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SKIN CANCER

A Rare Case of Metastatic Spiradenocarcinoma With *CDKN2A* Mutation

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EGFR+ mNSCLC WILL FIND THE BACK ROADS

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

Staying ahead of *EGFR*+ mNSCLC is important

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

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

Burden of *EGFR*+ mNSCLC mutations limits survival

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

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

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

Acquired resistance drives disease progression[8]

up to 50%

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

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

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

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Our Board Members Have Been Busy!

Take a look to see what they've been up to.

John L. Marshall, MD

Gastrointestinal Cancer Editorial Board Member

Marshall has been inducted into the 12th Annual Giants of Cancer Care presented by *OncLive*®, a sister brand of *ONCOLOGY*. Currently, Marshall Marshall is the director of the Otto J. Ruesch Center for the Cure of Gastrointestinal Cancers. The organization is focused on improving the lives of patients with gastrointestinal cancer through research, advocacy, and personalized medicine. Congratulations Dr Marshall on this amazing achievement!

The Giants of Cancer Care Award ceremony took place prior to the 2024 American Society of Clinical Oncology Annual Meeting in Chicago, Il. To view the full list of inductees or nominate a leader or mentor in oncology visit giantsofcancercare.com

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ONCOLOGY is seeking to expand its list of ad hoc reviewers to provide constructive feedback on manuscripts that have received initial editorial approval. Comments and criticisms are a necessary and invaluable part of the journal's process, and our need for more willing experts grows in step with the journal.

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Current Applications and Future Use of Artificial Intelligence in Oncology

Neil M. Iyengar, MD,
Associate Attending Physician,
Breast Medicine Service
Memorial Sloan Kettering
Cancer Center
New York, NY

Nearly all areas in our lives and the lives of our patients are impacted by the growing use of artificial intelligence (AI), whether we are explicitly aware of it or not. In medicine, AI-based tools have already been clinically implemented across a variety of specialties, such as radiology, pathology, and dermatology. Significant growth in capabilities and an increase in the associated applications have propelled AI use from predominantly diagnosis and screening to prognostication, therapeutic monitoring, and even treatment selection. Leveraging the increasing availability of "big data" sets, AI use in the research setting has expanded to include novel applications for radiographic and histologic assessments, drug discovery and development, novel biomarker and genomic prediction algorithms, and more. Such applications have further expanded the possibility of developing tumor-agnostic therapeutics targeted to novel genomic and/or microenvironment signatures. Finally, the use of AI at the systems level has the potential to improve health care delivery across a growing number of diverse communities affected by cancer.

Digitization of histology slides has also expanded the use of AI in pathology. The Cancer Genome Atlas is one of the largest biorepositories; it contains more than 10,000 digital pathology images across more than 20 types of cancers with associated clinical and genomic data. Several studies have utilized it and other repositories to develop diagnostic, prognostic, and predictive AI models that identify subtle histologic features and patterns. This approach has led to the development of novel digital pathology and genomic biomarkers that could be leveraged for diagnosis and treatment monitoring purposes once validated. For example, with the increasing use of immunotherapy and recently approved antibody-drug conjugates (eg, trastuzumab deruxtecan; Enhertu), AI technology could assist treatment selection by accurately quantifying PD-1 expression in the tumor microenvironment or tumor cell expression of HER2 at low or even ultralow levels in digital pathology images. Finally, the use of AI technology for analyzing genomic biomarkers (apart from histology) has been an exciting area of development for treatment selection and may be pivotal for advancing novel screening technologies that rely on genomic patterns detected in cell-free DNA—ie, the coveted "cancer screening blood test."

Perhaps one of the most exciting but challenging arenas for the use of AI in oncology is treatment selection and monitoring. Several platforms are currently in use for early drug discovery, which involves the processing of clinical, genomic, and proteomic data to identify therapeutic targets and associated molecule selection for further development. In the clinical setting, AI tools can assist with predicting treatment resistance based on patient and tumor features as well as ex vivo testing on biopsy samples. Incorporation of novel biomarker datasets beyond bulk tumor sequencing, such as single-cell sequencing to differentiate tumor and microenvironment components, may reduce the need for tissue samples in future AI-based treatment prediction tools. Individualized drug dosing is yet another exciting potential use of AI in oncology, and current tools under development utilize large datasets that include host factors (eg, body mass index, comorbidities, functional status), patient-reported outcomes, and adverse effect profiles in addition to traditional clinicopathologic features.

Despite AI's promise, some key challenges need to be addressed for AI technologies to continue expanding in clinical implementation. First, datasets—including digitized images—must be standardized in terms of variables, quality, processing and storage procedures, and other parameters to maximize the potential of deep learning. Next, many AI-derived diagnostic and prediction models require validation before larger-scale clinical implementation is possible. To include broader, more diverse data sets in AI modeling, transparency and trust regarding privacy and data use must be well established. The legal and ethical implications of AI use in medicine are evolving and should continue to be centrally addressed as AI applications grow. Related to privacy and trust, it is imperative that underrepresented and minority populations are included in learning datasets or that there are dedicated datasets that can be included in machine learning to generate equity in the application of AI. Finally, the framework in which AI is implemented should augment rather than overshadow oncologists and patient-centered decision-making. The potential for AI in oncology is highly promising across multiple domains, yet it is human ingenuity that is required to maximize this potential. ■

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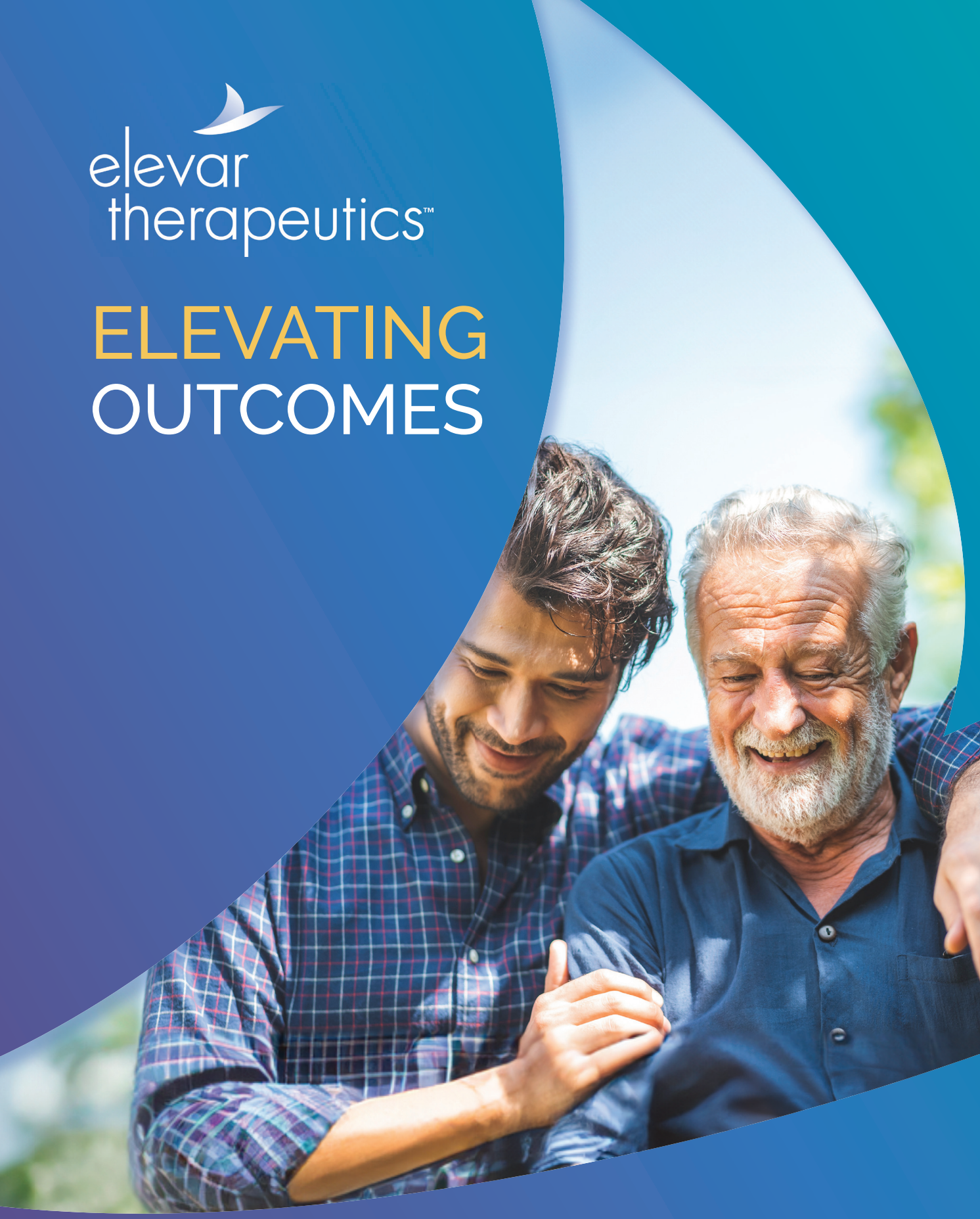

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SKIN CANCER

A Rare Case of Metastatic Spiradenocarcinoma With *CDKN2A* Mutation

Jonathan Q. Trinh, MD; Shristi Upadhyay Banskota, MBBS; Alissa S. Marr, MD

ABSTRACT Spiradenocarcinomas are rare malignant skin adnexal tumors. We describe a novel case of a patient with an aggressive *CDKN2A*-mutated spiradenocarcinoma who responded to a CDK4/6 inhibitor. This case highlights the unique nature of spiradenocarcinomas as well as the potential benefit of targeted therapy.

