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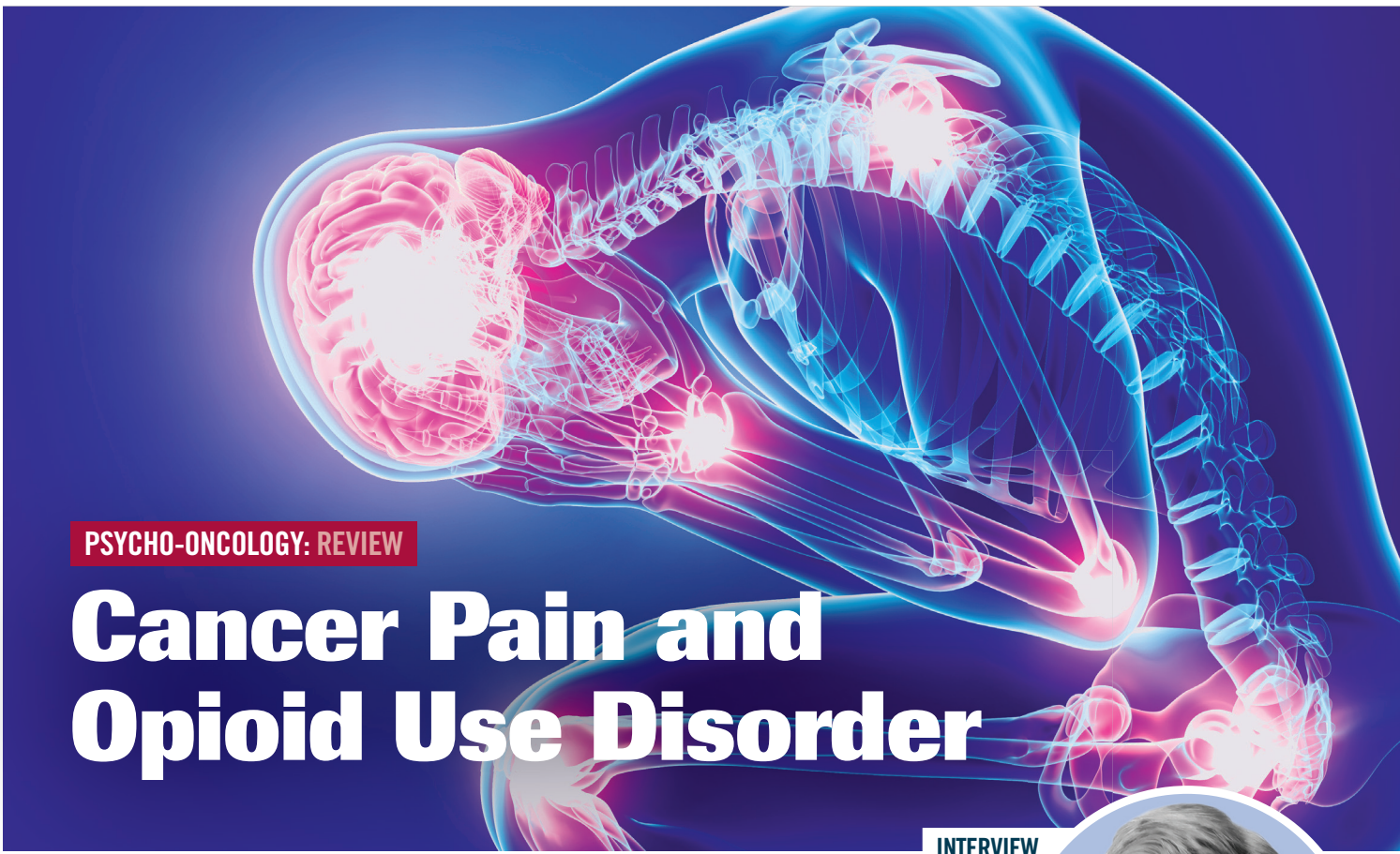

PSYCHO-ONCOLOGY: REVIEW

Cancer Pain and Opioid Use Disorder

INTERVIEW

Mark A. Socinski, MD, on Progression of Lung Cancer Treatment

MARK A. SOCINSKI, MD

ONCOLOGY® SEPTEMBER 2022 VOL. 36 NO. 09

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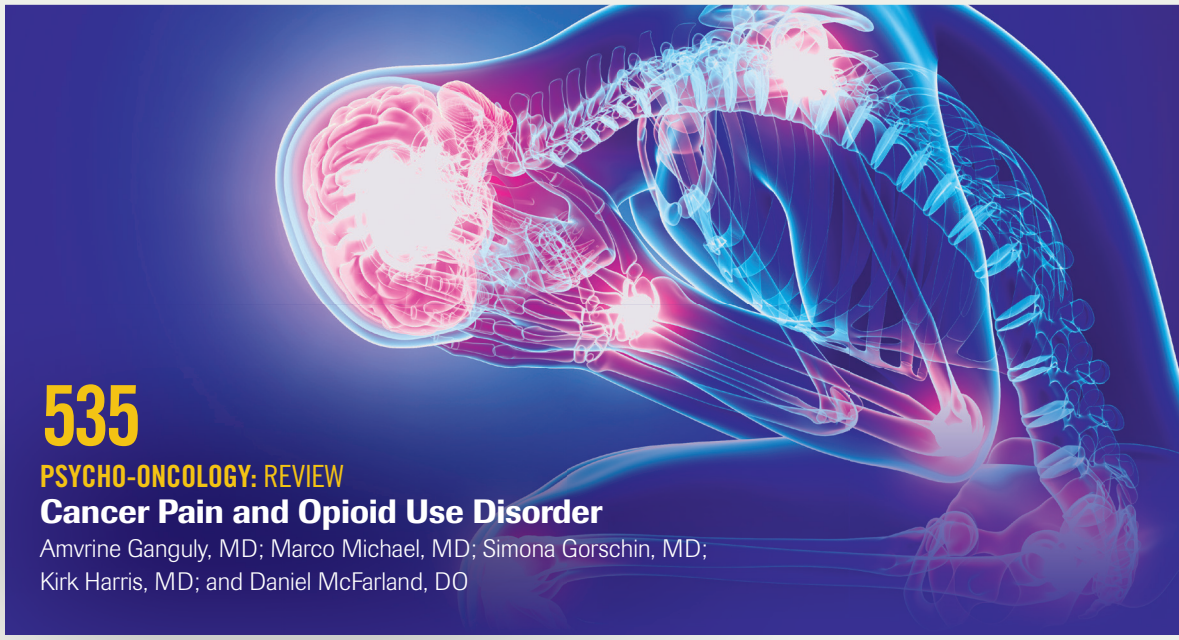

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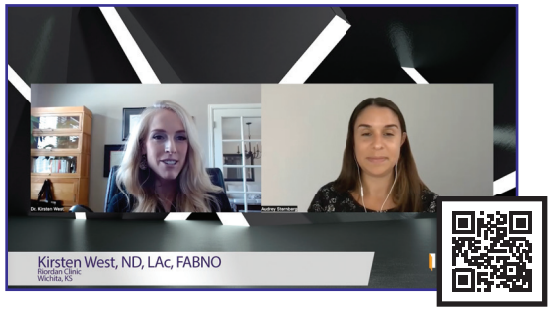

INSIDE THE PRACTICE

INSIDE INTEGRATIVE ONCOLOGY

CancerNetwork® with Kirsten West, ND, LAc, FABNO, a naturopathic doctor who specializes in integrative oncology and recently joined the Riordan Clinic based in Wichita, Kansas. In the interview, West dives into the field of integrative oncology by explaining its importance to the overall cancer care paradigm. She details recent advances in the field and spotlights how she and her colleagues play an important role in the multidisciplinary oncology team.

TO WATCH VISIT: **bit.ly/3e71Mze**

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PRACTICAL, PEER-REVIEWED PERSPECTIVES
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SEPTEMBER 2022 ▪ VOL. 36 ▪ NO. 09

Howard S. Hochster, MD
ASSOCIATE DIRECTOR FOR CLINICAL RESEARCH,
RUTGERS CANCER INSTITUTE OF NEW JERSEY
DIRECTOR OF ONCOLOGY RESEARCH,
RWJBARNABAS HEALTH

Is Drug Price Negotiation a Concept Whose Time Has Come?

As I write this, the US Congress has just approved the Inflation Reduction Act of 2022, which includes a provision that Medicare be allowed to negotiate drug prices with pharmaceutical companies. The first steps will not happen until 2026, when 10 of the most popular drugs will be subject to drug price negotiation. Additional provisions of the bill will make key changes to reimbursement to patients enrolled in Medicare Part D.

Why is this important? Currently, according to US regulations and law, Medicare must pay for any drug approved by the FDA. Prices are set by the drug companies. That's it. We pay the price the drug companies set, which is mainly related to the price set for the last drug approved for the indication or disease, plus an incremental cost. There is no relationship to complexity of the drug, cost of manufacture, or developmental costs. The incremental costs have doubled the cost of some drugs over a few years. And surprisingly, for those who studied economics, even with more competition (eg, all the anti–PD-1 drugs now available), the prices do not come down.

This pricing structure stands in contrast to almost every other country where drug prices are negotiated with the regulatory agencies. In England, for example, a second process to assess the cost effectiveness of the agent is required by the National Institute for Health and Care Excellence committee for reimbursement by the National Health Service. One way to improve cost effectiveness is to reduce cost. And that explains why brand-name drugs are generally cheaper in every other country. This also explains why many patients order "gray market" drugs from Canada, Mexico, or Europe, which may be even cheaper than their co-pay amounts in the United States. For example, a newer colon cancer drug for refractory disease, Lonsurf (trifluridine/tipiracil), can cost $20,000 per month for 70 mg twice daily. A patient I saw recently could not afford the $3000 per month co-pay, and he had too much income to qualify for patient assistance. He was stuck and had to take out a second mortgage on his house to get the necessary funds. And who hasn't experienced heartbreak and major dismay such as when a patient tells you that she did not take her pain medications this month because the choice was either paying for the drugs or feeding her family? These are examples of the economic toxicity we see in our daily practice.

With the new legislation, price negotiation won't start for another few years and only for the top 10 prescription drugs, which are unlikely to include chemotherapy agents. This is a small step in the direction of leveling the playing field, because patients in the US pay more than their fair share.

In addition, Medicare only paid for drugs administered in the doctor's office before Medicare "part D" was enacted in 2006 (following compromises with industry lobbyists). The system is far from perfect. Patients are left with a "donut hole," or coverage gap, after a basic amount is paid, at which point they have a 25% co-pay. In 2022, Medicare part D (outpatient pharmacy benefits) covers an initial cost of approximately $4330 then has a donut hole up to $6550 for which the patient co-pay is 25%. Patients falling into that coverage gap will have major outlays. The new legislation eliminates this coverage gap and the 5% co-pay after $7000.

Many commentators have opined that this will cause seriously decreased innovation and new drugs. This is unlikely to be the case. Too much is at stake for these companies to stop new drug development. Furthermore, much of new drug discovery occurs by licensing novel technology from universities. These discoveries and their intellectual property may be licensed by biotech firms, and sometimes these biotech firms are bought out by large pharmaceutical companies. You, the taxpayers of the United States, are paying for much of this basic academic research leading to new drugs, yet you don't see many of the benefits.

Here are some ways to save money: end direct-to-consumer advertising; remove pharmacy benefit managers to bring down purchase costs; make biosimilars interchangeable (just as with interchangeable generic small molecule drugs as allowed by the Hatch-Waxman Act) and end branded biosimilars; and end the process of prior authorization, which costs more to the health care system than it saves.

Other countries pay less for their medications, and we in the United States end up paying more than our fair share. Negotiations by Medicare and the VA system should help rebalance our costs vis-à-vis what everyone else in the world pays. ■

NCCN RECOMMENDED

National Comprehensive Cancer Network® (NCCN®)–recommended treatment option for certain patients with RET+ mNSCLC and RET+ advanced or metastatic thyroid carcinoma[2,3]*†

*See the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC and thyroid carcinoma for detailed recommendations, including other preferred treatment options.

†For select patients with recurrent/persistent locoregional or distantly metastatic RET mutation-positive medullary thyroid carcinoma; for structurally persistent/recurrent locoregional or distantly metastatic RET fusion-positive differentiated thyroid cancer not amenable to RAI therapy; and for metastatic RET fusion-positive anaplastic thyroid carcinoma.

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

RAI=radioactive iodine.

INDICATIONS

GAVRETO® (pralsetinib) is indicated for the treatment of:

- Adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
- Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

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

ARROW study design

Efficacy and safety with GAVRETO (400 mg orally once daily) were evaluated in patients with RET fusion+ mNSCLC, advanced or metastatic RET-mutant MTC, and advanced or metastatic RET fusion+ thyroid cancer in the ARROW study, a phase 1/2, single-arm, multicohort, multicenter clinical trial.[1,4] All patients must have had a non-resectable RET-altered solid tumor or MTC per local assessment of tumor tissue and/or blood.[4] The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR), as assessed by a blinded independent central review (BICR) according to RECIST v1.1.[1]

IMPORTANT SAFETY INFORMATION

Interstitial Lung Disease (ILD)/Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3/4, and 0.5% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD.

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity.

Please see additional Important Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.

Efficacy and safety data of GAVRETO in advanced thyroid cancers[1]

Select baseline characteristics from the U.S. Prescribing Information (USPI)[1]

MTC: cabozantinib- and vandetanib-naïve patients (n=29): The median age was 61 years (range: 19-81); 72% were male and 14% had a history of CNS metastases.

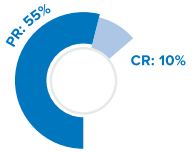
MTC: previously cabozantinib- and/or vandetanib-treated patients (n=55): The median age was 59 years (range: 25-83); 69% were male and 7% had a history of CNS metastases.

RET fusion-positive thyroid cancer (n=9): The median age was 61 years (range: 46-74); 67% were male and 56% had a history of CNS metastases.

For additional baseline characteristics, refer to the USPI.
CNS=central nervous system; RECIST=Response Evaluation Criteria in Solid Tumors.

GAVRETO demonstrated robust and durable response in advanced or metastatic RET-mutant MTC and advanced or metastatic RET fusion+ thyroid cancer[1,5]

MTC: cabozantinib- and vandetanib-naïve (n=29)*

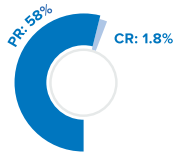


66% ORR
(95% CI: 46%-82%)

Median DoR (n=19): NR
(NE-NE)

- 84% of patients continued to respond to treatment at 6 months†
- Median time to first response was 3.7 months (range: 1.7 months-11.1 months)[5]

MTC: prior cabozantinib and/or vandetanib (n=55)‡



60% ORR
(95% CI: 46%-73%)

Median DoR (n=33): NR
(15.1 months-NE)

- 79% of patients continued to respond to treatment at 6 months†
- Median time to first response was 3.7 months (range: 1.8 months-12.9 months)[5,6]

RET fusion+ thyroid cancer (n=9)§

89% ORR
(95% CI: 52%-100%)

Median DoR (n=8): NR
(NE-NE)

- 100% of patients continued to respond to treatment at 6 months†
- Median time to first response was 1.9 months (range: 1.8 months-5.5 months)[5,6]

Patients enrolled by July 11, 2019. Data cutoff: May 22, 2020.

*Twenty-eight percent (28%) had received up to 3 lines of prior systemic therapy (including 10% PD-1/PD-L1 inhibitors, 10% radioactive iodine, 3.4% kinase inhibitors).

†Calculated using the proportion of responders with an observed duration of response at least 6 months or greater.[1]

‡Patients had received a median of 2 prior therapies (range: 1-7).

§All patients (100%) had papillary thyroid cancer. Patients had received a median of 2 prior therapies (range: 1-8). Prior systemic treatments included prior radioactive iodine (100%) and prior sorafenib and/or lenvatinib (56%).

CI=confidence interval; CR=complete response; NE=not estimable; NR=not reached; PD-1/PD-L1=programmed cell-death protein 1/programmed death-ligand 1; PR=partial response.

Safety of GAVRETO in 138 patients with RET-altered thyroid cancers

The most common adverse reactions (≥15%) and Grades 3-4 laboratory abnormalities (≥2%) were[1]:

- Musculoskeletal pain‖ (42%), constipation (41%), hypertension (40%), fatigue‖ (38%), diarrhea‖ (34%), edema‖ (29%), cough‖ (27%), rash‖ (24%), headache‖ (24%), pyrexia (22%), dyspnea‖ (22%), peripheral neuropathy‖ (20%), dizziness‖ (19%), abdominal pain‖ (17%), dry mouth (17%), stomatitis‖ (17%), nausea (17%), dysgeusia‖ (17%), and decreased appetite (15%)
- Decreased lymphocytes (27%), decreased neutrophils (16%), decreased hemoglobin (13%), decreased calcium (corrected) (9%), decreased phosphate (8%), increased AST (4.3%), increased ALT (3.6%), decreased platelets (2.9%), and decreased sodium (2.2%)

‖For grouped terms, please refer to the USPI.
ALT=alanine aminotransferase; AST=aspartate aminotransferase.

IMPORTANT SAFETY INFORMATION

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.1% of patients treated with GAVRETO. Increased aspartate aminotransferase (AST) occurred in 69% of patients, including Grade 3/4 in 5% and increased alanine aminotransferase (ALT) occurred in 46% of patients, including Grade 3/4 in 6%. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years). Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity.

Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event. Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage.

Please see additional Important Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.

Efficacy and safety data of GAVRETO® (pralsetinib) in RET fusion+ mNSCLC[1]

Select baseline characteristics from the USPI[1]

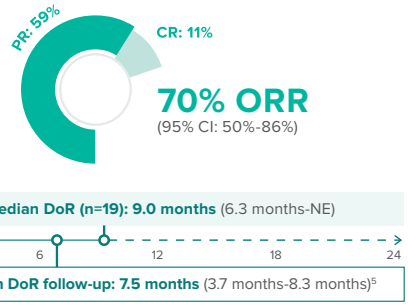
Treatment-naïve (n=27): The median age was 65 years (range: 30-87); 48% were male and 37% had either a history of or current CNS metastasis.

Previously platinum-treated (n=87): The median age was 60 years (range: 28-85); 51% were male and 43% had either a history of or current CNS metastasis.

For additional baseline characteristics, refer to the USPI.

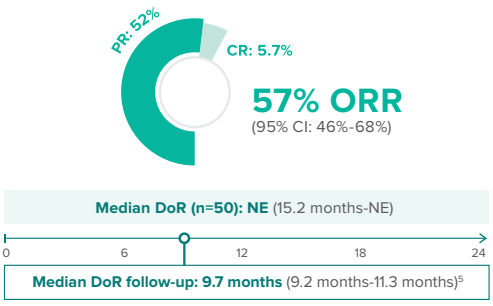
GAVRETO demonstrated robust and durable response in RET fusion+ mNSCLC patients treated with GAVRETO from the USPI[1,5]

Treatment-naïve patients (n=27)



- 58% of patients continued to respond to treatment at 6 months*
- Median time to first response was 1.9 months (range: 1.4 months-5.6 months)[5]

Previously platinum-treated patients (n=87)†



- 80% of patients continued to respond to treatment at 6 months*
- Median time to first response was 1.8 months (range: 1.3 months-9.1 months)[5]

Per initial protocol, treatment-naïve patients were included if they were deemed not eligible for platinum-based chemotherapy based on investigator assessment[7]

Patients enrolled by July 11, 2019. Data cutoff: Feb 13, 2020.
*Calculated using the proportion of responders with an observed duration of response at least 6 months or greater.[1]
†Patients received a median of 2 prior systemic therapies (range: 1-6); 45% of patients had prior anti-PD-1/PD-L1 therapy and 25% had prior kinase inhibitors.

Safety of GAVRETO in 220 patients with RET fusion+ mNSCLC

The most common adverse reactions (≥15%) and Grades 3-4 laboratory abnormalities (≥2%) were[1†]:

- Fatigue‡ (35%), constipation (35%), musculoskeletal pain‡ (32%), hypertension‡ (28%), diarrhea‡ (24%), cough‡ (23%), pyrexia (20%), edema‡ (20%), pneumonia‡ (17%), and dry mouth (16%)
- Decreased lymphocytes (19%), decreased neutrophils (16%), decreased phosphate (11%), decreased hemoglobin (9%), decreased sodium (7%), decreased platelets (3.2%), increased AST (2.3%), and increased ALT (2.3%)

†The safety of GAVRETO 400 mg orally once daily was evaluated in both treatment-naïve and previously platinum-treated mNSCLC patients.
‡For grouped terms, please refer to the USPI.

