFS was not reached (NR; 95% CI, 44.7-NR) with pembrolizumab plus chemoradiation vs 46.6 months (95% CI, 27.5-NR) with chemoradiation alone, failing to meet the superiority threshold of a 1-sided alpha of 0.0242 (HR, 0.83; 95% CI, 0.68-1.03; P = .0429). The 24-month EFS rate was 63.2% with pembrolizumab/chemoradiation vs 56.2% with chemoradiation alone; the 36-month EFS rates were 77.9% and 76.8%; the 36-month OS rates were 79.1% and 73.0%, respectively.

In a post hoc analysis of EFS and OS in patients with a PD-L1 CPS of at least 20, the addition of pembrolizumab to chemoradiation appeared to result in greater benefit compared with chemoradiation alone. Here the median EFS was NR in either arm but demonstrated a 24-month EFS rate of 71.2% with pembrolizumab/chemoradiation vs 62.0% with chemoradiation alone; the 36-month EFS rates were 66.7% and 57.2%, respectively (HR, 0.73; 95% CI, 0.49-1.06). The median OS was also NR in either arm, but indicated a 24-month OS rate of 83.3% with pembrolizumab/chemoradiation vs 79.9% with chemoradiation alone; the 36-month OS rates were 79.1% and 73.0%, respectively (HR, 0.67; 95% CI, 0.43-1.04).

In this study, pembrolizumab given as a lead-in dose, concomitantly with chemoradiotherapy and then adjuvantly for 1 year, failed to deliver a statistically significant improvement in EFS as a primary end point when compared with placebo. Even though there was a trend in favor of the pembrolizumab arm in the intention-to-treat and PD-L1-positive populations, the current study [data] cannot be interpreted as an indication for use of anti–PD-1 therapy in combination with chemoradiotherapy in any patient group. Indeed, in light of the recent presentations of negative findings from the JAVELIN Head and Neck 100 [NCT02952586], REACH [NCT02999087], and PembroRad [NCT02707588] studies, these data should signal the need for a change in thinking in how to design optimal combination regimens. Focus is now likely to shift to neoadjuvant and true adjuvant therapy approaches."

**READ MORE:** [bit.ly/3Di7DM8](bit.ly/3Di7DM8)

**Solangé Peters, MD, PhD**
Centre Hospitalier Universitaire Vaudois (CHUV)

**Osimertinib as adjuvant therapy in patients (pts) with resected EGFR-mutated (EGFRm) stage IB-IIIA non–small cell lung cancer (NSCLC): Updated results from ADAURA (Abstract LBA 47)**

Adjuvant osimertinib (Tagrisso) resulted in a 77% reduction in the risk of disease recurrence or death in patients with EGFR-mutated, stage II to IIIA non–small cell lung cancer (NSCLC), with a disease-free survival (DFS) improvement observed irrespective of prior adjuvant chemotherapy or disease stage, according to updated findings from the phase 3 ADAURA trial (NCT02511106).

At a median follow-up of 44.2 months (range, 0-67) with osimertinib (n = 233) and 19.6 months (range, 0-70) with placebo (n = 237), the median DFS was 65.8 months (95% CI, 54.4-not calculable [NC]) vs 21.9 months (95% CI, 16.6-27.5), respectively, in the population of patients with stage II/IIIA disease (HR, 0.23; 95% CI, 0.18-0.30).

In the overall population, osimertinib (n = 339) resulted in a median DFS of 65.8 months (95% CI, 61.7-NC) vs 28.1 months (95% CI, 22.1-35.0) with placebo (n = 343), translating to a 73% reduction in the risk of disease recurrence or death (HR, 0.27; 95% CI, 0.21-0.34). In this group, the median follow-up for those who received osimertinib was 44.2 months (range, 0-69) and 27.7 months (range, 0-70) for those given placebo.

Notably, the DFS benefit provided by osimertinib over placebo was observed across all predefined subgroups. In those who received prior adjuvant chemotherapy (n = 410), the HR for DFS was 0.29 (95% CI, 0.21-0.39); the HR was 0.36 (95% CI, 0.24-0.55) in those who did not (n = 272). The HRs for those with stage IB (n = 212), stage II (n = 236), and stage IIIA (n = 234) disease, per criteria according to the AJCC Cancer Staging Manual, 7th edition (American Joint Committee on Cancer/Union for International Cancer Control), were 0.41 (95% CI, 0.23-0.69), 0.34 (95% CI, 0.23-0.52), and 0.20 (95% CI, 0.14-0.29), respectively.

**READ MORE:** [bit.ly/3eNMjoi](bit.ly/3eNMjoi)

**Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-mutant metastatic non–small cell lung cancer (NSCLC): Interim results from the phase 2 DESTINY-Lung02 trial (Abstract LBA 55)**

The clinical benefit and tolerable safety profile of fam-trastuzumab deruxtecan-nxki (Enhertu) was maintained at 5.4 kg/mg vs 6.4 kg/mg in patients with HER2-mutated non–small cell lung cancer (NSCLC), confirming the benefit-risk ratio of the FDA-approved dose, according to findings from an interim analysis of the DESTINY-Lung02 trial (NCT04644237).

