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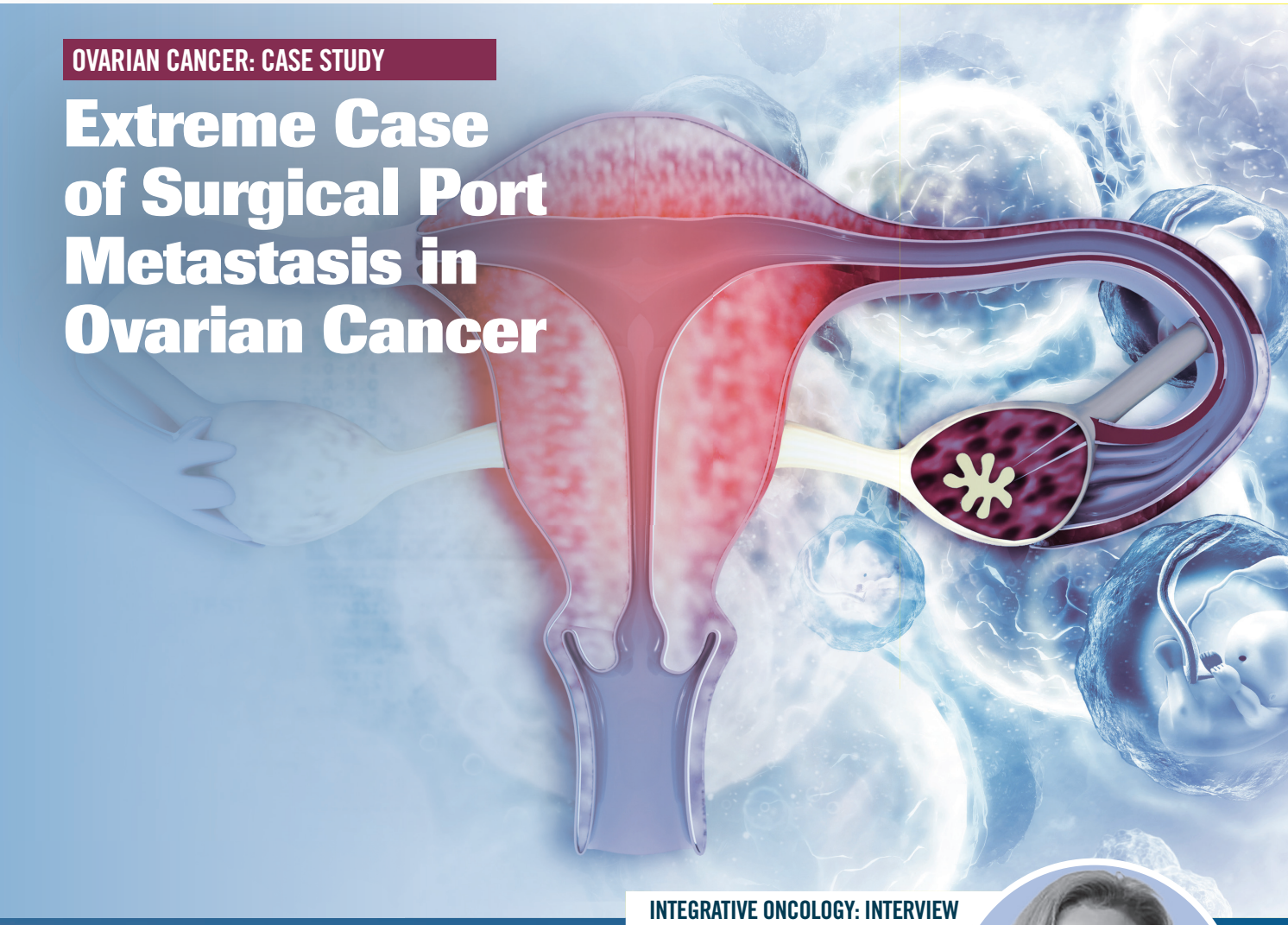

INTEGRATIVE ONCOLOGY: INTERVIEW

Linda E. Carlson, PhD, RPsych

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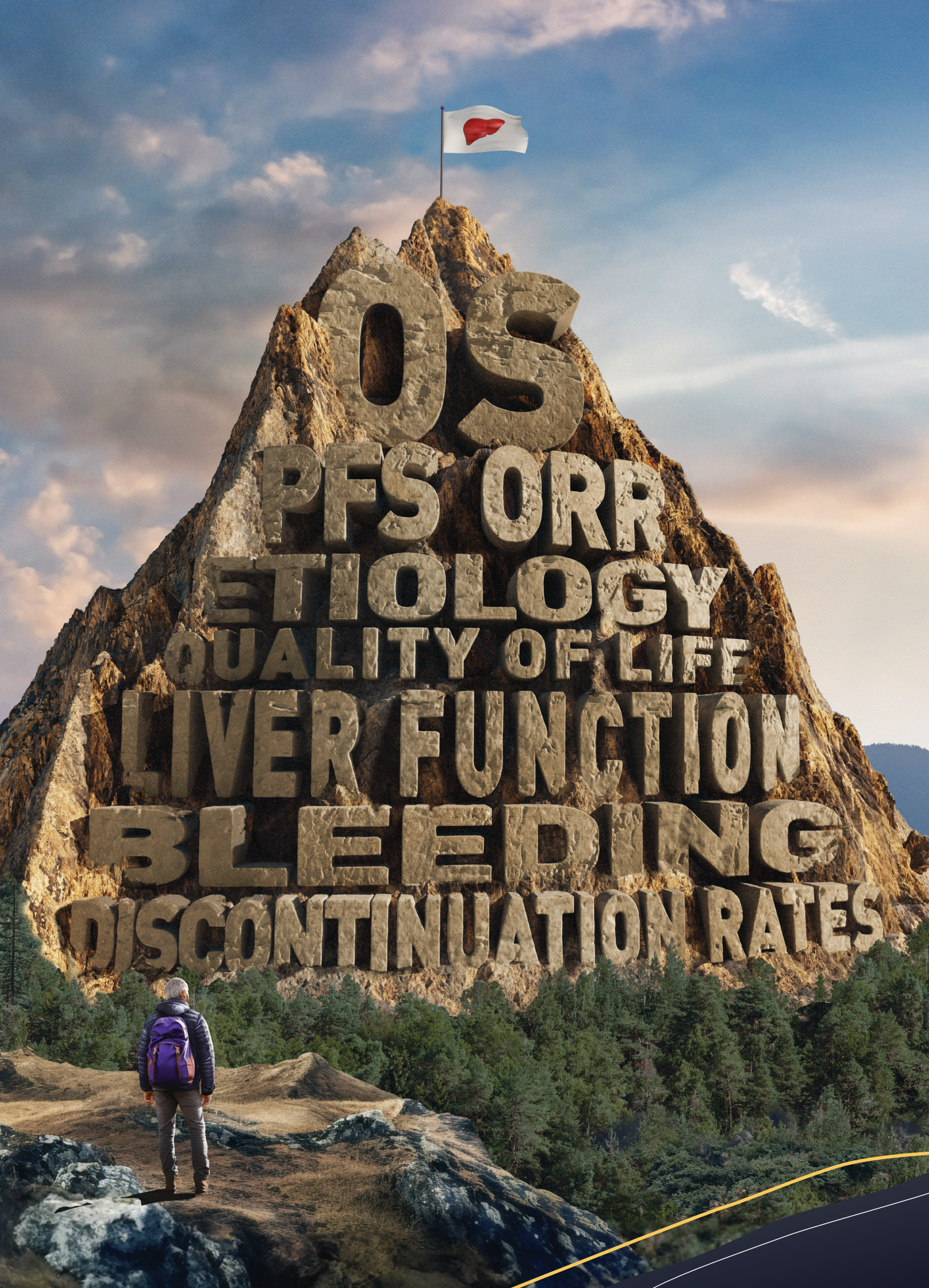
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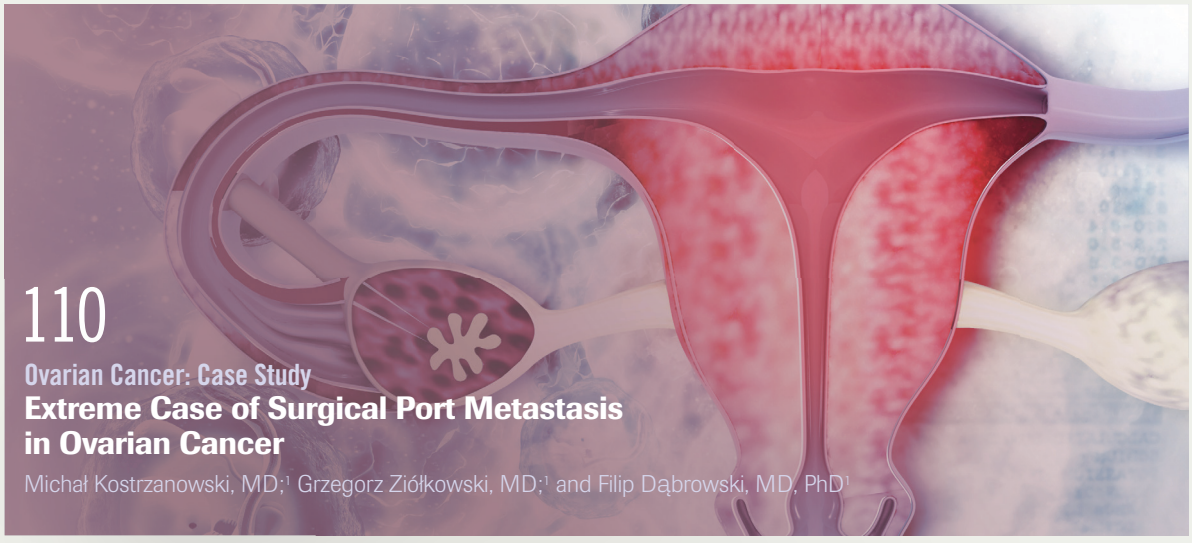

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OUR BOARD MEMBERS HAVE BEEN BUSY! TAKE A LOOK TO SEE WHAT THEY HAVE BEEN UP TO.

C. Ola Landgren, MD, PhD
Hematologic Malignancies Tumor Chair

Landgren and colleagues collaborated to develop a prediction model that determines individualized risk in multiple myeloma. The model, IRMMa, uses artificial intelligence (AI) and collects data from other cases of multiple myeloma to create a personalized treatment plan. Landgren noted that IRMMa can use AI to predict a patient's survival outcomes based on tumor biology, clinical data, and planned treatment.

