Value of Geriatric Assessment in Patients With Genitourinary Carcinoma

Modern Treatment Standards Require State-of-the-Art Molecular Profiling

Prostate Cancers
Germline Testing in Prostate Cancer: When and Who to Test

Colorectal Cancer
Addressing Resistance to Targeted Therapies in Metastatic Colorectal Cancer

Hematology CME
“Off-the-Shelf” Allogeneic CAR T-Cells

CHARU AGGARWAL, MD, MPH
NOW APPROVED

EXKIVITY™

mobocertinib

40 mg capsules

The first oral therapy for EGFR Exon20 insertion+ mNSCLC patients post platinum-based chemotherapy

INDICATION

EXKIVITY 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 confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

WARNING: QTc PROLON...
TORSADES DE POINTES occurred in 1 patient (0.4%). Clinical trials of had a change-from-baseline QTc interval >60 msec. Grade 4 1.2% of patients had a QTc interval >500 msec and 11% of patients who had scheduled and unscheduled electrocardiograms (ECGs), In the 250-patient subset of the pooled EXKIVITY safety population EXKIVITY can cause life-threatening heart rate–corrected QT (QTc) QTc Prolongation and Torsades de Pointes WARNINGS AND PRECAUTIONS • EXKIVITY can cause life-threatening heart rate–corrected See full prescribing information for complete boxed warning. TORSADES DE POINTES WARNING: QTc PROLONGATION and prolonged. withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity. Diarrhea EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population, diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days, but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly. Advise patients to start an anti-diarrheal agent (eg, loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake. Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity. Embryo-Fetal Toxicity Based on findings from animal studies and its mechanism of action, EXKIVITY 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 nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY. ADVERSE REACTIONS The most common (>20%) adverse reactions are diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium. DRUG INTERACTIONS CYP3A Inhibitors Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations, which may increase the risk of adverse reactions including QTc interval prolongation. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce the EXKIVITY dose and monitor the QTc interval more frequently with ECGs. CYP3A Substrates Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors decreased mobocertinib plasma concentrations, which may reduce EXKIVITY antimumor activity. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. Prolonged QT Interval EXKIVITY can cause QTc interval prolongation. Coadministration of EXKIVITY with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation. Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product Prescribing Information. USE IN SPECIFIC POPULATIONS Pregnancy Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Advise pregnant women of the potential risk to a fetus. Females and Males of Reproductive Potential Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY. Advise females of reproductive potential to use effective nonhormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose. Lactation There are no data on the presence of mobocertinib or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose. To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-846-217-4468 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Please see Brief Summary of Prescribing Information, including Boxed Warning, on the following pages. EGFR, epidermal growth factor receptor; mNSCLC, metastatic non-small cell lung cancer.
1 INDICATIONS AND USAGE
EXKIVITY 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 [see Dosage and Administration (2.1)]. This indication is approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
Select patients with locally advanced or metastatic NSCLC for treatment with EXKIVITY based on the presence of EGFR exon 20 insertion mutations [see Clinical Studies (14)]. Information on FDA-approved tests is available at: http://www.fda.gov/CompanionDiagnostics. Withholding, reducing the dose, or permanently discontinuing EXKIVITY based on the severity of QTc prolongation [see Dosage and Administration (2.2)].

2.2 Recommended Dosage
The recommended dosage of EXKIVITY is 160 mg orally once daily until disease progression or unacceptable toxicity. If a dose is missed by more than 6 hours, skip the dose and take the next dose the following day at its regularly scheduled time. If a dose is vomited, do not take an additional dose. Take the next dose as prescribed the following day.

2.3 Dosage Modifications for Adverse Reactions
EXKIVITY dose reduction levels for adverse reactions are summarized in Table 1.

Table 1: Recommended EXKIVITY Dose Reductions

<table>
<thead>
<tr>
<th>Dose Reductions</th>
<th>Dose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose reduction</td>
<td>120 mg once daily</td>
</tr>
<tr>
<td>Second dose reduction</td>
<td>80 mg once daily</td>
</tr>
</tbody>
</table>

Recommended dosage modifications of EXKIVITY for adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>EXKIVITY Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc Interval Prolongation and Torsades de Pointes</td>
<td>Grade 2</td>
<td>First Occurrence: Withhold EXKIVITY until ≤ Grade 1 or baseline. Upon recovery, resume EXKIVITY at the same dose. Recurrence: Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>[see Warnings and Precautions (5.1)]</td>
<td>Grade 3</td>
<td>First Occurrence: Withhold EXKIVITY until ≤ Grade 1 or baseline. Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY. Recurrence: Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>[see Warnings and Precautions (5.1)]</td>
<td>Grade 4</td>
<td>Interstitial Lung Disease (ILD)/pneumonitis [see Warnings and Precautions (5.2)] Any grade</td>
</tr>
<tr>
<td>Decreased Ejection Fraction or Heart Failure</td>
<td>Grade 2 decreased ejection fraction</td>
<td>First Occurrence: Withhold EXKIVITY until ≤ Grade 1 or baseline. If recovered to baseline within 2 weeks, resume EXKIVITY at the same dose or the next lower dose. If not recovered to baseline within 2 weeks, permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>[see Warnings and Precautions (5.3)]</td>
<td>Grade 2</td>
<td>First Occurrence: Withhold EXKIVITY until ≤ Grade 1. If recovered to baseline within 2 weeks, resume EXKIVITY at the same dose or the next lower dose. If not recovered to baseline within 2 weeks, permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>Decreased of Grade 3 or 4 decreased ejection fraction</td>
<td>Grade 4</td>
<td>First Occurrence: Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the next lower dose. Recurrence: Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>[see Warnings and Precautions (5.4)]</td>
<td>Grade 3</td>
<td>First Occurrence: Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the next lower dose. Recurrence: Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>Diarrhea [see Warnings and Precautions (5.4)]</td>
<td>Intolerable or recurrent Grade 2 of Grade 3</td>
<td>First Occurrence: Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the next lower dose. Recurrence: Permanently discontinue EXKIVITY.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Grade 4</td>
<td>First Occurrence: Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the next lower dose. Recurrence: Permanently discontinue EXKIVITY.</td>
</tr>
</tbody>
</table>
| Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions (cont’d)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity*</th>
<th>EXKIVITY Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Adverse Reactions</td>
<td>Intolerable or recurrent Grade 2 or Grade 3</td>
<td>Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the same dose or the next lower dose.</td>
</tr>
</tbody>
</table>

First Occurrence

Grades 4

• Withhold EXKIVITY until ≤ Grade 1.
• Resume EXKIVITY at the next lower dose if recovery occurs within 2 weeks.
• Permanently discontinue EXKIVITY if recovery does not occur within 2 weeks. Recurrence
• Permanently discontinue EXKIVITY.

5.4 Diarrhea
EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population (see Adverse Reactions (6.1)), diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an antidiarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake.

Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity (see Dosage and Administration (2.3)).

5.5 Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Oral administration of motesanib to pregnant rats during the period of organogenesis resulted in embryolethality at maternal exposures 1.7 times the human exposure based on area under the curve (AUC) at the 160-mg once-daily clinical 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 EXKIVITY (see Drug Interactions (7.2)) and for 1 month after the last dose. Advise females who are not of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY (see Use in Specific Populations (8.1, 8.3)).

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 pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to EXKIVITY as a single agent at a dose of 160 mg orally once daily in 256 patients, including 114 patients with EGFR exon 20 insertion mutation–positive locally advanced or metastatic NSCLC from Study AP32788-15-101, and patients with other solid tumors. Forty-eight percent (48%) were exposed for 6 months or longer and 12% were exposed for greater than 1 year. The most common (>20%) adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (>2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

EGFR Exon 20 Insertion Mutation–Positive Locally Advanced or Metastatic NSCLC Previously Treated with Platinum-Based Chemotherapy

The safety of EXKIVITY was evaluated in a subset of patients in Study AP32788-15-101 with EGFR exon 20 insertion mutation–positive locally advanced or metastatic NSCLC who received prior platinum-based chemotherapy (see Clinical Studies (14)). Patients with a history of interstitial lung disease, drug-related pneumonitis, radiation pneumonitis that required steroid treatment, significant, uncontrolled, active cardiovascular disease; or prolonged QTc interval were excluded from enrollment in this trial. A total of 114 patients received EXKIVITY 160 mg once daily until disease progression or unacceptable toxicity; 60% were exposed for 6 months or longer and 14% were exposed for greater than 1 year.

Serious adverse reactions occurred in 46% of patients who received EXKIVITY. Serious adverse reactions in >2% of patients included diarrhea, dyspnea, vomiting, pneumonia, hyperthyroidism, acne, and allergic reaction. Fatal adverse reactions occurred in 1.8% of patients who received EXKIVITY, including cardiac failure (0.9%), and pneumonitis (0.9%). Permanently discontinued occurred in 17% of patients who received EXKIVITY. Adverse reactions requiring permanent discontinuation of EXKIVITY in at least >2% of patients were diarrhea and nausea.

Dosage interruptions of EXKIVITY due to an adverse reaction occurred in 51% of patients. Adverse reactions which required dosage interruption in >5% of patients included diarrhea, nausea and vomiting.

Dose reductions of EXKIVITY due to an adverse reaction occurred in 25% of patients. The adverse reaction requiring dose reduction in >5% of patients was diarrhea.
Table 3: Adverse Reactions (≥10%) in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>EXKIVITY (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades* (%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>92</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>46</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>39</td>
</tr>
<tr>
<td>Nausea</td>
<td>37</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>18</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>15</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>78</td>
</tr>
<tr>
<td>Paronychia*</td>
<td>39</td>
</tr>
<tr>
<td>Dry skin</td>
<td>32</td>
</tr>
<tr>
<td>Pruritus</td>
<td>24</td>
</tr>
<tr>
<td>Alopecia</td>
<td>19</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>34</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>29</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>24</td>
</tr>
<tr>
<td>Upper respiratory tract infection*</td>
<td>16</td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>15</td>
</tr>
<tr>
<td>Rhinorhea</td>
<td>13</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Ocular Toxicity*</td>
<td>11</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>QTc interval prolongation*</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>10</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
</tr>
</tbody>
</table>

* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5).

** Events of Grade 3 only (no Grade 4 occurred).

a Stomatitis includes angular cheilitis, aphthous ulcer, cheilitis, mouth ulceration, mucosal inflammation, odynophagia, and stomatitis.

b Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.

c Rash includes acne, dermatitis, dermatitis acneliform, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, rash postular, and urticaria.

d Paronychia includes nail bed tenderness, nail disorder, nail infection, onycholysis, and paronychia.

e Musculoskeletal pain includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.

f Fatigue includes asthenia, and fatigue.

g Cough includes cough productive, cough productive, and upper-airway cough syndrome.

h Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, and upper respiratory tract infection.

i Dyspnea includes dyspnea and dyspnea exertional.

j Ocular toxicity includes dry eye, eye pruritis, abnormal sensation in eye, eye discharge, blepharitis, trichiasis, conjunctival hemorrhage, vitreous floaters, blurred vision and corneal edema.

k QTc interval prolongation includes electrocardiogram QT prolonged and ventricular arrhythmia.

I Hypertension includes blood pressure increase and hypertension.

Clinically relevant adverse reactions in <10% of patients receiving EXKIVITY included edema (9%), acute kidney injury (6%), peripheral neuropathy (7%), palmar-plantar erythrodysaesthesia (4.4%), pneumonitis (2.6%) and cardiac failure (2.6%).

Table 4 summarizes the laboratory abnormalities in Study AP32788-15-101.

Table 4: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients with EGFR Exon 20 Insertion Mutation–Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>EXKIVITY** (N = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades* (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Decreased red blood cells</td>
<td>59</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>52</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>26</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>25</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>52</td>
</tr>
<tr>
<td>Increased amylase</td>
<td>40</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>35</td>
</tr>
<tr>
<td>Decreased potassium</td>
<td>28</td>
</tr>
<tr>
<td>Increased alkaline phosphate</td>
<td>25</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>23</td>
</tr>
<tr>
<td>Decreased magnesium</td>
<td>23</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>22</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>21</td>
</tr>
<tr>
<td>Decreased sodium</td>
<td>20</td>
</tr>
</tbody>
</table>

* Grades per NCI CTCAE v5.0

** The denominator used to calculate the rate varied from 93 to 113 based on the number of patients with a baseline and at least one post-treatment value. The laboratory abnormalities are values that reflect worsening from baseline.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on EXKIVITY

**Strong or Moderate CYP3A Inhibitors**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations [see Clinical Pharmacology (12.3)], which may increase the risk of adverse reactions, including QTc interval prolongation.</em></td>
<td><em>Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce the EXKIVITY dose and monitor the QTc interval more frequently with ECGs [see Dosage and Administration (2.4), Warnings and Precautions (5.1)].</em></td>
</tr>
</tbody>
</table>

**Strong or Moderate CYP3A Inducers**

<table>
<thead>
<tr>
<th>Clinical Impact</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Coadministration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations [see Clinical Pharmacology (12.3)], which may reduce EXKIVITY anti-tumor activity.</em></td>
<td><em>Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.</em></td>
</tr>
</tbody>
</table>
7.2 Effect of EXKIVITY on Other Drugs

<table>
<thead>
<tr>
<th>CYP3A Substrates</th>
<th>Clinical Impact</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coadministration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates [see Clinical Pharmacology (12.3)], which may reduce the efficacy of these substrates.</td>
<td>Avoid concomitant use of hormonal contraceptives with EXKIVITY [see Warnings and Precautions (5.5), Use in Specific Populations (8.3)]. Avoid concomitant use of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product prescribing information.</td>
</tr>
</tbody>
</table>

7.3 Drugs that Prolong the QTc Interval

<table>
<thead>
<tr>
<th>Drugs that Prolong the QTc Interval</th>
<th>Clinical Impact</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXKIVITY can cause QTc interval prolongation [see Warnings and Precautions (5.1), Clinical Pharmacology (12.2)]. Coadministration of EXKIVITY with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation [see Warnings and Precautions (5.1), Clinical Pharmacology (12.2)].</td>
<td>Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, monitor the QTc interval more frequently with ECGs [see Warnings and Precautions (5.1)].</td>
<td></td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology (12.1)], EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in maternal toxicity at plasma exposures approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose (see Data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In an embryo-fetal development study, once-daily oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in maternal toxicity (reduced body weight gain and food consumption) at 10 mg/kg (approximately 1.7 times the human exposure based on AUC at the 160-mg once-daily clinical dose). Adverse effects on embryo-fetal development at this dose level included embryo lethality due to post-implantation loss (embryo-fetal death) and effects on fetal growth (decreased fetal weights). There was no clear evidence of fetal malformations at the high-dose level (10 mg/kg).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

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

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. EXKIVITY may render hormonal contraceptives ineffective [see Drug Interactions (7.2)].

Males

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

Infertility

Based on animal studies, EXKIVITY may impair fertility in males and females of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 114 patients [see Clinical Studies (14)] who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (69% vs 47%) and serious adverse reactions (64% vs 35%) in patients 65 years and older as compared to those younger than 65 years.

8.6 Renal Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² by Modification of Diet in Renal Disease [MDRD] equation). The recommended dosage of EXKIVITY has not been established for patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin >1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin >2.5 to 3 times ULN and any AST). The recommended dosage of EXKIVITY has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) [see Clinical Pharmacology (12.3)].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved patient labeling (Patient Information). QTc Interval Prolongation and Torsades de Pointes

Inform patients of the risk of QTc prolongation. Symptoms that may be indicative of significant QTc prolongation include dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their healthcare provider about the use of any heart medications [see Warnings and Precautions (5.1)].

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risks of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms such as cough, shortness of breath or chest pain [see Warnings and Precautions (5.2)].

Cardiac Toxicity

Inform patients of the risk of heart failure. Advise patients to contact their healthcare provider immediately if they experience any signs or symptoms of heart failure such as palpitations, shortness of breath, chest pain, and syncope [see Warnings and Precautions (5.3)].

Diabetes

Inform patients that EXKIVITY may cause diabetes, which may be severe in some cases and should be treated promptly. Advise patients to have antidiabetic medication readily available and promptly start antidiabetic treatment [e.g., insulin or sulfonylurea] if weight gain is unavoidable, increase the CYP3A substrate dosage where minimal concentration changes may increase the risk of diabetes [see Warnings and Precautions (5.2)].

Diabetic Ketoacidosis

Advise patients to contact their healthcare provider immediately if they experience any signs or symptoms of heart failure such as palpitations, shortness of breath, chest pain, and syncope [see Warnings and Precautions (5.3)].

Embryo-Fetal Toxicity

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

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose [see Use in Specific Populations (8.3)]

Lactation

Advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose [see Use in Specific Populations (8.3)].

Infertility

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

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions (7.2)]. Inform patients to avoid grapefruit or grapefruit juice while taking EXKIVITY.

Missed Dose

Advise patients that if a dose of EXKIVITY is missed by 6 hours or if vomiting occurs, resume treatment as prescribed the next day [see Dosage and Administration (2.2)].
ONCOLOGY® Remembers Dr Franco Muggia
Mike Hennessy Sr

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ONCOLOGY Remembers Dr Franco Muggia

Every step of the editorial process on the journal ONCOLOGY®—including conceptualization, manuscript drafting, an arduous review processes, and final approval—is completed with the oversight of the publication’s editorial advisory board of research pioneers and industry thought leaders.

In September 2021, the board lost one of its leading members, Franco Muggia, MD, who was a fixture at New York University (NYU) Langone’s Perlmutter Cancer Center and a leader in the study and treatment of patients with gynecologic cancers. He was 85.

Over a career lasting more than 50 years, Dr Muggia had a hand in developing important chemotherapeutic drugs, including bleomycin, nitrosoureas, taxanes, and his key area of interest, platinum compounds. During his time as associate director of the Cancer Therapy Evaluation Program at the National Cancer Institute, he played a crucial role in getting these agents incorporated into the standard of care for clinical practice and coordinated the early clinical development of chemotherapy for patients with leukemia and lymphoma, and breast, lung, ovarian, testicular, and gastrointestinal cancers.

Throughout his career, Dr Muggia was recognized as a worldwide thought leader in ovarian cancer therapeutics and played a leading role in the formation of the Gynecologic Oncology Group. He also helped found the New York Gynecologic Oncology Group and the New York Phase 1 Trials Group. In recent years, he led the Chemotherapy Foundation and helped to organize its annual meeting, the Chemotherapy Foundation Symposium, a program organized by Physicians’ Education Resource®, LLC.

Dr Muggia joined NYU School of Medicine in 1979 as professor of medicine and director of the Division of Medical Oncology. In 1986, he moved to the University of Southern California-Norris Comprehensive Cancer Center and continued his work optimizing intraperitoneal platinum and liposomal doxorubicin therapies for patients with ovarian cancer. He returned to NYU as director of the former Kaplan Cancer Center at NYU Medical Center from 1996 to 1997, before serving as director of the Division of Medical Oncology at NYU Langone Health’s Perlmutter Cancer Center until 2009.

After stepping down as division chief, he served as a senior faculty member and continued his commitment to clinical care, research, and educating the next generation of physician-scientists. The treatment landscape would not be the same without his contribution and he will be truly missed by his patients and colleagues alike.

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A FARNESYLTRANSFERASE INHIBITOR STUDY

4-8% of patients with HNSCC have HRAS mutations. HRAS mutations can be detected by most commercially available NGS panels. There are currently no FDA-approved therapies that target HRAS-mutant head and neck squamous cell carcinoma (HNSCC).

ABOUT TIPIFARNIB

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ABOUT AIM-HN

AIM-HN is a pivotal, registration-directed study designed to evaluate the efficacy and tolerability of tipifarnib in HRAS-mutant HNSCC.

KEY INCLUSION CRITERIA

• At least 18 years of age.
• Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology not amenable to local therapy with curative intent.
• Documented treatment failure from most recent prior therapy (eg, tumor progression, clinical deterioration, or recurrence), and from at least one prior platinum-containing regimen, in any treatment setting. The most recent prior and platinum-based therapy may be the same regimen.
• Known tumor missense HRAS mutation.
• Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
• Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
• Acceptable organ function.

KEY EXCLUSION CRITERIA

• Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous, or nonsquamous histologies (eg, mucosal melanoma).
• Concomitant disease or condition that could interfere with the conduct of the study or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.

PRIMARY OUTCOME

• Objective response rate

KEY SECONDARY OUTCOMES

• Duration of response
• Time to response
• Progression-free survival
• Overall survival
• Safety & tolerability

For your patients who are positive for HRAS mutation(s), AIM-HN may be right for them. Learn more about AIM-HN trial enrollment at kuraoncology.com/clinical-trials-aim. ClinicalTrials.gov identifier: NCT03719690


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As more and more targeted therapy options emerge in the cancer space, investigators continue to see positive impacts on long-term outcomes. However, this wider, advanced, individualized range of treatment options that may be offered to patients requires more sophisticated molecular testing techniques.

In an interview with ONCOLOGY®, Charu Aggarwal, MD, MPH, discussed this topic as it relates to her ongoing research, as well as how it may carry to other areas of oncology care outside of her area of expertise in the lung cancer space. She is the Leslye M. Heisler Associate Professor for Lung Cancer Excellence in the Department of Medicine at the University of Pennsylvania’s Perelman School of Medicine and co-chair of the 6th Annual International Congress of Immunotherapies in Cancer™, hosted by Physicians’ Education Resource, LLC (PER®).

Aggarwal spoke about how liquid biopsies, rather than invasive procedures, can help determine treatment prognosis. She also detailed how immunotherapy has evolved as a mainstay of treatment and how clinicians are now looking at adverse effects (AEs) as a positive sign of treatment efficacy.

Q: Can you discuss the benefits of liquid biopsies vs tissue sampling?

A: Molecular genotyping is becoming extremely important in non–small cell lung cancer. At least 9 biomarkers must now be tested at initial diagnosis, and the gold standard for testing has been to use tissue-based testing. However, it’s often a problem to get tissue because these biopsies are small and sometimes not enough tissue or not enough DNA is present on these samples. So then we asked, “Could we complement our ability to test for these mutations using tissue alone by adding in plasma-based sequencing?” We conducted a follow-up trial with about 300 patients here [at the University of Pennsylvania] and found that by adding plasma-based approaches, using 2 tubes of blood, we could get [results] relatively easier compared with tissue-based sequencing. We were able to increase our detection of molecular alterations from about 20% to about 36%—a significant increase. This means that more patients were able to get targeted therapy, receive a drug based on their molecular profile, and have significant benefit. Patients were able to avoid chemotherapy or immunotherapy.

We are currently doing much more with liquid biopsies [and are] really looking at the dynamics of circulating tumor DNA [ctDNA], to guide whether patients are responding to
In other words, you can regularly draw blood to see how the therapy is progressing?

A: Exactly. That's the point: We can [check progress] in a minimally invasive way.

How can you learn so much through liquid biopsies for solid tumors in lung cancer?

A: Lung cancer is among the leading cancer subtypes where liquid biopsies are being used. That's because a significant amount of ctDNA is shed into the bloodstream in patients with advanced disease. Also, lung cancer has so many different [molecular, actionable] subtypes that now have targetable drugs. We can say [to a patient], “You have an EGFR mutation” or “You have a MET exon 14 [skipping] mutation—I’m going to give you a pill.” There is more actionability in lung cancer than in other diseases. However, breast cancer, gastrointestinal cancer, and genitourinary cancer are all now [using] liquid biopsies and expanding the space to utilize it in the clinical setting.

Are we getting closer to being able to substitute liquid biopsies for tumor samples?

A: I think we are getting there. We’re not completely there, because we still need a few things from tissue samples. We can never characterize the cell type or the architecture of a tumor, which are still very necessary, with a liquid biopsy. Looking at tissue is still extremely important, no matter what. I think plasma or liquid biopsies will be essential to give us information about the rest of the tumor. In fact, it sometimes gives us a clearer picture of the heterogeneous nature of the tumor, so we can get a sense of the cells that may have more metastatic potential and may have a slightly different mutational profile. We can gather that [information] much better than we can with a single small biopsy.

How can you determine how well a treatment is going?

A: The most obvious indication that [a treatment is working is] less tumor. However, we’re also looking at other things like methylation signatures, RNA sequencing, and changes in mutational profile over time that may help us eventually [determine how treatment is going].

Can you discuss when to use targeted therapy vs immunotherapy to treat lung cancer?

A: We have learned a great deal about when to use targeted therapy in lung cancer. We need to know a patient’s molecular subtype. One way we [learn] that is by using both tissue and plasma sequencing, which is a must. Once we know the molecular subtype, the next question is how we utilize the information to guide therapy. In my mind, the question is not who should get chemotherapy, but who can avoid chemotherapy in this day and age. I feel that with the explosion of immunotherapy, we can now deliver immunotherapy safely with a survival benefit for most of our patients. There will always be a subset who don’t get immunotherapy, but the vast majority of our patients can, and we use PD-L1 testing to determine which patients can get immunotherapy alone. Again, that’s only for a small subset of patients; for [the rest, we’re still] using a combination of chemotherapy and immunotherapy.

What have you learned about the mechanism of action for immunotherapies? Does that affect the strategy for deploying them against lung cancer?

A: The premise of immunotherapy is reactivating the immune system and harnessing the power of T cells during cancer treatment. We know that our T cells as well as our bodies are inherently programmed to fight cancer. However, cancer cells may express inhibitory molecules; these can then be inhibited using PD-L1 inhibitors, potentially creating the immune response again. That’s the premise; the immune activation that’s inherent in the immune system to fight cancer.

What have we learned about managing immune-related AEs (irAEs)?

A: Many guidelines now help us with managing irAEs in a stepwise fashion, including guidelines from the National Comprehensive Cancer Network, the Society for Immunotherapy of Cancer, and the American Society of Clinical Oncology. I’d [like to] add that recent evidence suggests that the presence of irAEs in patients who receive immunotherapy may be related to better outcomes, depending on the grade of AEs. Preliminary data, at least, suggest that grade 2 and 3 AEs may be better in terms of predicting for an improved outcome to immunotherapy, which I think is very interesting. It’s reminiscent of the “old days” when we used to look at things like rash from EGFR inhibitors [to] tell us that the drug is working, [and] also that they are more likely to see a response.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

REFERENCES


Value of Geriatric Assessment in Patients With Genitourinary Carcinoma

Quirin Zangl, MD1; Julika Wirth, MD2; Alexander Karl, MD3; Christian Stief, MD4; Bernhard Zwissler, MD5; Vera von Dossow, MD6

ABSTRACT

OBJECTIVES: This work aims to evaluate comprehensive geriatric assessment (CGA) tools to better guide patients with urogenital carcinomas perioperatively and, consequently, to intensify or reduce hospital resource use.