IMPORTANT SAFETY INFORMATION

Tumor Lysis Syndrome (TLS): Cases of TLS have been reported in patients with medullary thyroid carcinoma receiving GAVRETO. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing. Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

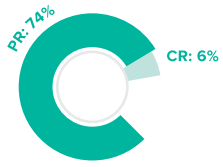
Please see additional Important Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.

Exploratory follow-up analyses of treatment-naïve mNSCLC patients[5]

These analyses include treatment-naïve patients enrolled through May 22, 2020, which include the patients from the pivotal analysis in the USPI. These results are not included in the GAVRETO labeling. **As these were not prespecified analyses, data must be interpreted with caution.**

All treatment-naïve patients

Overall Response Rate (n=68)



79% ORR
(95% CI: 68%-88%)

Duration of Response (n=54)

Median DoR: Not Reached (9 months-NR)
Median DoR follow-up: 7.4 months
(6.4 months-9.5 months)

Patients enrolled by May 22, 2020.
Data cutoff: Nov 6, 2020.

Post hoc analyses of treatment-naïve patients

Initially, the ARROW protocol included treatment-naïve patients who were not candidates for standard therapy. In July 2019, the protocol was amended to expand the eligibility criteria to include patients who were eligible for standard therapy.[7]

Pre-protocol amendment (n=43)

74% ORR

PR=65%, CR=9% (95% CI: 59%-87%)
Median DoR (n=32): 11 months
(7.4 months-NR)

Select baseline characteristics

- Median age: 65 years (30-87)
- Gender: female 44%, male 56%
- History of or current CNS metastases at baseline: 35%

Post-protocol amendment (n=25)

88% ORR

All responses were partial (95% CI: 69%-98%)
Median DoR (n=22): Not Reached
(NR-NR)

Select baseline characteristics

- Median age: 54 years (35-80)
- Gender: female 56%, male 44%
- History of or current CNS metastases at baseline: 28%

All other baseline characteristics were generally balanced between the pivotal data included in the USPI and exploratory follow-up populations.[1,5]

Adverse reactions (≥15%) and Grades 3-4 laboratory abnormalities (≥2%) in RET fusion+ mNSCLC patients (n=281) were generally consistent with the pivotal data included in the USPI[1,5]

IMPORTANT SAFETY INFORMATION

Based on findings from animal studies and its mechanism of action, GAVRETO can cause **fetal harm** when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose. Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose.

Common adverse reactions (≥25%) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. **Common Grade 3/4 laboratory abnormalities (≥2%)** were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased AST, increased ALT, decreased platelets and increased alkaline phosphatase.

Avoid coadministration of GAVRETO with **strong CYP3A inhibitors or combined P-gp and strong CYP3A inhibitors**. If coadministration cannot be avoided, reduce the GAVRETO dose. Avoid coadministration of GAVRETO with **strong CYP3A inducers**. If coadministration cannot be avoided, increase the GAVRETO dose.

You may report side effects to the FDA at **1-800-FDA-1088**. You may also report side effects to Genentech at **1-888-835-2555**.

Please see additional Important Safety Information throughout and Brief Summary of the full Prescribing Information for GAVRETO on adjacent pages.

References: 1. GAVRETO Prescribing Information. Genentech, Inc. April 2021. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed December 13, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Carcinoma V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed December 7, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **4.** Phase 1/2 study of the highly-selective RET inhibitor, pralsetinib (BLU-667), in patients with thyroid cancer, non-small cell lung cancer, and other advanced solid tumors (ARROW). ClinicalTrials.gov identifier: NCT03037385. https://clinicaltrials.gov/ct2/show/NCT03037385. Accessed June 2, 2021. **5.** Data on file. Blueprint Medicines Corporation. Cambridge, MA; 2020. **6.** Subbiah V, Hu MI, Wirth LJ, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. *Lancet Diabetes Endocrinol*. 2021;9(8):491-501. **7.** Gainor JF, Curigliano G, Kim DW, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol*. 2021;22(7):959-969.

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GAVRETO® (pralsetinib)
100 mg capsules, for oral use
Initial U.S. Approval: 2020

This is a brief summary of information about GAVRETO. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

1.1 Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer

GAVRETO is indicated for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.

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

1.2 *RET*-Mutant Medullary Thyroid Cancer

GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.3 *RET* Fusion-Positive Thyroid Cancer

GAVRETO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate).

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with GAVRETO. Pneumonitis occurred in 10% of patients who received GAVRETO, including 2.7% with Grade 3-4, and 0.5% with fatal reactions.

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold GAVRETO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue GAVRETO based on severity of confirmed ILD *[see Dosage and Administration (2.3)]*.

5.2 Hypertension

Hypertension occurred in 29% of patients, including Grade 3 hypertension in 14% of patients *[see Adverse Reactions (6.1)]*. Overall, 7% had their dose interrupted and 3.2% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate GAVRETO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating GAVRETO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue GAVRETO based on the severity *[see Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

Serious hepatic adverse reactions occurred in 2.1% of patients treated for GAVRETO. Increased AST occurred in 69% of patients, including Grade 3 or 4 in 5% and increased ALT occurred in 46% of patients, including Grade 3 or 4 in 6% *[see Adverse Reactions (6.1)]*. The median time to first onset for increased AST was 15 days (range: 5 days to 1.5 years) and increased ALT was 22 days (range: 7 days to 1.7 years).

Monitor AST and ALT prior to initiating GAVRETO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue GAVRETO based on severity *[see Dosage and Administration (2.3)]*.

5.4 Hemorrhagic Events

Serious, including fatal, hemorrhagic events can occur with GAVRETO. Grade ≥ 3 hemorrhagic events occurred in 2.5% of patients treated with GAVRETO including one patient with a fatal hemorrhagic event.

Permanently discontinue GAVRETO in patients with severe or life-threatening hemorrhage *[see Dosage and Administration (2.3)]*.

5.5 Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS) have been reported in patients with medullary thyroid carcinoma receiving GAVRETO *[see Adverse Reactions (6.1)]*. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

5.6 Risk of Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, GAVRETO has the potential to adversely affect wound healing.

Withhold GAVRETO for at least 5 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of GAVRETO after resolution of wound healing complications has not been established.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Hemorrhagic Events *[see Warnings and Precautions (5.4)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.5)]*
- Risk of Impaired Wound Healing *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

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

The pooled safety population in the WARNINGS AND PRECAUTIONS reflect exposure to GAVRETO as a single agent at 400 mg orally once daily in 438 patients with *RET*-altered solid tumors, including with *RET* fusion-positive NSCLC (n = 220), and *RET*-altered thyroid cancer (n = 138), in ARROW *[see Clinical Studies (14)]*. Among 438 patients who received GAVRETO, 47% were exposed for 6 months or longer and 23% were exposed for greater than one year.

The most common adverse reactions (≥ 25%) were constipation, hypertension, fatigue, musculoskeletal pain and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, decreased phosphate, decreased calcium (corrected), decreased sodium, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased platelets, and increased alkaline phosphatase.

RET Fusion-Positive Non-Small Cell Lung Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 220 patients with metastatic rearranged during transfection (*RET* fusion-positive) non-small cell lung cancer (NSCLC) in ARROW *[see Clinical Studies (14.1)]*. Among the 220 patients who received GAVRETO, 42% were exposed for 6 months or longer and 19% were exposed for greater than one year.

The median age was 60 years (range: 26 to 87 years); 52% were female, 50% were White, 41% were Asian, and 4% were Hispanic/Latino.

Serious adverse reactions occurred in 45% of patients who received GAVRETO. The most frequent serious adverse reaction (in ≥ 2% of patients) was pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia. Fatal adverse reactions occurred in 5% of patients; fatal adverse reactions which occurred in > 1 patient included pneumonia (n = 3) and sepsis (n = 2).

Permanent discontinuation due to an adverse reaction occurred in 15% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included pneumonitis (1.8%), pneumonia (1.8%), and sepsis (1%).

Dosage interruptions due to an adverse reaction occurred in 60% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, pneumonitis, anemia, hypertension, pneumonia, pyrexia, increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, fatigue, leukopenia, thrombocytopenia, vomiting, increased alanine aminotransferase (ALT), sepsis, and dyspnea.

Dose reductions due to adverse reactions occurred in 36% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, pneumonitis, neutrophil count decreased, fatigue, hypertension, pneumonia, and leukopenia.

Table 4 summarizes the adverse reactions in *RET* Fusion-Positive NSCLC Patients in ARROW.

Table 4: Adverse Reactions (≥ 15%) in *RET* Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

Adverse Reactions	GAVRETO N=220	
	Grades 1-4 (%)	Grades 3-4 (%)
General		
Fatigue[1]	35	2.3*
Pyrexia	20	0
Edema[2]	20	0
Gastrointestinal		
Constipation	35	1*
Diarrhea[3]	24	3.2*
Dry Mouth	16	0
Musculoskeletal Disorders		
Musculoskeletal Pain[4]	32	0
Vascular		
Hypertension[5]	28	14*
Respiratory, thoracic and mediastinal		
Cough[6]	23	0.5*
Infections		
Pneumonia[7]	17	8

[1] Fatigue includes fatigue, asthenia
[2] Edema includes edema peripheral, face edema, periorbital edema, eyelid edema, edema generalized, swelling
[3] Diarrhea includes diarrhea, colitis, enteritis
[4] Musculoskeletal pain includes back pain, myalgia, arthralgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal stiffness, arthritis, spinal pain
[5] Hypertension includes hypertension, blood pressure increased
[6] Cough includes cough, productive cough, upper-airway cough syndrome
[7] Pneumonia includes pneumonia, atypical pneumonia, lung infection, pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia influenza, pneumonia streptococcal
*Only includes a Grade 3 adverse reaction

Table 5 summarizes the laboratory abnormalities in ARROW.

Table 5: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in *RET* Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW

Laboratory Abnormality	GAVRETO N=220	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Increased AST	74	2.3
Increased ALT	49	2.3
Increased alkaline phosphatase	42	1.8
Decreased calcium (corrected)	39	1.8

Table 5: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in *RET* Fusion-Positive NSCLC Patients Who Received GAVRETO in ARROW (cont'd)

Laboratory Abnormality	GAVRETO N=220	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Decreased albumin	36	0
Decreased phosphate	35	11
Increased creatinine	33	0.5
Decreased sodium	29	7
Increased potassium	26	0.9
Hematology		
Decreased neutrophils	61	16
Decreased hemoglobin	58	9
Decreased lymphocytes	56	19
Decreased platelets	27	3.2

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 216 to 218 patients.

Clinically relevant laboratory abnormalities < 20% of patients who received GAVRETO included increased phosphate (10%).

RET-altered Thyroid Cancer

The safety of GAVRETO was evaluated as a single agent at 400 mg orally once daily in 138 patients with *RET*-altered Thyroid Cancer in ARROW *[see Clinical Studies (14.2, 14.3)]*. Among the 138 patients who received GAVRETO, 68% were exposed for 6 months or longer, and 40% were exposed for greater than one year.

The median age was 59 years (range: 18 to 83 years); 36% were female, 74% were White, 17% were Asian, and 6% were Hispanic/Latino.

Serious adverse reactions occurred in 39% of patients who received GAVRETO. The most frequent serious adverse reactions (in ≥ 2% of patients) were pneumonia, pneumonitis, urinary tract infection, pyrexia, fatigue, diarrhea, dizziness, anemia, hyponatremia, and ascites. Fatal adverse reaction occurred in 2.2% of patients; fatal adverse reactions that occurred in > 1 patient included pneumonia (n=2).

Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received GAVRETO. Adverse reactions resulting in permanent discontinuation which occurred in > 1 patient included fatigue, pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 67% of patients who received GAVRETO. Adverse reactions requiring dosage interruption in ≥ 2% of patients included neutropenia, hypertension, diarrhea, fatigue, pneumonitis, anemia, increased blood creatine phosphokinase, pneumonia, urinary tract infection, musculoskeletal pain, vomiting, pyrexia, increased AST, dyspnea, hypocalcemia, cough, thrombocytopenia, abdominal pain, increased blood creatinine, dizziness, headache, decreased lymphocyte count, stomatitis, and syncope.

Dose reductions due to adverse reactions occurred in 44% of patients who received GAVRETO. Adverse reactions requiring dosage reductions in ≥ 2% of patients included neutropenia, anemia, hypertension, increased blood creatine phosphokinase, decreased lymphocyte count, pneumonitis, fatigue and thrombocytopenia.

Table 6 summarizes the adverse reactions occurring in *RET*-altered Thyroid Cancer Patients in ARROW.

Table 6: Adverse Reactions (≥ 15%) in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

Adverse Reactions	GAVRETO N=138	
	Grades 1-4 (%)	Grades 3-4 (%)
Musculoskeletal		
Musculoskeletal Pain[1]	42	0.7*
Gastrointestinal		
Constipation	41	0.7*
Diarrhea[2]	34	5*

Table 6: Adverse Reactions (≥ 15%) in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW (cont'd)

Adverse Reactions	GAVRETO N=138	
	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal		
Abdominal Pain[3]	17	0.7*
Dry Mouth	17	0
Stomatitis[4]	17	0.7*
Nausea	17	0.7*
Vascular		
Hypertension	40	21*
General		
Fatigue[5]	38	6*
Edema[6]	29	0
Pyrexia	22	2.2*
Nervous System		
Headache[7]	24	0
Peripheral Neuropathy[8]	20	0
Dizziness[9]	19	0.7*
Dysgeusia[10]	17	0
Respiratory		
Cough[11]	27	1.4*
Dyspnea[12]	22	2.2*
Skin and Subcutaneous		
Rash[13]	24	0
Metabolism and Nutrition		
Decreased Appetite	15	0

[1] Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain
[2] Diarrhea includes colitis, diarrhea
[3] Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, epigastric discomfort
[4] Stomatitis includes mucosal inflammation, stomatitis, tongue ulceration
[5] Fatigue includes asthenia, fatigue
[6] Edema includes eyelid edema, face edema, edema, edema peripheral, periorbital edema
[7] Headache includes headache, migraine
[8] Peripheral neuropathy includes dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
[9] Dizziness includes dizziness, dizziness postural, vertigo
[10] Dysgeusia includes ageusia, dysgeusia
[11] Cough includes cough, productive cough, upper-airway cough syndrome
[12] Dyspnea includes dyspnea, dyspnea exertional
[13] Rash includes dermatitis, dermatitis acneiform, eczema, palmar-plantar, erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular
* Only includes a Grade 3 adverse reaction

Clinically relevant adverse reactions in < 15% of patients who received GAVRETO included tumor lysis syndrome and increased creatine phosphokinase.

Table 7 summarizes the laboratory abnormalities occurring in *RET*-altered Thyroid Cancer Patients in ARROW.

Table 7: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW

Laboratory Abnormality	GAVRETO N=138	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Decreased calcium (corrected)	70	9
Increased AST	69	4.3
Increased ALT	43	3.6

Table 7: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in *RET*-altered Thyroid Cancer Patients Who Received GAVRETO in ARROW (cont'd)

Laboratory Abnormality	GAVRETO N=138	
	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Increased creatinine	41	0
Decreased albumin	41	1.5
Decreased sodium	28	2.2
Decreased phosphate	28	8
Decreased magnesium	27	0.7
Increased potassium	26	1.4
Increased bilirubin	24	1.4
Increased alkaline phosphatase	22	1.4
Hematology		
Decreased lymphocytes	67	27
Decreased hemoglobin	63	13
Decreased neutrophils	59	16
Decreased platelets	31	2.9

Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 135 to 138 patients.

Clinically relevant laboratory abnormalities in patients who received GAVRETO included increased phosphate (40%).

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on GAVRETO

Strong CYP3A Inhibitors

Avoid coadministration with strong CYP3A inhibitors. Coadministration of GAVRETO with a strong CYP3A inhibitor increases pralsetinib exposure, which may increase the incidence and severity of adverse reactions of GAVRETO.

Avoid coadministration of GAVRETO with combined P-gp and strong CYP3A inhibitors. If coadministration with a combined P-gp and strong CYP3A inhibitor cannot be avoided, reduce the GAVRETO dose *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

Strong CYP3A Inducers

Coadministration of GAVRETO with a strong CYP3A inducer decreases pralsetinib exposure, which may decrease efficacy of GAVRETO. Avoid coadministration of GAVRETO with strong CYP3A inducers. If coadministration of GAVRETO with strong CYP3A inducers cannot be avoided, increase the GAVRETO dose *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, GAVRETO can cause fetal harm when administered to a pregnant woman. There are no available data on GAVRETO use in pregnant women to inform drug-associated risk. Oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in malformations and embryolethality at maternal exposures below the human exposure at the clinical dose of 400 mg once daily (see data). Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

In an embryo-fetal development study, once daily oral administration of pralsetinib to pregnant rats during the period of organogenesis resulted in 100% post-implantation loss at dose levels ≥20 mg/kg (approximately 1.8 times the human exposure based on area under the curve [AUC] at the clinical dose of 400 mg). Post-implantation loss also occurred at the 10 mg/kg dose level (approximately 0.6 times the human exposure based

on AUC at the clinical dose of 400 mg). Once daily oral administration of pralsetinib at dose levels ≥ 5 mg/kg (approximately 0.2 times the human AUC at the clinical dose of 400 mg) resulted in an increase in visceral malformations and variations (absent or small kidney and ureter, absent uterine horn, malpositioned kidney or testis, retroesophageal aortic arch) and skeletal malformations and variations (vertebral and rib anomalies and reduced ossification).

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Based on animal data, GAVRETO can cause embryolethality and malformations at doses resulting in exposures below the human exposure at the clinical dose of 400 mg daily.

Pregnancy Testing

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

Contraception

GAVRETO can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with GAVRETO and for 2 weeks after the final dose. GAVRETO may render hormonal contraceptives ineffective.

Males

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

Infertility

Based on histopathological findings in the reproductive tissues of male and female rats and a dedicated fertility study in which animals of both sexes were treated and mated to each other, GAVRETO may impair fertility.

8.4 Pediatric Use

The safety and effectiveness of GAVRETO have been established in pediatric patients aged 12 years and older for *RET*-mutant MTC and *RET*-fusion thyroid cancer. Use of GAVRETO in this age group is supported by evidence from an adequate and well-controlled study of GAVRETO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the pharmacokinetics of pralsetinib (see data), that the exposure of pralsetinib is expected to be similar between adults and pediatric patients aged 12 years and older, and that the course of *RET*-mutant MTC and *RET*-fusion thyroid cancer is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*.

The safety and effectiveness of GAVRETO have not been established in pediatric patients with *RET* fusion-positive NSCLC or in pediatric patients younger than 12 years old with *RET*-mutant MTC or *RET*-fusion thyroid cancer.

Animal Toxicity Data

In a 4-week repeat-dose toxicology study in non-human primates, physeal dysplasia in the femur occurred at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. In rats there were findings of increased physeal thickness in the femur and sternum as well as tooth (incisor) abnormalities (fractures, dentin matrix alteration, ameloblast/odontoblast degeneration, necrosis) in both 4- and 13-week studies at doses resulting in exposures similar to the human exposure (AUC) at the clinical dose of 400 mg. Recovery was not assessed in the 13-week toxicology study, but increased physeal thickness in the femur and incisor degeneration did not show evidence of complete recovery in the 28-day rat study.

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

8.5 Geriatric Use

Of the 438 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30% were 65 years or older. No overall differences in pharmacokinetics (PK), safety or efficacy were observed in comparison with younger patients.

8.6 Hepatic Impairment

GAVRETO has not been studied in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3.0 × upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin > 3.0 × ULN and any AST). No dose adjustment is required for patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

17 PATIENT COUNSELING INFORMATION

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

ILD/Pneumonitis

Advise patients to contact their healthcare provider if they experience new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

Hypertension

Advise patients that they will require regular blood pressure monitoring and to contact their healthcare provider if they experience symptoms of increased blood pressure or elevated readings *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Advise patients that hepatotoxicity can occur and to immediately contact their healthcare provider for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.3)]*.