The confirmed overall response rate in the prespecified early cohort (PEC) of the study was 53.8% (95% CI, 39.5%-67.8%) at the lower dose level (n = 52) and 42.9% (95% CI, 24.5%-62.8%) at the higher dose level (n = 28). The lower dose also showed superior safety and tolerability, including a lower rate of interstitial lung disease (ILD).

“Antibody-drug conjugates have 2 very important opportunities. First, if they are really targeted to a specific oncogene or molecular alteration of the tumor—such as HER2, which is dependent mainly on mutations in the exon 20 insertion in lung cancer, it’s a niche, something
that is very well defined molecularly—there is a potential here to move them to the frontline. We need to use them instead of chemotherapy, even as monotherapy. I hope that this strategy will move frontline. Trastuzumub deruxtecan has also been examined in HER2 expressing lung cancer, and there the response rate was not 50% it was 36%. This might not be enough to go frontline, but can we replace a toxic agent such as platinum or platinum-based chemotherapy, can we combine it with an anti-PD-L1/CTLA-4? When you are in this less actionable [arena] you might need to combine it.*

READ MORE: bit.ly/3zi0DIGI

Edward B. Baron, MD, MS
David Geffen School of Medicine at UCLA

**CANOPY-A: Phase III study of canakinumab (CAN) as adjuvant therapy in patients (pts) with completely resected non–small cell lung cancer (NSCLC) (Abstract LBA 49)**

Patients with completely resected non–small cell lung cancer (NSCLC) did not derive a significant benefit with adjuvant canakinumab vs placebo, according to data from the phase 3 CANOPY-A trial (NCT03447769). Disease-free survival (DFS) was 35.0 months vs 29.7 months, respectively (HR, 0.94; 95% CI, 0.78-1.14; one-sided P = .258), whose baseline disease characteristics and biomarkers of interest, showed there were no meaningful differences in DFS.

OS was not formally tested because DFS did not prove to be statistically significant; however, the data showed an OS HR of 0.722 (95% CI, 0.482-1.081). The lung cancer–specific survival was similar between the experimental and control arms, with an HR of 0.900 (95% CI, 0.534–1.517).

*The role of inflammation in lung cancer has been long studied, but to date, it has not been effectively therapeutically harnessed. Canakinumab is a high-affinity antibody directed against IL-1β, a key mediator of inflammation.*

**Evaluation of biomarker data from the entire CANOPY program, which in addition includes a neoadjuvant study as well as 2 studies in advanced disease—1 combined with chemotherapy in a frontline setting and 1 combined with chemotherapy in the second-line setting—will continue to be evaluated to try and further elucidate the role of IL-1β in NSCLC.”

READ MORE: bit.ly/3MONCjx

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**Phase III EMPower-Cervical 1/GOG-3016/ENGOT-cx9 trial of cemiplimab in recurrent or metastatic (R/M) cervical cancer: long-term survival analysis (Abstract 519MO)**

Cemiplimab (Libtayo) maintained an overall survival (OS) benefit vs chemotherapy as a second-line treatment for patients with recurrent or metastatic cervical cancer who received prior platinum-based chemotherapy, according to data from the long-term survival analysis of the phase 3 EMPower-Cervical 1 trial (NCT03257267).

In this study, investigators analyzed data from 608 patients with recurrent or metastatic cervical cancer after progression on first-line platinum-based chemotherapy. Patients were randomly assigned to receive either 350 mg of cemiplimab intravenously once every 3 weeks (n = 304) or investigator’s choice of single-agent chemotherapy (n = 304).

Compared with chemotherapy, treatment with cemiplimab significantly improved OS (11.7 months vs 8.5 months; HR, 0.656; 95% CI, 0.545-0.790; P < .00001). Cemiplimab reduced the risk of death by 34% in the overall population.

The effect was seen in patients with squamous cell carcinoma (10.9 months vs 8.8 months; HR, 0.69; 95% CI, 0.56-0.85; P = .00023), whose risk for death was reduced by 31%. In patients with adenosquamous carcinoma, cemiplimab treatment reduced the risk of death by 45%, thus increasing OS compared with chemotherapy (13.5 months vs 7.0 months; HR, 0.545; 95% CI, 0.365-0.814).

The median OS for patients in the PD-L1-positive group taking cemiplimab was 12.1 months vs 7.7 months for those who were PD-L1 positive and assigned chemotherapy (HR, 0.61; 95% CI, 0.45-0.83). For patients with PD-L1-negative status, the median OS with cemiplimab was 10.8 months compared with 7.0 months for those taking placebo, respectively (HR, 0.65; 95% CI, 0.43-0.98).