METHODS: After informed consent, 111 patients were included, all aged more than 65 years, with oncological surgery (with proof of a malignancy), a Mini Mental State Examination (MMSE) score of at least 23 points, and a prospective life expectancy of more than 2 months. Patients were divided into 2 groups: prostate cancer (n = 88) and distal urinary tract cancer (n = 29). Further CGA tools were Instrumental Activities of Daily Living (iADL), Activities of Daily Living (ADL), and the Charlson Comorbidity Index (CCI). The relationships between CGA and complications, hospital duration, death rate, and baseline characteristics were analyzed.

RESULTS: In comparison with the patients with prostate cancer, those with kidney/distal urinary tract cancer had higher CCI scores (median, 3 vs 2; \( P < .001 \)), MMSE scores (29 vs 28; \( P = .031 \)), complication rates (55.2\% vs 22.0\%; \( P = .001 \)), and hospital duration (16 vs 10 days; \( P < .001 \)), as well as more deaths in the group (8 vs 0). Comorbidities (6 vs 2; \( P < .001 \)), Physical Status Classification System (ASA state [3 vs 2; \( P < .001 \)]), and median age (74 vs 71 years; \( P = .008 \)) were all higher in the kidney/distal urinary tract group, and they had fewer problems with postoperative ADL items, which were significantly lower than those of the prostate group (\( P = .043 \)). Intra- and intergroup comparisons of preoperative and 1-year ADL/iADL values did not differ significantly.

CONCLUSION: These study results underscore the importance of CGA in patients with genitourinary carcinoma; most patients have high regenerative potential. Patients with kidney/distal urinary tract cancers are older, have more comorbidities, and have more postoperative impairments than patients with prostate cancer.

PERSPECTIVE: Nora Kovar, MD, MPH; and Melissa L. Teply, MD, provide perspective on page 624
1. Introduction
As life expectancy increases worldwide, so does the incidence of malignant tumors in surgical subspecialties like urology. While the surgical treatment of urological cancers is very standardized today, protocols that address individual life circumstances are still rare in clinical routine. If a patient already has problems managing the requirements of normal day-to-day life, exacerbated stress reactions due to an operation can undoubtedly worsen this. In contrast, an untreated malignant carcinoma usually causes death; therefore, it is critically important to address individualized perioperative therapy strategies. The expression “patient empowerment” is increasingly gaining clinical acceptance, meaning clinicians may focus on better adjusting treatment strategies individually, detecting patients who are at risk of being over- or under-treated, and possibly improving such outcome parameters as morbidity, mortality, length of hospital stay, and complication rates. Due to the increasing number of elderly people with malignant genitourinary carcinomas, comprehensive geriatric assessments (CGA), including the Activities of Daily Living score (ADL), modified by Barthel, and the Instrumental Activities of Daily Living score (iADL), promoted by Lawton and Browdy, are gaining increasing acceptance. Additional CGA instruments, like the Mini Mental State Examination (MMSE) and the Charlson Comorbidity Index (CCI), should help detect patients who are at increased risk for worse postoperative outcomes. Additional factors like age, medical comorbidities, psychosocial disorders, specific geriatric conditions, previous health care utilization, and private living situation are integrated into a holistic and therapeutic concept for patients 65 years and older. This article uses ADL and iADL as standardized tools to evaluate their efficacy in order to allocate resources properly during urological cancer surgery. The predictive value of ADL and iADL scores in geriatric patients with cancer has been long established. To the best of our knowledge, there is no literature around functional status in geriatric patients specific to genitourinary carcinomas. In the work below, we aim to evaluate the aforementioned CGA tools to better guide surgical patients with urogenital carcinomas perioperatively and, consequently, intensify or reduce hospital resource use.

2. Materials and Methods
2.1. Enrollment of patients, data collection, and inclusion and exclusion criteria
This trial is a substudy of the previously published PERATECS project (NCT01278537). All patients provided written informed consent for data collection and publication. The Institutional Review Board of the Charité - Universitätsmedizin Berlin approved the study protocol in January 2009 (EA1/241/08). The clinical substudy took place at the Department of Anesthesiology at Ludwig-Maximilians-University Munich. A total of 305 patients in the urologic ward were screened between April 2011 and July 2012, 111 of whom participated in this study (Ethic-Nr: 2011_095_11). All patients fulfilled the inclusion criteria, which included minimum age of 65 years, giving consent and written approval, oncological surgery (with proof of a malignancy), an MMSE score of at least 23 points, and a prospective life expectancy of more than 2 months.

Patients were excluded from the study if any of the following were missing: written informed consent, participation ability, accommodation in an institution on judicial or official order, emergency interventions and ambulant patients, lacking willingness to save and hand out data within the study or ability to understand the German language. Patients were also excluded if they were an employee of one of the study centers; had 2 or more carcinomas; were included in an adjuvant therapy study at some point during PERATECS; or participated in a different clinical study.

2.2. Investigators, time points, and CGA tools
All investigators received training before the onset of the study.

FIGURE 1. Perioperative Assessment Time Points
PREOPERATIVE ASSESSMENT → OP → POSTOPERATIVE ASSESSMENT → ASSESSMENT AFTER 12 MONTHS
ADL, Activities of Daily Living; iADL, Instrumental Activities of Daily Living; OP, surgical intervention
ADL examination per Bartel⁶ and iADL per Lawton and Brody⁴ were used in this trial. The ADL and iADL examinations took place using a standardized questionnaire at 3 time points: preoperatively; on the eighth day after surgery; and 12 months after hospital discharge (Figure 1). Additional and well-established CGA tools used in this trial were the MMSE⁵ and the CCI⁴ tests.

Additionally, Nursing Delirium Screening (NuDESC) was used as a clinically accepted standard tool to diagnose delirium. In each case, a 12-month follow-up after hospital discharge was performed. The ADL and iADL surveys were also performed after 1 year. Including the 12-month follow-up, the survey lasted until July 2013.

2.3. Additional clinical and demographic parameters
Age, body mass index (BMI), Physical Status Classification System of the American Society of Anesthesiologists (ASA) state, length of hospital stay, and the number of medications were analyzed, to be further correlated with the CGA results. Other registered perioperative characteristics included histological confirmation of malignancy and

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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>71 (IQR, 68-74)</td>
<td>74 (IQR,74-79.5)</td>
<td>.008</td>
</tr>
<tr>
<td>70-79</td>
<td>n = 30 (36.6%)</td>
<td>n = 7 (24.1%)</td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>n = 49 (59.8%)</td>
<td>n = 15 (51.7%)</td>
<td></td>
</tr>
<tr>
<td>Gender: Male</td>
<td>n = 82 (100%)</td>
<td>n = 20 (69.0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>n = 0</td>
<td>n = 9 (31.0%)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²:</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>18.5-19.9</td>
<td>25.92 ± 3.01</td>
<td>26.02 ± 3.83</td>
<td></td>
</tr>
<tr>
<td>20-21.9</td>
<td>n = 2 (2.4%)</td>
<td>n = 0</td>
<td></td>
</tr>
<tr>
<td>22-26.9</td>
<td>n = 3 (3.7%)</td>
<td>n = 4 (13.8%)</td>
<td></td>
</tr>
<tr>
<td>27-29.9</td>
<td>n = 43 (52.4%)</td>
<td>n = 12 (41.4%)</td>
<td></td>
</tr>
<tr>
<td>30-34.9</td>
<td>n = 25 (30.5%)</td>
<td>n = 9 (31.0%)</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ASA1</td>
<td>2 (IQR, 2-2)</td>
<td>3 (IQR, 3-3)</td>
<td></td>
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<tr>
<td>ASA2</td>
<td>n = 8</td>
<td>n = 0</td>
<td></td>
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<tr>
<td>ASA3</td>
<td>n = 61</td>
<td>n = 12</td>
<td></td>
</tr>
<tr>
<td>ASA4</td>
<td>n = 13</td>
<td>n = 16</td>
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</tr>
<tr>
<td>Number of daily medications</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0-2</td>
<td>2 (IQR, 1-4)</td>
<td>6 (IQR, 5-6.5)</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>n = 49 (59.8%)</td>
<td>n = 3 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>n = 26 (31.7%)</td>
<td>n = 11 (37.9%)</td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td></td>
<td></td>
<td>.031</td>
</tr>
<tr>
<td>25</td>
<td>29 (IQR, 28-30)</td>
<td>28 (IQR, 28-29)</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>n = 1</td>
<td>n = 0</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>n = 3</td>
<td>n = 2</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>n = 3</td>
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</tr>
<tr>
<td>29</td>
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<td>30</td>
<td>n = 28</td>
<td>n = 9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 29</td>
<td>n = 5</td>
<td></td>
</tr>
</tbody>
</table>

ASA, Physical Status Classification System by American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; MMSE, Mini Mental State Examination; NA, not applicable; NS, not significant.

Values in bold indicate statistical significance.
perioperative complications (eg, bleeding with hemoglobin levels lower than 2 g/dl, abdominal wound rupture); infections (eg, wound infections, body core temperature >39 °C); NuDESC score >2; cardiopulmonary complications (eg, acute respiratory distress syndrome, atrial fibrillation and other rhythm diseases, dyspnea, pleural effusion); musculoskeletal complications (eg, joint effusions); gastrointestinal complications (eg, meteorism, nausea, emesis, diarrhea, constipation); extraordinary pain (ie, Visual Analogue Scale score >5), and urogenital complications (eg, urinary stasis, urinary tract infections).

2.4. Data collection and statistical analysis
In total, 305 urologic patients were screened, of whom 199 fulfilled the inclusion criteria; subsequently, 17 declined to participate and 9 had histological confirmation of an oncocytoma, which is definitively nonmalignant. Sixty-two patients were lost to follow-up. The remaining 111 patients were subdivided into groups according to their diagnosis: Group 1: prostate cancer; and Group 2: kidney/distal urinary tract cancers (carcinomas of urinary bladder and ureter; Figure 2).

Statistical analysis was performed with SPSS 15.0 (IBM Statistics). After confirmation for normal distribution, continuous data were displayed as mean (SD) and further analyzed with a t-test. Without normal distribution, data were presented as the median, 25% and 75% quartile, and further analyzed with the Mann-Whitney U test. Descriptive statistics were used for additional clinical and demographic parameters, including age, BMI, ASA state, length of hospital stay, and the number of medications. For ADL and iADL, which are nonparametrical parameters, differences were observed between the states before the operation, directly after the operation, and 12 months postoperatively. For further ADL and iADL analysis, the Wilcoxon test was used. If 3 or more groups were analyzed, a Kruskal-Wallis test was used. A Spearman correlation test was performed to detect correlations among length of hospital stay, perioperative complications, and mortality. A P value below .05 was considered significant.

3. Results
3.1. Patient characteristics
Patients with kidney/distal urinary tract carcinoma were older (median age, 71 vs 74 years; P < .008). They also had significantly more comorbidities (median CCI score, 3 vs 2; P < .001), a higher ASA state (3 vs 2; P < .001), and significantly more preoperative medications (6 vs 2; P < .001). Preoperative MMSE scores were comparable (29 for prostate vs 28 for kidney/distal urinary tract; P = .031) (Table 1).
**Clinically Meaningful Outcome Measures: A Role for Geriatric Assessment**

The authors in the accompanying article employ function-based geriatric assessment in the pre- and postoperative evaluation of older adults. Traditionally, “preoperative risk assessment” refers to cardiac, pulmonary, or infectious risk, with mortality (for good reason) as the primary measure of surgical outcome. In geriatric patients, this approach often misses important aspects of the patient's condition (eg, functional dependence) that are relevant not only for care teams as they make treatment plans but also for patients as they anticipate what their course of treatment might look like. Ongoing emphasis on more comprehensive assessment—including functional status—will help to refine the evaluation of geriatric patients across disciplines and could improve conversations with patients and families regarding their care.

For both patients and their families, good recovery is closely linked with function. In studies from various surgical disciplines, poor postoperative functional status has been associated with lower quality-of-life scores for patients, as well as increased burden for their caregivers. Functional recovery also has important implications from a systems-based perspective, because postoperative functional deficits have also been associated with increased healthcare utilization and costs.

In recent years, geriatric assessment that is more comprehensive in scope has gained attention as part of preoperative evaluation and pretreatment evaluation of oncology patients more broadly and can be easily incorporated without abandoning more traditional outcome measures. For example, poor preoperative functional status has been associated with increased postoperative morbidity and mortality, higher rates of perioperative complications, increased length of stay, and discharge to a nonhome setting. Many researchers have also begun to explore “prehabilitation”—therapy aimed at enhancement of functional status before surgery—as an approach that might improve these outcomes.

Fewer studies include functional status (eg, activities of daily living [ADL] dependence) among their postoperative measures; however, available results have yielded useful insights. In recent studies of older surgery patients, including oncologic surgery patients, higher scores from a preoperative geriatric assessment tool that included functional status, mood, cognition, and mobility were associated with increased probability of both geriatric and surgical complications, increased length of stay, and increased postdischarge needs, including new functional dependence. Of note, the tool employed was able to be administered in a clinic setting in less than 10 minutes.

Creating a shared understanding of likely outcomes—including less traditional outcomes such as functional status—among providers, patients, and families is an important part of surgical planning.

The accompanying article evaluated patients’ functional status at 3 time points: preoperatively, at postoperative day 8, and 12 months after hospital discharge. This approach adds clarity to what patients can expect in their postoperative course and would provide useful information for providers to reference in approaching shared decision-making. Also of note is the significant correlation between ADL status and lethality in the distal urinary tract surgery group, particularly given that ADL assessment requires little more than completion of a questionnaire.

As the population ages and becomes more comorbid, performing thorough but efficient preoperative assessment will become increasingly critical. Moreover, these higher-complexity patients will require more nuanced conversations regarding potential risks and benefits of treatments. Incorporating more comprehensive geriatric assessment and focusing on practical, functional measures will aid providers not only in preparing to care for their patients but in setting realistic expectations for patients and families. Future research should include such measures not only preoperatively, but throughout the postoperative timeline.

**REFERENCES**


3.2. Daily life activities after the operation and after 1 year

Although both groups reached good levels of daily life activities after 1 year, there were significant differences in daily life activities (both ADL and iADL) directly after the operation and 1 year later. Both groups were taken together and statistically evaluated together here (Table 2).

iADL values were comparable in both groups preoperatively and after 1 year. ADL values decreased by 10 points in both groups postoperatively, with a significantly worse performance in the kidney/distal urinary tract group (P = .041). Nevertheless, the intergroup difference of ADL values diminished to a nonsignificant level again one year after surgery (Table 2).

3.3. Correlation of CGA values with outcome parameters

The correlation analysis accounted for both patient groups, and associations among mortality, complication rates, length of hospital stay, and comorbidities were investigated. Before the operations, there was a significant negative correlation between ADL values and mortality (P = .017). A lower ADL value after the operation was associated with longer length of hospital stay (P = 0). All other pre-and postoperative ADL and iADL values did not have significant correlations with relevant outcome parameters (Table 3).

3.4. Correlation of mortality with complication rates, comorbidities, and length of hospital stay

Eight patients in the kidney/distal urinary tract group died postoperatively, resulting in highly significant associations among perioperative complications (P = .004; r [correlation coefficient] = 0.268), length of hospital stay (P < .001; r = 0.524), and higher CCI score (P < .001; r = 0.649).

4. Discussion

This investigation was the first prospective and structured analysis of CGA for

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Tepli is an internist at the University of Nebraska Medical Center. She is Board Certified in Hospice and Palliative Medicine.
patients with genitourinary carcinoma who were undergoing surgery (prostate vs kidney/distal urinary tract cancer surgery). The associations of scores derived from geriatric assessment tools (ADL, iADL, MMSE, CCI), coexisting medical data (including age, ASA status, BMI, and regular medication), and morbidity, mortality, hospital length of stay, and complication rates were analyzed. CGA can help caregiver to use resources more effectively and possibly make better decisions for elderly patients.7,8

Patients with kidney/distal urinary tract cancer were shown to have much higher perioperative risks than those undergoing prostate cancer surgery. This was demonstrated by higher preoperative comorbidities (higher ASA state, more medications, older age, and lower MMSE) and worse postoperative performance (lower ADL values, longer hospital stays, and more complications).

Among this study’s main findings was the significant association in the kidney/distal urinary tract group between mortality and postoperative complications, higher CCI score, and length of hospital stay; no patients in the prostate group died. It must be noted that urinary bladder and ureter surgery usually is longer and more invasive (eg, affection of

### TABLE 2. Intergroup Comparison of Activities of Daily Living.

<table>
<thead>
<tr>
<th>Activities of daily life</th>
<th>Median value (both groups)</th>
<th>Median value prostate group</th>
<th>Median value distal urinary tract group</th>
<th>Intergroup comparison: P</th>
<th>Merged differences pre/post/12-month OP: P</th>
</tr>
</thead>
<tbody>
<tr>
<td>iADL preoperative</td>
<td>8 (IQR, 8-8)</td>
<td>8 (IQR, 8-8)</td>
<td>8 (IQR, 8-8)</td>
<td>NS</td>
<td>NA</td>
</tr>
<tr>
<td>iADL after 12 months</td>
<td>8 (IQR, 7-8)</td>
<td>8 (IQR, 7-8)</td>
<td>8 (IQR, 7-8)</td>
<td>NS</td>
<td>iADL pre -12-month P &lt; .001</td>
</tr>
<tr>
<td>ADL preoperative</td>
<td>100 (IQR, 100-100)</td>
<td>100 (IQR, 100-100)</td>
<td>100 (IQR, 100-100)</td>
<td>NS</td>
<td>NA</td>
</tr>
<tr>
<td>ADL postoperative</td>
<td>90 (IQR, 85-95)</td>
<td>90 (IQR, 90-95)</td>
<td>90 (IQR, 72.5-95)</td>
<td>.041</td>
<td>ADL pre -post OP P &lt; .001</td>
</tr>
<tr>
<td>ADL after 12 months</td>
<td>100 (IQR, 95-100)</td>
<td>100 (IQR, 95-100)</td>
<td>100 (IQR, 92.5-100)</td>
<td>NS</td>
<td>ADL pre -12-month P &lt; .001</td>
</tr>
</tbody>
</table>

ADL, Activities of Daily Living; iADL, Instrumental Activities of Daily Living; IQR, interquartile range; NA, not applicable; NS, not significant; OP, surgical intervention.

Values in bold are statistically significant.

Table 2 shows median preoperative, immediately postoperative, and 1-year postoperative iADL and ADL values. Merged group changes are displayed in column 6. According to the very large interquartile distances of ADL/iADL values, significant differences arose here. Comparison of both groups (prostate vs distal urinary) shows differences only in direct postoperative ADL values.

### TABLE 3. Correlation of CGA Values With Outcome Parameters

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Complications</th>
<th>Hospital length of stay</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL preoperative</td>
<td>P = .017</td>
<td>P = NS</td>
<td>P = NS</td>
<td>P = NS</td>
</tr>
<tr>
<td></td>
<td>r = -2.225</td>
<td>r = -.113</td>
<td>r = -.125</td>
<td>r = -.160</td>
</tr>
<tr>
<td>ADL immediately postoperative</td>
<td>P = NS</td>
<td>P = NS</td>
<td>P = .000</td>
<td>P = NS</td>
</tr>
<tr>
<td></td>
<td>r = -.084</td>
<td>r = -.161</td>
<td>r = -.336</td>
<td>r = -.178</td>
</tr>
<tr>
<td>ADL after 12 months</td>
<td>NA</td>
<td>P = NS</td>
<td>P = NS</td>
<td>P = NS</td>
</tr>
<tr>
<td></td>
<td>r = .133</td>
<td>r = .041</td>
<td>r = -.002</td>
<td>r = -.090</td>
</tr>
<tr>
<td>iADL preoperative</td>
<td>P = NS</td>
<td>P = NS</td>
<td>P = NS</td>
<td>P = NS</td>
</tr>
<tr>
<td></td>
<td>r = .038</td>
<td>r = -.057</td>
<td>r = -.031</td>
<td>r = -.147</td>
</tr>
<tr>
<td>iADL after 12 months</td>
<td>NA</td>
<td>P = NS</td>
<td>P = NS</td>
<td>P = NS</td>
</tr>
<tr>
<td></td>
<td>r = -.069</td>
<td>r = .000</td>
<td>r = -.147</td>
<td></td>
</tr>
</tbody>
</table>

ADL, activities of daily life; CGA, comprehensive geriatric assessment; iADL, instrumental activities of daily living; NA, not applicable; NS, not significant; r, correlation coefficient.

Table 3 shows the preoperative, immediately postoperative, and 1-year postoperative iADL and ADL values and their correlation with mortality, complications, length of hospital stay, and comorbidities. The only significant associations existed between preoperative ADL values and mortality (for both groups) and postoperative ADL value and hospital length of stay. Significant values are shown in bold. All other correlations were not significant.
bowel, adhesions, etc.). These findings point to the requirement to intensify geriatric care in this group due to their higher needs.\textsuperscript{3-10} Such a requirement is even more important when considering the utility of CGA implementation in possibly decreasing perioperative costs, as is well established in other surgical subspecialties.\textsuperscript{11-14} Prostate cancer is not often associated with many comorbidities in most patients,\textsuperscript{15-18} in contrast to patients with kidney cancer.\textsuperscript{16-18}

Both groups suffer from significant postoperative impairment in daily life activities, although impairment in patients with kidney/distal urinary tract cancers is generally worse. While ADL and iADL values tend to reach baseline values after 1 year, indicating the high regenerative potential of most individuals of both groups, median daily life performance is significantly worse immediately postoperatively.

An association already exists among comorbidity, number of medications taken, and worse outcome parameters for other critical patients (eg, those with ischemic stroke).\textsuperscript{15} In this study, we demonstrated a highly significant association between preoperative ADL value and mortality for the first time in patients undergoing urological surgery, as is already established in orthopedics,\textsuperscript{19} strongly highlighting the need for CGA. Another main finding was the significant association between lower postoperative ADL value and length of hospital stay, according to the existing knowledge of urological surgical treatment.\textsuperscript{20,21}

Operative protocols are very standardized today, but adjustments to do justice to the individual needs could possibly be better achieved by using CGA. Making these adjustments for urological patients might improve their outcomes, reduce costs, and improve their quality of life.\textsuperscript{2}

\textbf{DISCLOSURES AND CONFLICT OF INTEREST STATEMENTS:} All authors declare that there are no financial conflicts of or other conflicts of interest to disclose


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\textbf{KAY REFERENCES}

For references visit cancernetwork.com/Zangl_10.21
In the treatment of newly diagnosed, transplant-ineligible multiple myeloma:

**ADD TO THE MOMENTUM WITH DARZALEX® + Rd IN FRONTLINE**

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

**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 nausea. 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
**Powerful efficacy to start the treatment journey**

After a median ~30 months of follow-up, **mPFS was not reached** with DARZALEX® + Rd vs 31.9 months with Rd alone.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).1

**44% reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.56; 95% CI, 0.43–0.73; P=0.0001)

**Demonstrated safety profile** (median treatment duration of 25.3 months)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 asthenia.

- Serious adverse reactions with ≥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%).

**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.1

**Efficacy results in long-term follow-up**2,3 At median ~5 years of follow-up, **mPFS was not reached** with DRd vs 34.4 months with Rd alone.2

- 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).2

**47% reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.53; 95% CI, 0.43–0.66)

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

**Safety results in long-term follow-up** (median treatment duration of 47.5 months)2 At median ~5 years of follow-up2,3:

- Most frequent TEAEs ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthma, 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 IRRs ≥10% were pneumonia (DRd 54% vs Rd 29%), bronchitis (DRd 15% vs Rd 2%), pneumonia (DRd 11% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%).

CI=confidence interval. DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio. IRR=Injection-related reaction; mPFS=Median progression-free survival. 1

**CI=confidence interval. DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio. IRR=Injection-related reaction; mPFS=Median progression-free survival. 1**

**with an ~3 to 5 minute subcutaneous injection. DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab1,2**

These ~5-year analyses are not included in the current prescribing information.

**Visit FrontlineMomentum.com**

**With an ~3 to 5 minute subcutaneous injection. DARZALEX FASPRO® can be administered substantially faster than intravenous daratumumab**1,2

See the latest data rolling out.

**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.**

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

**DARZALEX FASPRO®: 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®.

**Systemic Reactions**

- In a pooled safety population of 832 patients with multiple myeloma (N=639) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 0.8%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 7 minutes to 3.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (85%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

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

- Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®.

**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 5.5 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, increased 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 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

Based on the mechanism of action, 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 areeligible 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.
**DARZALEX® (daratumumab) injection, for intravenous use**

**Brief Summary of Full Prescribing Information**

**INDICATIONS AND USAGE**

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

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are eligible 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 eligible 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.
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

**CONTRAINDICATIONS**

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation [see Warnings and Precautions].

**WARNINGS AND PRECAUTIONS**

**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 [see Adverse Reactions].

In clinical trials (monotherapy and combination: N=2,066), 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 on Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 72 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

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, oral or throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension [see Adverse Reactions].

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 rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4) [11%] with those reported in previous studies at Week 2 or subsequent infusions.

In EQUEULUS, patients receiving combination treatment (n=92) who were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 38% 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: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions 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 (2.4) in Full Prescribing Information]. 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 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 chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease [see Dosage and Administration (2.3) in Full Prescribing Information].

**Interference with Serological Testing**

Daratumumab binds to CD3 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 infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum [see References]. The determination of a patient’s ABO and Rh blood type are not impacted [see Drug Interactions].

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

**Neutropenia**

DARZALEX may increase neutropenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

**Thrombocytopenia**

DARZALEX may increase thrombocytopenia induced by background therapy [see Adverse Reactions].

Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

**Interference with Determination of Complete Response**

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

**Embyro-Fetal Toxicity**

Based on the mechanism of action, DARZALEX can cause fetal harm when administered to a pregnant woman. DARZALEX 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 and for 3 months after the last dose [see Use in Specific Populations].

The combination of DARZALEX 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.

**ADVERSE REACTIONS**

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

- Infusion-related reactions [see Warnings and Precautions].
- Neutropenia [see Warnings and Precautions].
- Thrombocytopenia [see Warnings and Precautions].

**Clinical Trials Experience**

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX in monotherapy. In this pooled safety population, the most common adverse reactions (≥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.
Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA (see Clinical Studies (14.1) in Full Prescribing Information). Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.44 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd 1%).

Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>Rd (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>57</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Anemia</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Chills</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>30</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX in combination with bortezomib, melphalan and prednisone was evaluated in ALCYONE (see Clinical Studies (14.1) in Full Prescribing Information). Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 14.7 months (range: 0 to 25.8 months) for daratumumab, bortezomib, melphalan and prednisone (D-VMP) and of 12 months (range: 0.1 to 14.9 months) for VMP.