Hemorrhagic Events

Advise patients that GAVRETO may increase the risk for bleeding and to contact their healthcare provider if they experience any signs or symptoms of bleeding *[see Warnings and Precautions (5.4)]*.

Tumor Lysis Syndrome

Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS *[see Warnings and Precautions (5.5)]*.

Risk of Impaired Wound Healing

Advise patients that GAVRETO may impair wound healing. Advise patients that temporary interruption of GAVRETO is recommended prior to any elective surgery *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective non-hormonal contraception during the treatment with GAVRETO and for 2 weeks after the final dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with GAVRETO and for 1 week after the final dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with GAVRETO and for 1 week after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

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

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, *including* prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7.1)]*.

Administration

Advise patients to take GAVRETO on an empty stomach (no food intake for at least 2 hours before and at least 1 hour after taking GAVRETO) *[see Dosage and Administration (2.2)]*.

Manufactured for:
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A Member of the Roche Group
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South San Francisco, CA 94080-4990

Jointly marketed by: Genentech USA, Inc. and Blueprint Medicines Corporation

MEET OUR EXPERT

Mark A. Socinski, MD medical director of Thoracic Cancer and executive medical director of the AdventHealth Cancer Institute in Orlando, Florida, as well as co-chair of the *20th Annual* Winter Lung Conference® hosted by Physicians' Education Resource®, LLC (PER®).

Mark A. Socinski, MD, on Progression of Lung Cancer Treatment

"Opportunities to escalate therapies that work well in stage IV into what we consider a more curative setting...are exactly what we need to be looking for."

The treatment of lung cancer has evolved greatly over the last 30 years. Recently, numerous therapy modalities have been tested and successfully implemented into earlier stages of treatment as either adjuvant or neoadjuvant therapy. Additionally, clinicians across the cancer care paradigm are learning how to better tailor treatment to patients based on their genetic makeup.

In an interview with *ONCOLOGY*®, **Mark A. Socinski, MD**, reviewed recent updates in lung cancer and the progression of lung cancer treatment throughout his career.

Additionally, Socinski spoke about finding ways to cure lung cancer when patients have earlier-stage disease, and which updates from recent conferences have the most potential to impact the standard of care.

Q: What are some major trends in the lung cancer space?

SOCINSKI: I started [treating lung cancer] in the 1980s, when editorials were being written to debate whether lung cancer was a treatable disease. Some providers believed you should treat it, while others thought it was not treatable and people should just go on hospice. That's where I started. Looking back over roughly 30 years, [it's difficult to] believe the advances that we've made in lung cancer. Cancer mortality figures in the United States show the greatest annual reduction in cancer mortality that has ever been seen, and that reduction was largely led by lung cancer and melanoma. The greatest advance in the disease is the understanding of biology. When we say lung cancer, specifically non–small cell lung cancer [NSCLC], we're dealing with up to 40 different diseases.

EGFR-mutant lung cancer is different from *ALK* fusion–positive lung cancer, which is different from disease that doesn't have a genomic driver but has high PD-L1 expression. Being able to take that pie and divide it up into various pieces helps you understand why treatment is more of a personalized approach—[it's] because of our understanding of the underlying biology. Lung cancer has become the poster child for targeted therapy, and that's led to a benefit in overall survival [OS] in NSCLC. That's been the biggest change over time that's allowed us to select the right treatment for the right patient at the right time; [we] realize that not every treatment, or not every new drug, will work for everybody. Rather, it probably will work well in 10%, 2%, or 20% of the patients; you just have to be able to find those patients at [diagnosis]. We do comprehensive genomic testing. If a patient does not have a genomic driver, the next important thing is a high PD-L1 expression. We now have the option of giving immunotherapy with good results, so those have been the biggest changes over the years.

Q: What strategies are being developed for earlier-stage NSCLC to avoid metastatic disease?

SOCINSKI: As a lung cancer doctor, most of my career has been spent treating patients with

stage IV NSCLC. I've counseled countless numbers of patients who have a treatable disease, but not a curable disease—but that's changing. [Some] patients who we thought were not curable may be cured. Most of my colleagues in lung cancer believe that this is true because we see it. When you have advances in the treatment of stage IV disease and lung cancer screening that will identify patients at an earlier stage, we'll hopefully see more of a stage migration in terms of when we treat patients. Most of my career has been spent treating stage III and IV diseases. If you look at breast cancer, patients are treated mostly at stage I or II, and we'd like to get [to that point] in lung cancer. Opportunities to escalate therapies that work well in stage IV into what we consider a more curative setting—the surgical setting, or the chemoradiotherapy setting in stage III disease—are exactly what we need to be looking for. We're beginning to see some payoffs from the various trials. The data we have [so far] show that there's a role for immunotherapy in the neoadjuvant or adjuvant setting, and there's a role for osimertinib [Tagrisso] in the adjuvant setting with an *EGFR* mutation. We'll see more of that as we move forward. We don't know the data yet for adjuvant trials that are exploring other immunotherapeutic agents. This is exactly what we need to do because even though we think surgery cures patients, it's not where it should be.

Q: Is there evidence of positive results for patients with targetable mutations receiving immunotherapy in the first line?

SOCINSKI: In the first-line setting, the general answer to that question is no. I always say that a [targetable mutation] trumps everything. FDA-approved targeted therapies in the targeted population are much more efficacious than chemotherapy as well as immunotherapy. In general, the patients who have these targeted DNA alterations tend to be lighter smokers or nonsmokers. Although that's not absolute, for the most part, immunotherapy is not very efficacious in these subsets relative to the targeted therapeutic options for patients. For patients with targetable alterations, most of them are given targeted therapy in the first-line setting. There are a couple of exceptions with alterations like *KRAS* G12C and *EGFR* exon 20 insertions, for which the standard of care is still first-line platinum-based chemotherapy plus or minus immunotherapy.

> **"...you don't need an academic medical center to build a cancer program...there's no reason that we can't be as good as every academic medical center, even a Comprehensive Cancer Center. That's what we aspire to."**

Q: What key findings were presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting that stood out to you?

SOCINSKI: Most of [the interesting data presented] were in early-stage disease. I had to give an ASCO review in July this year, and for the first time in my career, I started [the presentation by discussing] stage I surgical disease and made my way to stage IV at the end. It was a different approach, but it was mainly because from ASCO, the exciting data came from updates in adjuvant as well as the neoadjuvant therapies. Such updates included the CheckMate 816 [NCT02998528] and the NADINE [NCT03081689] trials.[1,2] Those are 2 new trials of neoadjuvant therapy. [These trials] come on the heels of having an FDA approval [of atezolizumab (Tecentriq)] in the adjuvant setting, and much like the PACIFIC trial [NCT01693562], it resparked the debate about neoadjuvant vs adjuvant therapy and who's the appropriate patient for each approach.[3,4] This brings up interesting questions and makes us rethink how we'll incorporate this into practice.

Q: What updates were seen at the 2022 World Conference on Lung Cancer?

SOCINSKI: We did see updated OS at the interim analysis for the IMpower010 trial [NCT02486718] looking at disease-free survival [DFS].[5] We can debate the most pertinent end point in the surgical setting, but most of us feel that it is OS, not DFS. Yes, there is nobility in delaying the recurrence of the disease, but you do surgery to cure the disease. Are we improving the cure rate? That is still a somewhat unanswered question.

An update was presented regarding the IMpower110 trial [NCT02409342] that looked at the OS advantage.[6] These high PD-L1 expressors appeared to have a promising OS benefit. At least in those patients with greater than 50% PD-L1 positivity and node-positive disease, immunotherapy is going to improve cure rates, which is what most of us want to see. We have a number of these trials ongoing. Like an HBO miniseries, whether we're in season 1, 2, or 3, we have to wait for it to play out.

Q: What made you want to treat lung cancer?

SOCINSKI: It was a combination of opportunity and mentorship. When I was a fellow, there was an opportunity in the lung cancer program at the Dana-Farber

Cancer Institute where I was trained. No one else wanted to do lung cancer, so that was my opportunity. It just so happens that one of my favorite attendings oversaw the lung cancer program, so he was my mentor. I viewed it as an opportunity to match with a mentor, and that's what drew me to lung cancer. I refer to those times as the dark times of lung cancer because we used relatively toxic therapy, which at that time was providing minimal benefits compared with what we can do nowadays.

Q: How are you using your previous experience in an academic cancer setting to build up the thoracic oncology program at AdventHealth, where you practice?

SOCINSKI: We throw around the term "pracademic," a combination of practice and academics. Academic medical centers have pros and cons. I trained in an academic medical center where I had 20-plus years of experience, so I understand the beast, as they say. But you don't need an academic medical center to build a cancer program. At AdventHealth, we're slowly accumulating people who have had successful careers in academic centers who are looking for a different model. I've been impressed with the quality of clinicians that we've been able to recruit since I've been here. If you look at the latest *US News and World Report* [rankings], for the first time in a long time, AdventHealth Cancer Institute was ranked [quite high, at] 30th. This reflects how we're building and how we're putting the processes and procedures in place to treat cancer in a way that's recognized. In my position as AdventHealth Cancer Institute's director, [I believe] there's no reason that we can't be as good as every academic medical center, even a Comprehensive Cancer Center. That's what we aspire to. ■

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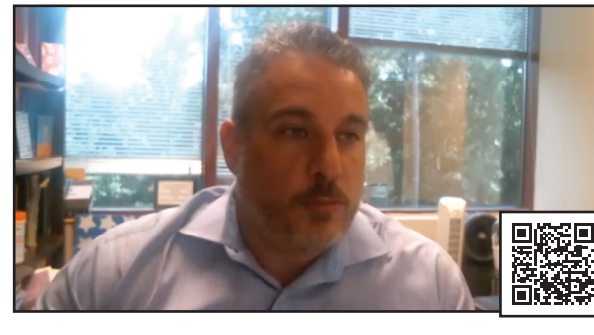
Hossein Borghaei, DO, MS, Discusses the Future of Biomarker Research for Immunotherapy in NSCLC

In an interview with *CancerNetwork*®, Hossein Borghaei, DO, MS, details the promising body of ongoing research assessing biomarkers in patients with non–small cell lung cancer who are candidates for treatment with immunotherapy.

cancernetwork.com/borghaei_9.22



Trevor M. Feinstein, MD, Reviews QOL Analysis of DUBLIN-3 Trial Comparing Docetaxel With or Without Plinabulin in NSCLC

Trevor M. Feinstein, MD, spoke about how quality of life was improved for patients with *EGFR* wild-type stage IIIB/IV non–small cell lung cancer receiving plinabulin in addition to docetaxel in the phase 3 DUBLIN-3 trial.

cancernetwork.com/Feinstein_9.22

Cancer Pain and Opioid Use Disorder

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ABSTRACT

Opioid use disorder (OUD) is increasingly recognized and co-present in patients with cancer. Unfortunately, OUD is not addressed or treated adequately in oncology settings. In addition, patients with cancer-related pain treated with narcotic pain medications are at risk for nonmedical opioid use (NMOU). More than two-thirds of patients with advanced cancer have pain. Both OUD and NMOU need to be concomitantly addressed alongside cancer-related pain management to avoid complications such as overdose. We review the approach to identifying and treating OUD and NMOU in patients with cancer and cancer-related pain.

Introduction

Primum non nocere. It is troubling to think that the medications, opioids specifically, meant to alleviate pain and suffering may inadvertently cause more harm than good. However, the harms caused by inappropriate opioid prescribing have been well documented in the noncancer population and help guide opioid prescribing in patients with cancer.[1] Of the cardinal ethical principles of medical care, respect for nonmaleficence can be particularly challenging when the vehicle of providing symptomatic relief for many patients carries the burden of addiction for some. On a national scale, responses to the opioid epidemic recapitulate similar anxieties about managing pain in the face of substance use disorders.[2]

Pain is highly prevalent in all patients with cancer (30%-50%); its presence is especially relevant for patients with advanced cancer (approximately 70%) managed primarily by medical oncologists.[3] Given the high lifetime prevalence of substance use disorders, many patients who develop cancer will have a preexisting opioid use disorder (OUD), and many more patients will be prone to nonmedical opioid use (NMOU) and other forms of what has been termed *chemical coping*.[4,5] Nonmedical opioid use encompasses a broad spectrum of nonprescribed opioid use that is particularly relevant for patients with cancer who also experience pain. The definition comes from the US National Survey on Drug Use and Health and includes use of opioids without a prescription, use with a prescription but not as prescribed, or use intended primarily for the purposes of the experience of feeling caused by opioids.[6] Consistent with the increasing prevalence of OUD in the general population, an increase in opioid-associated deaths was observed in patients with cancer specifically from 2006 to 2016.[7] In addition, patients may develop OUD during or after their treatment for cancer. Therefore, screening, assessments, and discussions about substance use should be routine and its management seamless given the logistical nuances of cancer care.[5]

The co-emergence of cancer and OUD develops from (1) patients with a history of OUD or other substance use disorders who develop cancer or (2) patients with cancer who develop OUD. The latter group originates from the iatrogenic development of OUD. Unfortunately, the iatrogenic contribution of opioid exposure to OUD and its etiology are not well understood.[8] Although iatrogenic development of OUD represents the minority of OUD, it certainly warrants further research. Even still, many patients taking opioids will not belong to either group but may be at high risk for NMOU, especially given the high prevalence of psychosocial stressors in patients with cancer.

Herein we review strategies for the management of pain in patients with cancer and concomitant OUD, either preexisting or developing while being treated for pain, and strategies for pain management in patients with cancer who are at high risk for NMOU.

Methods

We performed comprehensive searches of PubMed and Google Scholar for all relevant publications about OUD, more specifically in patients with cancer pain, using the following keywords: *oncology, cancer, opioid, opioid crisis, pain, palliation, opioid misuse, dependence, opioid use disorder*. We focused primarily on the studies that described oncological pain along with opioid use and current pharmacologic therapies to manage OUD. We excluded abstracts, comments, and non–English language articles.

Screening for Aberrant Opioid Use

Clinical practice guideline recommendations for active screening and monitoring of opioid pain management are conspicuously incomplete despite the importance of opioids to treat cancer pain and the risk of aberrant use.[5] A descriptive study of pain management practices found that clinicians were less likely to use urine toxicology screening while prescribing opioids or refuse opioid prescriptions for patients with cancer vs noncancer patients.[9] The National Comprehensive Cancer Network (NCCN) recommends the use of Risk Evaluation and Mitigation Strategy tools that have been put in place and are FDA approved for individual opioid products.[10] The NCCN recommends using state-run prescription drug monitoring programs and that clinicians are educated on aberrant use behaviors.[10] Briefly, these include such behaviors as compulsive use and preoccupation, overt cravings, and loss of control, as well as continued use despite harm.[11] In addition to patient education regarding opioid products and evaluating therapeutic response to opioids, the NCCN also recommends evaluating patients for risk factors associated with opioid misuse/abuse/diversion and monitoring for opioid misuse and abuse. Screening tools are available for this purpose but are not specific to cancer-related pain management.[12] A history of illicit drug, alcohol, or substance dependence, in addition to a family history of substance abuse, indicates higher risk of aberrant opioid use. In addition, younger patients with a history of legal problems, incarceration, or psychiatric disorders such as posttraumatic stress disorder, bipolar disorder, anxiety, and depression have an increased risk of aberrant opioid medication use.[12] The NCCN guideline recommendations encourage patients with a history of addiction to be treated for cancer-related pain in coordination with an addiction specialist. In addition, patients with high-risk factors for opioid misuse benefit from psychosocial education, support services, and cognitive behavior therapies that address problem-solving techniques and strategies to reduce the impact of modifiable risk factors.[10] Clinicians should consider interdisciplinary collaborations, including early referrals to interventional pain specialists, to maximize the use of nonopioid strategies for pain relief. Outpatient visits should be frequent, such as weekly, if possible, to reduce the quantity of prescribed opioids at any given time point.

Evaluation of Psychosocial Stressors

A global symptoms assessment is imperative for comprehensive pain management because depression, anxiety, and psychological distress worsen the severity, tolerability, and chronicity of perceived pain. At the same time, to be in pain is to be distressed, which may precipitate or worsen anxiety and depression. Also, depression lowers pain tolerance.[13] Complications, including changes in patterns of sleep, cognition, personality, or other substance use disorders, are both causes and consequences in this circular process that characterizes what has been termed *total pain* by palliative care founder Dame Cicely Saunders.[14-16] The purpose of structured symptom assessments is to untangle the bidirectional relationship between painful conditions and mental health and identify areas of dysfunction where intervention may decrease suffering.

Adequate management of OUD, in addition to cancer-related pain, requires appropriate attention to the constellation of concomitant neuropsychiatric symptoms (eg, depression, anxiety, insomnia, cognitive impairment) that often accompany pain. The American Society of Clinical Oncology and the NCCN have put forth guideline recommendations for screening and treatment of these symptoms.[10,17] Although concomitant psychiatric symptoms may abate while adequately addressing pain, it is generally recommended both are treated concomitantly. Psychoeducation plays a role in helping patients understand the relationships among pain, depression, insomnia, and poor executive function, for example. Patients should have an idea of when they are experiencing anxiety, for example, in the setting of pain or by itself, to facilitate the administration of as-needed medications. In addition, clinicians who treat cancer-related pain, especially in the setting of OUD, should be able to readily recognize affective disorders (eg, depression, anxiety) and cognitive disorders (eg, delirium). Diagnostic uncertainty and treatment trepidation should be met with prompt referral to mental health clinicians and symptom specialists. Comprehensive screening tools can expedite recognition and treatment of these concomitant symptom clusters.

Psychosocial screeners and multisymptom assessment tools should be collected concomitantly with opioid risk assessment tools, such as the Opioid Risk Tool or the Screener Opioid Assessment for Patients with Pain.[18,19] Psychological distress, anxiety, and depression could be assessed using the Distress Thermometer and Problem List, the Edmonton Symptom Assessment

Scale, or PROMIS (Patient-Reported Outcomes Measurement Information System) measures. PROMIS measures can be used to assess many psychosocial symptoms. They are derived from legacy measures and are validated in cancer settings. Insomnia may be addressed by questioning sleep hygiene habits and assessing for initial, middle, and terminal insomnia patterns. Cognitive impairment and delirium should be assessed by multiple time point assessments of awareness, orientation, and attention. Several brief self-report and clinician-administered scales measure attention and evaluate for cognitive impairment. The assessment of alcohol and other substance use disorders may be accomplished using PROMIS measures, and the CAGE (cut down, annoyed, guilty, eye-opener) screener for alcohol use may be extended to include substance use.[20] In addition, well-performing abbreviated and single-item screeners are available for alcohol (Alcohol Use Disorders Identification Test Consumption)[21] and other drug[22] use, which can trigger further screening with the full Alcohol Use Disorders Identification Test or referral to treatment.

Case Presentation

A 57-year-old man is being treated for recurrent small cell lung cancer with third-line chemotherapy. He notes increasing bony pain requiring escalating doses of short-acting hydromorphone in addition to the extended-release morphine formulation he is already taking. In addition to pain from bony metastasis, he has various psychological concerns, such as anxiety (likely precipitated by shortness of breath), initial and terminal insomnia, fatigue, and memory impairment. His clinicians have become frustrated with what seems to be inconsistent and excessive use of as-needed short-acting hydromorphone as he admitted taking more than prescribed to help with sleep and anxiety.

The patient has no personal or family history of drug use or alcoholism. He denies other significant psychosocial stressors aside from having lung cancer. Universal screening reveals the presence of partially treated pain, no evidence of cognitive impairment or delirium, a positive urine drug screen for opioids, and the presence of severe insomnia, anxiety, and depressive symptoms.

