Characterization of Blood-Based Molecular Profiling in Pancreatic Adenocarcinoma
Adverse reactions occurring more frequently in the NUBEQA arm and for 1 week after the last dose.

on placebo) and heart failure (2.1% vs 0.9% on placebo).

potential to use effective contraception during treatment with NUBEQA resistant prostate cancer.

The most frequent adverse reactions requiring dose interruptions included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%); the most frequent adverse reactions in ≥1% of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased AST (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3/4 for same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.

Study Design: The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter, phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of <10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (>955) or matching placebo (>554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BCR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, 99mTc bone scan by BICR, unacceptable toxicity, or withdrawal. The final analysis of OS was event-driven and conducted after 254 OS events had occurred and 14 months after MFS analysis.1-7

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

All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased AST (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3/4 for same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.

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Start new NUBEQA patients with 1 month free

MEN LIVED 2X LONGER WITHOUT CANCER SPREADING

with NUBEQA + ADT* vs ADT alone†

(40 months vs 18 months, respectively)

HR: 0.41; 95% CI: 0.34-0.50; P=0.001. *95% CI: 34.3-NE. †95% CI: 15.5-22.3.

Metastasis-free survival (MFS) was the primary endpoint.

REduced risk of death by NEARLY A Third

31% reduction in the risk of death with NUBEQA + ADT compared to ADT alone1-3

HR: 0.69 (95% CI: 0.53-0.88); P=0.003. Medians not estimable.

Overall survival (OS) was a key secondary endpoint.

INDICATION

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

IMPORTANT SAFETY INFORMATION

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

Adverse Reactions

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

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

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

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PROVEN TOLERABILITY

Three adverse reactions occurred more frequently with NUBEQA + ADT (≥2% over ADT alone): fatigue/asthenia (1.6% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%).11

Drug Interactions

Effect of Other Drugs on NUBEQA – Combined Pgp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined Pgp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of these substrates.

Review the prescribing information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

*The NUBEQA Free Trial Program provides 1 month’s supply of NUBEQA at no cost to patients who meet the program eligibility requirements and agree to the terms and conditions. For full terms and conditions and to enroll patients, please call Access Services by Bayer at 1-800-288-8374 or visit NUBEQAhcp.com.
NUBEQA® (darolutamide) tablets, for oral use

Initial U.S. Approval: 2019

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

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

4 CONTRAINICATIONS
None.

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

Advising males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1, 8.3)].

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

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

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

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

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

Table 1: Adverse Reactions in ARAMIS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grades ≥ 3 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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

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

Table 2: Laboratory Test Abnormalities in ARAMIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (N=954)</th>
<th>Placebo (N=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>AST increased</td>
<td>23</td>
<td>0.5</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on NUBEQA
Combined P-gp and Strong or Moderate CYP3A4 Inhibitor
Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inhibitor decreases darolutamide exposure which may decrease NUBEQA activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

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

7.2 Effects of NUBEQA on Other Drugs
Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates
NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C_{max} of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities.

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

References:
NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA [see Clinical Pharmacology (12.3)].

Review the prescribing information of the BCRP, OATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

Males

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

Infertility

Males

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

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

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

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

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

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

17 PATIENT COUNSELING INFORMATION

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

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

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

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

Embryo-Fetal Toxicity

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

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

Infertility

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

Manufactured by: Orion Corporation, Orion Pharma, FI-02101 Espoo, Finland

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

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For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

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Adjuvant Systemic Therapy Trends in 2021

As our understanding of systemic therapies expands with a greater breadth of research, established agents in the metastatic setting have begun to assert themselves as options in earlier stages of cancer care.

A big breakthrough in this regard came at the end of 2020 when osimertinib (Tagrisso) was approved as an adjuvant therapy for patients with non–small cell lung cancer (NSCLC) whose tumors harbored mutations in \( \text{EGFR} \) exon 19 deletions or exon 21 L858R. Results of the phase 3 ADAURA trial (NCT02511106) supported the FDA’s decision to grant this standard-of-care agent in the metastatic setting an addition indication for use in patients with stage IB to IIIA disease.

Since then, there have been multiple approvals of established agents for use in patients with early disease across multiple solid tumors malignancies. Both abemaciclib (Verzenio) and pembrolizumab (Keytruda) earned full approval for indications in early breast cancer. The CDK4/6 inhibitor may now be used in combination with endocrine therapy in the adjuvant setting for hormone receptor–positive, HER2-negative, node-positive early breast cancer at high risk of recurrence with a Ki-67 score of 20% or greater. Pembrolizumab is to be used as both a neoadjuvant treatment in combination with chemotherapy, then as a single agent in the adjuvant setting following surgery.

The PD-1 inhibitor nivolumab (Opdivo) earned an indication from the FDA as adjuvant treatment for patients with resected esophageal or gastroesophageal junction cancer who have residual pathologic disease and who previously received chemotherapy. In NSCLC, atezolizumab (Tecentriq) may now be used to treat patients with stage II to IIA NSCLC with PD-L1 expression of 1% or higher following complete resection and platinum-based chemotherapy. And recently, pembrolizumab won another FDA approval for the adjuvant treatment of patients with renal cell carcinoma who are determined to have intermediate- or high-risk disease following nephrectomy or following nephrectomy and resection of metastatic lesions.

Turning the page on a new year, news trends in oncology for 2022 are yet to be determined but are certainly anticipated to be as or even more exciting than what has already occurred in this space. As always, keep up with the latest issue of \textit{ONCOLOGY}® to stay up-to-date on the latest practical and timely clinical information necessary to deliver the highest level of patient care.
In this issue of ONCOLOGY®, Esther Drill, DrPH, et al from Memorial Sloan Kettering Cancer Center (MSKCC) report on the “real-world” experience of subcutaneously injected rituximab/pegylated-hyaluronidase (Rituxan Hycela). The article gives us pause to reflect on what this means precisely and what the authors have reported.

I had a recent discussion with a big data-crunching colleague about statistical validity and hypothesis testing in clinical research. He remarked that if all the data resided in a large dataset, we wouldn’t need hypothesis testing because we would have the answers from direct observation. Of course, he works with large public databases analyzing trends in public policy, so he really means “big data.” And yes, if we were equivalent to the National Security Agency and could access all the data in every electronic medical record and had the super-computer crunching power, we could probably answer many clinical questions directly and obviate the need for clinical research.

However, in absence of this, we have the current report and what people mean when they talk about “real-world experience.” Which data should we regard as falling under this category? First, we need a very large and wide data experience. A large retrospective review from 1 large center hardly qualifies. The surgeons at MSKCC and similar large institutions have been writing this kind of review for decades. Second, the database should be robust enough to explore correlations and provide analysts with the opportunity to dive deeper and make unexpected and penetrating observations. These may be “hypothesis-generating” observations, leading to further research.

Unfortunately, the current report, from MSKCC and its regional centers, falls short on both criteria. One only needs to have been on the staff at MSKCC and Bellevue Hospital, the flagship public hospital of the NYC Health + Hospitals system located a mere 2.1 miles down First Avenue in New York, to realize the “real world” in these institutions differs vastly. We can also see (see Table 1 on page 796) that the patient population of this study has only 4% Black participants and only 3% Medicare patients (reflective of the overall MSKCC patient population). Additionally, the article does not tell us which physicians participated and which opted not to participate, or why. We don’t know if all patients who were offered participation opted in and why some patients did not. We do not know how many patients tried subcutaneous injection but were not able to accomplish this on their own. What percentage of patients required home health care assistance and how much did that cost? Although a tendency was seen toward older patients, the mean age was still 68 years for the subcutaneous group. How did patients 75 years or older handle subcutaneous injections? Many such questions present themselves.

Finally, the authors conclude that subcutaneous rituximab saves chair time. This seems pretty obvious because home administration involves no “chair time.” The mean time saved was 93 minutes for combination therapy and 35 minutes for monotherapy. This is fine and the authors put this in context of savings to the health care system. However, they fail to mention that Rituxan Hycela is a brand agent on patent, whereas a number of rituximab biosimilars are available at lower cost. One estimate is that the brand subcutaneous agent would cost $4000 to $9000 more than intravenous biosimilars.

Finally, as a word of caution, this approach is now being adopted by more insurers, who are refusing to reimburse subcutaneous and intramuscular injections in clinics and forcing patients to receive such treatments at home. This kind of cost shifting to patients and home infusion agencies is not a helpful trend for those who still must come to clinics to see their physicians and are anxious about self-injection.

Real-world data may someday replace clinical trials, but we need very complete multi-institutional databases involving the full universe of patients being seen and treated. This study falls short on these criteria.

Reference
First-line maintenance treatment of urothelial carcinoma

BAVENCIO® (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

NCCN

Category 1 & Preferred

National Comprehensive Cancer Network® (NCCN®)

Recommendation

Avelumab (BAVENCIO) maintenance is the only NCCN CATEGORY 1 and PREFERRED immunotherapy option for both cisplatin-eligible and -ineligible patients with locally advanced or metastatic UC that has not progressed on first-line platinum-containing chemotherapy.1

Category 1-Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Preferred interventions—Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

IMPORTANT SAFETY INFORMATION (continues on following pages)

BAVENCIO 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.

BAVENCIO 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 4 (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.
**JAVELIN Bladder 100 Trial**—a Phase 3, randomized, open-label, multicenter study in patients with unresectable, locally advanced or metastatic urothelial carcinoma that did not progress with first-line platinum-containing chemotherapy (N=700)²

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

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

<table>
<thead>
<tr>
<th>Overall Survival Time (Months)</th>
<th>BSC (n=350)</th>
<th>BAVENCIO + BSC (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio (HR)</td>
<td>0.69 (95% CI: 0.56, 0.86);</td>
<td>2-sided <em>P</em>-value* = 0.001</td>
</tr>
<tr>
<td>14.3 months median OS (95% CI: 12.9, 17.9)</td>
<td>21.4 months median OS (95% CI: 18.9, 26.1)</td>
<td></td>
</tr>
</tbody>
</table>

- OS was measured post-randomization (after chemotherapy)

- OS in patients with PD-L1-positive tumors* (major efficacy outcome measure). BAVENCIO + 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 BAVENCIO + BSC vs BSC alone were:

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

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

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**Study design:** The JAVELIN Bladder 100 Trial was a Phase 3, 1:1 randomized, open-label, multicenter study of BAVENCIO as a first-line maintenance treatment in 700 patients with unresectable, locally advanced or metastatic UC who did not progress on 4 to 6 cycles of platinum-containing chemotherapy (gemcitabine + cisplatin and/or gemcitabine + carboplatin), and an ECOG PS of 0 or 1.² Patients with autoimmune diseases or medical conditions requiring systemic immunosuppression were excluded. Patients were randomized to BAVENCIO 10 mg/kg intravenous infusion every 2 weeks + best supportive care (BSC) (n=350) or BSC alone (n=350) until disease progression or unacceptable toxicity. Treatment was initiated within 4 to 10 weeks after chemotherapy. OS was the major efficacy outcome measure in all randomized patients and patients with PD-L1-positive tumors.³

* *P*-value based on stratified log-rank.

* Using the VENTANA PD-L1 (SP263) assay, PD-L1-positive status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, if none of these criteria were met, PD-L1 status was considered negative.³

† BSC was administered as deemed appropriate by the treating physician, and could include treatment with antibiotics, nutritional support, and other patient management approaches with palliative intent (excludes systemic antitumor therapy).³

§ PD-L1 expression was assessed in tumor samples using the VENTANA PD-L1 (SP263) assay.³

BICR=blinded independent central review; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group (ECOG) Performance Status; PD-1=programmed death 1 receptor; PD-L1=programmed death ligand.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.
References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V3 2021 © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their currentness or its use or application in any way. 2. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med. 2020;383(13):1218-1230.

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BAVENCIO® (avelumab) injection, for intravenous use
RX only
BREASTFEEDING: 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, Life-Threatening 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 1 (PD-L1), blocking the PD-1/PD-L1 pathway. These reactions are typically associated with high levels of immune activity.

BAVENCIO can cause severe, life-threatening immune-mediated adverse reactions. Systemic corticosteroids were required in 29% of patients (Grade 3-4: 10%, Grade 2: 19%). These reactions may occur in any organ system.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time during treatment with BAVENCIO and may be the result of a high immune mediator level. Immune-mediated adverse reactions usually occur during treatment with PD-1/PD-L1 blockers, but can occur after treatment has been stopped. Immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blockers.

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 for systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), and immune-mediated nephritis with renal dysfunction. Immune-mediated adverse reactions have been observed during treatment with BAVENCIO and may occur despite intervening therapy.

BAVENCIO can cause primary or secondary antithyroid antibodies. Thyroid disorders, including Grade 3-4 (0.1%) and Grade 2 (0.9%) adverse reactions, have occurred in patients treated with BAVENCIO, including hypothyroidism (0.1%), hyperthyroidism (0.1%), and thyroiditis (0.1%). Some patients required either thyroid hormone replacement therapy or immunosuppressant or hormone replacement therapy. Immunosuppressant or hormone replacement therapy was required in 0.1% (1/1738) of patients treated with BAVENCIO. Immune-mediated hypophysitis occurred in 0.1% (1/1738) of patients treated with BAVENCIO, including hypophysitis (0.1%), pituitary disorders (0.1%), and adrenal insufficiency (0.1%). Insulin as clinically indicated. Withhold BAVENCIO depending on severity. Immune-mediated adverse reactions may result in weakening of the immune system, reducing the body’s ability to fight infection. Instruct patients to report the following symptoms to their healthcare provider, as soon as possible:

- Fatigue
- Fever
- Sore throat

Other Immune-Mediated Adverse Reactions: While immune-mediated adverse reactions usually manifest during treatment with BAVENCIO, some may occur despite intervening therapy. Various grades of visual impairment, including blindness, can occur. If uveitis is observed, treatment with BAVENCIO can be temporarily withheld or discontinued. Various immune-mediated adverse reactions have been reported with BAVENCIO, including infusion-related reactions (Grade 3: 0.9%), acute kidney injury (5.0%), rash (6.1%), and diabetes mellitus (4.7%). Immune-mediated adverse reactions have been observed in patients treated with BAVENCIO, including hyperthyroidism (1.1%), hypothyroidism (1.8%), hypophysitis (0.1%), and adrenal insufficiency (0.1%).

Immune-mediated adverse reactions have been observed in patients treated with BAVENCIO, including hyperthyroidism (1.1%), hypothyroidism (1.8%), hypophysitis (0.1%), and adrenal insufficiency (0.1%).

Immune-mediated adverse reactions that may be severe or fatal can occur in any organ system.

Infusion-Related Reactions: BAVENCIO can cause severe or life-threatening infusion-related reactions. Premedicate with antihistamine and acetaminophen prior to the first 4 infusions. Monitor patients for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Initiate or stop the rate of infusion for mild or moderate infusion-related reactions. Stop the infusion and permanently discontinue BAVENCIO for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. Do not restart BAVENCIO in patients who have experienced Grade 4 infusion-related reactions. Thirty-three percent of patients received prednisone with antihistamine and acetaminophen. Eleven (9%) of the 12 patients with Grade 1-3 reactions were treated with prednisone, and 2 (17%) of the patients had infusion-related reactions that occurred after the BAVENCIO infusion was completed.

Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive alemtuzumab to reprogram hematopoietic progenitor cells to treat hematologic malignancies (HCL). While alemtuzumab can lead to a decrease in white blood cells, it is not indicated for use in patients with neutropenic fever. Alemtuzumab is not indicated for use in patients with neutropenic fever.

Embryo-Fetal Toxicity: It is known that a PD-1/PD-L1 blocking antibody administered to a pregnant woman can trigger the autoimmune process and can result in fetal loss. BAVENCIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid pregnancy.

Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO. Infusion-related reactions were observed in 9% of patients treated with BAVENCIO plus BSC.

Table 6: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 10% of Patients

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BAVENCIO</th>
<th>BAVENCIO plus BSC</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin decreased</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemoglobin increased</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelet count</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>30</td>
<td>30</td>
<td>0.01</td>
</tr>
<tr>
<td>Alanine transaminase</td>
<td>20</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>Aspartate transaminase</td>
<td>20</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>Blood cholesterol</td>
<td>20</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>Blood triglycerides</td>
<td>20</td>
<td>20</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Adverse Reactions in Patients with Hyperthyroidism

- Hyperthyroidism: BAVENCIO can cause hyperthyroidism, including hyperthyroidism (0.1%), hypothyroidism (0.1%), and thyroiditis (0.1%). Immune-mediated hypophysitis occurred in 0.1% (1/1738) of patients treated with BAVENCIO, including hypophysitis (0.1%), pituitary disorders (0.1%), and adrenal insufficiency (0.1%). Insulin as clinically indicated. Withhold BAVENCIO depending on severity. Immune-mediated adverse reactions may result in weakening of the immune system, reducing the body’s ability to fight infection. Instruct patients to report the following symptoms to their healthcare provider, as soon as possible:

- Fatigue
- Fever
- Sore throat

Other Immune-Mediated Adverse Reactions: While immune-mediated adverse reactions usually manifest during treatment with BAVENCIO, some may occur despite intervening therapy. Various grades of visual impairment, including blindness, can occur. If uveitis is observed, treatment with BAVENCIO can be temporarily withheld or discontinued. Various immune-mediated adverse reactions have been reported with BAVENCIO, including infusion-related reactions (Grade 3: 0.9%), acute kidney injury (5.0%), rash (6.1%), and diabetes mellitus (4.7%). Immune-mediated adverse reactions have been observed in patients treated with BAVENCIO, including hyperthyroidism (1.1%), hypothyroidism (1.8%), hypophysitis (0.1%), and adrenal insufficiency (0.1%).

Immune-mediated adverse reactions that may be severe or fatal can occur in any organ system.
Adverse reactions occurring in permanent discontinuation of BAVENCIO in >5% of patients were myasthenia gravis (including acute myocardial infarction and infarction T) led to 1.5% and -

>1.2%. Dose interruptions due to an adverse reaction, excluding temporary interruptions of BAVENCIO infusions due to infusion-related reactions, occurred in 41% of patients receiving BAVENCIO plus BSC. Adverse reactions leading to discontinuation of BAVENCIO in >5% of patients were urinary tract infection (including pyelonephritis) (4.7%) and blood creatinine increased (including acute kidney injury, renal impairment, and renal failure) (3.8%). The most common adverse reactions (2.0%) in patients receiving BAVENCIO plus BSC were fatigue, musculoskeletal pain, urinary tract infection, and rash. Thirty-one (9%) patients treated with BAVENCIO plus BSC received an oral prednisone dose equivalent to 2.4 mg daily for an immune-mediated adverse reaction. Table 5 summarizes adverse reactions that occurred in ≥10% of patients treated with BAVENCIO plus BSC.

Table 5: Adverse Reactions (≥10%) of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BAVENCIO plus BSC (N=134)</th>
<th>BSC (N=435)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15</td>
<td>0.3</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>24</td>
<td>1.2</td>
</tr>
<tr>
<td>Anklegia</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>24</td>
<td>1.2</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>17</td>
<td>0.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>12</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>10</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*Fatigue is a composite term that includes fatigue, asthenia, and malaise. Muscle pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain. Rash is a composite term that includes rash, rash maculo-papular, erythema, dermatitis acrodermatitis, eczema, erythema multiforme, rash erythematous, rash macular, rash papular, rash purpuric, drug eruption and ichthyosis planus.

**Urinary tract infection is a composite term that includes urinary tract infection, ureocelepy, cystitis, kidney infection, pyuria, pyelonephritis, bacteriuria, pyelonephritis acute, urinary tract infection bacterial, and Enchanchia urinary tract infection.**

*Cough is a composite term that includes cough and productive cough.

Patients received pre-medication with an anti-histamine and acetaminophen prior to each infusion. Infusion-related reactions occurred in 10% (Grade 3: 0.9%) of patients treated with BAVENCIO plus BSC.

Table 6: Selected Laboratory Abnormalities Worsening from Baseline Occurring in ≥10% of Patients Receiving BAVENCIO plus BSC (JAVELIN Bladder 100 Trial)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BAVENCIO plus BSC†</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Grade</strong></td>
<td><strong>Grade 3-4</strong></td>
<td><strong>Any Grade</strong></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>34</td>
<td>2.1</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>30</td>
<td>2.9</td>
</tr>
<tr>
<td>Blood sodium decreased</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST) increased</td>
<td>24</td>
<td>1.7</td>
</tr>
<tr>
<td>Blood potassium increased</td>
<td>24</td>
<td>3.8</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT) increased</td>
<td>24</td>
<td>2.6</td>
</tr>
<tr>
<td>Blood cholesterol increased</td>
<td>22</td>
<td>1.2</td>
</tr>
<tr>
<td>Serum amylase increased</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>C-PK increased</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>19</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: BAVENCIO plus BSC group (range: 339 to 344 patients) and BSC group (range: 329 to 341 patients).

**Immunogenicity:** As with all therapeutic proteins, there is potential for immunogenicity. The incidence of antibodies to BAVENCIO is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, a comparison of the incidence of antibodies to avilamab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. Of the 344 patients treated with BAVENCIO 10 mg/kg as an intravenous infusion every 2 weeks ± BSC, 32% were evaluable for treatment-emergent anti-drug antibodies (ADA) and 62 (19%) tested positive in the JAVELIN Bladder 100 trial. Patients testing positive for treatment-emergent ADA had decreased systemic BAVENCIO exposure. In exploratory analyses, the effect of ADA on the efficacy or safety could not be determined due to insufficient numbers of patients in the ADA-positive subgroup and controlling variables.

**TOXICITY MANAGEMENT GUIDELINES FOR ADVERSE REACTIONS:**

**Pregnancy:**

- **Risk Summary:** Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of BAVENCIO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Human IgG1 immunoglobulins (IgG1) are known to cross the placenta. Therefore, BAVENCIO has the potential to be transmitted from the mother to the developing fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to the fetus. In the U.S. general population, the estimated background risk for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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

- **Lactation:** Risk Summary: There is no information regarding the presence of avilamab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs and antibodies are excreted in human milk, advise a lactating woman not to breastfeed while taking BAVENCIO and for at least one month after the last dose of BAVENCIO due to the potential for severe adverse reactions in breastfeeding infants.

- **Females and Males of Reproductive Potential:** Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with BAVENCIO and for at least 1 month after the last dose of BAVENCIO.

- **Pediatric Use:** Safety and effectiveness of BAVENCIO have not been established in pediatric patients.

- **Geriatric Use:**

Locally Advanced or Metastatic Unresectable Carcinoma: Of the 344 patients randomized to BAVENCIO 10 mg/kg plus BSC in the JAVELIN Bladder 100 trial, 63% were 65 years or older and 24% were 75 years or older. No overall differences in safety or efficacy were reported between elderly patients and younger patients.

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

**Immunomediated Adverse Reactions:** Inform patients of the risk of immune-mediated adverse reactions requiring corticosteroids or hormone replacement therapy, including, but not limited to:

- **Pneumonitis:** Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath.
- **Colitis:** Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain.
- **Hepatitis:** Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of the abdomen, lethargy, or easy bruising or bleeding.
- **Endocrinopathies:** Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hyperthyroidism, hypothyroidism, and diabetes mellitus.
- **Nephritis with Renal Dysfunction:** Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis including decreased urine output, blood in urine, swelling in addition to loss of appetite, and any other symptoms of renal dysfunction.
- **Dermatologic Adverse Reactions:** Advise patients to contact their healthcare provider immediately for signs or symptoms of skin rash, itchy skin, rash with tiny spots and bumps, reddening of skin, blisters or peeling.

**Infusion-Related Reactions:** Advise patients to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

- **Complications of Allogeneic HSCT:** Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications.
- **Embryo-Fetal Toxicity:** Advise females of reproductive potential that BAVENCIO can cause fetal harm. Instruct females of reproductive potential to use effective contraception during and for at least one month after the last dose of BAVENCIO.

- **Lactation:** Advise nursing mothers not to breastfeed while taking BAVENCIO and for at least one month after the final dose.