Serious adverse reactions with at least a 2% greater incidence in the D-VMP arm compared to the VMP arm were pneumonia (D-VMP 11% vs VMP 4%), upper respiratory tract infection (D-VMP 5% vs VMP 1%), and pulmonary edema (D-VMP 2% vs VMP 0%).

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>DRd (N=364)</th>
<th>Rd (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td>13</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>84</td>
<td>41</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>84</td>
<td>41</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>4</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
| Key: D=daratumumab, Vmp=bortezomib-melphalan-prednisone

Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the D-VMP Arm in ALCYONE

<table>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>D-VMP (N=346)</th>
<th>VMP (N=354)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>16</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone

Atrial fibrillation, Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection
pneumonia, lung infection, pneumonia aspiration, pneumonia bacterial, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, and pneumonia sepsis.

- Infusion-related reaction includes terms determined by investigators to be related to infusion.

- Edema peripheral, generalized edema, peripheral swelling.

- Cough, productive cough.

- Dyspnea, dyspnea exertional.

- Hypertension, blood pressure increased.

Laboratory abnormalities worsening during treatment from baseline listed in Table 4.

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in ALCYONE

<table>
<thead>
<tr>
<th>Body System</th>
<th>D-VMP (N=346)</th>
<th>VMP (N=354)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>88</td>
<td>27</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>84</td>
<td>34</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>85</td>
<td>46</td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td>18</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone.

Newly Diagnosed Multiple Myeloma Eligible for Autologous Stem Cell Transplant Combination Treatment with Bortezomib, Thalidomide and Dexamethasone (DVTd)

The safety of DARZALEX in combination with bortezomib, thalidomide and dexamethasone was evaluated in CASSIOPEIA [see Clinical Studies (14.1) in Full Prescribing Information]. Adverse reactions described in Table 5 reflect exposure to DARZALEX up to day 100 post transplant. The median duration of induction/ASCT/consolidation treatment was 8.9 months (range: 7.0 to 12.0 months) for DVTd and 8.7 months (range: 6.4 to 11.5 months) for VTd.

Serious adverse reactions with a 2% greater incidence in the DVTd arm were bronchitis (DVTd 2% vs VTd <1%) and pneumonia (DVTd 6% vs VTd 4%).

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DVTd Arm in CASSIOPEIA

<table>
<thead>
<tr>
<th>Body System</th>
<th>DVTd (N=536)</th>
<th>VTd (N=538)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactionsa</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectionb</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Bronchitisc</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, VTd=bortezomib-thalidomide -dexamethasone.

- a Infusion-related reaction includes terms determined by investigators to be related to infusion.

- b Laryngitis, Laryngitis viral, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection.

- c Bronchitis, Bronchitis, Bronchitis chronic, Respiratory syncytial virus bronchitis, Tracheobronchitis.

- d Cough, Productive cough.

Note: Hematology laboratory related toxicities were excluded and reported separately in the table below.
DARZALEX® (daratumumab) injection

Laboratory abnormalities worsening during treatment from baseline listed in Table 8.

<table>
<thead>
<tr>
<th>Table 8: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>47</td>
<td>5</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactionsa</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>Peripheral edema b</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectionc</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughd</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnæa e</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

Combination Treatment with Twice-Weekly 20/56 mg/m² Carfilzomib and Dexamethasone

The safety of DARZALEX in combination with twice weekly carfilzomib and dexamethasone was evaluated in CANDOR (see Clinical Studies [14.2] in Full Prescribing Information). Adverse reactions described in Table 11 reflect exposure to DARZALEX for a median treatment duration of 16.1 months (range: 0.1 to 23.7 months) for the carfilzomib-dexamethasone (DKd) group and median treatment duration of 5.3 months (range: 0.9 to 25.0 months) for the daratumumab-carfilzomib-dexamethasone (DKd) group.

Serious adverse reactions occurred in 14% of patients who received DARZALEX in combination with Kd and 42% of patients who received Kd.

The most frequent serious adverse reactions reported in the DKd arm as compared with the Kd arm were pneumonia (DKd 14% vs Kd 9%), pyrexia (DKd 4.2% vs Kd 2.0%), influenza (DKd 3.9% vs Kd 1.3%), sepsis (DKd 3.3% vs Kd 1.3%), anemia (DKd 2.3% vs Kd 0.7%), bronchitis (DKd 1.9% vs Kd 0.7%), and diarrhea (DKd 1.6% vs Kd 0%). Fatal adverse reactions within 30 days of the last dose of any study treatment occurred in 10% of 398 patients who received DARZALEX in combination with Kd versus 5% of 153 patients who received Kd. The most frequent fatal adverse reaction was infection (4.5% vs 2.6%).

Permanent discontinuation of DARZALEX due to an adverse reaction occurred in 9% of patients. Adverse reactions (≥1%) which resulted in permanent discontinuation of DARZALEX included pneumonia.

Infiltration-related reactions that occurred on the day of administration of any DARZALEX dose or on the next day occurred in 18% of patients and that occurred on the day of administration of the first DARZALEX dose or the next day occurred in 12%.

<table>
<thead>
<tr>
<th>Table 11: Adverse Reactions (≥15%) in Patients Who Received DARZALEX in Combination with Carfilzomib and Dexamethasone (DKd) in CANDOR</th>
<th>DKd (N=308)</th>
<th>Kd (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3 or 4 (%)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactionsa</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>Fatigueb</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
<td>1.9</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infectionc</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>17</td>
<td>2.6</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopeniab</td>
<td>37</td>
<td>25</td>
</tr>
<tr>
<td>Anemiaa</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>3.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughd</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnæa e</td>
<td>20</td>
<td>3.9</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>18</td>
<td>3.9</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>16</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

Laboratory abnormalities worsening during treatment are listed in Table 10.
Key: D=daratumumab; Kd=carfilzomib-dexamethasone

- The incidence of infusion related reactions is based on a group of symptoms (including hypertension, pyrexia, rash, myalgia, hypotension, blood pressure increased, urticaria, acute kidney injury, bronchospasm, face edema, hypersensitivity, rash, syncope, wheezing, eye pruritus, eyelid edema, renal failure, swelling face) related to infusion reactions which occurred within 1 day after DKd or Kd administration.
- Fatigue includes fatigue and asthenia.
- Respiratory tract infection includes respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection and viral upper respiratory tract infection.
- Thrombocytopenia includes platelet count decreased and thrombocytopenia.
- Anemia includes anemia, hematocrit decreased and hemoglobin decreased.
- Cough includes productive cough and cough.
- Includes fatal adverse reactions.

**Adverse Reactions Occurring at a Frequency of < 15%**

- **Blood and lymphatic system disorders**: neutropenia, lymphopenia, leukopenia, febrile neutropenia
- **Cardiac disorders**: atrial fibrillation
- **Gastrointestinal disorders**: vomiting, constipation
- **General disorders and administration site conditions**: peripheral edema, asthma, chills
- **Infections**: influenza, urinary tract infection, sepsis, septic shock
- **Metabolism and nutrition disorders**: decreased appetite, hyperglycemia, hypocalcemia, dehydration
- **Musculoskeletal and connective tissue disorders**: muscle spasms, arthralgia, musculoskeletal chest pain
- **Nervous system disorders**: headache, dizziness, peripheral sensory neuropathy, paraesthesia, posterior reversible encephalopathy syndrome
- **Respiratory, thoracic and mediastinal disorders**: pulmonary edema
- **Skin and subcutaneous tissue disorders**: rash, pruritus

Combination Treatment with Once-Weekly (20/70 mg/m²) Carfilzomib and Dexamethasone

The safety of DARZALEX in combination with once-weekly carfilzomib and dexamethasone was evaluated in EQUULEUS [see Clinical Studies (14.2) in Full Prescribing Information]. Adverse reactions described in Table 12 reflect exposure to DARZALEX for a median treatment duration of 19.8 months (range: 0.3 to 34.5 months).

Serious adverse reactions were reported in 48% of patients. The most frequent serious adverse reactions reported were pneumonia (4.7%), upper respiratory tract infection (4.7%), basal cell carcinoma (4.7%), influenza (3.5%), general physical health deterioration (3.5%), and hypercalcemia (3.5%). Fatal adverse reactions within 30 days of the last dose of any study treatment occurred in 3.5% of patients who died of general physical health deterioration, multi-organ failure secondary to pulmonary aspergillosis, and disease progression.

Permanent discontinuation of DARZALEX due to an adverse reaction occurred in 8% of patients. No adverse reactions which resulted in permanent discontinuation of DARZALEX occurred in more than one patient.

Infusion-related reactions that occurred on the day of administration of any DARZALEX dose or on the next day occurred in 44% of patients. For patients who received the split-first dose of DARZALEX, infusion-related reactions that occurred in 36% and 4% on the first and second day of administration of DARZALEX, respectively. Adverse Reactions Occurring at a Frequency of < 15%

- **Blood and lymphatic system disorders**: neutropenia, lymphopenia, leukopenia, febrile neutropenia
- **Cardiac disorders**: atrial fibrillation
- **Gastrointestinal disorders**: pancreatitis
- **General disorders and administration site conditions**: peripheral edema, chills
- **Infections**: pneumonia, urinary tract infection, sepsis, septic shock
- **Metabolism and nutrition disorders**: decreased appetite, hyperglycemia, dehydration, hypocalcemia
- **Musculoskeletal and connective tissue disorders**: muscle spasms, musculoskeletal chest pain, arthralgia
- **Nervous system disorders**: dizziness, paraesthesia, peripheral sensory neuropathy
- **Skin and subcutaneous tissue disorders**: pruritus, rash

Combination Treatment with Pomalidomide and Dexamethasone

The safety of DARZALEX in combination with pomalidomide and dexamethasone was evaluated in EQUULEUS [see Clinical Studies (14.2) in Full Prescribing Information]. Adverse reactions described in Table 13 reflect exposure to DARZALEX, pomalidomide and dexamethasone (PdD) for a median treatment duration of 6 months (range: 0.03 to 16.9 months).

The overall incidence of serious adverse reactions was 49%. Serious adverse reactions reported in ≥5% patients included pneumonia (7%). Adverse reactions resulted in discontinuations for 13% of patients.

### Table 12: Adverse Reactions (≥15%) of Patients Who Received DARZALEX in Combination with Carfilzomib and Dexamethasone in EQUULEUS (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DKd (N=85)</th>
<th>All Grades (%)</th>
<th>Grades 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>88</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>29</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td><strong>General disorder and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>54</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>52</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>37</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>53</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>17</td>
<td>3.5</td>
<td></td>
</tr>
</tbody>
</table>
Laboratory abnormalities worsening during treatment are listed in Table 14.

### Table 14: Treatment-Emergent Hematology Laboratory Abnormalities in EQUULEUS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DPd (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>95</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>94</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75</td>
</tr>
<tr>
<td>Anemia</td>
<td>57</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Pd=pomalidomide-dexamethasone.

Laboratory abnormalities worsening during treatment are listed in Table 14.

### Table 13: Adverse Reactions With Incidence ≥10% Reported in EQUULEUS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DPd (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>50</td>
</tr>
<tr>
<td>Infusion-related reactions&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
</tr>
<tr>
<td>Chills</td>
<td>20</td>
</tr>
<tr>
<td>Edema peripheral&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>15</td>
</tr>
<tr>
<td>Pain</td>
<td>11</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50</td>
</tr>
<tr>
<td>Pneumonia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>15</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Cough&lt;sup&gt;e&lt;/sup&gt;</td>
<td>43</td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;f&lt;/sup&gt;</td>
<td>33</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>16</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
</tr>
<tr>
<td>Constipation</td>
<td>33</td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>26</td>
</tr>
<tr>
<td>Back pain</td>
<td>25</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>15</td>
</tr>
<tr>
<td>Bone pain</td>
<td>13</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>23</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>21</td>
</tr>
<tr>
<td>Tremor</td>
<td>19</td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>16</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Pd=pomalidomide-dexamethasone.

### Table 15: Adverse Reactions With Incidence ≥10% in Patients With Multiple Myeloma Treated With DARZALEX 16 mg/kg

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
</tr>
<tr>
<td>Chills</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>27</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Cough&lt;sup&gt;e&lt;/sup&gt;</td>
<td>21</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>17</td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;f&lt;/sup&gt;</td>
<td>15</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>15</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>15</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
</tr>
</tbody>
</table>

Key: D=daratumumab, Pd=pomalidomide-dexamethasone.

#### Monotherapy

The safety of DARZALEX was evaluated in 156 adult patients with relapsed and refractory multiple myeloma in three open-label, clinical trials. Patients received DARZALEX 16 mg/kg. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months).

Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (8%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 15. Table 16 describes Grade 3-4 laboratory abnormalities reported at a rate of ≥10%.

### Table 16: Treatment-Emergent Grade 3-4 Laboratory Abnormalities (≥10%)
**Interactions**

**Effects of Daratumumab on Laboratory Tests**

**Interference with Indirect Antiblobulin Tests (Indirect Coombs Test)**

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies 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 monocolonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent 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**

**Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)**

**Hepatitis B Virus (HBV) Reactivation**

Hepatitis B virus reactivation has been reported in less than 1% of patients following daratumumab administration. It is important to monitor patients for evidence of HBV reactivation and to initiate antiviral therapy as appropriate. If evidence of HBV reactivation is suspected, continue daratumumab with antiviral therapy and monitor for signs of hepatitis flare. If evidence of HBV reactivation is confirmed, discontinue daratumumab and antiviral therapy and refer the patient to a hepatologist for management.

**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. Deferring administration of live vaccines to neonates and infants exposed to DARZALEX in utero until a hematologic evaluation is completed.

**Lactation**

There is no data on the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, 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 Males of Reproductive Potential**

**Drug Interactions**

**Interactions**

**Infections**

**Cytomegalovirus, Listeriosis**

Inactive controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

**Fatal infections (Grade 5)** were reported as follows:

- **Relapsed/refractory patient studies: DvD: 1%, DvD: 2%; DvD: 2%, DvD: 3%; DvD: 3%, DvD: 0%**
- **where carfilzomib 20/56 mg/m² was administered twice-weekly**
- **where carfilzomib 20/56 mg/m² was administered once-weekly**
- **Newly diagnosed patient studies: DvM-P: 23%, VMP: 15%; DvD: 32%, Rd: 23%; DvD: 22%; Vd: 20%**

**Pneumonia** was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

**Diabetes** may occur for patients with IgG kappa myeloma protein impacting initial CD38 expression levels.

**Interference with Serum Protein Electrophoresis (SPE)** and Immunofixation Tests (IFE)**

Mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding (see References) or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies 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 Indirect Antiglobulin Tests (Indirect Coombs Test)**

**Hepatitis B Virus (HBV) Reactivation**

Hepatitis B virus reactivation has been reported in less than 1% of patients following daratumumab administration. It is important to monitor patients for evidence of HBV reactivation and to initiate antiviral therapy as appropriate. If evidence of HBV reactivation is suspected, continue daratumumab with antiviral therapy and monitor for signs of hepatitis flare. If evidence of HBV reactivation is confirmed, discontinue daratumumab and antiviral therapy and refer the patient to a hepatologist for management.
DARZALEX® (daratumumab) injection

in older than in younger patients [see Adverse Reactions]. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DXd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. 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 the patient to read the FDA-approved patient labeling (Patient Information).

Infusion-Related Reactions
Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, 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].

Interference with Laboratory Tests
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].

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation
Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again [see Adverse Reactions].

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

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX and for 3 months after the last dose [see Use in Specific Populations].

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

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864

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cp-60865v6
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Summary of Full Prescribing Information

INDICATIONS AND USAGE

Multiple Myeloma

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

- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
- in combination with bortezomib, 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 pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor.
- in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Light Chain Amyloidosis

DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone is indicated for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis.

This indication is approved under accelerating approval based on response rate [see Clinical Studies (14.1) in Full Prescribing Information]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

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 832 patients with multiple myeloma (N=639) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a system administration-related reaction (Grade 2: 3.5%, Grade 3: 0.8%). Systemic administration-related reactions occurred in 8% of patients, with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 3 minutes to 2.5 days). Of the 129 systemic administration-related reactions that occurred in 74 patients, 110 (85%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

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

Pre-medicate patients with histamine-1 receptor antagonist, acetylsalicylic acid and corticosteroids [see Dosage and Administration (2.5) in Full Prescribing Information]. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reactions or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and/or other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions [see Dosage and Administration (2.5) in Full Prescribing Information].

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred as early as median of 5.5 minutes (range: 0 minutes to 6.5 days) after starting the 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, cyclophosphamide and dexamethasone [see Adverse Reactions]. Serious cardiac reactions occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

DARZALEX FASPRO in combination with pomalidomide and dexamethasone is contraindicated in patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

Daratumumab may increase neutropenia induced by background therapy [see Drug Interactions].

Monitor complete blood count cells periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy [see Adverse Reactions].

Monitor complete blood count cells periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause deletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations].

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

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum [see References (15)]. The determination of a patient's ABO and Rh blood type are not impacted [see Drug Interactions].

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

Interference with Determination of Complete Response

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

Adverse Reactions

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

- Hypersensitivity and Other Administration Reactions [see Warning and Precautions].
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis [see Warning and Precautions].
- Neutropenia [see Warning and Precautions].
- Thrombocytopenia [see Warning and Precautions].

Clinical Trials Experience

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

Newly Diagnosed Multiple Myeloma

In Combination with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone was evaluated in a single-arm cohort of PLEIADES (see Clinical Studies (14.1) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 6 months or longer and 19% were exposed for greater than one year.

[Continued...]

[References (15)]

[Drug Interactions]

[Warning and Precautions]

[Warning and Precautions]

[Warning and Precautions]

[Warning and Precautions]
**DARZALEX FASPRO®** (daratumumab and hyaluronidase-fihj) injection

Serious adverse reactions occurred in 39% of patients who received DARZALEX FASPRO. Serious adverse reactions occurred in 3% of patients. Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia.

The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

### Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (DARZALEX FASPRO-VMP) in PLEIADES

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection†</td>
<td>39</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>16</td>
</tr>
<tr>
<td>Pneumonia‡</td>
<td>15</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>13</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue§</td>
<td>36</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34</td>
</tr>
<tr>
<td>Edema peripheral†</td>
<td>13</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>34</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Cough†</td>
<td>24</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>22</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>21</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>12</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>13</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
</tr>
</tbody>
</table>

* Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.

† Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, pneumonia, and pneumonia bacterial.

‡ Abdominal pain includes abdominal pain, and abdominal pain upper.

§ Fatigue includes asthenia, and fatigue.

† Edema peripheral includes edema, edema peripheral, and peripheral swelling.

‡ Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone included:

- **General disorders and administration site conditions:** infusion reaction, injection site reaction, chill
- **Infections:** herpes zoster, urinary tract infection, influenza, sepsis
- **Musculoskeletal and connective tissue disorders:** arthralgia, muscle spasms
- **Nervous system disorders:** headache, paresthesia
- **Metabolism and nutrition disorders:** hypocalcemia, hyperglycemia
- **Respiratory, thoracic and mediastinal disorders:** dyspnea, pulmonary edema
- **Cardiac disorders:** atrial fibrillation

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Decreased leucocytes</td>
<td>96</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>53</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>53</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>88</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48</td>
</tr>
</tbody>
</table>

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADES (see Clinical Studies (14.2) in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for longer than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 3 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue†</td>
<td>52</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>18</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection§</td>
<td>43</td>
</tr>
<tr>
<td>Pneumonia§</td>
<td>22</td>
</tr>
<tr>
<td>Bronchitis§</td>
<td>14</td>
</tr>
<tr>
<td><strong>Urinary tract infection</strong></td>
<td>11</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea†</td>
<td>22</td>
</tr>
<tr>
<td>Cough†</td>
<td>14</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>17</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
</tbody>
</table>

See Full Prescribing Information for a complete list of adverse reactions.
Table 4 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

- Fatigue includes asthenia, and fatigue.
- Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
- Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
- Bronchitis includes bronchitis, and bronchitis viral.
- Dyspnea includes dyspnea, and dyspnea exertional.
- Cough includes cough, and productive cough.

Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:

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

Table 4 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

Table 5: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DARZALEX FASPRO-Pd Arm in APOLLO

Table 6: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Table 7: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Pomalidomide and Dexamethasone (DARZALEX FASPRO-Pd) or Pomalidomide and Dexamethasone (Pd) in APOLLO
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Monotherapy

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

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

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

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

Table 7 summarizes the adverse reactions in COLUMBA.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO</th>
<th>Intravenous Daratumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥3 (%)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Infusion reactionsb</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 8 summarizes the laboratory abnormalities in COLUMBA.

Table 8: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Receiving DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>65</td>
<td>19</td>
<td>57</td>
<td>14</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>59</td>
<td>36</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>55</td>
<td>19</td>
<td>43</td>
<td>11</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>43</td>
<td>16</td>
<td>45</td>
<td>14</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>42</td>
<td>14</td>
<td>39</td>
<td>16</td>
</tr>
</tbody>
</table>

* Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=256).

Light Chain Amyloidosis

In Combination with Bortezomib, Cyclophosphamide and Dexamethasone

The safety of DARZALEX FASPRO with bortezomib, cyclophosphamide and dexamethasone (DARZALEX FASPRO-VCd) was evaluated in ANDROMEDA [see Clinical Studies (14.2) in Full Prescribing Information]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity or a maximum of 2 years. Among patients who received DARZALEX FASPRO-VCd, 74% were exposed for 6 months or longer and 32% were exposed for greater than one year.

Serious adverse reactions occurred in 43% of patients who received DARZALEX FASPRO in combination with VCD. Serious adverse reactions that occurred in at least 5% of patients in the DARZALEX FASPRO-VCd arm were pneumonia (9%), cardiac failure (8%), and sepsis (5%). Fatal adverse reactions occurred in 11% of patients. Fatal adverse reactions that occurred in more than one patient included cardiac arrest (4%), sudden death (3%), cardiac failure (3%), and sepsis (1%).

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 5% of patients. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than one patient were pneumonia, sepsis, and cardiac failure.

Dose interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 38% of patients who received DARZALEX FASPRO. Adverse reactions which required a dosage interruption in ≥3% of patients included thrombocytopenia, and hypertension.

The most common adverse reaction (≥20%) was upper respiratory tract infection, diarrhea, peripheral edema, constipation, fatigue, peripheral sensory neuropathy, nausea, dyspnea, and cough.

Table 9 below summarizes the adverse reactions in patients who received DARZALEX FASPRO in ANDROMEDA.

Table 9: Adverse Reactions (≥10%) in Patients with AL Amyloidosis Who Received DARZALEX FASPRO with Bortezomib, Cyclophosphamide and Dexamethasone (DARZALEX FASPRO-VCd) with a Difference Between Arms of ≤5% Compared to VCD in ANDROMEDA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO-VCd</th>
<th>VCD (N=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td>Pneumoniaa</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Cough</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>
DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

### Table 9: Select Hematology Laboratory Abnormalities Worsening Post-Baseline

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO-VCd (N=193)</th>
<th>VCd (N=188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>30 6</td>
<td>18 4</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>46 3</td>
<td>40 4</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>60 7</td>
<td>46 4</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>66 6</td>
<td>70 6</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>81 54</td>
<td>71 46</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions:</td>
<td>infusion reaction, chills</td>
<td></td>
</tr>
<tr>
<td>Dermatologic disorders:</td>
<td>rash, pruritus</td>
<td></td>
</tr>
<tr>
<td>Neurologic disorders:</td>
<td>paresthesia</td>
<td></td>
</tr>
<tr>
<td>Head and neck disorders:</td>
<td>nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders:</td>
<td>diarrhea</td>
<td></td>
</tr>
<tr>
<td>Hematopoietic disorders:</td>
<td>anemia, neutropenia</td>
<td></td>
</tr>
</tbody>
</table>
| Postmarketing Experience

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

#### Immune System: Anaphylactic reaction; systemic administration reactions (including death)

**Gastrointestinal:** Pancreatitis

**Infections:** Cytomegalovirus, Listeriosis

### DRUG INTERACTIONS

**Effects of Daratumumab on Laboratory Tests**

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Interference with daratumumab results from the binding of samples to the reagents in the assay. The degree of interference is dependent on the concentration of target protein in the sample.

#### Interference with Serum Protein Electrophoresis

**Pancreatitis:**

**Gastrointestinal:**

**Postmarketing Experience**

#### Risk Summary

**Pregnancy**

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

**Daratumumab** 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 knock-out animal models. There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk.
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 also 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) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Refer 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 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice) and early embryonic development (frogs).

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

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

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, 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 from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

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

Preparation 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 prior to initiating treatment in females of reproductive potential.

Pediatric Use

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

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and ≤65 years (n=160). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, anemia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see Clinical Pharmacology (12.3) in Full Prescribing Information].

REFERENCES


PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Adverse Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see Warnings and Precautions].

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific recommendations regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program [see Use in Specific Populations].

Interference with Laboratory Tests

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

Advise patients that DARZALEX FASPRO may affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see Warnings and Precautions].

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform their healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [see Adverse Reactions].

Product of Switzerland

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044.
U.S. License Number 1864

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Germline Testing in Prostate Cancer: When and Who to Test

Alexandra O. Sokolova, MD1,2; and Heather H. Cheng, MD, PhD3,4

ABSTRACT: The results of multiple studies have shown that a substantial proportion of men with advanced prostate cancer carry germline DNA repair mutations. Germline testing in prostate cancer may inform treatment decisions and consideration for clinical trials. There are 2 FDA approved PARP inhibitors (PARPi), olaparib (Lynparza) and rucaparib (Rubraca), for the treatment of advanced prostate cancer with DNA repair deficiency. Increasing demand for germline testing in prostate cancer and a shortage of genetic counselors have created a need for alternative care models and encouraged oncologists to take a more active role in performing germline testing. This article summarizes recommendations for germline testing in prostate cancer and describes care models for providing counseling and testing.

Introduction
Genetic testing in men with prostate cancer has become more widespread since the discovery that men with metastatic prostate cancer are more likely to carry germline DNA repair gene mutations and the approval of PARP, or poly adenosine diphosphate-ribose polymerase, inhibitors (PARPi) for prostate tumors with DNA repair deficiency. The resulting substantial increase in men with prostate cancer who are eligible for germline testing, with time-sensitive treatment implications, challenges the traditional in-person, time- and resource-intensive cancer genetics care delivery model, and calls for alternative approaches. Urologists, oncologists, and other medical providers are encouraged to take a more active role in delivering germline testing, and they should be aware of current guidelines and optimal pretest and posttest counseling components. This article focuses on the implementation of germline testing in the care of patients with prostate cancer.