“[EMPower-Cervical1 data] showed that cemiplimab vs [physician] choice chemotherapy in the first recurrent space, had a really convincing improvement in OS. That benefit was seen not just in PD-L1 positive advanced [disease], but also in those with PD-L1 negative-disease. That wasn’t the case in the original New England Journal of Medicine paper, but we are seeing that now in the presentation with longer follow-up. Pembrolizumab is approved... in the newly diagnosed, advanced setting and cemiplimab [confirms benefit] of the upfront immunotherapy for advanced disease.”

READ MORE: bit.ly/3FijтаH

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**Overall survival (OS) at 7-year (y) follow-up (f/u) in patients (pts) with newly diagnosed advanced ovarian cancer (OC) and a BRCA mutation (BRCAm) who received maintenance olaparib in the SOL01/GOG-3004 trial (Abstract 517O)**

Two years of olaparib (Lynparza) maintenance therapy elicited a long-term overall survival (OS) benefit vs placebo in patients with newly diagnosed, advanced ovarian cancer harboring a BRCA mutation, according to 7-year follow-up findings from the phase 3 SOL01/GOG-3004 trial (NCT01844986).

As of the data cutoff, the median OS was not reached with olaparib treatment vs 75.2 months with placebo treatment (HR, 0.55; 95% CI, 0.40-0.76; P = .0004). The 7-year OS rates were 67.0% in the olaparib arm and 46.5% in the placebo arm. The median duration of follow-up in the olaparib and placebo arms were 88.9 months (range, 85.7-93.6) and 87.4 months (range, 84.3–91.7), respectively.

In total, 45.3% of patients in the olaparib arm and 20.6% in the placebo arm still had not received a first subsequent treatment, while 44.3% of patients given placebo received a PARP inhibitor in a subsequent line of therapy vs 14.6% of patients in the olaparib group.

The time to first subsequent therapy or death was also substantially delayed with olaparib, compared with placebo (median, 64.0 months vs 15.1 months; HR 0.37; 95% CI, 0.28-0.48). This benefit extended beyond first subsequent therapy into the time to second subsequent therapy or death (TST) (93.2 months vs 40.7 months; HR 0.50; 95% CI, 0.37-0.67).

*These results support the use of maintenance olaparib to achieve long-term remission in women with newly diagnosed advanced ovarian cancer and a BRCA mutation.*

ESMO 2022, CONTINUED ON PAGE 73 ▶
For appropriate patients faced with relapsed/refractory multiple myeloma

FORGE AHEAD
WITH A BOLD APPROACH

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

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

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

IMPORTANT SAFETY INFORMATION

WARNING: OCULAR TOXICITY
BLENREP caused changes in the corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer, and symptoms such as blurred vision and dry eyes. Conduct ophthalmic exams at baseline, prior to each dose, and promptly for worsening symptoms. Withhold BLENREP until improvement and resume, or permanently discontinue, based on severity.

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

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

Learn more at BLENREPHCP.com
IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

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

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

Visual Acuity Changes: A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/200 or worse in the better-seeing eye in 14% of patients. 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 8%, and Grade 4 in 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%, 2.8%, and 0.5% of patients, respectively. Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fatal adverse reactions included cerebral hemorrhage in 2 patients. Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity.

Infusion-Related Reactions: Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8%, Grade 4 in 17%. The median time to resolution of the first thrombocytopenic event was 26.5 days. Infusion-related reactions occurred in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively. Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

Embryo-Fetal Toxicity: Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

ADVERSE REACTIONS

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP; keratopathy (21%) 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 dose interruption in >3% of patients included keratopathy (47%), blurred vision (5%), dry eye (3.2%), and pneumonia (3.2%). Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in >3% of patients included keratopathy (23%) and thrombocytopenia (5%).

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.

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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 (14.1) of full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

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.

5.2 Thrombocytopenia

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 15%, 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%, 2.8%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fetal 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].

5.3 Thrombocytopenia

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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.

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<th>Event</th>
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<th>All Grades (%)</th>
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<tr>
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</tbody>
</table>

6.2 BLENREP REMS

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

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for opthalmic 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.

5.4 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].

6.3 Embryo-Fetal Toxicity

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

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

6.4 Lactation

It is known that antibodies can be transferred to human infants following the ingestion of breast milk, and it is recommended that mothers not breastfeed during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

6.5 Opening the Vial

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) formation and response to therapeutic effect may be influenced by several factors, including sheep immunoglobulin, human immunoglobulin, and therapeutic protein inhibitor, MMAF) and it targets actively dividing cells.