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February 2021 US-AVE-00577

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Since the first information regarding single-agent PD-1 inhibitors were presented at the American Society of Clinical Oncology Annual Conference a decade ago, immune checkpoint inhibitors (ICIs) have been widely used in the treatment of non–small cell lung cancer (NSCLC).

In an interview with ONCOLOGY®, Julie R. Brahmer, MD, MSc discussed her integral role in developing these therapies and how she overcame doubts that they wouldn’t work in certain patient populations.

Brahmer spoke about the development of the PD-1 inhibitor nivolumab (Opdivo) and how her career progressed since working on a pivotal trial that brought it to the lung cancer space. She also revealed what she believes are next steps in ICI research, detailed potential new therapies that could be practice-changing in the lung cancer space, and shared why she doesn’t think more anti–PD-1 agent are necessary.

Q: Ten years ago, did you have any idea how big the research around PD-1 inhibitors would become?
A: Throughout my career of being a part of drug development teams, I certainly was used to being principal investigator on many phase 1 first-in-human trials that just never went anywhere or didn’t show activity. [Some] drugs would make it out of the phase 1 trials and into further development. With the advent of PD-1 [inhibitors], seeing an inkling of activity was exciting to be a part of since, particularly in NSCLC, most investigators in the community at large felt that lung cancer was not an immunogenic cancer and immune therapy of any type would never work. That [overarching] feeling, at least for the oncology community, continued until the [results of the first phase 3 study to show efficacy]. And even at that point, a lot of clinicians felt it was a fluke. Now, seeing that there are groups of patients within lung cancer being significantly affected—as well as patients with other cancers, such as [those with] microsatellite instability [MSI]–high colon cancer or [other] MSI-high tumors—it’s certainly exciting and gratifying to know that I was a small part of the development of something that could have an effect on patients who otherwise had minimal treatment options.
Q: When did you allow yourself to stop being skeptical about how the trials were progressing?
A: For me, it was [initially] during the phase 2 trials, where we saw consistent activity, and then in the first phase 3 trials in the second-line treatment setting, where it clearly did outperform chemotherapy. As an oncologist, I felt comfortable when it was in phase 3 trials, but even before that, when we saw patients whose disease had melted away and did not come back for months to years, I felt like this was something that would be around [for a while] and we just had to figure out who should receive it.

Q: What was your specific role in these trials?
A: I’m a medical oncologist and I do phase 2 drug development in oncology, and my subspecialty is specifically in patients with thoracic malignancies: lung cancer and mesothelioma. Those are the patients who I see in clinic. I was the principal investigator at Johns Hopkins of the first-in-human phase 1 trial of nivolumab [NCT00441337]. Back then it was MDX-1106, so it didn’t even have a name. I was also a part of the next phase 1 trial, and then with other investigators took that into a phase 3 study [NCT01642004] comparing it with chemotherapy in patients with metastatic lung cancer [in the second-line setting].

Q: Was this your first time working through a phase 3 trial?
A: Yes, it was. That was always a career goal—to be part of something that was just coming out of the lab, being tested for the first time, then taking that drug into a phase 3 setting, and then getting it approved. Certainly, having the opportunity to work within the industry and then seeing a drug translate into clinical benefit in the clinic was very exciting and gratifying.

Q: The most recent approval of an ICI came in October with atezolizumab (Tecentriq) in the adjuvant setting for NSCLC. How quickly do you think this will be utilized, and will there be reluctance in this setting?
A: Particularly in the second-line treatment setting where immunotherapy first got started, it was easily taken up because people are looking for something new to use. [They want] something that is touted to be less toxic, or toxic in a completely different way [than traditional therapies], and that has a clinical benefit [showing] that if it works, it will last for a long time, not just for a few months.

Obviously, that led to taking these agents into the first-line treatment setting. Realizing that a subset of patients benefited from the single-agent PD-1 or PD-L1 antibodies and trying to increase the response and duration of response in more patients, led to combining it with chemotherapy. Seeing the power in the metastatic setting [resulted in] bringing those sorts of drugs into the locally advanced setting, and now into the adjuvant setting after surgery.

My colleague, Heather Wakelee, MD, [deputy director of the Stanford Cancer Institute and the division chief of medical oncology at Stanford University], presented the atezolizumab study at the American Society of Clinical Oncology Annual Meeting this year. It’s great to be able to see immunotherapy [have an] impact on patients with early-stage disease NSCLC. We’re seeing the power of immunotherapy and that the immune system does play a role in disease control. Hopefully, at least early on, we’re seeing increased chances of a cure or at least disease-free survival in that early-stage disease as well.

Q: What are we learning about adverse effects (AEs) of ICIs and the proper way to manage them?
A: For the most part, oncologists are getting comfortable in treating patients with these inhibitors. Certainly, the toxicities are typical for immune responses. There are always nuances to these toxicities, and certainly the guidelines help give us a framework to treat or mitigate the AEs. We’re learning more about who we can safely treat or how to best use these therapies in patients with preexisting autoimmune diseases, as well.

Q: Regarding molecular testing strategies, what new tests are available and useful because of these agents?
A: Since we have targeted therapy, or tyrosine kinase inhibitors [TKIs], that have been developed specifically for multiple different mutations, [the presence of] EGFR mutations are now being used in the adjuvant setting [to guide therapy]. We want to go over testing, who to test, and what tests are best in the metastatic setting. We always struggled with finding if we have enough tumor tissue, and then trying to get those results as quickly as possible so that we can get the patients on the right treatment to begin with and control their disease. Now, sometimes, we do use blood-based cell-free DNA testing platforms to try to get those results quickly.

Q: Looking forward, what are the next steps in immunotherapy research?
A: [To start, we need to] drill down on who can get away with receiving just single-agent immunotherapy and who will be those long-term
responders. We’ve done [a lot] thus far with driver mutations—coming up with what we call “precision medicine” for those patients—and [we now need to] switch that over to develop precision medicine for the other patients receiving immunotherapy. We’re on the road, but over the next 10 years, we’ll accomplish that, and then we’ll also have a better idea of which combinations patients should receive.

A bunch of different combination ICIs are being tested, looking at a cellular therapy, and who should receive that, as well as which patients still need to rely on chemotherapy to get their disease under control. We’ll see these answers over the next 5 to 10 years. In the short term, we’ll see how best we should sequence [therapy], [figure out if] we should give everything upfront to these patients to give them their best chance of response, and [determine if] that affects their long-term disease control. Studies are ongoing there.

Q: Can you discuss the PD-1 and PD-L1 inhibitors in development, those that aren’t FDA approved yet?

A: I don’t think we need more drugs that target PD-1 or PD-L1. However, we all hope that having more drugs in the marketplace that act on the same pathway, and act in very similar fashion, will help drive down prices for our patients. We also must be practical when talking about drug development. For some companies, it’s easier to have their own PD-1 or PD-L1 antibody and start adding to it rather than trying to contract with other companies and deal with the complexity of having to use another company’s [agent], so I get why it’s being done. If it were just automatically free, you could use whatever you wanted and have no legal issues or data rights. We probably don’t need ten PD-1 or PD-L1 inhibitors in the clinic. I’m in favor of trying to do anything we can to speed up development of some of these newer checkpoints beyond PD-1 and PD-L1 inhibitors.

Q: If a patient has a genetic alteration that has a targeted drug, might a clinician ever be able to give immunotherapy first instead? Is any research being done?

A: Patients with driver-mutated tumors who were never smokers are typically given a TKI. Where it gets harder is in patients with KRAS G12C mutations; there, ICIs as a single agent have [resulted in] a decent response rate, in the 30% to 40% range. That’s where we need a study to be able to compare head-to-head what is best to give these patients first.

Many of us are a bit hesitant about potential AEs when we’re giving immunotherapy first in these patients for whom we plan to give a TKI next. Just because you stop an immunotherapy agent doesn’t mean that its effects will be gone quickly. It takes a while for the antibody to get out of your system—let alone the effects on the immune system that can last for months to years. Sometimes when we add a TKI and these patients stop immunotherapy, we can see more unusual AEs or increased AEs or more liver function abnormalities than we would typically expect; in some cases, [there are] risks and what we call pneumonitis inflammation of the lungs. [Pneumonitis inflammation] is complex in some of those patients, but the standard patient with an EGFR mutation, RET fusion, or ALK fusion tends to not do well with single-agent immunotherapy. We really rely on TKIs and feel that those patients, because of the high response rate to TKIs, can receive those first.

Q: What trials in the lung cancer space have the potential to be practice-changing?

A: I’m excited to see some of the ICIs called TGIT [T-cell immunoreceptor with immunoglobulin and ITIM domains]. Some anti-TGIT antibodies are being added to PD-1 or PD-L1 antibodies. Some of the early phase 2 studies show increased response rates in patients with PD-L1–high disease who do not need chemotherapy at all to achieve that response. I’m excited to see those results in that group of patients and seeing more drugs that we can use to target some of these driver mutations and ways to get around [any] resistance that occurs. I’m excited to see a lot of these drugs in this space, particularly the KRAS space [and] the EGFR space. There’s an opportunity to improve care for these patients, and I’m excited to see some of the new drugs that are being developed.

References

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Characterization of Blood-Based Molecular Profiling in Pancreatic Adenocarcinoma

Christine Chung, DO; Rachael Galvin, DO, MPH; Ella Achenbach; Oliwier Dziadkowiec, PhD; and Shiraj Sen, MD, PhD

ABSTRACT

BACKGROUND: Molecular profiling is being explored in pancreatic adenocarcinoma (PDAC) as a tool to assist with early detection, prognosis, and patient selection in targeted therapy clinical trials. Due to the challenges and risks of traditional tissue biopsies in pancreatic adenocarcinoma, the utility of blood-based molecular profiling is now being explored more broadly. However, given its novelty, what value blood-based molecular profiling may provide to oncologists caring for individuals with PDAC remains unknown. Herein, we characterize the mutational landscape of metastatic PDAC using blood-based circulating tumor DNA (ctDNA) collected in patients with refractory, metastatic PDAC who were referred to an oncology drug development unit in Denver, Colorado, between August 2014 and May 2019.

METHODS: We retrospectively analyzed results of blood-based molecular profiling that was performed on 77 consecutive patients with metastatic PDAC who underwent Guardant-360 testing for whom results were available.

RESULTS: In our data set, 55% of patients (41/77) were men, median (SD) age was 66 (9.3) years (range, 44-83). Of 77 patients, 34 (44%) had 1 or more somatic alterations. Variants reported as being of unknown significance were not included in the analyses. The total number of alterations were 119 (nonunique) and 96 (unique). The median number of alterations per patient was 3 and the median mutant allele frequency was 0.5%. TP53 was the most commonly altered gene (29 unique alterations), followed by KRAS (27 unique alterations). Of the patients with any alteration, 34% had 1 or more actionable alterations that could be potentially targeted in a clinical trial.

CONCLUSIONS: Detection of genomic alterations in ctDNA from patients with metastatic PDAC is feasible and reveals a wide range of genomic alterations, the actionability of which is being explored in clinical trials. Further investigation is needed to determine the extent to which blood-based molecular profiling can provide clinical utility in helping to select patients into clinical trials and determine its impact on survival.

KEYWORDS: molecular profiling, ctDNA, pancreatic adenocarcinoma
Introduction
Most cases of pancreatic adenocarcinoma (PDAC) are diagnosed in the metastatic or locally advanced stage. It is the fourth leading cause of cancer death in the United States, with a 5-year overall survival (OS) around 10% in this country despite years of research and therapeutic development. For those patients with unresectable or refractory PDAC, locoregional and systemic chemotherapies remain the main treatment options outside of a clinical trial. In December 2019, the FDA approved the first targeted therapy, olaparib (Lynparza), in the maintenance setting for individuals with metastatic pancreatic adenocarcinoma whose tumors harbored a deleterious or suspected deleterious germline BRCA mutation. Since 2010, a large body of transcriptomic and immunophenotypic research done in PDAC has led to the development of numerous targeted- and immunotherapy-based clinical trial options as well, many of which are biomarker-driven and are predicated on the identification of a specific genetic or immunologic signature.

While tissue-based assays remain the mainstay for molecularly characterizing PDAC, 2 limitations for the application of these assays are access to tissue and tumor heterogeneity in metastatic sites. Tumor-based biopsies can lead to ambiguous or inconclusive samples and thus may underestimate the mutational burden of heterogeneous tumors. Spatially separated heterogeneous somatic mutations and chromosomal imbalances translating into phenotypic intratumor diversity have been described across tumor types as well. Furthermore, there is often neither a safe nor feasible area to biopsy an individual’s tumor due to anatomical factors. Novel blood-based sequencing platforms have emerged and are now FDA approved in malignancies such as non–small cell lung cancer. These assays allow for molecular profiling based on circulating tumor DNA (ctDNA) that is released into the blood via apoptosis, necrosis, and active secretion.

Previous studies have suggested that the presence of ctDNA may be prognostic in both localized and advanced PDAC and that ctDNA concentration may be correlated with recurrence after tumor resection. Similarly, high ctDNA concentration has been found to be associated with distant organ metastases. Whether ctDNA dynamics will aid in treatment decision-making or be associated with response to therapy in PDAC, as has been found in other cancers, remains to be seen. Few data are currently available that characterize the genomic landscape in individuals with metastatic PDAC using blood-based assays. Herein, we characterize the mutational landscape of patients with metastatic PDAC who received blood-based molecular profiling.

Materials And Methods
We performed a retrospective review of 77 consecutive patients with refractory, metastatic PDAC who were referred to the Sarah Cannon Research Institute (SCRI) at HealthONE, an oncology drug development unit in Denver, Colorado, between August 2014 and May 2019. This analysis includes all patients with metastatic PDAC who were referred to SCRI, who elected to undergo blood-based molecular profiling, either before or after the initial referral; and had a full report available. Data for those tested prior to referral were not available, and thus it was unknown at what stage those patients were tested. We evaluated patient demographics; prior medical history, including initial stage at diagnosis, comorbidities, and prior cancer-related therapies (surgery, radiation, and systemic chemotherapies or prior clinical trial data); and source of referral (academic vs community). As a proxy for defining academic vs nonacademic practices, we classified each referring oncologist based on whether they are affiliated with a National Cancer Institute–designated cancer center. Blood samples were evaluated at the Clinical Laboratory Improvement Amendments–licensed and College of American Pathologists–accredited clinical laboratories of Guardant Health, Inc for ctDNA analysis.

Clinical outcomes and variables evaluated in our analysis include all alterations identified at the time of testing; percent ctDNA (% ctDNA) present in the bloodstream; and potential actionability of alterations. The determination of whether an alteration was potentially actionable or not via a clinical trial is based on the actionable gene list created by the Institute for Personalized Cancer Therapy—Precision Oncology Decision Support team at The University of Texas MD Anderson Cancer Center. These standards mandate that a gene is potentially actionable if there is supporting evidence that the gene is a driver for tumorigenesis, where any action on the gene can either determine sensitivity or resistance to drugs, and that it applies to all alteration types. Additionally, there must be a clinically available agent targeting the gene that is in at least preclinical development.

Based on the aforementioned criteria, the following genes were considered actionable based on their sensitivity to respective targeted agents: AKT1, ALK, ARAF, ARID1A, ATM, BRAF, BRCA1, BRCA2, CCND1, CCND2, CDK4, CDK6, CDKN2A, CDKN2B, EGF, ERBB2, FGFR1, FGFR2, FGFR3, HRAS, IDH1, IDH2, JAK2, JAK3, KIT, KRES, MAP2K1, MAP2K2, MET, MPL, MYC, NF1, NOTCH1, NRAS, NTRK1, PDGFR, PIK3CA, PTEN, PTPN11, RET, ROS1, SMO, STK11, and TSC1. The following genes were deemed actionable based on context-specific criteria: CCNE1 (sensitivity to CDK2 inhibitors; resistance to CDK4/6 inhibitors); ESR1 (presence is sensitizing to...
hormone therapy; mutations cause resistance to antihormone therapy); NRAS (sensitivity to MEK inhibitors; resistance to cetuximab [Erbitux] and panitumumab [Vectibix]); RAF1 (activating alterations cause sensitivity to MEK inhibitors and resistance to RAF inhibitors; inactivating alterations cause resistance to dasatinib). Only AR and RB1 were deemed actionable solely because of their resistance to antihormone therapy and to CDK4/6 inhibitors, respectively. The following were considered nonactionable: TFE3, CTNNB1, APC, GNAS, NFE2L2, MLH1, RIT1, SMAD4, HNF1A, CDH1, GATA3, VHL, FBXW7, and RhoA. Co-occurring alterations were also analyzed using descriptive methods. Data analysis was performed using R Studio.14 We used the Mann-Whitney U test to compare the mean number of comorbidities and mutations between individuals who died and those who were still alive. To calculate median survival, we calculated the number of months between initial diagnosis and either death or last date of contact. This research was approved by the HealthOne HCA institutional review board.

Results
As seen in Table 1, all patients had refractory disease after
pancreaticoduodenectomy, chemotherapy, and/or radiation therapy. Of 77 patients, 41 (55%) were men. Median (SD) age was 66 (9.3) years (range, 44-83). Patients had between 0 and 7 medical comorbidities (median, 2). Functional status was determined by ECOG performance score (PS), ranging from ECOG PS 0 to 3, with 69% (53/77 patients) scoring ECOG PS 1. Additionally, 28 of 77 patients (39%) were smokers whereas 41 (57%) were not, and 3 had unknown status (4%). Initial staging varied from stage I to stage IV, but the largest proportion of patients, 37 of 77 (48%), had stage IV disease at diagnosis and had de novo disease. As seen in Table 1, surgical intervention prior to referral occurred in 18 of 77 patients (23%), including 13 pancreaticoduodenectomies, 1 distal pancreatectomy, 1 segmental pancreatectomy, and 1 total pancreatectomy. Ninety-seven percent of patients (75/77) underwent chemotherapy prior to referral, which consisted of either gemcitabine and nab-paclitaxel (Abraxane), FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin), fluorouracil, or a combination of these. Eleven patients (14%) had enrolled in another clinical trial prior to referral and 22 received radiation.

Blood from 34 of 77 patients (44%) was found to harbor 1 or more genetic alterations, 7 patients (9%) had no alterations. Forty-seven patients (61%) underwent Guardant-360 testing; however, the stage in which they were tested was not available in those who were tested prior to referral. Thirty-two patients (42%) were referred to our clinic with stage IV disease, and 20 of these patients with stage IV disease (26%) were tested after referral. Of the patients with alterations, 36% (28/77) had 1 or more potentially actionable alterations, most commonly BRCA2 (12%), STK11 (2%), PIK3CA (1%), NF-1 (1%), EGFR (1%), and TP53 (30%). The number of alterations were 119 (total, nonunique) and 96 (unique), and the median number of alterations per patient was 4. Median mutant allele frequency (% ctDNA) was 0.5% (range, 0.09%-75.2%). Table 2. Genes Sequenced by Guardant360

<table>
<thead>
<tr>
<th>Gene</th>
<th>Specific mutations</th>
<th>Frequency</th>
<th>Potentially actionable</th>
<th>Targeted agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>G12c, G12d</td>
<td>23</td>
<td>Yes</td>
<td>G12c- AMG510, MRTX849</td>
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<td>SMAD4</td>
<td>W524, R445, R361H, S242, R378fs</td>
<td>4</td>
<td>No</td>
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<td>BRCA1</td>
<td>L1392F</td>
<td>1</td>
<td>Yes</td>
<td>Olaparib, rucaparib, niraparib</td>
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<tr>
<td>BRCA2</td>
<td>H1022R, D1484fs, N1603N, N1784fs, N1544fs, E1550fs, T630fs</td>
<td>9</td>
<td>Yes</td>
<td>Olaparib, rucaparib, niraparib</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>N71S, R80, E69, V82fs</td>
<td>4</td>
<td>Some data supports</td>
<td>Palbociclib, ribociclib</td>
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<tr>
<td>STK11</td>
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<td>Some data supports</td>
<td>Cardiac glycosides causing inhibition of ATP1A1 function</td>
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<td>APC</td>
<td>D1512N, R230C</td>
<td>3</td>
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<tr>
<td>GNAS</td>
<td>R201C, Q227E, R201H</td>
<td>3</td>
<td>Unknown</td>
<td>-</td>
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<tr>
<td>PIK3CA</td>
<td>R398C</td>
<td>2</td>
<td>Yes</td>
<td>mTOR inhibitor, everolimus, alpelisib</td>
</tr>
</tbody>
</table>

The number of alterations were 119 (total, nonunique) and 96 (unique), and the median number of alterations per patient was 4. Median mutant allele frequency (% ctDNA) was 0.5% (range, 0.09%-75.2%). TP53 was the most commonly altered gene (23 alterations, 23/77 patients [30%]), followed by KRAS (37 alterations, 27/77 patients [34%], with 1/77 being the potentially actionable G12c [1%] and 12/77 [16%] being G12D, BRCA2 (9 alterations, 7/77 patients [9%]), SMAD4 (4 alterations, 2/77 patients [3%]), and CDKN2A (4 alterations, 4/77 patients [5%]). Of the patients with alterations, 36% (28/77) had 1 or more potentially actionable alterations, most commonly BRCA2 (12%), STK11 (2%), PIK3CA (1%), NF-1 (1%), EGFR (1%), and TP53 (30%).
FGFR (1%), NRAS (1%), and KRAS G12C (1%). In these genes, mutations (vs amplifications, deletions, or others) occurred most frequently. Table 2 outlines the data to support actionability of notable mutations given the utility of specific treatments found to act on these genes. Table 3 provides a comprehensive list of the single nucleotide variants, copy number amplifications, fusions, and indels evaluated for, in selected genes.

Given the association between mechanisms of resistance to targeted therapies and co-occurring alterations, we also assessed patterns of co-occurring alterations in this data set, which are detailed in Table 4. We noted that KRAS co-occurred with various mutations in 10 different combinations: KRAS as G12D with TP53 mutations 9 times, with TP53 and SMAD4 five times, as G12V with TP53 four times, as G12D with CDKN2A four times, with BRCA2 four times, and as G12D in combination with CDKN2A and TP53 three times.

A total of 24 patients in our data set were diagnosed with other cancers within their lifetimes, and 6 of the 24 patients were found to harbor mutations in the blood that had therapies associated with them based on the Guardant360 test. Two patients had basal cell skin cancer, and 1 patient had an unspecified skin cancer. The mutations identified in these 24 patients included NF1, BRCA2, GNAS, and CDKN2A. One patient with prostate cancer had a BRCA2 mutation. One patient with colorectal cancer had both CDKN2A and KRAS mutations.

At the time of retrospective review, 20 individuals were still alive, 30 individuals had died, 23 individuals had an unknown status, and 4 individuals had missing status information. Based on the information in our data set, the median survival was 21 months (range, 3–68 months). It should be noted that 1 patient in the “alive” groups has been alive for 126 months, which is an outlier. This was a healthy man with no other medical problems, aged 72 years, who underwent treatment with FOLFIRINOX as well as with gemcitabine/nab-paclitaxel but had disease progression with both treatments. He completed 2 clinical trials (with entrectinib (Rozl)trek), a Trk/ALK/ROS1 inhibitor, and niraparib (Zejula), a PARP inhibitor), both with no success, so he transitioned to hospice. He did not undergo any molecular profiling testing as he had already transitioned to hospice at the time.

