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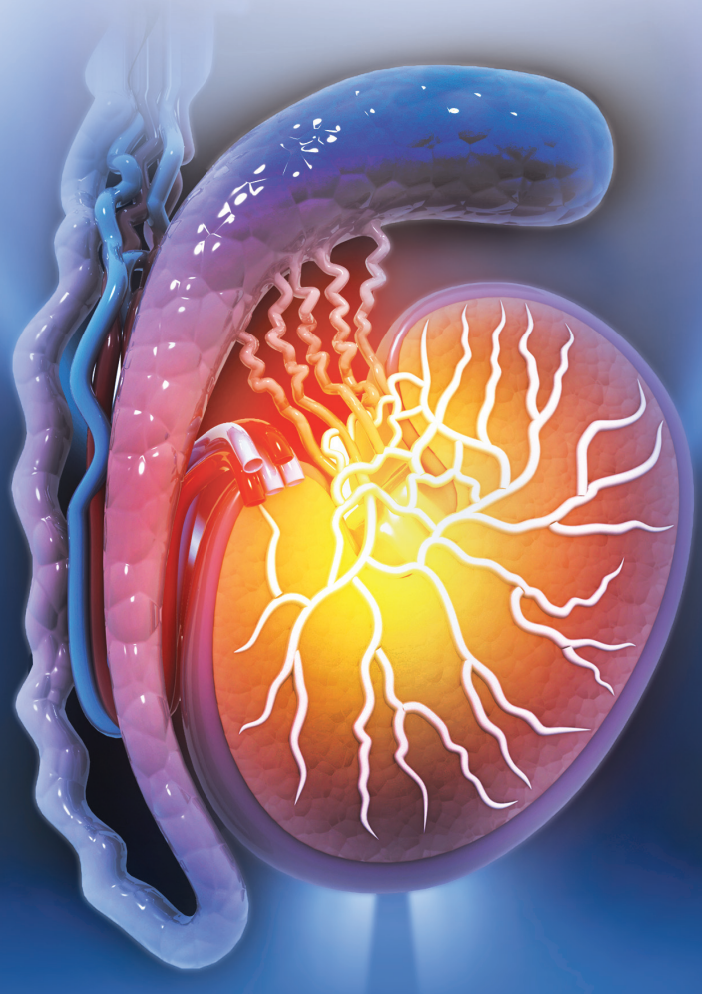
CLINICAL QUANDARY

Testicular Cancer

Evaluation and Management After Late Relapse



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Robert A. Winn, MD

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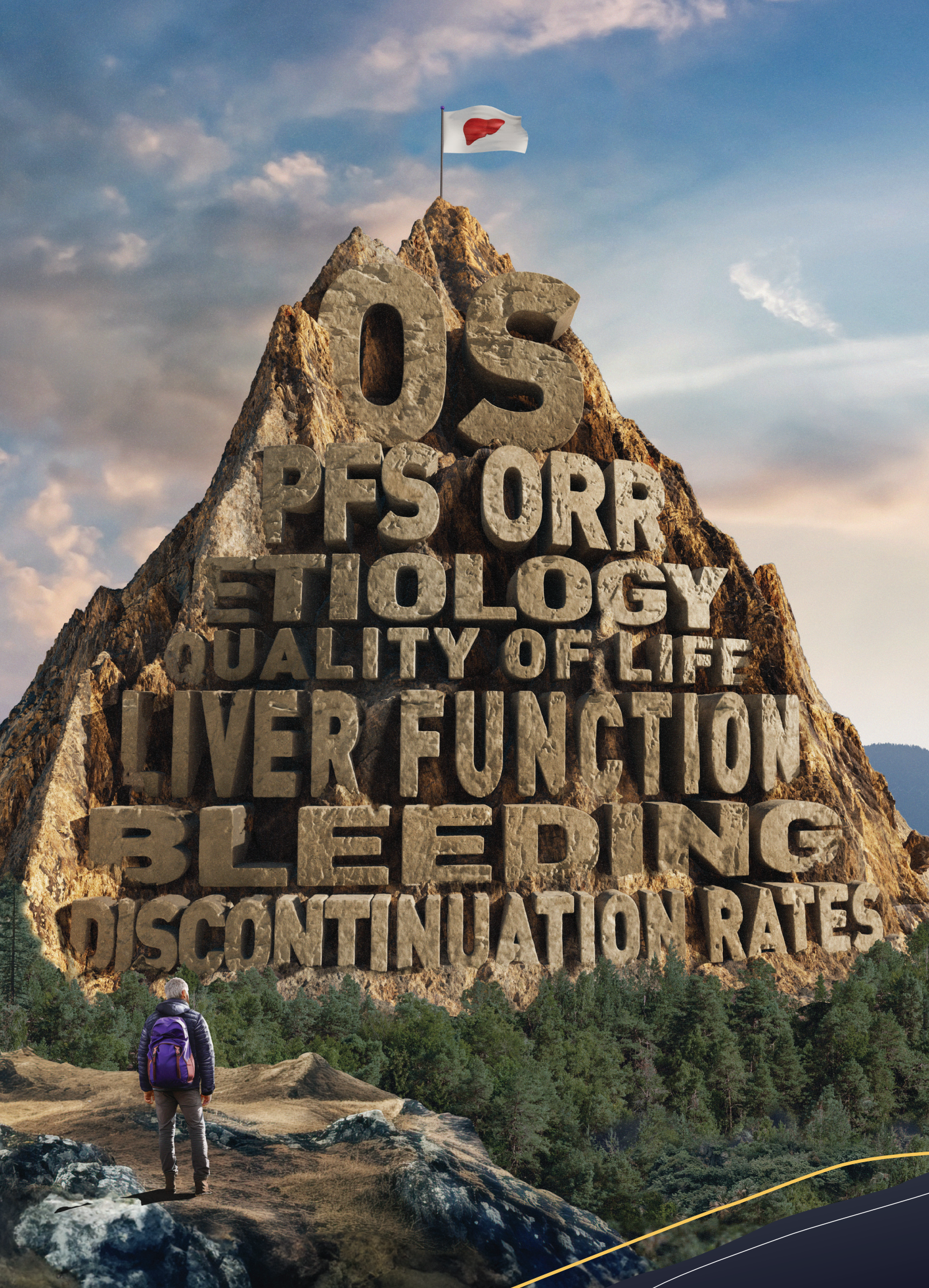
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Updates in Breast Cancer Care From the 41st Annual Miami Breast Cancer Conference

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The 41st Annual Miami Breast Cancer Conference in March 2024 highlighted a wealth of new and evolving data in the field. Key abstracts and presentations focused on novel endocrine therapies for hormone receptor (HR)–positive metastatic breast cancer (MBC), postmastectomy radiation after pathologic complete response (pCR), sequencing of antibody-drug conjugates (ADCs) in HER2-zero and HER2-low tumors, and emerging agents to manage HR-positive tumors after progression on CDK4/6 inhibitors. Attendees also reviewed and contextualized practice-changing data reported at recent congresses. Below are key points from some of these updates.

Several novel endocrine therapies recently have been made available or are under development for the treatment of patients with HR-positive MBC. Updated data for the oral selective estrogen degrader (SERD) elacestrant (Orserdu) provided insights regarding efficacy by duration of prior CDK4/6 inhibitor treatment.[1] In the phase 3 EMERALD trial (NCT03778931), patients with HR-positive/HER2-negative MBC who had prior CDK4/6 inhibitor exposure were randomly assigned to receive elacestrant (n=239) or standard of care (endocrine therapy or fulvestrant; n=239). Patients with a longer duration of prior CDK4/6 inhibitor therapy had longer progression-free survival (PFS) when subsequently treated with elacestrant (median PFS, 5.45 months; 95% CI, 2.33-8.61) compared with standard endocrine therapy (median PFS, 3.29 months; 95% CI, 1.87-3.71) when prior CDK4/6 inhibitor exposure was 18 months or more. The observed benefit of elacestrant with longer prior CDK4/6 inhibitor exposure was even greater in patients with *ESR1*-mutated tumors. The median PFS with elacestrant was 8.61 months (95% CI, 5.45-16.89) vs 2.10 months (95% CI, 1.87-3.75) with standard endocrine therapy. No new safety signals were identified, with low-grade nausea observed as a common adverse effect (AE) of elacestrant. Elacestrant is the only FDA-approved oral SERD for breast cancer treatment, although, with many ongoing oral SERD trials in the pipeline, this space will rapidly evolve.

