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ONCOLOGY®

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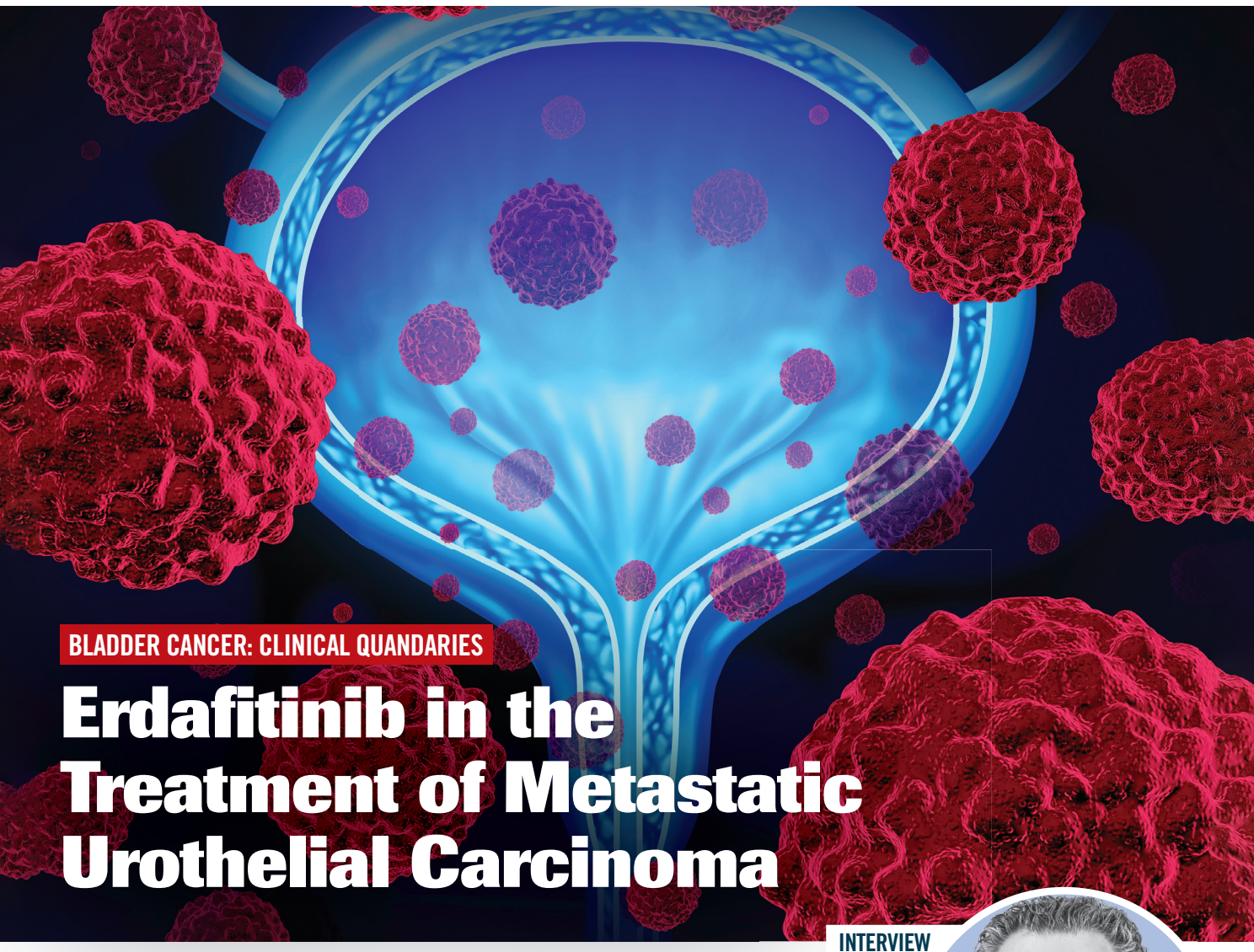

BLADDER CANCER: CLINICAL QUANDARIES

Erdafitinib in the Treatment of Metastatic Urothelial Carcinoma

INTERVIEW

Researchers Seek More Treatment Options for Gastrointestinal Cancer

TANIOS S. BEKAII-SAAB, MD

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MF=myelofibrosis; OS=overall survival.

References: 1. Kramann R et al. *Blood*. 2018;131(19):2111-2119. **2.** Palandri F et al. Poster EP1092 presented at: EHA2021; June 9-17, 2021; Virtual Congress. **3.** Tefferi A et al. *Mayo Clin Proc.* 2012;87(1):25-33. **4.** Gangat N et al. *J Clin Oncol.* 2011;29(4):392-397. **5.** Pettit K et al. *Curr Hematol Malig Rep*. 2017;12(6):611-624.

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MFTAKESHOLD

Beyond the surface of symptoms

MYELOFIBROSIS TIGHTENS ITS GRIP

MYELOFIBROSIS PROGRESSION
is often incessant and not always apparent[1,2]

≈60% of patients will have **intermediate-2 or high-risk disease at diagnosis**[3]

≈1.3 years and ≈2.9 years median OS for high-risk and intermediate-2 MF, respectively[4,5]

LEARN MORE ABOUT THE CONSEQUENCES OF MF PROGRESSION FOR PATIENTS

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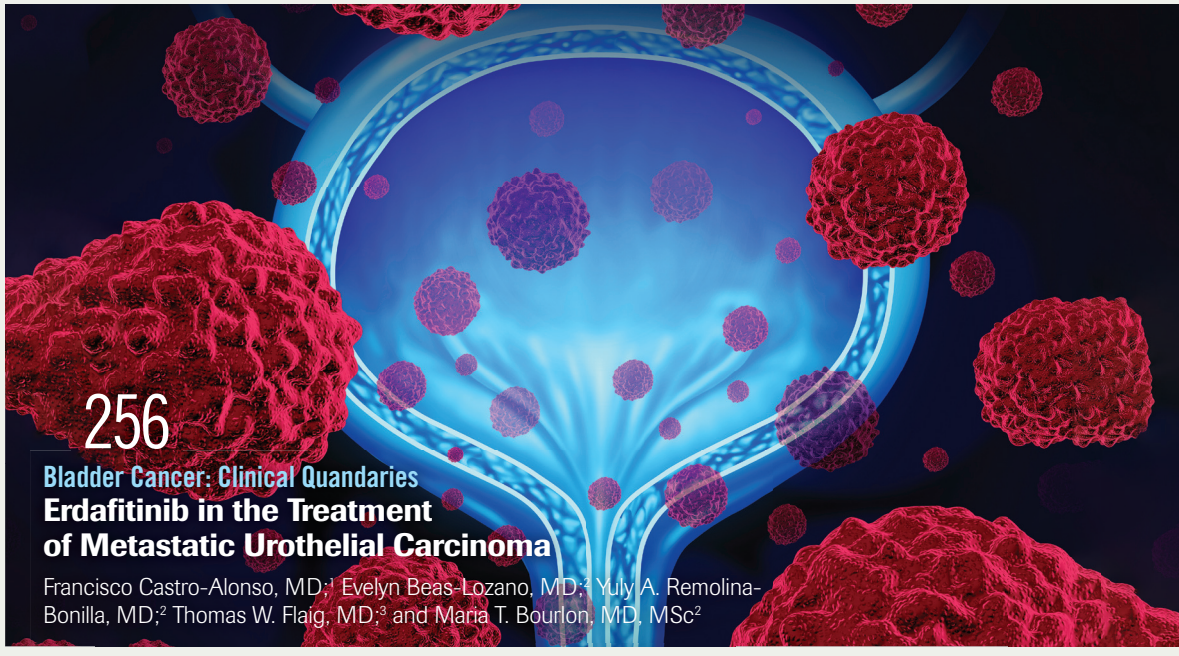

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OUR BOARD MEMBERS HAVE BEEN BUSY! TAKE A LOOK TO SEE WHAT THEY HAVE BEEN UP TO.

John L. Mulshine, MD
Lung Cancer Editorial Board Member
In a recently published article in *Annals of the American Thoracic Society*, of which Mulshine was the lead author, CT scans may help to detect emphysema. The study enrolled over 79,000 patients, of which scans detected emphysema in 23.8%. Investigators are hoping these results will better engage patients in monitoring and early detection, as well as living an overall healthy lifestyle.

Hossein Borghaei, DO, MS
Thoracic Malignancies Tumor Chair
At the 2023 European Lung Cancer Congress, Borghaei presented findings from part 1 of the phase 3 CheckMate 227 (NCT02477826) and the phase 2 CheckMate 568 (NCT02659059) exploratory studies. Those who had solid histologic, metastatic, nonsquamous non–small cell lung cancer had long-term survival benefits when nivolumab/ipilimumab were given.

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Care Plans, Education Improve Long-term Quality of Life

With 1 in 3 individuals receiving a cancer diagnosis sometime during their lifetime, we all are likely to experience cancer ourselves or to have a relative or close friend with cancer. Fortunately, there have been vast improvements in treatments and care for patients with cancer. But with those successful treatments often come short- and long-term toxicities that must be managed.

In 2006, the Institute of Medicine and the National Academies established a committee to examine the range of medical and psychosocial issues faced by cancer survivors needed to improve their health care and quality of life.[1] The committee set out 10 recommendations that fit into 4 broad categories: prevention, surveillance, intervention, and coordination.[1] One big part of the recommendations was that each patient who had received cancer therapy should receive a survivorship care plan written by the team providing the cancer care. These plans should be developed systematically and on evidence-based clinical practice guidelines, the committee noted. Many of these plans have been developed as a shared-care model in which specialists work collaboratively with primary care providers. This model is likely the most successful because much of the cancer survivor's health care is provided by their primary care network.

In addition to evaluations for cancer recurrence, services are needed for cancer screenings and evaluation of secondary effects such as organ dysfunction or secondary malignancies. Educating patients on primary and secondary prevention services, such as smoking cessation or regular cancer screening tests, is an important part of cancer survivorship. Cancer survivors also should receive additional lifestyle education such as how to maintain a healthy weight or increase activity. Some vital issues that are difficult to address include the need for services from psychologists or social workers. Even though the American Disabilities Act, has offered cancer survivors some protections from discriminatory practices, there are still many cases of health-related discrimination. Survivorship is an essential part of cancer care and benefits should be available based on evidence-based medicine.

The written survivorship care plan that is done at the end of active treatment for a patient with cancer does not guarantee a smooth transition or adequate education. It is an outline or road map for the patient, family, and primary care physician to follow. It should be a short, concise document that contains relevant information but does not overwhelm the patient or family. A specialty team trained to deliver the survivorship care plan is particularly beneficial in assisting patients with the transition.

A follow-up national cancer policy forum workshop in 2017 examined the implementation of the 2006 recommendations.[2] Although many of the original recommendations have been implemented, some are less universal, such as protections from health-related discriminatory practices.[2] Investing in research to improve cancer survivorship also was called out in the recommendations, particularly research on mechanisms of the late effects, prevalence of the risk of late effects, and interventions to improve the quality of life of all cancer survivors, their families, and caregivers. As a community of hematologists/oncologists, we owe it to our patients to not only improve our anticancer therapies but also to decrease the short- and long-term effects of the therapies we recommend for our patients. ■

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1. Institute of Medicine and National Research Council. *From Cancer Patient to Cancer Survivor: Lost in Transition.* The National Academies Press; 2005.