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

7 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 216 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 = 99). 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 (4%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

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

Dose interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP. Adverse reactions which required a dose 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 lymphocytopenia decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

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

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

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

† Keratopathy was based on slit lamp eye examination, characterized as corneal epithelial changes with or without symptoms.
‡ Visual acuity changes were determined upon eye examination.
§ Blurred vision included diplopia, vision blurred, visual acuity reduced, and visual impairment.
∥ Dry eyes included dry eye, ocular discomfort, and eye pruritus.
∥ Fatigue included fatigue and asthenia.
¶ Infusion-related reactions included infusion-related reaction, pyrexia, chills, diarrhea, nausea, asthma, hypotension, 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: Albuminuria.

Table 2 summarizes the laboratory abnormalities in DREAMM-2.

Table 2. Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43</td>
</tr>
<tr>
<td>Glucose increased</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25</td>
</tr>
<tr>
<td>Creatinine phosphokinase increased</td>
<td>22</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20</td>
</tr>
</tbody>
</table>

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, 9/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxid compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta, therefore, belantamab mafodotin-blmf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus.

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

Data
Animal Data: Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
8.2 Lactation
Risk Summary
There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 4 months after the last dose.

8.3 Females and Males of Reproductive Potential
BLENREP can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

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

Contraception
Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.
Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Nonclinical Toxicology (13.1) of full Prescribing Information].

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

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

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

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

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

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ocular Toxicity
• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].
• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3) of full Prescribing Information, Warnings and Precautions (5.1)].
• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
The potential for cure may also be enhanced. The OS benefit was seen despite over 40% of patients in the placebo group receiving subsequent PARP inhibitor therapy.

Ten-year survival in women with newly diagnosed advanced epithelial ovarian cancer is 17%.

Neoadjuvant versus adjuvant pembrolizumab for resected stage III-IV melanoma (SWOG S1801) (Abstract LBA 6)

Compared with adjuvant pembrolizumab (Keytruda) alone, the addition of neoadjuvant pembrolizumab significantly improved event-free survival (EFS) outcomes for patients with stage III-IV melanoma with an HR of 0.58 (95% CI, 0.39-0.87; \( P = .004 \)), according to data from the phase 2 SWOG S1801 trial (NCT03698019).

The landmark 2-year EFS rate was 72% in the neoadjuvant arm (n = 159) compared with 49% in the adjuvant arm (n = 154).

Twelve patients had disease progression that precluded surgery and 10 patients had residual disease or developed a metastasis prior to adjuvant therapy in the neoadjuvant arm. In comparison, 17 patients in the adjuvant arm experienced residual disease or developed metastasis prior to starting therapy.

Pembrolizumab in the neoadjuvant arm also improved EFS in all key subgroups in comparison with the adjuvant group. In particular, patients who were 66 years old or older had an HR of 0.4 (95% CI, 0.21-0.74), male patients had an HR of 0.48 (95% CI, 0.29-0.8), patients with stage IIIIC disease had an HR of 0.4 (95% CI, 0.22-0.75), and patients with BRAF-mutated disease had an HR of 0.44 (95% CI, 0.21-0.91).

Overall survival was also looked at in the study, but data were not mature at the time of presentation with only 36 deaths reported on the trial (HR, 0.63; 95% CI, 0.32-1.24; \( P = .18 \)).

Relapsed advanced ovarian cancer is typically incurable, highlighting the need for effective first-line therapies that delay relapse, prolong survival, and enhance the potential for cure. Seven years of follow-up is a clinically relevant time point for survivorship, and the longest follow-up for any PARP inhibitor in newly diagnosed advanced ovarian cancer. These 7-year results provide further confirmation that the benefit of maintenance olaparib extends well beyond its 2-year treatment cap.*

**READ MORE:** bit.ly/3DixbZw

**Neoadjuvant cemiplimab in patients (pts) with stage II–IV (MO) cutaneous squamous cell carcinoma (CSCC); Primary analysis of a phase II study (Abstract 7890)**

Cemiplimab (Libtayo) produced pathologic complete responses (pCRs) as a neoadjuvant treatment in more than half of patients with resectable, stage II to IV cutaneous squamous cell carcinoma (CSCC), according to a primary analysis of a phase 2 trial (NCT04154943).

In total, 63.3% of patients (95% CI, 51.7%-73.9%) experienced near or complete disappearance of their tumors when treated with the anti-PD-1 monotherapy, representing the highest response rates to this type of therapy in solid tumors.

Investigators observed a pCR in 40 patients (50.6%; 95% CI, 39.1%-62.1%) and a pathologic major response (pMR) in 10 patients (12.7%; 95% CI, 6.2%-22.0%) under independent central pathologist review. Twenty patients (25.3%) experienced no pCR or pMR, and 9 patients (11.4%) did not undergo pathologist evaluation.

Moreover, 54 patients demonstrated an objective response on imaging (68.4%; 95% CI, 56.9%-78.4%), which included 5 patients with CRs (6.3%) and 49 with partial responses (62.0%).

