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RENAL CELL CARCINOMA

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and the Use of mTOR Inhibitors

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Product Profile
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EGFR+ mNSCLC WILL FIND THE BACK ROADS

Despite advancements, *EGFR*+ mNSCLC still outmaneuvers today's strategies, leaving patients with limited PFS and at risk of disease progression.[1-8]

Staying ahead of *EGFR*+ mNSCLC is important

25% to 39% of patients with *EGFR*+ mNSCLC never receive 2L therapy, according to multiple studies.[9-11]

Range includes patients who died or discontinued the assigned therapy without receiving 2L therapy during follow-up.

Burden of *EGFR*+ mNSCLC mutations limits survival

Less than **one-fifth of patients** with *EGFR*+ mutations in mNSCLC will survive 5 years, as demonstrated by real-world data.[12]

Based on a real-world analysis of 2,833 adult patients with confirmed *EGFR* mutations treated with a 1st-, 2nd-, and 3rd-generation EGFR TKI in the advanced NSCLC Flatiron registry EHR database between January 1, 2011, and May 21, 2020.[12]

2L, second line; *EGFR*+, mutations in epidermal growth factor receptor; EHR, electronic health records; MET, mesenchymal-epithelial transition; mNSCLC, metastatic non-small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Acquired resistance drives disease progression[8]

up to 50%

MET amplification is a common mechanism of off-target acquired resistance to 3rd-generation EGFR TKIs, accounting for **up to 50% of all cases.**[8,13-16]*

*The detection rate of *MET* amplification can differ based on the sensitivity of the employed testing method and the specific cutoff point in each study.

Learn more about the **unmet need in patients with *EGFR*+ mNSCLC** by visiting **EGFRRoutes.com** or **scanning the QR code.**

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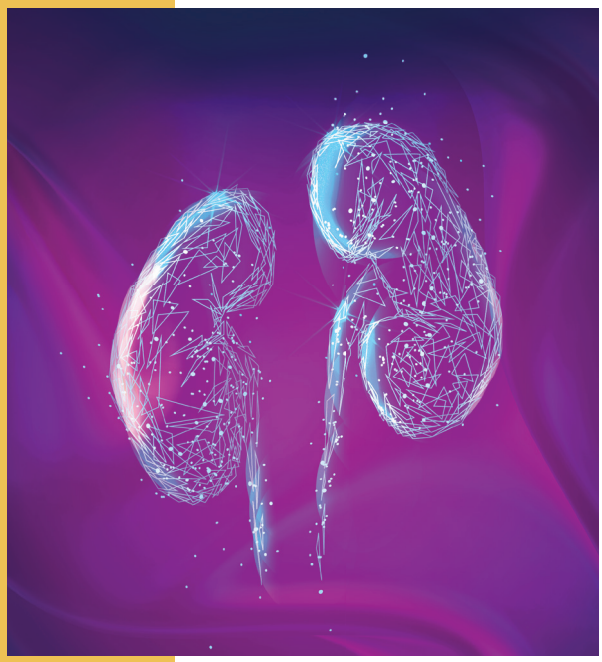

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Clinical Quandary: Renal Cell Carcinoma

Hereditary Renal Tumor Syndromes and the Use of mTOR Inhibitors

José Luis Rodríguez-Olivares, MD; Héctor Raúl González-Sánchez, MD; Evelyn Lilian Beas-Lozano, MD; Jazmin Arteaga-Vázquez, MD; Elaine T. Lam, MD; María Teresa Bourlon, MD, MSc, FASCO

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Breast Cancer Breakthroughs: 2024 ESMO Highlights

Neil M. Iyegar, MD, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Department of Medicine, Weill Cornell Medicine, New York, NY

The incredible pace of advancements in breast cancer therapeutics was again demonstrated at the 2024 European Society for Medical Oncology (ESMO) Congress. At the forefront of these advances were new data for several antibody-drug conjugates (ADCs) and molecular therapeutics. Here are some of the impactful presentations and data sets that are immediately practice-changing or provide important updates in the development of novel treatments.

KEYNOTE-522

The final overall survival data from the phase 3 KEYNOTE-522 trial (NCT03036488) were perhaps the most impactful data presented at ESMO, confirming the benefit of adding pembrolizumab (Keytruda) to neoadjuvant chemotherapy for early-stage triple-negative breast cancer.[1] At a median follow-up of 75.1 months, 14.7% (115/784) of patients in the pembrolizumab arm had died vs 21.8% (85/390) of patients in the control arm (HR, 0.66; 95% CI, 0.50-0.87; *P* =.0015). The 5-year overall survival (OS) rates were 86.6% vs 81.7%, and the 5-year event-free survival rate was 81.2% in the pembrolizumab arm vs 72.2% in the placebo arm (HR, 0.65; 95% CI, 0.51-0.83). However, it is important to note that careful patient selection is critical due to the risks of immune-related toxicities and further studies are needed to identify clinically useful biomarkers.

NATALEE

The 4-year update from the NATALEE trial (NCT03701334) of adjuvant ribociclib (Kisqali) for high-risk primary breast cancer was arguably the headliner of breast cancer data presented at ESMO.[2] In the phase 3 NATALEE trial, the addition of ribociclib to adjuvant aromatase inhibition for stage II and III hormone receptor–positive early breast cancer led to an improvement in invasive disease–free survival (iDFS). Eligible patients had anatomic stage IIA (either N0 with additional risk factors or N1 [1-3 axillary lymph nodes]), IIB, or III breast cancer. Patients were randomly assigned to receive ribociclib at 400 mg daily, 3 weeks on and 1 week off for 3 years plus a nonsteroidal aromatase inhibitor, or aromatase inhibitor alone. At the data cutoff of April 29, 2024, 63% of patients completed 3 years of ribociclib, while 20% stopped early due to adverse effects. With a median follow-up time of 44.2 months, the addition of ribociclib demonstrated a significant iDFS benefit (HR, 0.715; 95% CI, 0.609-0.840; *P* < .001). Ribociclib added a 4-year absolute iDFS improvement of 4.9%, an increase from the previously presented improvement of 2.7% at 3 years. Notably, the 4-year absolute iDFS benefit was 5.1% in the N0 population and 5.0% in the N+ population. No new safety signals were identified. On the basis of data from the NATALEE trial, ribociclib plus endocrine therapy received FDA approval for use in the adjuvant setting on September 17, 2024.[3]

DESTINY-Breast12

The DESTINY-Breast12 trial (NCT04739761) was a phase 3b/4 multicenter trial in which patients with HER2-positive metastatic breast cancer who received up to 2 lines of therapy in the metastatic setting and had stable or active brain metastases were treated with the HER2-directed ADC, trastuzumab deruxtecan (T-DXd; Enhertu).[4] In patients with brain metastases, the 12-month progression-free survival (PFS) rate was 61.6% (95% CI, 54.9%-67.6%) and the 12-month central nervous system PFS was 58.9% (95% CI, 51.9%-65.3%). The rates were similar in patients with stable (57.8%; 95% CI, 48.2%-66.1%) and active (60.1%; 95% CI, 49.2%-69.4%) brain metastases. The rates of interstitial lung disease (ILD) were similar to previously reported rates (16% all-grade ILD in the brain metastasis cohort, including 6 [2.3%] grade 5 events). These results demonstrated significant intracranial activity of T-DXd.

ICARUS-BREAST01

Phase 2 results from the ICARUS-BREAST01 trial (NCT04965766) testing the novel HER3-directed ADC patritumab deruxtecan (HER3-DXd) were also presented.[5] Patients with hormone receptor–positive, HER2-negative metastatic breast cancer who had progression on CDK4/6 inhibitor and 1 line of chemotherapy were enrolled. At the data cutoff, 99 patients were included and 19 patients were still on treatment. At a median follow-up of 15.3 months, the confirmed objective response rate was 53.5% (95% CI, 43.2%-63.6%) and the median PFS was 9.4 months (95% CI, 8.1-13.4). The most frequent treatment-related adverse effects were nausea (all grade, 75%; grade 3, 5%) and diarrhea (all grade, 53%; grade 3, 1%), and 6 patients had ILD (grade 1, n=5; grade 2, n=1). These results support the continued development of this novel ADC.

Quality of Life

Finally, multiple trials were presented demonstrating the beneficial effects of exercise on symptom management/quality of life, weight loss, and even improvements in invasive breast cancer–free survival and OS with 16 weeks of high-intensity interval training plus resistance training during chemotherapy for early breast cancer.[6-9] These studies provide welcome adjunctive data emphasizing the importance of lifestyle interventions to support standard cancer therapies.

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Cancer Rehabilitation Medicine
"Bridging the Gap" With Supportive Care

Jessica Cheng, MD, Assistant Clinical Professor in the Department of Supportive Care Medicine at City of Hope

Finding ways to improve quality of life outcomes is always a goal for oncologists. Those in the emerging field of cancer rehabilitation medicine have the opportunity to bridge a gap in oncology care.

Jessica Cheng, MD, described cancer rehabilitation as a strategy to improve function, whether that involves doing day-to-day activities or overcoming an unexpected challenge. She noted that finding solutions to these issues brings her joy.

Cheng, assistant clinical professor in the Department of Supportive Care Medicine at City of Hope, highlighted that cancer rehabilitation medicine is a subspecialty of physical medicine and rehabilitation (PM&R) and is a viable option for any patients who need to increase their strength or are experiencing toxicity-related events from treatment.