Nonmedical Opioid Use

The National Institute on Drug Abuse defines NMOU as "taking an opioid in a manner or dose other than prescribed, taking someone else's prescription opioid, even if for a legitimate medical reason, or taking prescription opioids for the feelings that it produces."[23] Chemical coping and NMOU are related concepts. Chemical coping refers to the use of opioid medications to treat psychological suffering or emotional distress.[24] It is a controversial term that was first used to described drug-seeking behaviors of patients with end-stage alcoholism.[25] This nomenclature may be experienced as stigmatizing, and, therefore, it may be more helpful and appropriate to address unresolved distress. Of course, pain is intimately related to psychological distress. Pain relief may alleviate distress; therefore, patients may use opioids in excess of what is needed to treat pain if distress is also ameliorated vis-à-vis opioid medication. Education regarding appropriate use of opioids and adequate screening for psychological comorbidities are key principles for addressing NMOU and chemical coping. Nonmedical opioid use may occur as a form of chemical coping or opioid use for other non–pain-related reasons. It may result from opioid availability and lack of mental health resource or psychoeducation availability, and the presence of mental health stigma. Oversight of NMOU and chemical coping requires not only limiting opioid medication availability but also providing needed psychoeducation, screening and triaging for psychosocial distress, and making nonstigmatizing mental health referrals. In fact, assessing for NMOU is an opportunity to assess psychosocial distress as well.

The problem with NMOU is the inappropriate use of potentially dangerous and addictive medication to suboptimally treat psychological symptoms. Anxiety, depression, and insomnia are more safely and effectively treated with appropriate (non)psychopharmacologic agents to target those symptoms. This syndrome is more common among young, male patients with a history of alcohol use, drug use, and smoking.[26,27] Patients who rapidly escalate the opioid dose, frequently complain of pain with intensity of 10 of 10, or are at risk for chemical coping should be referred to a supportive care/palliative care team for interdisciplinary management usually consisting of a pain management specialist and counselors. Addressing the most pertinent issue should help limit chemical coping and NMOU. At other times, patients will have a known history of OUD, which may be uncovered or develop while dealing with the stresses of cancer. By definition, patients with OUD are at high risk for losing control of their opioid use and will have higher rates of other psychosocial factors that generally make pain more severe, and they tend to be more intolerant of pain (this abates to some extent when they are treated for OUD), requiring higher doses of opioids for pain control. Patients with OUD should be treated for OUD while receiving treatment for cancer-related pain.[28]

In the case presentation, it is likely that NMOU would abate with psychoeducation and adequately addressing anxiety, depression, and insomnia.

Opioid Use Disorder

A person is defined as having an OUD when there is a pathologic pattern of behaviors related to opioid use, which is a combination of cognitive, behavioral,

and physiologic symptoms.[29] The person continues substance use despite emerging substance-related problems, which causes significant impairment or distress. The full diagnostic criteria are given in **Table 1**. A patient must meet at least 2 diagnostic criteria, and severity is stratified as mild, moderate, or severe if they meet 2 or 3, 4 or 5, or more than 6, respectively. A limitation of these diagnostic criteria is that severity is based on frequency of criteria rather than on impairment. A person could meet 7 criteria (severe) yet have little functional impairment, and someone else could meet 3 criteria (mild) and have significant functional impairment.

Tolerance or withdrawal (often termed *physiologic dependence*) may occur during the appropriate use of opioid therapies and should not be counted toward a diagnosis of OUD when opioids are used solely under appropriate medical supervision. Because many clinicians and patients are concerned with the possibility of opioid dependence, this is a key distinction that is diagnostically relevant. Furthermore, many patients exhibit signs of pseudoaddiction, a term coined in 1989 by Weissman and Haddox[30] to describe an "iatrogenic syndrome that mimics the behavioral symptoms of addiction" in patients with inadequate pain control. Although the existence of pseudoaddiction, as defined, is controversial, the concept remains present in the medical literature and seems to highlight a clinically relevant concept. These patients are usually identified by notable behaviors such as demanding specific opioids to treat their pain or other classic signs of drug-seeking behavior, but these behaviors should cease once adequate pain control is achieved. Therefore, patterns of drug use, including route of administration (intravenous or intranasal), frequency, impairment (ie, social, personal, professional), and other substance use should be explored.

TABLE 1. ***DSM-5* Criteria for Opioid Use Disorder**

Category	*DSM-5* criteria
Impaired control	**1.** Larger amounts or longer period of opioid use than was intended **2.** Persistent unsuccessful efforts to decrease or control opioid use **3.** Excessive time spent obtaining, using, or recovering from use of opioids **4.** Craving, or a strong desire to use opioids
Social impairment	**5.** Failure to fulfill major work, school, or home obligations due to recurrent opioid use **6.** Persistent or recurrent social or interpersonal problems due to opioid use or continued opioid use despite these problems **7.** Reduced or forfeited important social, occupational, or recreational activities due to opioid use
Risky use	**8.** Recurrent opioid use in physically hazardous situations **9.** Continued opioid use despite knowledge of a persistent physical or psychological problem that is likely caused or exacerbated by opioid use
Pharmacologic properties[a]	**10.** Tolerance (the need to increase amounts to achieve intoxication or desired effect or a markedly diminished effect despite continued use of an opioid of the same dose) **11.** Withdrawal (cessation or reduction of opioid use or opioid antagonist use that resulted in at least 3 of the following symptoms: dysphoric mood; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever; insomnia)

DSM, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
[a]Criteria not met when taken under appropriate medical supervision.

A complete history with necessary collateral information is needed to entertain a diagnosis of OUD: a physical examination in addition to full social and mental health histories should be acquired from the patient.[31] The physical examination may reveal a patient in intoxication (confusion, miosis, hypersomnia, nausea, euphoria, constipation, decreased pain perception) or withdrawal. Urine drug tests are necessary during initial and follow-up visits to ascertain the type of opioid substance used and other comorbid substance use, as well as to monitor remission and maintenance.[32] In most areas it is now necessary to include urine testing for fentanyl, which is often not included in standard urine drug test batteries.[33] If the patient has a history of intravenous drug use, tests such as infectious screening (HIV, hepatitis B, hepatitis C) are recommended; echocardiography to rule out endocarditis should be ordered for those with a history of bacteremia.[31]

Complex persistent opioid dependence (CPOD) can develop from long-term opioid dependence and shares many features with OUD, including the biological mechanisms associated with UOD. Complex persistent opioid dependence develops in the setting of opioid therapy that has not been effective but does not meet the criteria for OUD. It exists on a continuum between simple physical dependence and OUD. Complex persistent opioid dependence should be considered when long-term opioid use and tapering are not effective. Interestingly, CPOD may respond to buprenorphine treatment, which can also be used in a chronic pain setting. Delineating the diagnostic entity associated with dysfunctional or inappropriate opioid use has underlying treatment implications. Universally, psychosocial factors, along with nonpharmacologic management of pain, should be considered in all cancer-related pain treatment plans.

Management of Opioid Therapies in Patients With Cancer Who Have OUD

Given that approximately one-half of patients with cancer were prescribed an opioid during the year of their initial diagnosis, safe and effective pain management needs to be achieved while considering the management of OUD. Although the focus of this review is safe opioid prescribing in patients with OUD, one might consider the phenomenon of opioid misuse as a continuum, with chemical coping, NMOU, or CPOD being an early stage of substance use disorders.[34,35] In the early stages when patients use opioids to treat anxiety, depression, or sleep disorders, these actions can often be countered with compassionate use of motivational interviewing to assist them in gaining insight into their behaviors and to appropriately treat their emotional distress. Early identification is necessary.[35,36] The cancer setting (eg, type, stage) and whether the patient is being treated with curative intent play a role in prediction of ongoing pain and concomitant neuropsychiatric symptoms. Although early identification of pain, along with adequate treatment strategies, are still paramount, the concomitant considerations vary based on treatment setting. In the curative setting, the clinician may be most worried about addressing cancer-related pain and OUD to facilitate adherence with anticancer treatments, whereas quality of life and symptom management may be further prioritized in the palliative setting.

In addition, nonpharmacologic measures should be instituted just as would be appropriate for a patient with cancer but without OUD. These modalities include psychoeducation regarding activity and addressing pain management strategies proactively, exercise therapy as tolerated, mindfulness and stress reduction, group support activities, spinal manipulation, acupuncture, yoga, and other multimodal integrative therapies, as well as nonopioid analgesics such as nonsteroidal anti-inflammatory drugs, selected anticonvulsants (eg, gabapentin and pregabalin), and selected antidepressants (eg, duloxetine for peripheral neuropathy, amitriptyline for insomnia and irritable bowel syndrome types of pain).[37-39] Despite the widespread use of medical marijuana in patients with cancer and its potential use in addressing OUD, the evidence base is lacking, and, therefore, medical marijuana cannot be recommended to offset opioid-based medications for OUD (MOUDs).[40,41]

Patients with ongoing, untreated substance use disorders require more complex care than can usually be provided in an oncology setting without significant interdisciplinary support.[42] The goal may be the provision of pain control while using "harm reduction," which means the highest level of safe and effective care. The priorities of the harm reduction model of care for OUD are prevention of overdose and other consequences of unsafe use (eg, accidents, infections), increased control over use (ie, decreasing the total amount used), and preventing diversion.[43] A week's supply of opioid may be prescribed, rather than 1 month, and frequent urine screening may be used. Interdisciplinary care is warranted. Furthermore, people with a medical history of substance use disorder and those who are in recovery may present a unique challenge. Fears of relapse when presented with an opioid for the treatment of cancer pain may lead the patient to refuse these medications. Available evidence does not support an increased risk of relapse for patients treated with opioid analgesics who are maintained on medications for OUD.[44-46] Having thoughtful discussions about use of opioids, trying nonopioid analgesics, using interventional therapies, and incorporating the patient's sponsor or case manager can help provide effective relief while limiting the risk of relapse.

Currently, there are 2 evidence-based MOUDs: buprenorphine and methadone, which are also approved for pain.[47,48] Buprenorphine acts as a partial mu receptor agonist with high affinity and slow dissociation and may precipitate withdrawal as it may displace other opioids. It is combined with naloxone in most formulations approved for OUD, to prevent inhalation or injection use of the products. Methadone is a full mu

TABLE 2. **Combination of Cancer Pain Management With Medications for Opioid Use Disorder**

Expectation of cancer-related pain management		Patients with opioid use disorder	
		Buprenorphine-naloxone	Methadone
Prognosis	Weeks to months	1. Continue at twice- or thrice-daily dosing 2. Continue buprenorphine-naloxone and add a full agonist opioid[a] 3. Discontinue and start methadone thrice daily, if QT interval is normal	1. Continue methadone prescribed by methadone clinic; discuss adding a full agonist opioid[a] to the methadone 2. Switch to split-dose methadone prescribed by you
	Months to years	1. Continue at thrice-daily dosing 2. Discontinue and start methadone thrice daily, if QT interval is normal	1. Switch to split-dose methadone prescribed by you

[a]Oxycodone, morphine, hydromorphone, fentanyl

receptor agonist with a long half-life. Both medications blunt euphoria, decrease craving, and are medically safe. They reduce risk of overdose, acute and chronic infections, and suicide.[49,50] In general, patients with cancer have at least double the risk of suicide, but the risk becomes exceedingly pronounced with pain and the first few weeks to months after diagnosis or other cancer-related crises.[51] Buprenorphine and methadone have different dosing schedules for OUD treatment and analgesia: for pain management, they are prescribed at lower doses several times daily, as opposed to once-daily dosing for OUD. Use of these medications to treat OUD is highly regulated. Buprenorphine prescribers need to receive a Drug Enforcement Agency waiver with limitations on the number of patients to be enrolled in the clinic, whereas methadone maintenance treatment must be administered in a federally approved treatment program. These restrictions do not apply to prescriptions intended to treat pain. There is a dearth of evidence regarding dual treatments for co-occurring OUD and cancer pain. Therefore, in 2021, Merlin and colleagues[52] conducted an online modified Delphi approach to develop consensus for managing cancer pain in patients with OUD from experts in the discipline of hospice and palliative medicine, pain medicine, and addiction medicine. Experts agreed that nonopioid pharmacologic and nonpharmacologic treatments should be maximized before adjustments of MOUDs. The summary of the recommendation is highlighted in **Table 2**.

In both cases, experts agreed that it would be inappropriate to switch buprenorphine-naloxone to a methadone maintenance treatment program, and vice versa. Experts suggested switching buprenorphine-naloxone to split doses of methadone as appropriate due to perceived weaker pain control, although research by Neumann and colleagues[53] has shown both medications to be equally analgesic when initiated in patients identified as being addicted to other opioids. Stopping OUD treatment completely and starting a full agonist opioid was discouraged.

Patients who are taking a full agonist opioid to treat cancer pain but who also meet the criteria for OUD may benefit from a switch to methadone or buprenorphine as a primary analgesic therapy. Often, patients are reluctant to switch pain medications due to concerns of inadequate pain control. It is important to reassure patients that good alternatives exist, and physicians should focus on addressing the patient's pain management while also reducing potential adverse effects from full agonist opioids and unsafe drug use. If the patient is willing to consider buprenorphine, a low-dose initiation protocol can be implemented to prevent withdrawal symptoms.[54] Edens et al[47,55] present their home buprenorphine initiation protocol, which has been shown to minimize adverse effects and reach therapeutic doses for both pain management and OUD by day 5 (**Table 3**).

Despite the recommendation that patients with OUD and cancer-related pain continue taking MOUDs, there are situations in which the clinician may need to consider also prescribing a full opioid agonist (**Sidebar**). For patients already established on MOUDs, mechanisms of tolerance and hyperalgesia may prevent adequate analgesia from buprenorphine or methadone alone.[56] Uncontrolled pain plays a significant role in patients with OUD returning to or continuing opioid use.[46] Concurrent prescribing of a short-term full agonist

TABLE 3. **Recommendations for the Initiation of Buprenorphine While Receiving Cancer-Related Pain Management With a Full Agonist Opioid**

Day	Buprenorphine-naloxone dose	Total daily buprenorphine dose	Full agonist opioid
1	0.5 mg twice daily	1 mg	Continue full dose
2	1 mg twice daily	2 mg	Continue full dose
3	1 mg thrice daily	3 mg	Continue full dose
4	2 mg thrice daily	6 mg	If taking >200 MME, decrease by 25%; if not, continue full dose
5	4 mg thrice daily	12 mg	Stop full agonist; assess patient to monitor withdrawal
≥6	Adjust based on symptoms	Patients with chronic pain respond to doses of 6-16 mg	—

MME, morphine milligram equivalents.

SIDEBAR.

WHEN TO CONSIDER FULL OPIOID AGONISTS IN PATIENTS WITH OUD DURING HOSPITALIZATION

1. To treat acute pain when pain is not controlled by methadone or buprenorphine alone
2. To treat withdrawal and cravings while initiating methadone or buprenorphine
3. For short-term management of withdrawal and cravings for those who refuse methadone or buprenorphine, to avoid higher-risk illicit drug use

has been shown to reduce withdrawal and craving, address pain adequately, and prevent patients from turning to illicitly obtained opioids.[57] From a harm reduction perspective, compassionate, effective care through adequate pain management minimizes the risks of unsupervised opioid use.

Conclusion

Management of cancer-related pain in patients who have OUD or are at risk for OUD requires an individualized approach based on the patient's substance use history and pain management needs. In addition to making an accurate diagnosis of substance use disorder, a comprehensive assessment and an understanding of opioid and MOUD therapies are necessary to provide adequate patient-centered pain management. Clinicians should be aware that opioids might be misused, either inadvertently (eg, for its hypnotic and anxiolytic effects) or purposefully by those with substance use disorders; however, compassionate care and harm avoidance principles will support the cautious use of opioid medications when nonopioid and nonpharmacologic options are inadequate. ■

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For references visit
cancernetwork.com/Ganguly_9.22

KEY TAKEAWAYS

- Universal precautions can support adherence and prevent diversion. Interdisciplinary care, with input from supportive oncology/palliative care and addiction specialists, helps in caring for patients with OUD.
- Clinicians should not abandon nonpharmacologic options (eg, stress reduction techniques, psychoeducation) and nonopioid medications (eg, gabapentin, duloxetine) when managing pain in patients with OUD.
- In patients with untreated OUD, judicious use of a short-acting full agonist may be initiated in a hospital setting before switching to long-term treatment with buprenorphine or methadone.
- If patients are currently in maintenance treatment, consensus agreement exists to adjust to split dosing to address pain. In patients with OUD who are already taking buprenorphine or methadone, cancer-related pain should be managed using the existing agents, if possible.
- Pain management with a full-dose agonist may be necessary if methadone or buprenorphine do not control pain, if withdrawal and cravings are precipitated during partial agonist initiation, or for patients who refuse methadone and buprenorphine. Once adequate pain control is achieved, interdisciplinary efforts should be made to restart OUD medication management.

DARZALEX® (daratumumab) injection for intravenous infusion 100 mg/5 mL, 400 mg/20 mL | DARZALEX *Faspro*® (daratumumab and hyaluronidase-fihj) Injection for subcutaneous use | 1,800mg/30,000units

In the treatment of newly diagnosed, transplant-ineligible multiple myeloma[1]:

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, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

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

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

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

Powerful efficacy to start the treatment journey[1,4]

After a median ~30 months* of follow-up, **mPFS was not reached** with DARZALEX® + Rd vs 31.9 months with Rd alone.[1,4]

- **70.6% of patients had not progressed** with DRd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0–75.4; Rd: 95% CI, 49.5–61.3)†

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

Demonstrated safety profile (median treatment duration of 25.3 months)[1]

- The most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, IRRs, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia
- Serious adverse reactions with 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.[1]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; IRR=injection-related reaction; mPFS=median progression-free survival; PFS=progression-free survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.

*Range: 0.0-41.4 months.[4]

†Kaplan-Meier estimate.

‡Range: 0.03-69.52 months.[3]

§TEAEs are defined as any adverse event (AE) that occurs after start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered drug related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

‖3 to 5 minutes refers to the time it takes to administer DARZALEX *FASPRO*® and does not account for all aspects of treatment. For intravenous daratumumab, median durations of 16 mg/kg infusions for the first, second, and subsequent infusions were approximately 7, 4, and 3 hours, respectively.[1,5]

Efficacy results in long-term follow-up[2,3]

At median ~5 years (56 months)‡ 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)†

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

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

Safety results in long-term follow-up (median treatment duration of 47.5 months)[2]

At median ~5 years of follow-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 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

These ~5-year analyses are not included in the current Prescribing Information.

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

See the latest data rolling out.
Visit FrontlineMomentum.com

appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

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

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

DARZALEX *FASPRO*®: Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX *FASPRO*® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX *FASPRO*® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 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, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS

DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

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

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

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

cp-248517v3

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Janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

DARZALEX 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 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision *[see Adverse Reactions]*.

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4:<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 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 corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX infusion. If ocular symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

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 on 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 as monotherapy. In this pooled safety population, the most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

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

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

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

Body System Adverse Reaction	DRd (N=364)			Rd (N=365)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders						
Diarrhea	57	7	0	46	4	0
Constipation	41	1	<1	36	<1	0
Nausea	32	1	0	23	1	0
Vomiting	17	1	0	12	<1	0
Infections						
Upper respiratory tract infection[a]	52	2	<1	36	2	<1
Bronchitis[b]	29	3	0	21	1	0
Pneumonia[c]	26	14	1	14	7	1
Urinary tract infection	18	2	0	10	2	0
General disorders and administration site conditions						
Infusion-related reactions[d]	41	2	<1	0	0	0
Peripheral edema[e]	41	2	0	33	1	0
Fatigue	40	8	0	28	4	0
Asthenia	32	4	0	25	3	<1
Pyrexia	23	2	0	18	2	0
Chills	13	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Back pain	34	3	<1	26	3	<1
Muscle spasms	29	1	0	22	1	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea[f]	32	3	<1	20	1	0
Cough[g]	30	<1	0	18	0	0
Nervous system disorders						
Peripheral sensory neuropathy	24	1	0	15	0	0
Headache	19	1	0	11	0	0
Paresthesia	16	0	0	8	0	0
Metabolism and nutrition disorders						
Decreased appetite	22	1	0	15	<1	<1
Hyperglycemia	14	6	1	8	3	1
Hypocalcemia	14	1	<1	9	1	1
Vascular disorders						
Hypertension[h]	13	6	<1	7	4	0

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

[a] Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[b] Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis

[c] Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis

[d] Infusion-related reaction includes terms determined by investigators to be related to infusion

[e] Generalized edema, Gravitational edema, Edema, Peripheral edema, Peripheral swelling

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

	DRd (N=364)			Rd (N=365)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Leukopenia	90	30	5	82	20	4
Neutropenia	91	39	17	77	28	11
Lymphopenia	84	41	11	75	36	6
Thrombocytopenia	67	6	3	58	7	4
Anemia	47	13	0	57	24	0

Key: D=daratumumab, Rd=lenalidomide-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 *[see Clinical Studies (14.2) in Full Prescribing Information]*. Adverse reactions described in Table 3 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 3: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

Adverse Reaction	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Infections						
Upper respiratory tract infection[a]	65	6	< 1	51	4	0
General disorders and administration site conditions						
Infusion-related reactions[b]	48	5	0	0	0	0
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0

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

[a] 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

[b] Infusion-related reaction includes terms determined by investigators to be related to infusion

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Lymphopenia	95	42	10	87	32	6
Neutropenia	92	36	17	87	32	8
Thrombocytopenia	73	7	6	67	10	5
Anemia	52	13	0	57	19	0

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

Herpes 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.