2. Kline RM, Arora NK, Bradley CJ, et al. Long-term survivorship care after cancer treatment - summary of a 2017 National Cancer Policy Forum workshop. *J Natl Cancer Inst.* 2018;110(12):1300-1310. doi:10.1093/jnci/djy176

MEET OUR EXPERT

Tanios S. Bekaii-Saab, MD, FACP, is the leader of the gastrointestinal cancer program, medical director of the Cancer Clinical Research Office, and vice chair and section chief for medical oncology in the Department of Internal Medicine at the Mayo Clinic in Phoenix, Arizona. He is also the cochair of the *20th Annual* Meeting of the International Society of Gastrointestinal Oncology®, hosted by Physician's Education Resource®, LLC.

Researchers Seek More Treatment Options for Gastrointestinal Cancer

"We're starting to see a lot of benefits with targeted therapies [and] immunotherapies. Unfortunately, these [benefits] remain limited to a small subset of patients across GI [gastrointestinal] [malignant tumors]. One of the biggest challenges is how to expand those benefits to the majority of patients."

In the current landscape of gastrointestinal (GI) cancer treatments, questions persist about whether targeted therapies or immunotherapies are better for various subsets of the population. As new treatments and combinations emerge, it is still unclear how they may affect the standard of care.

Tanios S. Bekaii-Saab, MD, FACP, discussed the current landscape and provided insight into the unmet needs of this population. Additionally, he reviewed upcoming FDA actions and how they might alter clinical practice. Bekaii-Saab also touched upon the biggest takeaway from the forthcoming meeting he chairs and why multidisciplinary practice is so important in the GI space.

Q: What are some unmet needs in the GI space?

BEKAII-SAAB: We're starting to see a lot of benefits with targeted therapies [and] immunotherapies. Unfortunately, these [benefits] remain limited to a small subset of patients across GI [malignant tumors]. One of the biggest challenges is how to expand those benefits to the majority of patients. [Can we do it] by breaking down those various cancers that [are segmented] into smaller and smaller subgroups? With immunotherapy, can we identify better biomarkers for those [with] non–microsatellite instability–high [disease]? It is obvious that there's a small subgroup of patients who may benefit [from immunotherapy]; it is yet to be determined [how best to identify them]. How do we best move forward with those patients while at the same time creating new ways to bring immunotherapy closer to many of these cancers? [We ask the] same [questions] with targeted therapies.

Q: How might the potential FDA approval for pembrolizumab (Keytruda) plus chemotherapy in locally advanced unresectable or metastatic gastroesophageal junction adenocarcinoma affect the current standard of care?

BEKAII-SAAB: It just consolidates the current standard [of care]. The current standard is chemotherapy plus immunotherapy. In [this type of] cancer, tumors with a higher propensity for a CPS [combined positive score] of 5 or more respond better than [those with a score of] 10 or more. For responders [with a CPS] between 1 and 5, it's [more] mixed, and you need more of the chemotherapy. [If a patient had a CPS of] less than 1, [they are not likely to be a good candidate] for immunotherapy. Overall, immunotherapy is now part of the treatment plan for more than 60% of patients with this cancer.

Q: How important is a multidisciplinary team in the GI space?

BEKAII-SAAB: In every aspect of our care, a multidisciplinary team is important but more in the earlier stages of the disease. In HCC

[hepatocellular carcinoma], for example, the multidisciplinary team remains committed to the patient all the way through until the disease becomes more advanced. You need to have pathology; you need an interventional radiologist because you need an early assessment. We're [reclassifying] some patients [disease] from transplant ineligible to transplant eligible, from unresectable to resectable. You want that team to be present at all times.

Our modalities in HCC include locoregional approaches, [and] we're examining the [use] of combining locoregional with systemic approaches. We heard about data from the phase 3 IMbrave050 study [NCT04102098], [which means that] adjuvant therapy with atezolizumab [Tecentriq] plus bevacizumab [Avastin] is likely to become a standard option for our patients.[1] Now more than ever, there's a need for multidisciplinary involvement.

[This is also the] same in [pancreatic cancer], at least in the early stages of the disease, and in colon cancer. Oligometastatic disease is a multidisciplinary problem and needs to be addressed with locoregional and systemic therapy in the earlier stages of the disease. Every aspect of our care in GI [cancer] requires some level of involvement from the multidisciplinary team, [and] for some aspects of our care, you need the full involvement of the multidisciplinary team to optimize outcomes and survival.

Q: What do you hope your colleagues take away from this conference?

BEKAII-SAAB: What we would like [the audience] to do is understand how the treatment paradigm continues to shift and learn how to adapt [these shifts] to the current [clinical] practice. [This conference should also] stimulate and excite folks about what's coming next. We hope that what's coming next is not just a checkbox that we're going to wait on but [invites] wider participation into thinking about clinical trials and [improves] referrals for trials, which continue to advance the [treatment landscape]. How are things affected in the current practice? How can we participate or create solutions for practice in [the coming years]? How can we continue to shift this landscape through participation or [by] creating new standards? ■

Reference

1. Chow P, Chen M, Cheng AL, et al. IMbrave050: phase 3 study of adjuvant atezolizumab + bevacizumab versus active surveillance in patients with hepatocellular carcinoma at high risk of disease recurrence following resection or ablation. Abstract presented at: American Association for Cancer Research Annual Meeting 2023; April 14-19, 2023; Orlando, FL. Abstract CT003.

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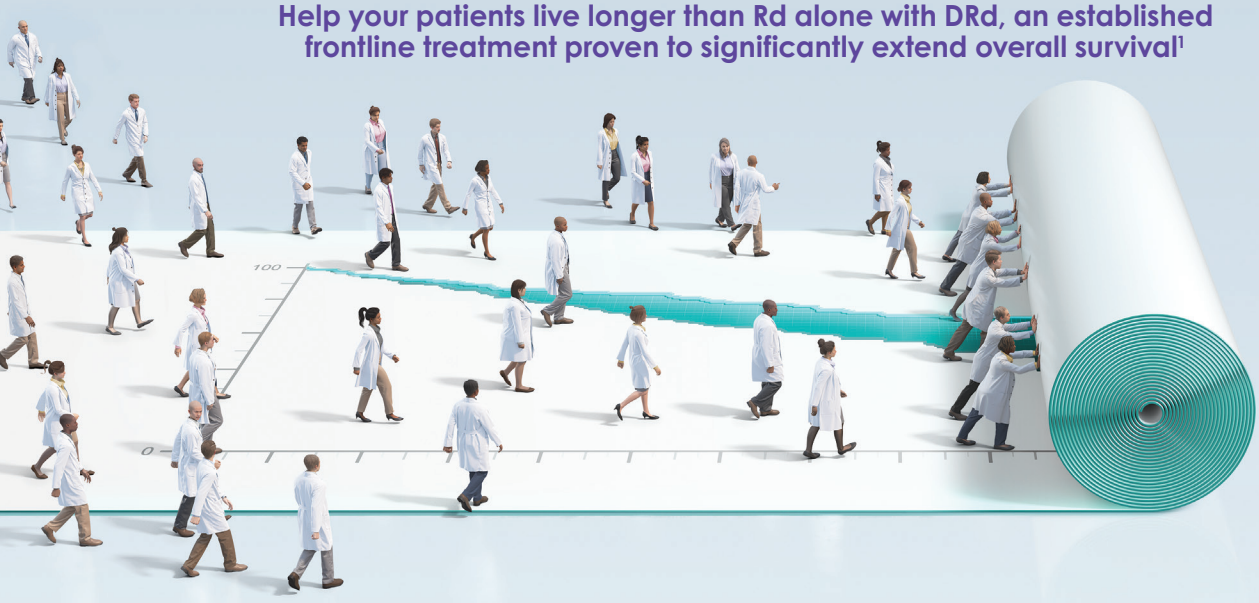
Help your patients live longer than Rd alone with DRd, an established frontline treatment proven to significantly extend overall survival[1]



At ~5 years: 32% reduction in the risk of death with DRd vs Rd alone in the MAIA trial
(HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013; mOS not reached in either arm).[1]*

*Median follow-up was 56 months in the DRd group (range: 53.0-60.1 months) and in the Rd group (range: 52.5-59.4 months)[1,2]

DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

IMPORTANT SAFETY INFORMATION AND INDICATIONS

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.

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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 progression-free survival and OS was a secondary endpoint.[1]

Powerful efficacy to start the treatment journey[1,3]

At follow-up of ~30 months*, **median progression-free survival (mPFS) was not reached** with **DARZALEX® (daratumumab) + Rd** vs 31.9 months (95% CI, 28.9 to not reached) with Rd alone

- **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)

Secondary endpoint of overall survival (OS)[1,2]

At ~5 years (56 months) of follow-up:

- 66% of patients were still alive with DRd vs 53% with Rd alone (DRd: 95% CI, 60.8–71.3; Rd: 95% CI, 47.2–58.6)‡
- Median follow-up was 56 months. Median OS was not reached for either arm

32% **reduction in the risk of death** in patients treated in the DRd arm vs Rd alone (HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013)

Demonstrated safety profile[1]

(median treatment duration of 25.3 months)

- The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, vomiting, upper respiratory tract infection, bronchitis, pneumonia, infusion-related reactions, peripheral edema, fatigue, asthenia, pyrexia, back pain, muscle spasms, dyspnea, cough, peripheral sensory neuropathy, and decreased appetite
- 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%)

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

At ~5 years (56 months)‡ of follow-up, **mPFS was not reached** with DRd vs 34.4 months with Rd alone.

- **52.5% of patients had not progressed** after ~5 years of treatment with DRd vs 28.7% with Rd alone (DRd, 95% CI: 46.7, 58.0; Rd, 95% CI: 23.1, 34.6)†

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 (PI). No conclusions should be drawn.

Safety results in long-term follow-up[2]

(median treatment duration of 47.9 months)

At median ~5 years of follow-up:

- Most frequent TEAEs§ for DRd ≥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 (18% vs 10%), 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 in the current PI. Treatment-emergent adverse events are reported as observed. These analyses have not been adjusted for multiple comparisons and no conclusions should be drawn.

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.

*Range: 0.0-41.4 months.[3]

†Kaplan-Meier estimate.

‡Range: 0.03-69.52 months.[2]

§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.

See the rolled-out data. Visit darzalexhcp.com

IMPORTANT SAFETY INFORMATION (CONTINUED)

DARZALEX®: Infusion-Related Reactions

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*® (daratumumab and hyaluronidase-fihj): 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*®.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj): Hypersensitivity and Other Administration Reactions

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.

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

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(11):1582-1596. doi:10.1016/s1470-2045(21)00466-6 **3.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104-2115.

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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, 0.35% (6/1,713) of patients developed treatment-emergent anti-daratumumab antibodies. Of those, 4 patients tested positive for neutralizing antibodies.

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
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cp-271933v3

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]*.

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).