Vered Stearns, MD
Breast Cancer Editorial Board Member

Stearns was coauthor of the recently published article "Entinostat, Nivolumab and Ipilimumab for Women With Advanced HER2-Negative Breast Cancer: A Phase Ib Trial." The trial (NCT02453620) found an overall response rate of 25%, 40% in those with triple-negative breast cancer, and 10% in those with hormone receptor–positive breast cancer. The clinical benefit rate was 40%, and the progression-free survival rate at 6 months was 50%. Full results can be found published in *Nature Medicine*.

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Electronic Medical Records and Physicians: A Love-Hate Relationship

As the use of the electronic medical record (EMR) has greatly expanded over the past couple of decades, it has (partially) improved communication among health care professionals and allowed data to be available more reliably for test results and information. Despite these advantages, there are also several disadvantages and issues regarding the use of EMRs. With each institution or oncology practice having its own EMR, information does not easily flow among providers or systems. The 21st Century Cures Act of 2016 aimed to make access easier for patients and providers. However, the information available among different EMR systems is sometimes incomplete and displayed in a cryptic format that makes interpretation difficult. Studies have shown that clinicians spend as much as two-thirds of their time documenting in the EMR, which has been recognized as a major contributor to physician burnout.[1]

This is particularly true in the United States, where the clinical documentation requirement for billing is pervasive and mandatory for physicians to get paid for their expertise and time.[2] The notes in the US are 3 to 5 times longer than in many other countries due to these differences in requirements for billing.[3] These required statements often add to the length of the note without adding any information to help with the patient's care. If clinicians were instead paid for documenting a small list of key elements in a standardized format, this would be a win-win situation for everyone.

Another aspect of EMRs is the ability of patients to access their notes and test results. In theory, this practice would allow patients to get information faster and decrease the number of phone calls from the health care providers to the patients. However, shared decision-making between health care providers and patients is not a new concept. As originally conceptualized by Charles et al, this practice would provide information exchange, deliberation, and negotiation about a health care or treatment decision.[4] Patients' right to access their records was codified under the Health Insurance Portability and Accountability Act of 1996. The passing of the Cures Act legislation aimed to make access easier and virtually unrestricted. To increase interoperability across EMR platforms, the Cures Act requires vendors and users to enable the development of computer and smartphone applications that give patients full access to their health care information. As of April 2021, the information blocking rule of the Cures Act dictates that 8 categories of clinical notes created in an EMR must be immediately available to patients through a secure online portal. These categories include physician notes, imaging, laboratory results, and pathology reports.

Like many things in life, there are advantages and disadvantages to the patients accessing EMRs. Patient portals can assist with appointments, educational content, and telehealth visits. The patients do need to have the equipment and technical ability to sign into the portal to take advantage of these services. However, test results often need interpretation by a medical professional, and with the patients receiving this information in a vacuum and not at the time of a medical visit, confusion and misinterpretation can occur. This can lead to stressful situations for some patients, particularly with pathology or radiology reports. Patient portals often contain an extensive list of questions and concerns directed to the health care team. With the number of queries increasing exponentially, many systems are warning patients that if there is an excessive number of portal messages, they may receive a charge for this service. Hopefully, with future improvements and upgrades, the details of the EMR can be improved to help more with patient care. ■

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Diagnosing and Treating Blastic Plasmacytoid Dendritic Cell Neoplasm in a Resource-Limited Setting

Fiza Khan, MD;[1] Foorquan Hashmi;[1] Nerses Ghahramanyan, MD;[2] Elen Baloyan, MD;[1-3] Gevorg Tamamyan, MD, MSc, DSc;[1-3] Marina Konopleva, MD, PhD;[4,5] Naveen Pemmaraju, MD;[5] and Astghik Voskanyan, MD[2,3]

ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematological malignancy with limited treatment options and poor prognosis. This case report presents the clinical course and management of a 62-year-old man with BPDCN in a resource-limited setting. The patient presented with constitutional symptoms and abnormal complete blood count findings. Initial treatment was performed with an acute lymphoblastic leukemia–based chemotherapy regimen, and the patient achieved complete remission, but the disease recurred 7 months after the initial diagnosis was confirmed in April 2022. The subsequent therapy was not effective, and the patient died during treatment. This case highlights the challenges in managing BPDCN and the need for further research to improve outcomes.

KEYWORDS

BPDCN, blastic plasmacytoid dendritic cell neoplasm, resource-limited setting, GMALL

Case Presentation

A 62-year-old man was admitted to Yeolyan Hematology and Oncology Center in Yerevan, Armenia, with worsening fatigue, generalized weakness, loss of appetite, shortness of breath on exertion, and hematochezia. The patient had a history of alcohol use disorder over the past decade. Although he previously had been treated for pneumonia in another hospital, abnormal complete blood count (CBC) results prompted a referral to this hospital, the main referral center in Armenia, for further evaluation and management.

Physical examination showed that the patient had an ECOG performance status of 2. A singular bruiselike cutaneous lesion was identified on his chest, with no other skin or mucosal abnormalities. The patient had swollen eyelids, although fever and scleral icterus were absent. The patient had bloody stools and constipation. Examination disclosed a nontender, distended abdomen with palpable peripheral lymph nodes of the left axillary region.

Initial laboratory and imaging findings were significant for the following:

- CBC results showed anemia
- Hemoglobin: 9.5 g/dL
- Platelets: 64×10^9/L
- White blood cells: 18.6×10^9/L

Abdominal ultrasound revealed an enlarged liver (18.5 × 7.5 cm) and spleen (21 × 8.5 cm). Enlarged lymph nodes were also identified, with the largest in the right inguinal region (2.6 × 2.0 cm), followed by nodes in the left axillary and cervical regions. Bone marrow immunophenotyping with flow cytometry showed 73% of blast cells expressing CD4, CD7, CD56, CD38, CD43, HLA-DR, and CD123, indicating blastic plasmacytoid dendritic cell neoplasm (BPDCN). A lack of expression for specific negative markers (MPO, lysozyme, CD3, CD14, CD19, CD34) excluded T- or B-lymphoblastic leukemia and acute myeloid leukemia (AML).

Chemotherapy with the German Multicenter Acute Lymphoblastic Leukemia (GMALL) regimen for patients

aged 55 to 75 years was initiated (dexamethasone, vincristine, daunorubicin, cytarabine, cyclophosphamide, methotrexate, PEG-asparaginase plus colony-stimulating factor). Induction chemotherapy led to complete remission (CR). Bone marrow aspiration showed no blasts with cell recovery. The patient had no central nervous system involvement and had received intrathecal chemotherapy according to protocol. The patient was in CR for 7 months but relapsed and continued maintenance therapy with methotrexate and 6-mercaptopurine.

Recurrent symptoms included fatigue and swollen masses in the axillary and neck regions. Blast cells were identified in CBC and bone marrow testing. Second-line induction therapy, incorporating azacitidine and venetoclax, was initiated. After the second cycle, a partial response was observed. After 2 months, because of loss of response, the patient received venetoclax plus bendamustine, which was not effective. The patient died at home 1 year after receiving the diagnosis.

Considering the constraints and limited resources of the setting, what treatment approach for BPDCN is most suitable for this case?

a. ALL regimen
b. AML regimen
c. Lymphoma regimen
d. CD123-targeted tagraxofusp
e. Allogeneic stem cell transplant

(turn to p. 106 for answer)

Discussion

BPDCN is a rare and aggressive hematological malignancy derived from plasmacytoid dendritic cells. Due to its elusive origin, its nomenclature was not standardized in the past. In 2008, the World Health Organization (WHO) initially categorized BPDCN as a subtype of AML, but it was later recognized as a distinct entity in the 2016 revision.[1,2] In the 2022 WHO Classification of Hematolymphoid Tumors, 5th edition, the disease is recognized under myeloid/histiocytic/dendritic neoplasms.[3] Although BPDCN can affect individuals of all ages and sexes, it most commonly affects older patients, with a median age of diagnosis in the sixth decade of life and a male-to-female ratio of 3:1.[3,4]

Diagnosis of BPDCN is based on a combination of clinical presentation, immunophenotyping, and histopathological findings. BPDCN cells express CD4, CD56, and specific plasmacytoid dendritic cell antigens, including CD123, TCL-1, and CD303. Notably, CD123 overexpression is a consistent feature of BPDCN.[5] According to the WHO 2022 guidelines, the diagnosis of BPDCN requires the presence of CD123 and at least 1 other pDC marker (CD123, TCL1, TCF4, CD304, or CD303), along with either CD4 or CD56 expression.[6] In the cases described above, immunophenotyping using flow cytometry demonstrated the characteristic expression of CD4, CD7, CD56, CD38, CD43, HLA-DR, and CD123. Additionally, for a confirmed diagnosis, a lack of expression for specific negative markers (MPO, lysozyme, CD3, CD14, CD19, and CD34) should be present. That condition was met in this particular case, which excluded T-lymphocyte, B-lymphocyte, and myeloid leukemias.[7] The disease often involves multiple organs, including the skin, bone marrow, blood, and lymph nodes, with clinical manifestations varying based on the site of involvement.[8] The patient in this case presented with constitutional symptoms, cytopenia, hepatosplenomegaly, lymph node, and skin involvement, which are commonly observed in BPDCN.

The rarity and aggressiveness of BPDCN have posed challenges in establishing a standard of care. The typical approach involves chemotherapy in conjunction with allogeneic stem cell transplantation (allo-SCT), which can extend survival.[9,10] Recent research conducted by Brüggen et al substantiated the benefits of allo-SCT compared with any form of chemotherapy regimen.[11] Despite the substantial supporting evidence, we couldn't proceed with this treatment method because adult patients in Armenia did not have access to allo-SCT at that time, and the patient couldn't afford to travel to another country for the procedure due to financial constraints.

According to results of recent studies, tagraxofusp monotherapy has shown excellent clinical results in patients with relapsed/refractory BPDCN.[12,13] During the course of this patient's treatment, tagraxofusp, a targeted therapy specifically approved for BPDCN, was not mentioned as part of the treatment plan. Tagraxofusp is a targeted therapy that was granted accelerated approval by the FDA in 2018 for the treatment of BPDCN in patients 2 years and older.[14] Tagraxofusp is a CD123-directed cytotoxin and has shown promising results in clinical trials,

In our case, the preferred treatment option was:

a. ALL regimen

with response rates and CR rates of 100% and 70%, respectively, in patients who are treatment naive, and 70% and 10%, respectively, in patients who were previously treated.[15] In a recent study by Pemmaraju et al, survival rates at 18 and 24 months were 59% and 52%, respectively.[16] Because this drug is expensive and not readily available in Armenia, we did not treat the patient with this medication.