Sixteen patients had stable disease (20.3%), 8 had progressive disease (10.1%), and 1 patient had no imaging-based evaluation (1.3%). The disease control rate was 89% (95% CI, 80%-95%).

The most common AEs of any grade were fatigue (30.4%), as well as diarrhea, nausea, and maculopapular rash (13.9% each).

**Approximately one-third of patients who are PD-L1 negative have a deep pathologic response, suggesting that this biomarker alone may be insufficient for segregating patients for treatment. This underscores the need for histologic confirmation of response. Still, hopefully, we’ll have biomarkers in the future that can help better direct us.**

The take-home message is that we have very early data, only pathologic response at the moment, but also very promising data. Maturation is needed to learn whether CSCC [pathologic response] rate is a surrogate marker for event-free survival.

Then, do we really need 4 doses of cemiplimab? Can we also achieve the same result with 2 doses? I hope we will see, as soon as possible, a randomized trial to establish this therapy approach in cutaneous squamous cell carcinoma.*

**READ MORE:** bit.ly/3scTfhQ
Tucatinib (Tukysa) plus trastuzumab (Herceptin) improved radiographic response rates in patients with metastatic HER2-positive colorectal cancer (CRC) initially treated with tucatinib monotherapy who later crossed over to receive doublet therapy, further supporting the regimen’s use in this setting, according to updated data from cohort C of the phase 2 MOUNTAINEER trial (NCT03043313).

Prespecified analyses for cohort C included objective response rate (ORR) by 12 weeks and disease control rate (DCR) by blind independent committee review (BICR); confirmed ORR by BICR for patients who crossed over from the monotherapy to combination regimen; and safety. Patients in cohort C received tucatinib at 300 mg twice daily.

Among the 30 patients treated with tucatinib, ORR by 12 weeks was 3.3% (95% CI, 0.1%-17.2%) and DCR was 80.0%. Overall, cohort C comprised patients with 1 partial response (PR; 3.3%) and DCR was 80.0%. ORR by 12 weeks was 3.3% (95% CI, 0.1%-17.2%) and DCR of 82.1%.

In total, 28 patients crossed over to the combination regimen, inducing a confirmed ORR of 17.9% (95% CI, 6.1%-36.9%) and DCR of 82.1%. Among patients who crossed over, 5 (17.9%) had PRs, 18 (64.3%) had SD, and 5 (17.9%) had PD.

In cohort C, 93.3% of patients experienced any-grade adverse events (AEs), with 21.4% experiencing grade 3 or higher AEs. Two patients had serious AEs. The most common AE was diarrhea (35.7%), of which all events were grade 1 or 2. Also in this group, the most common grade 3 or higher AEs include ALT/AST increase (7.1% and 10.7%, respectively). Two patients in the crossover group discontinued treatment because of AEs.

FRESCO-2: a global phase 3 multiregional clinical trial evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer (Abstract LBA25)

Fruquintinib (HMPL-013) resulted in a significant and clinically meaningful improvement in survival vs placebo in heavily pretreated patients with metastatic colorectal cancer (mCRC), according to data from the phase 3 FRESCO-2 trial (NCT04322359).

The trial met its primary end point of overall survival (OS) and key secondary end point of progression-free survival (PFS). Patients treated with fruquintinib achieved a median OS of 7.4 months (95% CI, 6.7-8.2) vs 4.8 months (95% CI, 4.0-5.8) with placebo (HR, 0.66; 95% CI, 0.549-0.800; P < .001). Moreover, treatment with fruquintinib resulted in a median PFS of 3.7 months (95% CI, 3.5-3.8) vs 1.8 months (95% CI, 1.8-1.9) with placebo (HR, 0.321; 95% CI, 0.267-0.386; P < .001). Not only was the drug effective, but it was also well tolerated, with investigators observing only 4% grade 3/4 immune-related adverse events (irAEs).

The nonrandomized, multicenter NICHE-2 trial was initiated by investigators after 32 patients with nonmetastatic dMMR colon cancer in the NICHE-1 trial (NCT03026140) showed 100% pathologic complete responses (pCRs) and none have disease recurrence to date. This treatment was also well tolerated, with investigators observing only 4% grade 3/4 immune-related adverse events (irAEs).

Four weeks of treatment with nivolumab (Opdivo) plus ipilimumab (Yervoy) elicited major pathologic responses (MPRs) in 95% of patients with mismatch repair-deficient (dMMR) colon cancer, according to findings from the NICHE-2 trial (N158483.031.16, EudraCT 016-002940-17).

Additionally, 67% of patients demonstrated pathologic complete responses (pCRs) and none have disease recurrence to date. This treatment was also well tolerated, with investigators observing only 4% grade 3/4 immune-related adverse events (irAEs).
patients undergoing timely surgery and meeting the safety end point of the trial.

This stands in stark contrast to data from neoadjuvant chemotherapy in this same patient population [that had] only 7% pathologic responses.