A 70-year-old woman with no prior oncologic history presented with a rapidly enlarging growth on the first dorsal web of her right hand. She initially noticed it 2 years prior and received a diagnosis of ganglion cyst. A few months prior to presentation, she noticed the growth had reddened with increased vascularity and grown to approximately 1.3 × 2.5 cm. At this time, an excisional biopsy was pursued. Pathology results demonstrated a spiradenoma with adjacent cords and nests of atypical cells with a high nuclear-to-cytoplasmic ratio and areas of tumor necrosis. Immunophenotyping was positive for SOX10 and GATA3 and negative for chromogranin, synaptophysin, and CK20. Based on the histologic features and immunohistochemical staining, the diagnosis of spiradenocarcinoma was made. This was followed by a wide local excision with 1.5- to 2-cm margins around a 5-cm transverse incision tumor bed along with sentinel lymph node biopsy after lymphoscintigraphy mapped to a deep right axillary level 2 node. Pathology of the primary site confirmed residual spiradenocarcinoma present in the center of the specimen, extending to the deep margin. Staining of the right axillary lymph node demonstrated a 5.5-mm focus of metastatic carcinoma with extracapsular extension.

A staging PET-CT scan only showed postoperative changes with no distant disease. Comprehensive level 1 to 3 radical axillary lymph node dissection was performed and showed no evidence of carcinoma. One month later, the patient developed a 1- to 2-cm mobile, palpable nodule in the thenar area on the dorsal aspect of her right hand. Punch biopsies of this mass showed spiradenocarcinoma at deep and lateral margins. The PET-CT scan did not demonstrate any other sites of disease. This was followed by a resection of the recurrent tumor, 4 to 5 cm deep into the hand with 2-cm margins, along with excisional biopsies of 2 epitrochlear lymph nodes. Pathology did not show any evidence of malignancy. A repeat ultrasound of the epitrochlear area 3 weeks later showed an abnormal right epitrochlear lymph node, suspicious for metastasis. A biopsy demonstrated malignant cells morphologically similar to the previously resected spiradenocarcinoma. Resection of epitrochlear lymph node with deep forearm dissection showed a 1.3-cm focus of metastatic spiradenocarcinoma with the presence of focal extranodal soft tissue, positive for SOX10 and GATA3.

Jonathan Q. Trinh, MD; Shristi Upadhyay Banskota, MBBS; Alissa S. Marr, MD
Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE

Shristi Upadhyay Banskota, MBBS; Alissa S. Marr, MD
Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE

The patient was treated with 5000 cGy of adjuvant radiation therapy to the epitrochlear region. The patient opted to forgo radiation treatment to the primary tumor site due to concerns of impairment with her surgical skin graft. The PET-CT scan did not show recurrence or metastases at that time. Six months later, a repeat scan showed a new hypermetabolic mediastinal lymph node concerning for metastatic disease. Flexible bronchoscopy and video-assisted thoracoscopy intraoperatively showed several pleural and parenchymal nodules, leading to a right lower lobe wedge resection and 2 pleural biopsies. The pathology of all samples returned as metastatic spiradenocarcinoma.

FoundationOne testing was performed and demonstrated the presence of a nonsense-substitution *CDKN2A* mutation. PD-L1 testing was negative (<1%), tumor mutational burden was low, and microsatellite status was stable. The patient was then started on paclitaxel 200 mg/m^2 and carboplatin of area under the curve (AUC) 6 every 3 weeks. Interval CT scans showed stable disease, and the regimen was stopped after 4 cycles due to grade 3 peripheral neuropathy. A follow-up PET-CT scan approximately 3.5 months after the patient stopped chemotherapy showed integral progression of multifocal lesions with new mediastinal, right hilar, right lung parenchyma, right pleural, and right lateral chest wall lesions with a maximum standard uptake value of 14.5. The patient was then treated with carboplatin AUC 6 and pemetrexed 500 mg/m^2. After 4 cycles, a PET-CT scan showed interval progression of extensive right lung parenchymal, right pleural, and right chest wall metastatic disease.

Given the finding of *CDKN2A* mutation, the patient was enrolled into the palbociclib arm of the nonrandomized phase 2 TAPUR trial (NCT02693535), which is exploring targeted anticancer drugs for patients with potentially actionable genomic alterations.[1] The patient received 125 mg daily of palbociclib for 21 days on a 28-day cycle.[1] CT scans of the chest, abdomen, and pelvis after 2 cycles showed decreased size of pulmonary nodules, decreased pleural thickening, decreased size of right hilar mass, decreased mediastinal lymphadenopathy, and overall response to treatment. During the third cycle, she developed chest pain and dyspnea. CT angiogram showed severe narrowing of the right upper lobe pulmonary artery branch and near complete occlusion of the right anterior lower lobe bronchus due to tumor compression, along with increased size and number of bilateral pulmonary nodules. Meeting RECIST criteria for disease progression, palbociclib was discontinued and she was started on palliative radiation to the right hilum and mediastinum. PET-CT scan showed extensive worsening of metastatic disease with extensive new metastases throughout the spine, liver, spleen, and skeleton, along with worsening of thoracic metastatic disease. The patient elected to enroll in hospice and was aged 73 years when she died, 5 years after initial diagnosis.

Discussion and Literature Review

Spiradenocarcinomas are rare malignant adnexal neoplasms arising from eccrine sweat glands, often from prior benign spiradenomas.[2] Histologically, they often exhibit areas of spiradenoma architecture with abrupt transition to malignant morphology, including evidence of nuclear atypia, increased mitotic activity, and necrosis.[3] They typically stain positive for most cytokeratins, with CK5-7 being the most frequently reported marker.[2]

Since spiradenocarcinoma's first description in 1972, fewer than 200 cases have been reported, including fewer than 30 metastatic cases.[2,4] Due to its rarity, no consensus on treatment guidelines currently exists. Although surgical resection for nonmetastatic disease with lymph node dissection of tumor-involved regional lymph nodes has demonstrated success, treatment for metastatic disease has been proven to be far more difficult.[5] Tamoxifen has shown significant success in a patient with estrogen receptor–positive spiradenocarcinoma.[6] Pembrolizumab has demonstrated a partial benefit in patients with positive PD-L1 expression.[6,7]

The *CDKN2A* tumor suppressor gene, first identified in 1994, was previously reported with different names (*p16ink4, p16ink4a, CDK41, MTS1,* and *p16*).[8] Loss of this gene contributes to the bypass of critical senescent signals and subsequent progression to malignant disease.[9] Its mutation or inactivation has been implicated in many types of cancers, such as melanoma and pancreatic cancer.[8]

Xenograft models of palbociclib, an oral low-nanomolar reversible inhibitor of CDK4/6, showed that tumor xenografts lacking *CDKN2A* were sensitive to the drug.[10] The role of *CDKN2A* levels in gauging response to targeted therapies has only been marginally explored, but now with highly targeted compounds antagonizing this pathway in clinical use, examining the impact of these levels in future studies may be beneficial for patient stratification. For instance, elevated *CDKN2A* levels may suggest a poor response to these compounds, aiding with patient exclusion from these treatments.[9]

To our knowledge, we present the first case of *CDKN2A*-mutated metastatic spiradenocarcinoma. After 2 regimens of combined chemotherapy failed, our patient was started on palbociclib, which led to improvement in multiple metastatic lesions. Her disease ultimately progressed, and our patient died. However, spiradenocarcinoma is incredibly rare and lacks clear answers on treatment in advanced disease. This case highlights the benefit of targeted therapy, if applicable, as systemic therapy. ■

CORRESPONDING AUTHOR
Jonathan Q. Trinh, MD
Department of Internal Medicine
982055 Nebraska Medical Center
University of Nebraska Medical Center
Omaha, NE
Email: jtrinh@unmc.edu

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Advancing Thoracic Surgery With Robotics and Video-Assisted Strategies

Richard Lazzaro, MD
Chief, Thoracic Surgery, RWJBarnabas Health, Southern Region
Toms River, NJ

Developments in robotic-assisted surgery such as Ion robotic-assisted bronchoscopy may be game changers in the surgical management of lung cancer, according to Richard Lazzaro, MD.

In an interview with *ONCOLOGY*, Lazzaro talked about how minimally invasive tools such as Intuitive's Ion have made thoracic surgery more effective by reducing complications and time to intervention for patients. He also highlighted other potential applications of robotic video-assisted surgical tools coming down the road, which may reduce the variability in surgery and close the skill gaps among surgeons with different degrees of medical experience.

Lazzaro also focused on the importance of multidisciplinary collaboration in the context of selecting appropriate treatment strategies for this patient population. According to Lazzaro, teamwork among radiation oncologists, medical oncologists, pathologists, and other physicians on the multidisciplinary thoracic tumor board can help determine the best type of adjuvant therapy for patients.

Q / Monmouth Medical Center recently highlighted your use of the robotic-assisted platform Ion.[1] How has this tool impacted your practice?

Lazzaro / Lung cancer affects so many patients; there are more than 230,000 new diagnoses in the United States each year. In addition to patients with lung cancer, about 1.6 million [individuals] each year are found to have a nodule in the lung. When you look at those nodules, you want to determine whether they are suspicious or whether they can be followed. A large number of nodules are suspicious. You can do probability testing by looking at the size of the nodule to see if it's grown from previous scans, and if there has been any activity on PET scans, which assess the function of a nodule. Is it inert, or is it biologically active? Is it in a patient with chronic obstructive pulmonary disease? Is the patient older? Is the nodule in the upper lobe? Does the nodule have irregular borders called spicules? Did it grow in each direction with the same symmetric radial growth?