The patient received induction therapy following the GMALL regimen, which is commonly used in the management of BPDCN.[17] Despite this multiagent chemotherapeutic regimen, the overall survival (OS) rate remains low, with relapse occurring mostly within 2 years after initial complete remission.[18-20] In a study by Huang et al, the survival rates at 1, 3, 5, and 10 years were 68.7%, 49.8%, 43.9%, and 39.2%, respectively.[16] Laribi et al demonstrated that patients receiving lymphoid-type treatment regimens followed by hematopoietic stem cell transplantation (HSCT) consolidation exhibited higher CRs and lower relapse rates. Specifically in their study, the ALL-based regimen achieved a 94% CR rate with a 13% relapse rate, whereas the non-Hodgkin lymphoma–type regimens achieved a 100% CR rate with a 33% relapse rate. In contrast, patients treated with an AML-based regimen followed by HSCT consolidation had an 88% CR rate, but a higher relapse rate of 58%.[21]

In our case, due to financial constraints, we could only implement the ALL-based regimen without HSCT. Taylor et al, in a study comparing the use of these different regimens as a first-line treatment for BPDCN, analyzed 59 patients from 3 cancer centers in the United States. Patients treated with initial lymphoid-type regimens exhibited improved progression-free survival (PFS) compared with those treated with myeloid regimens (2-year PFS, 40% vs 11%, respectively; $P = .075$).[18] In our case, we opted for the ALL-based regimen, specifically the GMALL group for patients aged 55 to 75 years, which we believe is the optimal choice in this case, even though the patient experienced a relapse after 7 months of remission.

Recognizing the aggressive nature of and frequent relapses associated with BPDCN, the patient was subsequently treated with second-line induction therapy, which included subcutaneous azacitidine and oral venetoclax. Venetoclax, a BCL2 inhibitor, is being investigated as a potential therapeutic approach. Patients' partial and full responses to venetoclax monotherapy have shown promising results in case reports.[22] Venetoclax and hypomethylating drugs such as azacitidine are also being explored in combination.[23-25] This treatment approach had shown some response in this case, with a decrease in blast cell count and a reduction in lymph node size. However, the disease continued to progress, and the patient experienced further complications due to disease progression.

Unfortunately, despite the use of various treatment modalities and supportive care, the patient's health continued to deteriorate, and he eventually died at home. The dismal outcomes seen in this case highlight the challenges in managing this aggressive and refractory disease.

Conclusion

In this case report, we detailed the diagnostic journey, treatment approaches, and disease progression of a 62-year-old man with BPDCN, a rare and aggressive hematological malignancy. Despite the implementation of multiple treatment strategies, including the GMALL regimen for patients aged 55 to 75 years, the patient achieved only temporary complete remission before experiencing disease relapse. The unavailability of targeted therapies such as tagraxofusp, coupled with financial constraints, limited our treatment options. Furthermore, at that time the unavailability of allo-SCT was another major challenge, despite its proven superiority in clinical studies. This case highlights the urgent need for more accessible and effective treatment modalities for BPDCN, as well as the importance of additional research to improve outcomes for this challenging malignancy. The outcome of this case serves as a reminder of the aggressive and refractory nature of BPDCN, emphasizing the pressing need for novel therapeutic approaches and resources to better manage this disease and make the best available care accessible to a wider group of patients. ■

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cancernetwork.com/3.24_BPDCN

MEET OUR EXPERT

Linda E. Carlson, PhD, RPsych
Enbridge Research Chair in Psychosocial Oncology and professor in the Department of Oncology, Cumming School of Medicine at the University of Calgary, Alberta, Canada

Updated SIO/ASCO Guidelines Recommend Integrative Therapies to Reduce Anxiety/Depression in Patients With Cancer

Integrative therapies have been proven to help reduce the adverse effects (AEs) of anxiety and depression in patients with cancer, according to Linda E. Carlson, PhD, RPsych.

Carlson, Enbridge Research Chair in Psychosocial Oncology and a professor in the Department of Oncology, Cumming School of Medicine at the University of Calgary, Alberta, Canada, explained how different therapies, such as mindfulness-based interventions, yoga, and relaxation, could work in managing anxiety and depression in patients with cancer. Specifically, she talked about the new recommendations published by the Society for Integrative Oncology (SIO) in partnership with the American Society of Clinical Oncology (ASCO), which highlight integrative approaches to managing anxiety and depression AEs.[1]

Carlson is a past president of SIO and an editorial advisory board member of *ONCOLOGY*. During the interview, Carlson discussed the current guidelines, which the recommendations clinicians can begin to use in everyday practice, and what aspects future research should address.

Q: Why it is important to be aware of integrative approaches for the treatment of anxiety and depression in patients with cancer?

CARLSON: The first thing to understand is how frequent and common these AEs are. Many patients with cancer will [experience] high levels of anxiety and depression that extend well past treatment and into their period of survivorship. We know that anxiety and depression can interfere with [patients'] quality of life and even affect their treatment outcomes. It's important to have evidence-based treatments to help with these AEs. [In terms of] integrative therapies, these will include mind-body therapies, natural health products and physical therapies, and acupuncture. There's mounting evidence that these kinds of therapies can be helpful for dealing with these burdensome AEs of anxiety and depression. It's time to put together a guideline that can provide some guidance for clinicians around which integrative therapies are useful for patients with cancer and when.

Q: What was the multidisciplinary approach used to create these guidelines?

CARLSON: We use a rigorous systematic approach to writing guidelines that ASCO typically uses for its conventional mainstream guidelines. There was a panel of 16 experts convened from a variety of different backgrounds, [including] medical oncology, radiation oncology, palliative medicine, psychosocial oncology, integrative therapies, and people who are experts in natural health products and music therapy. We also had methodologists and biostatisticians who helped systematically review the literature of all the clinical trials in this area of integrative therapies for treating symptoms of anxiety and

depression. Then we went through them in a systematic way to review the evidence and come up with recommendations.

Q: Please discuss the recommendations outlined in this article.

CARLSON: There were over 400 different randomized controlled trials that we looked at. The recommendations were broken down into the following: anxiety during treatment and post treatment, and depression during treatment and post treatment. The strongest recommendations across both anxiety and depression, both during and after treatment, were for mindfulness-based interventions. The research has looked at multiweek programs, so 4 to 8 weeks, and group sessions, so groups of patients with cancer. They get training in mindfulness meditation and gentle yoga, and there's group discussion and support around maintaining regular meditation practice. Patients are assigned regular daily practice of meditation during these mindfulness-based interventions. They're based on a program called Mindfulness-Based Stress Reduction that many people are aware of from Jon Kabat-Zinn, PhD.[2] There are many adaptations that have been used for people with cancer. These mindfulness training programs are helpful for reducing both anxiety and depression, both during and after treatment. That's one of the strongest recommendations.

Another recommendation is for yoga, specifically more traditional yoga programs where people are doing different postures or asanas. Similarly, these are usually multiweek programs where a group of people do yoga training once or twice a week. There's less home practice with that. These yoga programs can be helpful for both anxiety and depression. Most of the research in that area has been with women with breast cancer, so the recommendations are stronger there. It doesn't mean it won't work for other patients; it just hasn't been studied as much.

During treatment, [there is a recommendation for] relaxation and imagery, or the idea of relaxing the body using pleasant images to bring [about] a state of physiological relaxation. Hypnosis is helpful, specifically during procedures, to reduce anxiety. Music therapy, either working with a music therapist or listening to or making music, can also help reduce anxiety. Reflexology is using pressure points either on the feet or the hands to work with the nervous system to reduce levels of physiological arousal of anxiety. The last one I would add is posttreatment [recommendations for] tai chi and qigong interventions. They both come from traditional Chinese medicine, and they're both physical, slow, meditative movement sequences coupled with specific breathing exercises. Those kinds of interventions can also be helpful.

Q: How can clinicians begin to implement these updated guidelines into their practice?

CARLSON: The No. 1 thing that clinicians can do is be aware that these are options for people. Many patients prefer a nonpharmacological and nondrug alternative to treating anxiety and depression. Often, patients will be handed a prescription for an antidepressant or a sedative, and that's not the best first-line treatment. I should also point out as an aside, there's a companion guideline that ASCO published around the same time on mainstream treatments for anxiety and depression in patients with cancer.[3] That covered things like cognitive behavior, therapy, exercise, and other interventions that are helpful. It might be good to look at that as well. In that guideline, it clearly states that first-line treatments are behavioral; they're not pharmacological. Which behavioral treatment and integrative therapy are up to the individual and what their personal preference is. Mindfulness-based interventions are available in person in many locations, but there are also online programs. Some apps are available and have been studied that can be helpful.

For the clinician, [it's important to understand] that these options are available and they're evidence based. Then [it's important to figure] out where in your local area these treatments are available. Many comprehensive cancer centers have integrative therapies; they have yoga, tai chi, mindfulness-based interventions, relaxation, and imagery. Many counselors can offer those services and cognitive behavioral therapy. Being aware that [these options are] effective and that they are first-line treatments, finding out where they're available, knowing how patients can access them, facilitating the treatments in whatever way [clinicians] can, and advocating for more of these programs within cancer treatment centers will be important.

Q: Have integrative approaches become more common in the practice of mitigating anxiety and depression regarding cancer treatment?

CARLSON: Absolutely. The numbers show that when you survey patients with cancer, half of them have used some form of complementary therapy since their diagnosis. Besides natural health products, such as herbs and supplements, the mind-body therapies are the most popular. [Already there are] many people doing this. In general, in the United States, the usage of yoga and meditation is quite popular across the population. It's a little higher in people dealing with health conditions. There are many people out there using these therapies; they're interested in them and they're asking about them. Now that we have

strong evidence that they're effective for helping with anxiety and depression, that will just increase.

Q: What are the next steps for researching integrative practices for patients with anxiety/depression symptoms?

CARLSON: There are quite a few therapies that people are interested in that aren't included in the recommendation because there's not enough evidence: massage, light therapy, energy therapies, and dietary supplements. There's a lot of interest in psychedelics, like psilocybin, as well. We don't have those in the recommendations because there hasn't been enough research. We also need to look at different types of cancers, not just women with breast cancer. We need to look at men. We need to look at less common cancers. We need to look at people who are not [White] and highly educated, because much of the research is in those populations. We need to look more diversely at the population, not just at academic medical centers but in the community. [We need to look] at different community groups, consider issues of health equity and access to these therapies, and make them more accessible to people broadly. There's still a lot of work to do.

Q: Is there anything else that you would like to add?

CARLSON: The patients themselves play an important role in improving and ensuring access to these therapies and advocating for their cancer treatment teams to make these available. In many cases, patients wield a lot more power than clinicians within the system. If the patients are demanding them and saying, "There's evidence and there are recommendations from ASCO and SIO saying that these are going to help me with my anxiety and my depression," that can go a long way to making these more accessible.