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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cp-267681v2

Squamous Cell Carcinoma of the Kidney: A Large Case Series

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ABSTRACT

Objectives: We present our experience with and data about a very rare neoplasm of the kidney, squamous cell carcinoma (SCC).

Methods: A total of 14 patients with a diagnosis of SCC were identified on the basis of a retrospective analysis of medical records of patients who underwent surgery for renal cancers between 2015 and 2021 at the Sindh Institute of Urology and Transplantation. IBM SPSS v25 was used to record and analyze data.

Results: Most patients found to have SCC of the kidney were male (71.4%). The mean (SD) patient age was 56 (13.7) years. Flank pain was the most common presenting symptom (n = 11; 78.6%) followed by fever (n = 6; 42.9%). Only 4 (28.5%) of the 14 patients had a preoperatively established diagnosis of SCC; the remaining 10 (71.4%) had an incidental finding of SCC on their histopathology specimen. The mean (SD) overall survival was 5 (4.5) months.

Conclusions: SCC of the kidney is a rare upper urinary tract neoplasm reported in the literature. The gradual onset of vague symptoms, lack of pathognomonic signs, and inconclusive radiological features make the disease unsuspected in most cases, therefore delaying diagnosis and treatment. It usually presents at an advanced stage, and the prognosis is often poor. A high index of suspicion is warranted in patients with chronic kidney stone disease.

Introduction

Squamous cell carcinoma (SCC) of the kidney is an extremely rare neoplasm and accounts for less than 1% of all malignant renal tumors.[1-4] The gradual onset of vague symptoms, lack of pathognomonic signs, and inconclusive radiological features make the disease unsuspected in most cases, therefore delaying diagnosis and treatment.[5] The disease is reported to be associated with renal calculi, radiotherapy, infections, and other factors that chronically irritate the urothelium. Because of its rarity and lack of specific clinical and radiological features, it is diagnosed only after a nonfunctioning kidney has been removed for local symptoms.[2,3,5] Here, we report a case series of incidentally detected SCC of the kidney. To the best of our knowledge, only a few similar cases have previously been published.

Methods

Among the 2534 patients who underwent nephrectomy at the Sindh Institute of Urology and Transplantation between January 2015 and December 2021, 14 cases of SCC of the kidney were identified. All patients' medical records were reviewed retrospectively. The majority of the patients had an incidental finding of SCC of the kidney on postoperative histopathological examination of the specimen for simple nephrectomy of the nonfunctioning or pyonephrotic kidney, secondary to long-standing kidney stone disease. All patients received regular laboratory and radiological evaluations, including an ultrasound of the renal bed and a plain chest x-ray on follow-up. Patients who had an incidental finding of SCC on histopathology underwent more extensive postoperative radiological examination with contrast-enhanced CT scans of the chest, abdomen, and pelvis to rule out local recurrence and distant metastasis. Contrast-enhanced CT scans were also

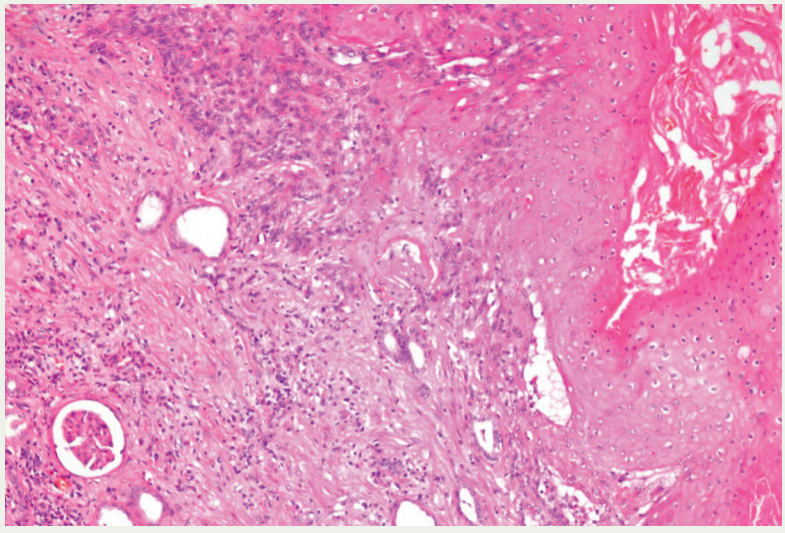

FIGURE 1. Medium-power view of kidney tissue with an infiltrating neoplastic lesion exhibiting nests and sheets of atypical squamous cells and abundant keratin formation in the right upper corner of the photomicrograph. (H&E: 200X)

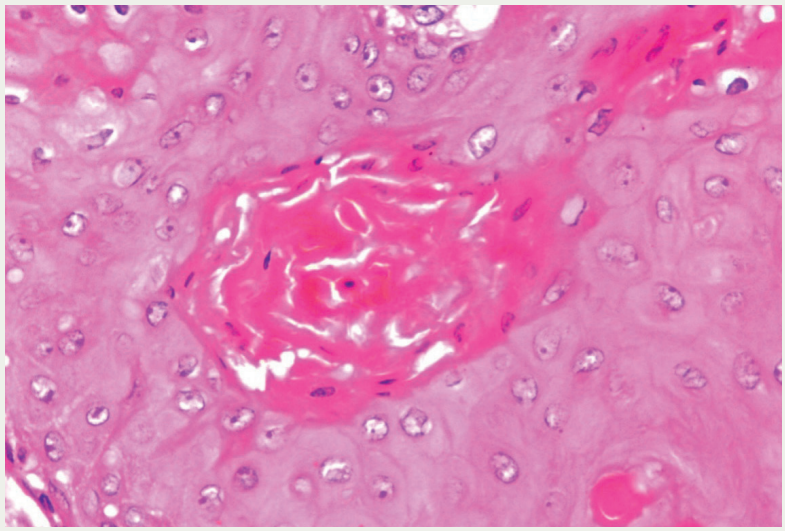

FIGURE 2. High-power view showing atypical squamous cells with abundant bright orangeophilic keratin pearl formation. (H&E: 400X)

performed for patients who had signs of recurrence on a follow-up ultrasound. The surgery and postoperative course of most patients remained uneventful; 2 patients developed purulent discharge from wounds that mimicked discharging sinus. Six patients whose nonfunctioning kidneys were surgically removed were found to have residual disease on postoperative radiological examination, and they underwent residual disease excision. Two of the 10 patients who had an incidental finding of SCC on histopathology (**Figure 1**) were found to have metastatic nodules in the lungs. None of the patients consented for chemotherapy; 6 patients received radiation therapy as part of pain management for secondary bony metastases. All 14 patients died because of extensive disease metastasis. IBM SPSS v25 was used to analyze the data.

Results

The mean (SD) age of the 14 patients was 56 (13.7) years, and 10 (71.4%) were male. Only 2 patients had reported comorbidities; one had diabetes and the other had hypertension. The modes of presentation were flank pain (n = 11; 78.6%), fever (n = 6; 42.9%), dysuria (n = 2; 14.3%), and wound discharge after surgery (n = 2; 14.3%). A history of renal stones was found in 9 (64.3%) patients, and 5 (35.7%) patients had renal failure. In 2 cases (14.3%), there was a suspicion of renal cell carcinoma (RCC), and in another 2 (14.3%) patients, transitional cell carcinoma of the kidney was suspected before surgery. The other 10 patients (71.4%) were having surgery to remove a nonfunctioning kidney; SCC was later diagnosed when the histopathological evaluation was completed (Figure 1 **and Figure 2**). The disease recurred in 6 (42.9%) of the patients. The mean (SD) overall survival (OS) of patients was 5 (4.5) months. For descriptive statistics see **Table 1**.

Discussion

Cancers of the kidney parenchyma and pelvis are the ninth and 12th most common causes of all cancer-related deaths.[6] SCC of the renal pelvis is an extremely rare, and an aggressive tumor that presents at an advanced stage and is known to arise from the collecting system. It accounts for less than 1% of all renal malignancies. Tumors arising from the urothelium of the renal pelvis and ureter are relatively rare neoplasms, making up 5% to 10% of all urothelial tumors.

TABLE 1. **Descriptive Statistics**

Patients in case series, N	14
Mean (SD) age, years	56 (13.7)
Male Female	10 (71.4%) 4 (28.6%)
Presentation	
Flank pain	11 (78.6%)
Fever	6 (42.9%)
Dysuria	2 (14.3%)
Wound discharge	2 (14.3%)
Other	6 (42.9%)
Preoperative diagnosis of malignancy	
Yes	4 (28.6%)
No	10 (71.4%)
Stones	
Yes	7 (64.3%)
No	4 (36.3%)
Side	
Right	6 (42.9%)
Left	8 (57.1%)
Comorbidities	
Diabetes mellitus	1 (7.1%)
Hypertension	1 (7.1%)
Recurrence	
Yes	6 (42.9%)
No	8 (57.1%)
Overall survival, mean (SD), months	5 (4.5)

Approximately 85% to 90% of upper urinary tract malignancies are urothelial carcinomas, while pure SCCs account for just 0.5% to 7.0%.[1,5,7]

Despite the rarity of this kidney tumor, this differential diagnosis should be investigated when a renal mass is accompanied by longstanding renal calculi. Factors that enhance the likelihood of SCC are chronic irritation, inflammation, and infections that promote squamous metaplasia of the renal pelvic epithelium. Chronic pyelonephritis or nephrolithiasis is frequently present in the pertinent medical history of SCC.[8]

Clinically, SCC tends to manifest in middle age (the fifth to seventh decades of life),[6,9] with a mean age at diagnosis of 56 years, and it affects males and females about equally. Our study found similar results, with a mean (SD) age of 56 (13.7) years. However, in our study, 10 of 14 of patients (71.4%) were male.

The modes of presentation reported in the literature include flank pain, hematuria, fever, anorexia, and weight loss.[5] These symptoms are often indistinguishable from those of the most common types of renal cancer. Most of the patients included in this series presented with flank pain, fever, dysuria, and wound discharge. Significantly, most instances of primary renal SCC are misdiagnosed, at least initially, because of the vague clinical symptoms and lack of distinct radiological diagnostic characteristics.[8,9]

The nonspecific nature of symptoms makes diagnosis and subsequent treatment difficult. There are currently no standard guidelines or treatment protocols for the management of patients with primary renal SCC.

According to research, factors that promote chronic urothelial injuries, such as renal calculi, radiotherapy, analgesic abuse, and infection, cause squamous metaplasia, which can progress to SCC.[10] In our study, renal stones were found in 64.3% of patients.