The next highest number of months being alive is 50. This patient, a man aged 78 years, was mostly healthy otherwise, had an ECOG PS of 1, and was diagnosed with pancreatic ductal adenocarcinoma in 2015. He had undergone treatment with FOLFIRINOX, capecitabine, and gemcitabine/nab-paclitaxel, as well 2 clinical trials, but progressed in his disease and was referred once he developed pulmonary and gastric metastases. The 2 clinical trials involved an aurora B kinase

Thanks to innovations in liquid biopsy platforms within the past decade, the oncology world is witnessing the transformation of precision medicine in cancer care. The first FDA approval of a liquid biopsy test was the CellSearch CTC enumeration platform in 2013, which is centered on the detection of circulating tumor cells (CTC) in blood. In 2016, the FDA approved the first circulating tumor DNA (ctDNA) blood test, cobas EGFR Mutation Test v2, to detect EGFR gene mutations in patients with non–small cell lung cancer (NSCLC). In 2020, the FDA approved 2 additional comprehensive genomic profiling liquid biopsy tests, Guardant360 CDx and FoundationOne Liquid CDx, which both utilize next-generation sequencing technology to detect tumor genomic alterations in cell-free ctDNA in blood. Although Guardant360 CDx can detect changes in more than 60 different genes that are relevant in solid tumors, FoundationOne Liquid CDx can identify mutations or alterations in 300 or more genes.

In this issue of the journal, Christine Chung, DO, and colleagues report on the biologic and clinical correlates of genomic alterations in 77 consecutive patients with pancreatic ductal adenocarcinoma (PDAC), utilizing the Guardant 360 CDx blood-based molecular profiling test. This timely article reflects the current momentum in the use of liquid biopsies as an alternative to traditional tissue biopsies. The current standard, tissue-based molecular profiling, is more invasive, not always easy to perform, and takes longer to produce results. Blood-based molecular profiling testing, on the other hand, is fairly new. Despite recent advances, there remain uncertainties; one is determining the standardization of the timing
of blood collection and extraction methods, and another is determining the assay cutoffs for ctDNA or CTC positivity. The possibilities of false-positive or false-negative results exist as well. Currently, the FDA recommends confirmation of negative results from Guardant 360 CDx or FoundationOne Liquid CDx tests with a tissue biopsy test. Similarly, the 2021 National Comprehensive Cancer Network Clinical Practice Guidelines state that cell-free ctDNA testing should not replace a histologic tissue diagnosis unless a patient is medically unfit for invasive tissue sampling. While in most instances a positive mutation, such as BRCA, BRAF, EGFR, or FGFR, directs the targeted treatment decision, confirmation of a negative mutation may also have implications for the treatment, as in the case of KRAS wild-type tumors in patients with colon cancer.

Although the guidelines are not well established, basic tumor biology principles may help in the liquid- vs tissue-biopsy decision. The higher the tumor burden, the higher the yield may be for the detection of ctDNA in blood-based molecular testing. In a patient with early-stage cancer, or in a patient with metastatic cancer whose tumor is responding well to current treatment, tumor shedding may not be high enough to detect ctDNA in blood. In this group of patients, tissue biopsy may be more appropriate. On the other hand, in a patient with metastatic cancer whose tumor is progressing while on or soon after treatment, blood-based molecular testing may be more applicable and may provide a quick answer for the next treatment choice.

In the retrospective review done Chung et al, initial staging of patients varied from stage I to IV; the largest proportion (48%) had stage IV disease at diagnosis. Blood from 35 of 77 (45%) patients showed 1 or more genetic alterations, with a median number of 3 alterations per patient. The most commonly altered gene was TP53, followed by KRAS, BRCA2, SMAD4, and CDKN2A. Of the patients with alterations, 36% had 1 or more potentially actionable mutation, most commonly BRCA2 (12%); this was followed by STK11, KRAS, PIK3CA, NF-1, EGFR, and FGFR.

The humbling fact is that so far, no agents have been approved against the most commonly identified mutations in PDAC, other than the PARP inhibitor olaparib (Lynparza). Clinical trials testing other agents are limited as well. In addition to finding targeted treatment options, other valuable uses of liquid biopsy technology can be the application of serial liquid biopsy testing in patients who are currently on treatment and assessing ctDNA quantitively to predict response and long-term clinical benefit. Likewise, monitoring patients who have completed curative therapy using blood-based molecular testing could be a valuable tool to determine risk of recurrence.

Despite the increasing popularity of liquid biopsy testing in cancer care, its current use seems to be mainly confined to advanced-stage patients as it is in this study by Chung et al. However, in addition to its potential in diagnosing cancer, guiding treatment decisions, and monitoring for treatment resistance, several studies are now underway to investigate how the commercial liquid biopsy tests might track minimal residual disease. Ongoing research is also exploring the utility of liquid biopsy in early-stage cancers as well as in detecting cancers in asymptomatic, average-risk individuals. Two liquid biopsy early-detection tests are making their way through clinical trials: The LUNAR-2 test is designed to detect colorectal cancer in asymptomatic, average-risk individuals, and the Galleri test may detect more than 50 types of cancer, including pancreatic cancer. An advantage of the Galleri test is that it may be able to pick up cancers for which we have no effective screening test, such as pancreatic cancer. It is encouraging to see that blood-based molecular testing is being increasingly integrated into a variety of pivotal clinical trials, supporting the view that this technology will be part of tomorrow’s standard of care.

For references visit cancernet.com/Copur_12.21

Copur is a medical oncologist/hematologist and medical director of oncology at Morrison Cancer Center, Mary Lanning Healthcare in Hastings, Nebraska, and is a professor at the University of Nebraska Medical Center adjunct faculty. He is also an Editorial Advisory Board member of ONCOLOGY®.
inhibitor and niraparib. He had the following blood-based mutations: TP53 A79fs, GNA11 D236D, ERBB2 (HER2) E147E, and APC D1571del. Interestingly, he also underwent FoundationOne tumor molecular profiling, which revealed the following tissue mutations: BRCA1 exon 10 K654fs, EGFR, FRCC1, KRAS exon 2 G12D, MGMT, TLE3, TOP2A, IOP01, TS, and THBBS.

The members of both the groups with individuals who had died and those who were still alive at the time of retrospective review had a median of 2 comorbidities. This, however, was not statistically significant ($P = .07$). The mean number of mutations between the 2 groups was almost identical and not statistically significant, and proportions of patients with each cancer stage were similar in progression trend. The data

<table>
<thead>
<tr>
<th>TABLE 3. Guardant360 Test Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Sequenced by Guardant-360</td>
</tr>
<tr>
<td>Analyzed for copy number amplifications</td>
</tr>
<tr>
<td>Analyzed for fusions/rearrangements</td>
</tr>
<tr>
<td>Analyzed for indels</td>
</tr>
<tr>
<td>Microsatellite instability (MSI)</td>
</tr>
<tr>
<td><strong>Actionable</strong></td>
</tr>
<tr>
<td><strong>Considered not actionable</strong></td>
</tr>
</tbody>
</table>

**Actionable based on criteria**

- **CCNE1** (sensitivity to CDK2 inhibitors; resistance to CDK4/6 inhibitors)
- **ESR1** (presence is sensitizing to hormone therapy; mutations cause resistance to antihormone therapy)
- **KRAS** (sensitivity to MEK inhibitors; resistance to cetuximab and panitumumab in colorectal cancer and to erlotinib and gefitinib in non–small cell lung cancer)
- **NRAS** (sensitivity to MEK inhibitors; resistance to cetuximab and panitumumab)
- **RAF1** (activating alterations cause sensitivity to MEK inhibitors and resistance to RAF inhibitors; inactivating alterations cause resistance to dasatinib)

Only AR and RB1 were deemed actionable solely because of their resistance to antihormone therapy and to CDK4/6 inhibitors, respectively.
we had on mutations in those who were still alive consisted of 32 patients (unknowns excluded). The median number of mutations for those alive was 2 (range, 0-4) and for those who had died was 3 (range, 0-15). The individual who had 15 is an outlier. The difference between groups in number of mutations was not statistically significant ($W = 132.4; P = .25$).

**Discussion**

Herein, we report the biologic and clinical correlates of genomic alterations among 77 patients with metastatic PDAC using blood-based ctDNA analysis. The majority of our patient population had metastatic disease prior to referral but had good performance status. Based on the information in our data set, the median survival was 21 months (range, 3-68). All patients had refractory disease after pancreaticoduodenectomy, chemotherapy, and/or radiation therapy. Patients had between 0 and 7 (median, 2) medical comorbidities. Functional status ranged from ECOG PS 0 to 3, with 69% (53/77) patients having ECOG PS 1. Additionally, 28 of 77 patients (39%) were smokers, whereas 41 (57%) were not, and 3 had unknown status (4%). Initial staging varied from stage I to stage IV, but the largest proportion of patients, 37 of 77 (48%), had stage IV disease at diagnosis and had de novo disease. As seen in Table 1, surgical intervention prior to referral occurred in 18 of 77 patients (23%). Ninety-seven percent of patients (75/77) underwent chemotherapy prior to referral, which consisted of either gemcitabine and nab-paclitaxel, FOLFIRINOX, fluorouracil, or a combination of these. Eleven patients (14%) had enrolled onto another clinical trial prior to referral and 22 received radiation.

Thus, this is consistent with the outcomes described in patients with PDAC referred to other phase 1 centers. Data from other institutions that do not enroll patients on early-phase trials would need to be analyzed to determine whether our data reflect the general population of those in early-phase trials would need to be analyzed to determine whether our data reflect the general population of those in-...
identified in PDAC. The prevalence of genetic testing is increasing, but there is a lower consistent prevalence of mutations and a limited number of treatments outside of clinical trials.

Historically, KRAS is known to be mutated in the majority of cases of PDAC and it is believed to be one of the earliest and most critical events of pathogenesis. It was initially thought to lack specificity, as it is often elevated in smokers and those with chronic pancreatitis. However, Groot and colleagues compared preoperative and postoperative KRAS ctDNA, with results revealing that an increase in ctDNA postoperatively correlated with tumor recurrence on imaging. Furthermore, Park and colleagues determined that ctDNA levels indicated the presence of cancer, and that they correlate well with clinical responses to treatment and progression in patients with PDAC. The KRAS mutation has been studied the most, has been associated with worse prognosis, and has been observed in 90% of cases of PDAC and specifically within 4 genetic alleles: G12V, G12D, G12R, and G61H.

In our study, however, KRAS mutations were found in only 34% of patients (26/77), with only 1% (1/77) possessing the only currently known potentially actionable mutation, KRAS G12C. Whether the presence or absence of KRAS in ctDNA has either prognostic or predictive implications remains to be seen.

The relevance of being able to detect KRAS alterations in the blood is underscored by the recent FDA approval of the first KRAS inhibitor, sotorasib (Lumakras), for KRAS G12C–mutated NSCLC. While the current approval is only in NSCLC, 7.1% of individuals with KRAS G12C–mutated colorectal cancer had confirmed response and 73% had disease control. Individuals with PDAC, as well, were noted to have responses to therapy and disease stabilization with sotorasib monotherapy. Other KRAS allele–specific inhibitors are currently in development, as are other MAPK-targeted inhibitors in monotherapy and in combination with sotorasib and other KRAS G12C inhibitors.

Kulemann and colleagues, for example, isolated and genetically characterized circulating tumor cells (CTC) in the blood that are hypothesized to be a means of systemic tumor spread. Blood from healthy donors and from otherwise healthy patients with PDAC were evaluated, and KRAS mutations in pancreatic CTCs were compared. It was found that those with more than 3 CTC/ml had a trend for worse median OS compared with patients with fewer or no detectable KRAS mutations. Unfortunately, because there is inconsistent detection, isolation, and characterization of CTC in PDAC, it is unclear to what extent these mutations shed CTCs into the bloodstream.

The incidence of detecting a KRAS mutation in our data set (27/77 patients; 35%) was vastly different from previous reports of KRAS being identified in tissue biopsies from approximately 92% of patients with PDAC. However, Patel and colleagues identified KRAS mutations in only 44% of PDAC and Kulemann and colleagues found KRAS in 58% of patients, both of which are more consistent with our findings. One potential discrepancy in our results and of those reporting higher KRAS mutation frequency is that many previous reports listed all KRAS mutations, not just potentially actionable ones. Another reason could be that not all KRAS mutations may shed into the bloodstream. These hypotheses require further investigation.

In our analysis, all patients had metastatic PDAC and had varying levels of ctDNA in the blood. It is still unclear what amount of ctDNA is meaningfully significant or what allelic fraction would be associated with an improved likelihood of response to a targeted therapy in PDAC. These questions remain outstanding. It is also worthwhile to note that even precancerous pancreatic lesions may shed ctDNA. The prevalence of KRAS mutations in low-grade precursor pancreatic intraepithelial neoplasia lesions, for example, is listed as greater than 90%. ctDNA has also been shown to be present in the bloodstream of patients with noninvasive pancreatic lesions, but these may never become carcinomas. The data we present here—as well as those presented by our colleagues who have described ctDNA findings in their advanced PDAC patient data sets in the past—must be examined in context of these collective findings. Moreover, these data raise further questions on whether ctDNA results may

<table>
<thead>
<tr>
<th>Table 4: Co-occurring Mutations</th>
<th>Frequency</th>
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<tr>
<td>KRAS G12D, TP53</td>
<td>9</td>
</tr>
<tr>
<td>TP53, KRAS, SMAD4</td>
<td>5</td>
</tr>
<tr>
<td>KRAS G12V, TP53</td>
<td>4</td>
</tr>
<tr>
<td>KRAS G12D, CDKN2A</td>
<td>4</td>
</tr>
<tr>
<td>KRAS G12D, CDKN2A, TP53</td>
<td>3</td>
</tr>
<tr>
<td>KRAS, TP43</td>
<td>16</td>
</tr>
<tr>
<td>KRAS, SMAD4</td>
<td>7</td>
</tr>
<tr>
<td>SMAD4, TP53</td>
<td>6</td>
</tr>
<tr>
<td>BRCA2, KRAS</td>
<td>4</td>
</tr>
<tr>
<td>KRAS, PIK3CA</td>
<td>4</td>
</tr>
</tbody>
</table>
play a future role in guiding the workup and management of patients with pancreatic masses.

We have also observed that many of our patients with \textit{KRAS} alterations harbored at least 1 co-alteration, including mutations in \textit{TP53}, \textit{CDKN2A}, \textit{BRCA2}, and \textit{SMAD4}. This was similar to the findings of Botrus and colleagues, who found that the most common co-occurring mutations were \textit{TP53} and \textit{KRAS} (n = 74), \textit{KRAS} and \textit{SMAD4} (n = 25), \textit{KRAS} and \textit{CDKN2A} (n = 12), and \textit{TP53} and \textit{SMAD4} (n = 20). Previous literature supports the concept that inactivating mutations in tumor suppressor genes such as \textit{CDKN2A/p16}, \textit{TP53}, and \textit{SMAD4} cooperate with \textit{KRAS} mutations to cause aggressive PDAC tumor growth. These observations suggest that co-targeting mutations may be an area of future research, and they highlight the need to better understand whether these genomic signatures simply play a prognostic role or whether they may also be predictive of response to therapies. Such ongoing analyses will be critical to understand the optimal mechanism by which to target \textit{KRAS} in PDAC in the ongoing \textit{KRAS} inhibitor combination studies.

In our data set, the median survival was 21 months (range, 3-68). It should be noted that 1 patient in the “alive” groups has been alive for 126 months, which is an outlier. The next highest number of months being alive is 50. Although the latter patient’s median survival is still higher than that of the typical patient with metastatic PDAC, it is unclear whether he had less aggressive disease, given that he had survived long enough to undergo 3 chemotherapy regimens (despite recurrent disease). This is likely due to a selection bias in patients who received blood-based molecular profiling in our analysis (which may have more indolent tumors), and it may not correlate well with the entire population of individuals with metastatic PDAC, who should also be explored. It is unclear what relevance this may have in terms of what mutations may be present in this subset of patients, or if ctDNA shed in the bloodstream varies among mutations.

The goal of identifying mutations is ultimately to determine if targeting them will lead to improved survival in patients with PDAC. Pishvaian and colleagues performed a retrospective analysis of patients with advanced PDAC who were treated with targeted agents specific to a mutation compared with unmatched therapies; the results suggested a survival improvement with the targeted agents. Of 1082 patients, 189 had actionable molecular alterations; 46 and 143 underwent matched and unmatched therapies, respectively. Those who went on to undergo matched therapy had significantly longer median survival. While this type of retrospective study can only be hypothesis generating, we think it identifies the potential of targeting alterations in PDAC. Our findings suggest that a blood-based approach to profiling PDAC may remain feasible and may help clinicians identify molecularly tailored therapy options and clinical trial recommendations for a subset of patients with PDAC.

Limitations

Our study has numerous limitations. First, the study was retrospective, with a small sample size of 77 patients. Second, it was a single-center study in which most patients were residents of a single county (Denver), which may limit the generalizability of our analysis. Third, these patients had advanced disease and thus short life expectancy, limiting our ability to study this population. At the same time, our survival data identify that the patients in this data set may also represent only a subset of patients with advanced PDAC who have a favorable prognosis; however, this data is consistent with those seen at other tertiary early-phase clinical trial centers. Additionally, as all of our patients had metastatic disease refractory to standard treatments, our results may or may not apply to individuals with early-stage PDAC. We did not look at the relationship among metastatic, refractory, and pancreatic adenocarcinoma that responded to standard treatment, to determine if each of the 3 groups had the same mutations. With our study’s relatively small number of patients, we were unable to calculate conclusions on OS in relation to genetic mutations or % ctDNA in a statistically meaningful manner.

Conclusions

We are hopeful that further research will allow the use of ctDNA to predict prognosis and estimate survival for patients diagnosed with PDAC. Further research will also be required to determine if these data are applicable to every patient with metastatic PDAC, if these data are being utilized for trial enrollment, whether FDA-approved therapies are effective in PDAC, and whether these markers are associated with response to therapy on trials.

Our study results show that ctDNA is seen in patients with metastatic PDAC; this fact may help select patients for clinical trials and may potentially help the future development of targeted therapies. More research is required to determine which patients should be tested, and when, and to define the implications for treatment.

AUTHOR AFFILIATIONS:
1. Department of Surgery, Swedish Medical Center, Englewood, Colorado, United States.
2. Department of Clinical Oncology Research, Sarah Cannon Research Institute at HealthONE, Denver, Colorado, United States.
3. Graduate Medical Education, HCA HealthCare, Denver, Colorado, United States

For references visit cancernetwork.com/Chung_12.21
Real-World Assessment of Patient Care and Practice Efficiency With the Introduction of Subcutaneous Rituximab

Esther Drill, DrPH1; Annie Qiu, BA2; Sheila Shapouri, PharmD, MS3; Tu My To, PhD, MPH1; Arliene Ravelo, MPH1; Jake Schade, BA2; Keith Dawson, DNP, MS4; and Matthew Matasar, MD2

ABSTRACT

INTRODUCTION: A subcutaneous (SC) formulation of the anti-CD20 monoclonal antibody, rituximab (Rituxan), is approved in diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia (CLL). Rituximab-SC (R-SC) has been associated with time and clinic resource savings vs the original intravenous formulation (R-IV). Insight into the resource implications of widening R-SC adoption in a US oncology setting is needed.

METHODS: A single-institution, retrospective observational analysis was conducted in adult patients with DLBCL, FL, or CLL. The primary outcome measure was chair occupancy time (difference between patient room-in and room-out times). Prescribing patterns were a secondary outcome.

RESULTS: Overall, 1190 patients were analyzed (treatment time frame: pre–R-SC adoption: n = 490 [41%], pre- and post R-SC adoption: n = 189 [16%], post R-SC adoption: n = 511 [43%]). Of the patients in the post–R-SC period, 374 (73%) received R-IV, 52 (10%) received R-IV and R-SC, and 85 (17%) received R-SC. When administered, R-SC reduced combination therapy chair time vs R-IV by a mean 37% (93.2 minutes; \( P < .001 \)). Monotherapy (any route) reduced chair time vs combination by a mean 35.2 minutes (\( P < .001 \)), with a further 40.2-minute reduction with R-SC (\( P < .001 \)), representing 62% (133.4-minute) total chair time savings vs R-IV. Doctors were more likely to prescribe R-SC to patients with FL than DLBCL.

CONCLUSIONS: R-SC is associated with significantly reduced chair time vs R-IV in a US oncology setting. Widespread adoption would be expected to improve practice efficiency and patient access to care, and to reduce health care resource burden.

KEYWORDS: Chronic lymphocytic leukemia, diffuse large B-cell lymphoma, follicular lymphoma, rituximab, subcutaneous, efficiency
Introduction

Rituximab (Rituxan; Genentech) is a chimeric anti-CD20 monoclonal antibody widely used in non-Hodgkin lymphoma (NHL) treatment. Worldwide, rituximab is recommended for a variety of B-cell malignancies, and it has a well-established efficacy and safety profile, with more than 4 million patients treated. In the United States, rituximab is approved for use in adults with non-Hodgkin lymphoma (NHL), including follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

The original intravenous (IV) formulation has prolonged infusion times and is associated with significant resource needs. The first infusion is given at a slower rate to reduce the risk of infusion-related reactions, which may be severe. This takes 4 or more hours, and although a 90-minute rapid infusion protocol was introduced in 2012 for second and subsequent infusions in which rituximab is coadministered with IV chemotherapy, infusion duration remains a challenge for patients and health care providers. Moreover, care provision during chemotherapy infusion requires significant resources, including pharmacy and nursing time, infusion facilities, and a relatively slow working pace.

To address this, a subcutaneous (SC) formulation, combining a 12-fold increase in concentration of the monoclonal antibody with recombinant human hyaluronidase (rHuPH20) to increase dispersion and absorption, has been developed (Rituxan Hycela; Genentech). This requires administration over 5 to 7 minutes, with 15 minutes of monitoring after administration. At flat doses, rituximab SC (R-SC) showed comparable efficacy and safety to rituximab IV (R-IV) in several clinical trials, and the US FDA (2017) and European Medical Association (2014 [FL and DLBCL] and 2016 [CLL]) have approved its use in DLBCL, FL, and CLL.

Patient preference and satisfaction, and time-motion data from clinical trials, favor SC formulation use. These data indicate that increased R-SC use is likely to result in time and resource savings, potentially leading to increased care access to health care providers for patients. Outside of clinical trials, data on patient care are limited, as are practice efficiency implications of widened use of R-SC in a US oncology setting. Using real-world US data, this analysis assesses patient care delivery and practice efficiency changes, measured by changes in chair occupancy time, as well as prescribing patterns before and after R-SC adoption. The research was carried out at Memorial Sloan Kettering Cancer Center (MSKCC), a comprehensive cancer center with locations in New York City (NYC), Long Island, Westchester County, and New Jersey.

Methods

Study Design

This was a single-center, retrospective, observational analysis. Patients were identified based on diagnosis and delivery of a rituximab-containing regimen; data were extracted for the period of September 2016 through September 2018 (R-SC was added to the hospital formulary at MSKCC in September 2017).

MSKCC’s Regional Care Network (RCN) sites outside of NYC are stand-alone outpatient clinics, staffed by MSKCC faculty that offer comprehensive oncology care. Each site sees a heterogeneous patient population across the spectrum of cancer diagnoses, although each site has at least 1 member of the lymphoma service delivering outpatient care to patients with B-cell lymphomas. The outpatient infusion suites in NYC (per the data reported herein) are more disease specific, and those chemotherapy units are often limited to a narrower range of diagnoses and treatments. Many physicians treat patients at more than 1 MSKCC site (typically both NYC and 1 regional location).

This research was approved by the MSKCC Institutional Review Board prior to initiation of study-related activity.

Eligible patients were those represented in MSKCC data with the following criteria: DLBCL, FL, or CLL diagnosis; receiving a rituximab-containing regimen for the qualifying diagnosis at MSKCC during the study period; and 18 years or older at the time of the rituximab-containing regimen initiation. Follow-up visits for rituximab-based treatment that were missing room-in or room-out times were excluded.

Data Collection

Data were collected from MSKCC’s clinical and institutional databases, including the Clinical Information System, Epic (scheduling software for patient arrival, room-in, and room-out times), and the electronic medical record (EMR).

Per approved prescribing information, patients receive R-IV as the first rituximab treatment at the initial visit, which usually takes longer than subsequent visits. Therefore, and as all patients receive the first dose as an IV infusion regardless of subsequent treatment route (R-IV/R-SC), each patient’s initial visit was excluded. Thus, if a patient only had 1 visit during the study period, that patient was not included.