The psychosocial piece is huge for patients. They say, "I don't want to just be cured of my disease; I want to have a good quality of life. I want to feel healed. I want to feel like a whole person. I want to be able to have a life beyond cancer." That's such a big piece of the cancer experience that often gets overlooked. ■

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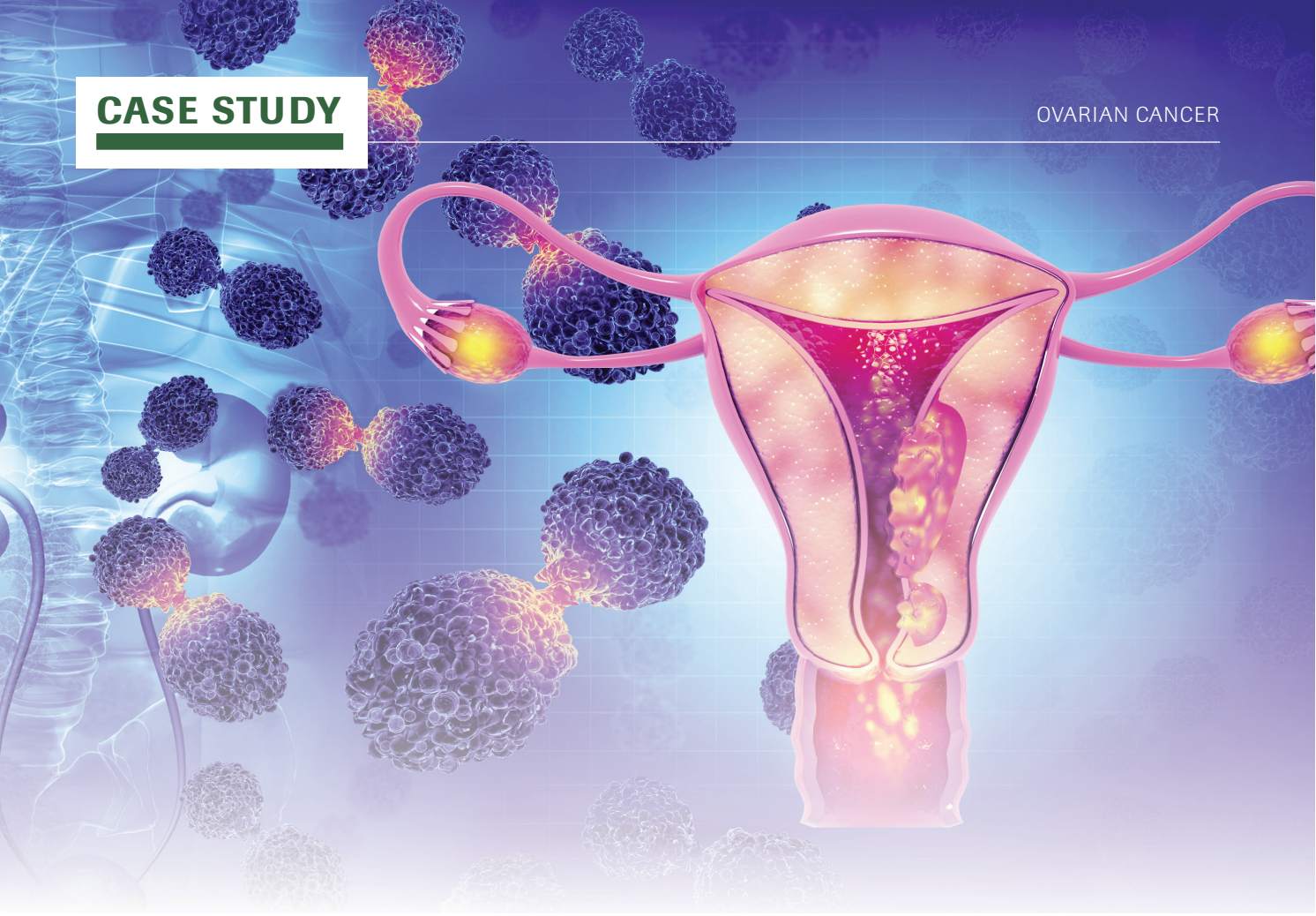

Extreme Case of Surgical Port Metastasis in Ovarian Cancer

Michał Kostrzanowski, MD;[1] Grzegorz Ziółkowski, MD;[1] and Filip Dąbrowski, MD, PhD[1]

ABSTRACT

Ovarian cancer accounts for more deaths than any other malignancy of the female reproductive system. Early diagnosis of this disease is difficult because there are no systematic opportunistic screening methods. At advanced stages, diagnostic laparoscopy is the first step in confirming disease advancement and obtaining samples for genetic and pathologic examination needed to start chemotherapy. Swiftly starting oncological treatment is crucial for increasing the survival rate in these patients. We present the case of a 51-year-old woman with metastatic International Federation of Gynecology and Obstetrics (FIGO) stage IIIC ovarian cancer who had delayed her therapy after initial laparoscopy due to COVID-19 infection and presented with an extreme case of surgical port metastasis.

KEYWORDS

Ovarian cancer; computed tomography scan, laparoscopy, metastases, surgical port

Ovarian cancer is one of the most common malignant diseases in women. The highest rates of new cases (11.4 per 100,0000) and deaths (6.0 per 100,0000) are seen in Eastern and Central Europe.[1] Looking at cancer-related deaths in the world, ovarian cancer ranks fifth, and for cancer-related deaths in Poland, it ranks fourth.[2,3] Worldwide, the disease typically presents in an advanced stage, when the 5-year survival rate is 29%.[1] Two-thirds of patients present with stage III or stage IV disease, which means upfront surgery is often not feasible.[4] Many patients require diagnostic laparoscopy to determine tumor genetic and histopathological status and neoadjuvant chemotherapy before cytoreductive surgery. The prolonged interval between laparoscopic biopsy and chemotherapy may lead to additional comorbidities.[5]

Case Presentation

In January 2023 a 51-year-old woman, gravida 3, para 2, was admitted to ambulatory care with symptoms of ascites. Her medical history included mild arterial hypertension, currently without treatment. One year ago, the patient was referred for ovarian cyst surgery (uniocular, anechoic, 7-cm diameter) but did not report for the procedure. The patient reported 10-kg weight loss in the previous 6 months. The risk of ovarian malignancy algorithm was 79%. During the physical examination, palpable solid lesions in the pelvis were found. On the transvaginal ultrasound scan, a solid cystic lesion measuring 11.0 cm × 9.0 cm × 7.5 cm was detected in the pelvis. The transabdominal ultrasound scan confirmed free fluid in the peritoneum and detected omental cake.

CT scans of the pelvis, abdomen, and thorax were performed. The CT scan found extensive pathological nodular lesions with a fluidlike structure extending from the level of the umbilicus to the pelvis in communication with the right adnexa. The lesion measured 19.0 cm × 11.5 cm × 14.5 cm. The thickness of the lesion at the anterior abdominal wall was approximately 3.5 cm. Numerous tumor implants in the greater omentum, along the wall of the small intestine, were suspected. Tumor implants and enlarged lymph nodes were suspected in the mesentery; there was a hypodense lesion in the sixth segment of the liver that measured 3.5 cm × 3.5 cm and an osteolytic lesion in the ischium with a diameter of 2.0 cm. The patient was qualified for laparoscopy with the intent of biopsy of a suspicious lesion.

During the surgery, node lesions in the corpus uteri, thick green fluid in the peritoneal cavity, and nodular implants in the liver recess, splenic recess, omentum, and peritoneum were found. The Fagotti score was 14 points.[6] A total of 120 mL of fluid from the peritoneal cavity, tissue slices from the omentum, and implants from the peritoneum were taken for histopathological and genetic examination.

The bleeding sites were coagulated, and a surgical drain was placed in the rectovaginal pouch. Surgical sutures were placed in the rectus sheath at the trocar site near the umbilicus and on the other 2 trocar sites. Single interrupted surgical sutures were placed in the skin.

During a histopathology examination, metastases of epithelial cancer and carcinosarcoma were found. Immunohistochemistry was positive for CK7, p53, PAX9, VIM, and CK19. Morphologically epithelial and spindle cells also were found.

The patient was urgently referred for chemotherapy, and her appointment in the clinical oncology department was scheduled 2 weeks after laparoscopy. Due to a viral infection of the upper respiratory tract and influenza, the patient was temporarily disqualified and did not return for reevaluation 2 weeks later.

In March 2023, the patient was admitted to the gynecologic emergency department. She had not returned to clinical oncology due to further COVID-19 infection and personal issues. In the physical examination, a new lesion measuring approximately 5.0 cm × 6.0 cm was found in the umbilical region. After removing the dressing from the umbilicus, attention was drawn to the bleeding from the lesion (**Figure 1**).

Umbilical jejunum hernia or metastasis of primary disease was taken into consideration. From the emergency department, the patient was referred for CT with contrast. The CT scans, compared with scans from the first admission, showed the thickness of the lesion at the anterior abdominal wall was 4.0 cm; it was 3.5 cm in January. Additionally, the tumor implant in the umbilicus now measured 5.2 cm × 6.3 cm (**Figure 2**); in January it was 1.9 cm × 1.8 cm (**Figure 3**).