When speaking with CancerNetwork, Cheng discussed the importance of PM&R and cancer rehabilitation, those who may benefit from it, and how she hopes to spread the word regarding this up-and-coming field.

"My heart's desire is that every institution that takes care of patients with cancer will recognize the importance of optimizing function and performance status from the beginning and throughout the cancer journey from prehabilitation to rehabilitation," said Cheng.

CancerNetwork / What is cancer rehabilitation medicine?

Cheng / A lot of times when [patients have] cancer, they have thoughts like, "Will I be able to go back to work? Can I go to my son's wedding? Can I keep golfing? My back hurts; it's hard to get off a chair. How am I going to get through this?" What I do in my practice in cancer rehabilitation medicine is I then ask a lot more questions about where these thoughts are coming from. I do an extensive physical exam, and I come up with a comprehensive, tailored, practical, and coordinated plan that aims to give the patient a measure of control over their life—to live their life to the fullest no matter where they are in their cancer journey.

A key part of being able to function and do the activities that they want to do is exercise. There can be a lot of barriers to exercise. It could be that back pain, fatigue related to cancer, neuropathy, or [something that makes them say,] "Why do I have to do that?" I seek to answer all those questions with my patients. That's one example of what a visit might look like. The part that I'm passionate about is cancer prehabilitation, and that's preparing for surgery, stem cell transplant, or whichever cancer treatment is coming up next. I had a patient who recently followed up with me after prehabilitation, and she followed everything I said in terms of exercise, nutrition, mental health, etc. [She said she] got out of the hospital faster, and she recovered much faster than she thought. The oncologist confirmed that was a quicker recovery than expected. That brings me joy.

CN / How does PM&R relate to cancer rehabilitation medicine?

Cheng / It is not well known in the cancer space. [PM&R] is my core specialty, and I subspecialize in cancer rehabilitation medicine. [PM&R] often gets confused with physical therapy vs physical medicine, or psychiatry vs physiatry. These are all important collaborators, but [PM&R] is not exactly those specialties either. PM&R is the only medical specialty that focuses on function. That's the keyword of everything I do: function.

Function is our ability to do things we care about, whether it's high level like sports or someone's job, or if it's getting off the toilet. Those are all activities that people do day-to-day. The body systems of focus are the musculoskeletal system, or muscle [and] bone joints, and the nervous system, like the brain, spinal cord, and the nerves throughout the body, as those are the ones that impact someone's function or ability to do things the most. We do a whole biological, psychological, social, whole-person approach, and

I would add an environmental approach because if you imagine getting someone to exercise, move better, or get up after a fall, it requires knowing everything about the patient.

Although we focus on the musculoskeletal and neurological systems, those are not the only systems we look at. We look at their blood pressure. If they're fainting, that's not going to help their function. Imagine all of that applied to the cancer world. Historically, the cancer world and the [PM&R] world have not mixed very much. The cancer rehabilitation medicine subspecialty is one of the fastest-growing subspecialties within PM&R, and the population of people who are surviving cancer is growing exponentially. Our [oncologists] are doing such a great job. With [PM&R], we can help empower patients to live longer with less disability and a better quality of life.

CN / What made you interested in this field of study?

Cheng / I started my medical journey with this appreciation of the mystery of healing. As with many people on the premedical journey, you learn a lot about organic chemistry and a lot about mechanisms. I shadowed some doctors with more of a holistic approach, and it was just very mysterious to me how osteopathic manipulation might be able to promote deeper levels of healing, like psychological, emotional, and spiritual healing.

When I found the specialty of PM&R, it seemed like a natural fit in that I like these body systems. It's focused on practical things. I love practical creative strategies married with medical complexities and the whole-person approach. It was innate to the [PM&R] field. The more I dug into the research about cancer rehabilitation, the more shocked I was at how high the unmet need was. A lot of people going into their cancer journey are already older and already have aches and pains or difficulty moving. For cancer treatment, oncologists look at their ability to move around and their performance status to see if they'll be able to handle their cancer treatment. It weighed on me that there's so much opportunity for my field to make a difference in someone's ability to even get cancer treatment. There's so much of a gap to bridge. There's so much headway to make in bringing these 2 fields together.

IMAGE BY BROOKE SPAULDING / MJH LIFE SCIENCES USING AI

CN / Is there a specific area of oncology that cancer rehabilitation focuses on?

Cheng / Cancer rehabilitation applies to all patients with any type of cancer or anyone with a body. Overall, because this field is on the more recent side with not too many specialists, there's a lot of room for research in every disease type and every stage of the disease. Personally, my interest is in cancer prehabilitation. The research has exploded exponentially and become an international phenomenon over the last 10 years.

I'm working on designing a trial for patients with breast cancer and gynecologic [cancers] who are undergoing chemotherapy before surgery so that we can catch them at the earliest time point. [This may allow us to] make them as fit as possible in their mind and body at the earliest point to give them the best chance with their cancer treatment. There has been a recent study that showed that in patients who are undergoing neoadjuvant chemotherapy for breast cancer, the [patients] who did an exercise and nutrition training program were able to achieve a good outcome with pathologic complete response in 53% of the cases

vs 28% of people who did not do the program.[1] [I spent] a lot of time talking with patients about how chemotherapy is not an excuse to not do exercise. It should be your push to exercise with all that you have in you to help the chemotherapy potentially work better. It's a way that they can have a measure of control over their cancer journey.

CN / What are some techniques that you implement to help improve a patient's quality of life?

Cheng / A patient example [may] help [better explain this]. On the rehabilitation end, a lot of times you have rehabilitation after an injury or something that causes some measure of disability. I had a patient with blood cancer who had a stem cell transplant. I saw her after treatment, and she was having difficulty eating and biting. She had pain in her masseter muscle, one of her chewing muscles. She had shoulder problems, [limited] range of motion, shoulder pain, and balance issues from the neuropathy. She couldn't sleep. It's this complex web [of symptoms], and they're all in 1 person. They all affect each other. There's lots of components to this because they all need to synergize to work. For that patient, it [involved] removing some medications and adding some medications for jaw pain, shoulder pain, and nerve issues. It [involved] doing some trigger point injections with [electromyography] guidance in the masseter muscle and working with outside physical therapy.

There are limitations in terms of how many things can be addressed at once. I would bridge the gap of rehabilitation care by giving some direction on exercises they can do at home in the meantime until they're ready to transition to the next item with a physical therapist [PT]. I would direct them to a PT [who] would work for them in terms of specialty, logistics, and what's feasible for them. If [the PT is] too far, it's just not going to work for them. [I also let] them know about any special precautions if they're on cancer treatment and if their blood values, platelets, or white blood cell counts are fluctuating. I would arm the patient to understand how to stay safe with the PT and to keep communicating with me and connect with the therapist to make sure that we can optimize their recovery as best as possible.

CN / How does cancer rehabilitation utilize the multidisciplinary care team?

Cheng / The core rehabilitation team consists of PM&R, PT, occupational therapy, and speech therapy. Those are the core rehabilitation team. With that said, because function and [a patient's] abilities to do things are so broad, my team includes everyone. Who is everyone? That could mean the rehabilitation team, recreational therapy, music therapy, acupuncture, supportive care, integrative medicine, interventional pain, neurology, orthopedics, and neurosurgery. It could mean the oncology team and communicating with them a lot. Every medical and supportive specialty is fair game. A lot of times, I am also trying to help the patient prioritize which referral in what timing makes the most sense, and then on the back end also trying to coordinate and streamline care in collaboration with the whole team.

CN / How do you hope this field grows and becomes implemented at more institutions across the country?

Cheng / I see the value of rehabilitation medicine as an integral part of the cancer space. My heart's desire is that every institution that takes care of patients with cancer will recognize the importance of optimizing function and performance status from the beginning and throughout the cancer journey from prehabilitation to rehabilitation. There's a lot of room for growth there.

CN / Where do you hope to see this field headed?

Cheng / My catchphrase recently is "prehab for all." I want everyone to be armed with this knowledge of what they can do that's in their control to optimize their abilities for meaningful activities throughout the cancer journey. I hope that oncologists and rehabilitation physicians alike will see that there's an opportunity with cancer prehabilitation to enable [patients] to get their cancer treatment, get through it better, and recover better. That's my hope: that this will just spread even more like wildfire than it already is.

CN / What do you hope your colleagues take away from this conversation?