Outcome Measures

Primary outcome measures were chair occupancy time before and after R-SC adoption, by treatment type (R-IV/R-SC), time of day and day of the week, and clinic location (NYC/RCN).
# TABLE 1. Patient Clinical, Demographic, and Treatment Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>R-IV</th>
<th>R-IV and R-SC</th>
<th>R-SC</th>
<th>P(^a)</th>
<th>Total (N = 1190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (% of total)</td>
<td>374 (73)</td>
<td>52 (10)</td>
<td>85 (17)</td>
<td>1190 (100)</td>
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<tr>
<td>Median age, years (range)</td>
<td>63 (53-71)</td>
<td>63 (54-71)</td>
<td>68 (57-76)</td>
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<td>64 (18-96)</td>
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<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
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<td>27 (52)</td>
<td>45 (53)</td>
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<td>Female</td>
<td>154 (41)</td>
<td>25 (48)</td>
<td>40 (47)</td>
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<td>Median BMI, kg/m² (range)</td>
<td>26.9 (24.0-30.6)</td>
<td>27.3 (23.9-31.6)</td>
<td>26.9 (24.2-29.7)</td>
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<td>Insurance status, n (%)</td>
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<td>2 (&lt;1)</td>
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<td>Qualifying diagnosis, n (%)</td>
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<td>40 (47)</td>
<td>688 (58)</td>
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<td>82 (22)</td>
<td>21 (40)</td>
<td>43 (51)</td>
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<td>CLL</td>
<td>38 (10)</td>
<td>7 (13)</td>
<td>2 (2)</td>
<td>110 (9)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>.748</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32 (9)</td>
<td>4 (8)</td>
<td>3 (4)</td>
<td>78 (7)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>84 (22)</td>
<td>7 (13)</td>
<td>15 (18)</td>
<td>147 (12)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13 (3)</td>
<td>1 (2)</td>
<td>4 (5)</td>
<td>29 (2)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (2)</td>
<td>0</td>
<td>1 (1)</td>
<td>9 (&lt;1)</td>
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<td>Unknown</td>
<td>239 (64)</td>
<td>40 (77)</td>
<td>62 (75)</td>
<td>927 (78)</td>
<td></td>
</tr>
<tr>
<td>Treatment location, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>.081</td>
<td></td>
</tr>
<tr>
<td>NYC</td>
<td>207 (55)</td>
<td>22 (42)</td>
<td>40 (47)</td>
<td>633 (53)</td>
<td></td>
</tr>
<tr>
<td>RCN*</td>
<td>142 (38)</td>
<td>29 (56)</td>
<td>37 (44)</td>
<td>473 (40)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>25 (7)</td>
<td>1 (2)</td>
<td>8 (9)</td>
<td>84 (7)</td>
<td></td>
</tr>
<tr>
<td>Treatment time frame, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre–R-SC adoption</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>490 (41)</td>
</tr>
<tr>
<td>Pre- and post R-SC adoption</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>189 (16)</td>
</tr>
<tr>
<td>Post R-SC adoption</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>511 (43)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenous; MSKCC, Memorial Sloan Kettering Cancer Center; NYC, New York City; R, rituximab; RCN, Regional Care Network; SC, subcutaneous.

*The following statistical tests were performed: \( \chi^2 \) test of independence, Fisher's exact test, and Kruskal-Wallis test.

*Includes worker's compensation.

*MSKCC's RCN includes stand-alone outpatient clinic sites outside of NYC, staffed by MSKCC faculty, which offer comprehensive oncologic care on Long Island and in Westchester County and New Jersey.

*Patients had multiple treatment visits spanning the periods pre- and post R-SC adoption.

*Statistically significant difference.
Chair occupancy was defined as the difference between patient room-in and room-out times as per the EMR timestamp data. Prescribing patterns were a secondary outcome, and they were assessed in patients treated exclusively in the post–R-SC adoption period. Outcomes are presented by overall population and stratified by combination vs monotherapy.

**Statistical Analysis**

A linear mixed-effects multivariable model with random intercept was used to analyze the association between treatment type and chair time in the year prior to, and the year following, R-SC adoption at MSKCC. Random intercept accounted for repeated measures within patients. Model covariates were sex, age, body mass index (BMI), treatment time (morning vs afternoon; effect of day of week), clinic location (regional vs local), months since SC implementation, and therapy type (monotherapy vs combination). Sex, age, BMI, therapy type, and months since SC implementation were determined a priori, and remaining covariates were selected if they were significant in the association between treatment type and chair time.

A logistic mixed-effects multivariable model was used to analyze the association between diagnosis and age on administration route. Prescriber was set as a random effect to account for clustering of patients at the doctor level; diagnosis and age were fixed effects. The model estimates the effects of both diagnosis and age, and it accounts for prescriber “tendency” on the prescribed route of rituximab administration.

Data were analyzed using R version 3.5.3 (The R Project for Statistical Computing).

**Results**

**Patient Characteristics**

Overall, 1190 patients were analyzed. Patient and treatment characteristics are outlined in Table 1. In total, 490 (41%) patients received all treatment pre–R-SC adoption, 511 (43%) received all treatment post R-SC adoption, and 189 (16%) received treatment both pre- and post R-SC adoption.

To fairly compare patient and treatment characteristics by rituximab administration route, we analyzed the 511 (43%) patients who received all treatment post–R-SC adoption (R-IV: n = 374 [73%]; R-SC: n = 85 [17%]; R-IV and R-SC: n = 52 [10%]). Most patients receiving R-IV had DLBCL (n = 254 [68%]), whereas the largest proportion of patients receiving R-SC had FL (n = 43 [51%]). Most patients with CLL were treated with R-IV (n = 38/47 [81%]), accounting for 10% of the R-IV arm. Except for age and qualifying diagnosis, baseline characteristics (Table 1) were similar between treatment groups. Patients receiving R-SC were older overall (median age, 68 years) than those receiving R-IV (median age, 63 years) and those receiving both R-SC and R-IV (median age, 63 years).

**Treatment Visit Data**

Data were collected over 5129 rituximab visits (pre–R-SC adoption: 2565; post R-SC adoption: 2564; Supplementary Figure). Of all visits, 4526 (88%) were for R-IV (combination therapy: 58%; monotherapy: 43%). R-SC accounted for 603 visits (12%; combination therapy: 54%; monotherapy: 46%).

**Chair Time Savings**

Patients receiving R-IV combination therapy had a mean chair time of 249.9 minutes. The linear mixed-effects model showed that R-SC reduced combination therapy chair time vs R-IV by a mean of 93.4 minutes (P < .001), equivalent to a 37% relative reduction (Figure; Table 2). Overall, monotherapy, regardless of administration route (R-IV/R-SC), reduced chair time by a mean of 35.2 minutes (P < .001) vs combination therapy. Mean chair time was further reduced by 40.2 minutes (P < .001) with R-SC monotherapy, resulting in total chair time savings of 133.4 minutes vs R-IV monotherapy (relative reduction, 62%; Figure). Reductions in chair time also increased over time following initial R-SC adoption (P = .004) (Table 2).

Since R-SC adoption in MSKCC (which occurred over the course of the year between September 2017 and September 2018), total predicted mean chair time savings were 30,039 minutes (R-SC combination therapy) and 37,240 minutes (R-SC monotherapy) in 603 visits, translating to 500.65 hours and 620.67 hours per year of chair time savings, respectively.

Comparisons based on days of the week showed the effect of patient volume/flux throughout a 7-day period, with a tendency for chair time to increase as the week progressed, and with substantially longer chair times on the weekends (Table 2). Treatment in the afternoon vs the morning was associated with a 20.8-minute mean reduction in chair time (P < .001).

**Prescribing Pattern**

Prescribing information was available for 506 of 511 (99%) patients treated exclusively in the period post R-SC adoption, with 1870 visits (R-IV: n = 1430 [76%]; R-SC: n = 440 [24%]). Overall, 408 (81%) patients were first prescribed R-IV, while 98 (19%) patients were first prescribed R-SC. Of the patients initially prescribed R-IV, 39 (10%) were switched to R-SC; of these, 3 (8%) patients were switched back to R-IV. Of the patients initially prescribed R-SC, 12 (12%) were switched to R-IV. Switching back to R-IV was per patient preference.

Twenty doctors prescribed for 15 or more patients who...
were treated exclusively in the post–R-SC adoption period; among these, heterogeneous patterns in R-SC prescribing were observed. There was a wide range, from 0% to 63% of the time, in the frequency of visits in which doctors prescribed R-SC. This difference can be partially explained by patient diagnosis and age. Doctors were more likely to prescribe R-SC to patients with FL than with DLBCL (odds ratio [OR], 2.38; 95% CI, 1.75-3.25; \( P < .001 \)), influenced by a service-level decision to favor R-IV for DLBCL, given the curative intent of therapy. Each additional year of a patient’s age increased the odds of prescribing R-SC by 2% (OR, 1.02; 95% CI, 1.01-1.03; \( P < .001 \)). Beyond this, there were large differences in prescriber “tendency” to prescribe R-SC vs R-IV as measured by random effect (least likely

### TABLE 2. Linear Mixed-Effects Multivariate Model on Chair Time in Minutes (room out-time minus room in-time) With Age, Sex, and BMI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>249.9</td>
<td>228.29 to 271.51</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Formulation (vs IV) SC</td>
<td>-93.2</td>
<td>-107.87 to -78.54</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Time of day (vs morning)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afternoon</td>
<td>-20.83</td>
<td>-24.93 to -16.73</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Day of the week (vs Monday)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>6.9</td>
<td>0.01 to 13.79</td>
<td>.050</td>
</tr>
<tr>
<td>Wednesday</td>
<td>11.95</td>
<td>3.52 to 20.38</td>
<td>.005</td>
</tr>
<tr>
<td>Thursday</td>
<td>15.16</td>
<td>8.51 to 21.81</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Friday</td>
<td>24.53</td>
<td>17 to 32.06</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Saturday</td>
<td>33.41</td>
<td>13.12 to 53.71</td>
<td>.001</td>
</tr>
<tr>
<td>Sunday</td>
<td>67.34</td>
<td>13.34 to 121.34</td>
<td>.015</td>
</tr>
<tr>
<td><strong>Therapy (vs combination)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>-35.24</td>
<td>-40.45 to -30.03</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Center location (vs NYC)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCN</td>
<td>4.03</td>
<td>-1.85 to 9.91</td>
<td>.179</td>
</tr>
<tr>
<td><strong>Sex (vs female)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7.69</td>
<td>1.42 to 13.96</td>
<td>.016</td>
</tr>
<tr>
<td>Patient age</td>
<td>0.1</td>
<td>-0.12 to 0.32</td>
<td>.374</td>
</tr>
<tr>
<td>Patient BMI</td>
<td>0.36</td>
<td>-0.18 to 0.9</td>
<td>.191</td>
</tr>
<tr>
<td>Months since SC implementation</td>
<td>-1.06</td>
<td>-1.78 to -0.34</td>
<td>.004</td>
</tr>
<tr>
<td>Type of therapy (mono vs combo) * route (SC vs IV) interaction</td>
<td>-40.2</td>
<td>-54.52 to -25.89</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Months since implementation * route (SC vs IV) interaction</td>
<td>-2.26</td>
<td>-4.34 to -0.17</td>
<td>.034</td>
</tr>
</tbody>
</table>

BMI, body mass index; combo, combination; IV, intravenous; mono, monotherapy; NYC, New York City; R, rituximab; RCN, Regional Care Network; SC, subcutaneous.
to prescribe R-SC [−2.42]; most likely to prescribe R-SC [2.30]). Of the 5 doctors who prescribed R-SC for fewer than 10% of their patients, 2 did not prescribe R-SC at all, and 3 prescribed R-SC only when a patient had already been started on R-SC by another member of the lymphoma service.

Discussion
Health systems and oncology practices need to balance the primary mission of delivering the highest quality care to patients with recognition of and response to an increasingly challenging economic and reimbursement landscape. Rapid growth in health care expenditures, with limitations on health care resources, necessitate intervention evaluations from a clinical resource management perspective. The economic significance of rituximab in B-cell lymphoma treatment has fueled initiatives such as the development of biosimilar agents and exploration of the SC administration route. While biosimilars have lower acquisition costs than the rituximab reference product, they require IV administration. SC administration offers the potential to administer rituximab in a manner that minimizes clinic resource use and time, while maximizing patient convenience and satisfaction.

From the perspective of clinical workflow, we found that R-SC adoption resulted in substantial time savings for both the patient and health system as measured by reduced chair time. Compared with R-IV, mean chair time was reduced by 37% when patients received R-SC as part of combination therapy, and by 62% when they received R-SC monotherapy.

Strategies to better leverage this reduction in chair time for individual practices may include assessment of variation across providers, histologies, and practice sites, as well as days of the week; at MSKCC, the observation that median chair times are longer later in the week affords a potential opportunity to align elective treatments with R-SC on these days.

Our findings mirror those obtained in clinics across non-US health care systems within the context of clinical trial-based care. A United Kingdom time–motion study, conducted alongside the phase 3b MabCute trial of maintenance R-SC in 276 patients with relapsed/refractory NHL, found patient time per session in the treatment room to be 263.8 minutes (95% CI, 236.6-294.3) for R-IV and 70.0 minutes (95% CI, 57.1-87.2) for R-SC, a reduction of 73%. R-SC was associated with savings of 174.8 minutes (95% CI, 172.5-177.1) in total active health care practitioner time and reduced total mean per-session staff costs by £115.17 (95% CI, 98.95-136.93).

A wider study across 30 oncology centers in Europe and South America, again conducted alongside MabCute, found reductions of 27% to 58% in health care provider time for the treatment process (including drug preparation; overall 32% reduction) and relative reductions in mean patient chair time of 53% to 91% (overall 74% reduction; \( P < .0001 \)) with R-SC vs R-IV. A systematic survey carried out in 17 Italian cancer centers found a reduction of 70% in mean administration time for every cycle where R-SC was used in place of R-IV in patients with NHL; over

![FIGURE. Adjusted* Mean Chair Time Among Patients Receiving R-IV or R-SC as Combination or Monotherapy](image)

*Adjusted for sex, age, BMI, treatment time, clinic location, and therapy type (monotherapy vs combination).

BMI, body mass index; R-IV, intravenous rituximab; R-SC, subcutaneous rituximab.
8 cycles, including the first IV dose, the reduction was 59%.

A chart review in Canada estimated a savings of more than 50,000 treatment suite hours in the third year following R-SC adoption. Time savings were estimated to be greater in FL patients than DLBCL patients, which was of interest as the prescribers in the current study were more likely to prescribe R-SC to FL patients.

The present results suggest that R-SC can result in substantial time savings for both patients and health systems, which may improve practice efficiency and allow more patients to be treated in a finite treatment space over a set period of time, ultimately improving patient care. From a societal perspective, the potential benefits for patients and caregivers are considerable. Reduced chair time would be expected to translate into reduced time in the infusion suite (assuming parity for other hospital-based activities for IV and SC processes), with associated improvement in convenience and patient burden. This aligns with the experience from the PrefMab study in 743 patients with previously untreated FL or DLBCL, which showed an overall patient preference for R-SC over R-IV; in turn, this was associated with increased patient-reported satisfaction.

The reductions in health care resource utilization that are likely to accrue from the adoption of R-SC over R-IV, as strongly indicated by the results of both this study and of other published literature, suggest that R-SC administration has the potential to impact routine clinical practice in FL, DLBCL, and CLL treatment. The adoption of fixed-dose SC administration reduces pharmacy work involved in IV medication preparation, chair utilization, and nursing hours required in medicine administration and posttreatment monitoring. Studies demonstrating the clinical equivalence and pharmacokinetic noninferiority of R-SC against R-IV suggest that these aims can be achieved without loss of efficacy.

Heterogeneous prescribing patterns were observed among doctors at MSKCC who prescribed R-SC, which were likely influenced by disease and prior route of rituximab administration. Large differences in doctors’ tendencies to prescribe R-SC over R-IV were noted; of the doctors with the most rituximab patients treated exclusively in the period post R-SC adoption, 25% either did not prescribe R-SC or prescribed it only to patients already receiving it. Heterogeneity in prescribing patterns can be problematic, particularly in the cases when it leads to avoidable health service costs and suboptimal patient care. This observation highlights the potential for higher center-level impact with further education for doctors on the availability and utility of R-SC, as well as the adoption of a standardized treatment approach.

**FIGURE S1.** Infusion/Injection Visits by Month Pre- and Post-R-SC Adoption

R-IV, intravenous rituximab; R-SC, subcutaneous rituximab.
While this study predated SARS-CoV-2 and the COVID-19 pandemic, implications for the improved workflow associated with R-SC may be magnified under current conditions. Given concerns regarding nosocomial risk—to patients and staff—the marked reduction in time that health care providers and patients must share close quarters, and the cumulative time that patients are in the infusion center, may be critically relevant.25

Limitations
This is the first US-based study to demonstrate time savings with the use of R-SC vs R-IV. Limitations are typical of analyses based on retrospective chart data. The information is reported as recorded by clinicians and is subject to potential data entry errors, and there is a risk that the retrospective EMR time stamp (used as a proxy for chair time) may not always be accurate. The generalizability of our results may also be limited to institutions with similar organizational structure to MSKCC, although the consistency of our results with those obtained in studies in several other jurisdictions suggests that this is unlikely to be a major concern. Institutional time savings will be dependent upon patient diagnoses and the relative proportion of patients receiving rituximab-based therapy.

Conclusions
In conclusion, we have demonstrated time savings associated with R-SC use in a high-volume US cancer center. Given the growing constraints on chair time available for infusion therapy in patients who are prescribed rituximab, increasing R-SC utilization is likely to improve practice efficiency, improve patient care access, and reduce health care resource burden, particularly when a substantial fraction of overall patient volume is composed of lymphoma treatment. Increased understanding of the impact of R-SC adoption on the ability to deliver efficient patient care will further inform key practice decisions in real-world settings.

AUTHOR AFFILIATIONS:
1. Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA
2. Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
3. Evidence for Access, Genentech, Inc, South San Francisco, CA, USA

DISCLOSURES:
ED, AQ, JS: No conflicts of interest to declare. SS, TMT, AR, KD: Employee of Genentech, Inc, stocks/stock options in Genentech, Inc/ F. Hoffmann-La Roche Ltd. MM: Research funding and honoraria from Genentech, Inc.

EQUAL CONTRIBUTION
ED and AQ contributed equally.

CORRESPONDING AUTHOR
Matthew Matasar, MD, Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065. Email: matasarm@mskcc.org; phone: 646-497-9137.

RESEARCH SUPPORT
This study was funded by Genentech, Inc. Third-party medical writing assistance, under the direction of Sheila Shapouri, was provided by Lynda McEvoy and Zoe Toland, of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd.

Key References

For references visit cancernetwork.com/Drill_12.21
**ABSTRACT:** Primary cutaneous carcinosarcoma is a rare malignant tumor composed of both an epithelial and mesenchymal cell population. We present a case of a man, aged 56 years, found to have a 26-mm exophytic lesion on the vertex scalp identified to contain a distinct population of basal cell carcinoma (BCC) as well as another population of spindled cells representing a poorly differentiated sarcomatous component. Five years after the removal of the primary lesion, the patient presented with metastatic BCC to the right scalp, right cervical nodes, lung, and rib. Next-generation sequencing of the lung metastasis was performed, revealing mutation of the patched gene (PTCH1) and prompting treatment with vismodegib (Erivedge). Cases of primary cutaneous carcinosarcoma with a basal cell epithelial component are rare and not much is known about their pathogenesis or clinical course. This case is unique in that metastatic BCC arose from a primary carcinosarcoma in which the carcinomatous component was basal cell. Furthermore, it has clinical significance in the successful use of a selective hedgehog pathway inhibitor.

**KEYWORDS:** Carcinosarcoma, basal cell carcinoma, vismodegib
intertwined. Immunostains including CD10, CD34, and S100 were negative throughout, speaking against a primary cutaneous sarcoma (including dermatofibrosarcoma protuberans and pleomorphic undifferentiated sarcoma). Ber-EP4, pancytokeratin, and p63 were negative in the spindle cell population, but positive within the basaloid component (Figure 2B). This primary tumor was classified as a carcinosarcoma with features of a spindle cell sarcoma and BCC. The adjacent satellite lesions displayed nests of basaloid keratinocytes with peripheral palisading and retraction artifact, which was compatible with a diagnosis of BCC. At the time, the vertex scalp lesion and adjacent nodules were deemed to represent separate primary tumors (Figure 2C). All lesions were treated by Mohs micrographic surgery.

Five years later, the patient developed shortness of breath and cough, and CT imaging revealed a left seventh rib destructive lesion, a right lower lobe cavitating mass, and a few scattered 3-mm pulmonary nodules, concerning for metastases. A bronchoscopy with endobronchial ultrasound and right lower lobe fine needle aspiration was performed, and histopathologic examination revealed a basaloid neoplasm displaying expression of pancytokeratin and Ber-EP4 compatible with metastatic BCC (Figure 3A). Next-generation sequencing (NGS) revealed targetable mutations in the PTCH1, PTEN, ARID1A, PDGFRA, and PIK3A genes. The patient’s staging PET scan displayed fluorodeoxyglucose-avid metastatic lesions to the right lower lung, cervical lymph nodes, and skeleton.

Through skin examination revealed a large irregular firm mass in the right supra-auricular areas as well as cervical lymphadenopathy. An incisional biopsy of the scalp lesion was performed and revealed features of nodular BCC (Figure 3B). When compared with the patient’s previously biopsied scalp lesions, this lesion revealed striking similarity in morphology. Notably, this new supra-auricular lesion did not contain a sarcomatous component, and additionally, it displayed a lack of connection to the overlying dermis, which is suggestive of a locoregional metastasis as opposed to de novo BCC.
The interesting case report: "Metastatic Basal Cell (BCC) Arising from a Primary Cutaneous Carcinosarcoma" summarizes the concept of carcinosarcoma (CS). Simply put, a CS has 2 different cancer types in one biopsy specimen. This case discusses specifically BCC as the carcinoma component and notes the importance of PTCH gene mutations in guiding the treatment choice of vismodegib (Erivedge). This is essential knowledge for medical oncologists and dermatologists who manage BCC. The initial pathology had a sarcomatous component as described but not in the recurrence that was biopsied. Only local therapy was given for the primary in the form of surgery with the patient refusing radiation. Based on this and the literature review, the authors suggest that the prognosis may be good. While the patient does have metastatic disease, a remission was achieved.

Despite modern genomic advances in cancer, we still heavily rely on the hematoxylin and eosin (H&E) stained biopsy slides, and the associated immunohistochemistry (IHC) that is provided to us by our pathologists. CS, especially cutaneous, is a rare entity as described and is fundamentally interesting from the standpoint of the origin of the 2 histologies. Do they come from 1 clone or do they come from 2 clones (divergent and convergent hypotheses)? An important point of the cutaneous CS is that they may not necessarily be of poor prognosis as in this case. But there is a broader fundamental problem that remains. Since the carcinoma and sarcoma can be any number of entities, this could lead to a difficulty in therapeutic and prognostic planning. Adding to the difficulty is that these uncommon entities are not usually studied in randomized trials. In general, prognosis may vary, and many noncutaneous sites are viewed as having a worse prognosis.

Further illustrating the challenge is that of systemic adjuvant therapy. What if this were recommended for a resected CS; there would be no easy solution. This is no different than thinking about squamous cell carcinoma (SCC) as a pathologic entity. To an extent, its treatment does depend on anatomy since potential morbidity, is in part, site dependent. It is simplest to think about operative therapy where, even if the disease had a biologically similar prognosis, the procedure may be more difficult based on location. For example, the complexity of surgical and radiation therapy of head and neck (HN) base of tongue SCC versus SCC of the scalp is clearly different. It is the oncologist that can reduce treatment plan to a binary problem of CNS involvement (that is protected by the blood-brain barrier) and non-CNS disease. Add the complexity of the 2 potential diagnoses of a carcinosarcoma combined with anatomy and you can see that it is not a trivial problem.