Unfortunately, a correct preoperative diagnosis of SCC is usually not made because patients' symptoms and radiological findings often mirror those of simple nonfunctioning kidneys secondary to stones or infection. SCC can be definitively diagnosed only when it is confirmed that a tumor exhibits squamous differentiation and specific histological signs, including the production of keratin pearls, intercellular bridges, and keratotic debris. A solid renal pelvic or ureteric mass, hydronephrosis, calcifications, or localized lymphadenopathy are radiological signs of renal pelvis SCC. These are nonspecific features that could be challenging to differentiate from those of other upper urinary tract neoplasms or other chronic inflammatory illnesses such as tuberculosis or xanthogranulomatous pyelonephritis.[11,12,13,14]

Ultrasonography typically reveals only hydronephrosis. However, CT is an important tool and can provide high-resolution imaging to evaluate masses and stages in renal malignancies.[13,15] Therefore ultrasound results only in incomplete staging and subsequent surgical planning for the removal of a presumed noncancerous kidney. In this series, only 4 cases (28.6%) were suspected of having malignancy—2 (14.3%) each of transitional cell carcinoma and RCC—before surgery, and the rest of the cases (71.4%) were operated on for a presumed nonfunctioning kidney. All of these cases turned out to be SCC after complete histopathological assessment.

Skin lesions caused by renal SCC are relatively uncommon. A fistula between the skin of the lumbar region and the kidney pole has been described in few case reports.[14] Two (14.3%) patients in our case series also developed postoperative cutaneous discharging sinus.

The cornerstone of SCC therapy has been radical surgery (ie, radical nephroureterectomy) for patients with disease localized to the kidney.[7-10,12,13,16] Nephrectomy is often necessary for metastatic disease to control symptoms and sometimes to establish the pathological diagnosis. Adjuvant cisplatin-based chemotherapy and palliative radiotherapy in metastatic cases have also been advocated for the control of symptoms, but their effect on survival is unknown.[5] Further large studies are required to establish the appropriate treatment for such patients. None of the patients in our case series consented for chemotherapy, but radiation therapy was offered to and received by 6 patients who had developed bony metastases.

It has been reported that the probability of 5-year survival is less than 10% and the mean OS is around 7 months.[17] In this series, disease recurrence was noted in 42.9% of patients at 3 months, and

the mean (SD) OS was 5 (4.5) months.

The scarcity of data, lack of guidelines, and retrospective nature of this case series remain the study's main limitations, which influenced our ability to draw conclusions regarding OS as well as to make concrete recommendations about when and how to apply diagnostic and treatment tools.

Conclusions

SCC of the renal pelvis is a rare tumor and is most often diagnosed postoperatively after nephrectomy for a presumed noncancerous kidney. The index of suspicion of malignancy should be high in cases of nonfunctioning kidneys with a long history of renal stones and infections. Such cases should be evaluated preoperatively by contrast-enhanced CT scans to establish the diagnosis of malignancy and achieve complete staging. ■

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(teclistamab-cqyv) Injection for subcutaneous use
10 mg/mL and 90 mg/mL

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For the 61.8% of patients who achieved ORR in MajesTEC-1

61.8%ORR*
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28.2% ≥CR† (n=31/110)
29.1% VGPR (n=32/110)
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*ORR: sCR+CR+VGPR+PR.
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INDICATION AND USAGE

TECVAYLI™ (teclistamab-cqyv) is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

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

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving TECVAYLI™. Initiate treatment with TECVAYLI™ step-up dosing schedule to reduce risk of CRS. Withhold TECVAYLI™ until CRS resolves or permanently discontinue based on severity.

Neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and serious and life-threatening reactions, can occur in patients receiving TECVAYLI™. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment and treat promptly. Withhold TECVAYLI™ until neurologic toxicity resolves or permanently discontinue based on severity.

TECVAYLI™ is available only through a restricted program called the TECVAYLI™ Risk Evaluation and Mitigation Strategy (REMS).

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome - TECVAYLI™ can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions. In the clinical trial, CRS occurred in 72% of patients who received TECVAYLI™ at the recommended dose, with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6%. Recurrent CRS occurred in 33% of patients. Most patients experienced CRS following step-up dose 1 (42%), step-up dose 2 (35%), or the initial treatment dose (24%).

Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI™. The median time to onset of CRS was 2 (range: 1 to 6) days after the most recent dose with a median duration of 2 (range: 1 to 9) days. Clinical signs and symptoms of CRS included, but were not limited to, fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation).

Initiate therapy according to TECVAYLI™ step-up dosing schedule to reduce risk of CRS. Administer pretreatment medications to reduce risk of CRS and monitor patients following administration of TECVAYLI™ accordingly. At the first sign of CRS, immediately evaluate patient for hospitalization. Administer supportive care based on severity and consider further management per current practice guidelines. Withhold or permanently discontinue TECVAYLI™ based on severity.

TECVAYLI™ is available only through a restricted program under a REMS.

Neurologic Toxicity including ICANS - TECVAYLI™ can cause serious or life-threatening neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

In the clinical trial, neurologic toxicity occurred in 57% of patients who received TECVAYLI™ at the recommended dose, with Grade 3 or 4 neurologic toxicity occurring in 2.4% of patients. The most frequent neurologic toxicities were headache (25%), motor dysfunction (16%), sensory neuropathy (15%), and encephalopathy (13%). With longer follow-up, Grade 4 seizure and fatal Guillain-Barré syndrome (one patient each) occurred in patients who received TECVAYLI™.

In the clinical trial, ICANS was reported in 6% of patients who received TECVAYLI™ at the recommended dose. Recurrent ICANS occurred in 1.8% of patients. Most patients experienced ICANS following step-up dose 1 (1.2%), step-up dose 2 (0.6%), or the initial treatment dose (1.8%). Less than 3% of patients developed first occurrence of ICANS following subsequent doses of TECVAYLI™. The median time to onset of ICANS was 4 (range: 2 to 8) days after the most recent dose with a median duration of 3 (range: 1 to 20) days. The most frequent clinical manifestations of ICANS reported were confusional state and dysgraphia. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

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

Choose TECVAYLI™, the first bispecific BCMA × CD3 T-cell engager given as an off-the-shelf subcutaneous injection for adult patients with RRMM who have received at least 4 prior lines of therapy, including a PI, an immunomodulatory agent, and an anti-CD38 monoclonal antibody[1,2]

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MajesTEC-1 study design:

The efficacy of TECVAYLI™ was evaluated in patients with RRMM in a single-arm, open-label, multi-center, phase 1/2 study. The study included patients who had previously received at least 3 prior therapies, including a PI, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.[1]

CD3, cluster of differentiation 3; CD38, cluster of differentiation 38; CI, confidence interval; CR, complete response; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; RRMM, relapsed or refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or permanently discontinue TECVAYLI™ based on severity per recommendations and consider further management per current practice guidelines.

Due to the potential for neurologic toxicity, patients are at risk of depressed level of consciousness. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI™ step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves.

TECVAYLI™ is available only through a restricted program under a REMS.

TECVAYLI™ REMS - TECVAYLI™ is available only through a restricted program under a REMS called the TECVAYLI™ REMS because of the risks of CRS and neurologic toxicity, including ICANS.

Hepatotoxicity - TECVAYLI™ can cause hepatotoxicity, including fatalities. In patients who received TECVAYLI™ at the recommended dose in the clinical trial, there was one fatal case of hepatic failure. Elevated aspartate aminotransferase (AST) occurred in 34% of patients, with Grade 3 or 4 elevations in 1.2%. Elevated alanine aminotransferase (ALT) occurred in 28% of patients, with Grade 3 or 4 elevations in 1.8%. Elevated total bilirubin occurred in 6% of patients with Grade 3 or 4 elevations in 0.6%. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TECVAYLI™ or consider permanent discontinuation of TECVAYLI™ based on severity.

Infections - TECVAYLI™ can cause severe, life-threatening, or fatal infections. In patients who received TECVAYLI™ at the recommended dose in the clinical trial, serious infections, including opportunistic infections, occurred in 30% of patients, with Grade 3 or 4 infections in 35%, and fatal infections in 4.2%. Monitor patients for signs and symptoms of infection prior to and during treatment with TECVAYLI™ and treat appropriately. Administer prophylactic antimicrobials according to guidelines. Withhold TECVAYLI™ or consider permanent discontinuation of TECVAYLI™ based on severity.

Monitor immunoglobulin levels during treatment with TECVAYLI™ and treat according to guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Neutropenia - TECVAYLI™ can cause neutropenia and febrile neutropenia. In patients who received TECVAYLI™ at the recommended dose in the clinical trial, decreased neutrophils occurred in 84% of patients, with Grade 3 or 4 decreased neutrophils in 56%. Febrile neutropenia occurred in 3% of patients.

Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local institutional guidelines. Monitor patients with neutropenia for signs of infection. Withhold TECVAYLI™ based on severity.

Hypersensitivity and Other Administration Reactions - TECVAYLI™ can cause both systemic administration-related and local injection-site reactions. Systemic Reactions - In patients who received TECVAYLI™ at the recommended dose in the clinical trial, 1.2% of patients experienced systemic-administration reactions, which included Grade 1 recurrent pyrexia and Grade 1 swollen tongue. Local Reactions - In patients who received TECVAYLI™ at the recommended dose in the clinical trial, injection-site reactions occurred in 35% of patients, with Grade 1 injection-site reactions in 30% and Grade 2 in 4.8%. Withhold TECVAYLI™ or consider permanent discontinuation of TECVAYLI™ based on severity.

Embryo-Fetal Toxicity - Based on its mechanism of action, TECVAYLI™ may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TECVAYLI™ and for 5 months after the last dose.

Adverse Reactions - The most common adverse reactions (≥20%) were pyrexia, CRS, musculoskeletal pain, injection site reaction, fatigue, upper respiratory tract infection, nausea, headache, pneumonia, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥20%) were decreased lymphocytes, decreased neutrophils, decreased white blood cells, decreased hemoglobin, and decreased platelets.

cp-322928v1

References: 1. TECVAYLI™ (teclistamab-cqyv) Prescribing Information. Janssen Biotech, Inc., Horsham, PA 19044. **2.** US Food and Drug Administration. FDA approves teclistamab-cqyv for relapsed or refractory multiple myeloma. Accessed November 9, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma

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Brief Summary of Prescribing Information for TECVAYLI™ (teclistamab-cqyv)

TECVAYLI™ (teclistamab-cqyv) injection, for subcutaneous use

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, can occur in patients receiving TECVAYLI. Initiate treatment with TECVAYLI step-up dosing schedule to reduce risk of CRS. Withhold TECVAYLI until CRS resolves or permanently discontinue based on severity *[see Dosage and Administration (2.1, 2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and serious and life-threatening reactions, can occur with TECVAYLI. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment. Withhold TECVAYLI until neurologic toxicity resolves or permanently discontinue based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Because of the risk of CRS and neurologic toxicity, including ICANS, TECVAYLI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TECVAYLI REMS *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

TECVAYLI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome

TECVAYLI can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions *[see Adverse Reactions]*.

In the clinical trial, CRS occurred in 72% of patients who received TECVAYLI at the recommended dose, with Grade 1 CRS occurring in 50% of patients, Grade 2 in 21%, and Grade 3 in 0.6%. Recurrent CRS occurred in 33% of patients. Most patients experienced CRS following step-up dose 1 (42%), step-up dose 2 (35%), or the initial treatment dose (24%). Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI. The median time to onset of CRS was 2 (range: 1 to 6) days after the most recent dose with a median duration of 2 (range: 1 to 9) days.

Clinical signs and symptoms of CRS included, but were not limited to, fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation).