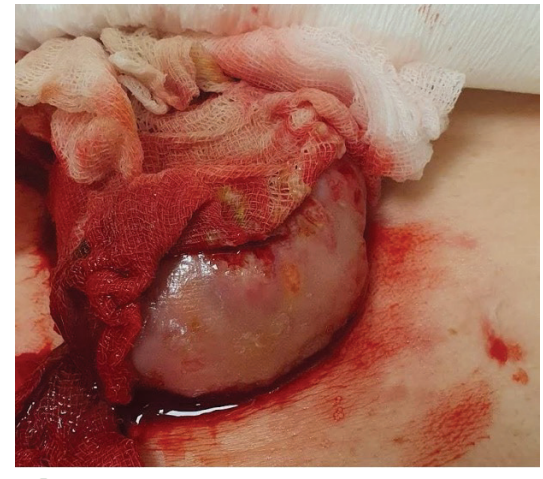

FIGURE 1. **Tumor Implants in the Umbilicus.**

The patient's C-reactive protein level was 205 mg/L, hemoglobin level was 7.9 g/dL, and leukocyte level was 16.5 µL. Due to anemia, 2 units of packed red blood cells were transfused. After surgical consultation, the authors decided

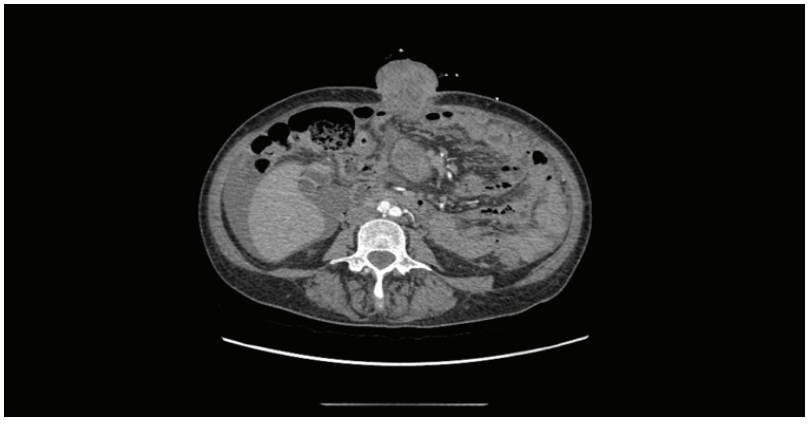

FIGURE 2. **Tumor Implants in the Umbilicus on CT Scan in March**

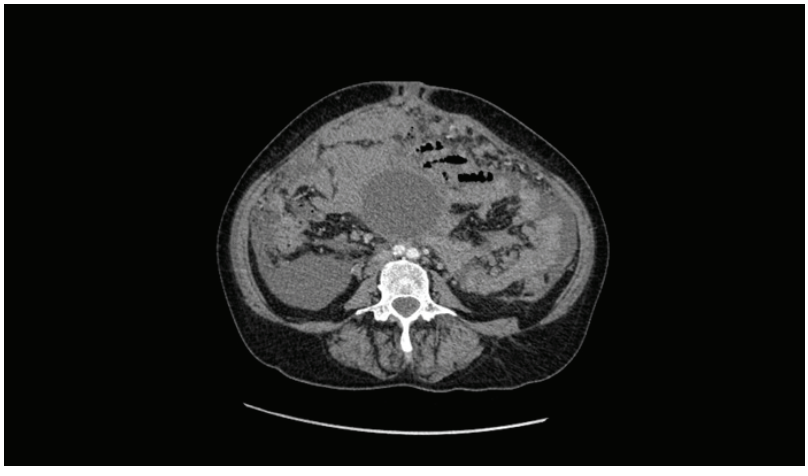

FIGURE 3. **CT Scan of the Abdomen at the Level of the Umbilicus in January**

to abandon the surgical treatment. The patient was referred for immediate radiation treatment of the tumor in the umbilicus and systemic chemotherapy.

Discussion and Review of the Literature

Ovarian cancer often presents with liver and splenic parenchymal metastases that contribute to International Federation of Gynecology and Obstetrics (FIGO) stage IV disease. This advanced type of cancer is present in 12% to 33% of the patients at initial diagnosis.[7] Study reports show the sites of distant metastases of ovarian cancer are pleural effusion/pulmonary metastases (ca. 40% of patients); abdominal wall metastases (ca. 40% of patients with FIGO stage IV disease); extra-abdominal lymph nodes (ca. 20%); liver metastases (ca. 14%); spleen metastases (ca. 6%); brain metastases (ca. 2%), and bone involvement (<2%).[8-10] Findings on the patient's CT scans, including tumor implants in the greater omentum and lesion in the liver, raised the suspicion of distant metastases of the disease; nevertheless, a laparoscopic biopsy would be needed to confirm the disease by histological examination of the lesion. Also, assessment of the extension of the disease during laparoscopy influences the primary treatment option for the patient.[5,11]

One of the most frequently used tools in the prediction of optimal cytoreduction is the Fagotti score. In this model, we consider the following parameters: omental cake, peritoneal carcinomatosis, diaphragmatic carcinomatosis, mesenteric involvement, bowel infiltration, stomach infiltration, and liver metastases.[6] The predictive index value for each positive parameter is 2. If the cut value is 8 or more, then the probability of converting the laparoscopy to laparotomy and optimal cytoreduction (residual tumor ≤ 1.0 cm) is equal to 0.[12] The presence of omental cake, peritoneal and diaphragmatic extensive carcinosis, mesenteric retraction, bowel and stomach infiltration, spleen and/or liver superficial metastasis was investigated by laparoscopy. By summing the scores relative to all parameters, a laparoscopic assessment for each patient was evaluated (total predictive index value = PIV).

Recently, more often the real destination of surgical treatment is complete cytoreduction (residual tumor = 0 cm). Then the cut value of Fagotti score is 10 or more points.[13]

In the literature, we found potential risk factors for abdominal wall metastases after laparoscopic surgery: FIGO stage IV disease, ascites volume higher than 500 mL, and peritoneal carcinomatosis.[14] These factors are closely correlated with the mechanism of the port-site recurrences. The starting point is when tumor cells are present within the abdominal cavity. The peritoneal wound by laparoscopic instruments breaches the mechanical protection provided by the mesodermal layer. Finally, the implantation of tumor cells into the laparoscopic port site could occur by direct contact, direct inoculation via laparoscopic instruments, or through

contaminated peritoneal liquid after the procedure. Additionally, local conditions in the abdominal wound, such as angiogenic growth factors, cell growth factors, and the presence of inflammation mediators, promote the growth of the tumor cells.[15]

The stimulatory effect of carbon dioxide (CO_2) on abdominal wall metastasis has a secondary role in clinical practice. Although we found a few studies in animal models showing that using gasless laparoscopy reduced the incidence of port-site recurrences, after thoracoscopy (during which no CO_2 is used) numerous port-site recurrences have also been described.[16,17] The presence of the tumor cells in the port sites is instead a result of direct contamination by the surgical instruments and not from the dispersal of the malignant cells by the CO_2.[18,19] The benefits of using gasless laparoscopy procedures remain controversial, and further research is needed in this area.

The other proposed way of dissemination of malignant cells to the abdominal wound is hematogenous spread. It might be that higher intra-abdominal pressure during laparoscopy facilitates the passage of malignant cells from the lymphatic to the venous system and causes implantation of neoplasm cells at trocar sites.[20] However, the other authors proved that only 1% of neoplasm cells that reach general circulation survive, and only 0.1% of these cells can cause metastases. Additionally, this mechanism does not explain the difference in wound metastases after laparoscopy and laparotomy, and the number of reported cases of metastases after open surgery is not as high as this mechanism would suggest.[21]

The incidence of abdominal wall metastases after diagnostic procedures varies among available scientific reports. We found 1 report that noted abdominal wall metastases appear in 47% of patients after laparoscopic interventions.[14] Another study proved that the risk of port-site metastases is 50% in patients with ovarian and primary peritoneal malignancies in the presence of ascites.[22] Other studies' results showed that the risk of port-site metastases is not as high as in the studies mentioned above: port-site metastases in 1 of 88 patients (1.14% per procedure) undergoing laparoscopic surgery for ovarian cancer and 1% per procedure for gynecologic malignancies in general.[23] However, Kruitwagen et al reported that the incidence of port-site metastases is 16% in patients with ovarian cancer undergoing laparoscopic procedures 9 to 35 days prior to the initial cytoreduction.[24]

When analyzing the articles and describing the correlation between abdominal wall metastases and risk factors, we found factors that could reduce the risk of recurrence of the disease at the port sites. In the study conducted by Van Dam et al, patients with abdominal implantations had a longer interval between primary laparoscopy and the debulking surgery or the start of chemotherapy.[25] Abdominal implantations developed in 0 patients in which cytoreductive surgery or chemotherapy was done within 1 week after a diagnostic laparoscopic procedure. The early onset of postoperative chemotherapy is correlated with the lower risk of the occurrence of port-site metastases.[26,27]

Van Dam et al also proved that proper surgical technique is very important.[25] Trocar site metastases appear in 58% of patients who underwent a closed laparoscopic procedure with a blunt trocar; the peritoneum and rectus sheath were not closed at the end of the operation, and the sutures were placed on the skin. Trocar site implantation metastases were found in only 2% of patients in whom an open laparoscopy was performed with careful closure of all layers of the abdominal wall.[28] An additional proven risk factor for early occurrence of port-site metastasis is the presence of ascitic fluid during the laparoscopic procedure.[28] Aspiration of all intraabdominal fluid before trocar removal, abdominal emphysema removal with trocar in place, and proper trocar fixation are other general recommendations proved in the scientific literature.[39]

In the other animal model, a significant reduction in port-site metastases was observed, when diluted povidone-iodine was instilled in the peritoneal cavity during laparoscopic procedure.[30]

A decrease in port-site metastases was also observed in the rat model of colon cancer. Irrigating the port sites with 5-fluorouracil at the time of procedure led to a decrease in occurrence of port-site metastases.[31] The harmfulness of irritative substances for the tissue and the benefits of minimizing the risk of port-site recurrences should be considered before using these agents.[32]

Port-site resection was another potential option to minimize the occurrence of port-site metastases. The authors analyzed the correlation between port-site resection and oncological outcome in advanced ovarian cancer: No better outcome in survival and higher prevalence of wound complications were observed.[33]

From the factors mentioned above, the delay of postoperative chemotherapy and the presence of ascites were the risk factors for developing port-site metastasis. The use of proper surgical technique of laparoscopy and proper wound closure in layers (rectus, sheet, and skin) did not protect the abdominal wall from metastasis in the place of the trocar site.

Conclusions

Although neoadjuvant chemotherapy may benefit patients in advanced stages of ovarian cancer, it is important to plan the treatment at the proper place after laparoscopic biopsy. Additionally, physcians and patients should make every effort not to delay proper therapy after the first stage of treatment, which is a diagnostic laparoscopy. ■

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Rising Prices and Lower Medicare Reimbursement Rates Create Outrage Among Clinicians

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Physician recruitment and retention have become a crisis. This crisis is borne of physician discontent and demoralization, which are especially high in the wake of the COVID-19 pandemic. Educational debt, the long training pipeline, and professional demands have made physician "burnout" a hot topic.

Releasing the final rules for 2024, the Centers for Medicare & Medicaid Services has imposed a 3.37% cut to the reimbursement rates for Medicare physicians. When adjusted for inflation, Medicare physician payments have decreased by 26% since 2001.[1] From 2020 to 2023, during and after the pandemic, the Medicare conversion factor decreased by 5.96%. The effect of this decrease in the Medicare conversion factor is compounded by an increased inflation rate since 2021.

The US inflation rate reflects the increase in prices compared with the prior year. Inflation increased by 7.0% in 2021 and 6.5% in 2022, and was at 3.4% in 2023, representing a cumulative inflation rate of about 14% since 2021.[2-5] Although the inflation rate has fallen from its high in 2021 and 2022, consumer and producer prices have not decreased to their prepandemic levels. In 2023, it took $1.14 to buy what $1.00 could purchase in 2021.