Science will continue to study differentiation and answer the question of single-cell origin versus multiple cellular origins with respect to entities such as CS. We will also continue to improve on common diagnostic clinical testing with techniques such as Oncogene sequencing and circulating tumor DNA. All of this will continue to make oncology challenging, in addition to the improvements in radiology and the natural consequence of lead time bias, overdiagnosis, and reclassification (pathologic and staging) of cancer.

In summary, CS is an entity that appears in multiple sites. The histology of the individual components is most important. Prior knowledge is important such as with the knowledge base on uterine CS. The case and its references provide insight into cutaneous CS suggesting that many entities may have a good prognosis but emphasize the general truth that rigorous clinical research is lacking in most CS diagnoses.

Reddy is a clinical assistant professor of medicine-oncology at Stanford University School of Medicine in California.
After careful review and diligent clinicopathologic correlation, the patient was diagnosed with metastatic BCC arising from a carcinosarcoma in which the carcinomatous component was basal cell. The patient was started on vismodegib 150 mg daily. Six weeks after initiation of therapy, the patient displayed near-complete resolution of the right supra-auricular mass. Six months into treatment, the patient is free of evidence of metastatic disease.

Discussion

Carcinosarcoma is a rare biphenotypic malignant tumor consisting of an epithelial as well as a mesenchymal component. Carcinosarcomas have been reported in numerous organs but primary cutaneous disease is rare. Furthermore, very few cases of cutaneous basal cell carcinosarcoma have been reported to date. There are 2 predominant theories for the origin of mixed malignant tumors such as carcinosarcoma: The convergence hypothesis (multiclonal hypothesis) suggests that the neoplasms arise from 2 or more stem cells, while the divergence hypothesis (monoclonal hypothesis) suggests that the neoplasm arises from a single totipotent stem cell that subsequently differentiates into both a mesenchymal component and an epithelial component. Some authors have more recently begun to favor the divergence hypothesis. One author reported on a basal cell carcinosarcoma in which both the epithelial and sarcomatous portions underwent DNA sequencing with NGS, and they were found to share multiple mutations, including a mutation in the PTCH1 gene in the hedgehog pathway, which suggests a common origin for the neoplasm.

Risk factors for the development of epithelial-derived (basal or squamous cell) carcinosarcomas have been identified as advanced age, male gender, and sun-damaged skin of the head and neck. Ultraviolet (UV) light has been suggested as an important causative factor. The results of one study suggest that the 5-year disease-free survival rate for patients with these tumors of 70%. Additionally, it has been shown that the prognosis is not affected by the type or the ratio of sarcomatous component. Results of another study showed that age less than 65 years, recent growth, longstanding skin tumor, and tumor size greater than 2 cm is correlated with more aggressive disease. These findings are pertinent to our patient, as he fits many of these categories and has had metastatic recurrence of disease 5 years after original resection. There is little evidence for effective treatment modalities for these rare malignancies. Vismodegib, a hedgehog pathway inhibitor (HHI), has been approved for treatment of metastatic BCC as well as locally advanced BCC. Cemiplimab (Libtayo), an anti–PD-1 antibody, has recently been approved for treatment of locally advanced and metastatic BCC in patients either previously treated with an HHI or in patients in whom an HHI is not appropriate.

Very careful clinicopathologic correlation was necessary in accurately classifying this patient's metastatic neoplasm, because choice of treatment modality is dependent on histogenesis. This patient's pulmonary metastasis was basaloid and displayed strong positivity for Ber-EP4, which is compatible with metastatic BCC. Furthermore, NGS of the metastasis revealed a high tumor mutational burden, which is often seen in UV-mediated carcinogenesis. Sequencing also highlighted a PTCH1 mutation, confirming that targeted therapy with an HHI would likely be effective. The patient was started on vismodegib and scheduled for a follow-up 6 weeks later, at which time the right supra-auricular mass was nearly resolved. Subsequent PET-CT imaging showed resolution of the lung mass but persistence of the rib lesions; for these, he was provided radiation therapy.

This case highlights an exceptional occurrence in which basal cell carcinosarcoma developed locoregional then distant metastasis and had an excellent response to hedgehog pathway inhibition.

CONFLICT OF INTEREST: None reported

FUNDING: None.

For references visit cancernetwork.com/Sterner_12.21
Management of Residual Disease After First-line Chemotherapy in a Patient With a Nonseminomatous Germ Cell Tumor

Regina Barragan-Carrillo MD1, Samantha Mateos-Corella MD1, Carlos Ortiz-Hidalgo MD2, Eva A Izquierdo-Echavarri MD3, Ricardo Castillejos-Molina MD4, Martín Angel5, Ignacio Barragan-Arteaga6, Thomas W Flaig7, María T Bourlon MD, MSc1

An 18-year-old man presented with a one-month history of a nonpainful right testicular enlargement. He had no family history of neoplasia, nor any relevant past medical history.

The physical examination was only remarkable for an enlarged right testicle. A testicular ultrasound revealed a 2.5-cm tumor.

FIGURE 1. Baseline and Follow-up Contrast Enhanced CT scans of a Nonseminomatous Germ Cell Tumor Before and After Systemic Treatment.

Baseline axial (A) and coronal (B) CT scans show a 2.07-cm retroperitoneal lymph node enlargement. (C, D) Follow-up axial and coronal CT scans after 4 cycles of bleomycin, etoposide, and cisplatin (BEP) show a partial response to systemic therapy with a residual retroperitoneal disease of 1.64 cm (arrow).

THE CASE

Which would be the most appropriate management of a residual disease larger than 1 cm in a patient with advanced NSGCT after first-line chemotherapy and tumor marker normalization?

A. Surgical resection with retroperitoneal lymph node dissection
B. Start surveillance
C. Continue with second line chemotherapy
D. Radiation therapy for the residual disease

SEE PAGE 817 FOR THE ANSWER AND A DISCUSSION OF THIS CASE BY EXPERTS.
and serum tumor markers revealed an elevated β-human chorionic gonadotropin (β-hCG), 22 mUI/L (normal, < 0.06 mUI/L); elevated alpha-fetoprotein (AFP), 329 ng/mL (normal, 0-9 ng/mL); and normal lactate dehydrogenase (LDH), 135 < /L (normal, 179 U/L).

A right radical inguinal orchiectomy was performed. Pathological examination revealed a 2.4 cm by 2 cm embryonal carcinoma with tumor invasion into the tunica albuginea. Postsurgical tumor markers obtained 3 weeks after orchiectomy were β-hCG, 100.5 mUI/L (normal, < 0.06 mUI/L); AFP, 1075 ng/mL (normal, 0-9 ng/mL); and LDH, 180 U/L (normal, 179 U/L). A chest, abdomen, and pelvis CT scan showed a 2.7-cm retroperitoneal lymph node enlargement, without visceral metastasis (Figure 1A and B).

Given the presence of node-positive disease with S2 serum markers, the diagnosis of a stage IIIB intermediate risk nonseminomatous germ cell tumor (NSGCT) was determined, and the patient underwent sperm banking. The patient was started on chemotherapy with 4 cycles of BEP (bleomycin, etoposide, and cisplatin), with a favorable tumor marker decline according to the Gustave-Roussy nomogram. After completion of the fourth chemotherapy cycle, serum tumor markers were negative, and 8 weeks after chemotherapy, the follow-up CT showed a 1.6-cm residual retroperitoneal lymph node conglomerate (Figure 1C and D).

**CORRECT ANSWER:** A. Surgical resection with retroperitoneal lymphadenectomy

**Discussion**

Outcomes in advanced testicular germ cell tumors are one of the success stories in modern oncology. Even in the context of a widespread visceral disease, they are amenable to cure after platinum-based chemotherapy, with a 5-year overall survival ranging from 71% in patients with a poor prognosis to 94% in patients with a good prognosis, according to the International Germ Cell Consensus Classification (IGCCC). Following first-line systemic therapy, 70% of patients with a stage II or higher NSGCT reach a complete biochemical and radiographic response. This leaves up to 25% to 30% of patients with advanced NSGCT with a residual mass on imaging evaluation, justifying the need of a follow-up postchemotherapy thoracic, abdominal, and pelvic CT scan. It is important to note that in order to avoid any false positive findings on cross sectional imaging, the CT scan should be performed 6 to 8 weeks following the last chemotherapy cycle, with concomitant measurement of serum tumor markers. Rising levels of tumor markers suggest the presence of progressive disease, in which case, second-line chemotherapy should be promptly started.

Lesions larger than 1 cm in the short axis in a cross-sectional imaging modality, with normal serum tumor markers could harbor 3 different histologies: 45% to 50% only have necrosis in the pathological examination, 40% are teratomas, and about 10% will persist with a viable tumor. Retropertitoneal nerve-sparing lymph node dissection (RPLND) is currently the standard of care for NSGCT residual masses equal to or larger than 1 cm, as the postchemotherapy histopathologic findings determine the need for further treatment or surveillance protocols. On the other hand, patients with lesions smaller than 1 cm can be only observed, as such patients have a very favorable prognosis with a 15-year cancer specific survival of up to 97%. Therefore answer A Surgical resection with retroperitoneal lymph node dissection is the best approach in this case.

Currently both the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend a full bilateral template lymph node dissection for postchemotherapy retroperitoneal residual disease. The anatomical borders for this type of resection are the renal hilar vessels, the ureters, and the common iliac arteries. The template-guided approach has been widely adopted in an effort to reduce the morbidity associated with this procedure, while also preserving the antegrade ejaculation and erectile function. Templates were developed under the rationale that retroperitoneal lymph drainage follow a characteristic lymph node spread, based on the laterality of the testicular primary, given the absence of crossover between the landing zones among patients with solitary metastases to either the left or right testicle. The main risk associated with a non-extended retroperitoneal dissection is a higher rate of locoregional recurrences. In the recently published RETROP cohort, the locoregional recurrence rate in patients with a 10 mm to 49 mm unilateral metastasis on CT scans was 0% for right-sided NSGCT and 4% for left-sided NSGCT; on the other hand, patients with a 10 to 49 mm bilateral metastasis should always undergo a bilateral...
templeted RPLND, as the metastatic lesions do not follow a predictable pattern of spread.16

As previously stated, 4 in 10 patients could be found to have a teratoma on resection. Although such tumors have a very low potential for distant invasion, they could undergo malignant transformation to somatic-type malignancy, grow progressively, and lead to local invasion.17,18 The clinical entity referred to as growing teratoma syndrome has been described in 2% to 8% of all NSGCT cases, and is characterized by increasing tumor size during or after chemotherapy, despite normalized or decreasing tumor marker levels.19 Therefore, surveillance is not an option, as teratomas are highly chemoresistant and radioresistant tumors. In such cases, surgery is the most reliable curative therapy, with an excellent disease-free survival of 75% to 80%.19 Therefore, option B Start surveillance, would not be an adequate option.

The presence of a viable tumor in the resected specimens is associated with a worse disease-specific survival.20 Data from the sCR2 trial supports the use of adjuvant chemotherapy post-RPLND in IGCCC’s intermediate- and poor-risk NSGCT residual viable tumors.21 In addition, data arising from retrospective analysis have shown an improvement in the 5-year progression-free survival among patients with disseminated NSGCT and viable residual disease, who receive postsurgical chemotherapy in comparison with those who do not (69% vs 52% respectively).22 Nonetheless, there has not been consistent evidence on the benefit of this strategy on overall survival.22

Key Points

• Following first-line chemotherapy, NSGCT residual masses equal to or larger than 1 cm are distributed as follows: 50% necrosis, 40% teratoma, and 10% viable tumor.
• RPLND is currently the standard of care in all NSGCT residual masses larger than 1 cm.
• Current guidelines recommend RPLND using a bilateral template in this setting. Although currently not the standard, more selective surgical approaches are being explored for highly selected patients.
• Even though teratomas have a lower potential for metastatic disease, their potential for local invasion justifies the need for surgical resection.
• In specimens with viable tumor cells, patients should receive 2 additional chemotherapy cycles with EP, TIP, VIP, or VeIP.
• NSGCTs are considered radioresistant tumors, and SBRT is considered a salvage therapy in chemorefractory inoperable patients.
Current guidelines recommend 2 further chemotherapy cycles with EP (etoposide and cisplatin), TIP (paclitaxel, ifosfamide and cisplatin), VIP (vinblastine, etoposide, ifosfamide, and cisplatin) in cases of a residual tumor with greater than 10% of viable tumor cells, choriocarcinomas, endodermal sinus tumors or seminomas. This recommendation is based on the rationale that residual disease could be partially resistant to first-line chemotherapy with BEP, and could be sensitive to other cytotoxic agents such as vinca alkaloids and taxanes.4,5,6 Therefore, answer C Continue with second line chemotherapy, is also inadequate, as only a minority of patients will need additional systemic therapy.

In contrast to seminomas, there are no imaging modalities capable of distinguishing between necrosis/fibrosis, teratomas, or viable tumors in NSGCT. Even novel functional imaging techniques, such as 18F-FDG PET, does not yield an adequate diagnostic accuracy in the prediction of absent viable tumors after first-line cisplatin-based chemotherapy.7 Moreover, to date, no validated clinical nor biochemical parameters currently exist to predict the histology of residual tumor masses. Some unsuccessful attempts have been made to identify this clinical dilemma, by developing predictive models that include the histology of the primary tumor, risk group at diagnosis, initial and postchemotherapy tumor markers, retroperitoneal lesion diameter, and regression percentage during chemotherapy.24,25 As expected, these models have not shown any statistical power to differentiate between viable tumor, teratoma, or necrosis.24,26 The latter further justifies surgical resection as the only reliable option to tailor the patients’ need for further cytotoxic treatment. This emphasizes the fact that option A) Surgical resection with retroperitoneal lymph node dissection, is the correct management strategy for this case.

In the context of a NSGCT, radiation therapy has a limited role. In contrast to a classic seminoma, the NSGCT is considered a radioresistant tumor.27 There have been few case reports exploring stereotactic body radiation therapy (SBRT) as a salvage therapy in inoperable patients with recurrent chemorefractory NSGCT, with overall positive results.28,29 Currently, the use of radiation therapy should only be considered in chemorefractory inoperable disease or in patients with very high surgical risk as a salvage strategy. Thus, answer D Radiation therapy for the residual disease, is also incorrect in this context.

**Outcome of This Case**

A bilateral nerve-sparing RPLND was performed without any surgical complications (Figure 2). The paracaval lymph nodes were resected, and pathological analysis was performed, which revealed a teratoma (Figure 2C). Further cytoxic therapy was foregone, and the patient started 3-monthly surveillance per guideline recommendations.

**AUTHOR AFFILIATIONS:**

1. Hematology-Oncology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.
2. Pathology Department, Hospital Médica Sur, Mexico City, Mexico.
3. Radiology Department, Hospital Médica Sur, Mexico City, Mexico.
4. Urológía Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.
5. Gastroenterology Unit, Instituto Alexander Fleming, CABA, Buenos Aires, Argentina.
6. Urológía Department, Hospital Country 2000, Guadalajara, Mexico.
7. University of Colorado Denver, School of Medicine, Aurora, CO.

**KEY REFERENCES**


For references visit cancernetwork.com/Bourlon_12.21

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EXPERT COMMENTARY ON THE PRODUCT PROFILE OF

Loncastuximab Tesirine

**Product Profile**

**Drug name:** Loncastuximab tesirine (Zynlonta)

**Date of approval:** April 23, 2021

**Initial indication:** For adults who have relapsed/refractory large B-cell lymphoma and have been treated with 2 or more lines of systemic therapy. This indication includes patients with diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

**Dosage and administration:** Given as an intravenous infusion over 30 minutes on day 1 of each 3-week cycle. Patients are given 0.15 mg/kg for 2 cycles and 0.075 mg/kg for subsequent cycles.

**How supplied:** Lyophilized powder in single-dose vial for reconstitution and further dilution

**Pivotal clinical trial:** LOTIS-2 (NCT03589469)

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**Trial Design of LOTIS-2**

**ELIGIBLE PATIENTS**

- Pathological diagnosis of DLBCL (DLBCL not specified, primary mediastinal large B-cell lymphoma, and high-grade B-cell lymphoma with MYC alterations and BCL2 and/or BCL6 rearrangements)
- Relapsed or refractory disease after 2 or more lines of treatment
- Biopsy-confirmed CD19 protein expression if CD19-directed therapy was used in a prior line
- Measurable disease defined by 2014 Lugano classification

**Intravenous infusion for 30 minutes on day 1 of each cycle at 150 μg/kg every 3 weeks for 2 cycles, then 75 μg/kg every 3 weeks for subsequent cycles for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria**

**PRIMARY END POINT**

ORR by 2014 Lugano classification

**KEY SECONDARY END POINTS**

DOR, RFS, PFS, and OS

DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival.
Q: Can you briefly describe the mechanism of action of loncastuximab tesirine?

HECHT: Loncastuximab tesirine is a new therapy indicated for [patients with] large B-cell lymphoma that has progressed after 2 lines of therapy. It’s a monoclonal antibody conjugate, meaning it has a monoclonal antibody component with a chemotherapy piece that’s attached to it. The monoclonal antibody targets CD19, which is over-expressed on the B cells, especially in B-cell malignancies. Then, the chemotherapy component acts like an alkylating agent. The antibody serves as a carrier; it takes that chemotherapy straight to the malignant cell where the complex is internalized by the cell, and the alkylating agent component produces cytotoxic interstrand cross-linking. With these conjugated monoclonal antibodies, we have a targeted delivery of a chemotherapy agent.

Q: What are some of the biggest concerns with this agent in the real-world treatment setting?

HECHT: What we’re seeing in the real-world setting is what was reported in the LOTIS-2 trial. The biggest safety concerns are [related to] the development of edema and effusion, such as pleural effusions or potential cardiac effusions. There is also a concern for increased liver enzymes, especially gamma glutamyl transferase, and development of a rash. Importantly, we should also look out for myelosuppression. Often when we talk about monoclonal antibodies, we don’t consider myelosuppression, but because [this agent] has that chemotherapy conjugate, myelosuppression is an adverse effect [AE].

To help with the AEs, patients should get a 3-day course of dexamethasone; it [should] start the day before the antibody and continue for 2 days after. There are specific recommendations on how to handle the edema and fluid retention using spironolactone. If a patient gains as much as a kilogram, they should start spironolactone to help combat that fluid retention.

Q: Are dosing modifications common with this agent?

HECHT: Loncastuximab tesirine is dosed using an every-3-week schedule with a planned dose reduction. [The investigators on LOTIS-2] did that because in the in the phase 1 trial, they saw a response as soon as 6 weeks after the initiation of therapy. The starting dose is 150 μg/kg for the first 2 cycles, which covers 6 weeks. To help mitigate the AEs, the dose reduces to 75 μg/kg for subsequent cycles. Beyond that planned decrease, dose reductions in the LOTIS-2 trial and in the real-world [setting] aren’t that common. Dose delays during the course of therapy are sometimes required to allow for the resolution of AEs between cycles. Patients with a body mass index of 35 kg/m² or higher should be dosed on an adjusted bodyweight schedule, and the formula for that is provided in the package insert and is included in the LOTIS-2 trial as well.

Q: What are the major drug interactions?

HECHT: With a lot of monoclonal antibodies, we’re not reliant on many metabolic pathways to eliminate the drug. Therefore, no known drug interactions have been identified with this agent so far.

Q: Have any barriers to administration or receipt by the patient emerged since this agent’s approval?

HECHT: With most of our new anticancer therapies, costs and reimbursements are always [a concern]. Most of our third-party carriers have adopted a prior authorization process to ensure that patients are only being offered loncastuximab tesirine for its approved indication, and a [certain] level of paperwork is involved in order to get the drug approved.

Q: Would you like to add anything else?

HECHT: I want to point out something that was included in the patient population were some patients with high-risk lymphoma features, such as double- or triple-hit lymphoma, or lymphoma that had transformed from a lower-grade to a higher-grade lymphoma. Just recently, at the International Conference on Malignant Lymphoma, [Pier Luigi Zinzani, MD, PhD, and colleagues] presented updates on these subgroups showing that they did as well as the general overall study population. The subgroups are small, but it’s encouraging to see patients with these high-risk lymphomas also deriving benefit, not just patients with standard-risk lymphomas.

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.

FOR REFERENCES visit cancernetwork.com/PP_12.21
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\(^1-^3\)

**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\(^1\)\(^4\)

After a median ~30 months\(^2\) 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 56.6% 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)\(^2\)

- 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 a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

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.\(^2\)

Efficacy results in long-term follow-up\(^2\)\(^3\)

At median ~5 years (56 months)\(^3\) 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)\(^1\)
- 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.

Efficacy results in long-term follow-up (median treatment duration of 47.5 months)\(^2\)

At median ~5 years of follow-up\(^2\)\(^3\):
- Most frequent TEAEs ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms
- Grade 3/4 infections were 41% for DRd vs 29% for Rd
- Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 45% for Rd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

Safety results in long-term follow-up

- Grade 3/4 IRRs ≥10% were pyrexia (21% vs 16%), respiratory infection, neutropenia, IRRs, and asthenia
- Grade 3/4 hospitalizations ≥10% were pneumonia (7% vs 6%) and lower respiratory tract infection (4% vs 4%)

MAIA-2 Study: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=372) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma. Treatment was continued until disease progression or death. The primary efficacy endpoint was median OS. Treatment was continued until disease progression or death (HR=0.57; 95% CI, 0.43–0.77; P<0.001)

MAIA-3 Study: A phase 3 global, randomized, open-label study, compared treatment with DRd (n=369) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma and an Hgb <11 g/dL at study entry. Treatment was continued until disease progression or death. The primary efficacy endpoint was mPFS. Treatment was continued until disease progression or death (HR=0.69; 95% CI, 0.53–0.92; P=0.011)

- Grade 3/4 infections were 40% for DRd vs 32% for Rd
- Grade 3/4 TEAEs ≥10% were neutropenia (52% vs 46%), anemia (15% vs 11%), pneumonitis (7% vs 4%), and nasopharyngitis (7% vs 5%)

Probability of Treatment Discontinuation

- Probability of treatment discontinuation was lower with DRd vs Rd: 17.0% vs 19.9% (P=0.008)
- Probability of discontinuation due to adverse events (AEs) was lower with DRd vs Rd: 11.1% vs 13.8%

MAIA Safety: MAIA Safety is similar to other prior daratumumab clinical trials.

- Adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

MAIA-2 Safety: MAIA-2 Safety is similar to other prior daratumumab clinical trials.

- Adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

MAIA-3 Safety: MAIA-3 Safety is similar to other prior daratumumab clinical trials.

- Adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

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, decreased platelets, and decreased hemoglobin.

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

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

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

**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, melphanal 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 at 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 4, 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, pharyngeal 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 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 splint 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 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 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 (2.3) 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 pre-medications 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 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 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.