Cheng / Engage in rehabilitation early. Give us a chance to optimize performance status, to help you do your work in oncology. To my PM&R colleagues, I would like them to know that you can impact cancer outcomes. ■

REFERENCE
Sanft T, Harrigan M, McGowan C, et al. Randomized trial of exercise and nutrition on chemotherapy completion and pathologic complete response in women with breast cancer: the lifestyle, exercise, and nutrition early after diagnosis study. *J Clin Oncol.* 2023;41(34):5285-5295. doi:10.1200/JCO.23.00871

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TABLETS

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RENAL CELL CARCINOMA

Hereditary Renal Tumor Syndromes and the Use of mTOR Inhibitors

José Luis Rodríguez-Olivares, MD; Héctor Raúl González-Sánchez, MD; Evelyn Lilian Beas-Lozano, MD; Jazmin Arteaga-Vázquez, MD; Elaine T. Lam, MD; María Teresa Bourlon, MD, MSc, FASCO

THE CASE A 47-year-old woman with a history of drug-resistant epilepsy during childhood presented to the emergency department with sudden dyspnea and chest pain. Upon admission, her oxygen saturation was 88%. A chest CT scan revealed pulmonary cystic lesions consistent with lymphangioleiomyomatosis and a right spontaneous pneumothorax (**Figure 1A**), which resolved with the placement of a chest tube. Physical examination revealed a hypopigmented macule on the skin of the lumbar region, facial angiofibromas, and periungual fibromas (**Figure 1B**). An abdominal MRI documented multiple bilateral renal tumors that were hypointense on T2-weighted imaging and showed a black boundary artifact, suggestive of fat-poor angiomyolipomas (AMLs) (**Figure 1C**). Subsequent percutaneous biopsy of the largest renal tumor confirmed the diagnosis of angiomyolipoma (positive for HMB-45 on immunohistochemistry). The brain MRI revealed subependymal nodules (**Figure 1D**). The pulmonary function tests showed a mild obstructive pattern. Germline genetic testing confirmed the suspected diagnosis, and the patient started oral systemic treatment with everolimus (Afinitor) 10 mg once daily, along with dexamethasone rinses for prophylaxis for mucositis.

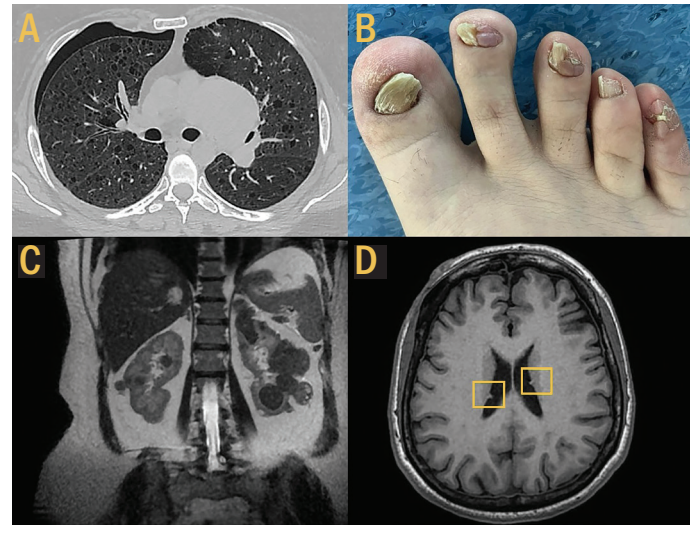

FIGURE 1. **Systemic Manifestations Associated With Hereditary Renal Angiomyolipomas** (**A**) Lung cysts and right spontaneous pneumothorax on CT scan. (**B**) Periungual fibromas (Koenen tumors) cause longitudinal grooves of the nail plate due to matrix compression. (**C**) Multiple bilateral renal and hepatic angiomyolipomas on MRI. (**D**) Subependymal nodules.

Which of the following hereditary cancer syndromes is associated with renal angiomyolipomas and the systemic findings presented by this patient?

A. Birt-Hogg-Dubé syndrome (BHD)
B. Cowden syndrome (CS) (*PTEN* hamartoma tumor syndrome [PHTS])
C. Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)
D. Hereditary papillary renal carcinoma (HPRC)
E. Tuberous sclerosis complex (TSC)

Turn to page 377 for the answer and a discussion of this case by experts

José Luis Rodríguez-Olivares, MD, Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Jazmin Arteaga-Vázquez, MD, Department of Genetics, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Héctor Raúl González-Sánchez, MD, Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Elaine T. Lam, MD, Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO

Evelyn Lilian Beas-Lozano, MD, Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

María Teresa Bourlon, MD, MSc, FASCO, Department of Hematology and Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

It is estimated that 6.4% of non–clear cell renal carcinoma cases are associated with hereditary cancer syndromes.[1] The National Comprehensive Cancer Network guidelines recommend genetic cancer risk assessment for individuals with a diagnosis of RCC aged 46 years and younger, with multifocal or bilateral tumors, with 1 or more first- or second-degree relatives with RCC, or meeting specific histologies and clinical features of a hereditary kidney cancer syndrome.[2] Therefore, oncologists must be mindful of potential hereditary kidney cancer syndromes and refer patients for genetic counseling. Genodermatoses are hereditary diseases characterized by distinctive skin lesions often accompanied by multiorgan effects. While these are often benign tumors, some of them predispose individuals to cancer.[3,4]

BHD is one of the main differential diagnoses for patients presenting with skin hamartomas, pulmonary cysts, pneumothorax, and renal tumors. These findings overlap with clinical features of other genodermatoses, especially TSC. The key findings to distinguish these 2 entities are the histologic findings of skin and renal tumors, as well as ruling out cardiac or central nervous system (CNS) manifestations that would be more common with TSC. BHD is caused by germline pathogenic variants (PVs) in *FLCN*, which encodes folliculin.[5] Unlike in this patient, the characteristic skin lesions of BHD are fibrofolliculomas and trichodiscomas, benign hair follicle tumors. However, BHD can also present less frequently with angiofibromas.[6] The histology of BHD renal neoplasms is diverse, the most common being chromophobe, followed by oncocytoma and, more rarely, hybrid chromophobe-oncocytoma.[7] Although 84% of individuals with BHD have lung cysts on a CT scan, and up to 38% have a history of spontaneous pneumothorax, the skin findings, histology of renal tumors, and history of CNS manifestations of this patient do not align with the diagnosis of BHD.[8] **Therefore, answer A is incorrect.**

CS is part of the PHTS spectrum, a group of diseases associated with germline PVs in *PTEN*, a tumor suppressor gene that encodes a phosphatase antagonizing cell cycle progression by intervening in the PI3K-AKT pathway.[9] The most common mucocutaneous characteristics of CS are multiple facial trichilemmomas and oral papillomas.[10] *PTEN* PVs have been associated with an increased risk of breast cancer in women, endometrial cancer, thyroid cancer, colon polyps, and familial kidney cancer.[11] The histopathological spectrum of renal neoplasms reported in individuals with CS is predominantly chromophobe and papillary RCC.[12] Although this patient has CNS involvement, she does not exhibit the classic manifestations associated with PHTS, such as Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum), macrocephaly, or autism spectrum disorder.[13] **Thus, answer B is incorrect.**

HLRCC is caused by heterozygous germline PVs in *FH* which encodes an enzyme that catalyzes the conversion of fumarate to malate in the tricarboxylic acid cycle.[14] The main manifestations

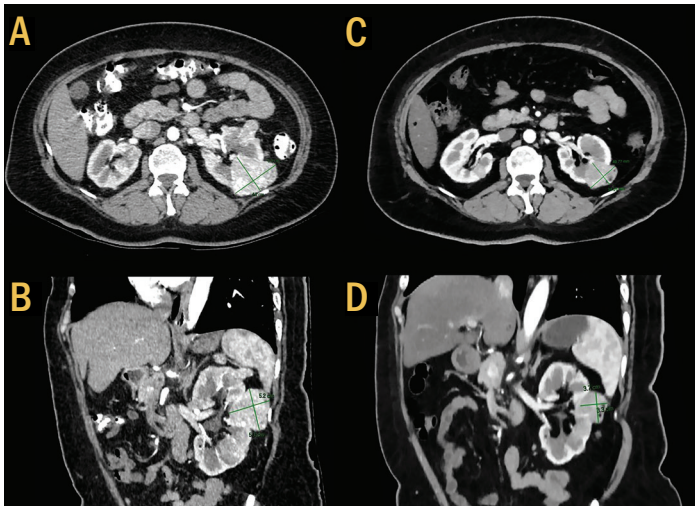

FIGURE 2. **Radiological Response With Everolimus.** Axial and coronal CT scans before (**A, B**) and after (**C, D**). Four months of treatment with everolimus showed a 25% reduction and less arterial enhancement in the largest angiomyolipoma.

of HLRCC are cutaneous leiomyomas, uterine fibroids, and type 2 papillary RCC.[15] Renal tumors associated with germline PVs in *FH* are of the papillary subtype, are unifocal, and have a high potential for developing early metastasis. The lifetime risk of developing renal cancer in carriers of PVs in *FH* is estimated to be 5.8% to 11.9%.[16] This patient did not have cutaneous or uterine leiomyomas and her renal tumors are more consistent with AML rather than papillary RCC, ruling out clinical suspicion for HLRCC. **Therefore, answer C is incorrect.**

HPRC is caused by germline PVs in *MET* that result in a gain of function of the kinase domain of c-MET (hepatocyte growth factor receptor), functioning as a driver in the tumorigenesis of papillary renal cancer.[17] Clinicians should suspect that an individual might be a carrier of a PV in *MET* in cases of papillary RCC type 1, bilateral/multifocal tumors, and a family history of papillary RCC.[18] To date, no associations have been made with extrarenal manifestations in HPRC.[19] **Thus, answer D is incorrect.**

Answer: E Tuberous sclerosis complex (TSC)

The patient fulfills the clinical diagnosis of TSC with multisystem involvement affecting the skin (facial angiofibromas, periungual fibromas, hypomelanotic spots); CNS (epilepsy, subependymal nodules); lungs (lymphangioleiomyomatosis [LAM] causing pneumothorax); and kidneys (AMLs).[20] **Answer E is correct.**