Although Medicare physician reimbursement continues to be cut, national health care expenditure (NHE) continues to burgeon. Before the pandemic, NHE increased from $1.365 trillion in 2000 to $2.029 trillion in 2005 to $3.795 trillion in 2019, representing 13.3%, 15.6%, and 17.7% of the gross domestic product (GDP), respectively.[6]

At the height of the pandemic in 2020 and 2021, health care expenditures increased to $3.9 trillion and $4.0 trillion, respectively, and accounted for 18.8% and 17.4% of the GDP, respectively.[7,8] In 2022 the NHE slowed, increasing only by 3.8%, and accounting for 17.2% of GDP.[9]

Part of this decline in NHE during postpandemic 2022 involved less health care utilization, reduced temporary federal government support, and an increase in GDP.[10] Less health care utilization represented not only the decline in COVID-19 care and hospitalizations but also the continued delay in the administration of routine health care. During the height of the pandemic in 2020, physician and clinical expenditures grew by 6.6%; after the introduction of the COVID-19 vaccine in 2021, these expenditures decreased by 5.6% to $864.6 billion.[11]

In this time of record federal spending and a debt of more than $34 trillion, cuts in the Medicare conversion factor will not balance the federal budget because Medicare physician services comprise only 14.9% of the total NHE.[12] Hospital care represents 31.1%, clinical services 5.4%, and prescription drugs 8.9% of the NHE. The Institute for Clinical and Economic Review identified 10 high-expenditure drugs that had "substantial 2022 net price increases" that "were not supported by new clinical evidence" for 8 of the 10 medications.[13] Most of these medications are used in oncology.

Compared with an 8.4% growth in 2021 during the pandemic, Medicare expenditures grew at a rate of 4.8% in 2022. This slower growth in Medicare expenditures is attributable to (1) lower rates of emergent care among Medicare fee-for-service beneficiaries, and (2) phased-in sequestration-based payment rate cuts of 1% from April to June 2022 and 2% per year from July 2022 onward; in 2021, due to the

pandemic, these rate cuts were suspended. Despite these physician rate cuts, Medicare expenditures for 2023 are projected to exceed $1 trillion and increase by an average of 7.8% from 2025 to 2031. Growth in Medicare spending is expected to slow in 2030 as (1) Medicare Advantage payments and hospital costs among fee-for-service beneficiaries decline; (2) provisions within the Inflation Reduction Act of 2022 are enacted; and (3) the last of the baby boomers enroll in Medicare in 2029.[14]

In 2020, more than 3600 US health care workers died from COVID-19. The median age of death from COVID-19 among patients was 78 years but was 59 years for health care workers. From March 2020 to December 2021, there were 622 additional deaths among physicians. Nurses and support staff members, who had greater patient contact, died in far higher numbers than physicians based on relative numbers and extent of patient interactions.[15,16] Like first responders, health care workers assumed these risks for themselves and their families based on their ethical commitment to patients.

Although first responders and health care providers were lauded during the pandemic, the continued cuts in Medicare reimbursement reflect how little their selfless service is valued. The only logical conclusion is that the federal government is counting on physicians' ethics regarding care of Medicare patients despite the ongoing reimbursement cuts. If physicians limit the number of Medicare patients in their practice due to fiscal restraints, physicians will be blamed. As a bonus, with mounting physician shortages, health care costs will decline as Medicare patients wait longer to see a physician.

Every budget reflects priorities. The federal budget, especially as it concerns provisions made during the sequestration of 2013 and the Inflation Reduction Act of 2022, continues to consider health care workers and Medicare patients as a low priority. In this election year, the calls to reverse cuts in Medicare reimbursement continue to be ignored by the federal government. Given the excess risks assumed during the pandemic, no wonder physician burnout is rampant.

There is an old adage in politics: "If you want less of something, cut its funding or tax it." What is the message to physicians and Medicare patients? Perhaps the nearly 1 million active physicians in the United States should demand that every bureaucrat be placed on the same pay-cut schedule as physicians treating patients on Medicare. ■

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RAPID REPORTER

ONCOLOGY Reviews Key Presentations From the
2024 Genitourinary Cancers Symposium

Enfortumab Vedotin Combo Improves Outcomes in Urothelial Cancer Subgroups

Patients with previously untreated locally advanced or metastatic urothelial carcinoma experienced improvements in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) with enfortumab vedotin-ejfv (Padcev) plus pembrolizumab (Keytruda) compared with chemotherapy, according to prespecified subgroup analysis findings from the phase 3 EV-302/KEYNOTE-A39 trial (NCT04223856).

These results showed that the PFS benefit with the combination in patients with visceral metastases (HR, 0.45; 95% CI, 0.37-0.55) and those with lymph node–only disease (HR, 0.40; 95% CI, 0.26-0.62) was consistent with that of the overall population (HR, 0.45; 95% CI, 0.38-0.54; 2-sided P <.00001). Moreover, OS benefit was similar to that of the overall population (HR, 0.47; 95% CI, 0.38-0.58; 2-sided P <.00001), regardless of the presence (HR, 0.47; 95% CI, 0.37-0.60) or absence (HR, 0.46; 95% CI, 0.27-0.78) of visceral metastases. In the visceral metastases cohort, the median OS was 25.6 months with the combination vs 13.6 months with chemotherapy. In the lymph node–only cohort, the median OS was not reached with the combination vs 27.5 months with chemotherapy.

Additional findings from the current analysis showed that consistent with the primary analysis, which showed an ORR of 67.7% with the combination vs 44.4% with chemotherapy, patients in all prespecified subgroups experienced superior response rates with the combination, surpassing at least 60% in all cases.

The most common treatment-related adverse effects (TRAEs) reported in the enfortumab vedotin/pembrolizumab arm (n = 440) included peripheral sensory neuropathy (any grade, 50.0%; grade ≥3, 3.6%), pruritus (39.8%; 1.1%), alopecia (33.2%; 0.5%), maculopapular rash (32.7%; 7.7%), fatigue (29.3%; 3.0%), diarrhea (27.5%; 3.6%), decreased appetite (26.8%; 1.1%), nausea (20.2%; 1.1%), anemia (13.9%; 3.4%), neutropenia (9.1%; 4.8%), and thrombocytopenia (3.4%; 5.0%).

In the enfortumab vedotin/pembrolizumab arm, 4 TRAEs led to death: asthenia, diarrhea, immune-mediated lung disease, and multiple organ dysfunction syndrome. In the chemotherapy arm, 4 TRAEs resulted in death: febrile neutropenia, myocardial infarction, neutropenic sepsis, and sepsis.

→ **For the full article, visit** cancernetwork.com/GU24_EV-302

Olaparib Combo Improves Survival vs Placebo in Metastatic CRPC

Significant improvements in progression-free survival (PFS) and overall survival (OS) were achieved with olaparib (Lynparza) plus abiraterone acetate (Zytiga) among those with homologous recombination repair (HRR)–mutated metastatic castration-resistant prostate cancer (mCRPC), according to post hoc analysis findings from the phase 3 PROpel trial (NCT03732820).

The clinical benefit with olaparib plus abiraterone was observed in patients with *BRCA2*, *ATM*, and *CDK12* mutations, the most prevalent single-gene HRR mutations across all patients treated. The radiographic PFS (rPFS) rate with the olaparib combination for patients with *BRCA2*, *ATM*, and *CDK12* mutations was 27% (HR, 0.20; 95% CI, 0.08-0.44), 29% (HR, 0.55; 95% CI, 0.20-1.38), and 42% (HR, 0.51, 95% CI, 0.20-1.18), respectively. Corresponding OS rates were 20% (HR, 0.20; 95% CI, 0.07-0.48), 43% (HR, 0.79; 95% CI, 0.33-1.77), and 47% (HR, 0.57; 95% CI, 0.24-1.27).

In the placebo arm, the rPFS rates for patients with *BRCA2*, *ATM*, and *CDK12* mutations were 71%, 50%, and 67%, respectively. Corresponding OS rates were 64%, 54%, and 71%. Notably, the analysis of treatment with the olaparib combination was limited in patients expressing other single-gene mutations due to their decreased incidence.

Overall, results were generally consistent with primary findings from the PROpel trial.

The PROpel trial previously met its primary end point of improved rPFS with the olaparib regimen compared with abiraterone and placebo in the intention-to-treat population. Previous data showed that the median rPFS with olaparib plus abiraterone was 24.8 months vs 16.6 months with abiraterone alone (HR, 0.66; 95% CI, 0.54-0.81; *P* <.0001). At the time of the final prespecified analysis, the median OS was 42.1 months with the olaparib combination vs 34.7 months with the placebo regimen. This difference was numerically, but not statistically, significant.

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Belzutifan Improves QOL and Disease Progression Time in Advanced Kidney Cancer

Belzutifan (Welireg) resulted in longer time to disease progression (TTD) and improvements in quality-of-life (QOL) scores in patients with advanced/metastatic clear cell renal cell carcinoma (RCC), as measured by the Functional Assessment of Cancer Therapy-Kidney Symptom Index Disease-Related Symptoms (FKSI-DRS) and the EORTC QLG Core Questionnaire (QLQ-C30) at 17 weeks compared with everolimus (Afinitor), according to findings from the phase 3 LITESPARK-005 trial (NCT04195750).

A total of 366 of 374 patients were randomly assigned to receive belzutifan, a first-in-class HIF-2 α inhibitor, and 354 of 372 patients were randomly assigned to receive everolimus in the randomized, open-label, phase 3 study were included in the patient-reported outcomes analysis population. Both the belzutifan and everolimus groups had high completion rates for FKSI-DRS and QLQ-C30 (>90% at baseline and >55% at week 17).

The median TTD with belzutifan was not reached in FKSI-DRS, 19.35 months in QLQ-C30 global health status/quality of life (GHS/QoL), and 19.32 months in QLQ-C30 physical functioning group compared with 11.99, 10.19, and 13.83 months with everolimus. Across the questionnaires, the TTD HRs were 0.53 (95% CI, 0.41-0.69), 0.75 (95% CI, 0.58-0.96), and 0.93 (95% CI, 0.72-1.20) and the 2-sided nominal *P* values were <.0001, .019, and .55, respectively.

Prior LITESPARK-005 data established belzutifan's efficacy in terms of progression-free survival (HR, 0.75; 95% CI, 0.63-0.90; *P* <.001) and overall response rate (estimated difference, 18.4; 95% CI, 14.0-23.2; *P* <.00001) vs everolimus in advanced kidney cancer.