For example, phase 2 data for another novel oral SERD, camizestrant, demonstrated promising efficacy.[2] SERENA-2 (NCT04214288) is a randomized, phase 2 trial evaluating the safety and efficacy of camizestrant compared with fulvestrant alone in patients with HR-positive/HER2-negative MBC. Participants were randomly assigned to receive camizestrant 75 mg (n=74), camizestrant 150 mg (n=73), camizestrant 300 mg (n=20), or fulvestrant (n=73). The trial met its primary end point of PFS, with a median PFS of 7.2 months and 7.7 months in the 75-mg and 150-mg arms, respectively (the 300-mg arm was not analyzed because enrollment in this arm was stopped early). Additionally, reductions in circulating tumor DNA (ctDNA) containing *ESR1* mutations were greater in the camizestrant arms compared with the fulvestrant arm. In addition to elacestrant and camizestrant, several novel endocrine therapies are under development as monotherapy or combination therapies. Combinations of oral SERDs with existing and novel molecular therapeutics also are being tested. Ultimately, oral SERD monotherapy or combinations with molecular therapies such as PI3K, AKT, and mTOR inhibitors will provide additional treatment options after treatment with CDK4/6 inhibition and endocrine therapy.

Regarding novel molecular therapeutics, phase 3 data for the oral AKT inhibitor capivasertib (Truqap) recently led to its FDA approval in November 2023.[3] The phase 3 CAPItello-291 trial

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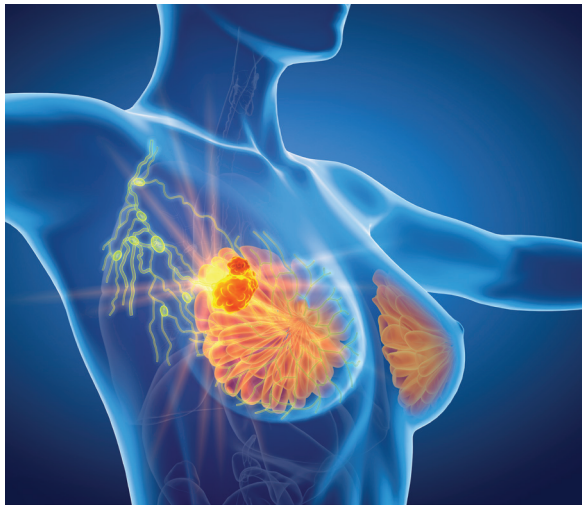

(NCT04305496) evaluated the efficacy and safety profile of capivasertib plus fulvestrant in patients with HR-positive/HER2-negative MBC and met the primary PFS end point.[4] Participants with at least 1 AKT pathway alteration (*PIK3CA*, *AKT1*, or *PTEN*) experienced a median PFS of 7.3 months (95% CI, 5.5-9.0) in the capivasertib arm vs 3.1 months (95% CI, 2.0-3.7) in the placebo plus fulvestrant arm. Approximately 70% of patients had been treated with a CDK4/6 inhibitor prior to study enrollment, which increases the relevance of these findings to current clinical practice. Overall, the toxicity profile was manageable, with diarrhea as the most common AE (all-grade rate, 72%). Hyperglycemia is a specific concern for agents that target this pathway. For example, the all-grade hyperglycemia rate was approximately 64% for patients treated with the PI3K inhibitor alpelisib (Piqray) in the phase 3 SOLAR-1 trial (NCT02437318). However, the all-grade hyperglycemia rate was only 16.3% with capivasertib in the CAPItello-291 trial despite a more lenient hemoglobin A_{1c} eligibility criterion. These results position capivasertib plus fulvestrant as a favored second-line treatment option in patients with AKT pathway–altered tumors. With increasing molecular therapeutic options, additional endocrine therapy partners are also needed. This need represents a potential space for oral SERDS that are under development.

Because of the availability and development of novel ADCs, there is a critical need to better understand the optimal sequencing of these agents, particularly for patients with HER2-low tumors. Currently, only observational data sets have been reported, and sequencing trials are underway. At the 2023 American Society of Clinical Oncology Annual Meeting, data from a single-institution, retrospective cohort study indicated the activity of ADCs after prior treatment with an ADC.[5] In a cohort of 35 patients, 8 of 12 (67%) had disease progression on the first assessment scan when the second sequential ADC contained the same antibody target but a different payload from the first ADC. When the second ADC contained a different antibody target and different payload than the first, 42% had disease progression on the first assessment scan, suggesting that a change in antibody target may represent a successful strategy for ADC sequencing. In another observational study of 84 patients treated with fam-trastuzumab deruxtecan-nxki (T-Dxd; Enhertu) and sacituzumab govitecan-hziy (SG; Trodelvy) sequentially, PFS was longer for the first ADC used, though some patients experienced more durable response with the second ADC.[6] Reassuringly, there were no safety concerns identified when sequencing T-Dxd and SG, although growth factor support was commonly required with SG treatment. These observational data sets have not identified reliable predictors of who *will* or *will not* respond to a second ADC, and data from ongoing trials are eagerly anticipated. For now, a conservative approach could include the use of treatments that have a different mechanism of action between ADC treatments.

These updates in breast cancer therapy and many more were discussed extensively during the Miami conference. The landscape of breast cancer therapy is rapidly changing with seemingly new shifts in standard-of-care guidelines after each major congress. We at *ONCOLOGY* will continue to bring the latest updates to our readers. ■

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TESTICULAR CANCER

Evaluation and Management of Testicular Cancer After Late Relapse

Joanna L. Langner, MS; Frederick Millard, MD; Vera Vavinskaya, MD; Haiyan Zhang, MD; Nuphat Yodkhunnatham, MD; Aditya Bagrodia, MD

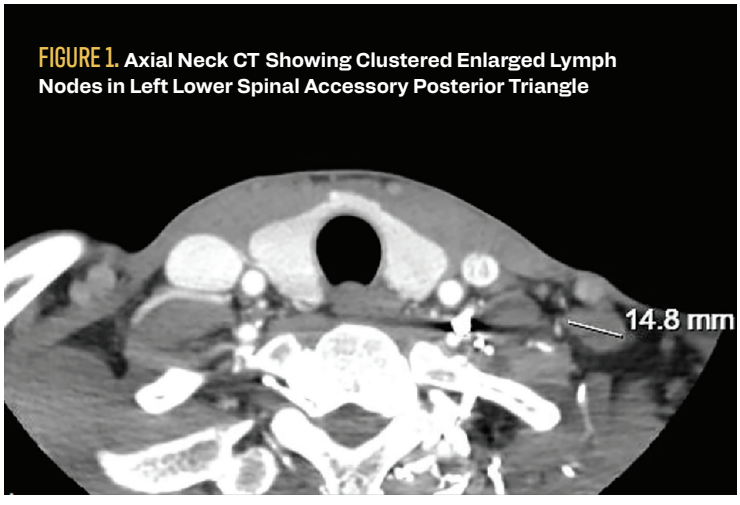

FIGURE 1. Axial Neck CT Showing Clustered Enlarged Lymph Nodes in Left Lower Spinal Accessory Posterior Triangle

What is the likely diagnosis based on the presenting illness and initial work-up?

A. Late relapse of NSGCTs with malignant germ cell elements

B. Late recurrence of teratoma

C. Somatic transformation/malignant degeneration of teratoma

D. Second primary germ cell tumor in left testis

E. New process unrelated to history of NSGCT, such as lymphoma, head and neck cancer, or a benign inflammatory condition

Turn to page 144 for the answer and a discussion of this case by experts

ABSTRACT

A 41-year-old man presented to his primary care physician with a 1-month history of left neck adenopathy in the context of a history of nonseminomatous germ cell tumors (NSGCTs). In 2011, the patient was treated for stage IB (T2N0M0S0) right-sided NSGCTs of the testis, which were 95% embryonal and 5% yolk sac tumors. He underwent a right radical orchiectomy and was followed until 2022 without recurrence.