TABLE 1. Studies Evaluating mTOR Inhibitors and Other Strategies in TSC Based on Selected Manifestations[27-28,30,33-35,39-40]

STUDY	TYPE	INTERVENTIONS	N	RESPONSE RATE (%)[a]	PFS
Subependymal giant cell astrocytomas					
EXIST-1	Phase 3, double blind	Everolimus 4.5 mg/m^2 vs placebo	117	35% at 6 months vs 58% at 48 months	89% at 3 years
Krueger et al	Phase 1/2	Everolimus 3 mg/m^2	28	32% at 6 months vs 52% at 60 months	92% at 5 years
EMINENTS	Single center, single arm, open label	Maintenance (reduced-dose) everolimus[b]	15	No difference in SEGA volume (0-60 months)	50% at 5 years
Angiomyolipomas					
EXIST-2	Phase 3, double blind	Everolimus 10 mg/day vs placebo	118	42% at 6 months vs 58% at 48 months	92% at 1 year 85.7% at 4 years
NCT00457808	Phase 1/2	Sirolimus[c] for 12 months	25	80% at 12 months	28% at 1 year after stopping sirolimus
Williams et al	Retrospective	Transcatheter transarterial embolization	16	Mean decrease volume, 56.1%	Not reported
Kothary et al	Retrospective	Selective arterial embolization	19	Not reported	78.7 months
Lymphangioleiomyomatosis					
MILES	Phase 3, double blind	Sirolimus vs placebo for 12 months	89	FEV_1, 46% vs 12% FVC, 54% vs 23%[d]	Not applicable
Treatment-resistant seizures					
EXIST-3	Phase 3, double blind	High-exposure vs low-exposure everolimus vs placebo	366	40.0% vs 28.2% vs 15.1%[e]	Not applicable

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PFS, progression-free survival; SEGA, subependymal giant cell astrocytoma; TSC, tuberous sclerosis complex.

[a]Response rate was defined as the proportion of patients with a reduction of 50% or more in target lesions with everolimus and 30% or more with sirolimus. [b]Patients with SEGA treated for 12 or more months with a standard dose received maintenance everolimus 3 times per week. [c]Titrated dose to maintain sirolimus blood levels at 1 to 5 ng/mL, escalating to a maximum of 10 to 15 ng/mL if no response is achieved. [d]FEV_1 and FVC values at or above baseline values at 12 months. [e]Proportion of patients with 50% or more reduction in seizure frequency.

Tuberous sclerosis complex is an autosomal dominant inherited disease associated with PVs in *TSC1* (encoding hamartin) and more frequently *TSC2* (encoding tuberin). The mTOR pathway aims to activate ribosomal complexes, allowing cell proliferation, while the TSC1-TSC2 heterodimer inhibits mTOR, controlling cell cycle progression.[21] This finding provided the rationale for the use of mTOR inhibitors for the treatment of patients with TSC-associated tumors (**Table 1**).

Although AMLs are often benign tumors, these patients require multidisciplinary management, ideally at a genitourinary-oncology clinic. These tumors can follow an indolent course, as shown in patients who received a placebo in earlier clinical trials. In light of this, active surveillance (AS) is an important strategy to discuss. The International TSC Diagnostic Criteria and Surveillance and Management Recommendations, updated in 2021, recommend MRI as the initial screening tool for renal AMLs because up to one-third may be fat-poor and not adequately identified with ultrasound.

TABLE 2. Common Adverse Effects Associated With Everolimus[31,33,37,40]

ADVERSE EVENT	ANY GRADE	GRADE ≥3
Stomatitis	48%-56%	1%-8%
Aphthous stomatitis	19%	3%
Mouth ulceration	16%	3%
Nasopharyngitis	24%	0%
Acnelike skin lesions	22%	0%
Hypercholesterolemia	20%	0%
Anemia	13%	0%
Diarrhea	13%	0%
Hyperglycemia	13%	4%
Hypophosphatemia	11%	0%
Leukopenia	10%	0%
Upper respiratory tract infection	10%	0%
Amenorrhea[a]	13%-22.6%	4.0%-5.5%

[a]Estimated proportion among female patients aged between 10 and 55 years.

For patients who are asymptomatic with AMLs less than 3 cm with a slow growth rate (typically less than 5 mm/year), it is reasonable to observe with annual MRI, monitoring blood pressure for potential secondary hypertension, as well as tracking proteinuria, hematuria, and glomerular filtration rate.[22,23]

In a meta-analysis involving individuals with predominantly sporadic AMLs, diverse AS protocols showed a low rate of spontaneous bleeding (2.3% to 3.1%) and the need for active treatment ranged from 2.2% to 13.1%.[24] In a single-center cohort, independent risk factors for AS discontinuation included AML size 4 cm or more (HR, 11.23; 95% CI, 3.41-37.03) and being symptomatic at diagnosis (HR, 3.74; 95% CI, 1.41-9.90).[25] When determining the eligibility of individuals for AS, it is important to consider that TSC-associated AMLs (approximately 10% of all cases), in comparison with sporadic cases, may have a faster growth rate and are more likely to require active treatment.[26]

Local treatment options for renal AMLs include selective arterial embolization or surgical resection, particularly when complications such as secondary retroperitoneal bleeding (Wunderlich syndrome), pain, or rapid growth arise. In settings where access to mTOR inhibitors is limited, and for patients who are not candidates for mTOR inhibitors, selective arterial embolization could be considered for the management of renal AMLs.[27,28] Patients with TSC are at a high risk of chronic kidney disease due to the replacement of normal renal parenchyma with multiple bilateral AMLs and renal cysts.[23] Therefore, if the multidisciplinary consensus agrees on surgical treatment, it should, whenever possible, adhere to the principles of nephron-sparing surgery[29] with the aim of delaying the need for renal replacement therapy.

The effectiveness of systemic treatment with mTOR inhibitors for TSC-associated manifestations has been demonstrated in several clinical trials. The phase 3 EXIST-2 trial (NCT00790400) included individuals 18 years or older with TSC or sporadic lymphangioleiomyomatosis and renal AMLs. The response rate at 24 weeks was 42% with everolimus vs 0% with placebo ($P < .0001$). The median time to response with everolimus was 2.9 months. The median time to AML progression was not reached with everolimus and 11.4 months with placebo. Interestingly, VEGF-D levels decreased with everolimus treatment and correlated with the reduction in AML size.[30] In the extended phase of the trial where crossover was permitted, the overall AML response rate was 58%, with a duration of response ranging from 3.0 to 55.5 months.[31]

Even though it is more commonly used for TSC-associated lymphangioleiomyomatosis, sirolimus administered for 1 year has also demonstrated effectiveness in reducing the volume of AMLs. In an open-label phase 2 trial (NCT00457808), at 12 months, 16 of the 20 patients had at least a 30% reduction in AML volume. However, at 6 and 12 months after stopping sirolimus, the mean AML volume had increased to 76.8% ± 27.5% ($P < .001$) and 85.9% ± 28.5% of the respective baseline volumes, highlighting the need for continuous treatment with everolimus.[32]

Although the EXIST-1 trial (NCT00789828) was a phase 3, double-blind study focused on patients with subependymal giant cell astrocytoma (SEGA), 38% had AMLs. Its primary end point was SEGA response rate defined as volume reduction of 50% or more.

In the initial analysis, with a median follow-up of 9.7 months, the SEGA response rate with everolimus was 35% vs 0% with placebo ($P < .0001$). Exploratory analysis also showed greater response rates in skin lesions (42% vs 11%) and AMLs (53% vs 0%).[33] In the extended follow-up, the median exposure to everolimus was 47.1 months. With longer follow-up, the overall SEGA response rate was 58%, and the 3-year progression-free survival was 89%. The overall response rate in AMLs also increased over time, reaching 73%, with a median duration of response of 42.3 months and no renal hemorrhage events.[34]

Lymphangioleiomyomatosis affects 30% to 40% of women with TSC and is associated with a risk of pneumothorax and progressive decline in lung function. The phase 3 MILES trial (NCT00414648) demonstrated a significant benefit of giving sirolimus for 1 year, stabilizing lung function compared with placebo (forced expiratory volume in 1-second slope 1 ± 2 mL/month vs –12 ± 2 mL/month with placebo, $P < .001$).[35]

Epilepsy is the most common neurological manifestation, with a higher risk of drug-resistant epilepsy compared with non-TSC-associated seizure disorders (60% vs 30% to 40%). EXIST-3 is the largest phase 3 clinical trial (NCT01713946) evaluating the use of everolimus for drug-resistant focal-onset seizures in patients with TSC. It demonstrated a lower frequency of seizures in patients treated with high everolimus exposure (14.9% vs 29.3% vs 39.6% with placebo, low [3 to 7 ng/mL], and high exposure [9 to 15 ng/mL], respectively; $P < .001$).[36]

The adverse effects (AEs) of mTOR inhibitors can limit their use. The most frequent AE is stomatitis, a class effect characterized by aphthous-like oral lesions. Stomatitis occurs in about 50% of cases at any grade and in 1% to 8% of cases at grade 3 or higher (**Table 2**). The best evidence on the prevention of oral mucositis comes from the single-arm phase 2 SWISH trial (NCT02069093). This study evaluated the efficacy of 0.5 mg/5 mL dexamethasone mouthwash 4 times a day in women who are postmenopausal and started everolimus plus exemestane for hormone receptor–positive/HER2-negative metastatic breast cancer. It showed that dexamethasone mouthwashes reduced the frequency of grade 2 or higher stomatitis at 8 weeks (2% in SWISH vs 33% in historical reports from the phase 3 BOLERO-2 study [NCT00863655]).[37] Fatigue, pneumonitis, rash, hyperglycemia, and hypertriglyceridemia are other important AEs of mTOR inhibitors.