Infections

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DVd: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DPd: 28%; DKd[a]: 37%, Kd[a]: 29%; DKd[b]: 21%

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly

[b] where carfilzomib 20/70 mg/m^2 was administered once-weekly

- Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%; VTd: 20%.

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

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%; DKd[a]: 5%, Kd[a]: 3%; DKd[b]: 0%

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly

[b] where carfilzomib 20/70 mg/m^2 was administered once-weekly

- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Fatal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials.

Other Clinical Trials Experience

The following adverse reactions have been reported following administration of daratumumab and hyaluronidase for subcutaneous injection:

Nervous System disorders: Syncope

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 may be misleading.

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 1,383 evaluable combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered 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.

Immune System disorders: Anaphylactic reaction, IRR (including deaths)
Gastrointestinal disorders: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

DARZALEX® (daratumumab) injection

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 *[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 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-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout 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 hematology evaluation is completed.

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

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

Pediatric Use

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

Geriatric Use

Of the 2,459 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 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

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

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, and blurred vision *[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]*.

Hereditary Fructose Intolerance (HFI)

DARZALEX contains sorbitol. Advise patients with HFI of the risks related to sorbitol *[see Description (11) in Full Prescribing Information]*.

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

cp-271933v2

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

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids *[see Dosage and Administration (2.5) in Full Prescribing Information]*. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. 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 *[see Dosage and Administration (2.5) in Full Prescribing Information]*.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone *[see Adverse Reactions]*. Serious cardiac disorders 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 CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References (15)]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

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

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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 diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in 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 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 Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Adverse Reaction	DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)	
	All Grades (%)	Grades ≥3 (%)
General disorders and administration site conditions		
Fatigue[a]	52	5#
Pyrexia	23	2#
Edema peripheral	18	3#
Gastrointestinal disorders		
Diarrhea	45	5#
Constipation	26	2#
Nausea	12	0
Vomiting	11	0
Infections		
Upper respiratory tract infection[b]	43	3#
Pneumonia[c]	23	17
Bronchitis[d]	14	2#
Urinary tract infection	11	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	31	2#
Back pain	14	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[e]	22	3
Cough[f]	14	0
Nervous system disorders		
Peripheral sensory neuropathy	17	2#
Psychiatric disorders		
Insomnia	17	5#
Metabolism and nutrition disorders		
Hyperglycemia	12	9#
Hypocalcemia	11	0

[a] Fatigue includes asthenia, and fatigue.
[b] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
[c] Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
[d] Bronchitis includes bronchitis, and bronchitis viral.
[e] Dyspnea includes dyspnea, and dyspnea exertional.
[f] Cough includes cough, and productive cough.
[#] Only grade 3 adverse reactions occurred.

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

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

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

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Laboratory Abnormality	DARZALEX FASPRO with Lenalidomide and Dexamethasone[a]	
	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	94	34
Decreased lymphocytes	82	58
Decreased platelets	86	9
Decreased neutrophils	89	52
Decreased hemoglobin	45	8

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

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 819 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 812 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 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.

Immune 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 dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-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 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.

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab *in utero* until a hematology 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), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

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

Pediatric Use

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

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

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 of age 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 ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

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

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

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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, and blurred vision *[see Warnings and Precautions]*.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

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

Interference with Laboratory Tests

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

Advise patients that DARZALEX FASPRO 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 FASPRO could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

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Psycho-Oncology and the Relevance of a Biopsychosocial Screening Program

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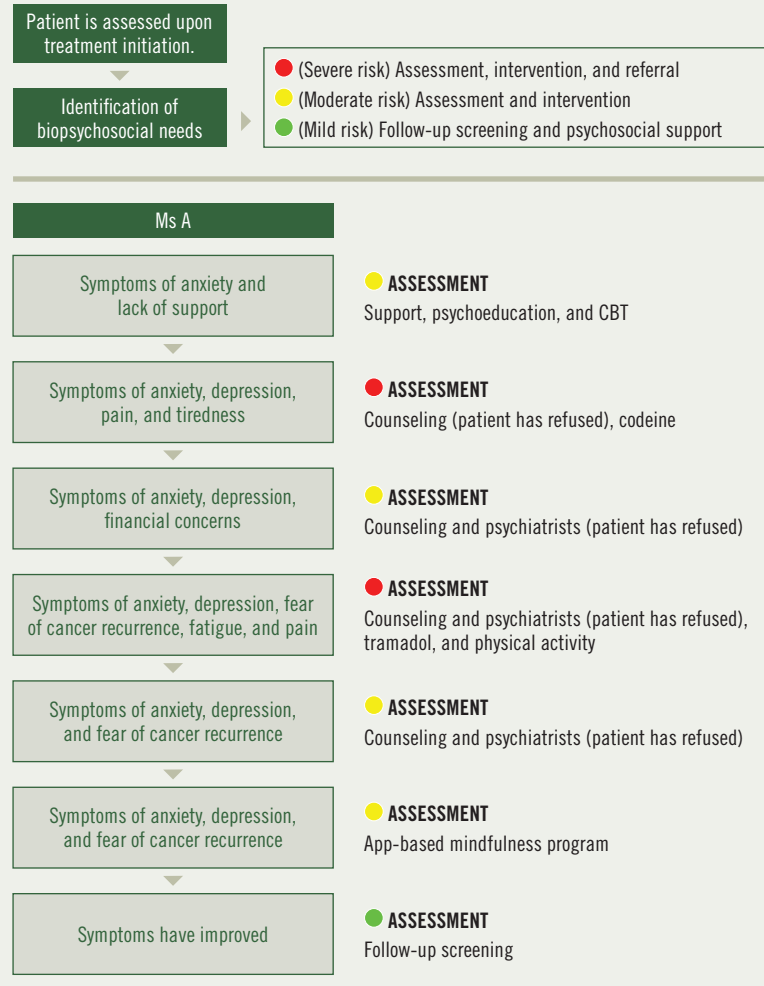
THE CASE

A 40-year-old unmarried Brazilian woman, Ms A, received a diagnosis of papillary renal cell carcinoma (RCC) in February 2020; she underwent nephrectomy the following month. In August, she began to experience generalized pain with subsequent scans revealing metastatic disease to the supraclavicular lymph node, liver, and vagina. In October 2020, Ms A started first-line systemic combination treatment with nivolumab (Opdivo; 3 mg/kg) plus ipilimumab (Yervoy; 1 mg/kg) every 3 weeks for 4 doses, followed by nivolumab (3 mg/kg) every 2 weeks, to be taken for 2 years. In April 2021, follow-up testing revealed a partial response to therapy, and a complete response was evident in August 2021.

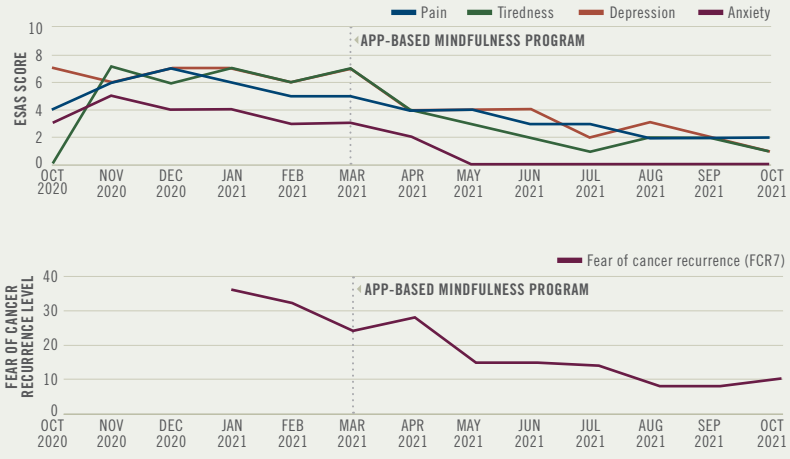
Ms A was first screened for biopsychosocial distress by the supportive care team in October 2020, and she completed the Edmonton Symptom Assessment System (ESAS) evaluation.[1] In the Centro de Câncer de Brasília where Ms A was treated, all patients are screened for biopsychosocial distress by the supportive care team before initiating treatment and at specific time points throughout treatment (**Figure 1**).[2] The unmet needs that are identified are discussed by the

FIGURE 1. **Flow Diagram of the Biopsychosocial Screening Program**



CBT, cognitive behavioral therapy.

FIGURE 2. **Most Common Symptoms Reported Over Time by Ms A**



ESAS, Edmonton Symptom Assessment System.

health care team (oncologist, nurse, psychologist, and nutritionist), with decisions made regarding the need for further assessments, treatment plan, or referrals.[2] At this time, the patient reported severe symptoms of anxiety, equating to an ESAS score of 7 (on a scale of 0 to 10, 10 indicating the worst possible severity). Upon further assessment, Ms A noted a lack of social support from family or friends. Support, psychoeducation, and cognitive behavioral therapy (CBT) were provided at this time, and she was told that further assessment would follow once she began immunotherapy treatment.

The supportive care team recontacted Ms A during her second cycle of treatment in November 2020 and administered the same ESAS screening. Ms A reported moderate symptoms of anxiety (ESAS score, 6) and depression (ESAS score, 5) as well as generalized pain (ESAS score, 6) and high levels of tiredness (ESAS score, 7). The patient was offered counseling, but she chose not to engage at that time. In addition, her oncologist assessed her pain symptoms and prescribed codeine for pain relief.

A psychologist further assessed Ms A using the Patient-Reported Outcomes Measurement Information System (PROMIS) screening measures. Her PROMIS-Anxiety score was 25 of a possible 40 (T-score, 63.5) and her corresponding PROMIS-Depression score was 20 of a possible 40 (T-score, 57.9). The psychologist administered the Brief Fatigue Inventory as well, and Ms A's score was 43 of a possible 90. The psychologist recommended that Ms A schedule an appointment with the counseling and support team.[3,4]

During her third treatment cycle in December 2020, Ms A was screened, and she reported levels of psychological impairment similar to those previously reported (**Figure 2**). The patient was once again offered counseling and was referred to a psychiatrist, but she declined both supportive care options. Ms A cited financial concerns and a lack of understanding as to why she had been referred to psychiatry.

During her fourth cycle of treatment in October 2020, the patient was assessed with the ESAS. During her medical visits, Ms A also expressed concern regarding her physical symptoms and admitted frequent self-monitoring for signs of recurrence or progression. As a result, she was assessed for clinically relevant fear of cancer recurrence or progression (FCR) using the Fear of Cancer Recurrence-7 (FCR-7).[5] At this time, Ms A reported a high level of anxiety and severe FCR (**Figure 2**) as well as ongoing fatigue (ESAS score, 7) and pain (ESAS score, 6). Her oncologist prescribed tramadol for pain and the supportive care team recommended increased engagement in physical activity. Upon further assessment, the patient reported a belief that her psychosocial symptoms, worry about recurrence or progression, and time spent self-monitoring were a normal part of her cancer experience.

In this case, what would be the best type of screening to capture the patient's whole experience during her cancer treatment?

A. Nothing; expected response to treatment

B. Ask the patient to respond to the question: *How are you doing?*

C. Biopsychosocial screening program

D. Physical symptom monitoring

TURN TO PAGE 554 FOR THE ANSWER AND A DISCUSSION OF THIS CASE BY EXPERTS.

CORRECT ANSWER: **C. Biopsychosocial screening program**

Discussion

The past 2 decades have been marked by dramatic advances in the treatment of cancer, especially advanced RCC. In this era of targeted agents and immunotherapy, overall survival of patients diagnosed with RCC has improved significantly, with previously unheard-of instances of complete responses to treatment. For example, in the CheckMate 214 (NCT02231749) trial of nivolumab plus ipilimumab, nearly 1 in 10 patients with advanced disease achieved a complete response.[6]

While such cases of complete response represent a great achievement in the treatment of advanced RCC, they also present challenges to the oncology community. To date, there has been limited success in identifying consistent markers of treatment response and thus, such cases remain unpredictable. This unpredictability presents a challenge to clinicians who are tasked with communicating prognostic information to their patients: The clinicians would like to engender hope but also manage realistic expectations of what may follow such a response.[7] In the RCC arena, patients' growing awareness of cases of complete responses with immunotherapy have shifted their expectations of cure. Indeed, results of a recent study noted that a significant proportion of patients receiving immunotherapy harbor inaccurate expectations of cure, although, interestingly, a more accurate expectation of cure was associated with lower rates of anxiety.[8] Undoubtedly, advances in treatment and reports of complete responses engender hope for patients, families, and the oncology community; however, the predictability of these outcomes remains uncertain. In the meantime, isolated examples of remission may paradoxically increase patients' distress, prompt unrealistic expectations, and further exacerbate fears of cancer recurrence.[9]

Germane to the case presented in this paper, patients with RCC often experience physical symptoms, including pain and fatigue, that are secondary to their treatment. Pain and fatigue are the most frequent symptoms reported by patients with RCC (more than 70%).[10] Importantly, fatigue is the most frequently reported treatment-related adverse effect of nivolumab plus ipilimumab. In the phase 3 CheckMate 214 trial, 93% and 46% of patients reported any-grade or grade 3/4 fatigue, respectively.[6] Identifying these symptoms associated with a comprehensive overview of potential factors associated with them are relevant to better determine treatment strategies. Study results have shown that psychological intervention and exercise treatment are generally effective for reducing pain and fatigue.[11,12] Psychosocial interventions—including counseling, CBT, psychoeducation, hypnosis, relaxation, and mindfulness—can also help manage these physical symptoms.[12]

Ms A also reported psychosocial symptoms during her cancer journey, including anxiety, FCR, lack of social support, and financial distress. Study results have shown that up to 77% of patients with a diagnosis of RCC report moderate-to-severe distress and 55% report moderate-to-severe FCR and that they are at moderate risk of suicide mortality, especially in the first year of being diagnosed with their disease.[13-16] As a result, ongoing research efforts have explored factors associated with biopsychosocial distress and FCR, in order to help identify and support those at high risk and to guide targeted supportive care programs. Previous study outcomes have also shown that financial comorbidity, lack of social support, and physical symptoms, such as pain and fatigue, can exacerbate distress and psychosocial comorbidity.[13,14,17] Demographic characteristics, including female gender and younger age, are also important risk factors for high levels of distress and FCR.[14,15]

Further, non–clear cell histology and presence of recurrence were associated with high levels of distress in patients with RCC.[14] These findings may be explained by the lack of information and treatments to each histological subtype, or by the poorer prognosis associated with disease recurrence.[14] Finally, an incomplete understanding of one's disease and prognosis has been associated with higher rates of FCR; evidence suggests that these FCR rates do not dissipate over time, in contrast with levels of distress.[15] Importantly, studies have shown that patients with untreated moderate-to-severe distress are more likely to use health care services—demanding more from their care team—and to visit emergency facilities.[18,19]

Biopsychosocial Screening for Distress

The cancer trajectory is marked by uncertainty and distress for patients, and efforts are underway to develop and implement effective symptom management and supportive care treatments. In the early 2000s, distress was deemed the sixth vital sign in care of patients with cancer, emphasizing its importance and the need for regular biopsychosocial screening.[20] Screening for distress programs have become an international standard of comprehensive cancer care. Accreditation Canada, the Association of American Physicians and Surgeons, and many other professional groups have established guidelines for routine biopsychosocial screening for distress.[21] As such, many cancer centers have developed and implemented a comprehensive approach in the care of patient throughout the cancer journey. Training programs have been

developed, research has been undertaken, and comprehensive programs have been accredited, and the newest models of care often seek to maximize resources and reduce barriers to services as part of whole-patient cancer care. However, despite recognition of the value of these advances, many cancer care programs nonetheless fail to screen patients routinely for distress and symptom burden.

Biopsychosocial screening programs have promoted greater levels of interdisciplinary cooperation and have helped shift the concept of disease-directed care to patient-centered care, beginning from the time of diagnosis.[22] Based on clinical guidelines, patients should receive biopsychosocial screening at several time points throughout the cancer journey, including at their first or second visit, during treatment, at the end of the treatment, and if their cancer status changes. Various screening questionnaires have been developed; some focus on the assessment of emotional symptoms (eg, anxiety and depression), while others are more comprehensive and assess multiple domains (ie, physical, emotional, practical, family/social). A biopsychosocial screening program should identify patients' unmet needs; then, a focused assessment should follow to determine the severity of symptoms, make appropriate referrals, and create supportive care engagement for those in need.[23-26] Research and health care system evaluations have shown that such programs are feasible and efficacious and help focus care resources.[27-30] These programs also actively engage patients, family members, and health care team members throughout the cancer journey, ensuring commitment to whole-patient care.

Cancer care involves state-of-the-art biomedical treatments and, as a result, often focuses primarily on physical symptom monitoring (response option D to our question above). The system as it currently stands often fails to address the psychosocial needs of patients. Biopsychosocial screening programs (response option C) are considered the most effective form of screening for patients across the cancer trajectory.[31] A biopsychosocial program has the ability to identify a variety of issues exacerbated by cancer, ranging from depression, anxiety, and constipation to lack of health literacy and financial difficulties that may cause additional suffering and reduce adherence to the treatment.[31] Identifying these unmet needs can assist the cancer care team in specifically assessing the gravity of the problem and determining the most appropriate treatment strategy and/or referrals.[31-33]

Screening for distress programs can also help guide the development of psychoeducational programs and interventions that target specific symptoms or vulnerable groups.[34] In contrast, clinically relevant psychosocial symptoms may be common but are not an expected response to treatment and thus should be treated accordingly (response option A). Previous study results have shown that only a small proportion of patients are inclined to ask for assistance; consequently, vague, open-ended questions can fail to capture patients' symptoms, meaning health care professionals miss the chance to intervene (response option B). Notably, biopsychosocial screening programs can provide an excellent opportunity to integrate psychosocial care into routine oncology care, providing psychosocial support for patients during the cancer care trajectory, including survivorship.[33] Although much research has been conducted and published on screening for biopsychosocial needs over the past 20 years, many cancer centers do not perform systematic screening or utilize this type of assessment. Regular follow-up and reassessments occur even less frequently.[33]

Once biopsychosocial needs are identified through screening programs, targeted, effective, and timely interventions—such as CBT, the standard of care for addressing emotional symptoms among those with a diagnosis of cancer—can be identified and provided.[35,36] In addition, there is evidence that supportive-expressive group psychotherapy, existential therapy, meaning-centered psychotherapy, mindfulness, and mindfulness stress reduction programs can be effective in managing certain symptoms or in specific contexts.[35,37-44] As evidence has emerged suggesting that FCR is highly prevalent and fails to dissipate in survivorship, targeted treatments have been developed to address this particular domain of distress.[36,45,46]

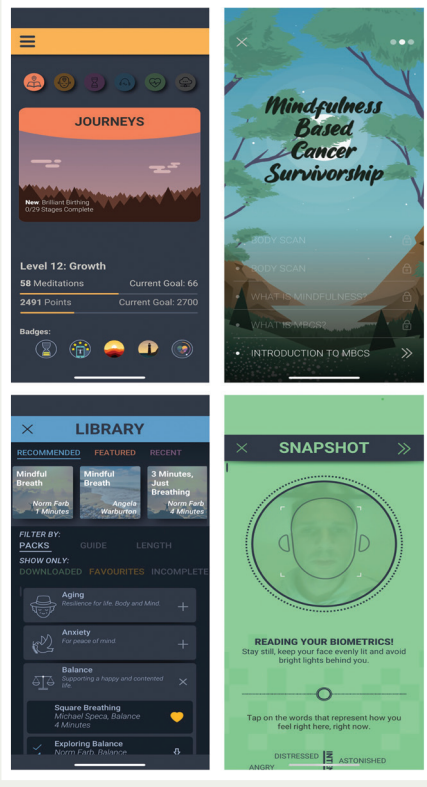
Case Conclusion

In compliance with emerging national and international comprehensive care guidelines in oncology, an evidence-based biopsychosocial screening program was implemented at the Centro de Câncer de Brasília in 2008 at no cost to patients.[2] Evidence has clearly shown that this type of program improves symptom management and is cost saving to the patient and the system.[18,47-49] This program includes routine biopsychosocial screening of patients' well-being and enables the health care team to identify and respond more effectively to those with unmet needs. Ms A participated in this screening for distress program, and her specific psychosocial, practical, and physical concerns were identified and discussed among the health care team (oncologist, psychologist, nutritionist, nurse, and palliative physician), as well as with Ms A. She was reporting symptoms of anxiety, fear of cancer recurrence or progression, pain, and fatigue during treatment. Pain medication was prescribed, and she reported mild symptom improvement. The health care team referred her to individual psychotherapy, but Ms A refused counseling or a referral to a psychiatrist for several reasons, including financial issues, time commitment, and fear of losing her job

if she took time to attend visits. In light of these barriers, the supportive care team offered the patient the opportunity to join a clinical trial for which she was eligible; it was examining the feasibility and effectiveness of an app-based mindfulness program for cancer patients and survivors.[49] The smartphone application, called AmDTx and adapted from a mindfulness-based cancer recovery program, provides guided meditations focused on 6 modules: introduction to mindfulness, stress resilience and cancer, calmness/self-possession, habits of thought, sleeping through the night, and fear of recurrence at enhancing mindfulness (**Figure 3**).[46] The patient agreed to participate, and over the study's 4 weeks, her symptoms of anxiety and FCR began to decrease (**Figure 2**). She also reported improvement in her physical symptoms of pain and fatigue, and she was able to stop taking the pain medication. Ms A has continued to use the app-based mindfulness program, although the trial is long over. She is about to complete her treatment course (2 years of nivolumab plus ipilimumab, as described earlier), her emotional symptoms have improved, and she is not experiencing any physical symptoms. Indeed, Ms A is now working as a patient advocate and helps other patients in their own journeys.