**Embryo-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 for use during pregnancy.

**ADVERSE REACTIONS**

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

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

**Clinical Trials Experience**

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

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, edema, nausea, cough, pyrexia, dyspnea, and asthenia.
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 at least 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>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
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<td></td>
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<td></td>
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<td>Diarrhea</td>
<td>57</td>
<td>7</td>
<td>4</td>
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<td>0</td>
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<td>Constipation</td>
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<td>1</td>
<td>&lt;1</td>
<td>36</td>
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<td>Nausea</td>
<td>32</td>
<td>1</td>
<td>&lt;1</td>
<td>23</td>
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<tr>
<td>Vomiting</td>
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<td>1</td>
<td>&lt;1</td>
<td>12</td>
<td>&lt;1</td>
<td>0</td>
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<tr>
<td><strong>Infections</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2</td>
<td>&lt;1</td>
<td>36</td>
<td>2</td>
<td>&lt;1</td>
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<td>3</td>
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<td>21</td>
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<td>0</td>
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<tr>
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<td>26</td>
<td>14</td>
<td>1</td>
<td>14</td>
<td>7</td>
<td>1</td>
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<td>Urinary tract infection</td>
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<td>0</td>
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<td><strong>General disorders and administration site conditions</strong></td>
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<td>Infusion-related reactions&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>33</td>
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<td>Anemia</td>
<td>32</td>
<td>4</td>
<td>0</td>
<td>25</td>
<td>3</td>
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<td>Pyrexia</td>
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<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
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<td>Muscle spasms</td>
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<td>22</td>
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<td>0</td>
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<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;f&lt;/sup&gt;</td>
<td>32</td>
<td>3</td>
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<td>20</td>
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<td>0</td>
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<tr>
<td>Cough&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>&lt;1</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>0</td>
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<td>Headache</td>
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<td>Hyperglycemia</td>
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<td>1</td>
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<td>Hypocalcemia</td>
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<td>1</td>
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<td>9</td>
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<td>1</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
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<tr>
<td>Hypertension&lt;sup&gt;h&lt;/sup&gt;</td>
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<td>6</td>
<td>&lt;1</td>
<td>7</td>
<td>4</td>
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</tbody>
</table>

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

Adverse reactions described in Table 2 reflect exposure to DARZALEX for a median treatment duration of 14.7 months (range: 0 to 25.6 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>
<thead>
<tr>
<th>Body System Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections</strong></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>5</td>
<td>0</td>
<td>28</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Pneumonia&lt;sup&gt;j&lt;/sup&gt;</td>
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<td><strong>General disorders and administration site conditions</strong></td>
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<tr>
<td>Infusion-related reactions&lt;sup&gt;k&lt;/sup&gt;</td>
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<td>4</td>
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<td>0</td>
</tr>
<tr>
<td>Peripheral edema&lt;sup&gt;l&lt;/sup&gt;</td>
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<td>1</td>
<td>&lt;1</td>
<td>14</td>
<td>1</td>
<td>0</td>
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<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cough&lt;sup&gt;m&lt;/sup&gt;</td>
<td>16</td>
<td>&lt;1</td>
<td>0</td>
<td>8</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>2</td>
<td>1</td>
<td>5</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
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<td></td>
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</tr>
<tr>
<td>Hypertension&lt;sup&gt;o&lt;/sup&gt;</td>
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<td>&lt;4</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
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</tbody>
</table>

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

Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 5.4 months (range: 1.4 to 9 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 5.4 months (range: 1.4 to 9 months) for Rd.

Serious adverse reactions with at least 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%).
pneumonia, lung infection, pneumonia aspiration, pneumonia bacterial, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, and pulmonary sepsis.

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

d. edema peripheral, generalized edema, peripheral swelling

e. cough, productive cough

f. dyspnea, dyspnea exertional

g. 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>Condition</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>
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<tr>
<td>Neutropenia</td>
<td>86</td>
<td>34</td>
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<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-thalidomide-dexamethasone.

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 POLLUX [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 compared with 42% in the Rd arm. Serious adverse reactions with at least a 5% greater frequency in the DRd arm versus 8% (n=22) in the Rd arm.

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm compared to the VTd arm were bronchitis (DVTd 2% vs VTd <1%) and pneumonia (DVTd 6% vs VTd 4%).

Table 6: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>95</td>
<td>44</td>
<td>15</td>
<td>91</td>
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<tr>
<td>Neutropenia</td>
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<td>57</td>
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<tr>
<td>Lymphopenia</td>
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<td>58</td>
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<tr>
<td>Neutropenia</td>
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<td>41</td>
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<tr>
<td>Anemia</td>
<td>36</td>
<td>3</td>
<td>0</td>
<td>35</td>
</tr>
</tbody>
</table>

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX. Adverse reactions described in Table 7 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

<table>
<thead>
<tr>
<th>Condition</th>
<th>DRd (N=283)</th>
<th>Rd (N=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Infections</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>51</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>43</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Upper respiratory tract infection includes terms determined by investigators to be related to infusion.

Musculoskeletal and connective tissue disorders

Cough includes terms determined by investigators to be related to infusion.

Nervous system disorders

Headache includes terms determined by investigators to be related to infusion.

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

Upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

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

cough, productive cough, allergic cough

dyspnea, dyspnea exertional

Note: Hematology laboratory related toxicities were excluded and reported separately in the table below.
Combination Treatment with Bortezomib and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in CANDOR (see Clinical Studies (14.2) in Full Prescribing Information). Adverse reactions described in Table 9 reflect exposure to DARZALEX for a median treatment duration of 15.1 months (range: 0.1 to 23.7 months) for the daratumumab-carfilzomib-dexamethasone (DKd) group and median treatment duration of 9.6 months (range: 0.1 to 10.8 weeks) for the carfilzomib-dexamethasone group (Kd).

Serious adverse reactions occurred in 56% of patients who received DARZALEX in combination with Kd and 46% 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 2.8%), and respiratory tract infection (DKd 7% vs Kd 3%). Adverse reactions with at least a 2% greater incidence in the DKd arm compared to the Kd arm were upper respiratory tract infection (DKd 5% vs Kd 2%), diarrhea, and atrial fibrillation (DKd 2% vs Kd 0% for each).

Adverse reactions in combination for 7% (n=18) of patients in the Vd arm versus 9% (n=22) in the Vd arm.

Table 8: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the Vd Arm CASTOR

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>47 5 0 38 6 1 1</td>
<td></td>
</tr>
</tbody>
</table>

General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Infusion-related reactions</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral edema</td>
<td>22 1 0 13 0 0</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 1 0 11 1 0</td>
<td></td>
</tr>
</tbody>
</table>

Infections

<table>
<thead>
<tr>
<th>Upper respiratory tract infection</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>44 6 0 30 3 3 1</td>
<td></td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Diarrhea</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32 3 1 22 1 0</td>
<td></td>
</tr>
</tbody>
</table>

Vomiting

<table>
<thead>
<tr>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>0 0 4 0 0</td>
</tr>
</tbody>
</table>

Respiratory, thoracic and mediastinal disorders

<table>
<thead>
<tr>
<th>Cough</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27 0 0 14 0 0</td>
<td></td>
</tr>
</tbody>
</table>

Dyspnea

<table>
<thead>
<tr>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 4 0 11 1 0</td>
<td></td>
</tr>
</tbody>
</table>

Table 9:  Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the Vd Arm CASTOR

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

Adverse Reaction | DVd (N=243) | Vd (N=237) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

<table>
<thead>
<tr>
<th>Laboratory abnormality</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>52 13 0 57 19 0</td>
<td></td>
</tr>
</tbody>
</table>

Table 11: Adverse Reactions (≥15%) in Patients Who Received DARZALEX in Combination with Carfilzomib and Dexamethasone (DKd) in CANDOR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DKd (N=308)</th>
<th>Kd (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DARZALEX® (daratumumab) injection

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

DARZALEX® (daratumumab) injection

Laboratory abnormalities worsening during treatment are listed in Table 10.

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

Table 10: Treatment-Emergent Hematology Laboratory Abnormalities in CASTOR

<table>
<thead>
<tr>
<th>Laboratory abnormality</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>52 13 0 57 19 0</td>
<td></td>
</tr>
</tbody>
</table>

Table 11: Adverse Reactions (≥15%) in Patients Who Received DARZALEX in Combination with Carfilzomib and Dexamethasone (DKd) in CANDOR

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DKd (N=308)</th>
<th>Kd (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DVd (N=243)</th>
<th>Vd (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Darzalex® (daratumumab) injection

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, asthenia, 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 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 administration.

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.

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopeniaa</td>
<td>88</td>
</tr>
<tr>
<td>Anemiab</td>
<td>52</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>31</td>
</tr>
<tr>
<td>Lymphopeniaa</td>
<td>29</td>
</tr>
<tr>
<td>General disorder and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatiguea</td>
<td>54</td>
</tr>
<tr>
<td>Infusion-related reactionsd</td>
<td>53</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>37</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infectiong</td>
<td>53</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>19</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18</td>
</tr>
<tr>
<td>Influenza</td>
<td>17</td>
</tr>
</tbody>
</table>

Key: D=daratumumab; Kd=carfilzomib-dexamethasone
- Thrombocytopenia includes platelet count decreased and thrombocytopenia.
- Anemia includes anemia, hematocrit decreased and hemoglobin decreased.
- Neutropenia includes neutrophil count decreased and neutropenia.
- Lymphopenia includes lymphocyte count decreased and lymphopenia.
- Fatigue includes fatigue and asthenia.
- 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 administration.
- Respiratory tract infection includes respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection and viral upper respiratory tract infection.
- 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, asthenia, 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 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 administration.

Respiratory tract infection includes respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection and viral upper respiratory tract infection.

Cough includes productive cough and cough.

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, asthenia, 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
- Skin and subcutaneous tissue disorders: rash, pruritus

Combination Treatment with Pomalidomide and Dexamethasone

The safety of DARZALEX in combination with pomalidomide and dexamethasone (DPd) for a median treatment duration of 6 months (range: 0.03 to 16.9 months).

DARZALEX, pomalidomide and dexamethasone (DPd) 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 were pneumonia (4.7%), upper respiratory tract infection, sepsis, septic shock

Fatigue includes fatigue and asthenia.

Infections: pneumonia, urinary tract infection, sepsis, septic shock

Musculoskeletal and connective tissue disorders: muscle spasms, arthralgia, musculoskeletal chest pain

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 (DPd) 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 13: Adverse Reactions With Incidence ≥10% Reported in EQUULEUS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DPd (N=103)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>50</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>50</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>25</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Edema peripheral</td>
<td>17</td>
<td>4</td>
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<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>11</td>
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<tr>
<td><strong>Infections</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>50</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>43</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>33</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>26</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>25</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>22</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Bone pain</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>13</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
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<tr>
<td>Insomnia</td>
<td>23</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>21</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>19</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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

* Infusion-related reaction includes terms determined by investigators to be related to infusion
* edema, edema peripheral, peripheral swelling.
* acute tonsillitis, bronchitis, laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, rhiinusitis, tonsillitis, upper respiratory tract infection
* lung infection, pneumonia, pneumonia aspiration
* cough, productive cough, allergic cough
* dyspnea, dyspnea exertional

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>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>95</td>
<td>36</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>94</td>
<td>45</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>57</td>
<td>30</td>
<td>0</td>
<td></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 (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulting 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 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>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>48</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>21</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>23</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

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

* Infusion-related reaction includes terms determined by investigators to be related to infusion
* Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Daratumumab 16 mg/kg (N=156)</th>
<th>All Grades (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>72</td>
<td>30</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>60</td>
<td>17</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>48</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>45</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Herspes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.
Interference with Serum Protein Electrophoresis and Immunofixation Tests
RhD-compatible RBCs per local blood bank practices. If an emergency transfusion is required, administer non-cross-matched ABO/blood group system is also sensitive to DTT treatment, supply K-negative units to disrupt daratumumab binding. Mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to treat CD38-positive RBCs, and for patients with multiple myeloma treated with DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Postmarketing Experience
The following adverse reactions have been identified during 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.

Gastrointestinal disorders:
- Pancreatitis

Immune System disorders:
- Anaphylactic reaction; IRR (including deaths)

Drug Interactions

Effects of Daratumumab on Laboratory Tests
Interference with Indirect Antiglobulin 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. 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 monoclonal 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-licensed daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

Use in Specific Populations

Pregnancy

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide 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 may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX in utero until a hematologic evaluation is completed.

Data

Animal Data
Mice that were genetically modified to eliminate all CD38 expression (CD38 null) and allowed to reproduce, demonstrated that daratumumab can cause fetal harm when administered to a pregnant woman. The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information for additional information.

Females and Males of Reproductive Potential
DARZALEX can cause fetal harm when administered to a pregnant woman (see Use in Specific Populations).

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

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

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

Geriatric Use
Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher for patients 75 years of age and older.
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 DKd 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].

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Horsham, PA 19044
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cp-60805v6
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 combination with 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 accelerated 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).

Limitations of Use

DARZALEX FASPRO is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or IV cardiac disease or Mayo Stage IIIA outside of controlled clinical trials [see Warnings and Precautions].

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).

ADVERSE REACTIONS

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, injection-site reactions occurred in 8% of patients. Of the 129 systemic administration-related reactions occurred in 8% of 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.

Monitor 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 Adverse Reactions].

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

Thrombocytopenia

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

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

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 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 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 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 are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Multiple Myeloma

In Combination with Bortezomib, 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, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting 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.
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>Laboratory Abnormality</th>
<th>DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone*</th>
<th>DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades ≥3 (%)</td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>53</td>
<td>84</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>53</td>
<td>42</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>86</td>
<td>49</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>48</td>
<td>19</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 greater 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 diabetes. 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 more than 1 patient were pneumonia and anemia.

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>All Grades (%)</td>
<td>Grades ≥3 (%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</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>Gastrointestinal disorders</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>Infections</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>Urinary tract infection</td>
<td>11</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>31</td>
</tr>
<tr>
<td>Back pain</td>
<td>14</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>22</td>
</tr>
<tr>
<td>Cough*</td>
<td>14</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>17</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></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.

* 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 bortezomib, melphalan and prednisone included:

- **General disorders and administration site conditions:** infusion reaction, injection site reaction, chills
- **Infections:** herpes zoster, urinary tract infection, influenza, sepsis
- **Musculoskeletal and connective tissue disorders:** arthropathy, 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 3: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES (Continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td>12</td>
<td>9$^{a}$</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td></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 include:

**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

**Infection and infestations:** sepsis, herpes zoster

**Metabolism and nutrition disorders:** decreased appetite

**Cardiac disorders:** atrial fibrillation

**General disorders and administration site conditions:** chills, infusion reaction, injection site reaction

**Vascular disorders:** hypotension, hypertension

**Respiratory, thoracic and mediastinal disorders:** chest pain

**Rash disorders:** cutaneous rash, rash, pruritus

**Skin and subcutaneous tissue disorders:** cutaneous rash, rash, pruritus

**Musculoskeletal and connective tissue disorders:** muscle spasms, musculoskeletal chest pain, arthralgia

**Psychiatric disorders:** insomnia

**Gastrointestinal disorders:** nausea, abdominal pain, vomiting

**Skin and subcutaneous tissue disorders:** rash, pruritus

**Musculoskeletal and connective tissue disorders:** muscle spasms, musculoskeletal chest pain, arthralgia

**Infections:** urinary tract infection, influenza, hepatitis B reactivation, herpes zoster, sepsis

**Vascular disorders:** hypertension, hypotension

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

Table 5 summarizes the adverse reactions in patients who received DARZALEX FASPRO-Pd. No adverse reactions resulting in permanent discontinuation occurred in more than one patient.

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

Table 6 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO-Pd or Pd in APOLLO.

Key: Pd=pomalidomide-dexamethasone

- Fatigue includes asthenia, and fatigue.
- Edema peripheral includes edema, edema peripheral and peripheral swelling.
- Pneumonia includes atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia respiratory syncytial viral.
- Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cough includes cough, and productive cough.

Only grade 3 adverse reactions occurred.

Key: Pd=pomalidomide-dexamethasone

Denominator is based on number of subjects with a baseline and post-baseline laboratory value for each laboratory test: N=148 for DARZALEX FASPRO-Pd and N=149 for Pd.

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>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grades ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leukocytes</td>
<td>94</td>
<td>34</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>82</td>
<td>58</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>86</td>
<td>9</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>45</td>
<td>8</td>
</tr>
</tbody>
</table>

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

In Combination with Pomalidomide and Dexamethasone

The safety of DARZALEX FASPRO with pomalidomide and dexamethasone compared to pomalidomide and dexamethasone (Pd) in patients who had received at least one prior line of therapy with lenalidomide and a proteasome inhibitor (PI) was evaluated in APOLLO (see Clinical Studies [14.2] in Full Prescribing Information). Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly for 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks from weeks 25 until disease progression or unacceptable toxicity in combination with pomalidomide and dexamethasone (n=148) or pomalidomide and dexamethasone (n=150). Among patients receiving DARZALEX FASPRO-Pd, 71% were exposed for 6 months or longer and 50% were exposed for greater than one year.

Serious adverse reactions occurred in 50% of patients who received DARZALEX FASPRO in APOLLO. The most frequent serious adverse reactions in >5% of patients who received DARZALEX FASPRO-Pd were pneumonia (15%) and lower respiratory tract infection (12%). Fatal adverse reactions occurred in 7% of patients who received DARZALEX FASPRO-Pd.

Permanent treatment discontinuation due to an adverse reaction occurred in 2% of patients who received DARZALEX FASPRO-Pd. No adverse reactions resulting in permanent discontinuation occurred in more than one patient.

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

Table 5 summarizes the adverse reactions in patients who received DARZALEX FASPRO 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 or daratumumab 16 mg/kg administered intravenously, each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FAS PRO, 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 FAS PRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure. Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FAS PRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FAS PRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FAS PRO. 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 7: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grade ≥3 (%)</th>
<th>All Grades (%)</th>
<th>Grade ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>24</td>
<td>1*</td>
<td>22</td>
<td>1*</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>5</td>
<td>10</td>
<td>6b</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>1*</td>
<td>11</td>
<td>0,4*</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>0,4*</td>
<td>11</td>
<td>1*</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>1*</td>
<td>16</td>
<td>2*</td>
</tr>
<tr>
<td>Infusion reactionsd</td>
<td>13</td>
<td>2*</td>
<td>24</td>
<td>5*</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>0</td>
<td>12</td>
<td>1*</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>0,4*</td>
<td>12</td>
<td>1*</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>2*</td>
<td>12</td>
<td>3*</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughb</td>
<td>9</td>
<td>1*</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>1*</td>
<td>11</td>
<td>1*</td>
</tr>
</tbody>
</table>

a Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, and upper respiratory tract infection.
b Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jiroveci pneumonia, and pneumonia.
c Fatigue includes asthenia, and fatigue.
d Infusion reactions include terms determined by investigators to be related to infusion.

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>Grades 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased leucocytes</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>56</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>

a Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=258).

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.

Dosage 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 cardiogenic shock, ischemic heart failure, pneumonia, sepsis, and cardiac failure.

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-VCd or Intravenous Daratumumab in ANDROMEDA

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
<th>All Grades (%)</th>
<th>Grades 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>40</td>
<td>1*</td>
<td>21</td>
<td>1*</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15</td>
<td>10</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>6*</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>34</td>
<td>2*</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>31</td>
<td>3</td>
<td>20</td>
<td>2*</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>28</td>
<td>3</td>
<td>20</td>
<td>4*</td>
</tr>
<tr>
<td>Coughb</td>
<td>20</td>
<td>1*</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>
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 (continued)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DARZALEX FASPRO-VCd</th>
<th>VCd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arhythmia</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions:
- Injection site reactions:
  - Grade 3: 11%
  - Grade 4: 0%

Musculoskeletal and connective tissue disorders:
- Only grade 3 adverse reactions occurred.
- Upper respiratory tract infection includes laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection, upper respiratory tract infection bacterial, and viral upper respiratory tract infection.
- Pneumonia includes lower respiratory tract infection, pneumonia, pneumonia aspiration, and pneumonia pneumococcal.
- Dyspnea includes dyspnea, and dyspnea exertional.
- Cough includes cough, and productive cough.
- Arrhythmia includes atrial flutter, atrial fibrillation, supraventricular tachycardia, bradycardia, atrial tachycardia, ventricular arrhythmia, ventricular extrasystoles, atrial tachycardia, ventricular tachycardia

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Cardiac Adverse Reactions in Light Chain (AL) Amyloidosis

Among patients who received DARZALEX FASPRO in combination with VCd, 72% of patients had baseline cardiac involvement with Mayo Cardiac Stage 1 (3%), Stage II (46%) and Stage III (51%). Serious cardiac disorders occurred in 16% of patients (8% of patients with Mayo Cardiac Stage I and II and 28% of patients with Stage III). Serious cardiac disorders in >2% of patients included cardiac failure (8%), cardiac arrest (4%) and arrhythmia (4%). Fatal cardiac disorders occurred in 10% of patients with Mayo Cardiac Stage I and II and 19% of patients with Stage III) who received DARZALEX FASPRO in combination with VCd. Fatal cardiac disorders that occurred in more than one patient in the DARZALEX FASPRO-VCd arm included cardiac arrest (4%), sudden death (3%), and cardiac failure (3%).

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading. In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 756 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 756 patients developed treatment-emergent anti-HuPH20 antibodies. The anti–HuPH20 antibodies did not appear to affect daratumumab exposure.

None of the patients who tested positive for anti-HuPH20 antibodies tested positive for neutralizing antibodies.

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.

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

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin 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 diethyldithioctetate (DDT) 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/ RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immuno-fixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE 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 DARZALEX FASPRO-treated 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

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

Table 10: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Cyclophosphamide and Dexamethasone (DARZALEX FASPRO-VCd) in ANDROMEDA

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DARZALEX FASPRO-VCd</th>
<th>VCd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Decreased lymphocytes</td>
<td>81</td>
<td>54</td>
</tr>
<tr>
<td>Decreased hemoglobin</td>
<td>66</td>
<td>6</td>
</tr>
<tr>
<td>Decreased leukocytes</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Decreased platelets</td>
<td>46</td>
<td>3</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>30</td>
<td>6</td>
</tr>
</tbody>
</table>

Denominator is based on the number of patients with a baseline and post-baseline laboratory value for each laboratory test, N=188 for DARZALEX FASPRO-VCd and N=186 for VCd. |
**REFERENCES**


**PATIENT COUNSELING INFORMATION**

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

**Hypersensitivity and Other Administration Reactions**

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

**Neutropenia**

Advise patients to contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [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 if they have ever had or might have a hepatitis B infection that DARZALEX FASPRO could cause hepatitis B virus to become active again [see Adverse Reactions].

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The estimated background risk of major birth defects and miscarriage for the indicated indication 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 developing child. Lenalidomide, thalidomide and pomalidomide are metabolized to renal-cleared metabolites available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information for 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), fetal-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embry-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].

**Pregnancy Testing**

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

**Contraception**

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

**Pediatric Use**

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

**Geriatric Use**

Of the 214 patients who received DARZALEX FASPRO as combination therapy with pomalidomide and dexamethasone or DARZALEX FASPRO as combination therapy with lenalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma, 43% were 65 to <75 years of age, and 18% were 75 years or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=85). Adverse reactions occurring at a higher frequency (>5% difference) in patients ≥85 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspepsia, 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 decline, 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, pancreatitis 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].
Evolving HER2+ Metastatic Breast Cancer Landscape

HER2-positive metastatic breast cancer has historically been considered a difficult-to-treat disease given that it is often more aggressive than other breast cancers. However, several recently established targeted treatment options that prolong survival and enhance quality of life now offer hope to patients and their care providers. And although these advancements are of great benefit to both patients and their treating clinicians, questions about choosing the appropriate therapy and sequencing different lines of treatment remain.

Four experts reviewed these new developments during an online discussion as part of an Around the Practice event hosted by CancerNetwork®, moderated by Andrew D. Seidman, MD, an attending physician for the breast medicine service at Memorial Sloan Kettering Cancer Center, who covered the current standard of care as well as novel and emerging therapies. The other panelists were Aditya Bardia, MD, MPH, a breast medical oncologist at Massachusetts General Hospital and assistant professor of medicine at Harvard Medical School in Boston, Massachusetts; Mark Pegram, MD, a professor of medical oncology at the Stanford University School of Medicine in California; and Ruta Rao, MD, who is associate professor in the Department of Internal Medicine, Division of Hematology, Oncology, and Cell Therapy at Rush Medical College; director, Coleman Foundation Comprehensive Breast Cancer Clinic; and medical director, Rush University Cancer Center, all in Chicago, Illinois. The discussion also included audience polls, which the speakers discussed as part of their program.