Germline vs Other Genetic Testing
Germline genetic testing evaluates for inherited mutations (otherwise known as pathogenic or likely pathogenic variants) that are found in virtually all cells of the body and are derived from the fundamental DNA of an individual. DNA from no cancerous, healthy cells (e.g., leukocyte or saliva/buccal swab cells) are used for germline genetic testing. The goals of germline genetic testing are to evaluate for an inherited cancer syndrome; to inform individual and family cancer risks; and to guide cancer prognosis and treatment decisions. Germline testing should be distinguished from recreational and somatic (tumor-specific) testing. Direct-to-consumer recreational genetic testing consists of an at-home test that is advertised to help understand the customer’s ancestry. Recreational genetic panels look for inherited variants in saliva/buccal swab cells to inform genealogy, and they are not primarily intended to guide medical decisions as they lack gene coverage and clinical-grade precision. None of the recreational genetic tests include a comprehensive assessment of the BRCA1/2 or other DNA damage repair genes and are inadequate for medical purposes. Somatic testing panels are designed to identify alterations in a tumor’s DNA. A somatic test may occasionally identify mutations expected to be germline, in which case follow-up dedicated germline tests are needed. Examples of somatic panels that...
report germline mutations include Tempus and UW-Oncoplex. However, many somatic panels use bioinformatics algorithms that may filter out, miss, and/or choose not to report germline mutations. Thus, in general, somatic panels should not be considered adequate for germline conclusions; at most, they should prompt confirmatory germline testing. This article focuses on dedicated clinical-grade germline testing.

**Heritable Risks of Prostate Cancer**

Germline testing in men with prostate cancer is being performed more often since an important number of prostate cancer cases have a heritable component.1,2 Germline mutations in DNA repair genes, such as *BRCA1/2*, contribute to hereditary prostate cancer risk and are present in up to 11.8% of men with metastatic prostate cancer;3 compared with 4.6% among men with localized prostate cancer and 2.7% in persons without a known cancer diagnosis.1,4

Germline *BRCA1/2* mutations are associated with increased risk of prostate cancer: up to a 3.8-fold increase with *BRCA1* and an 8.6-fold increase with *BRCA2* mutations.3 In men who carry germline *BRCA1/2* mutations are not only at increased risk of developing prostate cancer but are also at risk of a more aggressive prostate cancer phenotype.

In their study, Castro et al found that patients with prostate cancer with germline *BRCA1/2* mutations at the time of diagnosis were more likely to have higher Gleason score (≥8) and more advanced stage (T3/T4, nodal involvement, and metastases) compared with noncarriers. Men with germline *BRCA1/2* mutations also had shorter cancer-specific survival (CSS) than noncarriers (15.7 vs 8.6 years; *P* = .015).6 Men with localized prostate cancer and germline *BRCA1/2* mutations have worse outcomes after definitive treatment with surgery or radiation compared with noncarriers: 5-year metastasis-free survival, 72% vs 94%; *P* < .001; 5-year CSS, 76% vs 97%; *P* < .001.7 The prospective PROREPAIR-B study found that germline *BRCA2* status is an independent prognostic factor for CSS in patients with metastatic castration-resistant prostate cancer (mCRPC; 17.4 vs 33.2 months; *P* = .027).8

**NCCN Guidelines**

Based on the study results above and others, the current National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer (version 1.2022)9 recommend germline testing for the subsets of patients with prostate cancer who are more likely to have germline DNA repair mutations (Figure 1).

**The NCCN guidelines recommend offering germline testing to the following groups of patients with prostate cancer:**

1. Men with node positive, high-risk or very high-risk localized prostate cancer
2. Men with metastatic prostate cancer
3. Men meeting family history criteria (Table 1)

**NCCN recommends considering germline testing for men with personal history of prostate cancer and:**

1. Intermediate risk prostate cancer and intraductal/crcribriform histology
2. Personal history of exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract or small intestinal cancers

Several commercial vendors provide germline testing panels, including Invitae, Color, and Ambry. Further details and information on available panels can be found on the vendors’ websites. Panel sizes vary from dedicated *BRCA1/2* testing to 91-gene panels. The NCCN guidelines for prostate cancer9 recommend that germline testing panels include genes associated with Lynch syndrome (*MLH1, MSH2, MSH6, PMS2*) and homologous recombination genes (*BRCA1/2, ATM, PALB2, CHEK2*).10,11 Broader panels might

---

**TABLE 1. Family History Criteria for Germline Testing in Patients With Prostate Cancer**

- Family history of high-risk germline mutations (eg, *BRCA1/2*, Lynch syndrome)
- Ashkenazi Jewish ancestry
- Personal history of breast cancer
- ≥1 first-, second, or third-degree relative with: breast cancer at age <50y; male breast cancer; ovarian cancer; exocrine pancreatic cancer; metastatic, regional, very-high-risk, high-risk prostate cancer at any age
- ≥1 first-degree relative (father or brother) with prostate cancer at age ≥60 (but not clinically localized Grade Group 1)
- ≥2 first-, second-, or third-degree relative with breast cancer or prostate cancer (but not clinically localized Grade Group 1) at any age
- ≥3 first- or second-degree relatives with Lynch syndrome-related cancers, especially diagnosed at 50 years or younger: cancers of the biliary tract, endometrium, stomach, ovary, exocrine pancreas, upper tract urothelium, small bowel or colorectal cancer; or glioblastoma
be appropriate for men with mCRPC, especially if clinical trial participation is being considered. Average turnaround time for germline testing is between 10 and 30 days, which varies depending on the particular panel. The cost of germline testing varies depending on insurance coverage. Some companies offer provide testing for a flat out-of-pocket fee (eg, $250), and a benefit of participating in certain research studies may be no-cost testing.

**Delivery Care Models for Germline Testing**

NCCN guidelines recommend germline testing for a large subset of patients with prostate cancer, but the best care model to offer education and testing is unclear. The traditional clinical care delivery model for cancer genetics includes 2 in-person visits with a genetic counselor, the first for pretest risk assessment and education and the second to discuss the results. This is the most established pathway and, historically, has been utilized the most. However, broadening recommendations for germline testing create great demand that cannot be currently met in a timely fashion by the approximately 4000 genetic counselors in the United States.11,12 Therefore, oncologists and other providers are increasingly

**TABLE 2. Care Models to Deliver Germline Testing**

<table>
<thead>
<tr>
<th></th>
<th>Traditional</th>
<th>Provider-led</th>
<th>Hybrid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretest counseling</td>
<td>Genetic counselor</td>
<td>Provider (eg, oncologist)</td>
<td>Provider (eg, oncologist)</td>
</tr>
<tr>
<td>Ordering germline test</td>
<td>Genetic counselor</td>
<td>Provider (eg, oncologist)</td>
<td>Provider (eg, oncologist)</td>
</tr>
<tr>
<td>Posttest counseling</td>
<td>Genetic counselor</td>
<td>Provider (eg, oncologist)</td>
<td>Genetic counselor</td>
</tr>
</tbody>
</table>

**FIGURE 1. Recommendations for Germline Testing in Prostate Cancer**

(based on NCCN prostate cancer guidelines, version 1.2022)

**WHY TEST**

- Identify hereditary cancer syndrome, inform family cancer risks, determine clinical trial eligibility
- In some cases, may be helpful in active surveillance discussion
- Treatment implications are currently evaluated by several clinical trials
- PARPi, platinum candidacy

**WHO TO TEST**

<table>
<thead>
<tr>
<th>≥T3a</th>
<th>Grade Group ≥4</th>
<th>PSA &gt;20</th>
<th>N1</th>
<th>Intraductal/ductal histology</th>
</tr>
</thead>
</table>

NCCN does not now specify recommendations for BCR*

**WHICH GENES TO TEST**

MLH1, MSH2, MSH6, PMS2, BRCA1/2, ATM, PALB2, CHEK2**

BCR, biochemically recurrent prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; NCCN, National Comprehensive Cancer Network; nmCRPC, nonmetastatic castration-resistant prostate cancer; PARPi, PARP inhibitors; PSA, prostate-specific antigen.

*NCCN does not specify recommendations for BCR* Metastatic disease*

**Other genes may be indicated based on personal and family history**
performing pretest counseling, ordering genetic testing, and providing posttest counseling for their patients, or following hybrid models (Table 2). The provider-led germline testing model has been tested in breast and ovarian cancer but is new in prostate cancer. Scheinberg et al reported results of a multicenter prospective study evaluating provider-led germline testing for men with prostate cancer. Twelve oncologists received training about the role of germline testing and in counseling patients, and then offered germline testing to patients with mCRPC in their practice. Those patients who accepted germline testing received pretest counseling and educational materials, and later discussed test results in the oncologist's office. If a germline mutation was identified, the patient was referred to a genetic counselor to discuss the further implications of the results and to initiate cascade testing. Most patients (63 of 66; 95%) accepted the germline testing and high satisfaction rates were achieved among both oncologists and patients. A provider-led germline testing model in the Veterans Affairs health care system was also evaluated. Patients with

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Method of response assessment</th>
<th>Number of patients responding to PARPi, by mutation status</th>
<th>BRCA1/2</th>
<th>ATM</th>
<th>CDK12</th>
<th>Other HRD mut</th>
<th>No HRD mut</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROFOUNDED</td>
<td>Olaparib</td>
<td>Imaging</td>
<td>28/84</td>
<td>2/54</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Hussain et al, 2020)</td>
<td></td>
<td>PSA&lt;sub&gt;50&lt;/sub&gt;</td>
<td>66/153</td>
<td>7/90</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTC</td>
<td>29/97</td>
<td>12/56</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOPARP-A</td>
<td>Olaparib</td>
<td>Imaging, PSA&lt;sub&gt;50&lt;/sub&gt; CTC</td>
<td>8/8</td>
<td>4/5</td>
<td>N/A</td>
<td>2/3</td>
<td>2/33</td>
<td></td>
</tr>
<tr>
<td>(Mateo et al, 2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Olaparib</td>
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<td>7/19</td>
<td>5/20</td>
<td>8/27</td>
<td>N/A</td>
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<td>(Mateo et al, 2020)</td>
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<td>33/65</td>
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<td>0/10</td>
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<td></td>
<td>PSA&lt;sub&gt;50&lt;/sub&gt;</td>
<td>63/115</td>
<td>2/49</td>
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<td>7/26</td>
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CTC; circulating tumor cell DNA; imaging, radiographic response measured by RECIST criteria; mCRPC, metastatic castration-resistant prostate cancer; mut, mutations; N/A, not available; PARPi, PARP inhibitors; PSA<sub>50</sub>, decline of prostate-specific antigen by 50% from baseline; rPFS, radiographic progression-free survival.
metastatic prostate cancer were offered germline testing by their oncologists during regular clinic visits. Pretest counseling was provided by oncologists and study coordinators and saliva for the test was collected in the clinic. Posttest counseling sessions with genetic counselors were provided over the phone by the testing panel company. Again, most patients (190 of 227 approached veterans; 84%) accepted testing, and the test completion rate was 80% (182/227).\textsuperscript{20} Results of early studies suggest that provider-led germline testing in prostate cancer could be effective and satisfactory for both patients and providers.

The need to streamline germline testing also calls for the utilization of new technologies, such as video- or phone-based counseling. The EMPOWER study (NCT04598698) assessed men’s preference of in-person genetic counseling vs video-based genetic education\textsuperscript{21}; results indicated that in-person genetic counseling was preferred by men with less education and higher anxiety levels, and it resulted in greater improvement of cancer genetics knowledge. The rates of genetic testing uptake were similar for video-based and in-person counseling groups.\textsuperscript{21} Video-based counseling was also evaluated by Tong et al, who compared 2 models of streamlined germline testing in prostate cancer: (a) a take-home genetic kit provided by an oncologist, followed by referral to a genetic counselor if subsequent results are concerning; and (b) a genetic testing station, at which the patient participated in a video call from a genetic counseling assistant for genetics education and collection of family history, which was followed by saliva sample collection and, later, referral to a genetic counselor if any mutation was identified. The latter approach resulted in a lower rate of incomplete tests and a higher rate of follow-up with genetic counselors for positive results. Authors suggested that utilization of video education and involvement of genetic counseling assistants may improve access to germline testing among patients with prostate cancer.\textsuperscript{22} Several studies are ongoing to evaluate other care models to provide genetic testing in prostate cancer (eg, NCT02917798, NCT03076242, NCT03328091, NCT03503097).\textsuperscript{23}

### Components of Germline Testing Counseling

Oncologists who choose to perform germline testing need to be comfortable with several aspects of genetic counseling and to remain current on the ethics of informed consent and posttest counseling for germline testing (Figure 2). The 2019 Philadelphia Prostate Cancer Consensus Conference suggests that optimal pretest consent should include discussion of the purpose of testing, types of possible results (ie, pathogenic/likely pathogenic; benign/likely benign; variant of unknown significance; no variants identified), the possibility of identifying hereditary cancer syndrome and/or other cancer risks, testing’s potential cost, the importance of cascade family testing, and the Genetic Information Nondiscrimination Act (GINA) law.\textsuperscript{12} The GINA law protects against discrimination based on genetics in employment and health insurance; however, it is not applicable to life insurance, long-term care disability insurance, Indian Health services, and patients enrolled into federal employee, Veterans Administration, and US military health benefit plans.\textsuperscript{21,24} These gaps in protection by GINA law are important to discuss with patients, who may need to consider them before proceeding with the germline testing. Providers should also consider discussing the different panels available for testing, the privacy of genetic tests, and

**FIGURE 2. Germline Testing Steps**

![Germline Testing Steps](image-url)

**PRETEST COUNSELLING**

Should include discussion of:
- the goal for testing
- possible results
- potential to identify hereditary cancer syndrome and additional cancer risks
- cost of testing
- cascade family testing
- Genetic Information Nondiscrimination Act (GINA) law

**ORDER TEST**

When choosing a panel, consider:
- patient preferences
- genes included in the panel
- Out-of-pocket cost to patient
- data sharing/selling policies of genetic laboratories
- genetic counselor support provided by genetic laboratories

**POSTTEST COUNSELLING**

Should include discussion of:
- treatment implications
- implications of other cancer risks
- cascade genetic testing
- VUS reclassification potential
- family cancer risk based on family and personal history, if no mutation identified
genetic laboratories’ policies related to sharing and selling of data. Providers ordering germline tests also must accept responsibility to follow up with patients if reclassification occurs of a variant of (currently) unknown significance (VUS). VUS are reported in about 30% of men with prostate cancer who undergo germline testing. VUS results do not change clinical recommendations, and the majority of them end up being reclassified as benign. In the Find My Variant Study, 38 of 63 VUS (61%) were reclassified: 32 of 38 (84%) as benign/likely benign and 6 of 38 (16%) as pathogenic/likely pathogenic. In the rare case when a VUS is reclassified as pathogenic or likely pathogenic, the provider who ordered the test is notified and they are responsible for disclosing the reclassification to the patient. Regardless of the model used, genetic counselor referral is recommended if a patient has a germline mutation identified and/or if clinical suspicion is high for an inherited cancer predisposition. Collaborative efforts are needed to educate oncology providers on aspects of germline testing counseling and to create shared printed and video resources for patients to facilitate informed consent.

Cascade Testing
Germline testing in men with prostate cancer can potentially benefit not only the patient but also family members. If a germline mutation is identified in a patient, testing for the same mutation in family members (cascade testing) should be performed. For instance, identifying family members with BRCA1/2 mutations could inform potentially lifesaving risk-reducing interventions, eg, prophylactic salpingo-oophorectomy for female BRCA1 mutation carriers. The IMPACT study (Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted screening in BRCA1/2 mutation carriers and controls) evaluated the utility of prostate-specific antigen (PSA) screening in men aged 40 to 69 years with germline BRCA1/2 mutations compared with its utility in noncarriers. The study enrolled 3027 men with no personal history of prostate cancer: 919 BRCA1 carriers, 902 BRCA2 carriers, 709 BRCA1 noncarriers, and 497 BRCA2 noncarriers. Preliminary results, reported after 3 years of follow-up, showed that BRCA2 mutation carriers, compared with noncarriers, have a higher incidence of prostate cancer and a younger age of diagnosis. The results for BRCA1 carriers were not definitive, and further investigation is needed. The results from IMPACT suggest annual PSA screening for BRCA2 mutation carriers aged between 40 and 69 years, using PSA cutoff of 3.0 ng/mL. Studies evaluating the predictive value of lower PSA cutoff and prostate MRI are ongoing (eg, NCT03805919, NCT01990521).

Jun Gong, MD

An Evolving Relationship Between Medical Oncologists and Genetic Counselors in Prostate Cancer

The authors of this timely review are to be applauded for providing a comprehensive analysis of the current literature supporting guidelines-based indications for germline testing in prostate cancer. As they describe, germline mutations in DNA repair genes, including BRCA1/2, can be found in a clinically significant proportion of men with metastatic prostate cancer—up to 11.8%. The impact of these germline mutations on the modern care of the patient with prostate cancer is multifold. As the authors highlight, the presence of germline mutations in DNA repair genes can guide use of FDA-approved targeted agents in refractory and advanced prostate cancer, specifically the PARP inhibitors (PARPi) olaparib (Lynparza) and rucaparib (Rubraca). In the setting of DNA repair deficiency, sensitivity to platinum chemotherapy has also been well described. These associations have direct relevance to us, as medical oncologists, in our clinical management of patients with metastatic prostate cancer. It should be noted that 2 additional PARPi, talazoparib (Talzenna) and niraparib (Zejula), are separately undergoing phase 3 trials randomizing patients with metastatic castrate-resistant prostate cancer (mCRPC) who have not received systemic therapy in the castrate-resistant setting. Both of these trials seek to explore the effectiveness of moving PARPi to earlier settings in mCRPC with novel hormonal therapy in those with and without DNA damage repair deficiencies. As mentioned in the article, PARPi are also moving into the localized, high-risk prostate cancer setting; my group is participating in the NRG-GU007 (Nadir; NCT04037254) phase 2 trial in this setting, investigating niraparib in combination...
with standard-of-care radiation therapy and androgen deprivation therapy in patients with high-risk prostate cancer. As such, reasons for somatic and germline testing in prostate cancer are likely to evolve and expand in the near future.

Beyond the influence of germline testing on treatment decisions for our patients with metastatic prostate cancer, we cannot emphasize enough the importance of germline testing for patients’ families in patients who are positive for germline testing with our colleagues in genetic counseling. Here, the authors importantly highlight different care models to deliver germline testing. This topic has become increasingly relevant, given concerns for broadened recommendations for genetic testing and the resultant great demand that cannot be currently met by approximately 4000 genetic counselors in the United States.

One solution to this increased demand is the provider-led testing model, in which the oncologist performs the pretest counseling and discusses posttest results, with eventual referral to genetic counseling if there is a positive genetic test result. Similar models are also being described with primary care providers and genetic counselors. Such provider-led models are in accordance with the American Society of Clinical Oncology's genetic testing guidelines, in that experienced clinicians who are not geneticists may provide pretest counseling so long as prior informed written consent from the patient is obtained. Important to the success of this model would likely be the degree of clinician experience (ie, how comprehensive their genetic counseling training has been), the clinician’s comfort level, and the supporting staff or resources available to the clinician to operate a provider-led germline testing model.

Members of a consensus panel discussing germline testing have pointed out that clinicians who lack genetics training may experience numerous obstacles when counseling patients, in particular obstacles related to limited knowledge of the downstream impact of genetic testing, such as health insurance coverage, implications for life insurance, and protections afforded by the Genetic Information Nondiscrimination Act. Discussions about the importance and management of variants of unknown significance could be confusing for the patient even in the posttesting stage without appropriate knowledge and training on the clinician's part. In addition, genetic counseling may not always be reimbursed by some insurers, such as Medicare and Medicaid.

The hybrid model as presented by the authors may allow oncologists to shoulder some of the burdens of pretest counseling and ordering germline testing, while the experienced genetic counselors take over in the posttest counseling stage. To additionally lessen the burdens on genetic counselors, limiting the number of in-person visits by patients may be another option. As we have all learned throughout the COVID-19 pandemic, telemedicine does have certain advantages in clinical practice. Mauer et al have described the value of virtual counseling and technological adaptations, including billing practices and coordination of education and outreach opportunities, that have been made during the pandemic and have helped genetic counselors. Such adaptations represent only a few of the evolving strategies that we as medical oncologists, in conjunction with our health care team, must seek out and implement to help our genetic counseling colleagues reach an expanding population of prostate cancer patients in need of evidence-based germline testing.

REFERENCES

Gong is a is a medical oncologist of the Gastrointestinal Disease Research Group, Pancreatic Cancer Research Group, and Urologic Oncology Program in the Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai.
Oncologists are encouraged to take a more active role in performing germline testing, but the optimal approach is unclear. Joint efforts are needed to build collaborative relationships between oncologists and genetic specialists.

**Treatment Implications of Germline Testing**

**Advanced disease**

**PARPi.** Patients with DNA repair mutations have higher response rates to PARPi and platinum chemotherapy. In 2020, two PARPi received FDA approval for treatment of mCRPC with germline or somatic DNA damage repair gene mutations. Rucaparib was approved based on the phase 2 TRITON2 (NCT02952534) study; it reported a 51% (50/98) radiographic response rate among men with mCRPC and BRCA1/2 alterations. The benefit for men with non-BRCA DNA repair mutations was less clear, and rucaparib is currently approved only for carriers of BRCA1/2 mutations. The olaparib label includes a larger number of mutated genes eligible for treatment (BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L), based on results of the phase 3 ProFOUND study (NCT02987543). ProFOUND compared olaparib with enzalutamide or abiraterone and showed improved radiographic progression-free survival (5.8 months vs 3.5 months) with olaparib. Several other ongoing studies are evaluating the efficiency of PARPi monotherapy and combined therapies in mCRPC. Table 3 summarizes study results reporting response rates to PARPi in prostate cancer.

**Platinum chemotherapy.** Historically, platinum chemotherapy has been used to treat tumors, such as ovarian or pancreatic cancer, that have a high frequency of DNA repair mutations. Early data suggest that platinum chemotherapy is also effective in prostate tumors with DNA repair deficiency. A retrospective case series by Cheng et al showed that 3 of 3 patients with prostate cancer who had biallelic inactivation of BRCA2 had an exceptional response to platinum chemotherapy after progressing on several therapies. The results of a larger retrospective study supported this observation, reporting that 75% (6/8) of patients with mCRPC and with germline BRCA2 mutations had a PSA response (ie, decline of prostate-specific antigen by 50% from baseline) to platinum chemotherapy compared with 17% (23/133) of mCRPC patients without gBRCA2 mutations. Mota et al reported a 53% (8/15) PSA response to platinum chemotherapy among men with mCRPC and DNA damage repair mutations (ie, BRCA2, BRCA1, ATM, PALB2, FANCA, and CDK12).

**Localized Disease**

NCCN guidelines recommend considering DNA repair mutation status when discussing the possibility of active surveillance. Germline mutations in BRCA1/2 or ATM are associated with a higher likelihood of grade reclassification among men undergoing active surveillance. Mutation carriers should be closely monitored; they could potentially benefit from an earlier definitive treatment approach. BRCA1/2 carriers have worse outcomes with conventional definitive therapies. Castro et al evaluated the response of BRCA1/2 carriers with localized prostate cancer to 2 radical treatments—definitive radiation and radical prostatectomy—and reported that BRCA status is an independent prognostic factor for metastasis-free survival (HR, 2.36; \( P = .002 \)) and CSS (HR, 2.17; \( P = .016 \)). New treatment approaches in earlier disease stages are being evaluated in clinical trials for patients with prostate cancer and DNA repair deficiency. Targeted therapies, such as PARPi, are being actively investigated in the biochemically recurrent stage of prostate cancer (eg, NCT03047135, NCT03810105, NCT04336943, NCT0353394) and as neoadjuvant therapy in localized disease (eg, NCT04030559).

**Conclusions**

Germline testing is becoming more commonplace with advances in precision oncology and expanding treatment implications of the results of this testing. The NCCN prostate cancer guidelines recommend germline testing for men with high-risk or very high-risk localized prostate cancer; men with metastatic prostate cancer; patients with intraductal histology of the prostate; and patients meeting family history criteria. These recommendations have created a need for germline testing of many prostate cancer patients, which calls for a change in the traditional cancer genetics delivery model to meet the new demand. Oncologists are encouraged to take...
a more active role in performing germline testing, but the optimal approach is unclear. Until the results of larger trials focusing on various testing delivery models are available, joint efforts are needed to build collaborative relationships between oncolgists and genetic specialists. Further efforts are required to create dedicated resources to support providers in this new era of genetic testing and precision oncology in prostate cancer, which is marked by near-constant change.

AFFILIATIONS:
1 Division of Medical Oncology, Oregon Health Science University (OHSU).
2 OHSU Knight Cancer Institute.
3 Division of Medical Oncology, University of Washington.
4 Division of Clinical Research, Fred Hutch Cancer Research Center.

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Metastatic Colorectal Cancer

Metastatic colorectal cancer (mCRC) is the second most common cause of cancer-related death worldwide. In the mid-1980s, the median overall survival (OS) for patients with mCRC ranged from 10 to 12 months from the time of initial diagnosis. In more recent studies, this median has more than doubled and is commonly reported at more than 25 to 30 months. These improvements are due, in large part, to the introduction of multiple novel agents during the last 3 decades. Despite these improvements, however, nearly all patients treated with palliative chemotherapy will eventually develop resistance and ultimately succumb to progression of metastatic disease. Understanding the mechanisms by which malignant cells evade treatment could unlock novel therapeutic strategies that overcome resistance and improve survival. In this review, we will discuss some of the drivers of therapeutic resistance in patients with mCRC and present some novel strategies to overcome resistance.

Defining Primary and Secondary Resistance

Therapeutic resistance develops in nearly all patients with advanced cancer who are treated with palliative systemic therapy. Resistance to cancer-directed therapy is generally divided into primary and secondary (acquired) resistance. Primary resistance is defined as a lack of objective clinical or radiographic response to therapy. Secondary resistance is defined as therapeutic resistance that emerges after a period of disease stability or response. Although these terms will be used throughout this review, it is important to note that this simple division becomes less clear as the precision of surveillance imaging and/or blood-based tests improves. For example, biochemical or molecular assessment of response may be discordant with imaging studies, which may either be a function of disease natural history, imaging frequency, or—in the case of immunotherapy—pseudoprogression. Despite these caveats, it is helpful to understand therapeutic resistance fundamentally in terms of whether a therapy is “not effective” or “no longer effective” in order to better understand and target the underlying mechanisms driving resistance.