[The Ion platform can] utilize those tools to look at a nodule and determine whether it should not be observed and requires a biopsy. It gives you the ability to diagnose and add an additional tool called endobronchial ultrasound to stage [lung cancer]. In lung cancer, time to intervention is critical, and this robotic platform gives us a minimally invasive solution to lung biopsy. [Ion] overcomes some gaps [such as] traditional ways to utilize a bronchoscope, requiring the lesion to be in the central part of the chest. If it was a nodule in the periphery or the surface of the lung, where more than 70% of cancerous nodules are located, then the bronchoscopy couldn't biopsy that. We would require a CT scan–guided biopsy, which has a higher incidence of pneumothorax and bleeding.

This robotic platform gives us the ability to not only reach but [also] biopsy these nodules that are in the periphery of the lung and all the segments of the lung. It is a game changer for patients. In 2024, if you have a suspicious nodule, you should have some tissue on that [biopsied]. Now, for early lung cancer, there are times when we might forgo a biopsy. For the majority of patients, we want to have a biopsy before we make the treatment decision. Utilizing this technology and knowing the advances in systemic therapy and studies in immunotherapy, many patients nowadays are receiving treatment before

surgery. The ability to acquire tissue and do staging with fewer complications and up to a 95% chance of getting to that area and getting a diagnosis of cancer safely for patients gives us an opportunity to diagnose and treat patients earlier, which has always been shown to be beneficial in lung cancer. In essence, it's [a] quicker and less invasive [way to] get your diagnosis, your staging, and your treatment plan.

Q / What do current data or evidence show about the efficacy of Ion in this patient population?

Lazzaro / Data are operator dependent. How motivated are you, what tools do you utilize, and what lesions are you going after? If you go to biopsy something that's 3 cm, you're going to be up to 100% when getting a diagnosis on it. Sometimes, you may find smaller lesions that are under 10 mm that are more peripheral and challenging to get to. Additionally, does the operator confirm [the size by using] this robotic bronchoscopy platform and getting to the lesion?

I'm happy that we're over 95% successful in localizing the lesions. We utilize different tools, including fluoroscopy and body vision, which is utilizing the fluoroscopy machine while doing a simulated spin to develop a CT scan image to confirm that your biopsy instrument is in the lesion. The final tools that we use [are] something called radial EBUS [endobronchial ultrasound]. When you navigate to the lesion, you put a needle into it through a biopsy, and you take some of that fine-needle aspirate. As you're preparing it on slides for your pathologist, who's in the room with you, we're putting that radial EBUS probe in and we're looking for a signal that demonstrates that our tool is in the lesion. In addition to the bronchial ultrasound, fluoroscopy, and body vision, we take the material at the time of acquisition and have our pathologists look at the lesion material to make a diagnosis. We make sure we have enough to do all the molecular testing with next-generation sequencing for oncologists to make a treatment decision regarding systemic therapy.

Q / Are there any patients with lung cancer who may particularly benefit from treatment with Ion? Are there any patients for whom this approach would not be recommended?

Lazzaro / The patients who will get the biggest benefit are the ones for whom we're looking to give induction therapy. Being able to acquire a biopsy with Ion technology and having the pathologist there allows us…to confirm the disease stage and get all the pathology material in a very short period to make that treatment decision. For patients who are receiving induction therapy, it is our role to get tissue staging and molecular pathology.

> **"Anything that you can do to leverage technology to minimize the variability in surgery eliminates the skill gap so that novice surgeons may become as technically gifted as the intermediate surgeon or the master surgeon."**

The patients who would not benefit from undergoing bronchoscopy, in general, are the ones who have emphysema or contraindications. Emphysema is severe enough that they have low oxygen at baseline, so putting them under a general anesthetic would not be wise. It's the same thing if they have instability of their vital signs; maybe they have cardiac disease or a recent myocardial infarction or heart attack. Finally, if someone has a propensity toward bleeding or a bleeding disorder that needs to be addressed before the procedure is performed [they should not receive this treatment].

Q / Are there any other developments in robotic-assisted minimally invasive video-assisted thoracoscopic surgery that might hold promise in the field?

Lazzaro / Robotic surgery is a form of video-assisted thoracic surgery. We know that smaller incisions that preserve the concepts and the critical tenets of oncologic surgery never need to be changed. Doing maximal oncologic surgery in a minimally invasive way is the goal. With our system, we do more than 95% of our procedures as minimally invasive, usually with the Ion robot.

Future technology in the robot will include an augmented reality platform. We may have the ability to take a [patient's] imaging beforehand and have their CT scan with a 3-dimensional reconstruction alongside our operative field. The future of surgery will be much like when you drive your car and have GPS navigation and a highlighted map. The ability to recognize structures in the operating room and utilize the fusion of advanced imaging with the visual field will be an important consideration in the future. It is something that many companies are working on, and it will be a game changer.

Recently, Intuitive came out with its 5th-generation robot, [da Vinci 5].[2] You can see with 10 times the magnification and operate with 3 times the precision. You have more ability to move the instrument internally, and they described that with degrees of freedom. It's like having your hand inside the chest, and you can dissect the round structures. There's a whole field where you're operating,

and you can appreciate the tension and countertension that you apply to tissue to be able to perform surgery. The ability to manipulate a robotic instrument and be able to feel the tissue while you're controlling a $2 million robot is another game changer.

I believe that, in the future, the ability to record those movements of a surgeon's hands while an operation is being performed and the ability to observe a video recording of that operation will be used for training new physicians. They could watch a master surgeon perform an operation and have their hands strapped in. Not only would they see the operation, but their hands would be strapped into a machine that's taking their hands through the same movements that the master surgeon did. You would learn muscle memory and learn how to do those moves.

It's an exciting time because anything that you can do to leverage technology to minimize the variability in surgery eliminates the skill gap so that novice surgeons may become as technically gifted as the intermediate surgeon or the master surgeon. That's the goal of medicine: How can we get 99% of the people performing at the top 1%? That's by utilizing such technology to get a world of hyperperformers.

Q / How does multidisciplinary care factor into your treatment of patients with lung cancer at your clinic?

Lazzaro / Advances in lung cancer management have been tremendous. More patients can be treated [and experience] improvements in long-term survival. A lot of that comes from having a multidisciplinary thoracic tumor board that includes medical oncologists, radiation oncologists, pathologists, radiologists, pulmonary physicians, and thoracic surgeon oncologists. When you can review a [patient's] history, images, and pathology and relate them to clinical and pathologic staging, you can take that [patient's] current extent of disease and confirm the collective decision of the group in how you will treat these patients. Then you get to follow up and represent those patients for their response to treatment and then determine their next course of care. Sometimes it's surgery first, with no adjuvant therapy and just surveillance. Sometimes a patient has very early cancer and they're not a great surgical candidate because of an unhealthy heart, lungs, kidneys, or liver, making them a candidate for stereotactic body radiation therapy, stereotactic ablative radiotherapy, or CyberKnife.

A lot of patients are going to become candidates [for surgery] because they may [have] stage II or III disease, and they're going to become candidates for induction therapies. Our oncologists would do chemotherapy and immunotherapy before getting repeat imaging and discussing it again. It takes a little more work to get the team together, but we're not looking at it as work; we're looking at it as planning to develop the best treatment approach for patients. You want to take care of patients like that patient was your family member, but you are objective. That's the beauty of a multidisciplinary approach: It factors into all our patients. Maybe not every patient needs to be presented at a formal multidisciplinary tumor board, but every patient is discussed among thoracic oncologists, medical oncologists, and radiation oncologists. There is a shared decision-making that is disseminated and spoken with the patient so that they understand they have not one person but a team of physicians taking care of them.

Q / What do you hope your colleagues take away from this discussion?

Lazzaro / The management of lung cancer is different than it was even 5 years ago. If we can detect lung cancer early, we have options for treating patients today that we never had before. These options may significantly improve [chances for]a cure.

Speak with your patients, get them CT scans, and get them evaluated by some type of nodule clinic or a thoracic oncology clinic that includes pulmonary or medical oncology, radiation oncology, thoracic surgery, or all of the above. If we find things early, patients are easier to treat. If we find things more advanced, let's get that Ion bronchoscopy in. Let's do the mediastinal staging. Let's get the molecular pathology. Let's get them a multidisciplinary approach, some induction therapy, and a reassessment. This is the time when we really need to make a huge difference in lung cancer. ■

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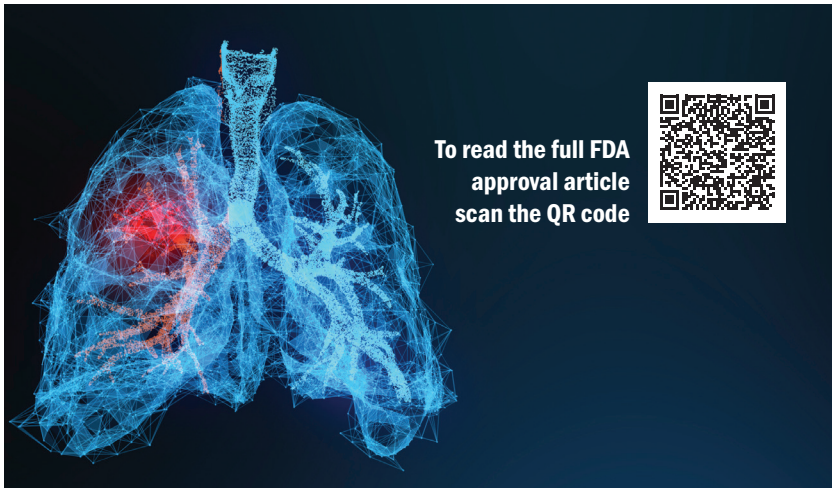
THE NEED-TO-KNOW

Amivantamab Plus Chemotherapy in Non-Small Cell Lung Cancer

In March 2024, the FDA approved frontline amivantamab-vmjw (Rybrevant) in combination with carboplatin and pemetrexed for adult patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) harboring *EGFR* exon 20 insertion mutations.[1] *ONCOLOGY* spoke with Misako Nagasaka, MD, PhD, associate clinical professor, Division of Hematology/Oncology, University of California, Irvine, and thoracic malignancies editorial advisory board member of *ONCOLOGY*, regarding the recent approval.