A Rapidly Changing Therapeutic Landscape

The discussion began with a review of current options for first- and second-line therapy in the treatment of HER2-positive metastatic breast cancer. Pegram, who runs a research lab focused on targeted metastatic breast cancer, discussed the regimen consisting of trastuzumab (Herceptin) and pertuzumab (Perjeta) combined with taxane chemotherapy,
usually paclitaxel. Oncologists favor this regimen because of the highly successful randomized double-blind phase 3 CLEOPATRA trial (NCT00567190), the updated results of which indicated that patients assigned to the active regimen had a median overall survival (OS) that was 16.3 months longer than that of patients assigned to placebo (HR, 0.69; 95% CI, 0.58-0.82).1

“That’s a huge survival benefit that has been persistent over the 8 years since that trial [was] first reported,” said Pegram. “Very impressive results and so far, nothing has been able to dethrone the CLEOPATRA regimen in the first-line setting.”

An established second-line treatment, trastuzumab emtansine (Kadcyla; TDM-1), has been recommended by guidelines and put into standard practice since the publication of the EMILIA trial (NCT00829166) in 2012, Pegram added. In a 2017 update, patients assigned to the study regimen experienced a superior survival benefit compared with controls assigned to capecitabine plus lapatinib (Tykerb).4

However, the results of an upcoming trial may displace the generally accepted CLEOPATRA regimen in the frontline setting, according to Pegram. In the DESTINY-Breast 09 study (NCT04784715), investigators will compare a regimen consisting of trastuzumab deruxtecan (Enhertu; T-DXd) with or without pertuzumab or placebo. The primary end point was progression-free survival (PFS) as determined by independent review; secondary outcomes included OS, PFS as determined by investigators, objective response rate, duration of objective response, and time to disease progression. The investigators found that the pertuzumab combination greatly extended median PFS (HR, 0.69; 95% CI, 0.58-0.81) and subsequently was found to have a dramatic benefit to OS, as Pegram mentioned at the beginning of the program.2

In a phase 3 KATHERINE (NCT01772472) trial, investigators assigned 1486 patients to either adjuvant trastuzumab or trastuzumab emtansine following surgery. The main outcome was invasive disease-free survival, with patients in the TDM-1 group demonstrating a 50% lower risk of recurrence of invasive breast cancer or death than those assigned to trastuzumab alone (HR, 0.50; 95% CI, 0.39-0.64; P < .001).2

In EMILIA, the efficacy of trastuzumab emtansine was compared with that of capecitabine and lapatinib; investigators randomly assigned 991 patients with previously treated, advanced disease to receive either therapy. The main outcome measures were PFS, OS, and safety. Trastuzumab emtansine was found to significantly improve PFS, and it lowered overall toxicity compared with capecitabine and lapatinib at the first analysis (HR, 0.65; 95% CI, 0.55-0.77; P < .001), with the final descriptive analysis revealing a 25% reduction in the risk of disease progression or death (HR, 0.75; 95% CI, 0.64-0.88).3,4

The 2021 American Society of Clinical Oncology meeting saw the presentation of updated results from the pivotal phase 3 HER2CLIMB study (NCT02614794) that randomized 612 patients with unresectable metastatic or locally advanced HER2-positive breast cancer in a 2:1 fashion to receive either trastuzumab and capecitabine alone or in combination with tucatinib (Tukysa). Investigators reported a survival benefit in the tucatinib group 15.6 months following the primary analysis, with patients assigned to tucatinib experiencing a 5.5-month improvement in OS compared with the placebo group (HR, 0.73; 95% CI, 0.59-0.90; P = .004).4

Data from DESTINY-Breast03 in 524 patients randomly assigned to T-DXd vs T-DM1 that were presented at the European Society for Medical Oncology 2021 Congress indicated that the median PFS was not reached in the trastuzumab deruxtecan group compared with 6.8 months in the T-DM1 group (HR, 0.28; 95% CI, 0.22-0.37; P = 7.8 × 10−22). Patients assigned to trastuzumab deruxtecan were also treated longer, at a median of 14.3 months compared with 6.9 months for those assigned to T-DM1. Both groups showed similar safety profiles of the agents.5

The NALA trial (NCT01808573),

Survival Outcomes in Recent Clinical Trials

Several trials in recent years have changed the way oncologists care for patients with metastatic HER2-positive breast cancer, and some ongoing trials may improve treatment in the near future.

In CLEOPATRA, investigators randomly assigned a total of 808 patients in a 1:1 fashion to chemotherapy and trastuzumab plus either pertuzumab or placebo. The primary end point was progression-free survival (PFS) as determined by independent review; secondary outcomes included OS, PFS as determined by investigators, objective response rate, duration of objective response, and time to disease progression. The investigators found that the pertuzumab combination greatly extended median PFS (HR, 0.69; 95% CI, 0.58-0.81) and subsequently was found to have a dramatic benefit to OS, as Pegram mentioned at the beginning of the program.2

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What’s more, patients with early HER2-positive breast cancer are already being treated with the dual-antibody pairing of trastuzumab and pertuzumab, and if these patients do not achieve a complete pathologic response, care providers may also administer postneoadjuvant TDM-1.6

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The TDM-1 regimen is also being challenged in the second line. Investigators recently reported findings from the phase 3 DESTINY-Breast 03 trial (NCT03529110) of T-DXd vs T-DM1 that could change the standard for HER2-positive metastatic breast cancer in this setting.2

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The NALA trial (NCT01808573),
a global, open-label phase 3 study of 621 patients with previously treated HER2-positive breast cancer, which included 3 men and compared survival with capecitabine plus either neratinib (Nerlynx) or lapatinib was discussed by Seidman. The study also included patients with stable, asymptomatic central nervous system (CNS) disease. The main outcomes were PFS and OS as determined by a blinded review, with statistically significant improvements in both end points noted in 2020. The HR for progression or death was 0.76 (95% CI, 0.63-0.93; stratified log-rank \( P = .0059 \)), and for survival the HR was 0.88 (95% CI, 0.72-1.07; \( P = .2098 \)). A 2021 update found that the neratinib combination outperformed lapatinib in terms of both PFS (7.8 vs 5.5 months; HR, 0.66; 95% CI, 0.41-1.05; \( P = .0741 \)) and OS (16.4 vs 15.4 months; HR, 0.90; 95% CI, 0.59-1.38; \( P = .6352 \)) in a subgroup of patients with CNS involvement.9,10

**Metastatic HER2-Positive Disease in Patient Cases**

After a discussion of these data for approved therapies to treat HER2-positive breast cancer, the panel turned to a series of case studies regarding third-line treatment options.

### Case 1
- A woman, aged 57 years, presented with a 1.8-cm left breast mass and 3 palpable axillary lymph nodes.
- Medical history: significant for chronic obstructive pulmonary disorder; a 20 pack-year history of smoking; active smoker
- Baseline pulmonary function tests: mildly impaired diffusing capacity of lungs for CO2 (83%)
- Biopsy: invasive ductal carcinoma; estrogen receptor–negative/progesterone receptor–negative; HER2 by immunohistochemistry testing, 3+
- CT of chest/abdomen/pelvis (CAP): 2 lung lesions (largest 1.6 cm)
- MRI of the brain: negative for metastasis
- The patient received 6 cycles of trastuzumab plus pertuzumab (HP) and taxane chemotherapy (THP), followed by HP alone. A partial response was observed in breast mass, as was a complete response in lung lesions.
- Ten months later, recurrence in 2 lung lesions were discovered (largest 0.9 cm).
- The patient received T-DXd with a partial response observed in both the breast and lung lesions.
- Eighteen months later, growth of 1 lung lesion and a new 1.2-cm liver metastasis were noted on CT CAP.

When polled about how they would treat a patient whose disease had progressed to the lung and liver after earlier treatments had cleared previous metastases, 50% of all audience members responded that they would use the HER2CLIMB regimen of tucatinib plus trastuzumab and capecitabine, making that regimen the most popular choice in the poll.

“I can say that there’s definitely more than 1 right answer. In the metastatic setting, we use therapy sequentially, so it’s about choosing 1 therapy [first],” Bardia said. “Then in the future, you’d be using other regimens. I’m not that surprised [by this response], given the excitement around HER2CLIMB. There’s a lot of interest in utilizing tucatinib, and maybe that is what prompted the use of trastuzumab, capecitabine, and tucatinib.”

Another popular response was T-DM1. “It’s very well tolerated and I think it is an agent that should be used in the metastatic setting. I’d personally either consider TDM-1 or tucatinib,” Bardia added.

Seidman then guided the conversation to a discussion of treatment options for a woman, aged 35 years, who “indicates that her main priority is to live as normally as possible,” without nausea or diarrhea.

### Case 2
- A woman, aged 35 years, with hormone receptor–negative, HER2-positive metastatic breast cancer, presented in the clinic.
- She completed first-line therapy with THP and then progressed while on maintenance HP.
- At that time, she was treated with T-DXd.
- Twenty months later, she has low-volume asymptomatic bone metastases.
- She has 2 children and says that her main priority is to live as normal a life as possible while being treated. She wants to spend her weekends at the soccer fields and doesn’t want to have nausea or diarrhea, AEs that would make that difficult.
At this point, Rao said it would be important to discuss adverse effect (AE) profiles of each available agent with the patient.

“In this particular case, if she’s telling you she doesn’t want to have nausea or diarrhea and you’re talking to her about the different options and the different AEs associated with each, you’re going to tell her about the rates of diarrhea and nausea seen with the HER2CLIMB regimen,” Rao said. “It’s really important to have that discussion with the patient about how we don’t know which of the 2 third-line treatment options is superior because they have not been compared head-to-head. But if you look at the AEs each one has and the desires the patient has, that will help make a decision.”

Pegram added that the patient could be given an antidiarrheal medicine as needed. “For tucatinib, it’s fine to use it as needed,” said Pegram. “They don’t need it prophylactically [since] the incidence of diarrhea isn’t that high. For T-DXd, they don’t need prophylactic antidiarrheal regimens either. The one area where you absolutely must use prophylactic treatment is the case of neratinib.”

Pegram also said that CNS metastases could play a major role in selecting a therapy. In particular, he said, the HER2CLIMB regimen would be an obvious choice for dealing with brain lesions.

“We now have level 1 evidence from a randomized phase 3 trial of an OS benefit of tucatinib-based treatment with the HER2-CLIMB regimen, specifically for HER2-positive CNS metastasis,”11 said Pegram. “Moreover, the FDA label language for the approval of tucatinib specifically calls out those patients with HER2-positive breast cancer brain metastases.”12 These are patients of particular interest for the tucatinib-based treatment.

**Sequencing of Therapies**

A final poll question asked audience members when they would use the most active regimens available to treat their patients. The response, Seidman noted, was unanimous: All participants responded that they would use the most active regimen available as early as possible. “We’ve got a strong preference to lead with your best foot,” he said.

The panelists had several reasons for leading with the most active therapy. “Both from the CLEOPATRA trial—with the significant improvement in OS—and even in the DESTINY-Breast03 trial, we’ve seen a significant improvement in PFS, [meaning] that these patients can do well for a long time, especially when we give them our most active regimens first,” Rao said.

Pegram noted that patients often tend to drop out of treatment as they move through lines of therapy, which could mean that they may never reach third-line therapy.

“If you’re going to save your best drug for a rainy day, that rainy day may never come because the patient may get too sick from their underlying disease to ever have the opportunity to take the best treatment available,” Pegram said. “That’s another reason why it’s wise to use your best drugs first.”

The panel ended with an acknowledgment of the great strides made in treating HER2-positive metastatic breast cancer in recent years. Seidman concluded, “Some people have said that we have an embarrassment of riches in HER2-positive metastatic breast cancer, but we all still have patients who are [dying] from advanced HER2-positive breast cancer. As much progress as we’ve made, we still have quite a way to go—but we certainly have reasons for optimism.”

**Key References**


Monitoring With ctDNA for Immunotherapy Response in Lung Cancer

In a recent OncView™ discussion, Roy S. Herbst, MD, PhD, chief of medical oncology at Yale Cancer Center and Smilow Cancer Hospital in New Haven, Connecticut, reviewed current strategies for determining success of immunotherapy in the treatment of non–small cell lung cancer (NSCLC).

Recent advances in diagnostic and treatment options are improving the outlook for this disease. Immune checkpoint inhibitors, for example, represented a fundamental change in the treatment of NSCLC and have led to improved patient outcomes with less toxicity than conventional chemotherapy.

In this program, Herbst discussed key considerations involved in selecting a treatment regimen for individual patients. He also described the monitoring parameters, such as circulating tumor DNA (ctDNA), which are measured to determine a patient’s response to therapy. Finally, Herbst offered his clinical expertise in determining treatment duration and when to give patients a drug holiday.

Selecting an Immune Checkpoint Inhibitor

Each year, multiple new drugs for the treatment of metastatic NSCLC are approved, with many others in clinical trials, according to Herbst. Treatment options depend on multiple factors, such as tumor size and location, involvement of pleura, tumor grade, lymphovascular invasion, and others.

Immunotherapies that are currently approved for NSCLC include nivolumab (Opdivo), pembrolizumab (Keytruda), durvalumab (Imfinzi), atezolizumab (Tecentriq), and cemiplimab (Libtayo).1 Herbst noted that almost “every patient who can get immunotherapy will get immunotherapy, because in metastatic lung cancer it really is the only way to see a long-term outcome.”

The selection of an immunotherapy depends on a patient’s PD-L1 expression, or tumor proportion score (TPS). Herbst described single-agent pembrolizumab, atezolizumab, and cemiplimab as “frontline” options in patients with a PD-L1 expression of 50% or greater. In patients whose PD-L1 expression is less than 50%, “most are using chemotherapy plus immunotherapy in that setting,” he noted. Pembrolizumab, he further explained, can be used in patients with at least 1% PD-L1 expression; however,
“those data suggest that the result is probably as good as chemotherapy, but not better.”

**Disease Monitoring**

Once started on immunotherapy, patients must undergo routine monitoring to ensure they are responding to therapy or at least not progressing, said Herbst. A multimodal approach may be used for patient monitoring, including evaluation of radiographs and circulating tumor DNA (ctDNA) levels, as well as the patient’s quality of life, their performance status, and any reported adverse effects. Herbst said he typically monitors patients every 2 months depending on their drug regimen, adding that “you usually do yourresting[again]before you decide to give another round of therapy.”

Radiographs are one form of monitoring that may be used for determining partial response, stable disease, or progressive disease. RECIST criteria are typically used to characterize tumors. According to Herbst, patients receiving immunotherapy can be difficult to evaluate using RECIST due to the possibility of pseudoprogression evident on images. The tumor may look bigger due to the influx of immune cells, or it may grow before it shrinks, he explained. By contrast, pseudoprogression, which he estimated to occur in about 5% of patients, is not very common. Finally, images may also be complicated by inflammation from infection.

Another “more sophisticated” form of monitoring is measuring ctDNA, which is released into the bloodstream when apoptosis occurs in tumor cells, Herbst stated. This minimally invasive method allows for early diagnosis, prognosis prediction, detecting mutations, identifying minimal residual disease, and monitoring therapy response. In addition to being a real-time monitoring technique, ctDNA also has high sensitivity and specificity. “It can give you a quantitative measurement [because] you’re actually measuring the tumor,” Herbst explained. He added that data from a recent study conducted by the Friends of Cancer Research out of Washington, DC, showed that a decrease in ctDNA correlated with survival in patients with lung cancer receiving immunotherapy.

Herbst further explained how ctDNA levels can be measured throughout the course of treatment to determine a patient’s response to therapy. “If you see ctDNA going down,” he stated, “it tells you the patient is most likely responding.” It can also show when the disease is stabilized. In this case, he said the ctDNA results may be a good indicator to stop therapy if the patient is no longer seeing any tumor shrinkage, adding that taking an x-ray is “a way to validate those markers.”

Furthermore, ctDNA measurements can help differentiate between pseudoprogression and progression. “In pseudoprogression, you would not see ctDNA going up. In progression, you would,” Herbst explained. Thus, if the tumor looks bigger but the ctDNA is stable, “that’s telling you it’s probably pseudoprogression.”

Measuring ctDNA also has benefits in minimal residual disease monitoring, Herbst added. “Why treat patients with adjuvant therapy after surgery or after chemoradiation if they don’t need it?” He cited the IMpower010 study (NCT02486718), whose results showed that ctDNA can be used to predict which patients will benefit from adjuvant therapy with atezolizumab after surgery. The findings demonstrated an improvement in disease-free survival in patients with stage II to IIIA NSCLC who were treated with adjuvant atezolizumab after surgery, with more pronounced benefit in patients with PD-L1 expression greater than 1% (HR, 0.66; 95% CI, 0.50-0.88; P = .004).2

Data from 2 recent studies showed that ctDNA was predictive of disease progression and immunotherapy response. Investigators in one study evaluated the use of ctDNA in 3 clinical trials—the phase 1/2 CD-ON-MEDI4736-1108 trial (NCT01693562), phase 2 ATLANTIC trial (NCT02087423), and phase 1 D4190C0010 trial (NCT02261220)—with the immune checkpoint inhibitor durvalumab, with or without tremelimumab.1 They found that pretreatment ctDNA could be used as a prognostic biomarker, and on-treatment ctDNA dynamics appeared to predict the benefit of immunotherapy. Similarly, findings from the phase 2 INSPIRE study (NCT02644369), examining patients with solid tumors who were treated with pembrolizumab, demonstrated that a reduction in ctDNA from the baseline was associated with immunotherapy benefit.4

The FDA recently approved 2 ctDNA blood tests, which are also called liquid biopsies: Guardant360 CDx and FoundationOne Liquid CDx.5,6 These are for use in patients with solid tumors and are the first FDA-approved assays to assess for multiple cancer-related genetic changes rather than a single gene mutation. “Most of those are looking at mutational profiles, but I believe that they can also look at quantitative amounts of DNA and correlate that with outcomes,” said Herbst.

**Determining Treatment Duration**

Patients who have stable disease after long-term treatment with immunotherapy may be eligible for a drug holiday. In patients who have undergone long-term treatment, Herbst said, “coming every 3 weeks is tough, and these drugs do produce some fatigue and adverse effects. So why not stop? If someone has gone for a year or 2 [on therapy] and they’re stable, have no evidence of
they’ve also had toxicity and have had “They’ve had great responses, but after 3 or 4 months due to toxicity. “Of those that do relapse, more than half of them respond again...if you give them pembrolizumab,” Herbst said. “My thought is that many of these patients could be, dare I say, cured after 2 years and if they’re not, we know we can rescue them or at least stabilize the disease by giving the immunotherapy again. So I am a proponent of stopping therapy if we can.”

In some instances, patients may have responded to therapy but still have an area that’s growing. “I’ve had some cases where I’ve actually either radiated or done surgery and then either stopped the drug or gone on with immunotherapy a little longer until things are stable,” Herbst said. He concluded that each patient needs to be treated on a case-by-case basis.

Choosing when to give patients a drug holiday is a difficult decision, as “there are very few studies,” Herbst admitted. Although he cited a study which favored treating patients longer with nivolumab therapy, Herbst said more data is needed to support these findings. However, conducting clinical trials to study drug holidays is difficult in this patient population and Herbst surmised that research may be done on a molecular level with ctDNA, “looking at how much tumor burden there is in a more molecular way.”

Treatment duration is patient specific, said Herbst, adding that some of his patients have stopped immunotherapy after 3 or 4 months due to toxicity. “They’ve had great responses, but they’ve also had toxicity and have had to stop pembrolizumab; [some are still] alive 5 or 6 years later.” On the other hand, he noted, “I’ve had patients I’ve treated for several years where they’ve never had a partial response, but they’ve been stable, and I [have] some people who I might have on therapy more than 3 or 4 years. 

Looking Ahead
In addition to ctDNA, other options are needed to determine appropriate treatment duration. One of those includes imaging, according to Herbst, such as PET scanning. Furthermore, future technology may allow for more advanced molecular testing. “I would predict that we’ll have ways to file T cells in the immune microenvironment and actually label CD8-positive T cells and look at those...or label PD-L1 so we can actually look at the immune microenvironment in a patient. That might help us determine sites and areas of tumors that have not been totally eradicated.”

After about 30 years in this field, Herbst remarked: “Only in the last decade have I seen the amazing results of immunotherapy. I would predict that in the next few years we’re going to start seeing new immune combinations that can be used in these settings.”

REFERENCES

Role of ctDNA in Monitoring Treatment Response in NSCLC
Roy S. Herbst, MD, PhD, provides an overview about what ctDNA testing results can indicate about a patient’s likelihood of responding to immunotherapy in NSCLC. Cancernetwork.com/Herbst_12.21
Recent Updates in the Treatment of Nonmetastatic Castration-Resistant Prostate Cancer

In a recent OncView™ discussion, Aaron Berger, MD, vice president and chief medical officer at Associated Urological Specialists in Chicago, Illinois, shared clinical experiences and perspectives regarding treatments of patients with nonmetastatic castration-resistant prostate cancer (nmCRPC).

Clinicians need to be aware of all the treatment options available in this space, as many FDA-approved indications have emerged in the past few years, Berger said. “There’ve been several new options for nonmetastatic castration-resistant prostate cancer to come to market,” he noted. “The first was enzalutamide [Xtandi] followed shortly thereafter by apalutamide [Erleada], and then most recently darolutamide [Nubeqa]. We’ve used all of them in our advanced prostate cancer clinic, and it’s certainly an improvement over the previous options [such] as first-generation antiandrogen therapies.”

Berger detailed his strategies for therapy selection in this patient population, including insights in baseline patient characteristics, clinical trial data, and toxicity profiles of each novel agent that guide his decisions.

Disease Monitoring in nmCRPC

Berger said his first consideration in a patient with nmCRPC is whether they need additional systemic therapy. Age, comorbidities, prostate-specific antigen (PSA) doubling time, and medication adherence are some of the factors that may incline a clinician to treat a patient with a newer antiandrogen medication.

“Some of these patients have a lot of other [medical] issues,” Berger said. “If they’re not excited about another medication or are worried about [adverse] effects, we may just observe them, especially if their [PSA is] rising somewhat slowly.”

Ultimately, the treatment goals in this setting are to prevent progression of disease from nonmetastatic to metastatic, as survival rates dramatically decrease in later stages of the disease. “Typically, we will check PSA and testosterone levels every 3 months,” Berger said. He noted that testosterone less than 50 ng/mL and a PSA doubling of 10 months or less was the threshold for administering medication to patients in clinical trials.

“That’s not in the labeling for all these medications. You certainly can use the medication if their doubling time is 11 months or 12 months, but...
normally it’s [with a PSA doubling time of] 10 months or less we’re really focused on,” he said.

For imaging in a patient with a significant PSA rise, Berger said he references the RADAR III guidelines, which recommend next-generation imaging techniques for detecting previously metastases (Table1).

“We would certainly consider doing conventional imaging initially, such as a CT scan or bone scan, and if it’s negative then we would likely continue observation,” Berger said. “I typically wouldn’t wait until PSA is 5, 10, or 20 ng/mL and just keep doing conventional imaging—we would likely move on to doing next-generation imaging studies earlier.” Some other factors that might motivate imaging sooner include pain in the back, hips, or legs; urinary symptoms; or obstructions in the kidneys.

**Therapy Selection**

Regarding the 3 available next-generation androgen receptor inhibitors that are available to treat patients in this setting, Berger said their mechanisms of action are similar but varying molecular sizes account for the biggest differences reflected in slightly different toxicity profiles.

“Darolutamide typically has less in the way of central nervous system effects—such as fatigue, light headedness, or dizziness—than what we sometimes may see [with the other agents],” Berger said. “But mechanistically, they work very similar.”

Regarding metastasis-free and overall survival (OS) rates, pivotal clinical trials that led to the approval of these agents reflect similar results. “The design of the studies are very similar and the results of the studies are very similar,” Berger said. “Sometimes there’s a reason why you may not use one versus the other, such as if a patient does have significant fatigue or has any other central nervous system issues such as gait abnormalities. Potentially, the darolutamide may be a better choice than enzalutamide or the apalutamide. But in my experience, they’re all tolerated pretty well.”