In summary, screening for distress is proving to benefit both the cancer care system and individual patients by enlisting each patient to respond to a questionnaire that asks about the most commonly experienced concerns across the cancer care trajectory. While identifying each patient's concerns is important, a timely response to those concerns by the appropriate professional is essential to improving outcomes and the patient's quality of life. ■

FIGURE 3. **AmDTx App-Based Mindfulness Intervention**



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For full reference list, visit
cancernetwork.com/Bergerot_9.22

In HER2+ MBC following 1L progression and beyond*

EMBRACE SUPERIOR SURVIVAL WITH PROVEN SAFETY

TUKYSA + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine

- **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 **(primary endpoint)**[1†]

More than 2 years median overall survival at follow-up analysis[2]

- **Primary analysis[‡]:** 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 **(secondary endpoint)**[1]
- **Follow-up analysis[§]:** 24.7 months (95% CI: 21.6-28.9) vs 19.2 months (95% CI: 16.4-21.4); HR = 0.73 (95% CI: 0.59-0.90); median follow-up: 29.6 months[2]

Follow-up OS analysis: Results of this prespecified exploratory analysis are descriptive but not conclusive, are not controlled for type 1 error, and should be interpreted with caution.

Safe and well tolerated[1,3]

- 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[1]
- 6% of patients discontinued TUKYSA due to adverse reactions vs 3% with placebo[3]

See additional follow-up data inside >

#1 PRESCRIBED

The TUKYSA regimen is the #1 prescribed treatment for patients with brain metastases in 2L+ HER2+ MBC[4‖]

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 Important Safety Information

- **The Prescribing Information for TUKYSA contains warnings and precautions** for diarrhea, hepatotoxicity, and embryo-fetal toxicity, some of which may be severe
- **The most common serious adverse reactions** in ≥2% of patients who received TUKYSA were diarrhea, vomiting, nausea, abdominal pain, and seizure

Study design: HER2CLIMB was a randomized (2:1) trial of TUKYSA or placebo each in combination with trastuzumab and capecitabine in 612 patients with HER2+ MBC, previously treated with trastuzumab, pertuzumab, and T-DM1. Primary endpoint was PFS per BICR in the first 480 patients enrolled. Secondary endpoints included OS. A prespecified exploratory analysis was included to evaluate OS at ~2 years. Please see additional study design on the following page.

*≥1 anti-HER2-based regimen in the metastatic setting.[1]
†Data from the first 480 patients.[1]
‡Primary analysis (data cutoff: September 4, 2019).[3]
§Prespecified exploratory analysis (data cutoff: February 8, 2021).[2]
‖Based on brand prescriptions from 10/20 to 05/21.[4]

1L = first-line; 2L = second-line; BICR = blinded 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; T-DM1 = ado-trastuzumab emtansine.

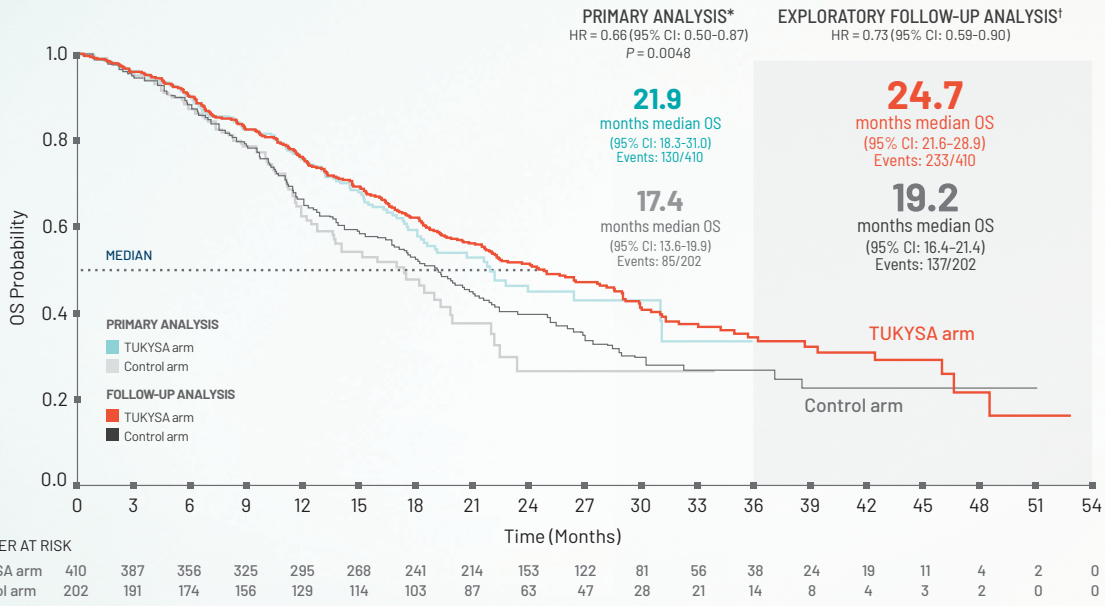
Please see full Important Safety Information on the following pages.

TUKYSA®
tucatinib
50 mg | 150 mg tablets

In combination with trastuzumab + capecitabine

TUKYSA ACHIEVED A MEDIAN OVERALL SURVIVAL OF MORE THAN 2 YEARS AT FOLLOW-UP ANALYSIS[2]*

OS in the total population (N = 612)[1,2]



Results of this prespecified exploratory analysis are descriptive but not conclusive, are not controlled for type 1 error, and should be interpreted with caution. Data cutoff for follow-up analysis was February 8, 2021.[2]

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 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.

- **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, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

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.

CONSISTENT SAFETY PROFILE AT FOLLOW-UP ANALYSIS[2†]

At the 2-year follow-up analysis[2]

The most common adverse reactions (≥20%) were diarrhea, PPE, nausea, fatigue, vomiting, decreased appetite, stomatitis, headache, AST increased, anemia, ALT increased, and blood bilirubin increased

TEAEs Grade ≥3
61% (245/404) in the TUKYSA arm vs
51% (101/197) in the control arm

TEAEs leading to death
2% (8/404) in the TUKYSA arm vs
3% (6/197) in the control arm

The rate of discontinuation due to adverse reactions for the TUKYSA arm remained consistent with the primary analysis[2,3†]

	TUKYSA		PLACEBO
PRIMARY ANALYSIS[3]	6%	vs	3%
FOLLOW-UP ANALYSIS[2]	6%	vs	4%

*Study design: HER2CLIMB was a randomized (2:1), double-blind trial of TUKYSA or placebo each in combination with trastuzumab and capecitabine in 612 patients with HER2+ MBC, previously treated with trastuzumab, pertuzumab, and T-DM1. Primary endpoint was PFS per BICR in the first 480 patients enrolled. Secondary endpoints assessed in the full study population included OS, PFS in patients with brain metastases, confirmed ORR, and safety.

The protocol included a prespecified exploratory analysis to evaluate OS, PFS (by investigator assessment), and safety in the total study population (N = 612) at ~2 years from the last patient randomized. After the primary analysis, 12.9% of patients in the placebo arm (26/202) crossed over to receive TUKYSA in combination with trastuzumab and capecitabine, with the first patient crossover in February 2020. Median overall study follow-up: 29.6 months (data cutoff: February 8, 2021). Because formal testing of all alpha-controlled endpoints was considered final at the primary analysis, data from this prespecified updated analysis are for descriptive purposes only.[1-3]

†Follow-up safety analysis was done as part of a prespecified exploratory analysis. Results are presented as descriptive data that are not intended to provide conclusions about safety and should be interpreted with caution.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ORR = objective response rate; TEAE = treatment-emergent adverse event.

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: 1. TUKYSA [Prescribing Information]. Bothell, WA: Seagen Inc. April 2020. **2.** Curigliano G, Mueller V, Borges V, et al. Updated results of tucatinib vs placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB). Poster presented at: American Society of Clinical Oncology Annual Meeting; June 4-8, 2021. **3.** Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med*. 2020;382(7):597-609. **4.** Data on file. Seagen Inc.

TUKYSAhcp.com

Seagen®

TUKYSA®
tucatinib
50 mg | 150 mg tablets

TUKYSA®
tucatinib
50 mg | 150 mg tablets

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.

DOSAGE 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/m^2 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

Dose Reduction	Recommended TUKYSA Dosage
First	250 mg orally twice daily
Second	200 mg orally twice daily
Third	150 mg orally twice daily

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

Table 2: Recommended TUKYSA Dosage Modifications for Adverse Reactions

Severity	TUKYSA Dosage Modification
Diarrhea[1]	
Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.
Hepatotoxicity[1,2]	
Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 ALT or AST (> 5 to 20 × ULN) OR Grade 3 bilirubin (> 3 to 10 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4 ALT or AST (> 20 × ULN) OR Grade 4 bilirubin (> 10 × ULN)	Permanently discontinue TUKYSA.
ALT or AST > 3 × ULN AND Bilirubin > 2 × ULN	Permanently discontinue TUKYSA.
Other adverse reactions[1]	
Grade 3	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.

1. Grades based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03
2. Abbreviations: 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, 81% 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 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.

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 of 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 seizure (2%). Fatal 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)

Adverse Reaction	TUKYSA + Trastuzumab + Capecitabine (N = 404)			Placebo + Trastuzumab + Capecitabine (N = 197)		
	Grade (%)			Grade (%)		
	All	3	4	All	3	4
Gastrointestinal disorders						
Diarrhea	81	12	0.5	53	9	0
Nausea	58	3.7	0	44	3	0
Vomiting	36	3	0	25	3.6	0
Stomatitis[1]	32	2.5	0	21	0.5	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia syndrome	63	13	0	53	9	0
Rash[2]	20	0.7	0	15	0.5	0
Hepatobiliary disorders						
Hepatotoxicity[3]	42	9	0.2	24	3.6	0
Metabolism and nutrition disorders						
Decreased appetite	25	0.5	0	20	0	0

Adverse Reaction	TUKYSA + Trastuzumab + Capecitabine (N = 404)			Placebo + Trastuzumab + Capecitabine (N = 197)		
	Grade (%)			Grade (%)		
	All	3	4	All	3	4
Blood and lymphatic system disorders						
Anemia[4]	21	3.7	0	13	2.5	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	0.5	0	4.6	0.5	0
Investigations						
Creatinine increased[5]	14	0	0	1.5	0	0
Weight decreased	13	1	0	6	0.5	0
Nervous System Disorders						
Peripheral neuropathy[6]	13	0.5	0	7	1	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	12	0	0	5	0	0

1. Stomatitis includes stomatitis, oropharyngeal pain, oropharyngeal discomfort, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysesthesia, tongue ulceration, and aphthous ulcer
2. Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema, skin toxicity, and dermatitis
3. Hepatotoxicity includes hyperbilirubinemia, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury
4. Anemia includes anemia, hemoglobin decreased, and normocytic anemia
5. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function
6. Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Table 4: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB

	TUKYSA + Trastuzumab + Capecitabine[1]		Placebo + Trastuzumab + Capecitabine[1]	
	All Grades %	Grades ≥3 %	All Grades %	Grades ≥3 %
Hematology				
Decreased hemoglobin	59	3.3	51	1.5
Chemistry				
Decreased phosphate	57	8	45	7
Increased bilirubin	47	1.5	30	3.1
Increased ALT	46	8	27	0.5
Increased AST	43	6	25	1
Decreased magnesium	40	0.8	25	0.5
Decreased potassium[2]	36	6	31	5
Increased creatinine[3]	33	0	6	0
Decreased sodium[4]	28	2.5	23	2
Increased alkaline phosphatase	26	0.5	17	0

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NCI-CTCAE v.4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NCI CTCAE v5.0).
2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
4. There is no definition for Grade 2 in CTCAE v.4.03.

Increased Creatinine: 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

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, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

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.

USE 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 ≥ 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 34% 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 in 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.

Seagen®

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Future Directions in the Management of Non–Small Cell Lung Cancer Harboring Driver Mutations

by Roy S. Herbst, MD, PhD

It has been 20 years since the discovery of *EGFR* mutations and almost 25 years since we first used EGFR inhibitors in the clinic. This resulted in a paradigm shift regarding the way we think about lung cancer. Now that we have drugs which target growth factor receptors, and we use them to slow the growth of tumors, giving rise to dramatic responses. Recently, these agents have moved forward to earlier stages of disease, and we are seeing large improvements in disease-free survival, such as in the recent phase 3 ADAURA trial (NCT02511106) of osimertinib (Tagrisso) as adjuvant therapy for patients with resected stage IB to IIIA *EGFR*-positive non–small cell lung cancer (NSCLC).[1]

The limitations continue, however, the activity of these drugs continues to improve, providing us with third- and fourth-generation agents. Our understanding of sensitivity, resistance, and tolerability very often allows patients to live with lung cancer and have a very manageable quality of life. Questions still remain, however: What are the next steps in this area? How can we continue to improve? That's where the next-generation agents will come in.

EGFR Mutations: A Brief History

Lung cancer is the leading cause of death in the United States, with more than 230,000 cases in the US and more than 2 million cases worldwide diagnosed annually.[2] *EGFR*-mutated lung cancer accounts for approximately 10% to 15% of the cases in the United States[2] and as many as 30% to 40% in Asia.[3,4] Clearly, targeting this pathway is important.

Through next-generation sequencing and other approaches, we have learned that mutations are canonically in exon 19 and 21, but there are also a host of aberrations in exon 20. The mutations in exon 21 may or may not be sensitive to the standard agents, a fact that requires continued drug discovery to understand how to better target them. Two agents—amivantamab (Rybrevant) and mobocertinib (Exkivity)[5,6]—are approved in the setting of metastatic NSCLC with *EGFR* exon 20 insertion mutations, and several others are in development.

Treatment Challenges

When targeting lung cancer with these personalized therapies, we see many responses, but they are often short-lived:

Patients develop resistance mechanisms and pathways. At the Yale Cancer Center, one of our approaches has been to rebiopsy patients at resistance. With this rebiopsy, we can learn if there is *EGFR* resistance, either on or off target. On-target resistance would mean a new mutation in the *EGFR* gene, and in that case we use a targeted agent that best targets that new pathway. In some cases, tumors transform to small cell lung cancer. New mutations, such as c-*MET*, can also develop. In fact, we see many patients who develop c-*MET, RET*, or other driver mutations.

How I Treat

I was closely involved in the initial trials examining EGFR inhibitors and in some of the work that led to the discovery of other driver mutations by creating databases and looking at biomarkers. In my practice, I have a very strong focus on biomarkers and precision medicine. Before I treat anyone with nonsquamous histology, especially a patient of Asian descent or with a light or nonsmoking history, I make sure I have EGFR testing results. If they have a mutation in exon 19 or 21, they get osimertinib as first-line therapy. Some trials in early stages, such as FLAURA2 (NCT04035486), are currently looking at targeted agents such as osimertinib plus chemotherapy. If a patient has a noncanonical mutation, meaning a mutation in exon 20 or a rare mutation in exon 19 or 21, I either consult my computer or one of the laboratory scientists who are working with these mutations in the laboratory to determine if it's an activating mutation. I want to know if it causes the lung tumor to grow or not, and if we have a drug that targets it. I predict that we will get much more personalized in how we target *EGFR* mutations in lung cancer in upcoming years.

Another consideration with these therapies is toxicity. Despite all the research, we still see a good deal of rash, diarrhea, dermatitis, paronychia on the nails, ingrown eyelashes, and other adverse effects (AEs) of therapy. Those require delicate management. It's important that patients are made aware of these AEs and possible ameliorators before they are treated. I make sure that the nurse practitioners and nurses in the office are familiar with the AE therapies, as well. This is clearly an area where scientists have gone from the clinic to the laboratory and back again, and we are making great headway.

Key Takeaways

1. Targeted therapy is here to stay. In lung cancer, we want to target all the actionable mutations, and certainly the most commonly occurring aberrations are in *EGFR* exon 19 and 21, followed by exon 20.
2. Drug development must continue. Having done this for more than a quarter of a century, I have treated many patients who have experienced amazing responses. However, I have never seen someone cured except perhaps in the adjuvant setting, such as in the ADAURA trial, and it's still too soon for that to be determined. We are waiting for the survival results from that trial; they will be available in the next few years. We continue to raise the bar and develop new and better drugs and combinations.
3. This research requires collaboration across the community, industry, and academia. We need large numbers of patients to figure out which drugs work best in which settings, and how to target the drugs together.
4. There is an issue with access. What good are all these therapies if we don't get them to the underserved populations? Some patients never get medical attention. These include patients with lung cancer who might see only a pulmonologist, never an oncologist—and the oncologist would be the one who'd have the most expertise to think about how these new therapies could best be molded for that patient's disease. This will be the challenge of the next several years: giving access to all patients.

In summary, it has been fantastic over my career to see targeted therapies, such as EGFR-targeting agents, being used routinely in oncology. Now we need to think about which agents should be used based on which mutation the patient has and how to target resistance because we must continue to ratchet up our clinical abilities and find better ways to manage lung cancer throughout the world. ■

FINANCIAL DISCOLSURES/ CONFLICTS OF INTEREST:

RSH receives consulting fees from AstraZeneca, Bolt Biotherapeutics, Bristol Myers Squibb, Candel Therapeutics, Inc., Checkpoint Therapeutics, Cybrexa Therapeutics, DynamiCure Biotechnology, LLC, eFFECTOR Therapeutics, Inc., Eli Lilly and Company, EMD Serono, Genentech, Gilead, HiberCell, Inc., I-MAB Biopharma, Immune-Onc Therapeutics, Inc., Immunocore, Janssen, Johnson & Johnson, Loxo Oncology, Merck and Company, Mirati Therapeutics, NextCure, Novartis, Ocean Biomedical, Inc., Oncocyte Corp, Oncternal Therapeutics, Pfizer, Regeneron Pharmaceuticals, Revelar Biotherapeutics, Inc., Ribbon Therapeutics, Roche, Sanofi, and Xencor, Inc. He receives research support to his institution from AstraZeneca; Eli Lilly and Company; Genentech, a member of the Roche Group; and Merck and Company. He serves in leadership roles for the American Association for Cancer Research (board member, committee chair), International Association for the Study of Lung Cancer (board member, committee chair), Society of Immunotherapy for Cancer (committee chair), and SWOG (committee chair, principal investigator). He serves on the board of directors for Immunocore (nonexecutive director) and Junshi Pharmaceuticals (nonexecutive, independent board member).