Q / How did the results of the PAPILLON trial help lead to the approval?

Nagasaka / The phase 3 PAPILLON study [NCT04538664] was a study dedicated to patients with *EGFR* exon 20 insertions. This is a rare subtype of *EGFR* mutations that do not respond to the usual *EGFR* tyrosine kinase inhibitors, which is the default for sensitizing mutations [such as *EGFR*] exon 19 deletion or L858R. PAPILLON compared amivantamab plus chemotherapy with chemotherapy alone, and it [showed] positive [results]. Subsequently on March 1, 2024, that PAPILLON regimen gained FDA approval.

A total of 308 patients [were randomly assigned,] with 153 receiving amivantamab plus chemotherapy and 155 receiving chemotherapy alone. The progression-free survival [PFS] was significantly longer in the amivantamab plus chemotherapy group than in the chemotherapy [alone] group. The median PFS was 11.4 months in the amivantamab plus chemotherapy group and 6.7 months in the chemotherapy group. The hazard ratio for disease progression or death was 0.40. The overall response rates were 73% vs 47%, respectively. In the interim overall survival analysis, which was only at 33% maturity, the hazard ratio for deaths for amivantamab plus chemotherapy as compared with chemotherapy was 0.67. It's trending in the right direction.

Q / What patient population is specified for this treatment combination?

Nagasaka / This is for [patients with] *EGFR* exon 20 insertion mutations. This indication is for the first line, and there are some patients who have not been treated previously, based on the forest plots that were available in *The New England Journal of Medicine* publication.[2] Among all of the subgroups, whether it be gender, race, history of

smoking, or having brain metastases or not, all of the subgroups benefited more from amivantamab and chemotherapy.

Q / Were any significant adverse effects (AEs) observed in the combination compared with standard-of-care chemotherapy?

Nagasaka / The predominant toxicities or AEs associated with amivantamab and chemotherapy were reversible hematologic changes and *EGFR*-related toxic events such as rash. Only 7% of patients discontinued amivantamab owing to AEs. When we think of amivantamab, we might think about infusion-related reactions. The rate of this was 42% in those in the amivantamab and chemotherapy group, and it was lower than what we saw in the phase 1 CHRYSALIS study [NCT02609776], probably due to the premedications that we give for chemotherapy.[3] The rates of chemotherapy-related AEs such as febrile neutropenia were similar, so [there were] no additional chemotherapy-related AEs. Having treated patients on the combination using amivantamab, I feel that long-term rash management is most important.

Q / How did the efficacy of this combination compare with other targeted therapies that are now emerging for this population in the frontline setting?

Nagasaka / Looking at the PFS, this combination of amivantamab plus chemotherapy for first-line therapy and patients with *EGFR* exon 20 insertion is a fantastic result that we have. However, it is intravenous therapy, and it is combined with chemotherapy. We have to be cognizant of that. The overall survival data are not matured yet, but hopefully, we will see more data come through for the overall survival as well. The difficulty is that outside of EXCLAIM-2 [NCT04129502], which was the phase 3 study using mobocertinib [Exkivity] vs chemotherapy,[4] I do not believe we have mature data on first-line specific treatment options for patients with *EGFR* exon 20 insertion, and as we all know, the EXCLAIM-2 study failed. There was no difference between using mobocertinib vs chemotherapy in the frontline setting.

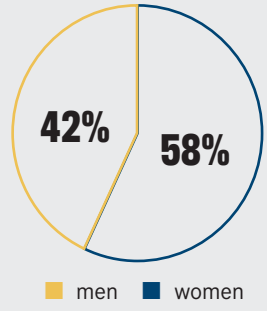
Q / What are the next steps for this combination?

Nagasaka / Mobocertinib did fail the study, but it was an oral regimen. Having a pill option is an advantage to patients. Hopefully, the axis of the medications will get easier. As far as amivantamab and PAPILLON go, [researchers] are developing a subcutaneous version of amivantamab. That might decrease the time required to be at the infusion site, although we're combining this with chemotherapy anyway. It's not going to be a chemotherapy-free option. Overall, the long-term toxicities of rash management are…important to find out. ■

STATS AT A GLANCE

308
Patients Enrolled

Men and Women Enrolled

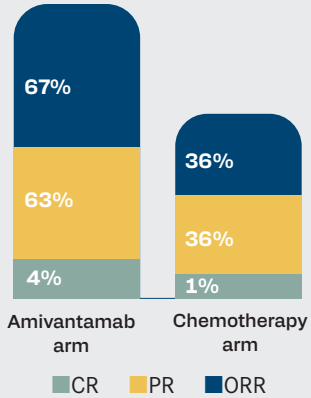


Progression-Free Survival

11.4 MONTHS
Amivantamab plus chemotherapy arm

6.7 MONTHS
Chemotherapy arm

Response Rates in the PAPILLON Trial



CR, complete response; ORR, overall response rate; PR, partial response

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NON–SMALL CELL LUNG CANCER

Amivantamab Plus Chemotherapy in *EGFR* Exon 20+ NSCLC

ONCOLOGY spoke with Tammy McClellan, PharmD, about the recent approval of amivantamab-vmjw (Rybrevant) plus chemotherapy. She focused on adverse effects patients may experience from the combination and how administration and dosing may play a role in any challenges observed.

PRODUCT PROFILE

DRUG NAME: Amivantamab-vmjw

DATE OF APPROVAL: March 1, 2024[1]

INITIAL INDICATION: Frontline therapy for locally advanced or metastatic non–small cell lung cancer harboring *EGFR* exon 20 insertion mutations

DOSAGE AND ADMINISTRATION[2]: The first dose is split between days 1 and 2

WEIGHT LESS THAN 80 KG: 1400 mg weekly for 4 weeks and then given every 3 weeks starting at Week 7 at the 1750 mg dose

GREATER THAN OR EQUAL TO 80 KG: 1750 mg weekly for 4 weeks and then given every 3 weeks starting at Week 7 at the 2100 mg dose

HOW SUPPLIED: Intravenous administration via a peripheral line on Weeks 1 and 2 followed by intravenous administration via a central line

PIVOTAL CLINICAL TRIAL: Phase 3 PAPILLON trial (NCT04538664)[3]

ELIGIBLE PATIENTS

Have an ECOG performance status of 0 or 1, agree to genetic characterization of tumor status through pretreatment biopsy and periodic blood samples for analysis of tumor mutation in the bloodstream.

CHEMOTHERAPY ADMINISTRATION

Arm A received 500 mg/m^2 of pemetrexed on day 1 of each 21-day cycle plus carboplatin for up to 4 cycles. Carboplatin area under the curve of 5 mg/mL was given intravenously on day 1 of each 21-day cycle. Arm B received matched treatment.

PRIMARY END POINT

Progression-free survival via RECIST v1.1 assessed by blinded independent central review.

KEY SECONDARY END POINTS

Objective response rate, duration of response, overall survival.

EXPERT COMMENTARY BY

Tammy McClellan, PharmD

Clinical Oncology Pharmacist, Riverside Healthcare, Kankakee, IL

Q / How is amivantamab dosed and administered alongside chemotherapy in the first-line setting?

McClellan / This is a weight-based drug, and the cutoff is 80 kg. To be more specific, if you're less than 80 kg, or if you're greater than or equal to 80 kg. [It's administered as] cycle 1 days 1, 2, 8, and 15. During cycle 1, day 1 all patients receive 350 mg of amivantamab.[For patients who weigh] less than 80 kg, 1050 mg on day 2 followed by 1400 mg weekly for 3 weeks during cycle 1, days 8 and 15, and cycle 2 day 1. Then it is given every 3 weeks

starting at Week 7 which is the same as cycle 3 Day 1 at the 1750 mg dose, with no doses during weeks 5 and 6. For patients who weigh greater than or equal to 80 kg, 1400 mg is given on day 2 followed by 1750 mg weekly for 3 weeks during cycle 1, days 8 and 15, and cycle 2, day 1. It is then given every 3 weeks starting at week 7 which is the same dose as cycle 3 day 1 at the 2100 mg dose, with no doses on weeks 5 and 6.

Q / Are there any adverse effects or toxicities that clinicians should be aware of with amivantamab?

McClellan / There is a higher incidence of infusion-related reactions. That is the reason why you would split your initial dose between days 1 and 2. It is also recommended that you do not use a central line for the first 3 doses- a peripheral line is used instead. This is a conscious effort to reduce the severity of infusion-related reactions. Other reactions include interstitial lung disease/pneumonitis, ocular toxicities (keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, uveitis)-which seem to be more and more common with the newer immunotherapy agents, dermatologic adverse reactions like dermatitis, pruritus, and dry skin. This drug may cause photosensitivity so patients would want to avoid/minimize exposure. This drug can cause nail toxicity, neurologic disorders, adverse gastrointestinal effects, peripheral neuropathy, mucositis, edema, fatigue, weight loss, and musculoskeletal pain. Amivantamab does have an adverse reaction of hemorrhoids. We hear about constipation, but not necessarily hemorrhoids and I wanted to point that out.

Q / What laboratory monitoring and treatment strategies are recommended for patients receiving amivantamab plus chemotherapy?