Berger then explored data from the phase 3 PROSPER (NCT02003924), ARAMIS (NCT02200614), and SPARTAN (NCT01946204) trials that led to the approvals of enzalutamide, darolutamide, and apalutamide, respectively.

“All 3 trials had very similar patient populations with a PSA doubling times of 10 months or less. All the patients had rising PSA that was confirmed on more than 1 occasion and castrate levels of testosterone less than 50 ng/mL,” Berger said. “They were all looking at metastasis-free survival as the primary endpoint.”

At the initial readout of the SPARTAN trial, metastasis-free survival (MFS) was statistically significantly improved with apalutamide versus the placebo group (HR, 0.28; 95% CI, 0.23-0.36; \( P < .001 \)). Similarly, MFS in PROSPER showed a 71% reduction in the risk of metastasis or death with enzalutamide compared with placebo (HR, 0.29; 95% CI, 0.24-0.35; \( P < .001 \)). In ARAMIS, patients treated with darolutamide derived a significant treatment benefit versus those treated in the placebo group (HR, 0.41; 95% CI, 0.34-0.50; \( P < .001 \)).

“In subsequent analyses, it is now

### TABLE 1. RADAR III Next-Generation Imaging Recommendations

<table>
<thead>
<tr>
<th>Prostate cancer disease state</th>
<th>Imaging recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>Biochemically recurrent</td>
</tr>
<tr>
<td><strong>Imaging recommendations</strong></td>
<td>Consider next-generation imaging for PSA ( \geq 0.05 ) ng/mL. ( PSA \leq 0.05 ) ng/mL can be considered based on specific performances of various next-generation imaging techniques.</td>
</tr>
</tbody>
</table>

CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen; RADAR, Radiographic Assessment for Detection of Advanced Recurrence.
borne out that they all do result in improvements in overall survival,” Berger said. OS results with next-generation agents versus placebo were statistically significant for SPARTAN (HR, 0.78; 95% CI, 0.64-0.96; P = .016), PROSPER (HR, 0.73; 95% CI, 0.61-0.89; P = .001), and ARAMIS (HR, 0.69; 95% CI, 0.53-0.88; P = .003).

**Adverse Effects of Therapy**

When discussing toxicity, Berger detailed each in the context of which adverse effects were commonly associated with each agent.

“We typically see with enzalutamide fatigue or asthenia. These patients are all on androgen deprivation therapy at baseline [and] they have low testosterone at baseline, which can certainly decrease their overall energy level to start with,” Berger said. “Adding the enzalutamide in some patients does zap their energy substantially to the point where some don’t really feel like they have any motivation and don’t want to get out of bed.”

For these patients, Berger said a slight dose reduction can have a profound effect on their energy levels. For example, reducing the dosage by 25% or switching a patient from a 4-pill dose to a 3-pill dose may help a patient’s experience without significant effects on their overall disease outcomes.

With apalutamide, full body rash 2 to 3 months into treatment may occur but often can be managed with oral antihistamines or topical corticosteroids. Rarely, patients have a severe full body rash that requires discontinuation of therapy.

“There’s also a slightly higher risk with apalutamide of hypothyroidism, but this is not typically something we screen for routinely,” Berger said. “It’s mainly for those patients who have a history of hypothyroidism and are on medications already for thyroid replacement that we’ll check a thyroid panel along with their PSA and testosterone.”

Regarding darolutamide, Berger said its toxicity profile is likely the most favorable of the 3 available agents with its lower rate of fatigue, with most symptoms occurring during treatment.

“The bottom line is to know what to potentially expect and let the patients know what to be on the lookout for,” he said.

**Comorbidities**

Berger said comorbid conditions, such as obesity or diabetes, may inform the decision to administer an androgen inhibitor but they do not necessarily preclude a patient from treatment.

“If they don’t have significant cardiovascular issues and haven’t had a heart attacks, stroke, or congestive heart failure issues, I’m not going to withhold a second-generation androgen inhibitor just because they’re a bit overweight,” Berger said.

In fact, the relatively manageable safety profile of these agents means that treatment can be given without many dose adjustments even to patients with renal insufficiencies, he said.

Neurologic issues that may be present, such as unsteadiness, dizziness, or a history of falls should be taken into consideration, Berger said. “Then the data would indicate that darolutamide may be a better option [because] there wasn’t an increased risk from falls and fractures in the ARAMIS trial.”

**Future Treatment Landscape in nmCRPC**

Regarding unmet needs in the treatment space, Berger said that guidance for prescribers on drug-drug interactions is lacking. “There are a lot of medications patients are on, whether it’s antihypertensives, diabetes medications, or cardiovascular medications, especially the anticoagulants that may have some interactions with these medications. And the guidance, as far as what we can glean from the studies, is not always clear about what’s safe and what may not be safe,” he said.

Another consideration is whether nmCRPC will continue to be a disease state in the future, as next-generation imaging techniques become more prevalent in the treatment landscape and reveal metastasis in patients who would have been formerly considered nonmetastatic.

“When you have a scan that can pick up an area of metastasis at [PSA of] 0.2 to 0.3 ng/mL, it may turn out that these patients are metastatic. All of these studies were done with conventional imaging,” Berger said. “The big question as far as this entire disease state is, will it still be a disease state 5 years from now?”

Overall, Berger said clinicians shouldn’t shy away from prescribing these medications to their patients, given their tolerability and ease of administration. “I would not be afraid of these medications because you can easily add them into your clinical practice without a lot of trepidation,” he said.

**REFERENCES**

Proteolysis-Targeting Chimera (PROTAC) Therapy for Cancer

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:
• Describe the mechanism of action of proteolysis-targeting chimera (PROTAC) therapy for the treatment of cancer.
• Explain the rationale for using PROTAC therapy for the treatment of cancer.
• Assess key data from ongoing clinical trials evaluating PROTAC therapy for the treatment of cancer.

INSTRUCTIONS FOR PARTICIPATION / HOW TO RECEIVE CREDIT

1. Read this activity in its entirety.
2. Go to http://www.gotoper.com/go/oncJdec21tfc to access and complete the posttest.
3. Answer the evaluation questions.
4. Request credit using the drop-down menu.
   You may immediately download your certificate.

FACULTY

Daniel P. Petrylak, MD
Professor of Medicine (Medical Oncology) and of Urology, Director, Genitourinary Oncology Research Program, Co-Director, Cancer Signaling Network Program, Yale School of Medicine, Yale Cancer Center, New Haven, CT

This activity was written by PER® editorial staff under faculty guidance and review. The Q&A portion of the activity was transcribed from a recorded interview with the faculty and edited by faculty and PER® editorial staff for clarity.

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RELEASE DATE: December 1, 2021
EXPIRATION DATE: December 1, 2022

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ACTIVITY

Targeted immunotherapies, such as small molecule inhibitors and monoclonal antibodies, have shown promise in the treatment of multiple cancer types. However, there are limitations to those approaches, including inability to cross cell membranes, off-target effects, and development of drug resistance.\(^1,2\) Novel therapeutic proteolysis-targeting chimeras (PROTACs) utilize proteasome-mediated degradation to target specific proteins expressed on cancer cells.\(^3,4\)

Compared with traditional drugs, PROTACs have increased selectivity for targeted proteins, are able to target proteins that are considered undruggable, can be reused after one round of protein degradation, require a reduced dose to achieve maximal benefit, and are associated with reduced off-target events.\(^1,3\)

PROTACs use hetero-bifunctional molecules consisting of 3 components: a ligand to bind a target protein, a ligand to bind E3 ubiquitin ligase, and a linker to connect the 2 ligands.\(^1\) Following the formation of the target protein-PROTAC-E3 complex, an E2 ubiquitin is recruited to transfer a ubiquitin molecule to the surface of the target protein.\(^1\) The target protein is then degraded via the ubiquitin-proteasome system.\(^1,5\)

In this article, Daniel P. Petrylak, MD, professor of medicine and urology, director of the genitourinary oncology research program, and co-director of the cancer signal transduction program at Yale Cancer Center and Yale School of Medicine in New Haven, Connecticut, discusses the mechanism of action, safety profile, and clinical data regarding PROTAC approaches for treating cancer.

Q: What are PROTACs, and how do they work?

PETRYLAK: The body has a natural way of degrading proteins. Of course, proteins have a certain time frame in terms of their viability, and we have a system that is able to recycle proteins and to degrade them for subsequent use of the amino

<table>
<thead>
<tr>
<th>Target protein</th>
<th>Disease type</th>
<th>PROTAC</th>
<th>Clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>Prostate cancer</td>
<td>ARV-110(^9)</td>
<td>Phase 1 and phase 2/ NCT03888612</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARV-766(^9)</td>
<td>Phase 1/ NCT05067140</td>
</tr>
<tr>
<td>ER</td>
<td>Breast cancer</td>
<td>ARV-471(^13)</td>
<td>Phase 1 and phase 2/ NCT04072952</td>
</tr>
<tr>
<td>BCL-XL</td>
<td>TCL</td>
<td>DT2216(^14,15)</td>
<td>Phase 1/ NCT04886622</td>
</tr>
<tr>
<td>BRD9</td>
<td>SS</td>
<td>FHD-609(^16)</td>
<td>Phase 1/ NCT04965753</td>
</tr>
</tbody>
</table>

AEs, adverse events; mCRPC, metastatic castration-resistant prostate cancer; NCT, National Clinical Trial number; PROTAC, proteolysis-targeting chimera; PSA, prostate-specific antigen; SAEs, serious adverse events; SS, synovial sarcoma; TCL, T-cell lymphoma; TEAEs, treatment-emergent adverse effects.
acids. This happens through the E3 ubiquitin ligase system. These proteins are bound to E3; they are ubiquitinated and then shuttled to the proteosome, where they are degraded into small peptides.6

**Q:** What is the rationale for the use of PROTACs in the treatment of cancer?

**PETRYLAK:** The rationale for the use of PROTACs is that you can specifically target proteins. In fact, you can target proteins that may be overexpressed or have different mutations and use PROTACs to degrade those proteins.6

Targets that are currently under clinical investigation include the androgen receptor (AR) and the estrogen receptor (ER).7,8 The thought is that since these target proteins may regulate growth that the growth may be shut off or the cells may die once these particular targets are eliminated.

**Q:** What PROTACs are currently being studied in clinical trials, and what proteins do they target?

**PETRYLAK:** There are a number of different PROTACs which target different proteins that may be involved in growth and regulation of cancer cells that are being studied in clinical trials for cancer. There are several different PROTACs that target the androgen receptor, such as ARV-110 and ARV-766.9,10 Both PROTACs target the AR in prostate cancer. Another molecule, AR-LDD, also targets a different portion of the AR.11 In other solid tumors, there are molecules such as DT2216 that target B-cell lymphoma extra-large protein (BCL-XL), KT-474 that targets interleukin-1 receptor-associated kinase (IRAK4), ARV-471 that targets the ER, and KT-333 that targets the signal transducer and activator of transcription 3 (STAT3) receptor.11

Another target, BRD9, which is degraded by FHD-609, is involved in synovial cell carcinoma.12 There are several PROTACs targeting different proteins, and I think this is a very, very exciting time, because this really is a new way of targeting mutations as well as differences in cancer cells compared to normal cells.

Information on phase 1/2 clinical trials investigating the safety and tolerability of PROTACs that target multiple proteins is summarized in Table 1.9,10,13-17

**Q:** Can you discuss the outcomes from some of the more promising clinical trials involving PROTACs?

**PETRYLAK:** The data that is publicly available about PROTACs is limited. I can discuss our experience with the ARV-110 compound. We presented the phase 1 trial data at the American Society of Clinical Oncology meeting in 2020.17 In our preliminary analysis, we found that patients previously treated with 2 or more agents for mCRPC, including enzalutamide and/or abiraterone, who have a specific mutation, the T878 or the H875Y mutation in the AR, had a 50% decline in prostate-specific antigen (PSA) levels.17 We presented 2 cases that showed a significant decline in PSA levels, and I case showed regression of soft tissue lesions.17

**Q:** What toxicities are associated with PROTACs?

**PETRYLAK:** ARV-110 is a PROTAC which targets the AR. In our first 22 patients, 1 patient receiving concomitant rosuvastatin had a grade 3 increase in aspartate aminotransferase (AST) and alanine transaminase (ALT) levels. Another patient on rosvastatin developed a grade 4 elevated AST/ALT and acute renal failure while on ARV-110 treatment.17 We have been able to correlate AST/ALT elevation with patients who are also receiving rosvastatin, a cholesterol-lowering drug. Concomitant use of ARV-110 and rosvastatin may affect the metabolism of ARV-110.17 Concurrent use of rosvastatin and ARV-110 is prohibited following the occurrence of these adverse events.17

I think we may see that the toxicities of the PROTACs will be unique to the individual drug and that depleting the target may have secondary effects. A summary of toxicities related use of PROTACs appears in Table 2.15,17,18

**Q:** Where do you envision PROTACs fitting into the future cancer treatment paradigm?

**PETRYLAK:** I believe this will open a huge avenue of particular targets that we’ve been unable to target in the past, and we can develop specific PROTACs to a number of different proteins. There are several different targets that can be envisioned. I see this as a broad application to multiple tumor types as well as other physiological processes.

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TABLE 2. Reported Toxicities of PROTACs in Select Clinical Trials

<table>
<thead>
<tr>
<th>Target protein</th>
<th>PROTAC</th>
<th>Reported toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>ARV-11017</td>
<td>Elevated AST/ALT, acute renal failure with concurrent use of rosvastatin</td>
</tr>
<tr>
<td>ER</td>
<td>ARV-47115,18</td>
<td>Nausea, arthralgia, fatigue, decreased appetite</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate aminotransferase; PROTAC, proteolysis-targeting chimera. 

**KEY REFERENCES**


For full reference list, visit

http://www.gotopaper.com/ga/oncldec211fc
4. There is no definition for Grade 2 in CTCAE v.4.03.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.

Effects of TUKYSA on Other Drugs

**CYP3A Substrates:** Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

**P-glycoprotein (P-gp) Substrates:** Concomitant use of TUKYSA with a P-gp substrate increased the plasma concentrations of P-gp substrate, which may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

**US IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information. Based on findings in animals and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures \( \geq 1.3 \) times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus.

**Lactation**

Risk Summary: TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information. There are no data on the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose.

**Females and Males of Reproductive Potential**

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

**Pregnancy Testing:** Verify the pregnancy status of females of reproductive potential prior to initiating treatment with TUKYSA.

**Contraception:**

- Females: Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.
- Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose.

**Infertility:** Based on findings from animal studies, TUKYSA may impair male and female fertility.

**Pediatric Use:** The safety and effectiveness of TUKYSA in pediatric patients have not been established.

**Geriatric Use:** In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were ≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 54% in patients ≥ 65 years compared to 24% in patients < 65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥ 65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

**Renal Impairment:** The use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (Clcr < 30 mL/min estimated by Cockcroft-Gault Equation), because capecitabine is contraindicated in patients with severe renal impairment. Refer to the Full Prescribing Information of capecitabine for additional information on severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [Clcr] 30 to 89 mL/min).

**Hepatic Impairment:** Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment. No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

**DRUG INTERACTIONS**

**Effects of Other Drugs on TUKYSA**

**Strong CYP3A Inducers or Moderate CYP2C8 Inducers:** Concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inducer decreased tucatinib plasma concentrations, which may reduce TUKYSA activity. Avoid concomitant use of TUKYSA with a strong CYP3A inducer or a moderate CYP2C8 inducer.

**Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor increased tucatinib plasma concentrations, which may increase the risk of TUKYSA toxicity. Avoid concomitant use of TUKYSA with a strong CYP2C8 inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

**Effects of TUKYSA on Other Drugs**

**CYP3A Substrates:** Concomitant use of TUKYSA with a CYP3A substrate increased the plasma concentrations of CYP3A substrate, which may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA with CYP3A substrates,
TUKYSA® (tucatinib) tablets, for oral use

Brief summary of Prescribing Information (PI). See full PI. Rx Only

INDICATIONS AND USAGE

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

DOSEAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of TUKYSA is 300 mg taken orally twice daily in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity.

Advise patients to swallow TUKYSA tablets whole and not to chew, crush, or split prior to swallowing. Advise patients not to ingest tablet if it is broken, cracked, or not otherwise intact.

Advise patients to take TUKYSA approximately 12 hours apart and at the same time each day with or without a meal. If the patient vomits or misses a dose of TUKYSA, instruct the patient to take the next dose at its usual scheduled time.

When given in combination with TUKYSA, the recommended dosage of capecitabine is 1000 mg/m² orally twice daily taken within 30 minutes after a meal. TUKYSA and capecitabine can be taken at the same time. Refer to the Full Prescribing Information for trastuzumab and capecitabine for additional information.

Dosage Modifications for Adverse Reactions

The recommended TUKYSA dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2. Refer to the Full Prescribing Information for trastuzumab and capecitabine for information about dosage modifications for these drugs.

Table 1: Recommended TUKYSA Dose Reductions for Adverse Reactions

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>Recommended TUKYSA Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>250 mg orally twice daily</td>
</tr>
<tr>
<td>Second</td>
<td>200 mg orally twice daily</td>
</tr>
<tr>
<td>Third</td>
<td>150 mg orally twice daily</td>
</tr>
</tbody>
</table>

Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally twice daily.

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Severity</th>
<th>TUKYSA Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea1</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 without anti-diarrheal treatment</td>
<td></td>
</tr>
<tr>
<td>Grade 3 with anti-diarrheal treatment</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>Hepatotoxicity2</td>
<td>Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 2 bilirubin (&gt;1.5 to 3 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.</td>
</tr>
<tr>
<td>Grade 3 ALT or AST (&gt; 5 to 20 × ULN) OR Grade 3 bilirubin (&gt; 3 to 10 × ULN)</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 4 ALT or AST (&gt; 20 × ULN) OR Grade 4 bilirubin (&gt; 10 × ULN)</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>ALT or AST &gt; 3 × ULN AND Bilirubin &gt; 2 × ULN</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
<tr>
<td>Other adverse reactions1</td>
<td>Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue TUKYSA.</td>
</tr>
</tbody>
</table>

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

2. Abnormalities: ULN = upper limit of normal; ALT = alanine aminotransferase; AST = aspartate aminotransferase

Dosage Modifications for Severe Hepatic Impairment: For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily.

Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors: Avoid concomitant use of strong CYP2C8 inhibitors with TUKYSA. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the TUKYSA dose that was taken prior to initiating the inhibitor.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 61% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 diarrhea and 0.5% with Grade 4 diarrhea. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of TUKYSA in 6% of patients and discontinuation of TUKYSA in 1% of patients. Prophylactic use of antidiarrheal treatment was not required in HER2CLIMB. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Hepatotoxicity: TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase > 5 × ULN, 6% had an AST increase > 5 × ULN, and 1.5% had a bilirubin increase > 3 × ULN (Grade ≥ 3). Hepatotoxicity led to dose reduction of TUKYSA in 8% of patients and discontinuation of TUKYSA in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Embryo-Fetal Toxicity: Based on findings from animal studies and its mechanism of action, TUKYSA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information for trastuzumab and capecitabine for pregnancy and contraception information.

ADVERSE REACTIONS

Clinical Trials Experience

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

HER2-Positive Metastatic Breast Cancer (HER2CLIMB)

The safety of TUKYSA in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB. Patients received either TUKYSA 300 mg twice daily plus trastuzumab and capecitabine (n=404) or placebo plus trastuzumab and capecitabine (n=197). The median duration of treatment was 5.8 months (range: 3 days, 2.9 years) for the TUKYSA arm. Serious adverse reactions occurred in 26% of patients who received TUKYSA. Serious adverse reactions in ≥ 2% of patients who received TUKYSA were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and sepsis (2%). Fetal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions leading to treatment discontinuation occurred in 6% of patients who received TUKYSA. Adverse reactions leading to treatment discontinuation of TUKYSA in ≥ 1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions leading to dose reduction occurred in 21% of patients who received TUKYSA. Adverse reactions leading to dose reduction of TUKYSA in <2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (>20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Table 3: Adverse Reactions (>10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥5% Compared to Placebo in HER2CLIMB (All Grades)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>TUKYSA + Trastuzumab + Capecitabine (N = 404)</th>
<th>Placebo + Trastuzumab + Capecitabine (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (%)</td>
<td>Grade (%)</td>
<td>Grade (%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>53</td>
<td>59</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Gastrointestinal disorders

- Diarrhea: 51
- Nausea: 58
- Vomiting: 36
- Stomatitis: 32

Skin and subcutaneous tissue disorders

- Palmar-plantar erythrodysesthesia syndrome: 63
- Rash: 20

Hepatobiliary disorders

- Hepatotoxicity: 42

Metabolism and nutrition disorders

- Decreased appetite: 25
ONC1221_852-CV4_Seagen.indd   854

Monitor ALT, AST, and bilirubin prior to starting TUKYSA.

Hepatotoxicity:
- **•**

**Warnings and Precautions**

**Important Safety Information**

**Warnings and Precautions**

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of anti-diarrheal treatment was not required in HER2CLIMB. If diarrhea occurs, administer anti-diarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN. 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

**Adverse Reactions**

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%). The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

**In combination with trastuzumab + capecitabine**

**TUKYSA extended overall survival**

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, PPE, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

**RAISING THE STANDARD FOR SURVIVAL**
If diarrhea occurs, administer antidiarrheal treatment as indicated.

**Warnings and Precautions**

**Important Safety Information**

**TUKYSA extended overall survival**

**NUMBER AT RISK**

**TUKYSA arm: 130/410**

**Control arm**

**NUMBER OF EVENTS**

**PFS AT 12 MONTHS**

**-3x as many patients were progression-free**

**TUKYSA ARM**

33% (33.1%; 95% CI: 26.6-39.7)

**CONTROL ARM**

12% (12.3%; 95% CI: 8.0-20.9)

*Study design: HER2CLIMB was a randomized [2:1], double-blind, placebo-controlled trial of 612 patients with HER2+ MBC who received TUKYSA + trastuzumab + capecitabine (TUKYSA arm: n = 410) or placebo + trastuzumab + capecitabine (control arm; n = 202). Primary endpoint was PFS (time from randomization to documented disease progression or death from any cause) in the first 480 randomized patients. Secondary endpoints assessed in all randomized patients included OS (time from randomization to death from any cause). PFS was evaluated in accordance with RECIST criteria, version 1.1, by means of BICR.*

This exploratory analysis is descriptive only. These are estimates and not exact numbers. HER2CLIMB was not powered to assess a statistical difference between treatment groups at this time point.

BICR = blind independent central review; CI = confidence interval; HER = human epidermal growth factor receptor; HR = hazard ratio; MBC = metastatic breast cancer; OS = overall survival; PFS = progression-free survival; PPE = palmar-plantar erythrodysesthesia; RECIST = Response Evaluation Criteria in Solid Tumors.

**Lab Abnormalities**

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.

The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

**Drug Interactions**

- **Strong CYP3A/Moderate CYP2C8 Inducers:** Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.

- **Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

- **CYP3A Substrates:** Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.

- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

**Use in Specific Populations**

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.

- **Renal Impairment:** Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.

- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see Brief Summary of Prescribing Information on adjacent pages.

**References:**


Indication
TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Select Safety Information
Warnings and Precautions

• Diarrhea: TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

Reduced risk of disease progression or death by 46%
Median PFS: 7.8 months (95% CI: 7.5–9.6) vs 5.6 months (95% CI: 4.2–7.1); HR = 0.54 (95% CI: 0.42–0.71); P < 0.00001
Extended median OS by 4.5 months
Median OS: 21.9 months (95% CI: 18.3–31.0) vs 17.4 months (95% CI: 13.6–19.9); HR = 0.66 (95% CI: 0.50–0.87); P = 0.0048

The trial studied patients who had received prior trastuzumab, pertuzumab, and T-DM1 in the neoadjuvant, adjuvant, or metastatic setting.1
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