For references visit
cancernetwork.com/Herbst_9.22

BAVENCIO® avelumab Injection 20 mg/mL

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 intervention=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.

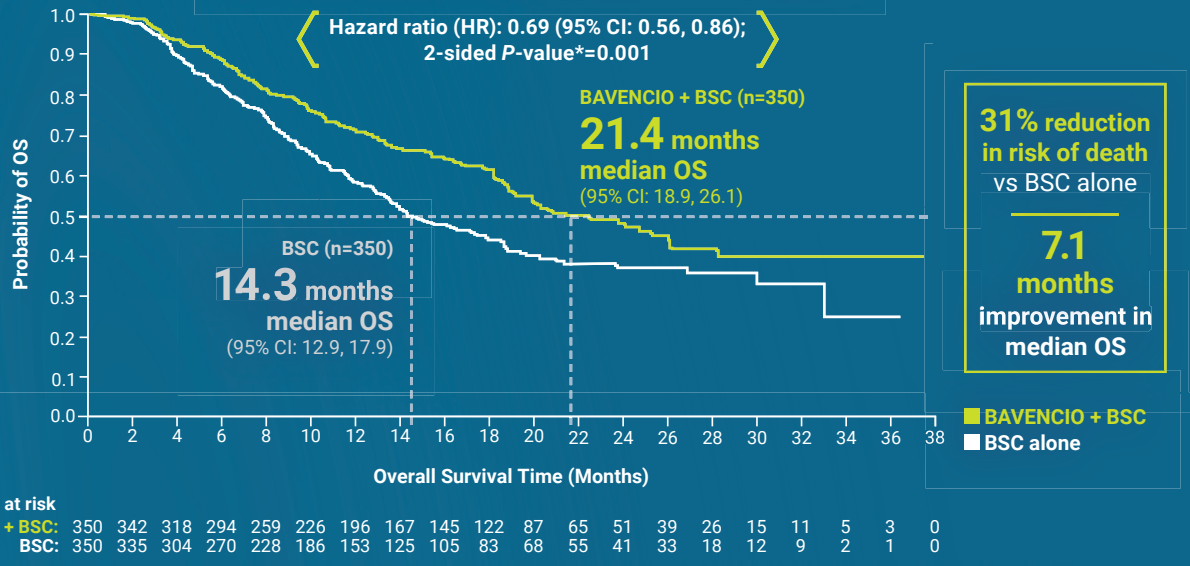
BAVENCIO can cause **immune-mediated pneumonitis**. Withhold BAVENCIO for Grade 2, and permanently discontinue for Grade 3 or Grade 4 pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.6%) adverse reactions. 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)



No. at risk

BAVENCIO + BSC:	350	342	318	294	259	226	196	167	145	122	87	65	51	39	26	15	11	5	3	0
BSC:	350	335	304	270	228	186	153	125	105	83	68	55	41	33	18	12	9	2	1	0

- 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.

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.§

**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.[2]

‡ 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).[2]

§ PD-L1 expression was assessed in tumor samples using the VENTANA PD-L1 (SP263) assay.[2]

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-1.

Please see additional Important Safety Information and Brief Summary of the Prescribing Information on the following pages.

IMPORTANT SAFETY INFORMATION (continued)

BAVENCIO® (avelumab) can cause **hepatotoxicity and immune-mediated hepatitis**. Withhold or permanently discontinue BAVENCIO based on tumor involvement of the liver and severity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin elevation. Immune-mediated hepatitis occurred with BAVENCIO as a single agent in 0.9% (16/1738) of patients, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in all (16/16) patients with hepatitis.

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

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

BAVENCIO can cause **immune-mediated thyroid disorders**. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold BAVENCIO for Grade 3 or Grade 4 endocrinopathies until clinically stable or permanently discontinue depending on severity. Thyroiditis occurred in 0.2% (4/1738) of patients, including Grade 2 (0.1%) adverse reactions. Hyperthyroidism occurred in 0.4% (7/1738) of patients, including Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hypothyroidism occurred in 5% (90/1738) of patients, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism.

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

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

BAVENCIO can cause **immune-mediated dermatologic adverse reactions**, including rash or dermatitis. Exfoliative dermatitis including Stevens Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold BAVENCIO for suspected and permanently discontinue for confirmed SJS, TEN, or DRESS. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions.

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

BAVENCIO can cause severe or life-threatening **infusion-related reactions**. Premedicate patients with an antihistamine and acetaminophen prior to the first 4 infusions and for subsequent infusions based upon clinical judgment and presence/severity of prior infusion reactions. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. Permanently discontinue BAVENCIO for Grade 3 or Grade 4 infusion-related reactions. Infusion-related reactions occurred in 25% of patients, including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids.

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

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

A **fatal adverse reaction** (sepsis) occurred in one (0.3%) patient with **locally advanced or metastatic urothelial carcinoma (UC)** receiving BAVENCIO + best supportive care (BSC) as first-line maintenance treatment. In patients with previously treated locally advanced or metastatic UC, fourteen patients (6%) who were treated with BAVENCIO experienced either pneumonitis, respiratory failure, sepsis/urosepsis, cerebrovascular accident, or gastrointestinal adverse events, which led to death.

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

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

Please see Brief Summary of Prescribing Information on following pages.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 3, 2021. 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 content or its use or application and disclaims any responsibility for 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.

LEARN MORE **at BAVENCIO.com**

May 2021 US-AVE-00615 V.2.1

BAVENCIO® (avelumab) injection, for intravenous use **Rx only**
BRIEF SUMMARY: Please see package insert for Full Prescribing Information

INDICATION AND USAGE

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Severe and Fatal 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, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

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.

Withhold or permanently discontinue BAVENCIO depending on severity. 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 (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis: BAVENCIO can cause immune-mediated pneumonitis. Immune-mediated pneumonitis occurred in 1.2% (21/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (0.3%) and Grade 2 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of BAVENCIO in 0.3% and withholding of BAVENCIO in 0.3% of patients. Systemic corticosteroids were required in all (21/21) patients with pneumonitis. Pneumonitis resolved in 57% (12/21) of the patients. Of the 5 patients in whom BAVENCIO was withheld for pneumonitis, 5 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of pneumonitis. With other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-Mediated Colitis: BAVENCIO can cause immune-mediated colitis. The primary component of the immune-mediated colitis consisted of diarrhea. Cytomegalovirus (CMV) 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. Immune-mediated colitis occurred in 1.5% (26/1738) of patients receiving BAVENCIO, including Grade 3 (0.4%) and Grade 2 (0.7%) adverse reactions. Colitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.5% of patients. Systemic corticosteroids were required in all (26/26) patients with colitis. Colitis resolved in 69% (18/26) of the patients. Of the 8 patients in whom BAVENCIO was withheld for colitis, 5 reinitiated treatment with BAVENCIO after symptom improvement; of these, 40% had recurrence of colitis.

Hepatotoxicity and Immune-Mediated Hepatitis: *BAVENCIO as a single agent*: BAVENCIO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.9% (16/1738) of patients receiving BAVENCIO, including fatal (0.1%), Grade 3 (0.6%), and Grade 2 (0.1%) adverse reactions. Hepatitis led to permanent discontinuation of BAVENCIO in 0.5% and withholding of BAVENCIO in 0.2% of patients. Systemic corticosteroids were required in all (16/16) patients with hepatitis. Hepatitis resolved in 56% (9/16) of the patients. Of the 3 patients in whom BAVENCIO was withheld for hepatitis, 3 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of hepatitis.

Immune-Mediated Endocrinopathies: *Adrenal Insufficiency*: BAVENCIO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement, as clinically indicated. Withhold BAVENCIO depending on severity. Immune-mediated adrenal insufficiency occurred in 0.5% (8/1738) of patients receiving BAVENCIO, including Grade 3 (0.1%), and Grade 2 (0.3%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in all (8/8) patients with adrenal insufficiency. Adrenal insufficiency did not resolve in any patient (0/8). Of the 2 patients in whom BAVENCIO was withheld for adrenal insufficiency, none reinitiated treatment with BAVENCIO. ***Hypophysitis:*** BAVENCIO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement, as clinically indicated. Withhold or permanently discontinue BAVENCIO depending on severity. Immune-mediated pituitary disorders occurred in 0.1% (1/1738) of patients receiving BAVENCIO which was a Grade 2 (0.1%) adverse reactions. Hypopituitarism did not lead to withholding of BAVENCIO in this patient. Systemic corticosteroids were not required in this patient. ***Thyroid Disorders:*** BAVENCIO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism, as clinically indicated. Withhold or permanently discontinue BAVENCIO depending on severity. ***Thyroiditis*** occurred in 0.2% (4/1738) of patients receiving BAVENCIO, including Grade 2 (0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation or withholding of BAVENCIO in any patients. No patients with thyroiditis required systemic corticosteroids. Thyroiditis did not resolve in any patients (0/4). ***Hyperthyroidism*** occurred in 0.4% (7/1738) of patients receiving BAVENCIO, including Grade 2 (0.3%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of BAVENCIO in any patients and led to withholding of BAVENCIO in 0.1% of patients. Systemic corticosteroids were required in 29% (2/7) of patients with hyperthyroidism. Hyperthyroidism resolved in 86% (6/7) of the patients. Of the 2 patients in whom BAVENCIO was withheld for hyperthyroidism, 2 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of hyperthyroidism. ***Hypothyroidism*** occurred in 5% (90/1738) of patients receiving BAVENCIO, including Grade 3 (0.2%) and Grade 2 (3.7%) adverse reactions. Hypothyroidism led to permanent discontinuation of BAVENCIO in 0.1% and withholding of BAVENCIO in 0.5% of patients. Systemic corticosteroids were required in 7% (6/90) of patients with hypothyroidism. Hypothyroidism resolved in 4% (4/90) of the patients. Of the 8 patients in whom BAVENCIO was withheld for hypothyroidism, none reinitiated BAVENCIO. ***Type I Diabetes Mellitus, which can present with Diabetic Ketoacidosis:*** Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold BAVENCIO depending on severity. Immune-mediated Type I diabetes mellitus occurred in 0.1% (2/1738) of patients receiving BAVENCIO, including Grade 3 (0.1%) adverse reactions. Type I diabetes mellitus led to permanent discontinuation of BAVENCIO in these two patients. Type I diabetes mellitus did not lead to withholding of BAVENCIO in any patient. Systemic corticosteroids were not required in any patient with Type I diabetes mellitus. Type I diabetes mellitus resolved in no patient and all patients required ongoing insulin treatment.

Immune-Mediated Nephritis with Renal Dysfunction: BAVENCIO can cause immune-mediated nephritis. Immune-mediated nephritis with renal dysfunction occurred in 0.1% (1/1738) of patients receiving BAVENCIO, which was a Grade 2 (0.1%) adverse reactions. Nephritis with renal dysfunction led to permanent discontinuation of BAVENCIO in this patient. Nephritis did not lead to withholding of BAVENCIO in any patient. Systemic corticosteroids were required in this patient. Nephritis with renal dysfunction did not resolve in this patient.

Immune-Mediated Dermatologic Adverse Reactions: BAVENCIO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue BAVENCIO depending on severity. Immune-mediated dermatologic adverse reactions occurred in 5% (90/1738) of patients receiving BAVENCIO, including Grade 3 (0.1%) and Grade 2 (2.0%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of BAVENCIO in 0.3% of patients and withholding of BAVENCIO in 0.4% of patients. Systemic corticosteroids were required in 29% (26/90) of patients with dermatologic adverse reactions. One patient required the addition of tacrolimus to high-dose corticosteroids. Dermatologic adverse reactions resolved in 41% (37/90) of the patients. Of the 7 patients in whom BAVENCIO was withheld for dermatologic adverse reactions, 3 reinitiated treatment with BAVENCIO after symptom improvement; of these, none had recurrence of dermatologic adverse reaction.

Other Immune-Mediated Adverse Reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received BAVENCIO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions. *Cardiac/Vascular:* Myocarditis, pericarditis, vasculitis. *Gastrointestinal:* Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis. *Nervous System:* Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy. *Ocular:* Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss. *Musculoskeletal and Connective Tissue:* Myositis/polymyositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis, polymyalgia rheumatic. *Endocrine:* Hypoparathyroidism. *Other (Hematologic/Immune):* Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

Infusion-Related Reactions: 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. Interrupt or slow 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. Infusion-related reactions occurred in 25% of patients treated with BAVENCIO including three (0.2%) Grade 4 and nine (0.5%) Grade 3 infusion-related reactions. Ninety-three percent of patients received premedication with antihistamine and acetaminophen. Eleven (92%) of the 12 patients with Grade ≥3 reactions were treated with intravenous corticosteroids. Fourteen percent of 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 allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity: Based on its mechanism of action, BAVENCIO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. If this drug is used during pregnancy, or if the patient becomes pregnant while taking BAVENCIO, inform the patient of the potential risk to a fetus. Advise females of childbearing potential to use effective contraception during treatment with BAVENCIO and for at least one month after the last dose of BAVENCIO.

ADVERSE REACTIONS

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

- Severe and fatal immune-mediated adverse reactions
- Infusion-related reactions
- Complications of allogeneic HSCT

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to BAVENCIO 10 mg/kg intravenously every 2 weeks as a single agent in 1738 patients enrolled in the JAVELIN Merkel 200 and JAVELIN Solid Tumor trials and to BAVENCIO 10 mg/kg intravenously every 2 weeks in combination with axitinib 5 mg orally twice daily in 489 patients enrolled in the JAVELIN Renal 100 and JAVELIN Renal 101 trials. In the BAVENCIO monotherapy population, 24% of patients were exposed for ≥ 6 months and 7% were exposed for ≥ 12 months. The following criteria were used to classify an adverse reaction as immune-mediated: onset within 90 days after last dose of BAVENCIO, no spontaneous resolution within 7 days of onset, treatment with corticosteroids or other immunosuppressant or hormone replacement therapy, biopsy consistent with immune-mediated reaction, and no other clear etiology.

Locally Advanced or Metastatic Urothelial Carcinoma
First-Line Maintenance Treatment of Urothelial Carcinoma
The safety of BAVENCIO was evaluated in the JAVELIN Bladder 100 trial where patients received BAVENCIO 10 mg/kg every 2 weeks plus best supportive care (BSC) (N=344) or BSC alone (N=345). Patients with autoimmune diseases or conditions requiring systemic immunosuppression were excluded. In the BAVENCIO plus BSC arm, 47% were exposed to BAVENCIO for > 6 months and 28% were exposed for > 1 year. The median age of patients treated with BAVENCIO plus BSC was 69 years (range: 37 to 90), 63% of patients were 65 years or older, 76% were male, 67% were White, and the ECOG performance score was 0 (61%) or 1 (39%). A fatal adverse reaction (sepsis) occurred in one (0.3%) patient receiving BAVENCIO plus BSC. Serious adverse reactions occurred in 28% of patients receiving BAVENCIO plus BSC. Serious adverse reactions in ≥ 1% of patients included urinary tract infection (including kidney infection, pyelonephritis, and urosepsis) (6.1%), pain (including abdominal, back, bone, flank, extremity, and pelvic pain) (3.2%), acute kidney injury (1.7%), hematuria (1.5%), sepsis (1.2%), and infusion-related reaction (1.2%). Permanent discontinuation due to an adverse reaction of BAVENCIO plus BSC occurred in 12% of patients.

Adverse reactions resulting in permanent discontinuation of BAVENCIO in > 1% of patients were myocardial infarction (including acute myocardial infarction and troponin T increased) (1.5%) and infusion-related reaction (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 interruption of BAVENCIO in > 2% 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 (≥ 20%) 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 ≥ 40 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)

Adverse Reactions	BAVENCIO plus BSC (N=344)		BSC (N=345)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
General Disorders and Administration Site Conditions				
Fatigue[a]	35	1.7	13	1.7
Pyrexia	15	0.3	3.5	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[b]	24	1.2	15	2.6
Arthralgia	16	0.6	6	0
Skin and Subcutaneous Tissue Disorders				
Rash[c]	20	1.2	2.3	0
Pruritus	17	0.3	1.7	0
Infections and Infestations				
Urinary tract infection[d]	20	6	11	3.8
Gastrointestinal Disorders				
Diarrhea	17	0.6	4.9	0.3
Constipation	16	0.6	9.0	0
Nausea	16	0.3	6	0.6
Vomiting	13	1.2	3.5	0.6
Respiratory, Thoracic and Mediastinal Disorders				
Cough[e]	14	0.3	4.6	0
Metabolism and Nutrition Disorders				
Decreased appetite	14	0.3	7	0.6
Endocrine disorders				
Hypothyroidism	12	0.3	0.6	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	10	0.9	0	0

[a]Fatigue is a composite term that includes fatigue, asthenia and malaise.
[b]Musculoskeletal pain is a composite term that includes musculoskeletal pain, back pain, myalgia, and neck pain.
[c]Rash is a composite term that includes rash, rash maculo-papular, erythema, dermatitis acneiform, eczema, erythema multiforme, rash erythematous, rash macular, rash papular, rash pruritic, drug eruption and lichen planus.
[d]Urinary tract infection is a composite term that includes urinary tract infection, urosepsis, cystitis, kidney infection, pyuria, pyelonephritis, bacteriuria, pyelonephritis acute, urinary tract infection bacterial, and Escherichia urinary tract infection.
[e]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)

Laboratory Abnormality	BAVENCIO plus BSC*		BSC*	
	Any Grade %	Grade 3-4 %	Any Grade %	Grade 3-4 %
Chemistry				
Blood triglycerides increased	34	2.1	28	1.2
Alkaline phosphatase increased	30	2.9	20	2.3
Blood sodium decreased	28	6	20	2.6
Lipase increased	25	8	16	6
Aspartate aminotransferase (AST) increased	24	1.7	12	0.9
Blood potassium increased	24	3.8	16	0.9
Alanine aminotransferase (ALT) increased	24	2.6	12	0.6
Blood cholesterol increased	22	1.2	16	0.3
Serum amylase increased	21	5	12	1.8
CPK increased	19	2.4	12	0
Phosphate decreased	19	3.2	15	1.2
Hematology				
Hemoglobin decreased	28	4.4	18	3.2
White blood cell decreased	20	0.6	10	0
Platelet count decreased	18	0.6	12	0.3

*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 detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to avelumab 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 plus BSC, 325 were evaluable for treatment-emergent anti-drug antibodies (ADA) and 62 (19.1%) tested positive in the JAVELIN Bladder 100 trial. Patients who tested 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 confounding variables.

USE IN SPECIFIC POPULATIONS

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

Data. ***Animal Data:*** 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 avelumab in human milk, the effects on the breastfed infant, or the effects on milk production. Since many drugs including antibodies are excreted in human milk, advise a lactating woman not to breastfeed during treatment and for at least one month after the last dose of BAVENCIO due to the potential for serious adverse reactions in breastfed infants.

Females and Males of Reproductive Potential, Contraception: 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 Urothelial 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).

Immune-Mediated 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 abdomen, lethargy, or easy bruising or bleeding.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypothyroidism, hyperthyroidism, 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 ankles, 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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RAPID REPORTER®

ONCOLOGY® Reviews Key Presentations From the 2022 International Association for the Study of Lung Cancer World Conference on Lung Cancer

ES-SCLC Responds to Temozolomide Plus Nivolumab Following Prior Chemotherapy

Patients with extensive-stage small cell lung cancer (ES-SCLC) previously treated with chemotherapy had impressive responses following therapy with temozolomide (Temodar) plus nivolumab (Opdivo), according to results of a multicohort, open-label phase 2 trial (NCT03728361). However, investigators found that only those with platinum-sensitive disease realized a benefit with the combination.

Twenty-five patients with ES-SCLC who progressed following first-line chemoimmunotherapy with treated and untreated brain metastases were included in the findings. The overall response rate (ORR) was 28% (95% CI, 12%-49%) at a median follow-up of 6.3 months. The response rate among platinum-sensitive patients (n = 15) was 47% (95% CI, 21%-73%) compared with 0% (95% CI, 0%-31%) among platinum-resistant patients (P = .057). The ORR was 20% (95% CI, 3%-56%) among patients who had brain metastases (n = 10) and 33% (95% CI, 12%-62%) among those who did not (n = 15; P = .659).