In the work-up for his adenopathy, laboratory results for human chorionic gonadotropin, lactate dehydrogenase, and α-fetoprotein were normal. CT scans confirmed clustered enlarged lymph nodes in the left lower spinal accessory posterior triangle, enlarged left lower neck lymph nodes, and several foci of enlarged left retroperitoneal periaortic lymph nodes. Fine needle aspiration of a left neck lymph node identified malignant tumor cells. A left neck dissection showed embryonal carcinoma in 12 of 28 nodes. Immunostaining showed the tumor cells were positive for SALL4 and CD30 but negative for CD117.

This patient likely had a contralateral late relapse of his original right NSGCT after 11 years of remission. The patient's original cancer was on the right side, with recurrence surrounding the aorta on the contralateral side, representing an atypical pattern of spread.

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Case Report

A 41-year-old Asian man presented to his primary care physician (PCP) in January 2023 with a 1-month history of left neck adenopathy in the context of a prior history of nonseminomatous germ cell tumors (NSGCTs). In 2011, the patient was treated for stage IB (T2N0M0S0) right-sided NSGCTs of the testis. The patient had multifocal tumors, 2.9 cm and 1.3 cm in greatest dimension, which were 95% embryonal and 5% yolk sac tumors. He underwent a right radical orchiectomy and was followed until 2019 under surveillance without evidence of recurrence. In July 2022, the patient had normal tumor markers and in September 2022 had normal CT scans. The patient is married and a nonsmoker, with no alcohol history and no history of undescended testis or infant surgery. At the time of this visit with his PCP to discuss the left neck adenopathy, he had no recent history of an upper respiratory infection and denied bladder changes, bleeding or bruising, bowel changes, cough or hoarseness, fatigue, night sweats, weight loss, pain, and persistent fever.

Soft tissue ultrasound in January 2023 revealed enlarged left neck lymph nodes that could be either pathological or reactive, with a decrease or loss of fatty hilum. The largest lymph node was 1.8 × 1 × 1.5 cm. His laboratory results were normal with a human chorionic gonadotropin (hCG) level of less than 1 IU/L, lactate dehydrogenase (LDH) level of 164 U/L, and α-fetoprotein (AFP) level of 2.9 µg/L; neoplastic syndrome was not indicated. A subsequent CT scan of his neck 3 weeks later confirmed clustered enlarged lymph nodes in the left lower spinal accessory posterior triangle, with left lower neck lymph nodes measuring up to 1.6 cm and a paratracheal cystic lesion measuring 1.8 cm in greatest dimension **(Figure 1)**. A CT scan of the chest/abdomen/pelvis 1 month after the CT scan of the neck confirmed the neck lymphadenopathy as well as several foci of left retroperitoneal periaortic lymph nodes that were enlarged, all less than 2 cm in greatest dimension **(Figure 2)**. Scrotal ultrasound at this time showed diffuse left testis microlithiasis that was otherwise normal, and tumor markers were notable for an LDH level of 303 U/L (elevated), AFP level of 3.4 µg/L, and an undetectable hCG level.

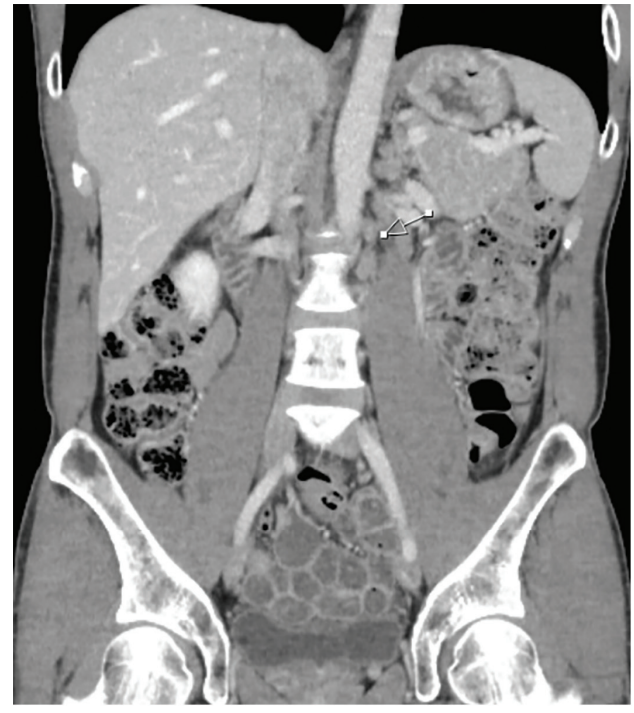

FIGURE 2. Coronal CT Abdomen and Pelvis Showing Several Foci of Periaortic Lymphadenopathy

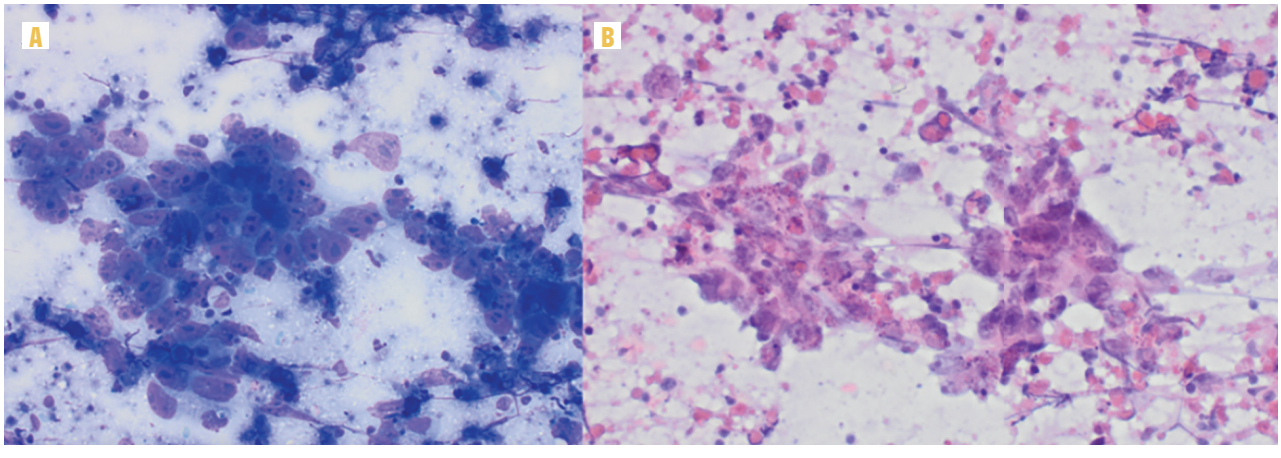

FIGURE 3. Staining Results **(A)** Diff-Quik stain (×20): Pleomorphic malignant cells with large irregular nuclei, coarse chromatin, prominent irregular nucleoli, vacuolated cytoplasm, and indistinct cell borders (syncytial growth pattern). **(B)** Papanicolaou stain (×20): Syncytial cluster of pleomorphic malignant cells with coarse chromatin and prominent nucleoli in a background of necrotic debris.

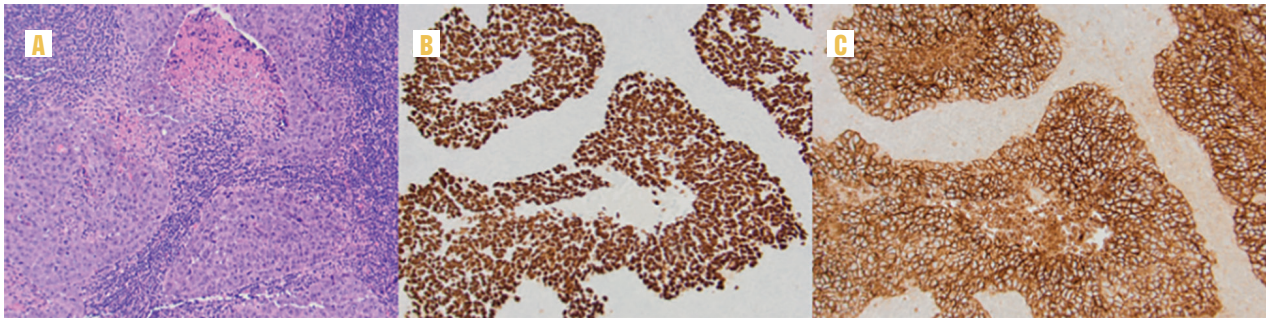

FIGURE 4. Additional Results **(A)** Hematoxylin and eosin stain (×100): Solid nests of malignant cells with synthetical growth pattern, prominent nucleoli, and tumor necrosis in a background of lymphoid tissue. **(B)** SALL4 immunostain stain (×100): Strong nuclear positivity. **(C)** CD30 immunostain stain (×100): Strong and diffusely membranous positivity.