McClellan / The standard complete blood count is needed to account for the different types of myelosuppression and/or infection. The comprehensive metabolic panel is needed to assess the various electrolyte imbalances, serum glucose abnormalities, hepatotoxicity, nephrotoxicity, albumin, magnesium and gamma-glutamyl transferase (GGT) levels. GGT levels can be controversial but I would like to mention that so Healthcare Providers can make their own decisions in light of the reported data.

Q / Are there any significant drug interactions between amivantamab and commonly used medications in patients with cancer?

McClellan / In the package insert,[2] there are no drug interactions listed. However, it is given in combination with pemetrexed [and carboplatin], which do have known interactions with nonsteroidal anti-inflammatory drugs. When given in combination [with another drug], I would look at the possibilities of synergistic adverse effects by assessing the administration of concurrent hepatotoxic and nephrotoxic agents. However, [because] it does have some parallel toxic effects, I would monitor any other concurrent hepatotoxic drugs that may be administered, just for that synergistic effect, if you will.

Q / Because this treatment was recently approved, have there been any access or logistical challenges associated with administering amivantamab plus chemotherapy?

McClellan / I would like to mention the infusion times and likelihood of the heightened incidence of the infusion reactions. The precautions that we are aware of include initial split dosing, several administration rates, and long infusion times until you reach the plateau-you have to take your time with this. With that, just be diligent and watch your patient. You most definitely should have a 1:1 nurse-to-patient ratio, if not a 2:1, so one [nurse can administer] while the other one is helping out [during the infusion], to at least get through the first administration on days 1 or 2.

[This treatment is given in the outpatient setting], however, [it is important to have] everything in place, making sure the premedications are given within the recommended times: diphenhydramine at 25 mg to 50 mg or equivalent and acetaminophen at 650 mg to 1000 mg- prior to each infusion, dexamethasone at 20 mg or equivalent- for the first infusion followed by dexamethasone 10 mg or equivalent for the second dose and thereafter optional use per the manufacturer.

Consideration of an H2 blocker to provide a different mechanism of action to combat infusion reactions is warranted. We express to the patient the importance of if you feel anything report it.

Q / How might the role of amivantamab or similar targeted therapies evolve in the treatment landscape for *EGFR*-mutated NSCLC?

McClellan / I am biased when it comes to non–small cell lung cancer as I would describe this disease state as one of the best examples when it comes to implementing precision medicine, targeted therapy, and genetic testing through the use of identifying relevant biomarkers and all that oncology health care providers are trying to accomplish. Fighting this cancer by treating it specifically, limiting the adverse effects, and giving the patient the best chance at obtaining a cure or an improvement in their quality of life. It excites me to have a great collaboration of precision medicine and targeted therapy for the individual all while providing tailored health care. ■

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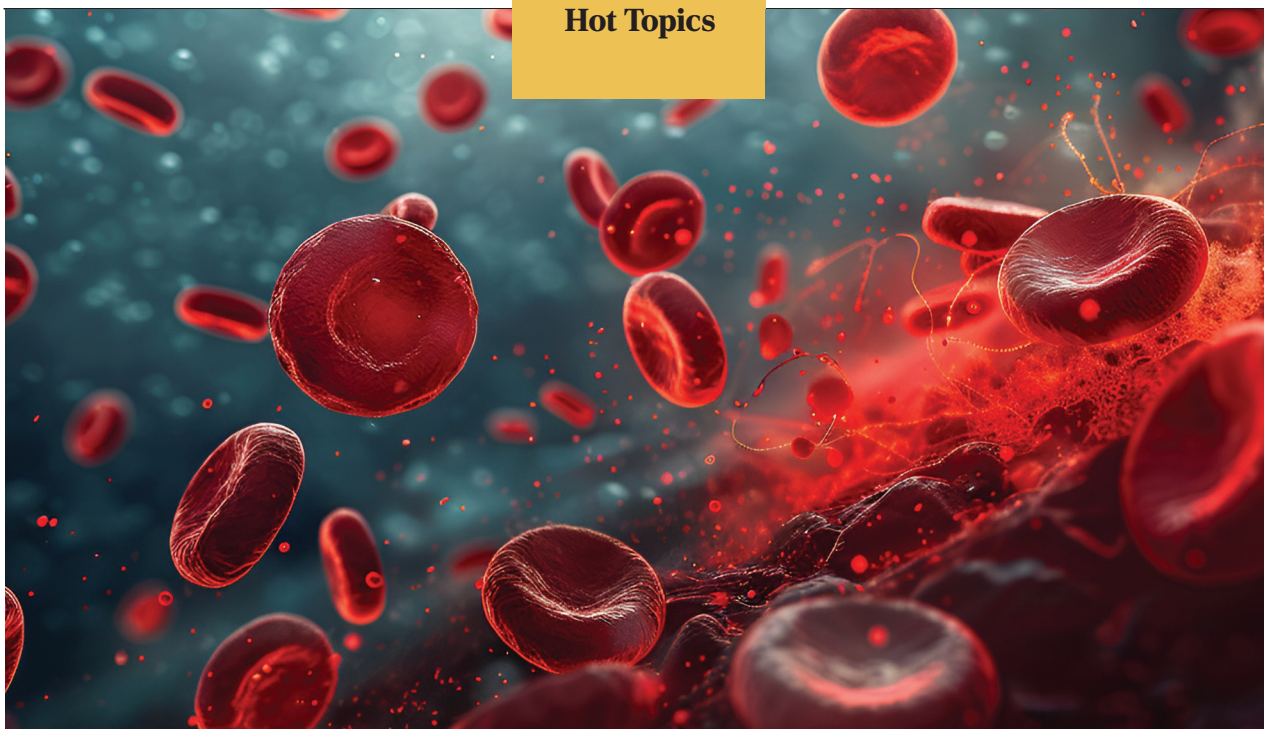

Continued Success of Venetoclax in t(11;14) Multiple Myeloma Despite Negative Trials

Zachary M. Avigan, MD; and Joshua Richter, MD, FACP

Multiple myeloma (MM) is a plasma cell neoplasm that remains incurable despite significant recent advances in novel and immune-based therapies.[1] Although cytogenetic assessment has improved disease classification and prognostication,[2] there are no currently approved mutation-targeted agents for myeloma. The t(11;14) chromosomal translocation between the *IGH* locus and *CCND1* represents the most common primary translocation in plasma cell disorders, found in 16% to 24% of patients with MM and approximately 50% of patients with light chain amyloidosis.[3] Patients with t(11;14) disease have increased dependence on B-cell lymphoma 2 (BCL-2) for cellular survival, which represents a rational therapeutic target for relapsed/refractory MM (RRMM).[3] However, despite efficacy in early models, venetoclax (Venclexta)–based therapy has yielded 2 negative phase 3 trials with an increased mortality signal and incidence of severe infections,[4,5] and it was not approved for use in MM by the FDA. Nonetheless, venetoclax remains in the National Comprehensive Cancer Network guidelines as a therapeutic option for patients with RRMM with t(11;14) and continues to be widely used off-label.[6,7] We here review the mechanism of venetoclax activity in t(11;14) disease, the rationale for off-label use, and ongoing trials of novel venetoclax combination therapies.

BCL-2 Inhibition in t(11;14) Disease

The BCL-2 family regulates cellular apoptosis and survival through interactions between antiapoptotic (BCL-2, BCL-xL, and MCL-1) and proapoptotic proteins (eg, BIM, NOXA), which modulate mitochondrial pore formation via the activity of BAX and BAK.[8] Both normal plasma cells and typical MM cells depend primarily on MCL-1 for survival.[9,10] However, a subset of myeloma cells have instead shown increased reliance on and higher expression of BCL-2 compared with other antiapoptotic proteins,[11,12] creating a mechanistic basis for BCL-2 inhibition in these patients.

Venetoclax and other BCL-2 inhibitors, such as navitoclax, have shown efficacy in multiple preclinical models in the subset of MM cells with high *BCL-2:MCL-1* ratio or with preferential binding of the proapoptotic protein BIM to BCL-2 instead of MCL-1.[13-16] Notably, this BCL-2–dependent phenotype is enriched in patients carrying t(11;14),[11-13,15,16] making this cytogenetic abnormality a more easily accessible biomarker than BCL-2 expression alone for venetoclax sensitivity. Further, transcriptional and epigenetic evaluation of t(11;14) MM cells has shown enrichment of a B-cell–like signature

Zachary M. Avigan, MD; and Joshua Richter, MD, FACP
The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

with increased BCL-2 dependence; in addition, acquired venetoclax resistance is associated with loss of the B-cell–like transcriptional pattern or copy number gains of *MCL1*.[12,17]

Venetoclax additionally shows synergistic efficacy with multiple other MM agents. The corticosteroid dexamethasone increases BIM expression and causes preferential binding to BCL-2, increasing sensitivity to BCL-2 inhibition.[18-20] The proteasome inhibitors bortezomib (Velcade) and carfilzomib (Kyprolis) upregulate the proapoptotic protein NOXA, which neutralizes MCL-1 and increases BCL-2 dependence.[14,21-24] Despite lower surface expression of CD38 in t(11;14) cells due to their B-cell–like phenotype,[25] the addition of venetoclax to monoclonal antibodies such as daratumumab (Darzalex) augments antibody-dependent phagocytosis of tumor cells.[26] These data provide a physiologic basis for clinical trials of venetoclax-based combinations in t(11;14) RRMM.