The median progression-free survival (PFS) for all 27 patients was 2.4 months (95% CI, 1.9-3.4). The median overall survival (OS) was 6.3 months (95% CI, 3.7-9.2).

All enrolled patients in the ES-SCLC cohort (N = 27) received 480 mg nivolumab and 150 mg/m^2 temozolomide for 5 days of each 28-day cycle. Two patients were not evaluable for ORR.

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Pembrolizumab Plus Lenvatinib Confers Promising Efficacy in Malignant Pleural Mesothelioma

Patients with malignant pleural mesothelioma (MPM) treated with pembrolizumab (Keytruda) plus lenvatinib (Lenvima) experienced promising clinical activity and safety, according to results from the phase 2 PEMMELA trial (NCT04287829).

In patients with MPM, there is a large unmet need for effective second-line treatment options. The PD-1 receptor blocker, pembrolizumab, has shown a response rate up to 20% as monotherapy whereas lenvatinib, a multiple tyrosine kinase inhibitor with mostly vascular endothelial growth factor receptor blocking properties, has synergistic interactions with PD-1 blocking in other tumors.

Preliminary results indicated that the objective response rate was 58%, and 76% of patients required dose reductions. At data cutoff on March 31, 2022, 22 of 38 patients had reached partial response (PR) as best overall response (95% CI, 41%-74%; P < .0001), 15 had a confirmed PR (95% CI, 24%-57%; P = .07). Among the 7 patients who had an unconfirmed PR, 3 can still reach a confirmed PR.

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Tislelizumab Maintains OS Benefit vs Docetaxel in Previously Treated NSCLC

Tislelizumab (BGB-A317) given in the second- or third-line setting resulted in improved overall survival (OS) compared with docetaxel for patients with non–small cell lung cancer (NSCLC), according to results of the phase 3 RATIONALE-303 trial (NCT03358875).

Median follow-up was 16.0 months and 10.7 months for the tislelizumab and docetaxel arms, respectively. The median OS for patients in the intention-to-treat population who received tislelizumab (n = 535) was 16.9 months (95% CI, 15.2-19.1) compared with 11.9 months (95% CI, 9.6-13.5) for those who received docetaxel (n = 270; HR, 0.66; 95% CI, 0.56-0.79; $P < .0001$). The 12- and 24-month OS rates for tislelizumab were 62.1% and 36.8%, respectively, and 49.7% and 23.7%, respectively, for docetaxel.

Patients with PD-L1 expression of at least 25% of tumor cells (PD-L1 positive) treated with tislelizumab (n = 227) had a median OS of 19.3 months (95% CI, 16.5-22.6) vs 11.5 months (95% CI, 8.2-13.5) with docetaxel (n = 116; HR, 0.53; 95% CI, 0.40-0.70; $P < .0001$). The 12- and 24-month OS rates were 67.4% and 42.3%, respectively, for patients in the tislelizumab arm compared with 47.8% and 22.3%, respectively, for patients in the docetaxel arm.

The previously reported interim analysis of the trial showed that tislelizumab significantly prolonged OS vs docetaxel. This led to the agent's approval in China in January 2022 for patients with advanced NSCLC who experienced disease progression after chemotherapy.

→ **For the full article, visit** CancerNetwork.com/2022WCLC_RATIONALE-303

Efficacy, Safety With Datopotamab Deruxtecan Plus Pembrolizumab Regimen Observed in Advanced NSCLC

Results from the phase 1b TROPION-Lung02 trial (NCT04526691) indicated that treatment of advanced/metastatic non–small cell lung cancer (NSCLC) without actionable genomic alterations was possible with the antibody-drug conjugate (ADC) datopotamab deruxtecan (DS-1062a) plus pembrolizumab (Keytruda), plus or minus platinum-based chemotherapy.

Data showed that patients who received the combination of datopotamab deruxtecan, pembrolizumab, and chemotherapy (the triplet) as first-line therapy (n = 20) achieved an overall response rate (ORR) of 50%, including a confirmed partial response (PR) rate of 35% and a pending PR rate of 15%. Additionally, 40% of patients had stable disease, for a disease control rate (DCR) of 90%.

Patients administered datopotamab deruxtecan plus pembrolizumab without chemotherapy (the doublet) as first-line therapy (n = 13) experienced an ORR of 62%, with all 8 responders achieving a confirmed PR. Furthermore, 39% of patients had stable disease, for a DCR of 100%.

As a second-line therapy, the doublet and triplet produced ORRs of 24% and 29%, respectively. In all patients who received the doublet and triplet, the ORRs were 37% and 41%, respectively. The overall DCR for both regimens was 84%.

Datopotamab deruxtecan consists of a TROP2 IgG1 monoclonal antibody linked to a topoisomerase I inhibitor payload by a tetrapeptide-based cleavable linker. The ADC is being evaluated in the TROPION-Lung02 trial at 2 dose levels in the doublet and the triplet regimens. In the dose-confirmation portion of the study, patients were required to have received no more than 2 lines of prior therapy. For the dose-expansion portion, no more than 1 prior line of therapy was permitted in cohorts 1 and 2, and cohorts 3 through 6 consisted of previously untreated patients.

→ **For the full article, visit** CancerNetwork.com/2022WCLC_TROPION

Addition of Tremelimumab to Durvalumab Regimen Induces Greater Survival Outcomes in PD-L1–Negative mNSCLC

Results from the phase 3 POSEIDON trial (NCT03164616) demonstrated that better survival and clinical benefit was possible when patients with PD-L1–negative metastatic non–small cell lung cancer (mNSCLC) were treated with tremelimumab plus durvalumab (Imfinzi) and chemotherapy vs either durvalumab plus chemotherapy or chemotherapy alone.

Median overall survival (OS) favored the tremelimumab plus durvalumab and chemotherapy group, and OS benefit was greater in patients with a tumor proportion score (TPS) of at least 1% vs those with a TPS less than 1%, who received one or both immunotherapy agents plus chemotherapy. The median OS for patients with PD-L1 TPS of 1% or greater was 15.6 months (95% CI, 11.6-18.1) with the doublet

plus chemotherapy, 14.4 months (95% CI, 11.8-17.5) with durvalumab plus chemotherapy, and 12.6 months (95% CI, 10.4-15.2) with chemotherapy alone. Median OS for patients with PD-L1 TPS less than 1% was 12.7 months (95% CI, 9.9-15.5) with the doublet plus chemotherapy, 10.9 months (95% CI, 8.1-13.5) for durvalumab plus chemotherapy, and 11.0 months (95% CI, 8.7-12.7) with chemotherapy alone.

Patients with mNSCLC (N = 1013) were randomized 1:1:1 to receive 75 mg of tremelimumab plus 1500 mg of durvalumab plus chemotherapy once every 3 weeks for 4 cycles, 1500 mg of durvalumab plus chemotherapy once every 3 weeks for 4 cycles, or chemotherapy once every 3 weeks up to 6 cycles.

The median progression-free survival (PFS) for patients with a PD-L1 TPS of 1% or greater was 6.2 months (95% CI, 5.0-6.6) with the doublet and chemotherapy, 6.4 months (95% CI, 4.9-6.7) with durvalumab and chemotherapy, and 4.9 months (95% CI, 4.9-6.0) with chemotherapy alone. The median PFS for patients with PD-L1 TPS less than 1% was 6.1 months (95% CI, 4.6-6.5), 4.6 months (95% CI, 4.0-5.0), and 4.7 months (95% CI, 4.6-6.2), respectively.

In patients with PD-L1 TPS of 1% or greater, those who received the doublet plus chemotherapy had an objective response rate (ORR) of 40.0%. Patients who received durvalumab and chemotherapy had an ORR of 49.1% and those who received chemotherapy alone had an ORR of 27.6%.

→ **For the full article, visit** CancerNetwork.com/2022WCLC_POSEIDON

CONTINUING MEDICAL EDUCATION (CME)

Broadening the Impact of Adjuvant Immunotherapy in Melanoma

FACULTY

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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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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Assess the latest clinical trials on current and emerging treatment options for melanoma
- Outline optimal management protocols for the treatment of melanoma
- Identify important toxicities related to immunotherapy in patients with melanoma

RELEASE DATE: September 1, 2022
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The development of BRAF directed targeted therapies and immune-checkpoint inhibitors (ICIs) have significantly improved outcomes for patients with advanced and metastatic melanoma. These agents have also demonstrated benefit in the stage III setting reducing rates of recurrence and becoming standard-of-care approaches.[1] Recently, the use of adjuvant therapy has shifted to earlier stages of melanoma, including for stage IIB and IIC disease.

This shift has expanded treatment options to reduce eventual melanoma recurrence; however, it will also impact considerations for patients who ultimately develop metastatic disease.[2] In this article, Jason J. Luke, MD, director of the Immunotherapy and Drug Development Center at UPMC Hillman Cancer Center in Pittsburgh, Pennsylvania, reviews the latest advances in current and emerging treatment options for melanoma.

Q: How do you balance efficacy versus potential toxicity of ICIs in stage II melanoma?

LUKE: KEYNOTE-716 demonstrated approximately a 35% improvement in relpase-free survival and distant-metastasis free survival in patients with stage IIB/C melanoma when comparing pembrolizumab treatment versus placebo. Given that the melanoma-specific survival and risk of recurrence for patients with stage IIB/C melanoma is approximately the same as stage IIIA/B, the clinical impact can be considered approximately the same in these populations.[3,4] Considering that then, use of adjuvant therapy for stage II isn't really any different than [that] for stage III. And what we think about is, what is the absolute reduction in the risk of recurrence with the administration of adjuvant therapy, and what is the absolute risk of an irreversible toxicity associated with immunotherapy?

When I consider this for my patients, I want to make sure that there's at least an equivalent potential for benefit as there is for [adverse] effects. We see that in stage IIB, IIC, IIIA, [and] IIIB, actually, you are reducing the risk on the order of about 5% to 10%.[3,4] When we think about those irreversible toxicities from immunotherapies, mostly the endocrinopathies [(eg,] hypophysitis, type 1 diabetes), we want to make sure that we're not risking those at a greater amount than what we would see in terms of improving the outcomes for patients.[5,6]

This is really the balancing act that we have to keep in mind as we talk with patients, because patients come from a perspective of commonly being, frankly, quite frightened about the cancer coming back. We want to level set with them to make sure [that] they're choosing what they believe to be right for them, both now and into the future, depending on what could happen to them thereafter.

Q: Do you think the findings of recent pivotal trials in stage II disease impact the use of sentinel lymph node biopsy?

LUKE: This is a great question, and, in fact, highly controversial. It's worth pointing out that in the melanoma oncology, medical oncology, and surgical oncology realms, the use of sentinel lymph node biopsy has been an established standard for a decade or more. However, in the dermatology community, there's actually been controversy around the use of sentinel lymph node biopsy. A substantial number of providers, especially Mohs surgeons, stopped doing sentinel lymph node [biopsy] an extended period ago. The results of KEYNOTE-716 [showed] that … the risk of recurrence is driven by the depth and ulceration of the primary lesion. Thus, whether or not a sentinel node is required anymore is now up in the air. The reason for that is if you have a deep primary, the adjuvant therapy that would be recommended for consideration would be anti–PD-1 [therapy] with pembrolizumab, whether or not you had a sentinel node.

Some people argue that we should still be doing sentinel lymph node biopsies, because the availability of BRAF inhibition as an adjuvant therapy is only available in the stage III setting. Others argue that [its] utility to risk stratification has an intrinsic value despite the lack of therapeutic intent associated with it. [Thus,] we've written that the use of sentinel lymph node biopsy is in flux.

My opinion is that we'll see an increasing group of patients who no longer pursue that procedure. And that's already started to become the case in my clinic. We still recommend it for most patients, as we have a number of clinical trials ongoing. But, certainly, I'm quite frank with patients that if they're not interested in going on a clinical trial, the utility of doing it, to me, is becoming a little bit less clear.

Q: As adjuvant immunotherapy is used for more patients with operable melanoma, what will the treatment landscape look like for patients who eventually develop metastatic disease?

LUKE: This is a very important question for our field, although one that we only have a little bit of experience with. We've had anti–PD-1 immunotherapy now for about 7 years. And, certainly, we've had to manage patients who progress on frontline anti–PD-1 [treatment] in the metastatic setting. Roughly speaking, that's about the same as what we see for patients who progress on adjuvant therapy. We are aware now that for patients who progress on anti–PD-1 monotherapy—so for example, pembrolizumab—if we continue anti–PD-1 [therapy] and add [an] anti–CTLA-4 [agent]with ipilimumab, we can get approximately a 30% response rate.[7]

We published a clinical trial investigating pembrolizumab plus low-dose

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ipilimumab after initial PD-1 [inhibitor] failure, but, subsequent to that, other groups published retrospective data confirming that 30% response rate.[7,8] The SWOG clinical trials group also published a prospective, randomized study demonstrating the same thing.[9] So we could transition over to a PD-1/CTLA-4 [blocker combination] at the time of progression. Obviously, for patients who have BRAF mutations in the tumor, they would have availability of BRAF inhibition in that setting. And then there are a number of molecules that are in early development that are looking quite promising.

One I'd really highlight would be tumor infiltrating lymphocyte (TIL) therapy delivered as adoptive cell transfer.[10] In 2 different cohorts, lifileucel has demonstrated a response rate of approximately 30% in PD-1-inhibitor–refractory melanoma.[11] Importantly, from the data that we've seen so far, it seems that the patients who benefit the most from TIL therapy are those who derive the least amount of benefit from anti–PD-1 [therapy (ie], people who progressed right away while getting anti–PD-1 [treatment]).[12] For patients who progress on adjuvant therapy, you start to think that a priority might be to harvest the tumor for TIL manufacture right away, despite the fact that we might want to give an interval therapy with a PD-1 [blocker] plus [a] CTLA-4 [inhibitor] while that TIL is being prepped.

Beyond that, there are number of other approaches. We have the recent approval of nivolumab and relatlimab for metastatic disease and melanoma.[13,14] How effective that therapy would be after progression on adjuvant therapy is an unknown question. But there are other molecules in the field that are also a high priority, including the use of VEGF blockade with lenvatinib plus pembrolizumab, which has looked exciting with about a 30% response rate after PD-1 [blockade] failure.[15]

There's an opportunity for that rapid drug development in the neoadjuvant setting, where we have a period of short exposure, and we can get a sense of what the activity looks like prior to surgery. That's a really exciting area that's evolving in the field, both as a primary modality [and] a drug development tool.

Q: What are the key ongoing developments in the adjuvant therapy setting?

LUKE: For stage III melanoma, there's RELATIVITY-098, comparing nivolumab monotherapy with nivolumab plus relatlimab.[16,17] That study is open for accrual currently, and [it] really hearkens back to this question about sentinel lymph nodes, because [it] is predicated on having a positive node [(ie], stage III [disease)]. But many people are excited about that study given the activity of nivolumab plus relatlimab in the metastatic setting. For stage II disease, there are 2 studies that are likely to impact standard of care. One of them is Checkmate 76K, which is a randomized study of nivolumab versus placebo in the same stage IIB and IIC population that KEYNOTE-716 established for pembrolizumab.[3,18]

[The other is the COLUMBUS-AD] study from the [European Organisation for the Research and Treatment of Cancer] ... which is investigating encorafenib and binimetinib—BRAF and MEK inhibitors—versus placebo, again, in that stage IIB and IIC melanoma setting.[19] Now that's a very interesting study, because they're also incorporating the use of gene expression profiling to try to predict who's at high risk.

Q: Are there any other key unanswered questions that remain regarding use of adjuvant immunotherapy for melanoma?

LUKE: Well, absolutely. And I think, in fact, we're only rather neophyte and at the beginning of our understanding of the optimal use for adjuvant therapy in melanoma. A major issue is the massive overtreatment of the population when we think about administering this to the total group of patients who land in stage IIB all the way through resected stage IV setting. We would much prefer to know exactly [who is going to experience recurrence] and who would benefit from that adjuvant therapy. The development of biomarkers to predict which patients need adjuvant therapy is, perhaps, the most important question in the field, given that now we're massively overtreating the population with our available therapies.

Q: How should we incorporate novel emerging treatment approaches in the metastatic disease setting when these therapies have been developed in patients naive to immunotherapy?

LUKE: It's a difficult question, because many of the [combinations] that we see coming forward [(eg,] the LAG3 [inhibitor combined] with relatlimab), may be substantially less active if patients have already had exposure to [an] anti–PD-1 [therapy]. Maybe that won't be a great therapy for refractory disease after progression on an adjuvant. So that highlights that we need novel mechanisms and new approaches that are not so dependent on PD-1 [inhibition] as the primary modality.

In other words, we've been developing PD-1 [inhibitor] plus X combinations

for a long time in the field. We really need to emphasize those [combinations] that bring in a new mechanism of action. We talked about TIL therapies, and that's a differentiated approach with adoptive cellular transfer. There's an opportunity for that rapid drug development in the neoadjuvant setting, where we have a period of short exposure, and we can get a sense of what the activity looks like prior to surgery. That's a really exciting area that's evolving in the field, both as a primary modality [and] a drug development tool.

Q: How do you view neoadjuvant therapy in the context of moving immunotherapy into stage II melanoma? Are there patients for whom you would prefer adjuvant to neoadjuvant therapy today, given what we know?

LUKE: The emerging data for neoadjuvant therapy in melanoma is quite exciting. In patients who are treated with neoadjuvant immunotherapy and who develop a major pathological response, few and, perhaps, none of those patients ever [experience recurrence]. That truly is exciting, because the patients who have participated in neoadjuvant trials to date really have high-risk lesions—palpable nodes that need to be surgically removed. Neoadjuvant therapy hasn't quite risen to the point of being a standard of care. [However], there [is] a randomized study ongoing through the SWOG Cooperative Group trying to establish that. If the question is, 'Do we prefer neoadjuvant versus adjuvant?' I think the answer is, 'Well, it depends.'

It depends on the individual patient in front of us realizing that the vast majority of patients currently are not eligible for neoadjuvant therapy, because they don't have palpable or recurrent disease. In the population where neoadjuvant [therapy] is possible, participation in a clinical trial is a high priority given the emerging data that we have. For the vast majority of patients, however, it's not relevant currently. Certainly, our standard of care [and] clinical workflows, from dermatology to surgery to medical oncology, lend themselves to the use of adjuvant therapy. That will continue to be the case, probably at a minimum, for the next 5 years. ■

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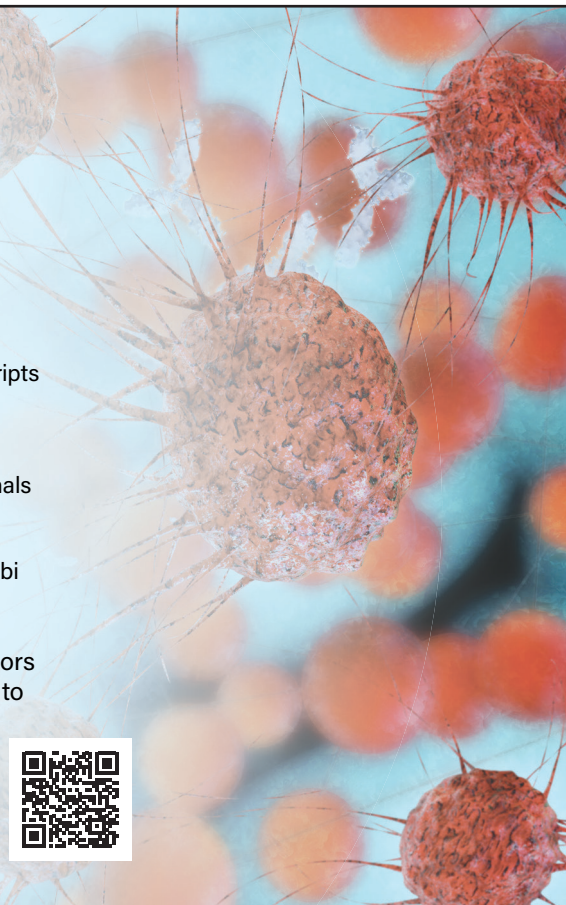

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