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AUGUST 2024 | Vol 38 • No 8

CASE STUDY | LEUKEMIA

Navigating a Paradigm Shift

Venetoclax Treatment Redefines Landscape of Acute Myeloid Leukemia

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Our Board Members Have Been Busy!

Take a look to see what they have been up to.

María T. Bourlon, MD, MSc

Genitourinary Cancer Editorial Board Member

Bourlon is now one of the Tres Uromigas! She and 2 other colleagues will be cohosting the Spanish-speaking podcast focused on updates in genitourinary cancer. This comes on the expansion of the *Uromigos* podcast hosted by other influential genitourinary oncologists.

Ting Bao, MD

Integrative Oncology Editorial Board Member

In early July, Harvard Medical School hosted a breast cancer course. Bao was one of the speakers presenting on integrative oncology. She specifically focused on its use for adverse effect management. Other topics from the course included antibody-drug conjugates in estrogen receptor–positive breast cancer and male breast cancer. To view the full list of topics and presenters search #HarvardBreastCancerCourse on X.

Call for Reviewers and Papers

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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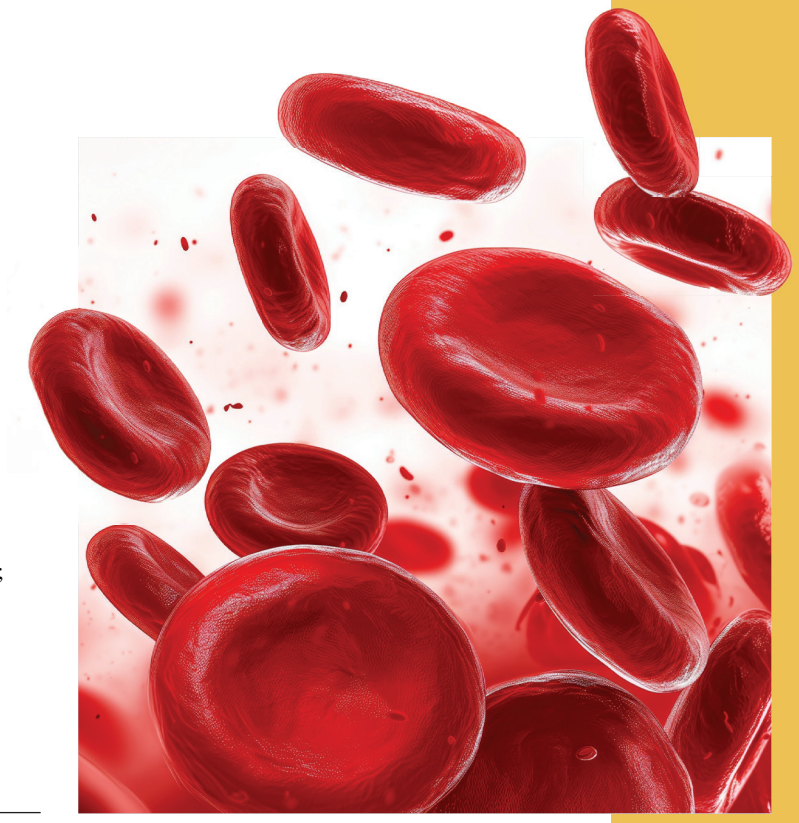

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Exercise Treatment as Part of Multidisciplinary Whole Person Care in Oncology

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[2]Department of Medicine, Weill Cornell Medicine, New York, NY

Several national agencies, including the American Society of Clinical Oncology (ASCO), recommend the prescription of exercise for patients diagnosed with cancer.[1,2] The evidence base for this recommendation is derived from studies that showed exercise-related improvements in patient-reported outcomes (PROs), treatment-associated adverse effects, cardiorespiratory fitness (CRF), and overall physical functioning.[3-6] Additionally, exercise may have direct anticancer effects and indirect effects by synergizing standard cancer therapies.[7,8] Despite these benefits, the implementation of exercise oncology practice guidelines in the United States has been limited. A major barrier to the implementation of exercise therapy and other "whole person interventions" is the increasing complexity of clinical decision-making due to the greater availability of novel cancer therapeutics with clinical benefits ranging from low to high impact.