In summary, mTOR inhibitors act as disease modifiers in individuals with TSC, halting the progression of associated tumors (SEGAs, AMLs, LAM, skin lesions), delaying respiratory function deterioration, and improving epilepsy control, all of which converge to enhance quality of life. This case illustrates how personalized management can significantly improve clinical outcomes in rare diseases.[38]

Outcome

Multigene panel testing showed a heterozygous germline pathogenic variant in *TSC2* [c.2172_2176del p.Thr725Profs*35]. After 16 weeks on everolimus 10 mg/day and primary prophylaxis with dexamethasone mouthwash, the patient did not experience any episodes of stomatitis or biochemical abnormalities. She achieved a 25% reduction in the size of the renal AML, with the largest tumor decreasing from 6 cm to 4.5 cm (**Figure 2**).

CORRESPONDING AUTHOR

María Teresa Bourlon, MD, MSc
Department of Hematology and Oncology
Instituto Nacional de Ciencias Médicas y Nutrición
Salvador Zubirán
15 Vasco de Quiroga Street
Section XVI, Tlalpan
Ciudad de Mexico 14080, Mexico
Email: maitebourlon@gmail.com

CONFLICT OF INTEREST

José Luis Rodríguez-Olivares, MD: None
Héctor Raúl González-Sánchez, MD: None
Evelyn Lilian Beas-Lozano, MD: None
Elaine T. Lam, MD: None
María Teresa Bourlon, MD, MSc: Speaker for Merck Sharp & Dohme, Merck, Ipsen, Bristol Myers Squibb, Pfizer and Eisai
FINANCIAL DISCLOSURES: None

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NON–SMALL CELL LUNG CANCER

Expert Commentary on the Product Profile of Lazertinib in NSCLC

Jenan Dailey, PharmD, BCAP, spoke about the approval of lazertinib (Lazcluze) plus amivantamab-vmjw (Rybrevant) as first-line treatment for patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with *EGFR* exon 19 deletions or exon 21 L858R substitutions detected by an FDA-approved test.[1] She also highlighted known resistance mechanisms to the combination and adverse effects (AEs) that were most significant.

PRODUCT PROFILE

DRUG NAME: Lazertinib (Lazcluze)

DATE OF APPROVAL: August 19, 2024[2]

INITIAL INDICATION: Locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitutions

DOSAGE AND ADMINISTRATION: 240 mg orally once daily with or without food given in combination with amivantamab[3]

HOW SUPPLIED: Orally, on the same day but prior to amivantamab

PIVOTAL CLINICAL TRIAL: Phase 3 MARIPOSA trial (NCT04487080)

DESIGN OF THE PHASE 3 MARIPOSA TRIAL

END POINTS

Primary: Progression-free survival

Secondary: Overall survival, objective response rate, and duration of response

INCLUSION CRITERIA

- Newly diagnosed histologically or cytologically confirmed disease
- Mandatory submission of unstained tissue from the tumor
- Toxicities from prior treatment resolved
- One measurable lesion present

COMMENTARY

Jenan Dailey, PharmD, BCAP
Riverside Healthcare
Bourbonnais, IL

Q / What is the mechanism of action of lazertinib?

Dailey / Lazertinib is a highly selective central nervous system [CNS] penetrant and third-generation tyrosine kinase inhibitor [TKI] targeting activating *EGFR* mutations exon 19 deletion and exon 21 L858R substitution. As with fellow third-generation EGFR TKI osimertinib [Tagrisso], lazertinib has demonstrated activity in *T790M* mutations that contribute to drug resistance in the targeted kinase. Lazertinib has also shown increased selectivity for mutated *EGFR* compared with osimertinib, which makes lazertinib's safety profile attractive for use in combination therapy settings. It is in combination with amivantamab, a bispecific EGFR and MET receptor–targeting antibody, that lazertinib has recently gained approval. This combination is indicated for first-line use in the treatment of adult patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations as detected by an FDA-approved test.

Q / How does this patient population benefit from the lazertinib plus amivantamab combination?

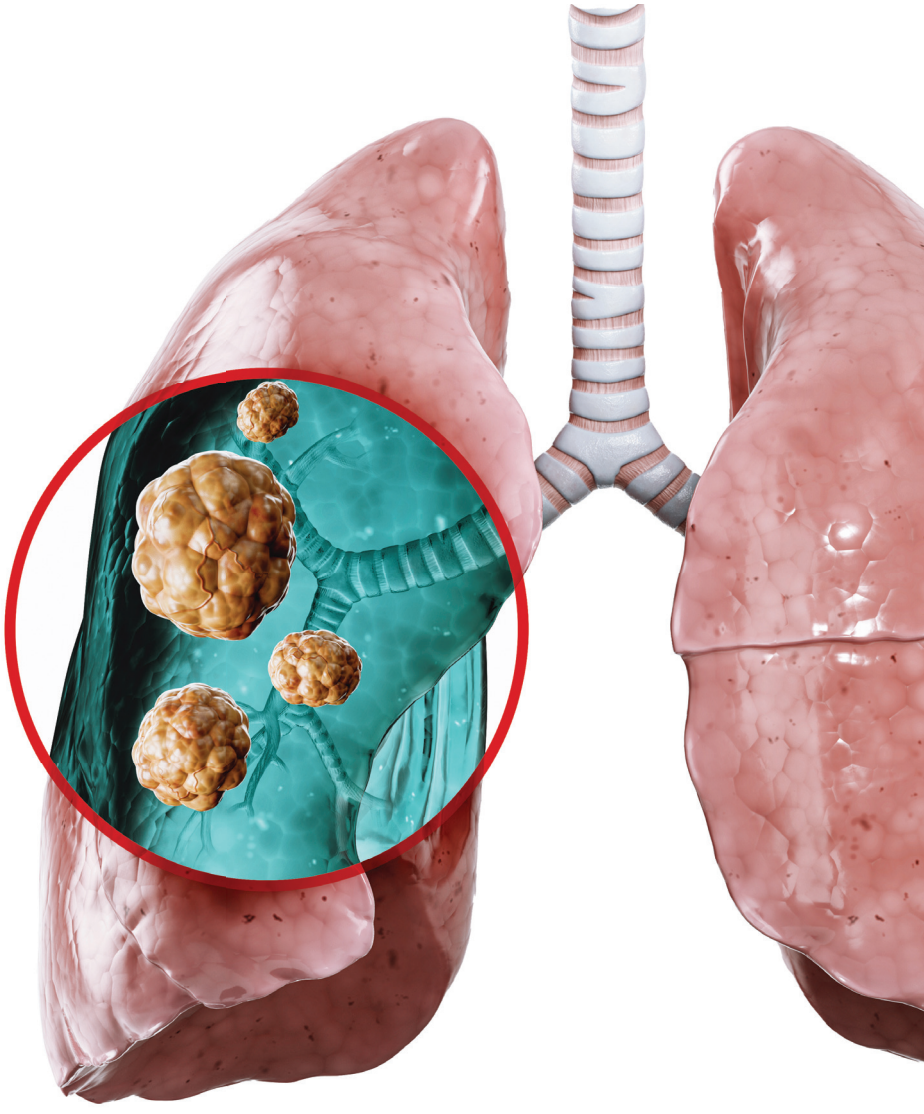
Dailey / This combination regimen is significantly more intense when compared with osimertinib monotherapy. Osimertinib monotherapy remains the National Comprehensive Cancer Network [NCCN] preferred first-line therapy for this subset of patients, and we know that patients generally do well on this therapy. Patients and providers will need to carefully consider who is most likely to benefit from the amivantamab and lazertinib treatment combination. Consideration can be given to patients with high-risk features associated with poorer outcomes and poor prognostic factors, as in those patients with known CNS metastases [and] *TP53* comutation, as well as those with baseline detectable circulating tumor DNA. These patients may be more willing to take on a more intense regimen and may be among those to derive more benefit from the multimodal therapy.

Q / Results from the MARIPOSA study showed a reduction in disease progression or death by 30%. How significant is this compared with other available treatments?

Dailey / In MARIPOSA, the primary end point was progression-free survival [PFS]. Comparing the median [PFS] for amivantamab and lazertinib with osimertinib, the combination group showed a significantly longer median PFS of 23.7 months vs 16.6 months in the osimertinib group. It is tempting to compare data from MARIPOSA with the combination therapy data found in the phase 3 FLAURA2 trial [NCT04035486], where osimertinib plus chemotherapy was compared with osimertinib monotherapy. However, direct comparison with data presented in the FLAURA2 trial is challenging. The primary end point was investigator-assessed PFS. The combination treatment in this study also recorded significantly longer PFS when compared with osimertinib monotherapy among patients with *EGFR*-mutated, advanced NSCLC.