Historical Limitations in Assessing Secondary Resistance

Until recently, there have been few attempts to study secondary therapeutic resistance in large-scale clinical trials. We will outline a few of the reasons why this research has been difficult to conduct but also why, in the age of targeted therapeutics, it is of utmost importance. The established clinical trial infrastructure is designed to assess the safety and efficacy of drugs largely based on objective response, progression-free survival (PFS), and OS. If a drug is effective at decreasing or controlling disease for an extended period of time, it is generally felt to be a positive outcome, which can lead to a regulatory approval. As clinical trials move more to response-based end points, it is possible that we will see more drugs that demonstrate excellent initial responses but lead to rapid development of secondary resistance. The need for rapid drug approval in this setting will have to be balanced against long-term outcomes of patients treated with novel therapeutics.

Historically, objective response rate (ORR) has been considered a surrogate for clinical benefit, even where OS
targeted inhibitors or chemotherapy, they develop acquired resistance. As tumors become more drug resistant, tumor DNA (ctDNA) is a technology that can be harnessed to monitor dynamic mutational profiles. The fact that ctDNA is noninvasive allows for repeated, longitudinal testing without the associated morbidity that tissue biopsies entail. As tumors progress, metastasize, or are exposed to stressors such as oxygen deprivation or to dynamic assessment of not only preexisting mutational profiles and those that are induced or unmasked by treatment. Fortunately, circulating tumor DNA (ctDNA) is a technology that can be harnessed to overcome most of these shortcomings and to provide a diagnostic tool for longitudinal, dynamic disease monitoring. Although the presence of cell-free DNA (cfDNA) was initially described in 1948 in healthy individuals, it was not until the past decade that commercial ctDNA assays have led to the initial development, and ultimately approval, of EGFR Inhibitors.

Mechanisms of Primary Resistance to EGFR Inhibitors

EGFR is commonly overexpressed in CRC. This knowledge led to the initial development, and ultimately approval, of the monoclonal antibodies cetuximab (Erbitux) and panitumumab (Vectibix) to treat mCRC. Despite these approvals, a large proportion of patients did not gain significant benefit from treatment with cetuximab or panitumumab. Multiple reports later identified KRAS mutations as driving primary resistance. The most obvious benefit of ctDNA-based molecular testing is its ability to provide a noninvasive mechanism for monitoring dynamic mutational profiles. The fact that ctDNA is noninvasive allows for repeated, longitudinal testing without the associated morbidity that tissue biopsies entail. As tumors progress, metastasize, or are exposed to stressors such as targeted inhibitors or chemotherapy, they develop acquired resistance to targeted therapies in the treatment of mCRC. The promise of targeted therapy—targeting only the gene or protein that is driving cellular proliferation—may become a liability when resistant subclones drive signaling through alternate pathways. A recurring challenge for drug development in mCRC is the rapid development of treatment resistance. For the vast majority of colon cancers, targeting a single mutation is either ineffective (primary resistance) or leads to relatively rapid disease progression after a period of response (secondary resistance). The future of clinical trials for mCRC will need to shift to dynamic assessment of not only primary resistance mechanisms but also those that develop in response to therapeutic inhibition.

Understanding mechanisms of secondary resistance is of utmost importance, but until recently such understanding has relied almost exclusively on postprogression tissue biopsies. Given the invasive nature of these biopsies, it is understandable that it has been difficult to conduct these ancillary studies in large-scale clinical trials. However, serial tissue biopsies are neither cost-effective nor practical. Furthermore, a single-site tumor biopsy is a relatively poor representation of the spectrum of intra- and intertumoral heterogeneity.

Noninvasive, longitudinal monitoring with ctDNA will continue to revolutionize clinical trial design. These advances have the opportunity to usher in new trials that allow for dynamic and adaptive treatment arms.
Most patients with metastatic colorectal cancer (mCRC) who receive palliative systemic therapy eventually develop resistance to treatment. Understanding the mechanisms by which malignant cells evade treatment could open novel therapeutic strategies that can overcome resistance and ultimately improve survival. In other words, a new challenge for drug development in mCRC is the development of treatment resistance.

For the vast majority of colorectal cancers, targeting a single gene alteration (mostly a mutation) is either ineffective (primary resistance) or leads to disease progression after a certain period of response (secondary resistance). Until recently, understanding the mechanisms of secondary resistance relied almost exclusively on post-progression tissue biopsies. However, it is not practical to conduct serial tissue biopsies because of both their invasive nature and poor cost-effectiveness. Furthermore, a single-site tumor biopsy is a relatively poor representation of the spectrum of intra- and intertumoral heterogeneity. As tumors progress, metastasize, or are exposed to stressors (such as targeted inhibitors or chemotherapy), they develop acquired gene alterations that are not uniformly distributed throughout single tumors or within multiple tumors in the same patient. If we are to reach the ultimate goal of successfully implementing precision oncology, we must understand the dynamic interplay between preexisting mutational profiles and those which are induced or unmasked by treatment.

Fortunately, analysis of circulating tumor DNA (ctDNA) is a noninvasive technology that can be harnessed to overcome most of these shortcomings and provide a diagnostic tool for longitudinal and dynamic disease monitoring. Indeed, this approach has allowed for the design of multiple novel clinical trial platforms that are tailored not only to a specific disease state or line of therapy but also to underpinnings of molecular resistance.

The COlorectal Cancer and Liquid BiOpsey Screening Protocol for Molecularly Assigned ThErapy trial (COLOMATE; NCT03765736), discussed by Jeremy C. Jones, MD, and John Strickler, MD, is a screening platform developed by the Academic and Community Cancer Research United Consortium for mCRC. COLOMATE utilizes Guardant360 (Guardant Health) molecular profiling, a comprehensive...
74-gene ctDNA sequencing assay, to identify potential patients for COLOMATE-associated studies. Three clinical studies are being conducted as part of the COLOMATE trial: (1) panitumumab (Vectibix) rechallenge (PULSE; NCT03992456) for secondary resistance to EGFR inhibitors; (2) tucatinib (Tukysa), trastuzumab (Herceptin), and TAS-102 (3T study) for secondary resistance to ERBB2 inhibition; and (3) rechallenge with encorafenib (Braftovi), cetuximab (Erbitux), and binimetinib (Mektovi) for secondary resistance to BRAF V600E inhibitors. Notably, across these studies, patients can participate in one trial and seamlessly switch to another at the first sign of resistance.

The authors also emphasized that this clinical trial approach will require rethinking clinical trials and statistical designs, in order to offer a novel approach to overcome resistance. However, if we can predict the gene alterations that will occur due to secondary resistance before treatment, clinical trial and statistical design of clinical development will change further—that is, it will allow the development of combination therapies that block the identical resistance gene alteration from the beginning. For this purpose, it is necessary to catalogue the gene alterations before and after treatment and develop an artificial intelligence–based predictor for the preemptive treatment strategy (Figure). It is my belief that the results of COLOMATE will be crucial to building a database and preparing for such next-generation clinical development.

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BRAF V600E mutations, occurring downstream of KRAS, appear to have a similar negative predictive effect to EGFR inhibitor (EGFRi) therapy. Di Nicolantonio and colleagues initially described a cohort of 79 patients with mCRC treated with panitumumab or cetuximab. The response rate in 11 patients with BRAF V600E–mutant mCRC was 0% compared with 32% in those patients with BRAF V600E and KRAS wild-type mCRC. This finding has been subsequently bolstered by multiple retrospective reviews; however, given the relative rarity of BRAF V600E mutations in mCRC, there was insufficient statistical evidence to preclude benefit from anti-EGFR therapies in this patient subset.17,18

HER2 amplification has also been implicated as a driver of primary resistance to EGFRi therapy.18,19 Similar to BRAF, the rarity of HER2 amplification in mCRC has limited the ability to make definitive conclusions regarding its role in EGFR resistance. Nonetheless, HER2 amplification is associated with significantly worse outcomes in patients treated with EGFR antibodies with or without cytotoxic chemotherapy.20,21 In one retrospective analysis, 74 patients with HER2-amplified mCRC had significantly worse ORRs (31.2% vs 46.9%) and median PFS times (5.7 vs 7.0 months).21

Secondary Resistance to EGFRi
All the causes of primary resistance mentioned above can also lead to secondary resistance in patients who are treated with EGFR antibodies. One novel class of mutations that develops as a mechanism of secondary resistance to EGFRi are the so-called EGFR ectodomain mutations, which arise within the receptor region of EGFR and alter cetuximab or panitumumab binding.22,23 Based on mathematical modeling, one can assume that there are numerous subclonal mutations in all patients with mCRC.24 The fact that these mutations generally remain subclonal suggests that they have some inherent growth disadvantage compared with the dominant (wild-type) clone in most cases. This dynamic is changed in the setting of targeted therapy, in which the dominant clone is selectively inhibited; this allows for growth of subclonal populations that are resistant to the inhibitor. When this selective pressure is removed, subclonal resistance mutations rapidly decay. This interplay between dominant and subclonal populations has been shown in a number of elegant preclinical and clinical studies.25-27 In one study that included 135 patients with RAS/BRAF wild-type mCRC who had progressed on anti-EGFR therapy, researchers were able to quantify the half-life of exponential decay of acquired mutations after withdrawal of an EGFRi. The half-life of clonal decay of acquired RAS mutations was 3.4 months, and the half-life of EGFR mutations was 6.9 months. Further, the investigators showed a nearly 20% improvement in ORR between those patients who were...
Secondary Resistance to HER2 Inhibition

HER2 amplification occurs in approximately 3% of patients with mCRC.24 Multiple trials have evaluated different anti-HER2-based therapies in patients with mCRC with varying degrees of success.28,31 Despite the impressive activity of this therapeutic strategy, nearly all patients develop primary or secondary resistance. The HERACLES trial (NCT03227926), patients with RAS, BRAF, or EGFR ecdomain mutations were excluded from EGFR rechallenge. In this trial, 27 patients were treated with single-agent panitumab. The ORR and DCR were 30% and 63%, respectively. The COLOMATE companion trial PULSE (NCT03992456) will assess panitumumab rechallenge in patients with mCRC who have progressed on prior anti-EGFR therapy and who meet rigorous molecular eligibility based on cfDNA profiling. Enrollment is ongoing.

Retreated with anti-EGFR therapy less than 1 half-life vs those who were retreated after more than 2 half-lives.25

The knowledge that acquired mutations decay after withdrawal of anti-EGFR therapy has spurred multiple trials aimed at EGFR rechallenge in patients who have developed secondary resistance to EGFRi. Two recent single-arm trials have provided evidence that EGFR rechallenge is a feasible and effective strategy for treatment of refractory mCRC. The 2 trials had similar designs and included patients who had an initial response to cetuximab-based chemotherapy followed by development of secondary resistance and exposure to a cetuximab-free regimen. In the CRICKET trial (NCT02296203), 28 patients were treated with cetuximab and irinotecan rechallenge. Although ctDNA was collected at the time of enrollment, patients were not excluded based on the presence of RAS, BRAF, or EGFR ecdomain mutations. The ORR and disease control rate (DCR) were 21% and 54%, respectively. In the CHRONOS trial (NCT03227926), patients with RAS, BRAF, or EGFR ecdomain mutations were excluded from EGFR rechallenge. In this trial, 27 patients were treated with single-agent panitumumab. The ORR and DCR were 30% and 63%, respectively. The COLOMATE companion trial PULSE (NCT03992456) will assess panitumumab rechallenge in patients with mCRC who have progressed on prior anti-EGFR therapy and who meet rigorous molecular eligibility based on cfDNA profiling. Enrollment is ongoing.

Primary and Secondary Resistance to BRAF V600E Inhibitors

BRAFV600E mutations occur in approximately 7% of patients with mCRC, and they are associated with significantly worse response to chemotherapy and poor prognosis.36,37 Several studies have sought to target BRAF V600E-mutated mCRC. Unlike patients with BRAFV600E-mutated melanoma, patients with mCRC appear to derive modest benefit, if any, from single-agent BRAF inhibitors.36,37 The mechanism of this primary resistance is due to EGFR-mediated reactivation of MAPK signaling through RAS, CRAF, and BRAF heterodimerization.36,38 Indeed, the combination of EGFR and BRAF inhibitors have led to significant improvements in responses, yet these responses tend to be short-lived due to relatively rapid development of secondary resistance. In the phase 3 BEACON trial, patients were treated with a combination of the BRAF inhibitor encorafenib (Braftovi) and cetuximab with or without the MEK inhibitor binimetinib (Mektovi) vs a control arm of irinotecan-based chemotherapy. ORRs (27% vs 20% vs 2%), median PFS (4.5 vs 4.3 vs 1.5 months) and median OS (9.3 vs 9.3 vs 5.9 months) were all improved with the targeted inhibitor combinations.42 Somewhat surprisingly, there was not a clinically significant difference in outcomes between patients who received triplet (BRAF, MEK, EGFR) vs doublet inhibition (BRAF, EGFR) despite a numerically increased response rate with the addition of KRAS, BRAF, or EGFR ecdomain mutations, those patients with PIK3CA mutations experience limited benefit from selective anti–HER2 strategies, a novel therapeutic strategy is needed. The current standard of care for these patients—regorafenib (Stivarga) and TAS-102 (trifluridine–tipiracil)—offers only limited survival benefit.33,34 The combination of tucatinib (Tukysa) and trastuzumab is active against RAS wild-type and HER2-amplified mCRC, but this selective anti-HER2 combination is unlikely to provide benefit in patients with concomitant resistance mutations. To target resistance mutations and HER2 amplification simultaneously, the 3T study will evaluate the safety, tolerability, and preliminary efficacy of tucatinib, trastuzumab, and TAS-102 in patients with PIK3CA-, RAS-, or BRAF-mutated and HER2-amplified mCRC. This will also be a COLOMATE companion trial.
of MEK inhibition.

As mentioned above, the development of secondary resistance in patients treated with targeted BRAF inhibitors is inevitable and generally rapid when compared with other targeted therapy approaches. Multiple pathways of secondary resistance have been identified in both in vitro and patient samples. The most common of these is the development of acquired RAS mutations or amplifications, which accounts for approximately 70% of patients who develop secondary resistance. Other documented causes of resistance include BRAF and MET amplifications, MAP2K1 mutations, and ARAF mutations as well as BRAF exon 2-8 deletions and EGFR ectodomain mutations, both of which decrease the affinity of BRAF and EGFRi binding. The common theme of all these alterations is reactivation of signaling through the MAPK pathway, which bypasses inhibition.

Since resistance mutations decay upon withdrawal of anti-EGFR therapies, it is hypothesized that similar changes would occur in BRAF V600E–mutant mCRC as well. Using this rationale, we have designed the BRAFV600E rechallenge arm of the COLOMATE trial, which will enroll patients with BRAF V600E–mutant mCRC who develop secondary resistance to targeted inhibition, are subsequently treated with chemotherapy, and are then rechallenged with encorafenib, cetuximab, and binimetinib. The addition of binimetinib in this setting allows for negative selective pressure downstream of BRAF, which will hopefully decrease the reemergence of secondary resistance mutations that bypass BRAF signaling.

**Understanding the mechanisms by which malignant cells evade treatment could unlock novel therapeutic strategies that overcome resistance and improve survival.**

### Non–V600 BRAF–Mutant mCRC

Non-V600 BRAF (BRAF non-V600) mutations occur in approximately 2% of all patients with mCRC, and these patients have a significantly better prognosis than those with the more common BRAF V600E mutations. BRAF non-V600 mutations are functionally divided into class II or class III, based upon their mechanism of signaling and RAS activation dependence. Whereas BRAF V600E mutations signal as RAS independent, activated monomer, class II BRAF non-V600 mutations signal as constitutively active mutant BRAF dimers that are relatively insensitive to negative RAS feedback inhibition. Class III BRAF non-V600 mutants have impaired or even absent kinase activity, but they can still amplify MAPK signaling in a RAS-dependent fashion through increased mutant/wild-type RAF heterodimerization. As mentioned above, class II BRAF non-V600 variants signal as constitutively activated dimers that are largely independent of RAS activation at baseline. Xenografts derived from patients with class II BRAF non-V600 variants who were exposed to dual BRAF/MEK inhibition showed significant shrinkage in 17 of 19 (89%) of tumors. Despite the preclinical evidence of benefit in this patient population, there has been limited success thus far in clinical trials evaluating dual BRAF-MEK inhibition in patients with class II mutations. One potential cause of resistance in patients with mCRC is EGFR upregulation/reactivation. Class II mutants are relatively insensitive to upstream activation (EGFR, RAS) at baseline due to ERK-mediated feedback suppression. However, in situations where this feedback suppression is eased, such as in the case of effective MEK/BRAF inhibition, one would expect rapid feedback reactivation as is seen in BRAF V600E mutations. Current RAF inhibitors selectively inhibit BRAF V600E–mutant monomers, but this can lead to modest ERK inhibition in patients with class II mutations. This is due to binding of the RAF inhibitor to one site in the dimer pair, leading to inhibition of that protomer while the other protomer remains activated. By itself, this modest inhibition is unlikely to provide any level of disease control; however, we hypothesize that the combination of modest BRAF inhibition combined with MEK and EGFR inhibition to prevent feedback reactivation will lead to improved disease control compared with other approved therapies.

Class III BRAF non-V600 mutations activate ERK signaling through amplification of mutant/wild-type RAF heterodimers. Class III mutants bind to RAS more effectively and activate wild-type CRAF, leading to downstream ERK activation. ERK activation in these mutants requires upstream activation by RAS, either by activating mutation or increased EGFR activity. This reliance on upstream activation can be exploited by effective EGFRI inhibition in patients with RAS wild-type disease. EGFR inhibition significantly decreases RAS signaling, while MEK inhibition has the potential to not only decrease downstream signaling but also to reduce the competitive advantage of emergent RAS or other upstream mutations. BRAF inhibitor treatment in this setting offsets toxicity from the MEK and EGFRi as it has opposing
effects in normal tissues. These patients with class II and class III BRAF non-V600 mutations will be eligible for the CO-LOMATE Umbrella trial to Evaluate Anti-BRAF Treatment Strategies, which will assess the safety and effectiveness of the combination of encorafenib, cetuximab, and binimetinib.

Future Directions

Although the mechanisms listed above are some of the most common pathways of resistance, they do not account for all the therapeutic targets driving secondary resistance. Noninvasive, longitudinal monitoring with ctDNA will continue to revolutionize clinical trial design. These advances have the opportunity to usher in new trials that allow for dynamic and adaptive treatment arms. In these studies, patients can be started on one trial and seamlessly switched to another at the first signs of resistance. This clinical trial approach will require rethinking clinical trial and statistical design, but it could offer a novel approach to overcoming resistance. We look forward to innovative clinical trial designs that will allow for this level of precision care for patients with mCRC.

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KEY REFERENCES


For references visit cancernetwork.com/Jones_10.21
**UNSILENCE AN EXPRESSIVE INSTRUMENT**

When is TAZVERIK® (tazemetostat) appropriate for your relapsed or refractory (R/R) follicular lymphoma (FL) patient?

**Important Safety Information**

- **Secondary Malignancies**
  The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LBL). Monitor patients long-term for the development of secondary malignancies.

- **Embryo-Fetal Toxicity**
  Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk.

**EZH2=enhancer of zeste homologue 2.**

**TAZVERIK is indicated for the treatment of:**
- Adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.
- Adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options.

These indications are approved under accelerated approval based on overall response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

**Important Safety Information continued on back page of this insert. Please see Brief Summary of the Prescribing Information on the adjacent pages.**
TAZVERIK (tazemetostat) tablets 200mg BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT THE PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

TAZVERIK (tazemetostat) is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies.

TAZVERIK is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options. These indications are approved under accelerated approval based on overall response rate and duration of response [see Clinical Studies]. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSEAGE AND ADMINISTRATION

Patient Selection - Select patients with relapsed or refractory (R/R) follicular lymphoma (FL) for treatment with TAZVERIK based on the presence of EZH2 mutation of codons Y646, A682, or A692 in tumor specimens [see Clinical Studies]. Information on FDA-approved tests for the detection of EZH2 mutation in relapsed or refractory follicular lymphoma is available at: http://www.fda.gov/CompanionDiagnostics.

Recommended Dosage - The recommended dosage of TAZVERIK is 800 mg orally twice daily with or without food until disease progression or unacceptable toxicity. Swallow tablets whole. Do not cut, crush, or chew tablets. Do not take an additional dose if a dose is missed or vomiting occurs after TAZVERIK, but continue with the next scheduled dose.

Dosage Modifications for Adverse Reactions - Table 1 summarizes the recommended dose reductions, and Table 2 summarizes the recommended dosage modifications of TAZVERIK for adverse reactions.

Table 1. Recommended Dose Reductions of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>600 mg orally twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>400 mg orally twice daily*</td>
</tr>
</tbody>
</table>

*Permanently discontinue TAZVERIK in patients who are unable to tolerate 400 mg orally twice daily.

Table 2. Recommended Dosage Modifications of TAZVERIK for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction [see Adverse Reactions]</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>Neutrophil count less than 1 x 10^9/L</td>
<td></td>
</tr>
<tr>
<td>• Withhold until neutrophil count is greater than or equal to 1 x 10^9/L or baseline.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• For first occurrence, resume at same dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• For second and third occurrence, resume at reduced dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Permanently discontinue after fourth occurrence.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count less than 50 x 10^9/L</td>
<td></td>
</tr>
<tr>
<td>• Withhold until platelet count is greater than or equal to 75 x 10^9/L or baseline.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• For first and second occurrence, resume at reduced dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Permanently discontinue after third occurrence.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia [see Adverse Reactions]</td>
<td>Hemoglobin less than 8 g/dL</td>
<td></td>
</tr>
<tr>
<td>• Withhold until improvement to at least Grade 1 or baseline, then resume at same or reduced dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other adverse reactions [see Adverse Reactions]</td>
<td>Grade 3</td>
<td></td>
</tr>
<tr>
<td>• Withhold until improvement to at least Grade 1 or baseline.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• For first and second occurrence, resume at reduced dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Permanently discontinue after third occurrence.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Withhold until improvement to at least Grade 1 or baseline.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• For first occurrence, resume at reduced dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Permanently discontinue after second occurrence.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dosage Modifications for Drug Interactions

Strong and Moderate CYP3A Inhibitors - Avoid coadministration of TAZVERIK with strong or moderate CYP3A inhibitors. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the TAZVERIK dose as shown in Table 3 below. After discontinuation of the moderate CYP3A inhibitor for 3 elimination half-lives, resume the TAZVERIK dose that was taken prior to initiating the inhibitor [see Drug Interactions, Clinical Pharmacology].

Table 3. Recommended Dose Reductions of TAZVERIK for Moderate CYP3A Inhibitors

<table>
<thead>
<tr>
<th>Current Dosage</th>
<th>Adjusted Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg orally twice daily</td>
<td>400 mg orally twice daily</td>
</tr>
<tr>
<td>600 mg orally twice daily</td>
<td>400 mg for first dose and 200 mg for second dose</td>
</tr>
<tr>
<td>400 mg orally twice daily</td>
<td>200 mg orally twice daily</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS - None.

WARNINGS AND PRECAUTIONS

Secondary Malignancies - The risk of developing secondary malignancies is increased following treatment with TAZVERIK. Across clinical trials of 729 adults who received TAZVERIK 800 mg twice daily, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 0.7% of patients. One pediatric patient developed T-cell lymphoblastic lymphoma (T-LL). Monitor patients long-term for the development of secondary malignancies.

Embryo-Fetal Toxicity - Based on findings from animal studies and its mechanism of action, TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure area under the plasma concentration time curve [AUC, 0-45h] at 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see Use In Specific Populations].

ADVERSE REACTIONS - The following clinically significant adverse reactions are described elsewhere in labeling: Secondary Malignancies [see Warnings and Precautions].

Clinical Trial Experience - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TAZVERIK was evaluated in two cohorts (cohorts 4 and 5) of study E7438-G000-101 that enrolled patients with relapsed or refractory follicular lymphoma [see Clinical Studies]. Patients received TAZVERIK 800 mg orally twice daily (n=99). Among patients who received TAZVERIK, 68% were exposed for 6 months or longer, 39% were exposed for 12 months or longer, and 21% were exposed for 18 months or longer. The median age was 62 years (range 36 to 87 years), 54% were male, and 95% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The median number of prior therapies was 3 (range 1 to 11). Patients were required have a creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula. Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions in ≥2% of patients who received TAZVERIK were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received TAZVERIK. Adverse reaction resulting in permanent discontinuation in ≥2% of patients was second primary malignancy. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received TAZVERIK. Adverse reactions requiring dosage interruptions in ≥3% of patients who received TAZVERIK were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received TAZVERIK. The most common adverse reactions (≥20%) were fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain. Table 6 presents adverse reactions in patients with relapsed or refractory follicular lymphoma in cohorts 4 and 5 of study E7438-G000-101.

Table 4. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-101

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection*</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Lower respiratory tract infection*</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection*</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain*</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Rash*</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory and mediastinal system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough*</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6 continues on the next page.
Table 6. Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Follicular Lymphoma Who Received TAZVERIK in Cohorts 4 and 5 of Study E7438-G000-100 (continued)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>50</td>
<td>7</td>
</tr>
<tr>
<td>Decreased white blood cells</td>
<td>41</td>
<td>9</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased glucose</td>
<td>53</td>
<td>10</td>
</tr>
<tr>
<td>Increased aspartate aminotransferase</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>21</td>
<td>2.3</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

*The denominator used to calculate the rate varied from 88 to 96 based on the number of patients with a baseline value and at least one post-treatment value.*

**DRUG INTERACTIONS**

**Effect of Other Drugs on TAZVERIK - Strong and Moderate CYP3A4 Inhibitors:** Co-administration of TAZVERIK with a strong or moderate CYP3A4 inhibitor increases tazemetostat plasma concentrations [see Clinical Pharmacology], which may increase the frequency and severity of adverse reactions. Avoid co-administration of strong or moderate CYP3A4 inhibitors with TAZVERIK. If co-administration of moderate CYP3A4 inhibitors cannot be avoided, reduce TAZVERIK dose [see Dosage and Administration]. Strong and Moderate CYP3A4 Inducers: Co-administration of TAZVERIK with a strong or moderate CYP3A4 inducer may decrease tazemetostat plasma concentrations [see Clinical Pharmacology], which may decrease the efficacy of TAZVERIK. Avoid co-administration of moderate and strong CYP3A4 inducers with TAZVERIK.

**Effect of TAZVERIK on Other Drugs** - CYP3A Substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates [see Use in Specific Populations, Clinical Pharmacology].