The associated decision-making paradigm requires highly nuanced conversations, planning, and more time for discussion between patients and their oncologists to develop an efficacious treatment approach that aligns with patient priorities while balancing potential toxicity. Within this context, the consideration of any additional treatment recommendation, such as exercise, is scrutinized against competing priorities to maximize clinical efficiency. Questions regarding the optimal use of exercise (eg, when to implement, type, and dosage of exercise) have made it challenging to prescribe exercise as part of a cancer treatment plan, relegating exercise to the realm of "general recommendations" that are mentioned but often forgotten.

Fortunately, guidelines from ASCO and the American College of Sports Medicine now include important details for exercise therapy implementation such as established safety and dosing information.[2] Several randomized control trials have demonstrated that exercise after completion of cancer therapy improves various PROs and CRF.[3,4] Additional studies have demonstrated that supervised exercise during chemotherapy is safe and tolerable.[9] Supervised exercise during chemotherapy also has early efficacy for mitigating chemotherapy-related decline in CRF.[10] Patients who initiate exercise after chemotherapy may also regain CRF and physical function to the same degree as those who started exercise during chemotherapy, which provides flexibility for patients unable to exercise. Exercise is also efficacious for improving fatigue, PROs, and other cancer-related symptoms in the setting of multimodality therapy such as chemoradiation.[10] Taken together, the extant data indicate that exercise may be implemented at nearly any point during the cancer treatment spectrum with favorable effects.

Adherence and tolerability are critical factors that impact the feasibility and efficacy of exercise therapy, perhaps even more so than pharmacologic therapies. For example, CRF recovery in patients who start supervised exercise after completing chemotherapy has been shown to catch up with that of patients who start exercise during chemotherapy but transition to home-based exercise after chemotherapy.[10] These findings suggest the superiority of supervised exercise over home-based exercise, though maintaining adherence can be a challenge. In this regard, smartphone mobile applications and other virtual/remote platforms could provide a scalable digital solution. Our group at Memorial Sloan Kettering Cancer Center recently demonstrated high engagement among survivors of breast cancer with a commercially

available smartphone application that led to an average weight loss of approximately 5% of baseline weight.[11]

In addition to smartphone applications, several existing web-based programs may be leveraged for patients with cancer. For example, the SurvivorSHINE program utilizes web-based diet and exercise counseling and has been shown to improve diet quality, increase physical activity, and reduce functional decline in cancer survivors.[12,13] The intervention consists of an interactive online program that has been subjected to rigorous formative research (focus groups, extensive beta testing, and stakeholder interviews) in diverse samples that informed and refined the yearlong intervention.[14] Website engagement data show weekly logins that are 2- to 3-fold higher than online lifestyle interventions of similar duration that are not tailored to oncology populations. Another important resource for implementing lifestyle interventions is the American Institute for Cancer Research, which offers continuous updates from published data and patient-facing educational information regarding diet and exercise.

Efforts are underway to include exercise oncology as a reimbursable service for cancer care. The success of such efforts stands to have a large potential impact on the availability and accessibility of exercise programs for patients with cancer throughout the US. Until exercise oncology programs become more accessible, it is our responsibility as oncologists to endorse the inclusion of exercise as part of cancer therapy and guide patients to appropriate resources. For now, the use of digital and web-based platforms provides an implementable and convenient approach to incorporating exercise therapy as part of whole person care in oncology. ■

FOR REFERENCES VISIT
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LYMPHOMA

Epcoritamab in Relapsed/Refractory Follicular Lymphoma

In June 2024, the FDA granted accelerated approval to epcoritamab-bysp (Epkinly) for patients with relapsed/refractory follicular lymphoma after 2 prior lines of therapy.[1] The approval was based on results from the phase 1/2 EPCORE NHL-1 trial (NCT03625037),[2] which were recently presented at the 2024 American Society of Clinical Oncology Annual Meeting.

Prior to the approval, *ONCOLOGY* spoke with Tycel Phillips, MD, associate professor in the Division of Lymphoma and Department of Hematology and Hematopoietic Cell Transplantation at City of Hope in Duarte, California. Phillips spoke about the implications of approval and how this will impact treatment options in the space.

Topline results included an overall response rate of 82% (95% CI, 74.1%-88.2%) and a complete response rate of 60%. The median duration of response was not reached (NR; 95% CI, 13.7-NR). At 12 months, an ongoing response occurred in 68.4% of patients (95% CI, 57.6%-77.0%). Two different cohorts were assessed—the pivotal and cycle 1, day 1 cohorts—with investigators analyzing the impact these different dosing regimens had on patients.

Q / What does the approval of epcoritamab mean for this patient population?