Initial fine needle aspiration (FNA) of a left neck node identified malignant tumor cells with clusters of pleomorphic malignant cells in a background of necrotic debris, with insufficient material for further characterization **(Figure 3).**

Four months after his first presentation at his PCP office, the patient underwent left neck dissection with pathology showing embryonal carcinoma in 12 of 28 nodes, with a maximum nodal size of 2.5 cm in greatest dimension. Immunostaining showed the tumor cells were positive for SALL4 and CD30 and negative for CD117 **(Figure 4)**.

Answer: A Late relapse of NSGCTs with malignant germ cell elements

Introduction

Testicular cancer is the most common cancer in young men, with 95% of testicular cancers being germ cell tumors (GCTs).[1] Within testicular GCTs, nonseminomas make up approximately 40% and the rest are seminomas.[1] The majority of patients with NSGCT are cured. However, late relapse of this cancer has been well documented and researched.[1]

Late relapse of testicular cancer is defined as occurring more than 2 years after initial diagnosis and surveillance or complete response to treatment.[1] In recent research, up to 7% of patients with NSGCT have had a late relapse, which is more common than previously thought.[1,2] The median number of years for late relapse of all testicular cancers is 6 years (range, 2-32).[1,3] In a 1994 *Urologia Internationalis* article, researchers described late relapse of NSGCT after orchiectomy and retroperitoneal lymph node dissection (RPLND) 40 months after surgery, with the only marker for recurrence being elevated AFP.[4] Reports of late relapse of NSGCT are found throughout the literature and may be on the rise.

In this report, we review a patient with a rare presentation of contralateral late-onset relapse of NSGCT after 11 years in remission. This case is unique in that the patient not only falls into the category of late relapse but also far surpasses the average relapse timeline of 6 years. Additionally, his presenting symptom was left neck adenopathy, with no other initial signs or symptoms of recurrence.

Late Relapse and Contralateral Retroperitoneal Recurrence

From the findings of the left neck dissection, the morphology and immune profile support the diagnosis of embryonal carcinoma **(answers B, C, and E are incorrect)**. Notably, the histological profile cannot reveal whether this is a late relapse or a secondary primary tumor. The lack of a discrete mass on scrotal ultrasonography, normal semen parameters, and normal gonadal function lead us to believe a burned-out or regressed metastatic left primary is less likely. Nevertheless, the presence of microlithiasis in a patient with a history of GCT must be considered as a risk factor for GCT. The timing and pattern of this patient's presentation are atypical for a NSGCT. Typically, we would expect right-sided tumors to primarily metastasize to the interaortocaval and paracaval lymph nodes. However, this patient had relapse in the para-aortic distribution and left supraclavicular region, which is more common in left-sided tumors.

For late relapses, clinical presentations vary, marked by serum tumor marker elevation, surveillance imaging, or symptoms. The most common place for testicular cancer to relapse is the retroperitoneum, making up 50% to 80% of relapses due to the shared embryology of the testis and kidney.[1,3] Late relapse may be seen in supraclavicular nodes and rarely in cervical nodes.[1] Researchers in a 2023 case study described an initial presentation of metastatic seminoma being neck/axillary lymphadenopathy.[5] Our patients'

periaortic and neck lymph nodes do follow these possible sites of metastatic spread, yet they are contralateral to what would be expected.

When it comes to laterality, left-sided tumors typically metastasize to left para-aortic nodes, and right-sided tumors metastasize to interaortocaval lymph nodes and paracaval lymph nodes.[1] It is important to note that because of the normal anatomical crossover of the abdominal lymphatics from right to left, a right-sided tumor can present with left para-aortic nodes, especially when bulky. However, this crossover is not extensively described in patients with late relapses.[1]

Although it is rare, this patient's original right-sided NSGCT has spread to left periaortic lymph nodes, likely in part due to the right-to-left crossover of abdominal lymphatics. His left neck lymph node is likely also a consequence of this crossover.

In the context of his diffuse left-sided microlithiasis, there is a raised concern for a left-sided primary secondary GCT. Results of a meta-analysis published in 2010 showed that testicular microlithiasis may represent an elevated risk of a testicular GCT in patients who are high risk, such as those with a history of GCTs. However, this risk has not been proven to be higher than the risk in patients without findings of testicular microlithiasis, and overall, it is still poorly understood.[6] Lastly, his paratracheal abnormality remains somewhat perplexing but has features suggesting it is a mediastinal cyst rather than a pathologic lymph node.

Based on the clinical presentation, results from the FNA, immunostains from the biopsy, imaging, and review of the historical data, it is likely that this patient has a contralateral late relapse of his original right NSGCT after 11 years of remission **(answer A is correct)**. However, we cannot fully rule out a secondary primary GCT in the left testis with 100% certainty without a left radical orchiectomy **(answer D is unlikely but cannot be ruled out completely)**. With the patient declining to undergo an additional surgery, the cause of his current cancer status may never be completely known.

Treatment

This patient had chemotherapy-naive late recurrence of NSGCT without evidence of teratoma or somatic transformation of teratoma in either the primary tumor from 2011 or supraclavicular lymph nodes. Reasonable options included chemotherapy, RPLND, or observation. The volume of involved supraclavicular lymph nodes and enlarged retroperitoneal lymph nodes made systemic therapy the most attractive option. Also, the retroperitoneal disease was small at this time, with a reasonable chance of regression with chemotherapy and avoidance of RPLND. Given that the patient had not been previously exposed to chemotherapy, the prognosis was optimistic. After a multidisciplinary discussion with the patient and shared decision-making, he completed 3 cycles of bleomycin, etoposide, and cisplatin. A CT scan of the chest/abdomen/pelvis taken 2 months after the patient completed chemotherapy showed that the retroperitoneal nodes had resolved and a 9-mm right paratracheal abnormality was present. This is the area where an 18-mm paratracheal cystic lesion was seen on the first neck CT after presentation with the neck mass. The waxing and waning of the paratracheal abnormality throughout chemotherapy again may signal that it is a cystic process. Three months later, the most recent CT scan of the chest/abdomen/pelvis found that the retroperitoneal lymphadenopathy was still resolved, a likely node measuring 1.1×0.7 mm between the aorta and the left adrenal had not significantly changed from prior exams, and the upper right paratracheal node appeared less conspicuous. Tumor markers continue to be negative.

When it comes to screening for relapse, CT surveillance is one of the best tools for identifying relapse at an early stage while also providing the opportunity for prognostics and early treatment.[1] As we have described in this paper, late relapse can present in many ways, with asymptomatic recurrence and/or contralateral retroperitoneal disease, making identification and diagnosis difficult. Patients need at least annual follow-up evaluations throughout their lives to identify late relapse.[2] That being said, some researchers have found that patients with stage I NCGCTs or seminomas do not need follow-up 5 years after remission.[7] However, in a patient such as the one described in this paper, there are no exact guidelines due to his unique case and presentation. This patient continues to be followed every 4 to 6 months with CT scans and tumor markers.

Patient Perspective and Testimonial

The patient was amenable to being interviewed about his experience with cancer as a part of this paper. After the patient received his initial diagnosis and was treated in 2011, he felt "very lucky that after the removal of the testicle, all the cancer biomarkers went down" and there were no signs of metastasis; years of negative scans followed. The patient changed his lifestyle after his cancer diagnosis, improving his diet and using meditation to help cope throughout his cancer journey, returning every 1 to 2 years for CT scans and laboratory testing. In 2023 when he presented to his PCP with concerns of left neck adenopathy, he was not immediately concerned that it was related to his cancer. He emphasized that he "[didn't] think the mass was related because [there was] no other sign; this was the only sign. I did not have weight loss; I did not have other things that I can think of that related to cancer." His most recent scans and laboratory results had been negative.