Initiate therapy according to TECVAYLI step-up dosing schedule to reduce risk of CRS *[see Dosage and Administration (2.1, 2.4) in Full Prescribing Information]*. Administer pretreatment medications to reduce risk of CRS and monitor patients following administration of TECVAYLI accordingly *[see Dosage and Administration (2.2, 2.4) in Full Prescribing Information]*.

At the first sign of CRS, immediately evaluate patient for hospitalization. Administer supportive care based on severity and consider further management per current practice guidelines. Withhold or permanently discontinue TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

TECVAYLI is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

Neurologic Toxicity including ICANS

TECVAYLI can cause serious or life-threatening neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) *[see Adverse Reactions]*.

In the clinical trial, neurologic toxicity occurred in 57% of patients who received TECVAYLI at the recommended dose, with Grade 3 or 4 neurologic toxicity occurring in 2.4% of patients. The most frequent neurologic toxicities were headache (25%), motor dysfunction (16%), sensory neuropathy (15%), and encephalopathy (13%).

With longer follow-up, Grade 4 seizure and fatal Guillain-Barré syndrome (one patient each) occurred in patients who received TECVAYLI.

In the clinical trial, ICANS was reported in 6% of patients who received TECVAYLI at the recommended dose *[see Adverse Reactions]*. Recurrent ICANS occurred in 1.8% of patients. Most patients experienced ICANS following step-up dose 1 (1.2%), step-up dose 2 (0.6%), or the initial treatment dose (1.8%). Less than 3% of patients developed first occurrence of ICANS following subsequent doses of TECVAYLI. The median time to onset of ICANS was 4 (range: 2 to 8) days after the most recent dose with a median duration of 3 (range: 1 to 20) days. The most frequent clinical manifestations of ICANS reported were confusional state and dysgraphia. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Monitor patients for signs and symptoms of neurologic toxicity during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or permanently discontinue TECVAYLI based on severity per recommendations and consider further management per current practice guidelines *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Due to the potential for neurologic toxicity, patients receiving TECVAYLI are at risk of depressed level of consciousness *[see Adverse Reactions]*. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

TECVAYLI is available only through a restricted program under a REMS *[see Warnings and Precautions]*.

TECVAYLI REMS

TECVAYLI is available only through a restricted program under a REMS called the TECVAYLI REMS because of the risks of CRS and neurologic toxicity, including ICANS *[see Warnings and Precautions]*.

Notable requirements of the TECVAYLI REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Prescribers must counsel patients receiving TECVAYLI about the risk of CRS and neurologic toxicity, including ICANS, and provide patients with Patient Wallet Card.
- Pharmacies and healthcare settings that dispense TECVAYLI must be certified with the TECVAYLI REMS program and must verify prescribers are certified through the TECVAYLI REMS program.
- Wholesalers and distributers must only distribute TECVAYLI to certified pharmacies or healthcare settings.

Further information about the TECVAYLI REMS program is available at www.TECVAYLIREMS.com or by telephone at 1-855-810-8064.

Hepatotoxicity

TECVAYLI can cause hepatotoxicity, including fatalities. In patients who received TECVAYLI at the recommended dose in the clinical trial, there was one fatal case of hepatic failure. Elevated aspartate aminotransferase (AST) occurred in 34% of patients, with Grade 3 or 4 elevations in 1.2%. Elevated alanine aminotransferase (ALT) occurred in 28% of patients, with Grade 3 or 4 elevations in 1.8%. Elevated total bilirubin occurred in 6% of patients with Grade 3 or 4 elevations in 0.6%. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Infections

TECVAYLI can cause severe, life-threatening, or fatal infections. In patients who received TECVAYLI at the recommended dose in the clinical trial, serious infections, including opportunistic infections, occurred in 30% of patients, with Grade 3 or 4 infections in 35%, and fatal infections in 4.2% *[see Adverse Reactions]*.

Monitor patients for signs and symptoms of infection prior to and during treatment with TECVAYLI and treat appropriately. Administer prophylactic antimicrobials according to guidelines *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Monitor immunoglobulin levels during treatment with TECVAYLI and treat according to guidelines, including infection precautions and antibiotic or antiviral prophylaxis *[see Dosage and Administration (2.2) in Full Prescribing Information]*.

Neutropenia

TECVAYLI can cause neutropenia and febrile neutropenia. In patients who received TECVAYLI at the recommended dose in the clinical trial, decreased neutrophils occurred in 84% of patients, with Grade 3 or 4 decreased neutrophils in 56%. Febrile neutropenia occurred in 3% of patients *[see Adverse Reactions]*.

Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local institutional guidelines.

Monitor patients with neutropenia for signs of infection.

Withhold TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Hypersensitivity and Other Administration Reactions

TECVAYLI can cause both systemic administration-related reactions and local injection-site reactions.

Systemic Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trial, 1.2% of patients experienced systemic-administration reactions, which included Grade 1 recurrent pyrexia and Grade 1 swollen tongue.

Local Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trial, injection-site reactions occurred in 35% of patients with Grade 1 injection-site reactions in 30% and Grade 2 in 4.8%.

Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

Embryo-Fetal Toxicity

Based on its mechanism of action, TECVAYLI may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with TECVAYLI and for 5 months after the last dose *[see Use in Specific Populations]*.

ADVERSE REACTIONS

The following adverse reactions are also described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions]*
- Neurologic Toxicity including ICANS *[see Warnings and Precautions]*
- Hepatotoxicity *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Neutropenia *[see Warnings and Precautions]*
- Hypersensitivity and Other Administration Reactions *[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

MajesTEC-1

The safety of TECVAYLI was evaluated in MajesTEC-1 *[see Clinical Studies (14) in Full Prescribing Information]* which included adult patients with relapsed or refractory multiple myeloma. Patients received step-up doses of 0.06 mg/kg and 0.3 mg/kg of TECVAYLI followed by TECVAYLI 1.5 mg/kg, subcutaneously once weekly (N=165). Among patients who received TECVAYLI, 47% were exposed for 6 months or longer and 7% were exposed for one year or longer.

The median age of patients who received TECVAYLI was 64 years (range: 33 to 84 years); 58% were male; 81% were White, 13% were Black or African American, and 2% were Asian.

Serious adverse reactions occurred in 54% of patients who received TECVAYLI. Serious adverse reactions in >2% of patients included pneumonia (15%), cytokine release syndrome (8%), sepsis (6%), general physical health deterioration (6%), COVID-19 (6%), acute kidney injury (4.8%), pyrexia (4.8%), musculoskeletal pain (2.4%), and encephalopathy (2.4%).

Fatal adverse reactions occurred in 5% of patients who received TECVAYLI, including COVID-19 (1.8%), pneumonia (1.8%), septic shock (0.6%), acute renal failure (0.6%), and hemoperitoneum (0.6%).

Permanent discontinuation of TECVAYLI due to adverse reactions occurred in 1.2% of patients. Adverse reactions resulting in permanent discontinuation of TECVAYLI included pneumonia (adenoviral and pneumocystis jirovecii pneumonia in the same patient) and hypercalcemia.

Dosage interruptions of TECVAYLI due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in >5% of patients included neutropenia, pneumonia, pyrexia, cytokine release syndrome, upper respiratory tract infection, and COVID-19.

The most common adverse reactions (≥20%) were pyrexia, CRS, musculoskeletal pain, injection site reaction, fatigue, upper respiratory tract infection, nausea, headache, pneumonia, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥20%) were decreased lymphocytes, decreased neutrophils, decreased white blood cells, decreased hemoglobin, and decreased platelets.

Table 1 summarizes the adverse reactions in MajesTEC-1.

Table 1: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1

Adverse Reactions	TECVAYLI (N=165)	
	Any Grade (%)	Grade 3 or 4 (%)
General disorders and administration site conditions		
Pyrexia	76	3#
Injection site reaction[1]	37	0.6#
Fatigue[2]	33	2.4#
Chills	16	0
Pain[3]	15	1.8#
Edema[4]	13	0
Immune system disorders		
Cytokine release syndrome	72	0.6#
Hypogammaglobulinemia[5]	11	1.2#
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[6]	44	4.2#
Bone pain	16	3#
Infections		
Upper respiratory tract infection[7]	26	2.4#
Pneumonia[8*]	24	15
Urinary tract infection[9]	11	5#

TECVAYLI™ (teclistamab-cqyv) injection

Table 1: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1 (continued)

Adverse Reactions	TECVAYLI (N=165)	
	Any Grade (%)	Grade 3 or 4 (%)
Gastrointestinal disorders		
Nausea	25	0.6#
Diarrhea	21	2.4#
Constipation	18	0
Vomiting	12	0.6#
Nervous system disorders		
Headache	25	0.6#
Motor dysfunction[10]	16	0
Sensory neuropathy[11]	15	1.2#
Encephalopathy[12]	13	0
Vascular disorders		
Hypotension	18	1.2#
Hemorrhage[13*]	12	1.8
Hypertension[14]	12	4.8#
Respiratory, thoracic, and mediastinal disorders		
Hypoxia	18	1.8
Cough[15]	15	0
Cardiac disorders		
Cardiac arrhythmia[16]	16	1.8
Metabolism and nutrition disorders		
Decreased appetite	11	0.6#
Renal and urinary disorders		
Acute kidney injury[17]	11	3.6

Adverse reactions were graded based on CTCAE Version 4.03, with the exception of CRS, which was graded per ASTCT 2019 criteria.

[1] Injection site reaction includes application site erythema, injection site bruising, injection site cellulitis, injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site edema, injection site pruritus, injection site rash, injection site reaction and injection site swelling.

[2] Fatigue includes asthenia and fatigue.

[3] Pain includes ear pain, flank pain, groin pain, oropharyngeal pain, pain, pain in jaw, toothache and tumor pain.

[4] Edema includes face edema, fluid overload, fluid retention, edema peripheral and peripheral swelling.

[5] Hypogammaglobulinemia includes hypogammaglobulinemia and hypoglobulinemia.

[6] Musculoskeletal pain includes arthralgia, back pain, muscle discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain and pain in extremity.

[7] Upper respiratory tract infection includes bronchitis, influenza like illness, nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection bacterial, rhinitis, rhinovirus infection, sinusitis, tracheitis, upper respiratory tract infection and viral upper respiratory tract infection.

[8] Pneumonia includes COVID-19 pneumonia, enterobacter pneumonia, lower respiratory tract infection, metapneumovirus pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia klebsiella, pneumonia moraxella, pneumonia pneumococcal, pneumonia pseudomonal, pneumonia respiratory syncytial viral, pneumonia staphylococcal and pneumonia viral.

[9] Urinary tract infection includes cystitis, cystitis escherichia, cystitis klebsiella, escherichia urinary tract infection, urinary tract infection and urinary tract infection bacterial.

[10] Motor dysfunction includes cogwheel rigidity, dysgraphia, dysphonia, gait disturbance, hypokinesia, muscle rigidity, muscle spasms, muscular weakness, peroneal nerve palsy, psychomotor hyperactivity, tremor and VIth nerve paralysis.

[11] Sensory neuropathy includes dysesthesia, hypoesthesia, hypoesthesia oral, neuralgia, paresthesia, paresthesia oral, peripheral sensory neuropathy, sciatica and vestibular neuronitis.