[The MARIPOSA] data [were] recorded with different criteria, utilizing the investigator-assessed PFS. Reported median PFS numbers were similar at 25.5 months for combination therapy and 16.7 months for monotherapy. In MARIPOSA, the primary end point of PFS was determined on the basis of a blinded independent central review according to RECIST. Serial imaging of the head was also performed in all patients, providing detailed accounts for the evaluation of treatment effects on CNS metastases; these study design features make cross-trial comparisons of PFS estimates between MARIPOSA and other trial designs not informative.

Looking at the key secondary end point of overall survival [OS] in



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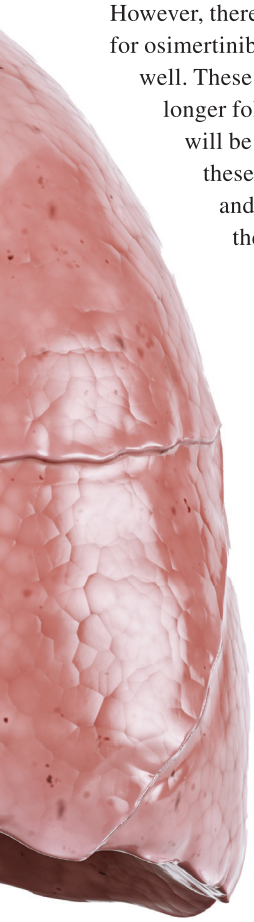
MARIPOSA, we cannot yet conclude that there will necessarily be a benefit in OS. This will require longer follow-up to achieve significance if the trend toward survival benefit continues. However, there may be a benefit in OS for osimertinib plus chemotherapy as well. These data will also require longer follow-up to conclude. It will be interesting to follow these regimens as more data and analysis further inform the treatment landscape.



Q / Were there any significant AEs noted with this combination?

Dailey / The combination of amivantamab and lazertinib is associated with significant toxicities classified as grade 3 or higher, which were reported in 75% of the patients in the combination group, compared with 43% of patients in the osimertinib monotherapy group. The most common AEs reported for the amivantamab and lazertinib group were paronychia in 68% of patients, infusion-related reactions in 63%, and rash in 62%. Surprisingly, venous thromboembolism was reported in 37% of patients on the combination vs 9% of patients assigned to osimertinib. The combination group saw 83% of patients with AEs leading to dose interruption, 59% leading to dose reduction, and discontinuation in 35%. These numbers far exceed the corresponding numbers for the osimertinib group at 39%, 5%, and 14%, respectively.

Q / Were there any resistance mechanisms observed with this treatment?

Dailey / Resistance to therapy is ever present, and not all patients will initially respond, and eventual loss of response is the expected outcome. The study rationale for combining amivantamab with lazertinib was designed to proactively address known mechanisms of resistance to current therapies. This stemmed from the findings that showed osimertinib with this activity against *T790M* mutation. The leading cause of resistance for first-generation EGFR TKIs was associated with improved PFS over the first-generation agents. This is in addition to the knowledge that resistance to third-generation EGFR TKIs does develop in almost all patients, with most known resistance mechanisms being secondary EGFR pathway alterations and MET pathway activation. Treatment with amivantamab and lazertinib offers broad coverage of these discussed resistance mechanisms with the consideration of preserving chemotherapy for use in later lines of therapy. Unfortunately, up to 50% of patients do not have identified resistance mechanisms to the standard of care osimertinib therapy.

Q / Where do you see this agent headed in the future?

Dailey / Lazertinib has only been approved in combination setting with amivantamab. This combination has now been added as an NCCN first-line therapy option for *EGFR* exon 19 deletion or exon 21 L858R mutations, either discovered prior to or during first-line systemic therapy. To date, osimertinib monotherapy remains the NCCN preferred first-line therapy in this space. If the combination does show an increased OS benefit with longer follow-up, this will become an increasingly attractive therapy option. Increases in PFS and OS must still be weighed against increases in toxicity and detriment to the quality of life for the patient; as always, shared decision-making will be critical.

Q / How do you expect to implement this treatment into your clinical practice?

Dailey / Patient selection for first-line treatment of NSCLC with amivantamab plus lazertinib will be based on the presence of *EGFR* exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test. Selection among the approved first-line therapy options will be tailored by patient-specific risk factors, performance, status, and shared decision-making. The amivantamab and lazertinib regimen demonstrates significant activity and benefit but comes with significant increases in time in the clinic, toxicity, and cost. ■

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To read more about the approval of lazertinib plus amivantamab visit **cancernetwork.com/approvalalert**

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MULTIPLE MYELOMA

Linvoseltamab Still Efficacious Despite CRL in Multiple Myeloma

"I don't think [the CRL] impacts how I look at the data that [are] publicly available or the long-term approval chances for linvoseltamab and how we might use it in the future," said Surbhi Sidana, MD.

Surbhi Sidana, MD, Associate Professor, Hematologist, Department of Medicine, Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University School of Medicine, California

The FDA recently issued a complete response letter (CRL) for the B-cell maturation antigen (BCMA) bispecific antibody linvoseltamab for patients with relapsed/refractory multiple myeloma.[1] The decision followed an issue discovered during an inspection of a third-party manufacturing facility involving packing the drug for storage and distribution. It has since been resolved; a reinspection is planned in the coming months.

CancerNetwork spoke with Surbhi Sidana, MD, an associate professor and hematologist in the Department of Medicine, Division of Blood and Marrow Transplantation and Cellular Therapy at Stanford University School of Medicine in California. She shared her thoughts on the recent FDA decision and phase 1/2 LINKER-MM1 trial (NCT03761108) findings, which evaluated linvoseltamab for patients with relapsed/refractory multiple myeloma and gave insight into developments occurring in the multiple myeloma space.[2]

Sidana began by assuring that the CRL was unrelated to the findings of LINKER-MM1. She expressed that the FDA rightfully decided to reinspect the manufacturing facility in the coming months before making a final decision. She reinforced the assurance by highlighting unprecedented efficacy results from the trial and a manageable safety profile congruent with similar bispecific antibodies and immunotherapies.

Furthermore, Sidana shared promising developments in multiple myeloma that she believes will impact clinical practice. She concluded the interview by addressing the incidence of infections following treatment, recommending an "aggressive" supportive care approach and potential dose reductions for patients to reduce high-grade infection frequency.

Q / How does the CRL from the FDA regarding linvoseltamab in relapsed/refractory multiple myeloma impact the treatment landscape?

Sidana / Linvoseltamab received a CRL from the FDA in response to its biologic license application. For those who are not familiar with what the CRL is, let me break it down. When a company submits an application for a new drug approval—in this case, Regeneron submitted for linvoseltamab, which is a BCMA CD3 bispecific antibody in myeloma—the FDA, when it has certain things it wants to course correct for the application itself, will issue a CRL. In this case, they showed a CRL in response to an inspection at a manufacturing facility where linvoseltamab [is partially] manufactured or filled, and they found some deficiencies.

It was not related to data, as I understand it, for linvoseltamab in the clinical trial per se but related to a third-party manufacturing facility. Now, in most cases, this is not unusual to receive a CRL. If the manufacturer and its affiliates can address the deficiency that is listed by the FDA, it then clears the path for FDA approval. This might be a delay for appropriate reasons that the FDA noted, but I do not think that this will lead to any long-term repercussions for linvoseltamab [regarding] FDA approval.

Q / Is the CRL a setback for this agent?

Sidana / In the big picture, CRLs are usually certain deficiencies that are noted by the FDA. In this case, it was at a manufacturing plant that was a third-party facility. Overall, the linvoseltamab program—yes, they have to address this. Yes, this might delay things for a certain period for FDA approval. In the big picture, I don't think this impacts how I look at the data that [are] publicly available, the approval chances long term for linvoseltamab, and how we might use it in the future. This is my read on the data that [are] publicly available.

Q / What benefit was observed with linvoseltamab in the LINKER-MM1 trial?

Sidana / LINKER-MM1 is a phase 1/2 trial of linvoseltamab, a BCMA CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma. I will focus more on the phase 2 portion that evaluated 2 doses of linvoseltamab: a 50-mg dose and a 200-mg dose; both were given intravenously [IV]. Over 100 patients were treated in both arms, and they wanted to evaluate the efficacy of these 2 doses. The step-up dosing was once a week IV with hospitalization for 24 hours after 2 step-up [doses]—week 1 and week 2. Starting week 3, patients received the full dose every week. Starting month 4 or week 16, it went to every other week. Now, there are some nuances in dosing, such that if [patients] were on the higher dose of 200 mg, starting week 24 approximately month 6 if [patients] were in a deep response, [very good partial response] or better with a 200-mg dose, [patients] could even go to every 4 weeks [to improve] patient convenience.

They did note that the responses were better in the 200-mg dose than in the 50-mg dose. The 200-mg dose was where the higher response rate was seen, even though responses were good in both arms, meeting the null hypothesis: about 50% in the 50-mg and 70% in the 200-mg [groups].

Q / Do you believe linvoseltamab has a place as an approved agent for relapsed/refractory multiple myeloma?