Venetoclax Monotherapy or in Combination With Dexamethasone

Venetoclax was initially evaluated as monotherapy for RRMM regardless of cytogenetics. In a phase 1 study, 66 patients—30 with t(11;14)—with a median of 5 prior lines of therapy were treated with venetoclax doses up to 1200 mg daily and showed an overall response rate (ORR) of 21%, including a 40% ORR in patients with t(11;14).[27] Response additionally correlated with high *BCL2*:*MCL1* and *BCL2*:*BCL2L1* mRNA expression ratios. The most common grade 3 or higher toxicities were cytopenias, including thrombocytopenia (26%), neutropenia (21%), and anemia (14%), with serious infectious adverse effects (AEs) including pneumonia (8%) and sepsis (5%).[27] Investigators in another study found a similar ORR of 44% in 25 patients with t(11;14) RRMM and AL amyloid using a lower dose of venetoclax 400 mg daily.[28]

Venetoclax also has been studied as a doublet with dexamethasone. In a phase 1/2 trial of venetoclax 800 mg daily with weekly dexamethasone, 51 patients with t(11;14) RRMM and a median of 3 to 5 prior lines of therapy were treated.[29] In the phase 2 cohort, grade 3/4 AEs included lymphopenia (19%), anemia (16%), thrombocytopenia (10%), and sepsis (10%). The ORR was similarly 48% with progression-free survival (PFS) of 10.8 months.[29] Based on these data, the randomized phase 3 CANOVA study (NCT03539744) of venetoclax-dexamethasone vs pomalidomide-dexamethasone enrolled 263 patients with early relapsed t(11;14) MM and 2 or more prior lines of therapy. The study did not meet statistical significance for its primary end point of PFS (9.9 vs 5.8 months, respectively; $P = .237$); however, venetoclax-dexamethasone showed significantly increased ORR (62% vs 35%; $P < .0001$), deeper responses with a higher rate of at least very good partial response (VGPR) (39% vs 14%; $P < .0001$), and a trend toward improved median overall survival (OS) (32.4 vs 24.5 months; $P = .067$).[5]

Venetoclax-Based Triplet Therapy

The phase 3 BELLINI trial (NCT02755597) evaluated a venetoclax triplet regimen in 291 patients with RRMM—35 with t(11;14) —and 1 to 3 prior lines of therapy.[4] Patients were randomly assigned 2:1 to receive bortezomib/dexamethasone with venetoclax 800 mg daily or placebo. The study showed promising efficacy with significantly increased median PFS (22.4 vs 11.5 months; $P = .01$) and rate of VGPR or better (59% vs 36%; $P = .00029$) in the overall cohort. However, the venetoclax group had increased rates of grade 3 or higher neutropenia (18% vs 7%) and pneumonia (16% vs 9%), and 8 patients developed fatal infections contributing to worse OS (HR, 2.03; 95% CI, 1.04-3.95; $P = .034$) in the venetoclax group.[4] Based on this mortality signal, the FDA briefly placed a clinical hold on all venetoclax-based MM trials and did not approve the drug.

However, there are multiple concerns about BELLINI's study design that may have contributed to mortality. Specifically, the trial included primarily patients who did not have t(11;14), and patients were given high venetoclax doses without antimicrobial prophylaxis. In the final updated analysis when restricted to patients with t(11;14) disease, median PFS was 36.8 months in the venetoclax group vs 9.3 months in the placebo group (HR, 0.12; 95% CI, 0.03-0.44) with an OS trend that favored the venetoclax group (HR, 0.61; 95% CI, 0.16-2.32),[30] suggesting that increased mortality with venetoclax may have been restricted to patients without t(11;14).

Ongoing randomized studies of venetoclax-based triplets have restricted inclusion to patients with t(11;14), included treatment arms with a lower 400-mg dose, and added fluoroquinolone prophylaxis for the first 90 days of therapy as well as for subsequent episodes of severe neutropenia. Based on encouraging early-phase data,[31] a randomized phase 2 study of carfilzomib-dexamethasone with or without venetoclax 400 mg or 800 mg (NCT02899052) is currently underway in patients with t(11;14) myeloma with 1 to 3 prior lines of therapy. Interim analysis of 58 patients showed increased ORR (92% vs 63%, respectively), depth of response (≥ VGPR, 82% vs 42%), and median PFS (23 months vs 17 months) favoring venetoclax, though with an ongoing signal of increased grade 3/4 infections (28% vs 11%), pneumonia (18% vs 11%), and sepsis (15% vs 0%).[32]

After similar phase 1 efficacy with daratumumab,[33] a randomized phase 1/2 study of daratumumab-dexamethasone combined with bortezomib vs venetoclax (400/800 mg) (NCT03314181) was

initiated in patients with t(11;14) RRMM with 1 or more prior therapies.[34] Preliminary results recently presented from the first 81 patients again showed higher ORR (96% vs 65%, respectively), VGPR or greater (93% vs 38%), minimal residual disease negativity (38% vs 8%, $< 10^{-5}$), and median PFS (46.1 months vs 15.5 months) in the venetoclax groups. Significantly, although venetoclax-treated patients had a higher incidence of grade 3/4 neutropenia compared with the bortezomib group (13% vs 0%), only 1 treatment-related death was noted after 49 cycles of therapy.[34]

Conclusion

Despite its lack of FDA approval and initial safety concerns, venetoclax remains widely used in patients with t(11;14) myeloma due to its established mechanism and clinical efficacy in this disease subgroup. With the evolving therapeutic landscape for RRMM and recent approvals of cellular therapy in early relapse, the future role of venetoclax remains uncertain pending more mature data from ongoing triplet studies. Nonetheless, with careful patient selection and appropriate antimicrobial prophylaxis, it remains an attractive targeted therapy for t(11;14) disease. ■

DISCLOSURES

ZMA declares no conflicts of interest. JR has consulted for both AbbVie and Genentech.

CORRESPONDING AUTHOR

Joshua Richter, MD, FACP
The Tisch Cancer Institute; Icahn School of Medicine at Mount Sinai
1470 Madison Ave
New York, NY 10029

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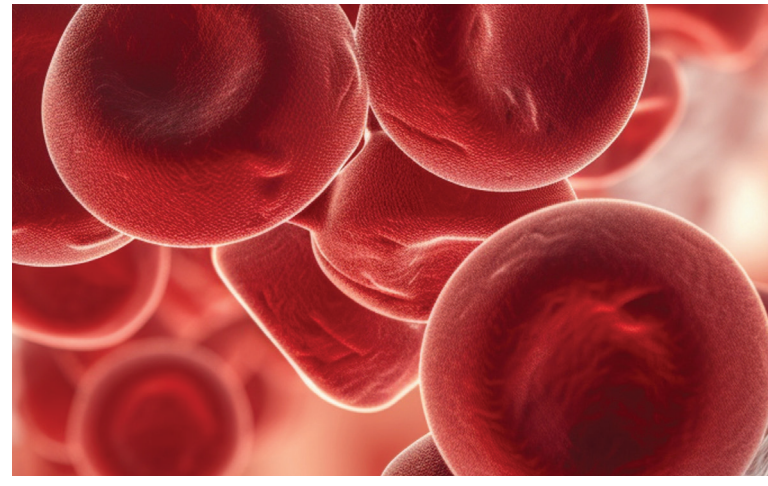
MULTIDISCIPLINARY CARE

ONCOLOGY reviews trials from the 2024 Oncology Nursing Society Congress. Highlights from presentations at the April meeting include adverse effects identified after chimeric antigen receptor T-cell therapy, ciltacabtagene autoleucel in myeloma, and a nurse-driven workflow for tocilizumab orders.



Cranial Nerve Palsy Is Present Across CARTITUDE Trials in Multiple Myeloma

A subgroup of patients with multiple myeloma receiving ciltacabtagene autoleucel (cilta-cel; Carvykti) across 3 CARTITUDE trials experienced cranial nerve palsy (CNP) at a median of 3 weeks post infusion.

CNP was experienced mostly by male patients, and most cases were low grade, with most resolving after a short time on corticosteroid treatment. Additionally, patients with cytokine release syndrome or immune effector-associated neurotoxicity syndrome were not found to be at a higher risk of having CNP.

The presentation assessed results from the phase 1/2 CARTITUDE-1 (NCT03548207), phase 2 CARTITUDE-2 cohorts A, B, and C (NCT04133636), and phase 3 CARTITUDE-4 (NCT04181827) studies. CARTITUDE-1 included 97 patients with relapsed/refractory multiple myeloma with 3 or more prior lines of therapy. Cohort A of CARTITUDE-2 included 20 patients with progressive multiple myeloma after 1 to 3 lines of prior therapy who were refractory to lenalidomide (Revlimid). Cohort B included 19 patients with progressive

multiple myeloma after early relapse. Cohort C included 20 patients with relapsed/refractory multiple myeloma. CARTITUDE-4 included 176 patients with lenalidomide-refractory multiple myeloma and 1 to 3 prior lines of therapy.

To grade CNP adverse effects, the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0 was used. For patients with CNP, cerebral spinal fluid analyses and MRI were performed at the investigator's discretion. Additionally, to assess CNP, flow cytometry was used for peripheral blood levels of cilta-cel and chimeric antigen receptor–positive T cells with memory phenotypes. A multiplex sandwich immunoassay measured the serum cytokine levels.

Across the 3 studies, CNP was observed in 6.3% of patients. Most CNP events were grade 2 and presented as facial nerve palsy. Three patients had impairment of an additional cranial nerve.

TO READ THE FULL ARTICLE, VISIT
cancernetwork.com/ONS24_CARTITUDE

Cilta-cel Shows High Responses for Lenalidomide-Refractory Myeloma in First Relapse

Ciltacabtagene autoleucel (cilta-cel; Carvykti) demonstrated a 99.4% objective response rate (ORR), along with an 86.4% complete response (CR)/stringent CR (sCR) rate in patients with lenalidomide (Revlimid)–refractory multiple myeloma as early as their first relapse, according to results of the phase 3 CARTITUDE-4 trial (NCT04181827).