The patient was an active participant in his care. He searched for answers, trying to understand his cancer and why it was such a unique case. The patient mentioned he had another physician at a renowned testicular cancer institution who believes his cancer is possibly a primary tumor on the left side, but for a definitive diagnosis, he would need a left orchiectomy and lifelong hormonal

therapy, which he was not interested in. This further emphasizes that we cannot know with 100% certainty whether there is a left-sided primary secondary GCT in this patient. However, we can use our best clinical judgment to guide care and share this unique case to further medical knowledge on this topic.

The patient ended with a strong statement pointing out the same questions that brought our clinical team to write up this case: "The interesting thing is that usually the tumor cell migrates through the same side, but this case is special. We don't know why it migrated to the other side. That's why we are having this conversation today. Hopefully, my case can help later research to see what kinds of things we can learn from here." The patient would like to tell all patients with cancer and readers that when it comes to a long journey with cancer, "Try not to stress out about everything; keep your mind calm." He emphasized that although the surgical treatment and chemotherapy have been life-changing, family support and meditation also have been very helpful.

Discussion

Although late relapse of NSGCT is rare, it has been on the rise, likely in part due to better treatment options and long-term survival.[1] Notably, this patient presented with late relapse after 11 years in remission with contralateral retroperitoneal disease. The patient's original cancer was on the right side, with recurrence surrounding the aorta on the contralateral side, representing an atypical pattern of spread for NSGCT. Based on this patient's rare presentation and other literature with findings of contralateral retroperitoneal recurrence, it is important to be aware of the variation and spectrum of relapse and how to better identify late relapse when we encounter it.

Outcome and Follow-Up

As of February 2024, the patient is recovering uneventfully from the acute toxicities of chemotherapy and is being followed by urology, oncology, and otolaryngology. ■

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

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

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

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

After 56 months: 32% reduction in the risk of death with DRd vs Rd alone in the MAIA trial
(HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013; mOS not reached in either arm).*[1]

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

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

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

DARZALEX® and DARZALEX *FASPRO*® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX *FASPRO*®), or any of the components of the formulations.

DARZALEX®: Infusion-Related Reactions

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

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

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

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

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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

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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]*.

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

For patent information: www.janssenpatents.com

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Striving for Health Care Equity by Closing the Cancer Care Gap

Robert A. Winn, MD, Director and Lipman Chair in Oncology at Virginia Commonwealth University (VCU) Massey Comprehensive Cancer Center, Senior Associate for Cancer Innovation, and Professor of Pulmonary Disease and Critical Cancer Medicine at VCU School of Medicine

"*If you were to ask me what the 1 magic thing would be, it would be that we would adopt a concept of 1 team, one fight nationally, and that we would be able to have our structures and our coordination of care.*"

In the ongoing fight against cancer, achieving equitable access to quality care is a critical challenge, according to Robert A. Winn, MD.

Winn recently wrote a 2024 forecast focusing on achieving health equity in the oncology space for the American Association for Cancer Research (AACR).

He spoke about the persistent disparities in cancer outcomes among different populations, and he emphasized the distinction between equity and disparity. Additionally, he noted the positive trajectory toward achieving health equity, outlining the crucial role of addressing systemic barriers and resource allocation in creating a level playing field for all patients.

Q / What does health equity mean or look like in the oncology space?

Winn / This is an important conversation about what equity looks like. Equity is more of a principle: When all obstacles are removed, people get the same care at the same time in the same manner, and even potentially get the same outcomes. I say that because when people talk about equity, that is something that we're striving for. What exists currently are disparities. We know that African American individuals [with multiple myeloma] tend to do less well. It turns out that work that's been done has shown that when you have the same access to care, when the barriers are removed like the social part, the structural parts are removed, you can obtain [equity]. African American individuals right now will have a different outcome than, say, their White counterparts. We call that a disparity because it's not something that may inherently be an issue of their biology, in the context of African American individuals are just "going to have worse outcomes with multiple myeloma." The disparity accounts for the fact that, whatever that biology is, there are additional forces and obstructions to being able to get the care. Equity is much more of a principle of having an even playing field. As we know, the unfortunate reality is that is not true everywhere.

Q / How can you see healthy equity impacting or changing for patients with cancer throughout 2024?

Winn / Several things on the horizon may be game changers for improving and moving toward equity. For example, the fact that, at some point, we allowed Medicaid to pay for clinical trials. This new ruling by the Centers for Medicare & Medicaid Services [CMS] that allows for the reimbursements of navigation—ie, getting people to navigate you from point A to point B—will also assist us in getting toward a more equitable society in the context of oncology. There's still work to do. We will always talk about when new drugs come out. There is usually a sort of nonintentional divide. For example, when immunotherapy came out, we wrote in *The New York Times* and everywhere else about the immunotherapy divide. New therapies, new technologies, and new screening mechanisms usually don't reach all communities equitably. That's still a struggle. We are making some good progress, but we need to make more progress in the area of biomarker testing, for example, in lung cancer and all these other [cancers]. With the reimbursements from CMS, Medicaid paying for clinical trials, and many other things that we could talk about, we are trending toward the health equity goal. We're not there yet.

Q / What should be the biggest focus for underserved populations to achieve health equity?

Winn / It's not so much that the [underserved populations often live in areas of] persistent poverty, rural areas, or areas where there are high populations of minorities…. I think it's the structures. When people say, "Well, what can be done? How do we make care more accessible? How do we make the quality of that care standard, so that whether you have $1 million or $1, you're getting equitable care?" That's a challenge because it takes resources. When people ask those questions, I say, "I don't know that we'll ever achieve a definitive equity." We can certainly do better. We can certainly work with, for example, federally qualified health centers in a different way than we are now in 2024. [We can make] sure that screening and follow-up care and survivorship...are embedded more in those federally qualified health centers or community health centers. I think we could do better by working with our community hospitals. This is what the Association of Community Cancer Centers and others are trying to do; [they are examples of] where you have your academic centers and the community health centers working together in partnership. If you were to ask me what the 1 magic thing would be, it would be that we would adopt a concept of 1 team, 1 fight nationally, and that we would be able to have our structures and our coordination of care better and more organized than we have it now.

Q / How do you hope to educate your colleagues on this issue?

Winn / The education part of this is exciting for us. I hope that the AACR Cancer Disparities Report is just 1 tool to not only get my colleagues but to also get people within the community and those people who are in charge of our resources a little bit more up to speed and aware. This report has, on its own, been substantiated. I was part of the first one in 2020 and the second one in 2022. I'm happy to be part of [the 2024] one as well and leading the charge of the 2024 report. That's one element that we hope will be able to help educate people and bring awareness. The other one is just [the] good old-fashioned [strategy of] having our professional bodies, whether they're AACR, AACI [Association of American Cancer Institutes], American Cancer Society, or ASCO [American Society of Clinical Oncology], all working on 1 accord, and that is to bring to the attention that cancer is not like it used to be in the 1950s. It is not necessarily a death sentence if you can get to the right place and get the right care at the right time.

Q / Is there anything you're focusing on at your institution that may break the mold that other institutions can follow?

Winn / We've philosophically flipped the script where it has always been in cancer, this focus on creating a molecule that becomes a medicine and then we stop. Once it becomes a medicine and it gets into a trial, how do we get people from diverse backgrounds, rural communities, areas of persistent poverty, and minority communities into our trials? In addition to focusing on the basic discovery that is the molecule becoming medicine, we have at Massey focused on the back half of that, and which is, how do these techniques get disseminated and diffused across communities? Can it result in an impact? We are a very proud comprehensive cancer center, which means that it starts with having a community focus and then having our research and support benefit those efforts to have a broader impact so everyone can benefit from the science we generate from our centers more equitably. ■