I believe that neoadjuvant immunotherapy has a very strong potential to become standard of care for patients with dMMR colon cancer. The future has never been brighter for this patient population and for that, I urge the pharmaceutical companies to please strive for registration of neoadjuvant immunotherapy.

READ MORE: bit.ly/3DfbA4i

KRISTAL-1: updated efficacy and safety of adagrasib (MRTX849) with or without cetuximab in patients with advanced colorectal cancer (CRC) harboring a KRAS G12C mutation (Abstract LBA 24)

Adagrasib (MRTX849) monotherapy and in combination with cetuximab (Erbitux) generated encouraging responses in patients with advanced colorectal cancer (CRC) harboring KRAS G12C mutations, according to data from the phase 1b/2 KRISTAL-1 trial (NCT03782449).

The combination of adagrasib and cetuximab was evaluated in the phase 1b portion of the trial, and at a median follow-up of 17.5 months, evaluable patients (n = 28) experienced an objective response rate (ORR) of 46%, with a disease control rate of 100%. All 13 responders had a partial response (PR), and 15 patients had stable disease.

The median duration of response (DOR) with the combination was 7.6 months, and the median time to response (TTR) was 1.4 months. The median progression-free survival was 6.9 months (95% CI, 5.4-8.1), and the 6- and 12-month PFS rates were 60% and 24%, respectively. The median OS was 13.4 months (95% CI, 9.5-20.1), with 6- and 12-month overall survival (OS) rates of 84% and 61%, respectively.

At a median follow-up of 20.1 months in the phase 2 portion of the trial evaluating single-agent adagrasib, evaluable patients (n = 43) achieved an ORR of 19% and a disease control rate of 86%. All 8 responders experienced a PR,

READ MORE: bit.ly/3CPTpkd

GU CANCERS

Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): results from patients with ≥ 12 mo of treatment in JAVELIN Bladder 100 (Abstract 1760P)

Findings from a subgroup analysis of the phase 3 JAVELIN Bladder 100 trial (NCT02603432), showed that at a median follow-up of 38 months, 118 of 350 patients in the avelumab arm (33.7%) received a minimum of 12 months of treatment. Among these patients, the median overall survival (OS) was not reached (95% CI, 50.9 months-not estimable [NE]), and the median PFS was 26.7 months (95% CI, 19.4-32.2).

The benefit was not limited just to the PD-L1-positive population of patients, as it spanned across all populations. If patients achieved a CR [complete response], PR [partial response], or stable disease [following chemotherapy, they benefited from avelumab]. It is important to remember that the patients who developed progression after 4 to 6 cycles of chemotherapy were excluded from the [randomized portion of the trial]. The impact of the trial resonates with the whole theme of maintenance avelumab treatment. For the patients who fit the eligibility criteria of JAVELIN Bladder 100, chemotherapy is still our best [ frontline] treatment option to this day. This includes treatment with gemcitabine/cisplatin or gemcitabine/carboplatin. If patients achieve either a CR, PR, or stable disease, they then go on to maintenance avelumab. For those patients able to go through prolonged treatment [with avelumab], they garner a [significant] benefit, which was seen in this latest subgroup analysis of JAVELIN Bladder 100.

The next step is [to see] if we can do better. We know that [patients can achieve] good responses and good maintenance therapy is available. Although up to one-third of patients are enjoying good responses and a good quality of life with maintenance avelumab, patients still had to leave the trial and were not able to continue with maintenance avelumab, [primarily] due to progression. We must work to fulfill this unmet need in this field.

READ MORE: bit.ly/3SqVTv4

Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC) of IMDC intermediate or poor risk (COSMIC-313) (LBA 8)

The phase 3 COSMIC-313 trial (NCT03937219) evaluated the triplet cabozantinib plus nivolumab plus ipilimumab vs nivolumab plus ipilimumab in previously untreated patients with intermediate-or poor-risk advanced renal cell carcinoma (RCC). In the final analysis of the primary intention-to-treat population the median progression-free survival (PFS) was not reached in the triplet arm vs 11.3 months in the control arm (HR, 0.73; 95% CI, 0.57-0.94; P = .013). The 12-month PFS rate was 57% vs 49%, respectively.

In terms of tumor response, the objective response rate among the 276 patients in the triplet arm was 43% vs 36% among the 274 patients in the control arm. Further, 55% of patients
had a tumor reduction of at least 30% with the addition of cabozantinib compared with 45% of patients who received nivolumab and ipilimumab only. Any tumor reduction was noted in 90% and 75% of patients, respectively. Of note, responses were more pronounced in the intermediate-risk group.

The objective response rate in the triplet arm was 43% compared with 36% in the control arm. The complete and partial response rates were 3% and 41% vs 3% and 32%, respectively. These translated to a disease control rate of 86% and 72%, respectively. The median duration of response was not reached in either arm. In terms of safety, the use of high-dose corticosteroids was 58% with the triplet compared with 35% with nivolumab plus ipilimumab.