At a median follow-up of 16.0 months (range, 3.8-27.3), findings showed that the responses deepened over time, with the median duration of response and median progression-free survival (PFS) not reached in the as-treated population with cilta-cel. Additionally, patients who were minimal residual disease (MRD)–evaluable (n=144) with an MRD-negative CR or higher showed improved PFS from infusion vs those who were MRD positive and/or had lower than a CR (P=.0196).

In an intent-to-treat (ITT) analysis of CARTITUDE-4, data showed that cilta-cel had a 73% reduction in the risk of disease progression or death compared with standard of care (SOC; HR, 0.26; P<.001). The ORR was 84.6% and 67.3%, respectively, and the CR or better rate was 73.1% and 21.8%.

Additional data showed that in the as-treated population, the very good partial response (VGPR) or higher rate was 96.0%, the VGPR rate was 9.7%, and the partial response (PR) rate was 3.4%. In the ITT population, the ORR was 84.6%, the CR/sCR rate was 73.1%, the VGPR or higher rate was 81.2%, the VGPR rate was 8.2%, and the PR rate was 3.4%. Finally, in the SOC population, the ORR was 67.3%, the CR/sCR rate was 21.8%, the VGPR or higher rate was 45.5%, the VGPR rate was 23.7%, and the PR rate was 21.8%.

Furthermore, the MRD-negativity rates were 72%, 61%, and 16% in the as-treated, ITT, and SOC populations, respectively. The 12-month PFS rates were 90%, 76%, and 49%, respectively, while 12-month OS rates were 92%, 84%, and 84%.

Investigators also evaluated the PFS following cilta-cel infusion in the as-treated patients by MRD-negativity status and best response in those who were MRD evaluable. Here, the median PFS was not reached (NR; 95% CI, 20.63-not estimable [NE]), and the 12-month PFS rate was 88.9% (95% CI, 80.8%-93.8%) in those with an MRD-negative CR or higher. In those with MRD-positive status and/or less than a CR, the median PFS was also NR (95% CI, 11.33-NE), and the 12-month PFS rate was 70.9% (95% CI, 48.8%-84.8%).

TO READ FULL THE ARTICLE, VISIT
cancernetwork.com/ONS24_CARTITUDE-4

Cilta-cel Yields Sustained Responses in R/R Multiple Myeloma

Treatment with ciltacabtagene autoleucel (cilta-cel; Carvykti) produced minimal residual disease (MRD) negativity and sustained responses in a cohort of patients with relapsed/refractory multiple myeloma, according to updated findings from the phase 2 CARTITUDE-2 trial (NCT04133636).

Overall, 100% of 17 evaluable patients in cohort A—which included those who were refractory to lenalidomide (Revlimid) and received 1 to 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug—achieved MRD negativity following treatment with cilta-cel. MRD-negative status was reported in 93.3% (n=14/15) of those in cohort B, which included patients with 1 prior line of therapy and progressive disease within 12 months following autologous stem cell transplantation or initiation of antimyeloma treatment.

Cilta-cel elicited an overall response rate (ORR) of 95.0% and 100.0% in cohort A and cohort B, respectively. Additionally, 85.0% and 68.4% of patients from each respective cohort had an MRD-negative complete response or better.

Investigators also reported ongoing responses at 24 months in 73.3% (95% CI, 47.2%-87.9%) of patients in cohort A and 70.5% (95% CI, 42.5%-86.7%) of those in cohort B. The median time to first response was approximately 1 month for both arms, and the median time to best response was approximately 3 months and 5 months in cohort A and cohort B, respectively.

The progression-free survival rate at 24 months was 75.0% (95% CI, 50.0%-88.7%) for patients in cohort A and 73.3% (95% CI, 47.2%-87.9%) for those in cohort B. Additionally, the overall survival rate at 24 months was 75.0% (95% CI, 50.0%-88.7%) and 84.2% (95% CI, 58.7%-94.6%), respectively.

Grade 3/4 treatment-emergent AEs (TEAEs) affected 95.0% of patients in cohort A and 94.8% of those in cohort B, and serious TEAEs occurred in 50.0% and 36.8% of patients, respectively. Common hematologic AEs in each cohort included neutropenia (95.0% vs 94.7%), lymphopenia (80.0% vs 47.4%), thrombocytopenia (80.0% vs 57.9%), anemia (75.0% vs 57.9%), and leukopenia (60.0% vs 31.6%), respectively.

TO READ THE FULL ARTICLE, VISIT
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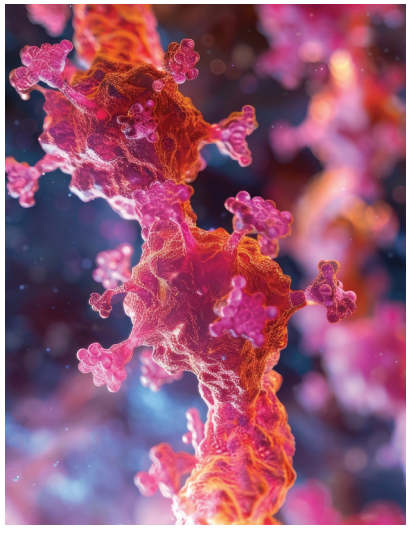

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New Tocilizumab Workflow Is More Effective for CRS Related to CAR T, Bispecific Antibodies

A nurse-driven, verbal workflow for placing tocilizumab (Actemra) orders for patients experiencing cytokine release syndrome (CRS) due to chimeric antigen receptor (CAR) T-cell therapy or bispecific antibody treatment for their lymphoma or multiple myeloma was shown to be efficient and timely, according to single-center results.

Of 38 tocilizumab doses ordered, 31 (82%) were given within 1 hour of the order being placed, and when the new workflow was utilized, the majority of nurses administered tocilizumab timelier, within 1 hour of the order entry (90.5%). However, tocilizumab administration was less timely when orders were placed by physicians (83.3%) or advanced practice nurses (60.0%). The 1 tocilizumab order placed by a pharmacist was administered within 1 hour of order entry.

"Creating a standardized verbal tocilizumab order workflow provided safe delivery of the drug," lead study author Andrea Wagner, MSN, RN, OCN, of Hackensack University Medical Center in New Jersey, and coinvestigators wrote in the poster presented during the meeting.

Verbal orders for immunotherapy, targeted therapy, and chemotherapy are not permitted, except to hold or stop treatment, according to Oncology Nursing Society Chemotherapy and Immunotherapy Guidelines and Recommendations for Practice. Although this policy aligns with Hackensack Meridian Health practices, the investigators noted that there is a potential urgent need for tocilizumab to help manage CRS from the use of CAR T-cell therapy or bispecific antibodies.

The investigators, who are from the institution's lymphoma and multiple myeloma units, examined the potential for developing a nurse-driven workflow in which the provider verifies tocilizumab's indication and dosage, while the nurse enters the order into the electronic medical record (EMR). This would theoretically facilitate verbal orders of tocilizumab and help streamline standard processes.

In the nurse-driven, verbal order workflow, which was coordinated between nurses and providers, the procedure was as follows:

- The provider obtains tocilizumab consent on admission.
- A physician communication order lists the indication, patient-specific dose of tocilizumab, and any other pertinent information regarding its use and administration for that individual patient.
- Following the provider's verbal communication in the CRS setting, the nurse places the tocilizumab order in the EMR with the use of the physician communication order.
- Tocilizumab is then administered.

Between March 2023 and March 2024, the 2 units treated a combined 68 patients with bispecific antibodies; 48 patients had lymphoma (70.6%) and 20 patients had multiple myeloma (29.4%). Thirty-eight doses of tocilizumab were administered, and 21 orders of the drug were placed via the new workflow.

Of the 38 tocilizumab doses, more than half of the orders were placed by nurses (55.3%; n=21), followed by advanced practice nurses (26.3%; n=10), physicians (15.8%; n=6), and a pharmacists (2.6%; n=1).

Investigators noted that there were no reported tocilizumab medication errors via the nurse-driven workflow. ■

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Continuing Medical Education

FACULTY

Thierry Facon, MD
Professor of Hematology
Lille University Hospital
Lille, France

Francesca Gay, MD, PhD
Associate Professor
Department of Molecular Biotechnology and Health Sciences
University of Turin
Turin, Italy

Pieter Sonneveld, MD, PhD
President, European Myeloma Network
Department of Hematology
Erasmus MC Cancer Institute
Rotterdam, The Netherlands

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CME PROVIDER CONTACT INFORMATION
Physicians' Education Resource®, LLC
2 Commerce Drive
Cranbury, NJ 08512
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New Combination-Based Approaches to NDMM

What Do the Data, the Experts, and Patients Say?

LEARNING OBJECTIVES

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

- Evaluate safety and effectiveness data from trials exploring novel combination therapies to guide treatment decisions for individuals with newly diagnosed multiple myeloma (NDMM) based on patient and disease-specific considerations
- Investigate the benefits and obstacles associated with shared decision-making with patients with NDMM

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3 Things You Should Know About Managing Newly Diagnosed Multiple Myeloma

Over 176,000 people worldwide are diagnosed with multiple myeloma each year.[1] Treatment regimens for newly diagnosed multiple myeloma (NDMM) have traditionally been divided based on whether a patient is eligible for autologous stem cell transplant (ASCT).[2,3] Recently published results from several randomized trials evaluating anti-CD38 monoclonal antibodies as part of triplet or quadruplet therapy are challenging the existing paradigms for both transplant-eligible and -ineligible patients.[4-9] Ongoing studies of using novel therapies seek to further improve outcomes. Here are 3 things you should know about new approaches to managing NDMM.