**USE IN SPECIFIC POPULATIONS**

**Pregnancy - Risk Summary:** Based on findings from animal studies and its mechanism of action [see Clinical Pharmacology], TAZVERIK can cause fetal harm when administered to pregnant women. There are no available data on TAZVERIK use in pregnant women to inform the drug-associated risk. Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure [AUC0-45h] at the 800 mg twice daily dose [see Data]. Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Data - Animal Data: In pregnant rats, once daily oral administration of tazemetostat during the period of organogenesis from gestation day (GD) 7 through 17 resulted in no maternal adverse effects at doses up to 100 mg/kg/day (approximately 6 times the adult human exposure at 800 mg twice daily). Skeletal malformations and variations occurred in fetuses at doses ≥50 mg/kg (approximately 2 times the adult human exposure at the 800 mg twice daily dose). At 200 mg/kg (approximately 14 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss, missing digits, fused vertebrae, doros heads and fused bones of the skull, and reduced fetal body weights. In pregnant rabbits, no adverse maternal effects were observed after oral gavage administration of 400 mg/kg/day tazemetostat (approximately 7 times the adult human exposure at the 800 mg twice daily dose) from GD 7 through 19. Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the adult human exposure at the 800 mg twice daily dose), with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the adult human exposure at the 800 mg twice daily dose). At 400 mg/kg (approximately 7 times the adult human exposure at the 800 mg twice daily dose), major findings included increased post implantation loss and cleft palate and snout.

**Lactation - Risk Summary:** There are no animal or human data on the presence of tazemetostat in human milk or on its effects on the breastfed child or milk production. Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

**Females and Males of Reproductive Potential - Pregnancy Testing:** Verify the pregnancy status of females of reproductive potential prior to initiating TAZVERIK [see Use in Specific Populations]. Risk Summary: TAZVERIK can cause fetal harm when administered to pregnant women [see Use in Specific Populations]. Contraception: Females - Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose. TAZVERIK can render some hormonal contraceptives ineffective [see Drug Interactions]. Males - Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for at least 3 months after the final dose.

**Pedicure Use - The safety and effectiveness of TAZVERIK in pediatric patients aged less than 16 years have not been established.**

**Juvenile Animal Toxicity Data -** In a 13-week juvenile rat toxicity study, animals were dosed daily from post-natal day 7 to day 97 (approximately equivalent to neonate to adulthood). Tazemetostat resulted in:

- T-LBL at doses ≥50 mg/kg (approximately 2.8 times the adult human exposure at the 800 mg twice daily dose)
- Increased tracheal bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose)
- Increased body weight at doses ≥50 mg/kg (approximately equal to the adult human exposure at the 800 mg twice daily dose)

**Geriatric Use -** Clinical studies of TAZVERIK did not include sufficient numbers of patients with relapsed or refractory follicular lymphoma aged 65 and over to determine whether they respond differently from younger subjects.

**Renal Impairment -** No dose adjustment of TAZVERIK is recommended for patients with mild to severe renal impairment or end-stage renal disease [see Clinical Pharmacology].

**Hepatic Impairment -** No dose adjustment of TAZVERIK is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 times upper limit of normal [ULN] or AST > ULN) who are treated in patients with moderate (total bilirubin > 1.5 to 3 times ULN) or severe (total bilirubin > 3 times ULN) hepatic impairment [see Clinical Pharmacology].

**NONCLINICAL TOXICOLOGY**

**Carcinogenesis, Mutagenesis, Impairment of Fertility -** Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL, MDS, and AML have been reported clinically and T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in animals, tazemetostat appears to have greater with longer duration dosing. Tazemetostat did not cause genetic damage in standard battery of studies including a screening and pivotal bacterial reverse mutation (Ames) assay, an in vivo micronucleus assessment in human peripheral blood lymphocytes, and in vitro micronucleus assessment in rats after oral administration. Fertility and early embryonic development studies have not been conducted with tazemetostat; however, an assessment of male and female reproductive organs were included in 4- and 13-week repeat-dose toxicity studies in rats and Cynomolgus monkeys. Oral daily administration of tazemetostat did not result in any notable effects in the adult and female reproductive organs in the toxicology studies [see Toxicology].

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

**Secondary Malignancies -** Advise patients of the increased risk of secondary malignancies, including AML, MDS, and T-LBL. Advise patients to inform their healthcare provider if they experience fatigue, easy bruising, fever, bone pain, or paleness [see Warnings and Precautions].

**Embryo-Fetal Toxicity -** Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see Use in Specific Populations]. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with TAZVERIK and for 6 months after the final dose [see Use in Specific Populations]. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose [see Use in Specific Populations, Nonclinical Toxicology].

**Lactation -** Advise women not to breastfeed during treatment with TAZVERIK and for 1 week after the final dose [see Use in Special Populations].

**Contraindications -** Advise patients to contact their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John’s wort, grapefruit, and grapefruit juice while taking TAZVERIK [see Drug Interactions].

Brief Summary [07/2020]  
T-ZL-BR-21-0025  
Rx Only  
© 2021 Epizyme®, Inc. All Rights Reserved.
Tazemetostat (TAZVERIK®) is recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as an option for appropriate patients with relapsed or refractory follicular lymphoma.¹

Learn more about the approval of TAZVERIK for R/R FL patients based on efficacy demonstrated in both MT and WT EZH2 populations studied.¹

Visit ExploreTAZVERIK.com today

Important Safety Information (continued)

Embyo-Fetal Toxicity (continued)
Administration of tazemetostat to pregnant rats and rabbits during organogenesis resulted in dose-dependent increases in skeletal developmental abnormalities in both species beginning at maternal exposures approximately 1.5 times the adult human exposure (area under the plasma concentration time curve [AUC0-45h]) at the 800 mg twice daily dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAZVERIK and for 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TAZVERIK and for 3 months after the final dose.

Adverse Reactions
In 99 clinical study patients with relapsed or refractory follicular lymphoma receiving TAZVERIK 800 mg twice daily. Serious adverse reactions occurred in 30% of patients who received TAZVERIK. Serious adverse reactions occurring in ≥2% were general physical health deterioration, abdominal pain, pneumonia, sepsis, and anemia. The most common (≥20%) adverse reactions were fatigue (36%), upper respiratory tract infection (30%), musculoskeletal pain (22%), nausea (24%), and abdominal pain (20%).

Drug Interactions
Avoid coadministration of strong or moderate CYP3A inhibitors with TAZVERIK, which may decrease the efficacy of TAZVERIK. Coadministration of TAZVERIK with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and reduced efficacy of CYP3A substrates.

Lactation
Because of the potential risk for serious adverse reactions from TAZVERIK in the breastfed child, advise women not to breastfeed during treatment with TAZVERIK and for one week after the final dose.

Before prescribing TAZVERIK, please read the Brief Summary of the Prescribing Information on the adjacent pages.

EZH2=enhancer of zeste homologue 2; MT=mutant type; WT=wild type.

References: 1. TAZVERIK (tazemetostat) Prescribing Information. Cambridge, MA: Epizyme, Inc., July 2020. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphomas V.3.2021, © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 1, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
Opsoclonus-Myoclonus–Associated Neuroblastoma With Bone Marrow Metastases: What Would Be the Best Treatment Option?

A 1.9-year-old girl was presented to the hospital with dancing eye movements, ataxia, and behavioral disorders. The MRI showed a retroperitoneal tumor (transversal size: 3.9 x 2.5 cm, craniocaudal size: 4.6 cm) extending from T12 to L3 vertebral bodies (Figure), which was suspicious for neuroblastoma. Afterwards, biopsy of the lesion and bone marrow was performed. The initial pathological evaluation (CD56+, PHOX2B+, NKX2-, Ki67 50%-55%, NSE+, CD99-) of the tumor and bone marrow confirmed the diagnosis of poorly differentiated, high-risk neuroblastoma.

What would be the best choice for further management of this patient?

A. Chemotherapy with further treatment including surgery and aHSCT
B. Surgical resection of the primary tumor
C. Observation
D. Radiation therapy

FIGURE. MRI Imaging of Neuroblastoma
Key Points

- Cancer in children with paraneoplastic OMS appears to have a better prognosis compared to cancer patients without paraneoplastic symptoms.
- OMS is thought to be caused by an autoimmune process, and early immunosuppressive treatment is recommended.
- High-risk NB prognosis is significantly better with high-dose chemotherapy and/or radiotherapy followed by transplantation of autologous bone marrow than chemotherapy alone.

Discussion
The “dancing eye syndrome,” or opsoclonus-myoclonus syndrome (OMS), is a rare disorder that affects the nervous system. OMS is characterized by rapid, multidirectional eye movements (opsoclonus), quick, involuntary muscle jerks, sleep disturbance, cognitive dysfunction, and behavioral changes. OMS typically occurs in association with tumors, usually with neuroblastoma (NB). Approximately half of pediatric OMS is related to NB. The incidence of OMS is rare; one of the prospective studies in the United Kingdom estimated 0.18 cases per million per year.

The literature states that OMS is caused by an autoimmune process for which it is recommended to provide early immunosuppressive treatment. In addition to corticosteroids, intravenous immunoglobulin (IVIG), cyclophosphamide, or rituximab can be also used. However, there is no standard combination or duration of immunomodulatory therapy.

Patients with cancer with paraneoplastic OMS tend to have higher survival than those without paraneoplastic OMS.

An earlier study showed that the typical characteristics of neuroblastoma differ among OMS children. Notably, the frequency of OMS associated with NB is the lowest among children aged 6 months or younger.

NB is the most common extracranial solid tumor in childhood. It can be categorized into different prognostic groups based on age, histological subtype, tumor grade, stage, the status of the MYCN oncogene, chromosome 11q status, and DNA ploidy. In addition, according to revised classification, segmental chromosome aberrations (loss or gain of a portion of a chromosome arm) also play a role in the classification system and are associated with unfavorable prognosis. Accurate staging plays a crucial role in treatment planning, as it is provided according to assigned risk groups.

There is a wide range of treatment approaches for patients with NB: observation, chemotherapy, myeloablative consolidation therapy (single or tandem), surgery, radiation therapy, immunotherapy. Surgical resection of the tumor is an essential part of the treatment of NB, however, in some cases, induction chemotherapy is needed in order to make the tumor amenable for surgical resection. Hence, initial surgical resection with negative margins and without any loss of neurological function is not always feasible. Performing surgery in patients with a disseminated disease does not assure achieving gross total resection of the primary tumor. In addition, in case of upfront surgical treatment, because the radiation volume is set at the resection, the radiation field is much bigger. Despite that, some recent studies suggest better treatment outcomes for complete resection. Surgery alone is a preferable option for most patients with low-risk disease. However, based on several studies, resection should be conducted after several courses of induction chemotherapy when the tumor becomes smaller in size and less invasive. Therefore, initial surgical treatment would lead to a number of complications and would not improve survival for this patient, making answer B (surgical resection of the primary tumor) a poor choice.

Despite the fact that OMS is associated with better outcome and low-risk disease, in this particular case the patient had disseminated disease and unfavorable histological type according to Shimada classification. Patients older than 18 months and those having disease dissemination or localized disease with unfavorable markers, such as MYCN amplification, are at the highest risk for disease progression and mortality. Therefore, answer C (observation) is not the preferred path for management for this patient since observation only would lead to disease progression.

Radiation therapy is another option for local control, along with surgical resection, and is a necessary part of the treatment of high-risk neuroblastoma. However, it has greater benefit in case of administration after surgical resection as part of further therapy. Moreover, radiation therapy at this young age would lead to a number of adverse effects and complications. Therefore, answer D (radiation therapy) is not the preferred option for this child.

Standard approach for high-risk neuroblastoma includes initial chemotherapy with further surgical treatment and aHSCT. These patients typically present with unresectable diseases. Thus, it is critical to provide induction chemotherapy to reduce tumor burden and continue with local control. In order to reduce the recurrence of the disease and reduce the symptoms of the nervous system.
system, children with OMS NB should be treated with the combined modality therapy, including surgery, chemotherapy, aHSCT, and/or radiotherapy. The current treatment approaches for OMS include immunomodulatory therapies, including steroids, IVIG, cyclophosphamide, and more recently, rituximab.13 Given this information, answer A (chemotherapy with further treatment including surgery and aHSCT) is the best treatment option for this patient.

Outcome
The child received 6 cycles of chemotherapy according to NB2004 protocol, after which complete surgical resection of the tumor was possible. After the first cycle of chemotherapy, symptoms of OMS were resolved; hence, no steroids or immunoglobulins were added to the treatment. Pathological examination of resected tumor showed histological differentiation (ganglioneuroma, CD56+, NSE+, Ki67 1%-2%). Afterwards, aHSCT was performed. Now the child is disease-free and has no neurological abnormalities due to OMS. ■

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**KEY REFERENCES**
First-line maintenance treatment of urothelial carcinoma

BAVENCO® (avelumab) is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

Based on overall survival (OS) data

The FIRST and ONLY immunotherapy approved in the first-line maintenance setting

BAVENCO can cause severe and fatal immune-mediated adverse reactions in any organ system or tissue and at any time after starting treatment with a PD-1/PD-L1 blocking antibody, including after discontinuation of treatment.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. No dose reduction for BAVENCIO is recommended. For immune-mediated adverse reactions, withhold or permanently discontinue BAVENCIO depending on severity. In general, withhold BAVENCIO for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue BAVENCIO for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. In general, if BAVENCIO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic corticosteroids (eg, endocrinopathies and dermatologic reactions) are discussed in subsequent sections.

BAVENCO can cause immune-mediated pneumonitis. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. Systemic corticosteroids were required in all (21/21) patients with pneumonitis. BAVENCIO can cause immune-mediated colitis. The primary component of immune-mediated colitis consisted of diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 colitis. Immune-mediated colitis occurred in 1.5% (26/1738) of patients, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in all (26/26) patients with colitis.
**BAVENCIÖ® (avelumab) + best supportive care (BSC) demonstrated superior OS vs BSC alone**

**All randomized patients (major efficacy outcome measure)**

Hazard ratio (HR): 0.69 (95% CI: 0.56, 0.86); 2-sided P-value* = 0.001

BAVENCIÖ + BSC (n=350)

- **21.4 months median OS** (95% CI: 18.9, 26.1)

BSC (n=350)

- **14.3 months median OS** (95% CI: 12.6, 17.9)

31% reduction in risk of death vs BSC alone

7.1 months improvement in median OS

- OS was measured post-randomization (after chemotherapy)

- OS in patients with PD-L1-positive tumors† (major efficacy outcome measure). BAVENCIÖ + BSC showed statistically significant improvement in OS vs BSC alone in patients with PD-L1-positive tumors (n=358, 51%); HR: 0.56, (95% CI: 0.40, 0.79; 2-sided P-value < 0.001)

- OS in patients with PD-L1-negative tumors‡ (exploratory analysis). In patients with PD-L1-negative tumors (n=271, 39%), the OS hazard ratio was 0.85 (95% CI: 0.62, 1.18)

**Most common adverse reactions in the JAVELIN Bladder 100 Trial**

The most common adverse reactions (≥20%) in patients receiving BAVENCIÖ + BSC vs BSC alone were:

- Fatigue (35% vs 13%)
- Urinary tract infection (20% vs 11%)
- Musculoskeletal pain (24% vs 15%)
- Rash (20% vs 2.3%)

For information on warnings and precautions, see Important Safety Information starting on the previous page.

**Study design:** The JAVELIN Bladder 100 Trial was a Phase 3, 1:1 randomized, open-label, multicenter study of BAVENCIÖ as a first-line maintenance treatment in 700 patients with unresectable, locally advanced or metastatic urothelial cancer that did not progress on first-line platinum-containing chemotherapy (N=700).2

*VALENCIÖ® (avelumab) + best supportive care (BSC) demonstrated superior OS vs BSC alone

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**Important Safety Information:** (continues on following pages)
BAVENCIO® (avelumab) can cause hepatotoxicity and immune-mediated hepatitis. Withhold or permanently discontinue BAVENCIO based on the severity of the laboratory abnormalities. Withhold BAVENCIO for severe or potentially life-threatening immune-mediated hepatitis. Systemic corticosteroids were required in 8% of patients with hepatitis.

BAVENCIO can cause primary or secondary immune-mediated adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients, including Grade 3 (0.1%) and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency.

BAVENCIO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold BAVENCIO for Grade 3 or 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction.

BAVENCIO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hyperthyroidism can follow hypothyroidism. Initiate hormone replacement for Grade 3 or 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (27/95) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (0.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

BAVENCIO can cause immune-mediated type I diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO for Grade 3 or 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated type I diabetes mellitus occurred in 1% (2/1738) of patients, including Grade 3 (0.1%) adverse reactions.

BAVENCIO can cause immune-mediated nephritis with renal dysfunction. Withhold BAVENCIO for Grade 2 or Grade 3, and permanently discontinue for Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients, which was a Grade 2 (0.1%) adverse reaction. Systemic corticosteroids were required in this patient.

BAVENCIO can cause immune-mediated dermatologic adverse reactions, including rash or dermatitis. Exfoliative dermatitis including blistering occurred in 13% (22/173) of patients, including Grade 3 (1.2%) and Grade 2 (1.2%) adverse reactions. Musculoskeletal pain occurred in 22% (41/173) of patients, including Grade 3 (1.2%) and Grade 2 (1.2%) adverse reactions. Systemic corticosteroids were required in 30% (2.9) of patients with dermatologic adverse reactions.

BAVENCIO can result in other immune-mediated adverse reactions. Other clinically significant immune-mediated adverse reactions occurred at an incidence of at least 1% in patients receiving BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. For myocarditis, permanently discontinue BAVENCIO for Grade 2, Grade 3, or Grade 4. For neurologic toxicities, withhold BAVENCIO for Grade 2 and irinotecan for Grade 3 or Grade 4.

BAVENCIO can cause severe or life-threatening infusion-related reactions. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 22% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

Fetal and other serious complications of allogeneic hematopoietic stem cell transplantation (HSCT) can occur in patients who receive HSCT before or after being treated with a PD-1 or PD-L1 antibody. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

BAVENCIO can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to a fetus including the risk of fetal death. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO. It is not known whether BAVENCIO is excreted in human milk. Advise a lactating woman not to breastfeed during treatment and for at least 1 month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

A fatal adverse reaction (sepsis) occurred in one (0.3%) patient with locally advanced or metastatic uterine cervical carcinoma (UC) receiving BAVENCIO plus BSC. Two deaths occurred in patients with locally advanced or metastatic UC receiving BAVENCIO. One patient died from an exacerbation of hemolysis-uremic syndrome occurring in a patient with type I diabetes mellitus. The other death resulted from a myocardial infarction.

The most common adverse reactions (all grades, ≥20%) in patients with locally advanced or metastatic UC receiving BAVENCIO plus BSC (vs BSC alone) as first-line maintenance treatment were fatigue (35% vs 13%), musculoskeletal pain (24% vs 15%), urinary tract infection (20% vs 11%), and rash (20% vs 2.3%). In patients with previously treated locally advanced or metastatic UC receiving BAVENCIO, the most common adverse reactions (all grades, ≥20%) were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection.

Selected laboratory abnormalities (all grades, ≥20%) in patients with locally advanced or metastatic UC receiving BAVENCIO plus BSC (vs BSC alone) as first-line maintenance treatment were blood triglycerides increased (34% vs 28%), alkaline phosphatase increased (30% vs 20%), blood sodium decreased (28% vs 20%), lipase increased (25% vs 16%), aspartate aminotransferase (AST) increased (24% vs 12%), alanine aminotransferase (ALT) increased (24% vs 12%), blood cholesterol increased (22% vs 16%), serum amylase increased (21% vs 12%), hemoglobin decreased (28% vs 18%), and white blood cell decreased (20% vs 10%).

Please see Brief Summary of Prescribing Information on following pages.
BAVENCIO® (avelumab) injection, for intravenous use

Rx only

BRIEF SUMMARY: Please see package insert for Full Prescribing Information

INDICATION AND USAGE
First-Line Maintenance Treatment of Urothelial Carcinoma

BAVENCIO is indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Severe Hypothyroidism:

Immune-mediated Adverse Reactions: BAVENCIO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the PD-ligand (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing the inhibition of the immune system. This may lead to worsening/preexisting organ-specific or organ-unknown immunemediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may occur in any patients treated with BAVENCIO. Important immune-mediated adverse reactions occurring during treatment with PD-1/PD-L1 inhibitors include pneumonitis, colitis, hepatitis, endocrinopathies, endocrine deficiencies, and toxic epidermal necrolysis (TEN), which can present with diabetic ketoacidosis. Monitor patients for adverse reactions. Systemic corticosteroids were required in 29% of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of BAVENCIO in any patient. Systemic corticosteroids were required in this patient.

BAVENCIO can cause immune-mediated endocrinopathies that can result in hyperthyroidism, hypophysitis, gastroenterocolitis, dermatitis herpetiformis, pancreatitis, and autoimmune hepatitis.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate patients with signs and symptoms of thyroid dysfunction at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude another etiology of the illness. Instruct medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue BAVENCIO depending on severity. In general, if BAVENCIO requires temporary discontinuation, reinitiate corticosteroids at a dose of 1 to 2 mg prednisone (or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of ofloxacin 400 mg orally twice daily, plus vancomycin IV 1 gram q24h, or another oral treatment if corticosteroid therapy is not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily have systemic corticosteroids (e.g., endocrinopathies and dermatopathies) are discussed below.

Immune-Mediated Pneumonitis:

BAVENCIO can cause immune-mediated pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (217/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients. Systemic corticosteroids were required in all (21/21) patients with pneumonitis. Pneumonitis resolved in 57% (121/212) of the patients. Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of pneumonitis. With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-Mediated Colsitis:

BAVENCIO can cause immune-mediated colitis. The primary composite adverse reaction comprised constipation, diarrhea, clostridium difficile (CDI) infection, rectal bleeding, rectal pain, vomiting, hypokalemia, and hypomagnesemia. CDI infection has been reported in patients treated with all PD-1/PD-L1 blocking antibodies. Withhold or permanently discontinue BAVENCIO in 0.5% and withholding of BAVENCIO in 0.5% of patients. Systemic corticosteroids were required in all (252/252) patients with colitis. Colitis resolved in 69% (185/267) of the patients. Of the 8 patients in whom BAVENCIO was withheld for colitis, 5 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of colitis.

Hypothyroidism and Immune-Mediated Hypothyroidism: BAVENCIO can cause primary or secondary hypothyroidism. For Grade 2 or higher hypothyroidism, discontinue BAVENCIO after symptom improvement, and led to permanent discontinuation of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in all (6/6) patients with hypothyroidism. Hypothyroidism resolved in 96% (16/17) of the patients. Of the 2 patients in whom BAVENCIO was withheld for hypothyroidism, none reinitiated treatment with BAVENCIO. Immunotherapy can cause thyroiditis, including subclinical to potentially severe autoimmune hypothyroidism.

Hypophysitis: BAVENCIO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis may present with diabetes insipidus, with or without hypothyroidism. Hypophysitis can follow hypothyroidism. Initiate hormone replacement for hypothyroidism or institute glucocorticoids at a low dose, as clinically indicated. Withhold or permanently discontinue BAVENCIO depending on severity. Withhold BAVENCIO in 0.1% (187/1738) of patients receiving BAVENCIO, including Grade 3 (0.4%) and Grade 2 (0.6%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% of patients and withholding of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency. Adrenal insufficiency did not resolve in any patient (0%). Of the 2 patients in whom BAVENCIO was withheld for adrenal insufficiency, none reinitiated treatment with BAVENCIO. Hypophysitis: BAVENCIO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis may present with diabetes insipidus, with or without hypothyroidism. Hypophysitis can follow hypothyroidism. Initiate hormone replacement for hypothyroidism or institute glucocorticoids at a low dose, as clinically indicated. Withhold or permanently discontinue BAVENCIO depending on severity. Withhold BAVENCIO in 0.1% (187/1738) of patients receiving BAVENCIO, including Grade 3 (0.4%) and Grade 2 (0.6%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% of patients and withholding of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency. Adrenal insufficiency did not resolve in any patient (0%). Of the 2 patients in whom BAVENCIO was withheld for adrenal insufficiency, none reinitiated treatment with BAVENCIO. Immunotherapy can cause thyroiditis, including subclinical to potentially severe autoimmune hypothyroidism.

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Adverse reactions resulting in permanent discontinuation of BAVENCIO in > 1% of patients were myasthenia gravis (20%), thyroiditis (17%), dermatologic adverse reactions (10%), and thyroiditis (17%). 20% of patients were exposed to BAVENCIO for > 6 months prior to or after an allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and infectious disease.

**WARNINGS AND PRECAUTIONS**

**CONTRAINDICATIONS**

BAVENCIO is contraindicated in patients with a known hypersensitivity to BAVENCIO or any of its excipients.

**PRECAUTIONS**

Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to identify the cause. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative causes.

**INTERACTIONS**

BAVENCIO can cause immune-mediated pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism. Hypothyroidism resolved in 4% (4/90) of patients treated with BAVENCIO plus BSC. Thyroiditis did not resolve in any patients (0/4).

**PATIENT COUNSELING INFORMATION**

Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath.

**DIAGNOSTIC TESTS**

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. The assay methodology, sample handling, timing of testing, and other factors may influence antibody detection. The assay may be influenced by several factors including assay methodology, sample handling, timing and other variables. The assay may be influenced by several factors including assay methodology, sample handling, timing and other factors. The assay may be influenced by several factors including assay methodology, sample handling, timing and other factors. The assay may be influenced by several factors including assay methodology, sample handling, timing and other factors. The assay may be influenced by several factors including assay methodology, sample handling, timing and other factors.
EXPERT COMMENTARY ON THE PRODUCT PROFILE OF

Umbralisib for Lymphoma

PRODUCT PROFILE

DRUG NAME: Umbralisib (Ukoniq)

DATE OF APPROVAL: February 5, 2021

INITIAL INDICATION1,2:
- Accelerated approval for patients with relapsed or refractory marginal zone lymphoma who have received at least 1 prior anti-CD20 based regimen
- Accelerated approval for patients with relapsed or refractory follicular lymphoma who have received at least 3 prior lines of systemic therapy

DOSE AND ADMINISTRATION: 800 mg orally once daily with food

HOW SUPPLIED: Orally

PIVOTAL CLINICAL TRIAL: UNITY-NHL (NCT02793583)

REFERENCES

DESIGN OF UNITY-NHL

ELIGIBLE PATIENTS
- Diagnosis of non-Hodgkin lymphoma, including follicular lymphoma, mantle cell lymphoma, and marginal zone lymphoma
- Relapsed or refractory disease to prior standard therapy and subjects who are not candidates for high-dose therapy or autologous stem cell transplant
- Mantle cell lymphoma requires 1 or more lines of therapy including at least 1 BTK inhibitor

Oral umbralisib at 800 mg once daily plus intravenous ublituximab (TGTX-1101)
Oral umbralisib at 800 mg once daily
Oral umbralisib at 800 mg daily plus ublituximab and bendamustine

PRIMARY END POINT
ORR

KEY SECONDARY END POINTS
PFS

BTK, Bruton tyrosine kinase; ORR, overall response rate; PFS, progression-free survival.
Q: What are some of the biggest concerns with umbralisib’s toxicity profile? Have any new safety concerns emerged in the real-world treatment setting?