Phillips / The biggest impact will be in centers that have picked 1 bispecific to keep on the formulary. Epcoritamab's approval in large cell lymphoma has allowed them to keep 1 bispecific agent or formulary and doesn't require them to have [multiple agents stocked].[3] In this situation, if they have a bispecific for diffuse large B-cell lymphoma [DLBCL] and an antibody specific for follicular lymphoma, it will require [the clinic] to have either epcoritamab, glofitamab-gxbm [Columvi], or mosunetuzumab-axgb [Lunsumio] for follicular lymphoma.

This potentially allows for ease of use in that situation. There are fewer difficulties with staff [and] infusion nurses, [as well as not having to deal] with different bispecifics and being more comfortable with dealing with 1 drug. In the long term, it is always better for the patients because it's easier to manage the toxicity that may come from this. There is [also] more familiarity with the step-up of dosing for epcoritamab, which is different from what we have with mosunetuzumab and glofitamab.

Some of the [adverse] effects that come from it, like cytokine release syndrome [CRS] and immune effector cell–associated neurotoxicity syndrome [ICANS], can be associated with this.

Q / How promising are the data from the EPCORE NHL-1 trial?

Phillips / The data are still a bit immature compared with what we see with CAR [chimeric antigen receptor] T drugs and even mosunetuzumab. The duration of response is still to be determined, as I'm sure [those] data [are] still maturing…. The overall response and complete response rates look very similar to what we see with mosunetuzumab. In that aspect, there are no major differences between the 2 drugs. The CRS events appear to be a little less than what we saw in large cell lymphoma but not drastically different.

The big takeaway [is the efficacy]. It's still to be determined how effective and durable this will be. Given that epcoritamab appears to be a more effective drug in large cell lymphoma than mosunetuzumab, I would hope that would translate into longer responses in follicular lymphoma, especially given some of the other aspects of the drug, which is treatment to progression. This is a little different from mosunetuzumab, and the CRS rates seem to be a bit higher in criteria than what we saw with mosunetuzumab.

STATS AT A GLANCE

Dosing regimen

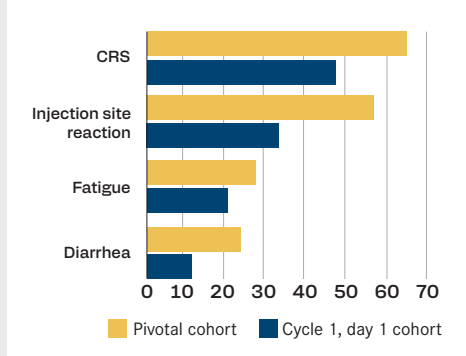
Pivotal cohort

0.16 mg of epcoritamab; the cycle 1, day 8 step-up dose was 0.8 mg; and the cycle 1, day 15 first full dose was 48.0 mg

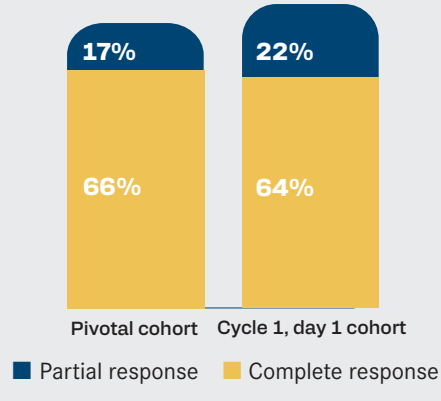
Cycle 1, day 1 cohort

0.16 mg of epcoritamab; the cycle 1, day 8 dose was 0.8 mg; cycle 1, day 15 was 3.0 mg; and cycle 1, day 22 was the first full dose of 48.0 mg