"This is the first trial using a modern control arm, that is contemporary and similar in terms of patient selection and outcomes. COSMIC-313 uses nivolumab and ipilimumab as the control arm, which have shown promising results in patients with mCRPC. The OS is immature with only 17 months follow-up. Responses were numerically higher, but we would like to see them be even higher, but we must wait and see.

One of the issues is how to manage adverse effects. We are adding TKI [tyrosine kinase inhibitors], we had higher risk of AEs overall in the triplet arm, especially around the injection site area, such as rash, mostly low grade. We are learning how to manage this regimen and we still have to find it a place. These data are too early this is the interim results with more analysis coming."

| READING MORE: bit.ly/3TFowWn |

Study EV-103 cohort K: antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC) [Abstract LBA 73]

The combination of enfortumab vedotin-ejfv (Padcev) and pembrolizumab (Keytruda) elicited a high overall response rate (ORR) and a manageable safety profile in patients with locally advanced or metastatic urothelial cancer, according to data from cohort K of the phase 1/2 EV-103 trial (NCT03288545).

"The patient population was predominantly male, and approximately 60% had impaired performance status. Visceral disease was presented more than 80% of patients, and approximately 40% were PD-L1 high; a proportion of patients were not evaluable because they did not have tumor to be submitted. A total of 149 patients were included in the study, 76 of whom were treated with enfortumab vedotin plus pembrolizumab and 73 who were treated with enfortumab vedotin alone. The confirmed ORR (95% CI) for enfortumab vedotin plus pembrolizumab was 64.5%, and median duration of response (DOR) was not reached. Confirmed ORR for enfortumab vedotin alone was 45.2%, with a median DOR of 13.2 months.

Regarding adverse events (AEs), 15.6% of patients receiving enfortumab vedotin plus pembrolizumab stopped treatment due to an AE, and 24.3% of patients receiving enfortumab vedotin alone stopped treatment due to an AE. The most common AEs seen in patients receiving enfortumab vedotin plus pembrolizumab included fatigue, peripheral sensory neuropathy, alopecia, and maculo-papular rash. Eighteen (23.7%) serious treatment-related adverse events (TRAEs) were seen in the combination therapy group and 11 (15.1%) were seen in the monotherapy group. Three TRAEs leading to death (3.9%) were seen in the combination group and 2 (2.7%) were seen in the monotherapy group. Rosenberg reported that skin reactions were more frequent with patients receiving enfortumab vedotin plus pembrolizumab, although none were serious."

"These data suggest that the combination of enfortumab vedotin and pembrolizumab is a viable treatment option for cisplatin-ineligible patients. Management of skin toxicity is an important topic for patients receiving enfortumab vedotin, and in my practice I try to see patients within the first several cycles that each visit to monitor the skin toxicity events closely [and] it’s important for medical oncologists to develop a relationship with a dermatologist who they can refer patients to for assistance with more significant skin toxicities."

"I’m optimistic that this will be a treatment option for patients in the future. In the meantime, EV-302 [NCT04223856] is recruiting [and] is a randomized phase 3 trial of enfortumab vedotin and pembrolizumab compared to gemcitabine and platinum as first-line therapy either cisplatin or carboplatin.

That will answer definitively whether patients will be receiving enfortumab vedotin and pembrolizumab in the long term regardless of platinum eligibility."
Sacituzumab govitecan-hziy (Trodelvy) generated statistically significant and clinically meaningful benefits in overall survival (OS) and responses vs physician’s choice of treatment in pretreated patients with hormone receptor-positive, HER2-negative metastatic breast cancer who were resistant to endocrine therapy, according to the second interim analysis from the phase 3 TROPICS-02 trial (NCT03901339).

Results showed that sacituzumab govitecan elicited a median OS of 14.4 months, compared with 11.2 months with treatment of physician’s choice (HR, 0.79; 95% CI, 0.65-0.96; P = .02).

The TROPICS-02 trial included 543 patients who were previously treated with taxane, endocrine therapy, CDK4/6 inhibitor, and 2 to 4 prior lines of chemotherapy. Participants were randomly assigned 1:1 to receive either sacituzumab govitecan (10 mg/kg on days 1 and 8 every 21 days; n = 272) or treatment of physician’s choice (n = 271) until progression or unacceptable toxicity. Follow-up was conducted at a median of 12.5 months.

OS improvements were consistent across most subgroups, including patients who had received 3 or more chemotherapy regimens for metastatic disease and those who received endocrine therapy in the metastatic setting for at least 6 months.

The objective response rate was greater in the sacituzumab govitecan group compared with the treatment of physician’s choice group (21% vs 14%; odds ratio [OR], 1.63; 95% CI, 1.03-2.56; P = .035). The clinical benefit rate was 34% for patients assigned sacituzumab govitecan and 22% for those assigned treatment of physician’s choice (OR, 1.8; 95% CI, 1.23-2.63; P = .003).