1. Not all transplant-ineligible patients are alike.

For the first-line treatment of transplant-ineligible NDMM, the European Hematology Association–European Society for Molecular Oncology 2021 MM guidelines recommend use of either Dara-Rd (daratumumab plus lenalidomide and dexamethasone), Dara-VMP (daratumumab plus bortezomib, melphalan, and prednisone), or VRd (bortezomib plus lenalidomide and dexamethasone) based on results of the phase 3 MAIA (NCT02252172), ALCYONE (NCT02195479), and SWOG S0777 (NCT00644228) trials, respectively.[2,4-6] When individualizing treatment for these patients, health care professionals should consider that patients with NDMM who are not intended for upfront ASCT consist of a heterogenous population. They include fit patients who are active and independent, those who perform limited activities, and frail patients who are dependent upon others.

The MAIA trial introduced the use of an anti-CD38 monoclonal antibody in triplet therapy for transplant-ineligible patients with NDMM. Updated results after a median follow-up of 56.2 months showed that use of Dara-Rd led to a significant improvement over Rd in 60-month overall survival rate (66.3% vs 53.1%, respectively; $P < .0001$).[4] A follow-up analysis evaluating the impact of frailty on outcomes found that the addition of daratumumab led to a progression-free survival (PFS) benefit across fit, intermediate, and frail subgroups.[10]

Quadruplet combinations are now being evaluated in fit patients who are ineligible or not intended for initial transplant. In the phase 2 GMMG-CONCEPT (NCT03104842) trial, Isa-KRd (isatuximab with carfilzomib, lenalidomide, and dexamethasone) was evaluated for induction and consolidation followed by Isa-KR maintenance in transplant-ineligible patients with high-risk NDMM.[6] The study met its primary end point—54.2% of transplant-ineligible patients achieved minimal residual disease (MRD) negativity at the end of consolidation. Several ongoing trials are investigating the use of other anti-CD38 monoclonal antibody-based quadruplets including Isa-VRd (isatuximab plus bortezomib, lenalidomide, and dexamethasone) and Dara-VRd (daratumumab plus bortezomib, lenalidomide, and dexamethasone).[7,11,12]

The future landscape for transplant-ineligible NDMM may include the use of novel immunotherapies (**Table**). For example, studies are comparing bispecific antibodies in combination with Dara-R (daratumumab plus lenalidomide) to Dara-Rd.[13,14]

TABLE. Select Ongoing Trials Evaluating Novel Immunotherapies in Patients With NDMM

PATIENT POPULATION	TRIAL (NCT NO.)	PHASE	TREATMENT ARM(S)	PRIMARY END POINT
Transplant ineligible or ASCT not intended for initial therapy	MajesTEC-7 (NCT05552222)[13]	3	Tec-DR vs DRd	· PFS · CR or better
	MagnetisMM-6 (NCT05623020)[14]	3	EDR vs DRd	· DLT · PFS · Sustained MRD-negativity rate
	CARTITUDE-5 (NCT04923893)[15]	3	VRd + Rd vs VRd + cilta-cel	· PFS
Transplant eligible	MajesTEC-4 (NCT05243797)[17]	3	Tec-Len vs Len	· PFS
	MagnetisMM-7 (NCT05317416)[18]	3	E vs Len	· PFS
	CARTITUDE-6 (NCT05257083)[19]	3	D-VRd + ASCT+D-VRd vs D-VRd + cilta-cel	· PFS · Sustained MRD-negative CR

ASCT, autologous stem cell transplant; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DLT, dose-limiting toxicity; DRd, daratumumab, lenalidomide, and dexamethasone; D-VRd, daratumumab plus bortezomib, lenalidomide, and dexamethasone; E, elranatamab; EDR, elranatamab, daratumumab, and lenalidomide; Len, lenalidomide; MRD, minimal residual disease; NCT, National Clinical Trial; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; Tec-DR, teclistamab, daratumumab, and lenalidomide; Tec-Len, teclistamab and lenalidomide; VRd, bortezomib plus lenalidomide and dexamethasone.

Upfront chimeric antigen receptor (CAR) T-cell therapy following VRd induction is also being evaluated.[15] In the future, this may offer patients a treatment option that does not require long-term maintenance therapy.

2. Quadruplet therapy with anti-CD38 monoclonal antibodies is the new standard of care for transplant-eligible patients with NDMM.

Two landmark, phase 3 clinical trials evaluating quadruplet therapy with an anti-CD38 monoclonal antibody combined with a proteasome inhibitor, lenalidomide, and dexamethasone recently reported positive findings. In the PERSEUS trial (NCT03710603), 709 transplant-eligible patients with NDMM were randomly assigned to receive either Dara-VRd as induction and consolidation with Dara-R maintenance or VRd induction and consolidation with R maintenance.[8] The study met its primary end point of prolonged PFS; the estimated 48-month PFS was 84.3% in the D-VRd group and 67.7% in the VRd group (HR, 0.42; $P < .001$). The addition of daratumumab improved rates of MRD negativity compared to VRd with a widening gap over time that was most evident at the deeper threshold of 10^{-6}. MRD negativity was also sustained at a high rate, allowing 64% of patients in D-VRd group to discontinue Dara maintenance per protocol design.

Results of the IsKia trial (NCT04483739) evaluating the addition of isatuximab to KRd as pre-ASCT induction and post-ASCT consolidation in 302 transplant-eligible patients also met the primary end point, which was improved rates of MRD negativity after consolidation.[9] Similar to results of the PERSEUS trial, the benefit in the Isa-KRd group was more pronounced at the 10^{-6} threshold (67% vs 48%; $P < .001$) than at the 10^{-5} threshold (77% vs 67%; $P = .049$). In all, 18% of patients had high-risk cytogenetics including 10% with 2 or more high-risk cytogenetic abnormalities (HRCAs). The Isa-KRd group demonstrated a drastic improvement (77% vs 27%) in postconsolidation MRD negativity at 10^{-6} in this very high-risk patient population.

Questions remain about the utility of MRD testing to guide treatment decisions, particularly for maintenance therapy. Randomized clinical data comparing maintenance therapies to observation are currently lacking. In the phase 2 MASTER trial (NCT03224507), outcomes were evaluated following treatment cessation in patients with NDMM who had 2 consecutive MRD-negative assessments following induction with Dara-KRd (daratumumab plus carfilzomib, lenalidomide, and dexamethasone) and ASCT with or without consolidation.[16] The patient population was enriched for those with high-risk disease. Overall, 71% of patients entered treatment-free surveillance. Among patients with 2 or more HRCAs, 27% had MRD resurgence or progression 12 months after cessation of therapy.

Novel immunotherapies are also being investigated in transplant-eligible patients with NDMM, including in trials of bispecific antibodies as maintenance therapy following ASCT (**Table**).[17,18] CAR T-cell therapy following Dara-VRd induction is also going head-to-head with ASCT, which may answer whether CAR-T therapy can one day replace ASCT and potentially cure some patients with MM.[19]

FIGURE. AI-Derived Insights Into Top Patient Concerns Related to NDMM

TOP PATIENT CONCERNS RELATED TO NDMM

1. Understanding combination therapy options
2. Adverse events from combination therapies
3. Understanding ASCT (ie, process and recovery)
4. Ambiguity around test results and diagnosis
5. Adverse events from ASCT
6. Clinical trial options and eligibility requirements
7. Financial barriers and insurance benefits

AI, artificial intelligence; ASCT, autologous stem cell transplant; NDMM, newly diagnosed multiple myeloma.

3. Patients need help understanding the plethora of combination therapy options.

Physicians' Education Resource used an artificial intelligence tool to conduct an analysis of patient concerns and questions regarding NDMM from posts across social media platforms (X, Reddit, YouTube, and TikTok) from March 2022 to March 2024. The identified topics were classified and sized to create a rank ordered list (**Figure**). The analysis revealed the importance of helping patients sort through all of the various combination therapy options for NDMM. Given the burdensome process and recovery period associated with ASCT and data demonstrating the efficacy of quadruplet therapies without upfront transplant, it is critical to engage in shared decision-making with patients and educate them on the latest data demonstrating unprecedented rates of sustained MRD negativity and durable PFS that can be achieved by adding ASCT.[6,8,9,20]

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To learn more about this topic, including expert commentary on the latest clinical trial data pertaining to newly diagnosed multiple myeloma, go to https://gotoper.com/emn24mm-activity

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

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

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

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

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

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

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

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

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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.

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IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Systemic Reactions

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

Local Reactions

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

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

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

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

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

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

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

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

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

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

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

DARZALEX®: ADVERSE REACTIONS

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

DARZALEX *FASPRO*®: ADVERSE REACTIONS

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

INDICATIONS

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

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

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

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

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

cp-248517v3

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

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

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

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

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

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

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

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

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

Interference with Serological Testing

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Interference with Determination of Complete Response

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

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

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

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

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

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

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

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

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

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

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

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

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

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

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

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

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

Herpes Zoster Virus Reactivation

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

Infections

Grade 3 or 4 infections were reported as follows:

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

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

Fatal infections (Grade 5) were reported as follows:

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

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

Hepatitis B Virus (HBV) Reactivation

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

Other Clinical Trials Experience

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

Nervous System disorders: Syncope

Immunogenicity

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

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

Postmarketing Experience

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

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

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

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

Neutropenia

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

Thrombocytopenia

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

Embryo-Fetal Toxicity

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

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

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

Hereditary Fructose Intolerance (HFI)

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

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

For patent information: www.janssenpatents.com

cp-271933v4

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

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

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

Local Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Embryo-Fetal Toxicity

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

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

Interference with Serological Testing

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

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

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity

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

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

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

Postmarketing Experience

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

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

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Data

Animal Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

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

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

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Janssen Biotech, Inc.
Horsham, PA 19044, USA
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