We haven’t seen anything that stood out beyond what we were already prepared for. Specifically, [events such as] diarrhea or nausea tend to be the most common, which is fine with us. ¹ My pharmacists, my nurses, and I do a very robust job with counseling our patients before they start therapy to make sure they understand what the potential adverse effects [AEs] are and how to manage them. We talk to patients about how to anticipate their diarrhea and how to manage nausea or fatigue, and we find that if we give them a little bit of education ahead of time, they can recognize [the AEs] when they happen. Being [proactive] about AEs helps patients get over the initial adherence barrier and helps them stay on the therapy longer. It seems to be working well.

Now, [AEs] like nephrotoxicity or colitis are out of our control. The important thing that we specify with our patients is to make sure that they don’t skip scheduled doctor’s appointments or lab appointments. Especially with [the COVID-19 pandemic], it’s been difficult. Patients are afraid to leave their houses or afraid to go to the clinic. With a drug like this and with a higher risk of issues, potentially for nephrotoxicity or colitis, it’s important that the doctor stay on top of that. Often, the only way to do that is to see the patient, do a scan, or do lab work. It is important to make sure we let those patients know that if they have lab appointments, it’s vital that they don’t miss them.

Q: How does this agent stand up to other PI3K inhibitors?

When we think of PI3K inhibitors, we think of a drug in another disease state but with a similar mechanism of action [that has its] own unique set of issues, specifically with hyperglycemia.² We must be very aggressive in monitoring our patients. It opens a whole other can of worms by having spent so much time working on treating and managing the AEs. Hyperglycemia is not an antibody-dependent enhancement [ADE] of this drug, which removes a significant amount of time and attention of focusing on ADE management and allows us to focus on the patient and their disease management.

Q: Are dosing modifications common with this agent?

With any drug, you [may] see issues with those limitations, whether it’s toxicities or kidney disease or hepatic impairment. We haven’t seen anything so far because, to my knowledge, I don’t think there [has been] any dose adjustment [due to] renal impairment, which is surprising [given] the agent’s potential for toxicity. The same thing [has been seen] with hepatic impairment as well: no dose adjustments. Any dose reductions [would be] due to AE management and those limiting toxicities. We have had a couple of patients who have been dose reduced based on AEs, but so far, no patients have discontinued therapy due to intolerability, so that’s been a good sign.

Q: Are there drug interactions clinicians should be aware of?

The package insert does not speak of any specific drug-related contraindication. [However], there always will be something, unfortunately, with any drug. Patients have comorbidities or allergies and sometimes they have advanced age, so they could be on 10 to 14 different medications. Interactions become an issue that we must be very careful about. We do a drug scan every time we fill a prescription for a patient beforehand to make sure that nothing will interact with or contraindicate the drug. We haven’t come across anything yet so far with umbralisib, thankfully.

Q: Would you like to add anything else?

Umbralisib is an interesting drug because it works in a unique way. From the trial results, it shows that patients are getting good results. Time will tell once we have some more patients on therapy. We are anticipating good long-term data [regarding] safety and efficacy. I’m excited to see where it’s going. We think it’s a good drug with a good space that offers patients an option where there wasn’t one offered in another line of therapy. Umbralisib provides a reasonable choice for those who can’t tolerate prior lines of therapy. It’s always great to know that these drug companies are coming up with more options for these patients.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
Physician Burnout May Correlate With Institutional Practices

BY JEFF BENDIX

Burnout has been gaining significance as physicians deal with greater stress due to heavy workloads and individual loss of autonomy. Efforts to combat burnout tend to focus on building resilience, but findings show that fighting burnout involves organization-level responses, such as creating values around teamwork, open communication, and process improvement.

Samuel Edwards, MD, an assistant professor of medicine at Oregon Health and Science University and a practicing internist with the Veterans Affairs Portland Health Care System, discusses the implications from burnout and how to reduce it.

*Medical Economics*®: What led you and your colleagues to undertake this study?

**EDWARDS:** This is part of a larger study, which was an evaluation of the EvidenceNOW initiative. Our group in Oregon was part of a large nationwide team funded to do an enterprise evaluation [of EvidenceNOW] called ESCALATES, [which stands for] Evaluating System Change to Advance Learning and Take Evidence to Scale.

We did surveys of practices and people in those practices at the start of the initiative in 2015, then several times throughout. One thing we wanted to understand was practice climate and burnout, since it’s such a common and concerning issue in primary care.

What did you find?

One of the things we were interested in understanding was how much of burnout is a practice-level phenomenon vs related to individuals, and we found definite evidence of a practice-level effect in burnout. We characterized practices by how much burnout they had in them.

What was interesting was we found that in 30% of our sample, none of the practice members said they had any burnout. Given the dire descriptions of burnout in medicine today, we thought that was an interesting finding, so we chose to focus on characterizing those zero-burnout practices vs a group of practices that were very high burnout to try to understand the differences.

We had this measure of practice culture, which we called adaptive reserve. It consists of 6 domains: facilitative leadership, work environment, teamwork, sense-making, culture of learning, and relationship infrastructure. These practices used more quality-improvement strategies, tended to be physician-owned solo practices, and didn’t participate in large transformation initiatives, such as accountable care organizations or the Transforming Clinical Practice Initiative. In general, we saw this signal that smaller practices with greater agency and a strong culture tended to have less burnout than other practices.

Why is practice culture such an important factor in the presence and level of burnout?

I think it’s intuitive to some extent. A place where you have strong leadership and good relationships among practice members has been shown to be associated with low burnout. One thing that stood out to us was that leadership is important—specifically, facilitative leadership, which is not traditional command and control, hierarchical leadership but more fostering relationships, enhancing communication, attending to power imbalances, focusing on psychological safety, and cultivating teamwork.

Can any of the features of zero-burnout practices be replicated from small and/or clinician owned to large health care institutions?

On the one hand, there are a surprising number of smaller practices still in existence, but I operate in a large-practice environment, and many doctors do nowadays. It’s certainly possible to maintain a strong practice culture within a large organization. Making larger organizations feel small by having smaller practice groups with more autonomy about how they run their day-to-day operation and have more control can make a big difference.

A version of this article was written by Jeff Bendix for *Medical Economics*®. To read the full article, visit: https://bit.ly/3oxJYQT
**MRD Has Potential to Predict Outcomes for Patients With Myeloma Post–Stem Cell Transplantation**

Minimal residual disease (MRD) negativity may predict outcomes for patients with multiple myeloma on maintenance therapy with lenalidomide (Revlimid) who previously underwent autologous stem cell transplantation, according to results from the Myeloma XI trial (NCT01554852).

The trial included 1248 patients with multiple myeloma who were eligible for autologous stem cell transplant (ASCT) and randomly assigned either maintenance therapy with (n = 730) or without lenalidomide (n = 518). MRD status was assessed at 3 months after transplant and 6 months after randomization.

Of the 750 patients with evaluable samples after transplantation, 63.3% were MRD-negative. In addition, of the 623 patients with evaluable samples 9 months after transplantation, 65.6% had a negative MRD status.

During a median follow-up of 32.9 months, patients with a positive MRD status had a median progression-free survival (PFS) of 24 months (95% CI, 21-28) compared with 44 months for those with a negative status (HR, 0.47; 95% CI, 0.37-0.58; P < .0001). Median overall survival (OS) was not reached in either group at the time of the analysis; at 3 years, OS rates were 78.7% in patients with an MRD-positive status and 86.5% in patients with negative MRD, leading to a statistically significant difference favoring those with a negative MRD status (HR, 0.59; 95% CI, 0.4-0.85).

Compared with patients assigned observation, patients assigned maintenance therapy with lenalidomide had significant improvements in PFS in both the MRD-positive groups (33 months vs 18 months; HR, 0.43) and MRD-negative groups (56 months vs. 36 months; HR, 0.62).

When MRD status was assessed 9 months after randomization, patients with negative MRD had a significantly longer median PFS compared with those with positive MRD (50 months vs 13 months; HR, 0.20; 95% CI, 0.13-0.31; P < .0001). Median OS was also not reached in either of these groups at this time point, although the difference between the groups was statistically significant (HR, 0.33; 95% CI, 0.15-0.75; P = .0077).

For the full article, visit cancernetwork.com/IMW_lenalidomide

**Treatment With KRd Plus Autologous Stem Cell Transplant Elicits Durable Survival Benefit in Myeloma**

A regimen consisting of carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone (KRd) plus autologous stem cell transplant (ASCT) plus maintenance carfilzomib-lenalidomide (KR) resulted in durable responses for patients with multiple myeloma with standard- or high-risk cytogenic abnormalities, according to data from the FORTE trial.

In addition, patients from both groups had improved progression-free survival (PFS) at 3 and 4 years.

The trial included 396 newly diagnosed patients with multiple myeloma who were transplant-eligible and younger than 65 years of age. Of the patients in this analysis, 243 had high-risk disease, 105 had double-hit myeloma, and 153 had standard-risk disease. They were randomized to receive KRd with ASCT (KRd-ASCT), carfilzomib plus
cyclophosphamide and dexamethasone (KCd) with ASCT (KCd-ASCT), or KRd without ASCT (KRd12). After the second consolidation, they were again randomized to receive either KR or lenalidomide maintenance therapy.

In the overall patient population, the KRd-ASCT arm had significantly prolonged progression-free survival (PFS) compared with the KRd12 and KCd-ASCT arms. KR maintenance also resulted in significantly prolonged PFS compared with R maintenance.

Among patients with high-risk disease, KRd-ASCT improved PFS compared with KRd12 (HR 0.6; P = .04) and KCd-ASCT (HR, 0.57; P = .01). There were 4-year PFS rates of 62%, 45%, and 45%, respectively. In patients with double-hit myeloma, KRd-ASCT improved PFS compared with KRd12 (HR, 0.53; P = .07) and KCd-ASCT (HR, 0.49; P = .03), with 4-year PFS rates of 55%, 31%, and 33%, respectively. Similarly, in patients with standard-risk disease, KRd-ASCT improved PFS when compared with KRd12 (HR, 0.47; P = .05) and KCd-ASCT (HR, 0.38; P = .01), with 4-year PFS rates of 80%, 67%, and 57%, respectively.

There was also PFS benefit in patients with del17p, t(4;14), and 1q gain who received KRd-ASCT compared with KRd12. Patients with del1p saw greater benefit from KRd-ASCT and KRd12 than KCd-ASCT. Patients with amp1q had the worst outcomes regardless of which treatment type they received.

For maintenance therapy, KR improved PFS in all 3 groups compared with lenalidomide alone, with 3-year PFS survival rates of 90% versus 73% in patients with standard-risk disease, 69% versus 56% in patients with high-risk disease, and 67% versus 42% in patients with double-hit myeloma.

There was more benefit with KR maintenance in patients with del17p, t(4;14), 1q gain, and del1p. Patients with amp1q had the worst outcomes and did not receive any benefit from KR compared with lenalidomide alone.

→ For the full article, visit cancernetwork.com/IMW_KRd

**Fixed-Volume Isatuximab-Based Combo Efficacy Is Confirmed in Newly Diagnosed Multiple Myeloma**

Updated results confirmed the safety and efficacy of the quadruplet regimen of fixed-dose isatuximab-irfc (Sarclisa) in combination with bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (Isa-VRd) for newly diagnosed multiple myeloma with no immediate intent for transplant in a phase 1b trial (NCT02513186).

Part B of the study assessed the efficacy of Isa-VRd in 46 patients who were ineligible or had no immediate intent for autologous stem cell transplant (ASCT). At a median follow-up of 15.24 months, the overall response rate was 97.8%, comprising a 53.3% complete response rate, a 37.8% very good partial response rate, and a 6.7% partial response rate.

Minimal residual disease (MRD) negativity was calculated using combined next-generation flow cytometry or sequencing methods at a threshold of 10^-5. Of 45 patients who had a response, 23 patients (51.1%) had MRD negativity.

Isatuximab 10 mg/kg was administered from a 250 mL fixed-volume infusion—the standard dilution volume of the approved indications for the CD38 monoclonal antibody—for 4 cycles of 6 weeks each with standard-dose VRd. This was followed by maintenance therapy with isatuximab, lenalidomide, and dexamethasone for 28 days or until progression, unacceptable toxicity, or patient willingness to discontinue.

The median duration of treatment for patients in part B was 15.3 months (range, 1.4-21.4), with patients receiving a median of 14 treatment cycles (range, 1-21).

A marked improvement was observed in the time for median duration of infusion, making the fixed-dose infusion a more convenient treatment option for patients. Specifically, in part B, the median duration of fixed-volume isatuximab infusion decreased from 3 hours and 41 minutes for the first infusion to 1 hour and 55 minutes for the second infusion to 1 hour and 20 minutes for the third infusion onward. The median durations of infusion in part A were 3 hours and 44 minutes, 2 hours and 49 minutes, and 2 hours and 17 minutes, respectively.

No new safety signals were reported with Isa-VRd.

→ For the full article, visit cancernetwork.com/IMW_isatuximab

Read this and more online at www.cancernetwork.com/conference
Clinical Activity Is Observed With Mobocertinib for EGFR Exon 20 Insertion–Positive NSCLC With or Without Prior Immunotherapy

Platinum-pretreated patients with EGFR exon 20 insertion mutation–positive non–small cell lung cancer (NSCLC) saw clinical activity with mobocertinib (TAK-788), regardless of prior PD-1/PD-L1 inhibitor history, according to results from a phase 1/2 trial (NCT02716116).

Results showed that in this patient subset (n = 114), the confirmed overall response rate (ORR) via an independent review committee (IRC) was 28% (95% CI, 20%-37%) and the disease control rate (DCR) was 78% (95% CI, 69%-85%). Additionally, among patients who received prior PD-1/PD-L1 therapy, the confirmed ORR via IRC was 25% (95% CI, 14%-40%) and 30% (95% CI, 20%-43%) in those who did not receive prior checkpoint blockade.

The confirmed ORR via investigator assessment in patients who received prior PD-1/PD-L1 therapy was 38% (95% CI, 24%-53%) and was 33% (95% CI, 22%-46%) in those without.

Additional data showed that in the platinum-pretreated subset of patients who did and did not receive PD-1/PD-L1 inhibition, the median duration of response with mobocertinib was 17.5 months (95% CI, 3.7-not estimable [NE]) and 11.0 months (95% CI, 3.8-17.5), respectively. The confirmed DCR in this subset of patients who previously received PD-1/PD-L1 inhibition was 77% (95% CI, 63%-88%) compared with 79% (95% CI, 67%-88%) for those who did not receive prior checkpoint inhibitors (n = 66).

The median progression-free survival in those who received PD-1/PD-L1 inhibition and those who did not was similar at 7.4 months (95% CI, 5.5-21.1 months) and 7.3 months (5.4-10.2 months), respectively. In addition, the respective median overall survival was 21.1 months (95% CI, 13.1-NE) and 24.0 months (95% CI, 13.1-NE).

Furthermore, no marked differences were reported between the 2 cohorts, regarding the best change from baseline in target lesion volume or duration of treatment in confirmed responders.

→ For the full article, visit cancernetwork.com/WCLC21_mobocertinib

Durvalumab and Chemotherapy, Plus or Minus Tremelimumab, Yields Survival Benefit in Frontline Treatment of Advanced NSCLC

A statistically significant improvement in progression-free survival (PFS) was noted with use of the first-line combination of durvalumab (Imfinzi) and chemotherapy, plus or minus tremelimumab, in patients with metastatic non–small cell lung cancer (NSCLC), according to findings from the international, open-label, multicenter phase 3 POSEIDON trial (NCT03164616).

The median PFS with durvalumab plus chemotherapy was 5.5 months (95% CI, 4.7-6.5 months) compared with 4.8 months (95% CI, 4.6-5.8 months) with chemotherapy alone, leading to a 26% reduction in the risk of disease progression or death (HR, 0.74; 95% CI, 0.62-0.89; P = .00093). However, the median overall survival (OS) was 13.3 months (95% CI, 11.4-14.7 months) with durvalumab/chemotherapy and 11.7 months (95% CI, 10.5-13.1 months) with chemotherapy alone—a difference that was not found to be statistically significant (HR, 0.86; 95% CI, 0.72-1.02; P = .07581).

When tremelimumab was added to durvalumab/chemotherapy, the median PFS was 6.2 months (95% CI, 5.0-6.5 months) vs 4.8 months (95% CI, 4.6-5.8 months) with chemotherapy alone, leading to a 26% reduction in the risk of disease progression or death (HR, 0.72; 95% CI, 0.60-0.86 months; P = .00031). The median OS was 14.0 months (95% CI, 11.7-16.1 months) and 11.7 months (95% CI, 10.5-13.1 months) in the 3-drug and chemotherapy-alone arms, respectively (HR, 0.77; 95% CI, 0.65-0.92; P = .00304).

Investigators explored durvalumab with or without tremelimumab in combination with the investigator’s choice of chemotherapy in the frontline treatment of patients with squamous or nonsquamous metastatic NSCLC (n = 1013). Patients were randomized 1:1:1 to receive durvalumab at 1500 mg plus chemotherapy every 3 weeks for 4 cycles, followed by maintenance durvalumab plus pemetrexed until disease progression (n = 330); durvalumab plus tremelimumab at 75 mg and chemotherapy every 3 weeks for 4 cycles, followed by maintenance durvalumab plus tremelimumab and pemetrexed until disease progression (n = 335); or platinum-based chemotherapy every 3 weeks for up to
6 cycles, followed by maintenance pemetrexed until disease progression (n = 332). Treatment discontinuation (20.4%, 22.1%, and 15.3%, respectively) and death rates (10.2%, 12.4%, and 9.0%, respectively) due to adverse effects were similar across all 3 arms.

→ For the full article, visit cancernetwork.com/WCLC21_durvalumab

**T-DM1 Plus Osimertinib Yields Minimal Responses in Resistant EGFR-Mutated NSCLC**

Interim data from the phase 2 TRAEMOS study (NCT03784599) indicated that the combination of ado-trastuzumab emtansine (Kadcyla; T-DM1) and osimertinib (Tagrisso) elicited limited efficacy in a population of patients with EGFR-mutated non–small cell lung cancer (NSCLC).

Findings showed that the combination induced an overall response rate (ORR) of 11% (n = 3/27) with a disease control rate (DCR) of 48% (n = 13/27) after 12 weeks. The median progression-free survival (PFS) for patients treated with the antibody-drug conjugate (ADC)/tyrosine kinase inhibitor (TKI) regimen was 2.7 months (95% CI, 2.1-3.5 months).

Data showed that the confirmed ORR was 46% at 12 weeks. Investigators observed the highest response rates in patients with a human epidermal growth factor receptor 2 (HER2) score of 3+ by immunohistochemistry (IHC; 67%) or HER2 copy number of 10 or higher (100%). However, the median PFS was only 2.3 months (95% CI, 0.5-5.8 months).

From January 2019 to April 2021, investigators enrolled 34 patients who had progressive disease on an EGFR TKI, 27 of whom were eligible for efficacy and safety assessments. HER2 status was assessed by IHC, and patients were required to be positive for HER2 overexpression (IHC2+ ≥ 10%), as well as have a World Health Organization performance status of 0 to 2.

Patients received 3.6 mg/kg of intravenous T-DM1 every 3 weeks, which was the recommended phase 2 dose, plus 80 mg of daily osimertinib. Patients received a median of 4 cycles of T-DM1 (range, 1-14 cycles).

The primary end points were ORR, and additional end points were 12-week DCR, PFS, and overall survival. Investigators assessed responses every 6 weeks.

The median number of T-DM1 cycles was 4 (range, 1-14 cycles). Regarding safety, investigators observed no grade 4/5 treatment-related adverse events (TRAEs). Twenty percent of patients experienced grade 2 and 19% experienced grade 3 TRAEs. Five patients discontinued participation due to toxicities, including pneumonitis in 2 patients, and decreased left ventricle ejection fraction, nausea, and stomach pain/fatigue in 1 each.

These are the first data combining T-DM1 and osimertinib in patients with EGFR-mutant NSCLC to target HER2 bypass track resistance. Nonetheless, according to the investigators, the findings suggest that the ADC is not worth pursuing in this patient population.

→ For the full article, visit cancernetwork.com/WCLC21_T-DM1
Updates in Therapies of Relapsed and Refractory Follicular Lymphoma

In a recent OncView™ discussion, Connie Lee Batlevi, MD, PhD, a medical oncologist focused on the treatment of Hodgkin and non-Hodgkin lymphomas at Memorial Sloan Kettering Cancer Center in New York, shared clinical experiences and perspectives regarding treatments in the follicular lymphoma space.

To begin the discussion, Batlevi said the risk of disease relapse in this population is high, and it is increasing as patients are living longer. “Follicular lymphoma is considered a noncurable indolent lymphoma,” she explained. “The goal of any treatment is to balance effectiveness of treatment, quality of life, and cost of care. In some longitudinal studies, about 50% of patients relapse after frontline therapy [with] more than a decade of observation. However, as patients are thankfully living beyond a decade, we know that patients are ultimately always at risk for a relapse.”

Batlevi detailed her rationale for therapy selection at each relapse and considerations for sequencing agents in this patient population.

**Therapy Selection Considerations at Each Relapse**

According to Batlevi, factors that may play into treatment selection at first relapse include a patient’s functional status, characteristics of their disease at relapse, disease volume on imaging, laboratory findings, metabolic activity on PET scan, and genetic and pathologic assessments.

“A biopsy is almost always an important aspect of disease assessment because it is key to identifying a transformation. If a transformation were to occur, where the follicular lymphoma changes to a diffuse large B-cell lymphoma, that would change the management,” said Batlevi.

Treatment selection also hinges on other factors, such as what therapy was used in the frontline setting.

In addition, certain treatments have backbones that may be too harsh for frail patients, such as bendamustine or the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone. Immune-based targeted therapies like lenalidomide (Revlimid) may not be optimal for patients whose lifestyles are not compatible with a rigorous administration schedule.

Some patients in first relapse, Batlevi noted, may in fact be better suited for observation. Clinical guidelines help determine who may be appropriate for this approach.

Batlevi said she likes to refer to the guidelines of the Groupe d’Etude des Lymphomes Folliculaires, “a set of clinical criteria that were validated to guide frontline treatment of patients with follicular lymphoma. Those criteria include having more than 3 lymph nodes that each mea-
sure more than 3 cm or any 1 lymph node measuring more than 7 cm,” plus other organ and laboratory measures for determining if immediate therapy is required.¹

In a patient who is receiving therapy in the third-line setting or beyond, Batlevi again stressed the importance of understanding that patient’s needs based on their lifestyle and life expectancy. Caring for these patients can be gratifying, she said, as she comes to understand their needs and is able to tailor an individualized treatment approach.

**Therapy Options For Third-line and Beyond Disease**

In the third line, clinicians may choose from several options, both with chemotherapy and without. “Classically, any chemotherapy remains an option, although it’s not likely going to be at the forefront of our resources. There are [also] autologous stem cell transplants, which use really high doses of chemotherapy,” Batlevi said. “The nonchemotherapy options fall into various classes, such as PI3K inhibitors, EZH2 inhibitors, immune-based therapies like chimeric antigen receptor T cells, and also allogeneic stem cell transplant, which is essentially an immune replacement therapy to control follicular lymphoma.”

Molecular testing is particularly useful for therapy selection for patients with this disease. For example, patients with EZH2-positive relapsed or refractory follicular lymphoma following 2 prior therapies may receive treatment with the recently approved agent tazemetostat (Tazverik).² Tazemetostat also may be used in other patients with follicular lymphoma who have no other satisfactory alternative treatment options.

“EZH2 is very important for B-cell development, [and it is mutated] in about 15% to 25% of follicular lymphomas,” said Batlevi. “In the phase 2 clinical trial that led to [tazemetostat’s] approval [Study E7438-G000-101; NCT01897571]...overall response rate was about [69% in patients with the mutations] and in wild type, it was about 35%.”² Notably, the overall disease control rate in the EZH2-mutant group was 98%, composed of 13% complete responses (CRs), 56% partial responses, and stable disease in 29%.

According to Batlevi, other benefits of tazemetostat include its tolerable safety profile. Fewer than 10% of patients require dose reductions due to treatment-emergent adverse effects (AEs) and fewer than 5% have to discontinue therapy for treatment-related causes.

“Tazemetostat is a very easy-to-give drug. It’s taken twice a day by mouth. There are no substantial neutropenias or leukopenias that are concerning, [which is] especially important given the COVID-19] pandemic,” said Batlevi. In terms of real-world use, patients with EZH2 mutations and frail patients with mutations are the most likely to receive benefit from this treatment compared with other available agents.

Turning to PI3K inhibitors, Batlevi described the 4 that are available to treat patients in the third-line setting and beyond: idelalisib (Zydelig), duvelisib (Copiktra), copanlisib (Aliqopa), and umbralisib (Ukonig).

“Each target is [for a] slightly different PI3K isoform. For example, idelalisib targets g and d and umbralisib is a d and CK1-e targeter. In general, responses are in the 50% range and CR [rates] are typically less than 10%.”²

Other considerations of treatment with PI3K inhibitors are their AE profiles. Both idelalisib and duvelisib have known risks of colitis and pneumonitis, whereas copanlisib, although generally more tolerable than the other 2, can result in hyperglycemia and hypertension.

The fourth, umbralisib, is newly approved for use in patients with relapsed or refractory marginal zone lymphoma, following at least 1 prior anti-CD20–targeting regimen, and in patients with follicular lymphoma who have had 3 prior lines of therapy.³ “Overall, fewer

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**REFERENCES**


**EDITOR’S NOTE:** Interview quotes slightly modified for readability.
Experts Discuss Third-line Treatment Options for HER2-Positive Advanced Breast Cancer

For what used to be a tumor type with very poor outcomes, HER2-positive advanced breast cancer now has a number of treatment options. In a recent edition of *Between the Lines*, Sara A. Hurvitz, MD, FACP, and Steven E. Vogl, MD, reviewed treatment standards for patients with advanced disease.1

As Hurvitz, director of the Breast Oncology Program at the David Geffen School of Medicine at the University of California, Los Angeles, explained, “We have 8 FDA-approved, HER2-targeted therapies for metastatic disease, and this review article very nicely takes us through the history of the approvals, what the standard first-line and second-line treatments are, and then dives into all the data relating to [the] third line and beyond.”

Although Hurvitz and Vogl agreed on standards for first- and second-line treatment, they noted that a clear treatment strategy in the third line was still needed. As such, the experts reviewed supporting data for available agents to clarify best use of each in clinical scenarios.