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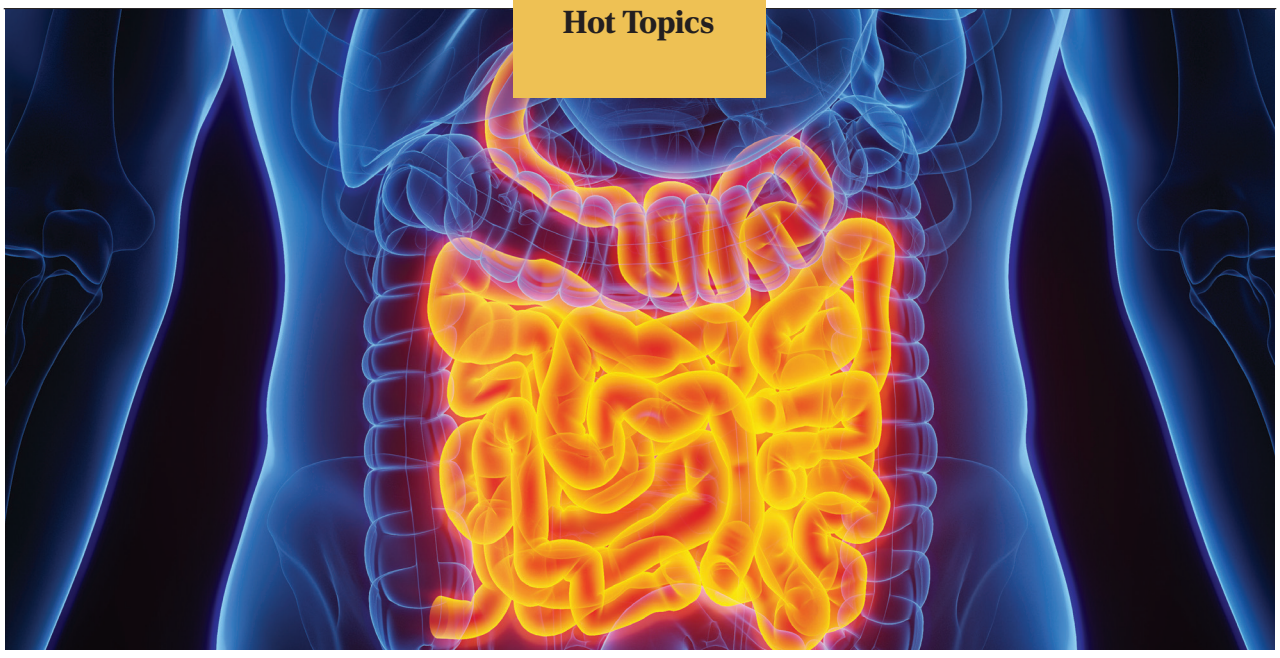
Experts forecast 2024, part 2: achieving cancer health equity. News release. AACR. January 12, 2024. Accessed February 16, 2024. https://shorturl.at/cMQR8



Identifying Indications for Neoadjuvant Therapy in Cholangiocarcinoma

Hilary R. Keller, MD; Laura Fluke, DO; Jared A. Forrester, MD; and Ronald F. Wolf, MD

The incidence of cholangiocarcinoma (CCA) is rising, and survival rates remain low. Recent randomized, controlled trials (RCTs) demonstrated improved survival with adjuvant chemotherapy and immunotherapy in the metastatic and postoperative settings. Neoadjuvant therapy is increasingly used for other cancers to achieve R0 resection and as an indicator of treatment response. Although there has not been an RCT for neoadjuvant therapy in CCA, there are multiple supportive retrospective studies. Data from the recent phase 2 NEO-GAP (NCT03579771) prospective trial for neoadjuvant chemotherapy in patients with resectable high-risk intrahepatic CCA demonstrated safety and the increased likelihood of R0 resection with a neoadjuvant approach.

CCA is biliary tract cancer classified by location: intrahepatic (iCCA) or extrahepatic (eCCA; perihilar and distal). The rising incidence of CCA is attributed to advancements in imaging, molecular testing, and pathologic diagnosis of iCCA.[1,2] The 5-year relative survival rate for all stages of iCCA is 9%, and 11% for extrahepatic CCA.[3] Surgical R0 resection remains the best chance for cure. However, only approximately 40% of patients are amenable to surgical resection, with only 30% to 35% of resections truly curative due to the high rate of recurrence.[4-10] Randomized, controlled trial results demonstrated a survival benefit in patients with resectable CCA after adjuvant capecitabine (phase 3 BILCAP [NCT00363584]),[11] in patients with locally advanced disease after gemcitabine/cisplatin with durvalumab (Imfinzi; phase 3 TOPAZ-1 [NCT03875235])[12], and in patients with metastatic disease after pembrolizumab (Keytruda; phase 3 KEYNOTE-966 [NCT04003636]).[13] Neoadjuvant therapy in CCA offers a strategy to reduce tumor size, promote resectability by increasing the likelihood of an R0 resection, treat occult metastatic disease, and assess tumor biology as a prognostic indicator of treatment response.[6]

Intrahepatic

Much of the evidence supporting neoadjuvant chemotherapy (NAC) in iCCA is retrospective. Accepted definitions of high-risk or locally advanced disease, data on patients likely to benefit from NAC, or any defined parameters regarding the adequacy of response are lacking. One study demonstrated improved overall survival (OS) without improved recurrence-free survival in resectable iCCA after NAC.[14] The authors argue that NAC may identify patients with stable or responsive disease as having favorable tumor biology, being less likely to have a recurrence, and being more likely to benefit from surgical resection.[14] Another retrospective study using the National Cancer Database (NCDB) found that patients with resectable stage II to III iCCA trend toward improved survival with NAC,[15] which is statistically significant after propensity score matching compared with up-front resection.[16] Utuama et al argue for NAC in patients

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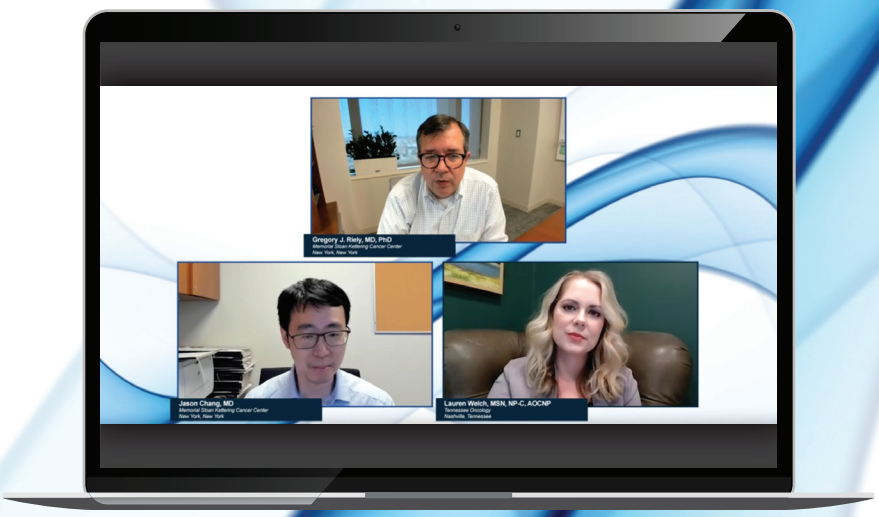

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with resectable but more advanced disease: stage II to III with high-risk features such as larger tumor size, vascular invasion, or lymph node (LN) involvement.[16] These findings are similar to the results of a multi-institutional international, retrospective study that found a nonsignificant improvement with outcomes in resectable iCCA after NAC upon propensity matching.[17]

In a retrospective analysis of a prospectively maintained database, patients who were high-risk with stage III resectable iCCA who underwent NAC exhibited extended OS; however, survival was not associated with pathologic response to NAC.[18] High-risk features were defined as including regional lymphadenopathy, multifocal disease, satellite lesions, and vascular involvement with either tumor embolus or arterial encasement.[18] The NEO-GAP trial determined the feasibility of NAC with gemcitabine, cisplatin, and nab-paclitaxel (Abraxane) for patients with resectable, high-risk iCCA.[7] Patients were considered high risk if their tumor size was greater than 5 cm or if they had multiple tumors, major vascular invasion, or LN involvement.[7] Investigators reported an R0 resection rate of 73%, comparable to the 62% R0 resection rate in the BILCAP trial.[6,7,11] Overall, there may be a benefit for NAC in resectable iCCA, especially in locally advanced disease and resectable disease with high-risk features.