With a median follow-up of 25.7 months (range, 16.8-39.1) at the data cutoff date at the second prespecified interim analysis of June 13, 2023, the median duration of treatment was 7.6 months (range, 0.1-35.8) with belzutifan, compared with 3.9 months (range, 0.0-33.2) with everolimus. A total of 84 (22.6%) and 18 (5.0%) patients remained on treatment across the 2 arms.

→ **For the full article, visit** cancernetwork.com/GU24_LITESPARK-005

Cabozantinib Combo Significantly Improves PFS vs NHT in Metastatic CRPC

Combining cabozantinib (Cabometyx) with atezolizumab (Tecentriq) demonstrated a clinically meaningful and statistically significant progression-free survival (PFS) improvement compared with second-line novel hormonal therapy (NHT) among patients with metastatic castration-resistant prostate cancer (CRPC), according to data from the phase 3 CONTACT-02 trial (NCT04446117).

Across the PFS intent-to-treat (ITT) population, the median PFS per blinded independent review committee (BIRC) assessment was 6.3 months (95% CI, 6.2-8.8) with the cabozantinib combination vs 4.2 months (95% CI, 3.7-5.7) in the NHT arm (HR, 0.65; 95% CI, 0.50-0.84; *P* = .0007). Additionally, the PFS rate in each respective arm was 60% vs 42% at 6 months and 25% vs 18% at 12 months.

The median PFS per BIRC across the ITT population was 6.3 months with cabozantinib plus atezolizumab vs 4.2 months with NHT (HR, 0.64; 95% CI, 0.50-0.81; *P* = .0002). Moreover, data highlighted a median radiographic PFS of 6.3 months vs 4.1 months in each respective arm in the PFS ITT population (HR, 0.62; 95% CI, 0.48-0.81).

The PFS benefit with the cabozantinib-based regimen extended to patients across most prespecified subgroups. Of note, the experimental combination led to a PFS improvement in those with liver metastases (HR, 0.43; 95% CI, 0.27-0.68), patients who previously received docetaxel (HR, 0.57; 95% CI, 0.34-0.97), and those with bone metastases (HR, 0.67; 95% CI, 0.50-0.88).

Findings from the interim overall survival (OS) analysis in the ITT population indicated a median OS of 16.7 months (95% CI, 15.1-20.9) in the cabozantinib arm compared with 14.6 months (95% CI, 11.6-22.1) in the NHT arm (HR, 0.79; 95% CI, 0.58-1.07; *P* = .13). The 6-month and 12-month OS rates in each arm, respectively, were 87% vs 79% and 62% vs 57%.

In the cabozantinib and NHT arms, the objective response rate was 14% vs 4%, and the disease control rate was 73% vs 55%. Partial responses were reported in 13% and 4% of patients; 1% of those in the cabozantinib arm had a complete response. Additionally, more patients in the cabozantinib arm experienced a reduction in the size of target lesions.

→ **For the full article, visit** cancernetwork.com/GU24_CONTACT-02

CONTINUING MEDICAL EDUCATION (CME)

The Impact of CAR T-Cell Therapy on Hematological Malignancies

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

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LEARNING OBJECTIVES

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

- Discuss advantages and disadvantages of CAR T-cell therapy in hematological malignancies
- Describe the opportunities for improvement in CAR T-cell therapy made possible by gene editing techniques

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Chimeric antigen receptor (CAR) T-cell therapy is a recent addition to the hematological oncology armamentarium. To create CAR T cells, gene editing renders natural T cells more active and more capable of binding to tumor cells. CRISPR technology allows for more precise gene insertions and several simultaneous modifications in T cells, which enhances their cancer-fighting abilities. In this article, Jae Park, MD, explores recent advances and future directions of CAR T-cell therapy that is being accelerated via evolving gene editing technologies.

Q: How has autologous CAR T-cell therapy transformed care for patients with hematologic malignancies?

PARK: Autologous CAR T-cell therapy has had a tremendous impact on treatment of patients with hematologic malignancy.[1] In cases of non-Hodgkin lymphoma, there are now several autologous CAR T-cell products approved, all targeting CD19. These products initially were studied in patients who had relapsed disease after chemotherapy and autologous transplant—high-risk patients with few treatment options available. Even in this setting, about half the patients were able to achieve a complete remission, and more remarkably, these patients were able to maintain the remission long term after one-time infusion of CAR T cells.[2] With the longer follow-up that we have now, we can comfortably call this a curative therapy. Based on that data, CAR T-cell therapy was subsequently studied in earlier lines in lymphoma, and now at least 2 products are approved in the second-line setting and some are under investigation for the first-line setting.[3,4]

In multiple myeloma, we have 2 approved products targeting BCMA.[5] These BCMA CARs can yield high response rates, reaching more than 80% in patients who have failed at least 3 prior lines of therapy, but the durability of the remissions is not as good as in lymphoma patients.[6] Whether CAR T-cell therapy could generate more durable responses in earlier lines of multiple myeloma is currently being investigated in ongoing clinical trials.

Leukemia is the third disease front where CAR T-cell therapy has made a big impact. We have 2 products approved targeting CD19 in acute lymphoblastic leukemia.[7,8] These patients are, again, highly refractory and relapsed patients, often after allogeneic bone marrow transplant. CD19-targeted CAR T-cell therapy can attain a high initial response rate and about half the patients are able to maintain the remission long term, again, after a single infusion.[9]

Q: What are some of the limitations of autologous CAR T-cell therapy?

PARK: Despite the huge success of autologous CAR T-cell therapy in hematologic malignancies, there are some limitations. First, there are unique adverse effects associated with CAR T-cell therapy such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS).[1]

CRS was a bigger problem when CAR T-cell therapy was initially used. Now we have learned a great deal about its pathophysiology, high-risk patient populations, management, and prophylactic strategies to minimize severe CRS.

ICANS is most commonly seen with the CD19 CARs in leukemia and lymphoma and is less common in patients with multiple myeloma.[3,10,11] ICANS is more challenging to manage because the pathophysiology is not as well understood and treatments have a lower response rate compared with CRS. Steroids remain the mainstay of therapy. Because severe cases of ICANS do not respond promptly to steroids and other managements, the key is to prevent ICANS altogether or keep it at low grades, ie, grade 1 and 2. We and others have studied several prophylactic strategies including the use of the IL-1 inhibitor anakinra to address those issues.[12]

The second limitation is that these are autologous CAR T cells, meaning the T cells are coming from the patients themselves. That can create challenges in selecting optimal timing for T-cell collection, ie, leukapheresis. Some patients might have just received chemotherapy or are on active immunosuppressants that can negatively impact the number of T cells retrieved, or compromise T-cell potency. In other cases, the disease is progressing so rapidly that patients cannot wait until they get scheduled for leukapheresis and then wait until the T-cell infusion, which can take several weeks.[1] This wait time limits which patients are able to get this therapy.

The third limitation is that this treatment is currently being administered in cell therapy specialty centers. Due to the possibility of CRS and ICANS, there are regulatory requirements on how closely these patients need to be monitored, and how close to the treatment center they must stay. That limits patients who do not have a caretaker or the financial means to travel to the centers. As the adverse effect profiles of new CAR products and prophylactic and management strategies improve, we are hoping these regulatory rules will be modified in the near future. We must work on improving access so that more patients can receive these potentially curative and life-prolonging therapies.

Q: How do gene editing techniques, including CRISPR, contribute to the development of CAR T-cell products?

PARK: Gene editing techniques such as CRISPR have enabled tremendous progress in the field of CAR T-cell development. CRISPR and other gene editing technologies are being used to knock-in, knock out, and/or knock down genes of interest to test how a combination of such specific gene modifications can improve the antitumor efficacy of CAR T cells.[13] Armored CAR T cells are modified to deliver inflammatory cytokines specifically at the tumor upon T-cell activation. With advancement of gene editing technologies, CAR T cells can function as a micropharmacy. Whatever we want the cells to deliver, we can build into them within a certain capacity. In addition, several investigators have used CRISPR and other gene editing technologies to insert

a CAR into a T-cell receptor (TCR) locus, creating allogeneic or donor-derived, off-the-shelf T cells, thereby expanding the available cell sources beyond autologous T cells for CAR therapies.[14]

Q: What advantages do allogeneic or off-the-shelf CAR products provide?

PARK: One advantage of the off-the-shelf CAR therapies is their immediate availability. Patients can bypass the leukapheresis and the bridging time from collection to infusion, saving them several weeks of wait time and a number of visits to the clinic and infusion centers as well as reducing the number of chemotherapy cycles that often get delivered while waiting for autologous cell delivery.[15] The second advantage is that it will allow treatment of patients who are currently not being considered for autologous CAR T-cell therapies due to recent T-cell suppressive chemotherapy exposure or for those who have an insufficient number of T cells or had prior autologous T-cell manufacturing failures. The third is that the T cells for off-the-shelf CARs come from a healthy donor, which means that the cells could be more active, and we do not need to worry about possible manufacturing failure or out of spec products. Lastly, we hope off-the-shelf CAR T cells will drive down the cost since it requires fewer steps in manufacturing and can be made in mass production, similar to antibodies and antibody-drug conjugates. Hopefully, in the future, reducing the regulatory hurdles and the amount of monitoring that the patient needs will reduce costs as well for both autologous and allogeneic CAR products.

Q: What are some of the challenges and limitations in using off-the-shelf CAR products for cancer treatments, and how can gene editing address some of those challenges?

PARK: Ideally, the T cells need to be present long enough to control the disease and eradicate tumor cells completely. But it is not yet clear what the optimal duration of T-cell persistence is, and it may depend on tumor burden, disease types, and CAR designs. Plus, we may not want the CAR T cells to persist forever, especially when they also target normal B cells or myeloid cells, which can then cause permanent immune suppression and potential infectious complications.[16] Ideally, we want these immune cells to be there long enough to get rid of all the tumor cells, but once the job is done, be gone. That is the holy grail.

With all these caveats in mind, there is a concern that off-the-shelf T cells may not persist as long as autologous CAR T cells due to potential immune-mediated rejections, and [they] may not clear out the tumor as completely.[13] To address these concerns, several investigators are conducting additional genetic editing to make allogeneic T cells less susceptible to host immune-mediated rejections and/or make them more potent to overcome the short persistence.

Q: Please describe the safety concerns associated with using gene editing in humans, and how are researchers working to improve its safety and precision?

PARK: Recently, we have heard a lot about secondary T-cell lymphomas that might have been caused due to viral integration into an oncogene site.[17] While incidences of these events are extremely rare and the benefit of autologous CAR T cells still outweighs this potential risk, this raises some anxiety. But, with CRISPR-edited CAR, that risk is even lower since we know exactly where the CAR is being inserted. However, when multiple gene edits are made, there is an increased risk of recombination events that can lead to unwanted or unanticipated outcomes. How many edits can we make and what are some of the safety effects of doing it? We need to follow these patients long term, not only for the efficacy perspective, but for the safety as well.