Sidana / Yes, I do believe linvoseltamab has a place in the relapsed/refractory multiple myeloma landscape as an approved agent. Now, we should note there are 2 FDA-approved bispecific antibodies that are already there: teclistamab-cqyv [Tecvayli], which was approved in late

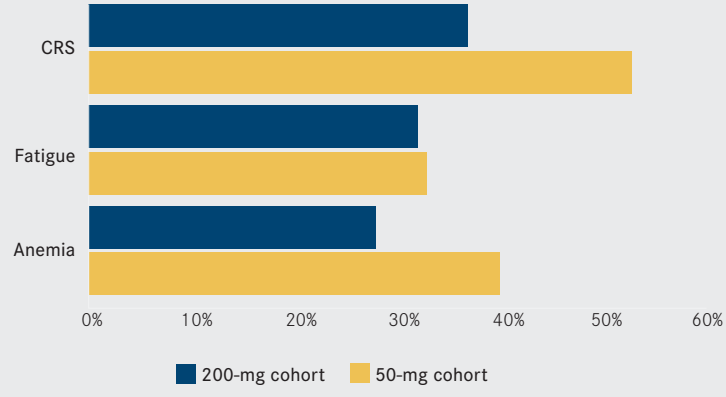
STATS AT A GLANCE

Overall response rate

64%
in the 200-mg cohort

50%
in the 50-mg cohort

The Most Common Treatment-Emergent Adverse Effects



Grade 3 or Higher ICANS

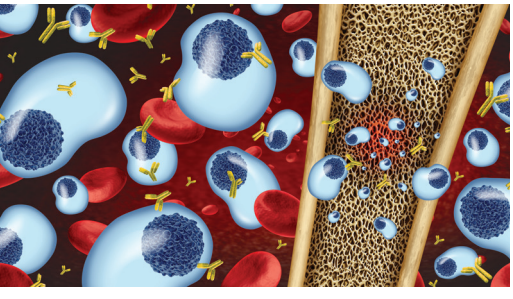
2%
in the 200-mg cohort

1%
in the 50-mg cohort

ICANS, immune effector cell–associated neurotoxicity syndrome.

2022, and elranatamab-bcmm [Elrexfio], which was approved in mid-2023. However, when we take examples from other cancers, there is a host of immunotherapy options [that] we might choose to use—one over the other, depending on center preferences, toxicity profile, convenience, and sometimes cost and formulary issues.

Certainly, there is a need for bispecific antibodies in multiple myeloma, and there are certain differences in schedule and administration. Of course, the cost remains to be determined. Yet we do not know anything about the cost, which may give it a place in the multiple myeloma treatment armamentarium.



Q / The FDA stated in the CRL that a reinspection will occur in the coming months. What do you believe are the next steps for this agent?

Sidana / The next steps would be waiting for that to happen and waiting for the FDA response. As I understand from the publicly available data, that is the only deficiency that has been raised to date. We expect that once that occurs, and if that's successful, we expect to see FDA approval for this agent.

Q / What other developments in multiple myeloma have the potential to impact clinical practice?

Sidana / We are living in exciting times in multiple myeloma. Over the [past] 3 to 4 years, we have had FDA approvals for 2 CAR [chimeric antigen receptor] T-cell therapies, idecabtagene autoleucel [ide-cel, Abecma] and ciltacabtagene autoleucel [cilta-cel, Carvykti], that target BCMA; [and] 3 bispecific antibodies, [including] 2 that target BCMA, teclistamab and elranatamab, and another that targets GPRC5D, talquetamab-tgvs [Talvey]. Now, we have other BCMA bispecifics, including linvoseltamab, that may get approved in the near future.

[There are] many other targets in development, both for bispecifics and CAR T, and other drugs, like CELMoDs [cereblon E3 ligase modulators] iberdomide and mezigdomide, [that] have shown promising data. We also had belantamab mafodotin-blmf [Blenrep], which was initially FDA approved. The accelerated approval was withdrawn based on a phase 3 study [DREAMM-3; NCT04162210].

Another phase 3 study shows very promising data that [were] presented in the summer meetings in 2024, so this is an exciting landscape—not only for the approval of new agents in late relapse but also for earlier line approval of agents like CAR T. Over the summer, we had early-line approval of both cilta-cel, after 1 prior line of therapy for patients who were [lenalidomide (Revlimid)]–refractory, and ide-cel after 2 prior lines of therapy.[3,4] Bispecifics are being investigated in earlier lines over the next couple of years. As those trial data come in, we would expect, hopefully, to get those moved into earlier lines.

Q / Is there anything else you would like to highlight regarding linvoseltamab as a treatment, the LINKER-MM1 trial, or the FDA decision?

Sidana / [What] I want to highlight about linvoseltamab and other BCMA bispecific antibodies and immunotherapy, in general, is the importance of good supportive care. These are very effective agents in terms of efficacy, but the lesson that we learned from the early trials was that infection is a big signal. We have to be aggressive, especially as these treatments move into the community where they might not have experience with clinical trials. We have to be aggressive with infection prophylaxis, including using drugs for zoster prophylaxis [and] PJP [*Pneumocystis jirovecii* pneumonia] prophylaxis because cases of PJP pneumonia were seen. We have to be aggressive with intravenous immunoglobulin, which is very effective in preventing grade 3 or higher infections in patients treated with BCMA bispecific antibodies. [We] have to be careful.

Also, in the real world, a lot of us are reducing the frequency of these agents. In the teclistamab trials, it was shown that, as you reduce the frequency the risk of infection does go down over time. [These are] very practical aspects that I want to highlight, with not just linvoseltamab, but all BCMA bispecific antibodies. ■

Stats at a Glance Reference

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Continuing Medical Education

The Evolving Landscape of Prostate Cancer Management

BRCA Testing and ctDNA as Diagnostic Tools and PSMA-Imaging and -Targeted Approaches

LEARNING OBJECTIVES

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

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- Evaluate the role of emerging biomarkers and targets, especially PSMA, in improving detection and treatment of metastatic castration-resistant prostate cancer.
- Assess how precision medicine has transformed prostate cancer care across the disease spectrum, from risk assessment to advanced disease management.

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FACULTY
Maha Hussain, MD, FACP, FASCO
Genevieve E. Teuton Professor of Medicine
Division of Hematology/Oncology
Deputy Director
Robert H. Lurie Comprehensive Cancer Center
Northwestern University Feinberg School of Medicine
Chicago, IL

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Prostate cancer remains the most common tumor type in males and the second leading cause of cancer deaths overall in the United States.[1] With an estimated 299,010 new cases expected in 2024, the average lifetime risk of diagnosis is about 17%, while the risk of dying from the disease is approximately 3%.

The landscape of prostate cancer management has been dramatically reshaped by precision medicine. This approach has evolved from focusing on individual risk assessment to guiding diagnostic procedures, treatment decisions, and management of advanced disease.[2]

Precision medicine now incorporates:

- **Risk assessment:** Utilizing genetic and molecular markers to identify high-risk populations
- **Diagnostic accuracy:** Employing advanced imaging techniques and biomarker analysis to enhance prostate biopsy procedures
- **Tailored treatments:** Optimizing therapy based on the genetic profile of the tumor, balancing efficacy with minimized adverse effects
- **Advanced care strategies:** Personalizing treatment for advanced prostate cancer using targeted therapies, immunotherapies, and hormone-based treatments aligned with the molecular characteristics of the tumor

Q / Which patient subpopulation would you test for *BRCA1/2* mutations?

HUSSAIN / Anytime we have patients who have metastatic disease, testing them for *BRCA* or *BRCA*-like genes is going to be important, potentially for therapeutic purposes and particularly in metastatic castration-resistant disease. Other than that, testing for germline mutations is important.

Q / How do you foresee the role of circulating tumor DNA (ctDNA) as a diagnostic and prognostic tool in prostate cancer?

HUSSAIN / Potentially, ctDNA will play different roles. In situations in which we are looking for insight into the genomics of the tumor, ctDNA is going to be helpful in that regard. When it comes to the actual diagnosis of prostate cancer or the staging of disease, ctDNA is not a mature biomarker at this point. For diagnostic purposes, we need the tissue either via biopsy from the prostate or, if a patient has metastatic disease, then biopsy from tissues affected by metastasis. As it relates to monitoring disease activity, prostate-specific antigen (PSA) continues to be the most useful biomarker. Any additional biomarkers, such as ctDNA, will have to be validated as they relate to early detection of metastatic disease or micrometastatic disease and potential response to therapy.

Q / How have PSMA diagnostics changed the way that prostate cancer is managed?

Despite these advancements, detecting recurrence and treating metastatic disease remain significant challenges.[3] Conventional imaging often falls short in early detection, and hormone-resistant tumors present a major clinical obstacle. However, new hope lies in targeting prostate-specific membrane antigen (PSMA), which is frequently overexpressed in prostate cancer.[4] PSMA-targeting molecules are being developed to both detect early metastasis and treat metastatic castration-resistant prostate cancer (mCRPC), potentially offering new avenues for managing this challenging stage of the disease.[5]

As research continues, the integration of these precision medicine approaches and novel targeted therapies promises to further improve patient outcomes and quality of life for those affected by prostate cancer.

HUSSAIN / From a therapeutic standpoint, it provides an option that we did not have for patients before. Since 2004, when the first drug that prolonged life in castration-resistant disease—docetaxel—was approved, we now have infinitely more agents available for our patients. I'm hopeful that at some point we're going to have potential cures for patients with metastatic disease.

Use of PSMA therapeutics, specifically, is an FDA-approved option based on impactful benefit with regard to progression-free survival and overall survival in the setting of end-stage mCRPC.