[12] Encephalopathy includes agitation, apathy, aphasia, confusional state, delirium, depressed level of consciousness, disorientation, dyscalculia, hallucination, lethargy, memory impairment, mental status changes and somnolence.

[13] Hemorrhage includes conjunctival hemorrhage, epistaxis, hematoma, hematuria, hemoperitoneum, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage and subdural hematoma.

[14] Hypertension includes essential hypertension and hypertension.

[15] Cough includes allergic cough, cough, productive cough and upper-airway cough syndrome.

[16] Cardiac arrhythmia includes atrial flutter, cardiac arrest, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, tachycardia and ventricular tachycardia.

[17] Acute kidney injury includes acute kidney injury and renal impairment.

Only grade 3 adverse reactions occurred.

* Includes the following fatal adverse reactions: hemorrhage (n=1), pneumonia (n=3).

Clinically relevant adverse reactions in <10% of patients who received TECVAYLI included febrile neutropenia, sepsis, ICANS, seizure, Guillain-Barré syndrome, hepatic failure, and new onset or reactivated viral infections (including adenovirus, hepatitis B virus (HBV), cytomegalovirus (CMV), varicella zoster virus (VZV), and herpes simplex virus (HSV)).

Table 2 summarizes laboratory abnormalities in MajesTEC-1.

Table 2: Select Laboratory Abnormalities (≥30%) That Worsened from Baseline in Patients with Multiple Myeloma Who Received TECVAYLI in MajesTEC-1

	TECVAYLI (N=165[1])	
Laboratory Abnormality	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology		
Lymphocyte count decreased	92	84
White blood cell decreased	86	41
Neutrophil count decreased	84	56
Platelet count decreased	71	22
Hemoglobin decreased	67	33
Chemistry		
Albumin decreased	68	6
Alkaline phosphatase increased	42	2.4
Phosphorus decreased	38	13
Gamma-glutamyl transferase increased	37	8
Sodium decreased	35	10
Aspartate aminotransferase increased	34	1.2
Calcium (corrected) decreased	31	1.2
Creatinine increased	30	3

[1] The denominator used to calculate the rate varied from 164 to 165 based on the number of patients with a baseline value and at least one post-treatment value.

Laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

DRUG INTERACTIONS

TECVAYLI causes release of cytokines *[see Clinical Pharmacology (12.2) in Full Prescribing Information]* that may suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. The highest risk of drug-drug interaction is expected to occur from initiation of TECVAYLI step-up dosing schedule up to 7 days after the first treatment dose and during and after CRS *[see Warnings and Precautions]*. Monitor for toxicity or concentrations of drugs that are CYP substrates where minimal concentration changes may lead to serious adverse reactions. Adjust the dose of the concomitant CYP substrate drug as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action, TECVAYLI may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. There are no available data on the use of TECVAYLI in pregnant women. No animal reproductive or developmental toxicity studies have been conducted with TECVAYLI. Teclistamab-cqyv causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, teclistamab-cqyv has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

TECVAYLI is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with TECVAYLI should be considered.

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.

Lactation

Risk Summary

There are no data on the presence of teclistamab-cqyv in human milk, the effect on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to TECVAYLI are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with TECVAYLI and for 5 months after the last dose.

Females and Males of Reproductive Potential

TECVAYLI may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

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

TECVAYLI™ (teclistamab-cqyv) injection

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 5 months after the last dose of TECVAYLI.

Pediatric Use

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

Geriatric Use

Of the 165 patients with relapsed or refractory multiple myeloma treated with TECVAYLI in MajesTEC-1 at the recommended dosage, 48% were 65 years of age or older, and 15% were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients 65 to 74 years of age compared to younger patients. There is an insufficient number of patients 75 years of age or older to assess whether there are differences in safety or effectiveness.

PATIENT COUNSELING INFORMATION

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

Cytokine Release Syndrome (CRS)

Discuss the signs and symptoms associated with CRS, including fever, hypoxia, chills, hypotension, sinus tachycardia, headache, and elevated liver enzymes. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of CRS. Advise patients that they will be hospitalized for 48 hours after administration of all doses within the TECVAYLI step-up dosing schedule *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neurologic Toxicity including ICANS

Discuss the signs and symptoms associated with neurologic toxicity, including ICANS, including headache, confusion, dysgraphia, motor dysfunction, neuropathy, or encephalopathy. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of neurologic toxicity. Advise patients to refrain from driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule and in the event of new onset of any neurologic toxicity symptoms until neurologic toxicity resolves *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

TECVAYLI REMS

TECVAYLI is available only through a restricted program called TECVAYLI REMS. Inform patients that they will be given a TECVAYLI Patient Wallet Card that they should carry with them at all times and show to all of their healthcare providers. This card describes signs and symptoms of CRS and neurologic toxicity which, if experienced, should prompt the patient to immediately seek medical attention *[see Warnings and Precautions]*.

Hepatotoxicity

Advise patients that liver enzyme elevations may occur and that they should report symptoms that may indicate liver toxicity, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions]*.

Infections

Discuss the signs and symptoms of infection *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Neutropenia

Discuss the signs and symptoms associated with neutropenia and febrile neutropenia *[see Dosage and Administration (2.4) in Full Prescribing Information and Warnings and Precautions]*.

Hypersensitivity and Other Administration Reactions

Advise patients to immediately seek medical attention for any signs and symptoms of systemic administration-related reactions. Advise patients that local injection-site reactions may occur and to report any severe reactions *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with TECVAYLI and for 5 months after the last dose *[see Warnings and Precautions and Use in Specific Populations]*.

Lactation

Advise women not to breastfeed during treatment with TECVAYLI and for 5 months after the last dose *[see Use in Specific Populations]*.

Manufactured by:
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Erdafitinib in the Treatment of Metastatic Urothelial Carcinoma

Francisco Castro-Alonso, MD;[1] Evelyn Beas-Lozano, MD;[2] Yuly A. Remolina-Bonilla, MD;[2] Thomas W. Flaig, MD;[3] and Maria T. Bourlon, MD, MSc[2]

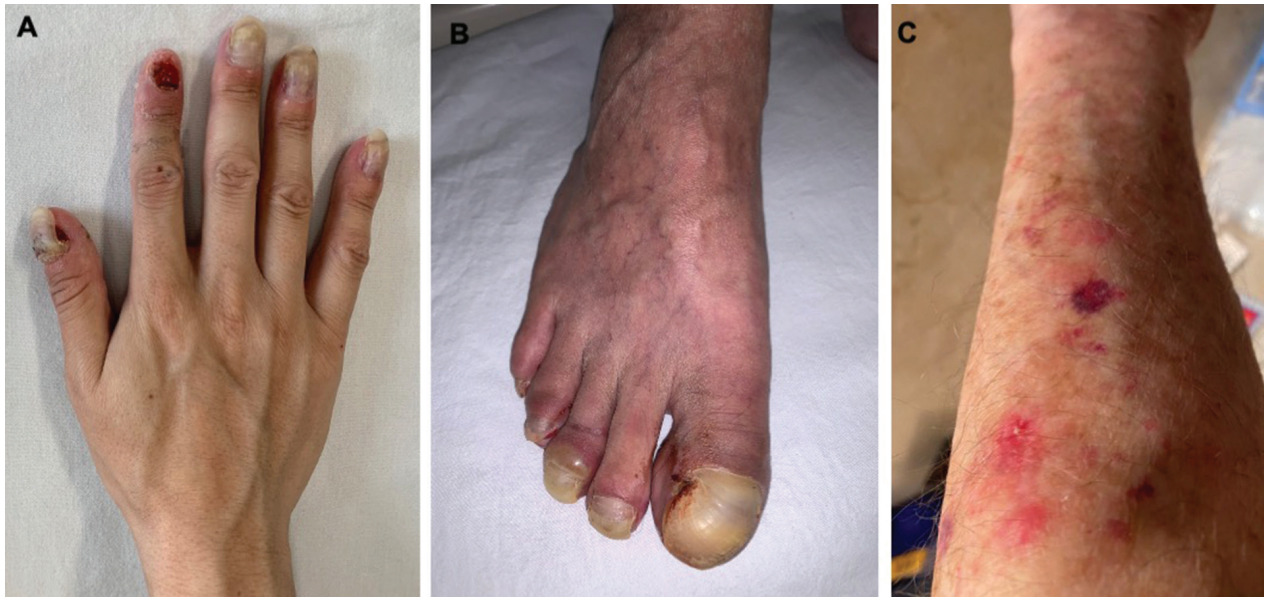

FIGURE 1. **Cutaneous Changes Presented With Erdafitinib. (A, B)** Onycholysis and onychomadesis affecting hands and feet. **(C)** Purpuric macules and skin erosions affecting the superior extremities.

THE CASE

A Hispanic man, aged 42 years, was diagnosed with stage IV metastatic urothelial bladder cancer (MUBC) with nonregional lymphadenopathies and lung, bone, and skin involvement. He received first-line treatment with gemcitabine and cisplatin for 6 cycles, achieving a partial response (PR). Next, he received immunotherapy maintenance with avelumab for 4 months until disease progression. A next-generation sequencing test of paraffin-embedded tumor tissue identified a fibroblast growth factor receptor 3 (*FGFR3*) S249C missense mutation.

The patient was started on erdafitinib 8 mg daily, and while he was on this dosage, he presented with grade 2 hyperphosphatemia of 8 mg/dL. Erdafitinib treatment was temporarily withheld until his phosphorus level reached less than 5.5 mg/dL, accomplished with dietary phosphate restriction to 600 to 800 mg/day; then, erdafitinib was restarted at the same dose. Thereafter, he experienced onycholysis, onychomadesis, Beau lines, and paronychia, with purpuric skin lesions and erosions (**Figures 1A-1C**). Grade 2 nail loss with superinfection was diagnosed and erdafitinib treatment was delayed for 14 days with weekly reassessment. He received oral trimethoprim/sulfamethoxazole for 2 weeks with improvement of symptoms to grade 1. Afterward, he restarted erdafitinib with a dose reduction to 6 mg daily, resulting in better tolerance. The patient achieved clinical response with reduction of metastatic bone lesions, and a CT scan at 10 weeks after he began erdafitinib revealed a PR according to RECIST criteria (**Figures 2A-2H**).

Which of the following statements about erdafitinib is incorrect?

A. Either *FGFR3* mutations or *FGFR2/3* fusions are required for its therapeutic use.

B. Phosphorus serum levels are recommended to guide dose titration.

C. Hyperphosphatemia is the most common adverse event (AE) associated with erdafitinib use.

D. FDA approval was based on a phase 2 trial for patients progressing after platinum therapy with or without immunotherapy.

E. Lower phosphorus levels are associated with better outcomes.

TURN TO PAGE 258 FOR THE ANSWER AND A DISCUSSION OF THIS CASE BY EXPERTS.