Q: Where do you see the future of gene-edited immune effector cell products for oncology in 5 to 10 years, and what current research is most promising?

PARK: The field has progressed tremendously over the last 5 years already. We now have several genetically engineered cellular products approved for several disease indications globally.[1] These immune effector cell therapies not only work where all other therapies have failed, they sometimes even cure the patients, which is the ultimate goal of any cancer therapy. In the next 5 or 10 years, we want to cure more patients with cancer and increase access to CAR T-cell therapy.

In order to increase the cure rate, we are moving the autologous CAR T-cell therapies currently being used in later lines of treatment to earlier lines. We have learned and seen that these therapies have the most single-agent antitumor activity and there is no reason to save them until other therapies fail. However, in order to do that, we do need to improve their safety, which is being addressed with better CAR designs.

Next, we are studying additional gene editing to create next-generation CARs that are more potent and overcome the limitation of current CARs. In the next 2 or 3 years, we are going to see many results of these studies being presented, and hopefully they can accelerate our quest to cure cancer once and for all.

Lastly, we will see these immune effector cells being used for nonlymphoid hematologic malignancies such as acute myeloid leukemia (AML) and for solid tumors. Several CAR clinical trials are now ongoing for relapsed AML, and TCR-enhanced therapies as well as the tumor-infiltrating lymphocytes in sarcoma and melanoma are getting very close to being approved. I am very excited for the future of immune effector cell therapies and the potential they [have] to change the landscape of cancer therapies. ■

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

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

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

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DARZALEX® (daratumumab) + Rd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma.

Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) and OS was a secondary endpoint.[1]

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

At follow-up of 28 months, **median progression-free survival (mPFS) was not reached** with DARZALEX® + Rd vs 31.9 months (95% CI, 28.9 to not reached) with Rd alone*

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

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

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

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

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

Secondary endpoint of overall survival (OS)[1,2]
After 56 months of follow-up:

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

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

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

- The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, upper respiratory tract infection, bronchitis, pneumonia, infusion-related reactions, peripheral edema, fatigue, asthenia, pyrexia, back pain, muscle spasms, dyspnea, cough, peripheral sensory neuropathy, and decreased appetite
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

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

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

- Most frequent TEAEs for DRd occurring in ≥30% of patients were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms‡
- Grade 3/4 infections were 43% for DRd vs 30% for Rd‡
- Grade 3/4 TEAEs occurring in ≥10% of patients were neutropenia (54% for DRd vs 37% for Rd), pneumonia (20% vs 11%), and anemia (17% vs 22%)‡

Treatment-emergent adverse events are reported as observed. These analyses have not been adjusted for multiple comparisons and no conclusions should be drawn.

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); FDA=U.S. Food and Drug Administration; HR=hazard ratio; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.
*Range: 0.0-41.4 months.[1,3]
†Kaplan-Meier estimate.[3]
‡Safety analysis set. TEAEs are defined as any adverse event (AE) that occurs after the start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

See the rolled-out data.
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IMPORTANT SAFETY INFORMATION (CONTINUED)

Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

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

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

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

Systemic Reactions

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

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

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

Local Reactions

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

DARZALEX® and DARZALEX *FASPRO*®: Neutropenia and Thrombocytopenia

DARZALEX® and DARZALEX *FASPRO*® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® or DARZALEX *FASPRO*® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX *FASPRO*®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX® and DARZALEX *FASPRO*®. Type and screen patients prior to starting DARZALEX® and DARZALEX *FASPRO*®.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Determination of Complete Response

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

DARZALEX® and DARZALEX *FASPRO*®: Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® and DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX *FASPRO*® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX *FASPRO*® and for 3 months after the last dose.

The combination of DARZALEX® or DARZALEX *FASPRO*® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

DARZALEX®: ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence ≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX® are neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

DARZALEX *FASPRO*®: ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX *FASPRO*® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS

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

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

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

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

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

cp-248517v3

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(11):1582-1596. doi:10.1016/s1470-2045(21)00466-6 **3.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med.* 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249 **4.** Kumar SK, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 MAIA study. Poster presented at: 64th American Society of Hematology (ASH) Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA.

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

DARZALEX can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported *[see Adverse Reactions]*.

In clinical trials (monotherapy and combination: N=2,066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

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

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

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

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

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

Neutropenia

DARZALEX may increase neutropenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

Thrombocytopenia

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

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

Interference with Determination of Complete Response

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

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX can cause fetal harm when administered to a pregnant woman. DARZALEX may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose *[see Use in Specific Populations]*.

The combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

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

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

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

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

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

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

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

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

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

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

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

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

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX *[see Clinical Studies (14.2) in Full Prescribing Information]*. Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd).

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

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

Table 3: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

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

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

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

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

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

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

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

Herpes Zoster Virus Reactivation

Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

Infections

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DVd: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DPd: 28%; DKd[a]: 37%, Kd[a]: 29%; DKd[b]: 21%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%; VTd: 20%.

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

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%; DKd[a]: 5%, Kd[a]: 3%; DKd[b]: 0%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

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

Hepatitis B Virus (HBV) Reactivation

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

Other Clinical Trials Experience

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

Nervous System disorders: Syncope

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products may be misleading.

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, 0.35% (6/1,713) of patients developed treatment-emergent anti-daratumumab antibodies. Of those, 4 patients tested positive for neutralizing antibodies.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX *in utero* until a hematology evaluation is completed.

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients *[see Adverse Reactions]*. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing, itching, and blurred vision *[see Warnings and Precautions]*.

Neutropenia

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

Thrombocytopenia

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

Interference with Laboratory Tests

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

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions]*.

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

Embryo-Fetal Toxicity

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

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

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

Hereditary Fructose Intolerance (HFI)

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

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

For patent information: www.janssenpatents.com

cp-271933v4

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

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids *[see Dosage and Administration (2.5) in Full Prescribing Information].* Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions *[see Dosage and Administration (2.5) in Full Prescribing Information].*

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

Local Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone *[see Adverse Reactions].* Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

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

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

Thrombocytopenia

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

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

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations].*

The combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide or pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References (15)].* The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions].*

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

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADES *[see Clinical Studies (14.2) in Full Prescribing Information].* Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

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

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

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

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

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

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

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

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

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

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 819 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 812 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

Postmarketing Experience

The following adverse reactions have been identified with post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System: Anaphylactic reaction, Systemic administration reactions (including death)

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

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

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

Of the 214 patients who received DARZALEX FASPRO as combination therapy with pomalidomide and dexamethasone or DARZALEX FASPRO as combination therapy with lenalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma, 43% were 65 to <75 years of age, and 18% were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=85). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

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

Interference with Laboratory Tests

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

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions]*.

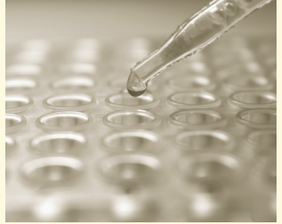
Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

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

For patent information: www.janssenpatents.com

cp-267681v3



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A reputation of providing world-class cancer care and groundbreaking research.

Together in partnership with IU School of Medicine, IU Health Medical Center provides world-class care and is known for leadership and groundbreaking research in the prevention, detection and treatment of cancer, notably breast, colon, pancreatic, genitourinary and hematologic cancers.

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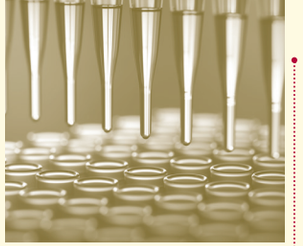

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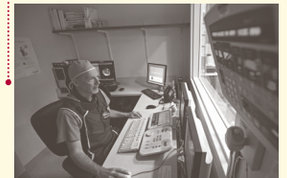
Pioneers on the leading edge of cancer care.



Indiana University Health

Over a century of clinical breakthroughs and excellence in treating every form of cancer.

1887
Indiana University School of Medicine established what is believed to be the country's first department of urology
founded by William N. Wishard, MD

1960
Pioneered the surgical technique of retroperitoneal lymph node dissection (RPLND) for patients with testis cancer
by John Donohue, MD

1970s
Led the country in developing and refining the medical approach to testis cancer

Developed the treatment and cared for first patient with testis cancer through cisplatin-based chemotheraphy
by Lawrence Einhorn, MD

Physicists and engineers at Indiana University School of Medicine pioneered high intensity focused ultrasound (HIFU) for treatment of prostate cancer
by Naren Sanghbi

1987
Use of Indiana Pouch for patients with bladder cancer or other urologic conditions published
by Richard Bihrle, MD and others at Indiana University School of Medicine

The first population based study for screening colonoscopy performed in the United States
by Douglas Rex, MD

1988
The first cord blood transplant made possible by the basic scientific proof-of-concept research at IU School of Medicine
by the late Hal Broxmeyer, PhD

1992
The National Cancer Institute (NCI) awards a planning grant to IU School of Medicine for a cancer center, establishing the Indiana University Cancer Center

1999
The IU Cancer Center earns National Cancer Institute designation.

2006
The IU Cancer Center becomes the Indiana University Melvin and Bren Simon Cancer Center to reflect the philanthropic support of Melvin and Bren Simon

2007
The Komen Tissue Bank is established at Indiana Univeristy Melvin and Bren Simon Cancer Center

First to publish on HIFU treatment for prostate cancer in the U.S.
by Michael Koch, MD and Thomas Gardner, MD

2010
One of the first five programs in the country to initiate robotic surgery for the pancreas, bile ducts and gallbladder

2016
One of the first in the U.S. to pioneer PSMA guided imaging for prostate cancer
Clint Bahler, MD

One of the first to perform focal HIFU procedure for treatment of prostate cancer
Michael Koch, MD

2017
Pioneered the regimen of high-dose chemotherapy with autologous peripheral-blood stem-cell transplantion for relapsed germ cell tumors
by Nabil Adra, MD, Rafat Abonour, MD, Sandra K. Althouse, MD, Costantine Albany, MD, Nasser H. Hanna, MD, and Lawrence H. Einhorn, MD

2019
The IU Simon Cancer Center earns Comprehensive Cancer Center status, the NCI's highest designation

2021
New England Journal of Medicine published findings on preventing a common complication to lifesaving blood stem cell transplantation in leukemia, acute graft-versus-host disease (GVHD)
Sherif Farag, MD, PhD

2022
The Indiana University Melvin and Bren Simon Comprehensive Cancer Center becomes a member of the National Comprehensive Cancer Network

2022
IU Health completed the first study using tumor gene fingerprints to define therapy in patients with high-risk disease for breast cancer

Indiana University Health