Median duration of response was prolonged at 8.1 months (95% CI, 6.7-9.1) with sacituzumab govitecan vs treatment of physician’s choice at 5.6 months (95% CI, 3.8-7.9).

There was also a significant improvement in quality of life with sacituzumab govitecan compared with treatment of physician’s choice. In particular, the median time to deterioration of global health status/quality of life was 4.3 months and 3 months, respectively (HR, 0.75; 95% CI, 0.61-0.92; P = .006). The median time to deterioration for fatigue was 2.2 months compared with 1.4 months (HR, 0.73; 95% CI, 0.60-0.89; P = .002), respectively.

This statistically significant and clinically meaningful benefit of sacituzumab govitecan over [treatment of physician’s choice] from the TROPICS-02 study supports the use of sacituzumab govitecan as a novel therapy for patients with pretreated, endocrine-resistant hormone receptor-positive, HER2-negative metastatic breast cancer.

Currently, international guidelines recommend sequential endocrine therapy combined with targeted agents for this patient population; however, optimal sequencing of therapy following endocrine resistance remains unclear. For patients who are resistant to endocrine therapy, sequential single-agent chemotherapy is the standard of care... although this treatment is associated with declining efficacy and increasing toxicity.

With this in mind, there remains a high unmet clinical need for novel, effective therapy options for patients with pretreated hormone receptor-positive, HER2-negative metastatic breast cancer in the late-line setting.

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Open-label, randomized study of lasofoxifene (LAS) vs fulvestrant (Fulv) for women with locally advanced/metastatic ER+/HER2- breast cancer (mBC), an estrogen receptor 1 (ESR1) mutation, and disease progression on aromatase (AI) and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (Abstract LBA 20)

Single-agent lasofoxifene (Fablyn) did not produce a statistically significant improvement in progression-free survival (PFS) vs fulvestrant (Faslodex) for patients with estrogen receptor (ER)-positive, HER2-negative metastatic breast cancer harboring ESR1 mutations, according to data from the phase 2 ELAINE 1 trial (NCT03781063).

However, investigators determined that lasofoxifene, a nonsteroidal selective estrogen receptor modulator (SERM), elicited a benefit in objective response rate (ORR) and clinical benefit rate. Patients who received lasofoxifene (n = 52) achieved a median PFS of 6.04 months (95% CI, 2.82-8.04) compared with 4.04 months (95% CI, 2.93-6.04) for patients who received fulvestrant (n = 51; HR, 0.699; 95% CI, 0.445-1.125; P = .138). The 6- and 12-month PFS rates in the lasofoxifene arm were 53.4% and 30.7%, respectively, vs 37.9% and 14.1% in the fulvestrant arm (P = .138), respectively.

Additional data showed lasofoxifene elicited an ORR of 13.2% compared with 2.9% for fulvestrant (P = .12). In the lasofoxifene arm, 1 patient achieved a complete response with a duration of 18 months. Four patients had partial responses (PRs) with a median duration of 13.75 months. One patient in the fulvestrant arm achieved a PR with a duration of 16 months.

The clinical benefit rate after 24 weeks in the lasofoxifene group was 36.5% vs 21.6% in the fulvestrant group (P = .12).

An exploratory circulating tumor DNA (ctDNA) analysis assessed the baseline and 8-week ctDNA samples of 61 patients for ESR1-mutant allele fraction. The median relative change for all variants in the lasofoxifene arm was –87.1% compared with –14.7% in the fulvestrant arm. In patients with ESR1 Y3375S mutations, the median mutant allele fraction change was –89% in the lasofoxifene arm and –82% in the fulvestrant arm.

Regarding safety, most adverse effects (AEs) were grade 1/2 and no thrombotic AEs were reported. The most common treatment-emergent AEs of any grade were nausea (27.5% and 18.8%) in the lasofoxifene and fulvestrant arms, respectively, fatigue (23.5% and 37.5%), arthralgia (21.6% and 22.9%), hot flush (21.6% and 10.4%), constipation (15.7% and 12.5%), dizziness (15.7% and 4.2%), hypertension (15.7% and 14.6%), and cough (15.7% and 10.4%).

Lasofoxifene did not statistically improve PFS, but we did see numerically superior outcomes in all of these primary and secondary areas, such as PFS and ORR.

ESR1 mutations in patients with ER-positive, HER2-negative breast cancer are associated with endocrine resistance, metastases, and poor prognosis. Selective estrogen degraders, such as fulvestrant, have displayed limited efficacy in this patient population.

Lasofoxifene is a third-generation oral SERM that improved tumor growth inhibition and metastases reduction vs fulvestrant in preclinical models. In terms of monotherapy, a larger trial is going to be needed to determine if lasofoxifene can be an alternative to fulvestrant.”

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