Because CCA is highly heterogenous and often possesses targetable mutations (eg, *KRAS*, *BRAF*, *EGFR*, *PI3k*, *FGFR*, *IDH1/IDH2*, *HER2/neu*), tumor molecular profiling can be useful for neoadjuvant treatment. Additional strategies include locoregional therapies such as transarterial radioembolization,[19-21] transarterial chemoembolization,[22] and hepatic arterial infusion.[23] Although there are fewer studies evaluating locoregional therapies, they demonstrate downstaging with the potential for surgical cure. Upcoming trials, including the use of neoadjuvant doublet immunotherapy (durvalumab/tremelimumab [Imjudo]) for resectable and high-risk iCCA, should provide more insight into the optimal neoadjuvant regimen.[24-28]

Extrahepatic

A retrospective study using the NCDB compared NAC with adjuvant chemotherapy in resectable stage I to III CCA (including both intrahepatic and extrahepatic), finding NAC associated with improved OS.[29] Similarly, when grouping all patients with CCA, receiving either neoadjuvant or adjuvant chemotherapy improved OS, even in patients with margin-negative and node-negative disease. However, there was no difference in survival between those receiving neoadjuvant or adjuvant chemotherapy.[30] These studies' results suggest a potential benefit for NAC in perihilar CCA.

Specifically for perihilar CCA, results of a single-institutional study demonstrated improved OS with NAC in patients with advanced disease, including disease that was resectable with LN metastasis, borderline resectable, or unresectable/locally advanced.[31] Investigators in a phase 2 trial in Japan treated patients with borderline resectable perihilar CCA with a combination of neoadjuvant gemcitabine and oral fluoropyrimidine derivative S-1, finding the regimen safe and feasible with an 81% R0 resection rate.[32] They defined borderline resectable hilar CCA as regional LN metastasis and pathologically confirmed vascular invasion, due to the significantly reduced survival rates.[33] For hilar CCA, there may be a role for NAC in patients who have borderline resectable disease, but additional prospective studies are needed.

NAC or chemoradiation for extrahepatic CCA also has been evaluated retrospectively in patients who are high risk. In distal CCA, Cloyd et al reported no difference in 5-year OS between up-front resection and NAC or chemoradiation.[34] However, receipt of either neoadjuvant or adjuvant therapy was associated with improved OS.[34] Further, LN positivity portended a poor prognosis, suggesting that there may be a role for neoadjuvant therapy in cases with high-risk features, such as LN involvement.[34] Similarly, advanced extrahepatic CCA was associated with improved OS and cancer-specific survival after NAC or chemoradiation. However, the majority of this retrospective Surveillance, Epidemiology, and End Results Program cohort was patients with gallbladder cancers.[35] Another study evaluating extrahepatic CCA, but excluding distal CCA, found that compared with up-front surgery, neoadjuvant chemoradiation was associated with improved postoperative outcomes, higher likelihood of an R0 resection, and improved median survival.[36]

Conclusion

The treatment of patients with CCA must be multidisciplinary and individualized. Surgeons should strive to standardize high-risk stratification. Although propensity-matching cohorts can improve comparisons, randomized clinical trials will best elucidate the ideal regimens and neoadjuvant/adjuvant strategies for both chemotherapy and immunotherapy. Tumor molecular profiling may add additional therapies targeting genetic mutations. Designing, developing, and enrolling clinical trials should be encouraged to optimize future patient care. ■

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Tumor-Infiltrating Lymphocyte Therapy Advances Into Melanoma

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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:
- Describe the challenges and advantages of tumor-infiltrating lymphocyte (TIL) therapy in melanoma.
- Integrate lifileucel into treatment paradigms for patients with melanoma.

RELEASE DATE: April 1, 2024 **EXPIRATION DATE:** April 1, 2025

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Harnessing the power of the immune system with tumor-infiltrating lymphocyte (TIL) therapy has emerged as a promising approach in cancer treatment. TIL therapy involves harvesting T cells that have naturally infiltrated the tumor microenvironment and that recognize tumor-specific antigens. These TILs are then isolated, expanded ex vivo to generate large numbers, and infused back into the patient following lymphodepletion chemotherapy. The reinfused TILs can then mount a potent antitumor immune response to recognize and attack cancer cells throughout the body. This personalized approach enhances the patient's own immune system, allowing for a highly targeted and potentially curative treatment strategy. Recently, the FDA's approval of lifileucel has offered a new therapeutic option for patients with metastatic melanoma. In this article, Omid Hamid, MD, delves into the intricacies of TIL therapy, shedding light on its clinical efficacy, future directions, and potential implications for melanoma management.

> As we become more familiar with [TIL therapy], I have no doubt that there will be a push to not only move it earlier into the therapeutic paradigm, also combine it with more tolerable combinations of immunotherapeutics.

Q / Who is the ideal candidate for TIL therapy today?

Hamid / Based on approval of TIL therapy, the ideal candidate is a patient in the second line and beyond who has experienced treatment failure with first-line therapy with a PD-1 backbone.[1] This patient could be of any age, have good cardiac and pulmonary function, and not have any contraindications (eg, ongoing infection, cytopenias).[2] This could be any patient independent of *BRAF* status, as BRAF inhibition had failed in patients who were on these trials. This patient could be part of an institution that does TIL therapy, and that is basically it.

Patients with a variety of other solid tumors would be fit for a clinical trial as the horizons of TIL therapy expand.[3] There are now first-line trials, such as TILVANCE-301 [NCT05727904], in advanced melanoma.[4] So, a whole host of patients should be considered for TIL therapy.

Q / Please walk us through a patient's experience with TIL treatment.

Hamid / The discussion about where TILs would fit in the patient's therapeutic paradigm for advanced melanoma is given.[2] The decision is made to move into a TIL trial. At that point, the patient's journey goes in multiple directions. The first is an evaluation of the cardiac status, pulmonary function, and baseline laboratory tests. The patient would then be evaluated by a surgical oncologist who has expertise in TIL therapy. Imaging is reviewed for the appropriate place to do a TIL harvest. As our experience has shown, that can be anywhere, whether it is a dermal metastasis, a subcutaneous area, lymph nodes, a visceral area, or other.

The patient undergoes a surgical procedure, and that tumor is harvested and sent out.[2] A discussion is then had with the manufacturer about when the TILs will be evaluated and ready for infusion, and then that clock starts. The therapeutic team at the treatment center would then schedule a time in the infusion center for lymphodepleting chemotherapy that prepares the patient by decreasing the T cells in the periphery that are not tumor specific. A plan is made for the patient to be hospitalized after the lymphodepleting chemotherapy; the patient is then hospitalized and given the TILs, which have been cryopreserved and shipped back to the therapeutic center.

Those TILs are thawed and infused into the patient. Shortly afterward, the patient enters a monitored area and receives infusions of up to 6 doses of IL-2.[2] That is to stimulate those T cells. The patient is then monitored until the blood counts recover until he or she is stable enough to be discharged home. They are discharged home with prophylactic antibiotics and follow-up appointments with their medical oncologist. We tell the patient to stay within the area if an adverse event (AE) occurs, whether that be cytopenias, fever, pain, or another effect. At our institution, we have oncologists on call who are familiar with the AEs of the therapy, and patients can call at any time and be seen.

Q / What safety concerns should be expected during the process of cell therapy?

Hamid / The major toxicities that occur with TIL therapy are associated with the lymphodepleting preparative regimen and the IL-2.[5] Those are mostly cytopenias (sometimes of long duration) and febrile neutropenia. Toxicities that we have seen with high-dose IL-2 can be related to fluid overload, such as cardiac or pulmonary events and renal insufficiency. Interestingly, the majority of those happen during the 2 weeks of TIL therapy. Once the patient is stable and discharged, there are very few AEs to be seen.

Q / Please discuss efforts to combine TILs with other immunotherapies.

Hamid / It seems that the whole history of TILs has begun now with lifileucel. It is very hard for people who have not been in the field or who are watching the field to understand that there have been combinatorial trials with TILs for many years.[6] At this point, the main focus is the combination of TILs with anti–PD-1 therapy.[3] There has been a phase 1/2 trial looking at a combination in untreated patients in whom we have seen high clinical benefit rates and tolerability.

TILVANCE-301, a randomized phase 3 trial in melanoma that is accruing patients, is looking at TIL therapy plus PD-1 inhibition versus PD-1 inhibition alone in patients with advanced melanoma.[4] It is moving TIL use earlier and earlier into treatment based on the results of some of the trials we have seen, including the results of 1 study that showed high response rates (48%) with TILs given to patients receiving second-line therapy.[7] The question is: Should we be seeing this earlier and earlier in our therapeutic regimen?