**FDA-Approved Regimens in Third-Line Setting**

Use of the antibody-drug conjugate (ADC) fam-trastuzumab deruxtecan-nxki (Enheru) has shown impressive activity in patients pretreated with ado-trastuzumab emtansine (Kadcyla). In the phase 2 DESTINY-Breast01 trial (NCT03248492), investigators reported a median progression-free survival (PFS) of 16.4 months among 184 heavily pretreated patients. Responses were observed in 112 patients (60.9%); the disease control rate was 97.3%.2

“As the authors of the article pointed out, the patients enrolled in the DESTINY-Breast01 study had a median of 6 prior lines of therapy, enormously heavily pretreated patients … we would expect, or get excited to see, an objective response rate [ORR] of 20%,” Hurvitz commented.

These data resulted in the FDA granting accelerated approval to trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive cancer who have received 2 or more prior anti-HER2-based therapies in the metastatic setting.3 Tucatinib (Tukysa) is another agent with proven efficacy when given as third-line treatment for HER2-positive advanced breast cancer. This drug was approved by the FDA for use with trastuzumab and capecitabine (Xeloda) in patients with unresectable or metastatic HER2-positive breast cancer, including those with brain metastases, who have been pretreated with at least 1 prior anti-HER2–based regimen in the metastatic setting.4 The approval was based on results from the phase 2 HER2CLIMB trial (NCT02614794),

**References**

in which 612 patients were randomized to receive trastuzumab plus capecitabine with either tucatinib or placebo.

Patients treated with the tucatinib combination experienced a statistically significant improvement in median PFS (7.8 months vs 5.6 months in the control group; \(P < .001\)) and median overall survival (OS; 21.9 months vs 17.4 months, respectively; \(P = .005\)). The ORR also favored use of the tucatinib combination when compared with placebo plus trastuzumab/capecitabine (40.6% vs 22.8%, respectively; \(P < .001\)).

Notably, patients with untreated brain metastases in the tucatinib group also experienced an improvement in intracranial PFS (10 months vs 4 months in those not given tucatinib; \(P < .0001\)), intracranial ORR (47% vs 20%, respectively), and OS (18 months vs 12 months, respectively; \(P = .005\)).

“I think tucatinib is the way to go, because it really gets into the brain. It’s a remarkably better treatment—the way it was given with capecitabine and trastuzumab—than anything we’ve had before for brain metastases in HER2-positive breast cancer,” explained Vogl, a medical oncologist at the Montefiore Medical Center in Bronx, New York.

Although the combination of neratinib (Nerlynx) and capecitabine was approved for treating HER2-positive advanced or metastatic breast cancer following 2 or more HER2-directed regimens, both Hurvitz and Vogl said they were hesitant to use it because of the toxicity.

Hurvitz explained, “We do think that starting neratinib at a low dose and escalating up slowly may mitigate that adverse effect, but it’s still bad. When you have a drug like tucatinib, of course, I’m going to use that earlier, and I think the authors agreed.”

In the phase 3 NALA trial (NCT01808573), 621 patients with centrally confirmed, HER2-positive metastatic breast cancer who had received at least 2 HER2-directed regimens were randomized to receive either neratinib plus capecitabine (750 mg/m² twice daily on days 1-14 of 21-day cycles) or lapatinib (Tykerb) plus capecitabine (1000 mg/m² twice daily on days 1-14 of 21-day cycles). The 12-month PFS rate was higher with use of the neratinib combination (28.8%) than with the lapatinib combination (14.8%), but there was no significant improvement in the 12-month OS rate (72.5% vs 66.7%, respectively; \(P = .2\)).

Grade 3 toxicities were twice as common among the group given neratinib (24%) than among those given lapatinib (13%), despite the lower capecitabine dose used in the neratinib group. The limited clinical benefits plus the high toxicity of neratinib make this agent a less appealing option when compared with other targeted therapies approved by the FDA, according to the NALA investigators.

**Alternative Therapeutic Options**

The anti-HER2 monoclonal antibody margetuximab-cmbk (Margenza) was approved in December 2020 in combination with chemotherapy to treat patients with metastatic HER2-positive breast cancer who previously received 2 or more prior anti-HER2 therapies, with at least 1 being for metastatic disease. The antibody was combined
with chemotherapy and compared with trastuzumab therapy in the phase 3 SOPHIA trial (NCT02492711). A total of 536 patients with HER2-positive metastatic breast cancer who had received 2 or more lines of therapy were randomized to receive margetuximab or trastuzumab. A statistically significant, yet clinically modest, improvement in investigator-assessed median PFS was noted with use of margetuximab as compared with trastuzumab therapy (5.7 months vs 4.4 months, respectively; \( P < .001 \)). The ORR also favored the margetuximab arm vs the trastuzumab arm (22\% vs 16\%, respectively; \( P < .001 \)).

“Margetuximab was designed to elicit an antibody-drug-mediated cellular cytotoxicity response,” Hurvitz explained. “It appears only to work in patients who have a particular genotype that puts them at a higher risk of not being able to generate that response. Although it’s available to us to use, we don’t have a way to test for that that genotype.”

Lastly, abemaciclib (Verzenio) plus trastuzumab and fulvestrant (Faslodex) was examined in the phase 2 monarchHER trial (NCT02675231), in which 237 pretreated patients with hormone receptor–positive, HER2-positive advanced breast cancer were randomized to treatment with either the triplet, the doublet of abemaciclib plus trastuzumab, or trastuzumab plus physician’s choice of chemotherapy. Significant improvement in PFS was noted in the triplet arm when compared with the chemotherapy arm (8.3 months vs 5.7 months, respectively; \( P = .03 \)); there was no statistically significant difference between the doublet and chemotherapy arms. The confirmed ORR was also improved in the triplet arm (33\%) when compared with the chemotherapy arm (14\%).

The triplet provided an intriguing chemotherapy-free option for this cohort of patients. Still, Vogl explained, the study was suboptimally designed due to limited data on the impact on patient response with the addition of abemaciclib to trastuzumab/fulvestrant.

The Future of Third-Line Therapies

“We’ve been spoiled by 2 extraordinary experiences, explained Vogl when discussing the recent use of these combination therapies. “Both tucatinib and trastuzumab deruxtecan are much better than anything we’ve had since we got pertuzumab for first-line therapy.”

As promising novel anti-HER2 treatments emerge, the monarchHER investigators suggested, the field will continue to revolutionize, with guidelines beginning to include novel treatment options in the third-line setting and thereafter.

“I think we’re going to see more data relating to [trastuzumab deruxtecan] compared with standard of care in the coming year,” Vogl said. He also suggested that investigators may look to established agents. These include everolimus (Afinitor) given with hormonal and HER2-targeted therapy in the second, third, and fourth lines for palliative treatment of patients with hormone receptor–positive, HER2-positive disease. Vogl commented that although obtaining funding for research involving palliative therapy may present a problem, the efforts will pay off in the end.

REFERENCES

EDITOR’S NOTE: Interview quotes slightly modified for readability.

“Between the Lines Breast Cancer”

“We’ve been spoiled by 2 extraordinary experiences [in this setting]. Both tucatinib and trastuzumab deruxtecan are much better than anything we’ve had since we got pertuzumab for first-line therapy.”

—SARA A. HURVITZ, MD, FACP
Preclinical Data Show Promise of Seribantumab in HER3-Positive Cell Lines

In this edition of Between the Lines, D. Ross Camidge, MD, PhD, and Alexander I. Spira, MD, PhD, examined preclinical data for seribantumab in patient-derived cell lines with NRG1 fusions.1

These early results for the anti-HER3 antibody in NRG1-rearranged lung and breast cancer cells demonstrated the agent’s ability to inhibit growth and signaling activation of 4 ErbB family members, which led to NRG1 fusion-dependent tumorigenesis in vitro and in vivo.

What HER3 does when it’s active, explained Camidge, director of the Thoracic Oncology Clinical and Clinical Research Programs at the University of Colorado in Aurora, “is partner with different members of the family—mostly HER2, but also [sometimes] with EGFR and HER4—causing signaling, and that seems to drive some cancers.”

“You’re actually not directly targeting the NRG1, but you’re targeting its partner, HER3, which is just a different way to think about things when you think about typical targetable mutations,” responded Spira, a director of Virginia Cancer Specialists. A challenge, he added, “is that we’re looking at a very small percentage of cancer patients. Probably fewer than 1% of patients with cancer have this targetable fusion, although like most targetable mutations, when you have it, it appears to be very active.”

Evidence of Activity of Seribantumab

In the study, cancer cell lines with NRG1 fusions or amplifications were compared with cells that did not harbor any aberrations in NRG1. Results indicated that treatment with either afatinib (Gilotif) or seribantumab resulted in reduced growth of NRG1 fusion-positive cell lines in a dose-dependent manner, whereas non-NRG1-altered cell lines saw minimal effect.

Additional examination into seribantumab’s effect on NRG1-β1 in one cell line—which caused increased phosphorylation of EGFR, HER3, and HER4 receptors in a dose-dependent manner—demonstrated that inhibition of HER3 with the agent was able to efficiently block NRG1-dependent cell proliferation. Other cellular processes suggest that seribantumab induces apoptosis of NRG1 fusion-positive breast and lung cancer cell lines and can inhibit phosphorylation of downstream mediators of NRG1-altered cells.

In patient-derived xenograft models of ovarian and non–small cell lung cancer (NSCLC), tumor regression of 50% to 100% was noted with seribantumab.

In postulating how these data might translate to the clinical setting, Spira
commented on the known effects of afatinib in patients. “I had to be reminded about afatinib. A lot of drugs are being studied [for treating tumors with] these NRG1 fusions, [and] we’re not hearing much about afatinib anymore. Given what we know about the toxicity of afatinib and the doses that [are being used] here, that’s probably not a sustainable dose in real life. This explains to me why, if anything, you have a better chance with seribantumab.”

Key Takeaways for the Clinic

Spira noted a key aspect of the research: the evidence of afatinib’s efficacy in NRG1-altered cell lines. “Afatinib, as a drug, has been around for a long time and has been studied typically in EGFR mutations, but we forget it’s a pan-HER drug. There is activity in these NRG1 fusions as a downstream effect. As I looked at some of the effects of it and where things are, my take-home is it might be a tough drug to give, thinking about the toxicity and the doses achievable.”

“The idea of coming at these from a different point of view with the anti-HER3 antibody is a lot more interesting,” said Camidge. “Seribantumab looks like it’s got the chops to do it; it downregulates the signaling and causes shrinkage.”

Both investigators said efficacy in patients remains to be seen, but ongoing trials are examining the use of seribantumab in patients with NRG1-altered tumors (TABLE).

**TABLE. Ongoing Clinical Trials of Seribantumab in NRG1-Altered Solid Tumors**

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Phase</th>
<th>Target enrollment</th>
<th>Protocol</th>
<th>Dosing and cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOHCC-OLIP-01 (NCT04790695)</td>
<td>2</td>
<td>1</td>
<td>Single-patient protocol for NRG1 fusion–positive metastatic pancreatic cancer</td>
<td>Weekly IV seribantumab at 3000 mg for 12 weeks as induction, then maintenance seribantumab as a 3000-mg infusion every 2 weeks starting approximately 14 days after induction.</td>
</tr>
</tbody>
</table>
| ELVCAP-001-01 (NCT04383210) | 2     | 75                | Open-label, international, multicenter study in adult patients with recurrent, locally advanced or metastatic solid tumors that harbor NRG1 gene fusions | Weekly seribantumab as a 1-hour IV infusion at varying doses every 2 weeks and every 3 weeks, during the induction, consolidation, and maintenance dosing phases.  
- Cohort 1 (n = 55): NRG1 gene fusion–positive tumors after standard treatment, excluding prior ErbB-directed therapy.  
- Cohort 2 (n = 10): NRG1 gene fusion–positive tumors after standard treatment, including prior ErbB-directed therapy.  
- Cohort 3 (n = 10): NRG1 gene fusion–positive tumors lacking an EGF-like domain after standard treatment, including prior ErbB-directed therapy. |

IV, intravenous

NRG1 as a Clinical Biomarker in Cancer

Alterations in NRG1 are extremely rare, accounting for only about 1% of all cases of NSCLC. However, the ability to successfully target and treat cancers with these alterations makes them important to screen for, lending greater significance to the need for genomic testing.

“It’s a reminder of the importance of next-generation sequencing. If you don’t test, you can’t find for these,” said Spira.

He cited a retrospective review presented at the 2021 American Society of Clinical Oncology Annual Meeting showing that fewer than 50% of patients with metastatic NSCLC in the US Oncology Network were tested for mutations in ALK, BRAF, EGFR, and ROS1, and for PD-L1 expression.2

“Many community-based hospitals and groups are still limiting the testing,” Spira said. “It’s important to make sure we’re testing everybody comprehensively, not just doing assays based on 1, 2, 3, or 5 tests. This is a reminder of how important it is to do broad-based testing.”

REFERENCES


EDITOR’S NOTE: Interview quotes slightly modified for readability.

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Chimeric antigen receptor (CAR) T-cell therapy has revolutionized immunotherapy for hematologic malignancies. The autologous type of CAR T-cell therapy is based on the patient’s own cells, and clinical trials have shown that it can lead to longer survival in patients with relapsed/refractory leukemia or lymphoma that would not respond to other therapies. However, autologous CAR T-cell therapy also carries concerns, such as not working in all the patients in whom it is attempted, the cost and time associated with developing the CAR-T products from autologous cells, a relatively high relapse rate, and a risk of adverse events such as cytokine release syndrome, cytopenias and neurological toxicity. There is growing interest in an alternative type of CAR-T therapy, known as allogeneic or “off-the-shelf” therapy, in which donor cells lead to availability of the CAR-T product in days rather than weeks, and there is a potential standardization of the product.

C. Ola Landgren, MD, PhD, reviews the major challenges surrounding the use of autologous CAR T-cell therapy, explains the rationale for continuing research into the development of allogeneic CAR T-cell therapy, and assesses key data from clinical trials evaluating “off-the-shelf” CAR T-cell therapy.

Q: What are the benefits of using autologous CAR T-cell therapy in hematologic malignancies?

LANDGREN: The benefit is that there is very strong proof that these types of therapies do work across all the different hematologic malignancies. There is also proof that they are safe. Unfortunately, every therapy—including autologous CAR T-cell—has side effects. I think there is an old saying, if there is no side effect, it usually doesn’t work. So, it’s more a matter of picking therapies with side effect profiles that match up with what the patient considers to be feasible or reasonable, and what the options are to control disease activity. The field is moving forward very fast and I think what we are starting to see now is that these therapies are going up in earlier lines. And you could potentially replace some of the older paradigms that have been around for a long time.

Q: How has the availability of idecabtagene vicleucel (ide-cel) impacted the care of patients with multiple myeloma?

LANDGREN: Ide-cel is the first autologous CAR T-cell therapy that is FDA approved for the treatment of multiple myeloma. It has given a lot of patients access to a therapy that previously was just not there and that can be given as a single infusion with a quite long duration in many patients. Unfortunately, for some patients the duration is shorter, but that’s also how every drug is. Some patients have great benefit. Some patients have less good benefits. Ide-cel in many patients had given great response. I think you could argue that this is one of few therapies for this disease where you can with one single dose achieve a very long and durable clinical benefit.

Q: What are the potential benefits of “off-the-shelf” CAR T-cell therapy compared with autologous CAR T-cell therapy?

LANDGREN: They are dramatically different. The name “autologous” implies that you have to take out these T cells from the person, who’s going to get these same cells after they have been exposed to the vector which transforms the T cells in the patient’s body into an “anti-myeloma drug” which can be given back to the same person a few weeks later. Allogeneic, on the other hand, they are the same allogeneic cells for any patient that’s being treated with this given therapy. The benefits, obviously, is that you now have an off-the-shelf product.
If you have CAR T-cells that are allogeneic, and you have a patient who comes to clinic, you could treat these patients in a few days. The autologous CAR T-cells, because they come from the same person who is going to receive them at the next point, you have to first harvest them, transduce them with this vector, prepare them, expand them, and then activate them. Then you have to have the patient come back and receive them. That vein to vein—which is usually the terminology that’s being used for the autologous T-cells—is about a month, while information from studies on allogeneic CAR T-cells shows that you can start therapy with allogeneic CAR T-cells on average two days after the decision is made. That’s a huge benefit for patients. With everything else being equal, it seems reasonable to speculate that allogeneic would be the winners. However, in reality, there are a lot of other aspects that also come into play.

Q: What are the potential risks of allogeneic CAR T-cell therapy?

LANDGREN: The allogeneic CAR T-cells, because they come from another person, when you give back the tissue from another person, that is truly a transplantation. And the immune system will now recognize this as foreign material. The immune system will try to fight these cells and try to get rid of them... Therefore, you have to develop ways to overcome these problems. For example, if you’re using CAR T-cells that are allogeneic, you could genetically modify them so they do not express something called CD52 on their surface. And then you could give an anti-CD52 targeted therapy before you infuse the allogeneic CAR T-cells, because CD52 will turn off other parts of the immune system, which means that the allogeneic CAR T-cells will not be recognized as foreign material and they will be left alone.

Based on existing data, allogeneic CAR T-cells can be given safely, and you will not turn off their efficacy if anti-CD52 targeted therapy is given. To my knowledge, there have not been any reports of opportunistic infections or severe infections related with these approaches. It will be important to monitor patients long-term to make sure there are no excess risks of infections.

Q: Would the availability of allogeneic therapy expand the population of patients who could benefit from CAR T-cell therapy?

LANDGREN: I think that the instant access will allow people to get the treatment right away. We talked about vein to vein before from the autologous, but it’s about the month’s turnaround time. And some centers may not have the capability of even doing all these things. It should be emphasized that managing patients with all these therapies right now will require a lot of infrastructure and expertise.

Just because you can get the allogeneic cells given in a day or two, that doesn’t mean that you will do them in the local office, like in the middle of nowhere. I do think that an off-the-shelf product will probably give more patients access to it, and it also will allow more centers to consider setting up the infrastructure.

Q: How might a reduction in vein-to-vein time in patients having CAR T-cell therapy affect patient outcomes?

LANDGREN: That is a very important practical detail when it comes to interpreting results. Now, if you have a patient who is considering an autologous T-cell therapy, that means that the person comes to the physician’s office with the intent to collect the CAR T-cells. In this scenario I’m outlining, you’re often talking about two months interval from the first discussion of it to actually receiving it. Here is an example of how it goes: at the first visit, there’s a decision to move forward with autologous CAR T-cells is made. The patient will be scheduled for a visit to come back and collect T cells. In the meantime, a “bridge therapy” is given. This may be 1 month of therapy. Then the patient comes back for collection of cells. After collection, the cells need to be transduced and turned into CAR T-cells, which takes another month. In the meantime, additional bridge therapy is given. After about 1 month, the cells are ready to be infused.

In contrast, for an off-the-shelf product, it is much quicker. For example, if a patient comes to receive an allogeneic CAR T-cell therapy on a Monday, let’s say. If the patient and the doctor agree that this could be a good therapy, let’s say on Wednesday the patient could be receiving this therapy. That’s drastically shorter.

That would also from a study perspective introduce a huge bias. That means in the first example, with 1 to 2 months of delay, patients that have a very aggressive disease, could progress, they may never collect the cells. So, they are not in the denominator when you evaluate the prognosis of how the patient’s being treated. They are not part of the treated cohort. In all the autologous CAR T-cell studies, we only hear about the patients who were treated. The patients who had more aggressive disease are typically not included because their disease did not stay calm during the 1-2 months of built-in delay.

In contrast, if you think about the patients coming to clinic for allogeneic...
CAR T-cells, most patients can receive therapy as planned without delay. Therefore, allogeneic CAR T-cell-treated patients include those with highly aggressive disease. Unfortunately, that could be patients that will have the disease maybe blowing through that therapy. And that would count against that therapy. For these reasons, it seems reasonable to believe that autologous CAR T-cells may look better than allogeneic CAR T-cells when you compare across studies with the two modalities – reflective of this inherent bias.

**Q:** Do T cells from healthy donors make a difference compared with T cells from a patient who’s undergone chemotherapy?

**LANDGREN:** In the autologous setting, you harvest T cells from someone who’s going to get his or her own T cells back when they have been transduced and turned into CAR T-cells. Typically, this person has had the disease for a while, has received several therapies, and now these T cells are the ones you take out and then you transduce them and give them back, versus the allogeneic, you could have a healthy donor. Presumably, from an effect point of view, the healthy T cells from healthy donors probably are better. We don’t have randomized studies to show these are the true benefits in terms of months or years, so. So for now, this is lab based.

**Q:** What is known about the long-term effects of CAR T-cell therapy?

**LANDGREN:** The current known long-term effects I think are some year or years [of data]. We don’t have like 10 or 20 years of follow-up. I think what we do know is that some patients who undergo autologous CAR T-cells have sustained anemia, neutropenia, thrombocytopenia. We have seen in patients’ follow-up for over one year in our clinical experience that there can be improvement after that. There seems to be some form of sustained suppression of the bone marrow. Some centers have, in selected patients, chosen to give a boost of the patient’s own stored stem cells (if he or she has collected plenty for prior high-dose melphalan therapies), that were collected from the peripheral blood. Typically, such stem cells are used in the setting of high-dose melphalan chemotherapy, so-called autologous stem cell transplant. If the patient has extra cells stored, sometimes they are given as a boost to try to help the counts to recover.

**Q:** If one type of T-cell therapy fails, for example autologous, could we then move to the other one, e.g. allogeneic? What is the sequence of therapies in your mind?

**LANDGREN:** There is not yet any firm data in the literature on sequencing of therapies in multiple myeloma. Unfortunately, I think the field is so crowded. There are so many therapies, both approved and in pipeline, ongoing in trials. It looks even more and more complicated going forward. If I use my hat of clinical experience for more than 20 years treating patients with myeloma, thinking about how I have sequenced patients in my clinic for many years, here are my 2 cents: in multiple myeloma, most of the drugs that work, they usually work if you try them again.

If you have a drug that works and then eventually unfortunately stops working, it’s not likely that that same drug or very similar drug with the same mechanism of action will work as the next line. But if you switch to another mechanism, you can have benefits. Now, if that eventually also fails, you can go back to the first line. I think if something works, it’s likely to work again in the future but you need some “recovery time” when you use other mechanisms of action. And I think one of the reasons why this is, is probably because the disease is highly biologically heterogeneous. We and others have done whole genome sequence of large numbers of patients with multiple myeloma, and we have seen that in the relapse setting, patients could have between 3000 and 10000 mutations in their myeloma cells. And if you start looking through individual cells, the same mutations are not present in every single myeloma cell. So if you now put these individual myeloma cells in different buckets, and you say you’re going to have certain mutational signatures in certain buckets, you’re going to end up with very many buckets.

I think what happens probably is that when we give the therapy, we can reduce the burden of the disease, and we can usually reduce the dominant clones of the disease in a given patient. We may actually already be able to cure some of these buckets if you want.

There is usually a small population of cells that you perhaps don’t see, or you do see in very low level, when the disease comes back. Using advanced technologies, it is possible to track the disease in full detail over time. After many lines of therapy, where a disease comes and goes, we have evidence that the distribution of subclones has been shifted compared to the distribution at diagnosis. Pressure generated by various therapies will lead to selection of clones. Likely, the path toward a cure for multiple myeloma includes a better understanding of the biology of these selected aggressive
clones, and the mechanisms which allow these clones to exist.

**Q:** How might the availability of other therapies currently in development, such as bispecific antibodies, impact the use of CAR T-cell therapy?

**LANDGREN:** These new bispecific antibodies have the ability of binding both to the target, the disease cell, as well as binding to T cells for example... They match up the disease cells, say myeloma, with the person's own T cells inside his or her body. There are very many of these bispecific antibodies far along in development across the board of hematologic malignancies.

The results look fantastic. I specialize in multiple myeloma. I think we have over 25 bispecific antibodies in development for multiple myeloma. We do not yet have an FDA-approved bispecific antibody, but that will probably happen in 2022. All the bispecific antibodies have response rates in the range of say 60% up to 80% overall response rates for multiple myeloma. And the majority of the already approved drugs, the already FDA-approved therapies we have for myeloma, when they were approved they were based on 20% to 30% overall response rate as a point of reference.

So this is another magnitude of efficacy. How long does it last? What happens when patients wean off of these? What therapies would you use then? How will these drugs be given? Will they be given in combination with other therapies? These are questions we don’t have any answers to yet. But there’s no doubt in my mind that the whole myeloma treatment field is undergoing a major transformation as we speak.

And I think what we’re going to see in the coming years is there will probably be chemotherapy-free therapies, that could be antibody only or could be cell therapies only, or that could be combinations of such therapies. And maybe that could be patients that could be cured. It’s a long process to go from developing a therapy to reach such a goal. But I think for the first time, we really have a shot on goal amid all these new therapies.

**Q:** One of the hopes for off-the-shelf CAR T-cell therapy is that it might reduce the cost. How do we weigh that against the use of health care resources such as specialized units and intensive care unit beds?

**LANDGREN:** Cost is always a barrier for anything in life, right? We always have to make sure that we can afford it. If it’s a great, great therapy but it’s so expensive that we can only treat one patient, then the other patients won’t benefit from it. The problem is obviously still there. So, these are very difficult aspects and as a treating physician and as a researcher, I’m not really sure how to solve this. These are things that probably are more related to insurance and the government and drug companies and things like that. But of course, whatever we can do on the treatment side and the research field to help, we are always happy to help. I think our contribution maybe can be in terms of developing treatment strategies for patients who can be treated more outpatient. We can try to help and design studies, so the need for advanced monitoring and things like that can be lower and that would help and bring down the costs.

**Q:** What are your final thoughts?

**LANDGREN:** We spend a lot of time thinking about ways to improve drugs and cell therapies, different types of concepts, for the intervention of diseases. But I think it’s also very important to emphasize the need for advanced monitoring and tracking to rule out residual disease. The role of minimal residual disease detection, I think, has to be moved up to a shared number 1, side by side with development of new treatments. And the reason I think so is because if we don’t have these tools and we continue to develop new therapies, we never really have the ability to answer if the therapies work until many years later.

So if you can achieve no detectable disease and you can repeat testing and show sustained no detectable disease, that’s when you know that you’re on the path towards a cure. There is an unmet need to develop new and better assays for MRD tracking in multiple myeloma, ideally for testing in the peripheral blood. New, effective drugs partnered with advanced MRD tracking—that is the path we need to pursue. We are all running against the clock. On our team, we are running as fast as we can—every day!

**KEY REFERENCES**


**For full reference list, visit** [https://www.gotoper.com/gobots21cartcell](https://www.gotoper.com/gobots21cartcell)
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