Platinum-based chemotherapy is the standard first-line treatment for patients with MUBC, with either cisplatin or carboplatin combinations.[1-4] In patients whose disease does not progress on chemotherapy, maintenance with avelumab is indicated.[4] This evidence comes from the JAVELIN-100 Bladder study (NCT02603432), a phase 3 randomized clinical trial that showed an overall survival (OS) improvement of 7.1 months (median OS, 21.4 vs 14.3 months; HR, 0.69) and a progression-free survival (PFS) benefit of 1.7 months (median PFS, 3.7 vs 2.0 months; HR, 0.62) when comparing avelumab with best supportive care.[5]

Despite these improvements in survival with avelumab, most patients will inevitably progress after chemotherapy and immunotherapy, warranting subsequent treatment options. In this scenario, treatments involving antibody-drug conjugates (ADCs) and tyrosine kinase inhibitors (TKIs) have shown promising results.[6-8] Among the ADCs, enfortumab vedotin (EV), an antinectin-4 antibody coupled to an antimicrotubule payload, has the strongest evidence, and is considered the standard of care in patients who progress after chemotherapy and immunotherapy. This is based on a phase 3 trial in which patients were randomly assigned to receive EV or investigator-chosen chemotherapy (docetaxel, paclitaxel, or vinflunine). Patients who received EV had significantly better OS (12.8 vs 8.9 months; HR, 0.7), PFS (5.5 vs 3.7 months; HR, 0.62), and overall response rate (ORR; 40.6% vs 17.9%).[6] Additionally, another ADC, sacituzumab govitecan (SG)—a Trop-2 antibody associated with a topoisomerase I inhibitor—was approved by the FDA in 2021 based on the results of cohort 1 of the TROPHY-U-01 study (NCT03547973). This phase 2 trial evaluated SG in patients who had already received platinum-based chemotherapy and a checkpoint inhibitor. The primary end point, ORR, was 27.7%; the mean duration of response was 7.2 months and the median PFS and OS were 5.4 and 10.9 months, respectively.[7]

Targeted therapies against driver mutations have been used in cancer treatment for more than 4 decades;[8] in MUBC, inhibition of *FGFR* alterations is of the utmost importance.[8,9] FGFR comprises a family of 4 transmembrane protein kinases that are normally involved in embryogenesis and tissue proliferation[10] and FGFR5 exhibits an absence of intracellular tyrosine kinase domain, resulting in the lack of receptor tyrosine kinase activity[22]. Cancer-cell alterations in this pathway cause constitutive activation of the receptor, resulting in cellular proliferation, migration, and survival.[10,11] Across different cancer types, urothelial carcinoma harbors the highest frequency of *FGFR* alterations (15%-20%),[8,10,11] with *FGFR3* point mutations being the most common, followed by *FGFR3* fusions.[12]

Efforts to inhibit *FGFR* alterations in MUBC are not new. The first attempt to target this receptor was with dovitinib, a multikinase TKI with FGFR activity. In 2013, results of a phase 2 trial (NCT00790426) reported that the drug had limited activity.[13] Newer, more specific FGFR inhibitors have since been developed, including the TKIs pemigatinib, rogaratinib, infigratinib, futibatinib, derazantinib, and AZD454, as well as the monoclonal antibody vofatamab.[9,14,15] Other than erdafitinib, all of these drugs are currently used only in clinical trials.

Erdafitinib's clinical benefit was first demonstrated in a phase 1 trial, from which 2 dosing strategies were recommended for further research: a continuous 9-mg daily dose, and an intermittent 10 mg/day schedule, alternating 7 days on and 7 days off.[16]

Erdafitinib was further studied in BLC2001, a phase 2 clinical trial that included 99 patients with unresectable, locally advanced or MUBC. All patients had either an *FGFR3* mutation or fusions of *FGFR2/3*, and all had progressed during or after 1 or more prior lines of chemotherapy and anti–PD-1 or anti–PD-L1 blockade. The primary end point was ORR. BLC2001 was initially designed as a 2-arm trial, with each arm studying the

CORRECT ANSWER: E

continuous and intermittent regimens previously recommended by the phase 1 trial. After a protocol amendment, however, a continuous daily 8-mg dose was selected, with the possibility of up-titration according to serum phosphate levels. After a median follow-up of 11 months, the ORR was 40%, with 3% complete responses and 37% PRs. The mean PFS and OS were 5.5 and 13.8 months, respectively.[17] Based on these unprecedented results, erdafitinib was authorized by the FDA in 2019 for the treatment of MUBC. **Therefore, answers A and D are correct.**

In BLC2001, 100% of patients reported having AEs of any cause; hyperphosphatemia was the most common (77%), followed by stomatitis (58%), diarrhea (51%), and xerostomia (46%). Grade 3, 4, and 5 AEs of any cause were reported in 67% of patients; hyponatremia and stomatitis were the most frequent (11% and 10%, respectively). The **Table** presents a more comprehensive list of AEs.[17] Real-world data show a similar profile. Of 12 patients in a Brazilian series who were receiving erdafitinib as a second-line treatment, 83% reported any-grade AEs, and 42% reported grade 3/4 AEs; again, any-grade hyperphosphatemia was the most common (33%).[18] **Thus, answer C is correct.**

The etiology underlying the development of hyperphosphatemia in a substantial proportion of patients receiving erdafitinib is related to the wide range of functions of FGFR, a tyrosine kinase expressed on the cell membrane involved in cell proliferation, survival, migration, and differentiation.[19] Physiologically, in the proximal renal tubule FGFR1 is activated by its interaction with its ligand in the presence of the Klotho transmembrane protein; this inhibits the reabsorption of phosphate by NaPi-2a, a sodium-phosphate cotransporter, and blocks the conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D. This limits the absorption of phosphate by the small intestine.[20] Hyperphosphatemia is so common that it is considered to be a marker of FGFR inhibition, and it is used for erdafitinib dose titration, with a target serum level of 5.5 to 7.0 mg/dL.[17] There is evidence that higher efficacy of erdafitinib correlates with high serum phosphorus level. In the pivotal phase 2 trial, when comparing patients with phosphorus levels greater than vs less than 5.5 mg/dL, the ORR was 42.7% vs 34.8%, respectively, median PFS was 5.6 vs 3.8 months (HR, 0.68), and median OS was not reached vs 6.7 months (HR, 0.35).[21] **Therefore, answer B is correct.**

Because higher phosphorus levels, rather than lower levels, are associated with better outcomes, **answer E is incorrect and thus is the question's proper response.**

Skin toxicity associated with erdafitinib, although it occurs less frequently than hyperphosphatemia, can represent more of a challenge. In the pivotal phase 2 trial evaluating erdafitinib for MUBC, 16% of patients underwent dose reductions due to skin toxicity.[17] Management of skin AEs associated with TKI use is different than management of those caused by chemotherapy; supportive measures include emollients and, if those are not effective, topical steroids.[22-24] Nail toxicity is particularly difficult to manage. The most common AEs reported in the BLC2001 trial were onycholysis (16%), nail dystrophy (16%), and paronychia (14%);

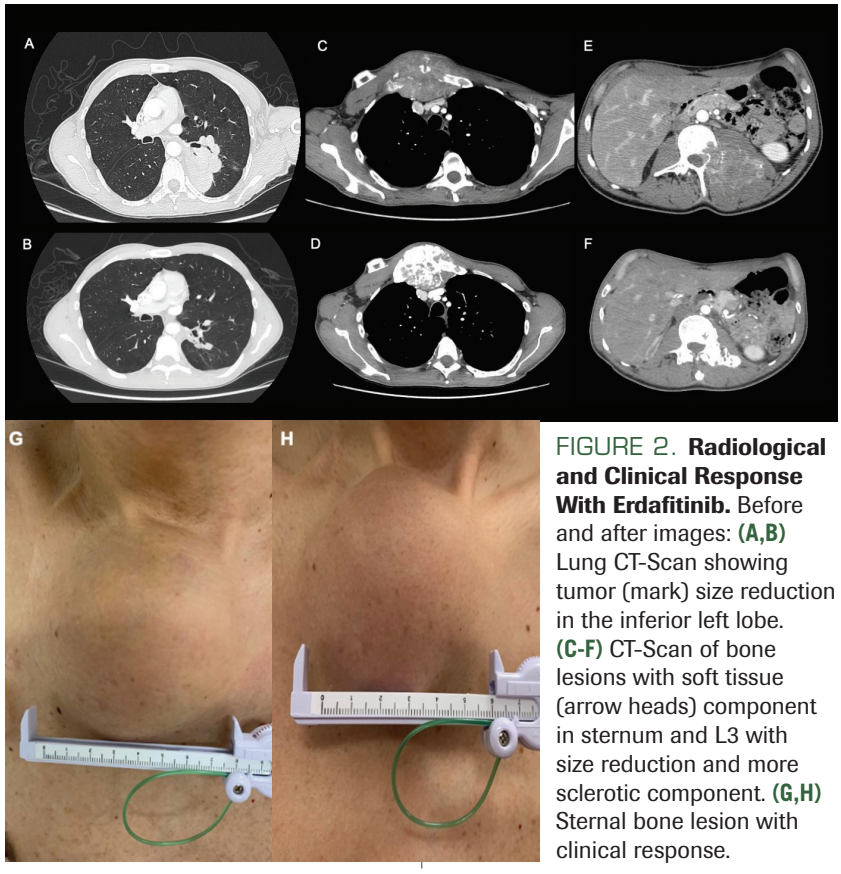

FIGURE 2. **Radiological and Clinical Response With Erdafitinib.** Before and after images: **(A,B)** Lung CT-Scan showing tumor (mark) size reduction in the inferior left lobe. **(C-F)** CT-Scan of bone lesions with soft tissue (arrow heads) component in sternum and L3 with size reduction and more sclerotic component. **(G,H)** Sternal bone lesion with clinical response.

TABLE 1. **Common Adverse Events Associated With Erdafitinib***

Adverse event	Any grade	Grade 3[3]
Hyperphosphatemia	77%	2%
Stomatitis	58%	10%
Diarrhea	51%	4%
Dry mouth	46%	0%
Decreased appetite	38%	0%
Dysgeusia	37%	1%
Fatigue	32%	2%
Dry skin	32%	0%
Alopecia	29%	0%
Constipation	28%	1%
Hand-foot syndrome	23%	5%
Anemia	20%	4%
Asthenia	20%	7%
Nausea	20%	1%
Dry eye	19%	1%
Onycholysis	18%	2%
Alanine aminotransferase increased	17%	2%
Paronychia	17%	3%
Blurred vision	17%	0%
Nail dystrophy	16%	6%
Urinary tract infection	16%	5%
Vomiting	13%	2%
Hyponatremia	12%	11%
Hematuria	10%	2%
Dyspnea	8%	2%
Nail disorder	8%	3%
Acute kidney injury	6%	2%
Cataract	6%	2%
Colitis	5%	2%
Keratitis	5%	3%
Aphthous ulcer	4%	2%
Urosepsis	3%	3%

*Adapted from reference 17.