Additionally, there are data with TIL therapy used in combination with BRAF agents that have been presented before.[8] As we become more familiar with it, I have no doubt that there will be a push to not only move it earlier into the therapeutic paradigm but also combine it with more tolerable combinations of immunotherapeutics. Once you have a drug that has shown single-agent activity with long-term durability, as this has shown, then the movement into combinations with proven agents is the next logical phase.

Q / Currently, lifileucel is approved in subsequent-line therapy. Could TILs play a role in first-line treatment?

Hamid / Absolutely. We see greater efficacy of TILs as the performance status of the patient is better and they can handle therapy better.[5] In the trials of lifileucel, in the initial cohorts 2 and 4, a significant proportion of patients were primary refractory to checkpoint inhibitors. The C-144-01 study [NCT02360579] updates have shown a high response rate (31.4%).[9] This is in 153 patients, and it is a response rate that is one of the highest—if not the highest—in patients with refractory disease. There is an early time to response (less than 2 months), median time to response, and long durations of response, with ongoing responses of nearly 4.5 years. Looking at patients early with an indication that they are not responding to checkpoint inhibition and then switching them to TILs is where this is going.

Q / How do you see lifileucel fitting into current therapeutic guidelines for melanoma treatment?

Hamid / Lifileucel will definitely be in any therapeutic paradigm with a big asterisk that says that the patients have to be well suited for it. We may exclude patients from receiving TIL therapy due to their cardiorespiratory status, their performance status, or the pace of the growth of their disease.[2] But the main point to be made with this approval is that we have opened the floodgates for patients to learn more about and be considered for any type of T-cell therapy, whether it be the ImmTACs [immune mobilizing monoclonal T-cell receptors against cancer], like the PRAME bispecific, or tebentafusp therapy.[10,11] These are therapies that redirect T cells into the tumor. Whether it is CAR-T trials or natural killer cell trials that are being looked at in melanoma, that field is now wide open.

Q / What are some of the most significant challenges that must be overcome in TIL therapy to have a greater impact on patients with melanoma?

Hamid / The main challenges for TIL therapy begin with the access to patients. We need to have centers that have the appropriate resources—the physicians, the medical oncologist, the surgical oncologist, the therapeutic center, the beds in the hospital, and the supportive care that is necessary in the wards and in the clinics.[2] There are about 50 Centers of Excellence set up so far. As physicians who have had a long-term relationship with this therapy, it behooves us to educate our colleagues to understand the need for more centers to provide TIL treatment. Of course, TIL therapy is something that takes time to make. It is usually 3 to 4 weeks to manufacture the TILs, and we are looking to have manufacturing centers that can meet the demand for TILs.

The main challenges for TIL therapy begin with the access to patients.

Additionally, we have to clarify what the cost is going to be and where the payers stand with this. With any recently approved therapy, the question is: Will this be reimbursed appropriately, and do we have the right pathways? That is the hesitancy.

Q / How is genetic engineering being used to improve the safety and/or efficacy of TILs?

Hamid / We are CRISPR-ing out certain genes that are deleterious to the immune response. If we can CRISPR out PD-1, we may not need to give TILs with a PD-1 inhibitor.[12] Then we do not need to deal with excess toxicities that occur when we combine immunotherapies or any type of therapy. There is an ongoing trial of the PD-1 CRISPR.[13]

Some groups are looking at whether we can decrease the amount of the preparative chemotherapeutic regimen. Others

are looking at the other side. For example, investigators associated with a phase 1 trial are looking at using IL-15 in a different capacity. Instead of IL-2, we may use IL-15 when we believe that the toxicities may be less and the stimulation of regulatory T cells may be less.[14] This could be a more manageable treatment that requires less time in the hospital.

Q / Where do you see the future of adoptive cell therapy heading?

Hamid / The future is bright for adoptive cell therapy. The future will be the realization of this modality as having a true value not only in melanoma but also in other solid tumors.[3] This is an extremely important therapeutic in patients with advanced cervical cancer, where we do not have second-line options. The data in an ongoing trial in non–small cell lung cancer are forthcoming, but early experience has shown responses and durability. Let us not forget that the combinations with PD-1 have looked at other solid tumors, including head and neck cancer.

There are responses in breast cancer and colorectal cancer, so a wide range of tumors are being looked at with this modality, including sarcomas.[3] We are at the beginning of the marathon with this new modality. We have to train our colleagues to be able to give this therapy and impress upon them every chance we get—at meetings, through print, through video—that this is a modality that should be considered for a multitude of solid tumor indications. ■

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A FAREWELL TO MBCC: Tripathy on His Years as Cochair

"The meeting has always been about, 'How am I going to treat the next patient I see?' It is very clinically oriented, very practical, and very utilitarian," Debu Tripathy, MD, said in an interview with CancerNetwork. "However, it's utilitarian on a high level. I want to know the science behind it. I want to know why that's the right thing to do. That's what the magic is about [attending the] meeting. You understand that it's not only because this is how we do it, but why it is, what the data behind it are, and how we might make it even better."

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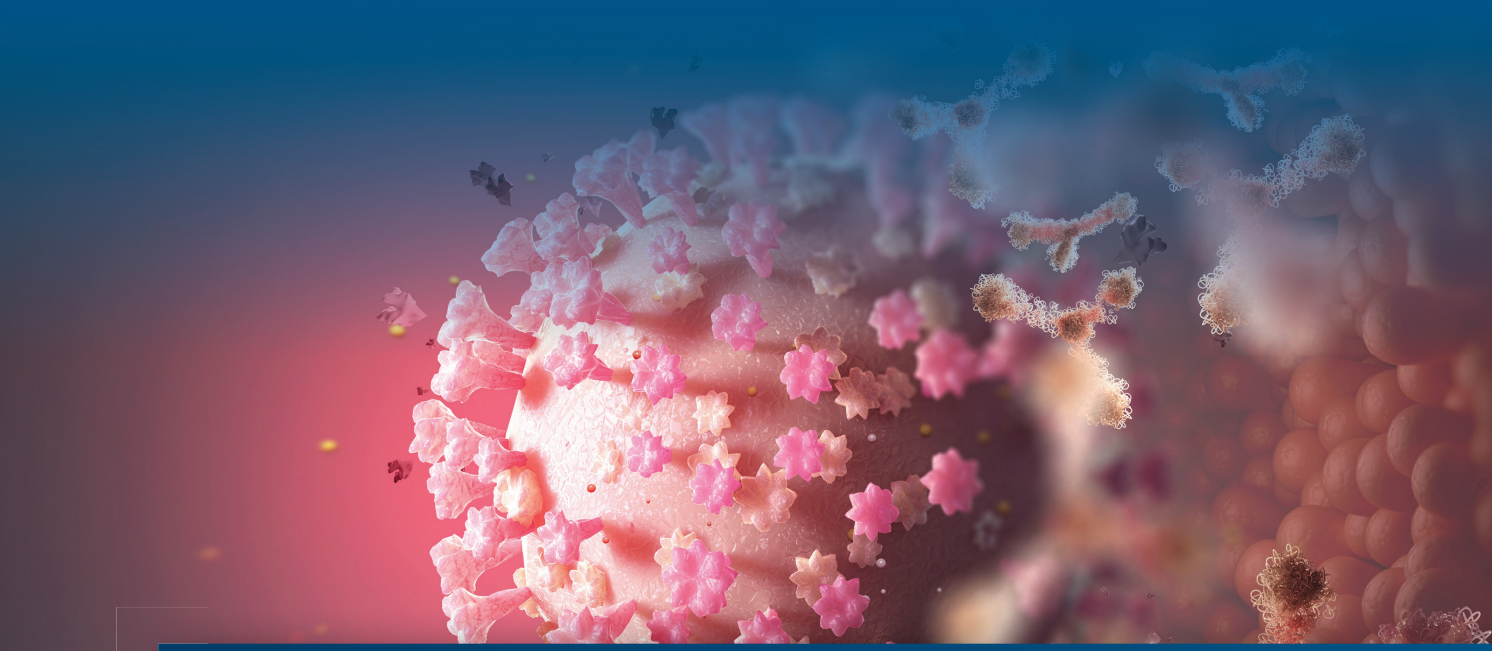

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