The imaging is very important. Ultimately, the goal is to detect cancer at a very early stage with the hope that we can target it, treat it appropriately, and potentially cure it. I do think that theranostics with regard to the imaging component is very helpful. However, it is clear that more research to define its impact on our treatment decisions is needed. Until now, when it comes to metastatic disease, all of the current data from key clinical trials that led to FDA approvals and guiding our therapy decisions were based on conventional imaging and not PSMA imaging.

I tell patients and my mentees: in reality, a tumor 1 cm^3 in size is comprised of a billion cancer cells. Clearly, even if the PSMA

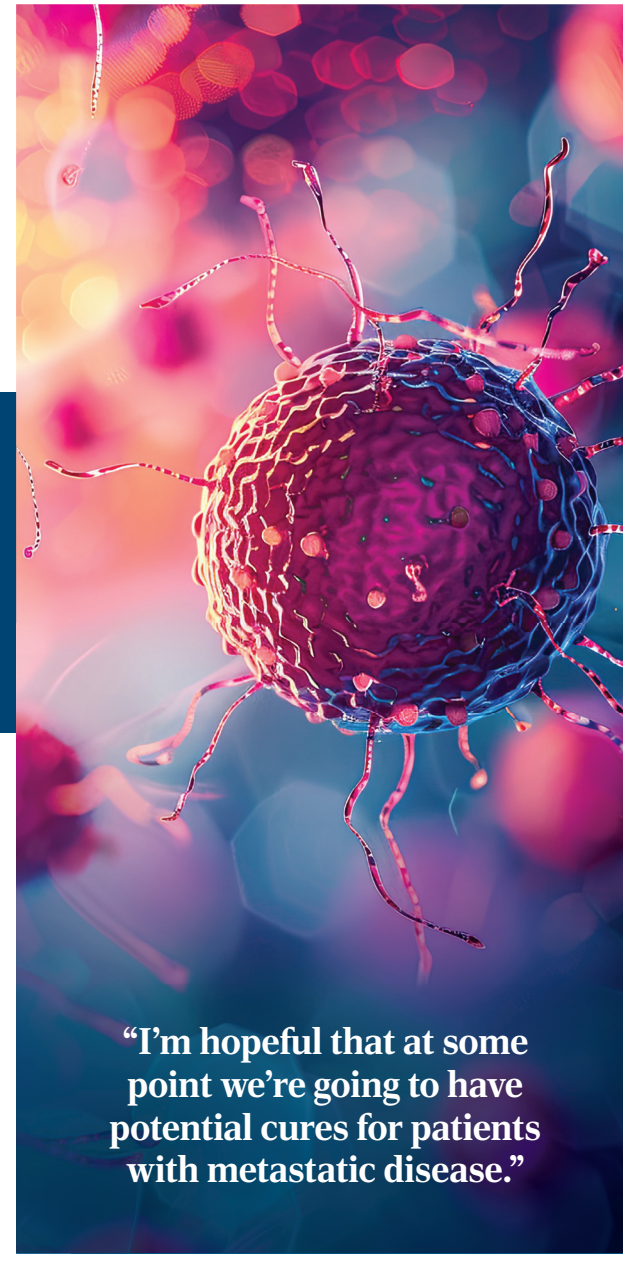
TABLE. Emerging Agents of Next-Generation Imaging in Prostate Cancer[4]

RADIOTRACER	ADVANTAGES	DISADVANTAGES	STATUS
^{68}GA-PSMA-11	· Lower uptake time. · Lower radiation exposure. · Extensively researched. · TLX591-CDx radiopharmaceutical cold kits will enable greater accessibility.	· ^{68}Ga generator–dependent production makes mass production relevant to ^{18}F-based agents. · Difficult to transport due to short half-life.	Received FDA approval (currently only covers UCSF and UCLA).
^{68}GA-PSMA-617	· Improved binding affinity. · Increased internalization into PCa cells vs ^{68}GA-PSMA-11. · PSMA-617 can be chelated with ^{177}Lu to enable pure theranostic pairs. · Companion agent (^{177}Lu-PSMA-617) is widely used and extensively researched.	· More research is necessary to evaluate use across multiple clinical settings.	—
^{18}F-DCFPyl	· Extensively researched; labeling with ^{18}F leads to commercialization. · Longer half-life and shorter position range leads to better image quality. · Lower hepatic background; may be advantageous in later stages of PCa.	· High uptake in the urinary system can lead to challenges in detecting small lymph nodes in pelvis.	Received FDA approval.
^{18}F-PSMA-1007	· Reduced urinary clearance offers elective assessment of the prostate.	· Higher detection of benign lesions vs ^{68}Ga-PSMA-11. · Higher uptake in liver makes it difficult to identify liver lesions.	—
^{18}F-rhPSMA-7	· Radiohybrid ligand allows for rapid labeling and pure imaging of theranostic pairs. · Rapid blood clearance; low urinary excretion.	· Uptake in bones, healing fractures, and degenerative changes not attributed to PCa can lead to false positives. · More research is necessary to evaluate agent in multiple clinical settings.	Trials underway: NCT04186819 and NCT04186845
CTT1057	· Similar biodistribution to urea backbone drugs with lower dose to kidneys and salivary glands · Companion therapeutic agent (CTT1403) is currently in clinical trials	· More research is necessary to evaluate use of this agent in multiple clinical settings	Phase 1 trial completed
^{64}Cu-PSMA-617	· Enables delayed imaging (up to 17 h postinjection). · Easier to transport to remote facilities.	· Potentially higher radiation exposure. · More research is necessary to evaluate ^{64}Cu-based imaging agents alongside ^{18}F- and ^{68}Ga-based imaging agents.	—

PCa, prostate cancer; PSMA, prostate-specific membrane antigen; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco.

imaging is negative and the PSA level is up, that does not mean that there is no micrometastatic disease. One cannot just 100% believe the negative imaging. There is cancer activity that has to be managed based on evidence-based standards of care and clinical judgment.

Detecting recurrence and treating metastatic disease are key challenges in prostate cancer.[3] Conventional imaging modalities struggle with early detection, and hormone-resistant tumors pose a major clinical hurdle. As PSMA is often overexpressed in prostate cancer, PSMA-targeting molecules are being developed to detect early progression and to treat mCRPC. Due to uptake of ligand-binding PSMA into tumor cells, a high-quality image is generated. **Table 1** presents several emerging PSMA-targeting molecules currently used and under development to detect and treat prostate cancer.[4]



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Q / Where do you see the field of prostate cancer going in the next 5 years?

HUSSAIN / Basically, the field is moving in a wonderful way with significant investment at all levels regarding research, science, clinical trials, and enrollment in different parts of the world, not just in Western countries. I think we are moving toward converting prostate cancer, when it comes to metastatic disease, from an imminently deadly disease to more of a chronic disease.

When I entered the field 3 decades ago, the median survival for men with metastatic hormone-sensitive disease was roughly 2.5 to 3 years. Now, it has doubled to nearly 6 years with a significant number of men living beyond 10 years. In fact, my practice includes several patients who have surpassed the 10-year mark since their initial diagnosis of metastatic hormone-sensitive disease.

We've seen similar progress in castration-resistant disease. The median survival was about 9 months when I started my clinical practice, but that has extended considerably. We've made substantial strides, and I'm optimistic that we're moving closer to managing this as a chronic disease with the ultimate goal of finding a cure. ■

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*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]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

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DARZALEX®: Infusion-Related Reactions

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

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

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

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions.

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DARZALEX® (daratumumab) + Rd (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 (PFS) and OS was a secondary endpoint.[1]

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

At follow-up of 28 months, **median progression-free survival (mPFS) was not reached** with DARZALEX® + 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)

Efficacy results in long-term follow-up[1,4]

After 64 months of follow-up, the median PFS was 61.9 months (95% CI: 54.8, not evaluable) in the DRd arm and 34.4 months (95% CI: 29.6, 39.2) in the Rd arm

45% **reduction in the risk of disease progression or death** with DARZALEX® + Rd vs Rd alone (HR=0.55; 95% CI, 0.45-0.67)

Secondary endpoint of overall survival (OS)[1,2]
After 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 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
(median treatment duration of 25.3 months)[1]

- The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, 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%)

Safety results in long-term follow-up
(median follow-up of 64.5 months)[4]

This information is not included in the current Prescribing Information and has not been evaluated by the FDA.

- Most frequent TEAEs for DRd occurring in ≥30% of patients 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 43% for DRd vs 30% for Rd‡
- Grade 3/4 TEAEs occurring in ≥10% of patients were neutropenia (54% for DRd vs 37% for Rd), pneumonia (20% vs 11%), and anemia (17% vs 22%)‡

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); FDA=U.S. Food and Drug Administration; HR=hazard ratio; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.
*Range: 0.0-41.4 months.[1,3]
†Kaplan-Meier estimate.[3]
‡Safety analysis set. TEAEs are defined as any adverse event (AE) that occurs after the 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 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.
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IMPORTANT SAFETY INFORMATION (CONTINUED)

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*®. 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.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

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. doi:10.1056/NEJMoa1817249 **4.** Kumar SK, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 MAIA study. Poster presented at: 64th American Society of Hematology (ASH) Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA.

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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, USA
U.S. License Number 1864

For patent information: www.janssenpatents.com

cp-271933v4

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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Janssen Biotech, Inc.
Horsham, PA 19044, USA
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For patent information: www.janssenpatents.com

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