Loriot Y, Necchi A, Park SH, et al; BLC2001 Study Group. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med.* 2019;381(4):338-348. doi:10.1056/NEJMoa1817323

of the 13 patients who suspended the treatment due to serious AEs, 2 did so due to nail AEs.[17] Patients can try to prevent these events with lifestyle measures, which include avoiding prolonged contact with water, wearing loose-fitting socks and footwear, wearing gloves to avoid trauma, and refraining from biting or cutting nails too short. Nail hardeners are a further option. Oral antibiotics are indicated if secondary infection develops.[22-24]

Level A evidence regarding treatment sequencing in MUBC is pending; however, we have retrospective evidence. In a single-center retrospective cohort of 80 patients who received EV, 26 patients harbored *FGFR3* alterations. Although 8 patients were exposed to erdafitinib before EV, only 1 patient received erdafitinib afterward. When compared with patients who were FGFR-negative, those who were FGFR-positive and had no prior exposure to erdafitinib had a significantly shorter median PFS and a trend to shorter median OS on EV: 2.5 vs 6.8 months (HR, 0.3; $P < .01$) and 4.9 vs 14.6 months (HR, 0.42; $P > .05$), respectively. In contrast, patients with FGFR-altered with prior erdafitinib exposure showed similar median PFS with EV compared with the entire cohort: 6.7 vs 5.2 months.[25] Tumor response also seems to be hindered in the patients who have *FGFR2/3* activating mutations. In a multicenter cohort of 40 patients exposed to EV without prior erdafitinib exposure, ORR differed widely from those who had an *FGFR2/3* mutations compared with those who did not (29% vs 55%), without statistical significance ($P = .4$) but larger studies are necessary to confirm this data.[26] Erdafitinib's place in the treatment sequencing in MUBC will be further studied in the ongoing THOR phase 3 multicohort trial (NCT03390504). In cohort 1, patients with *FGFR3* alterations with MUBC who previously received anti-PD-1/PD-L1 treatment and no more than 2 previous lines of systemic treatment, will be randomized to receive erdafitinib or chemotherapy with either docetaxel or vinflunine; in cohort 2, patients with *FGFR3* alterations with MUBC who progressed on chemotherapy will be randomly assigned to erdafitinib or pembrolizumab in the second-line setting.[27]

PERSPECTIVE BY

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Erdafitinib's Road to Approval and Use in Urothelial Carcinoma

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is the most common genitourinary malignancy and the sixth most common cancer in the United States.[1,2] Despite falling incidence rates over the past 10 years, death rates have remained stable. Survival varies significantly by stage of disease; patients with UC present with nonmuscle-invasive bladder cancer (NMIBC), MIBC, or metastatic UC (mUC), and 5-year survival rates range from 70% or greater, to 30% to 40%, to 5%, respectively. Despite the disease being one of the top mutated cancers, the roles of immunotherapies and targeted therapies have been limited until recent years.

Treatment selection for locally advanced or mUC is heavily influenced by performance status and the presence of comorbidities that may render patient's ineligible to receive platinum-based chemotherapy. The National Comprehensive Cancer Network (NCCN), recommends that patients who are able to tolerate platinum-based chemotherapy receive treatment in the frontline setting for advanced disease because of improved survival and response rates.[3] Immunotherapy has also made a drastic impact as a treatment option for patients who are platinum ineligible, following progression on platinum-based chemotherapy, or as maintenance following platinum-based chemotherapy.

FGFRs are widely distributed transmembrane tyrosine kinase receptors. Aberrations in the genes encoding FGFRs are common in a wide variety of cancers, with the majority being gene amplifications or activating mutations. They are involved in cell development, differentiation, survival, and migration, as well as angiogenesis and carcinogenesis. In humans, 4 FGFRs (*FGFR1-FGFR4*) share structural homology with vascular EGFRs, platelet-derived growth factor receptors, and other tyrosine kinase receptors, which has implications for pharmacologic therapy. FGFRs signal through several intracellular pathways, including the RAS/RAF/MEK and the PI3K-AKT pathways. Specific *FGFR* mutations have been observed in a proportion of bladder cancers, and *FGFR* aberrations occur in approximately 10% to 20% of mUC cases.

The FDA initially granted erdafitinib (Balversa) breakthrough designation status as a novel agent for the treatment

Combination strategies are also an active area of clinical research. Some authors consider FGFR-altered tumors to be less immunogenic than those without FGFR pathway aberrancies.[28,29] Combinations of FGFR inhibitors with anti–PD-1/anti–PD-L1 agents have been studied in several phase 2 studies, including the NORSE (erdafitinib plus cetrelimab; NCT03473743), FORT-2 (rogaratinib plus atezolizumab; NCT03473756), FIERCE-22 (vofatamab plus pembrolizumab; NCT03123055) and FIGHT-205 (pemigatinib plus pembrolizumab; NCT04003610) trials. Erdafitinib has also been studied in combination with EV in a phase 1B trial (NCT04963153).[15] Larger confirmatory trials are eagerly awaited, as these may change the way we treat MUBC.

Case Outcome

After a PFS of 5 months, the patient presented with clinical and radiological progression. At this point, because the patient did not have access to EV or SG, he was offered additional chemotherapy. He received 2 cycles of docetaxel, but he experienced progressive disease and further clinical deterioration. He then began receiving best supportive care and died within 1 month due to disease progression. ■

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of UC in March 2018.[4] The confirmed approval of erdafitinib occurred on April 12, 2019, making it the first FGFR inhibitor on the market, the first oral option in UC treatment, and the first targeted treatment option for UC.[5] Erdafitinib is indicated for adult patients with locally advanced or mUC who have an *FGFR3* or *FGFR2* genetic alteration and who have progressed during or following at least 1 line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Erdafitinib is dosed at 8 mg orally once daily with or without food, increasing to 9 mg daily if select parameters are met.

Updated data from the phase 2 BCL2001 trial (NCT02365597) in patients receiving 8 mg daily demonstrated similar efficacy to earlier trials.[6] The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR), as determined by blinded independent review committee. The median age of participants was 67 years (range, 36-87 years); 79% of patients were men and 74% were White. Most patients (92%) had a baseline ECOG Performance Status Scale score of 0 or 1. Eighty-four (97%) patients had received cisplatin or carboplatin previously; 56% had received only cisplatin-based regimens, 29% carboplatin-based regimens, 10% both regimens, and 5% were not defined. Three (3%) patients had disease progression following prior platinum-containing neoadjuvant or adjuvant therapy only. Twenty-four percent of patients had been treated with prior immune checkpoint inhibitors. The ORR was 32.2% (95% CI, 22.4%-42.0%), with complete responses in 2.3% of patients and PRs in 29.9%. The median DOR was 5.4 months (95% CI, 4.2-6.9).

In the BCL2001 trial, (NCT02365597) there were 2 treatment regimens: 10 mg once daily, 7 days on and 7 days off, and 6 mg once daily for 28 days. The analysis showed that both dosing schedules had promising efficacy and tolerability, and the investigators decided to optimize the dosing in the trial at 8 mg daily (continuous), with a dose increase to 9 mg once daily in patients whose serum phosphate levels were below the target of 5.5 mg/dL between days 14 and 17. Among the 87 patients treated in BCL2001, the most common adverse effects (AEs), in 20% or more of patients, included abdominal pain, alopecia, decreased appetite, and constipation. Grade 3 or higher AEs occurring in 1% or more of patients were hyperphosphatemia, keratitis, nail disorder, nail dystrophy, onycholysis, palmar-plantar erythrodysesthesia syndrome, paronychia, and stomatitis.

Of note, a dose increase occurred in only 41% of patients. Ocular toxicities may occur with erdafitinib and may be severe. Central serous retinopathy/retinal pigment epithelial detachment was reported in 25% of patients in the trial, with a median time to first onset of 50 days. Thirteen percent of patients had resolution and in 13% the condition was ongoing at data cutoff. Dry eye symptoms occurred in 28% of patients. Ophthalmological exams should be conducted during the first 4 months of therapy and every 3 months after.

Erdafitinib offers a first-in-class oral option for patients with advanced bladder cancer with select *FGFR* mutations. Clinicians should be well versed in the management of patients to ensure optimal and safe outcomes. ■

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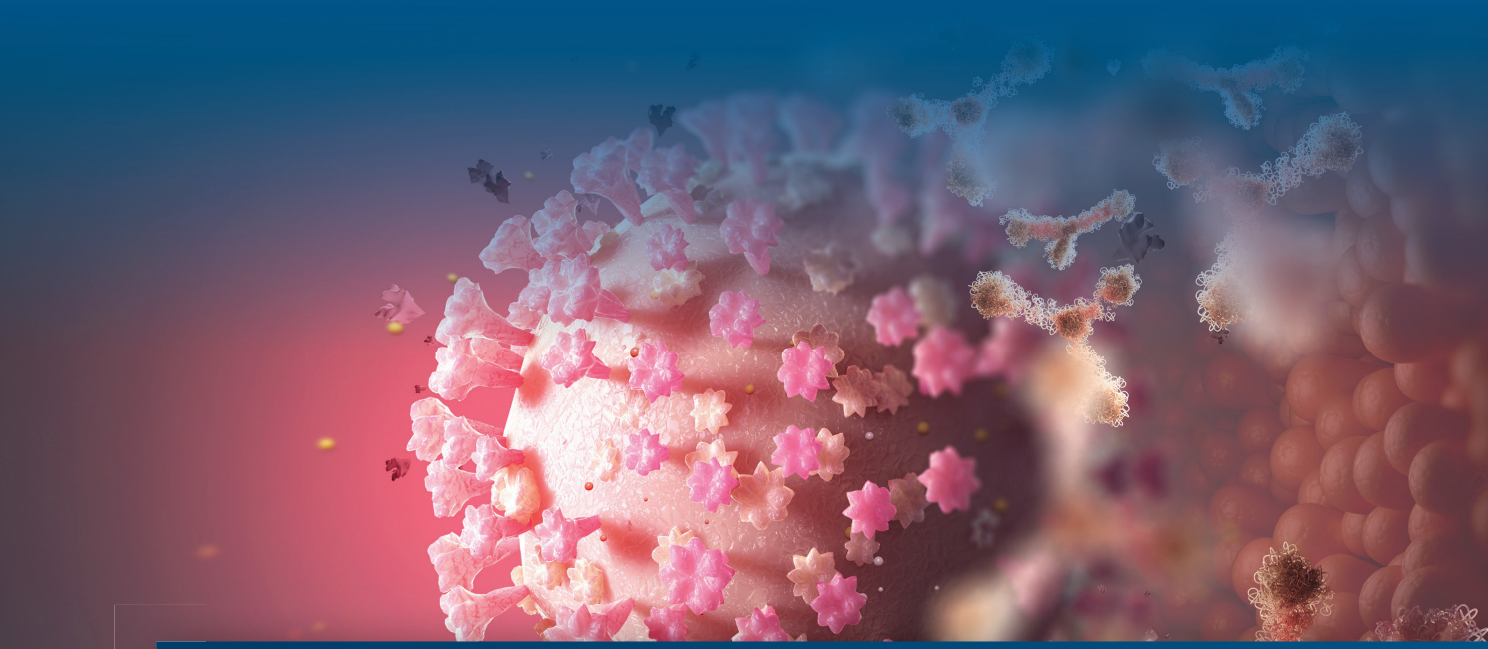

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