Grade 1/2 treatment-emergent adverse effects



Response rates



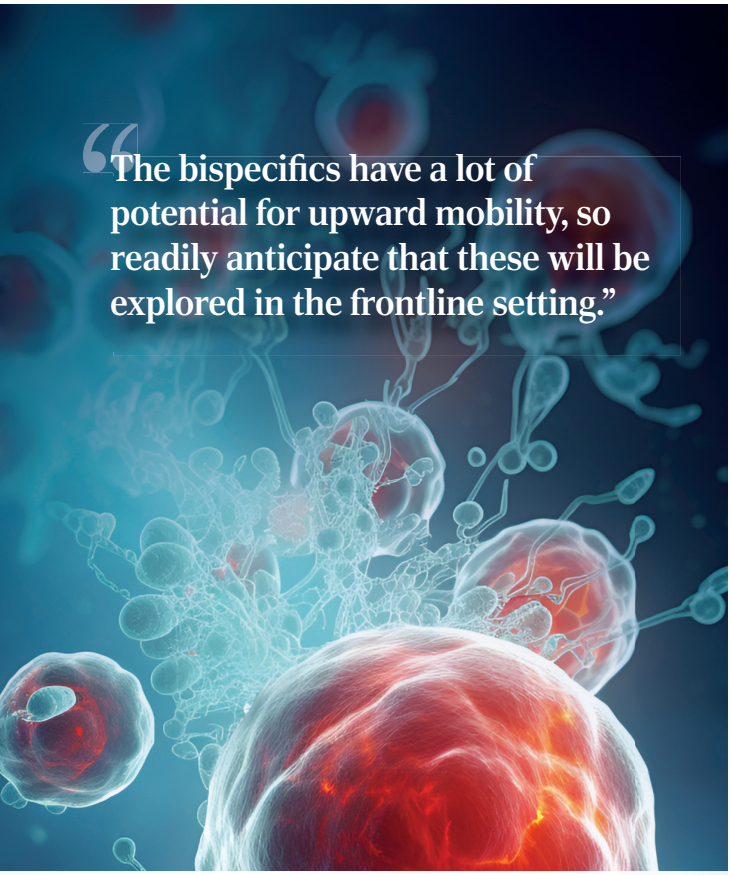
To justify that, you would want to hope for a longer duration of response with this drug.

Q / Are there any unmet needs that epcoritamab would help to reduce?

Phillips / As we try to transition these bispecifics into the community setting, having these drugs available allows patients [the opportunity] who can't [receive] CAR T-cell therapy or can't get to other academic centers for clinical trials. This provides them with a more effective option, especially with the loss of the PI3K inhibitors in relapsed/refractory follicular lymphoma. When chemotherapy or lenalidomide [Revlimid] fails these patients, there's a bit of a void there as far as agents that could provide some durability of response. Having this fills that void, [as well as] being able to be off the shelf and readily available for patients who live in situations where they can't get access to CAR T-cell therapy or get to a major academic center. These drugs could bridge that gap and give these patients adequate response durability. And after dealing with step-up dosing and safety, these drugs are quite promising, especially compared with the now-defunct Δ inhibitors of chemotherapy. Some of these other drugs may be coming down the line.

Q / How would you implement this treatment into your clinical practice?

Phillips / This is an effective therapy that we can use in a third-line setting, or even in patients who may have progression of disease after



24 months [of treatment. Patients with] early progression tend to have poor outcomes, especially when given more cytotoxic agents like chemotherapy. Ideally, this treatment does not appear to be impacted by that prognostic factor. It does allow utilization in that situation. If patients are to get lenalidomide or rituximab [Rituxan] in the frontline setting, this allows the use of this drug after that…. There's just 1 real agent—tazemetostat [Tazverik][4]—that has the current approval [in the third-line setting as of right now. Epcoritamab] allows for a more effective therapy and a more durable response than what we see with tazemetostat.

Q / Are there any significant toxicities that stand out to you?

Phillips / Besides the CRS, it's the ICANS. That's one thing we always keep an eye on. The rates of those are much less with the bispecifics than we will see with CAR T-cell therapy. Infections are [another] thing we will have to keep an eye on because of how bispecifics work; so you're more prone to viral infections. The good news is that after the COVID-19 pandemic, we've come a long way, and those infections can be managed and treated. We're not having nearly as many fatalities as we have in the early parts of the pandemic. We're keeping an eye on the patient's immunoglobulin levels and repeating those, if necessary, to prevent more recurrent viral infections, which is important.

Anytime we constantly keep patients on treatment, we run the risk of other things that may come up [later down the line] that we may not anticipate. At least in the short term, infection, ICANS, and CRS are the biggest things to be concerned about with this type of treatment. This is a little different from what we see with chemotherapy, where you get the nausea, vomiting, bacterial infections, and the secondary malignancies that come along with it.

Q / Are there any other plans to further research epcoritamab in this patient population or perhaps those with other types of cancer?

Phillips / The bispecifics have a lot of potential for upward mobility, so readily anticipate that these will be explored in the frontline setting. Epcoritamab and the other bispecifics have already been explored in the second-line setting in combination with lenalidomide. I'm sure that combination as a single agent—and probably lenalidomide—will be explored in untreated or newly diagnosed patients.

We're sort of seeing the same phenomenon in [DLBCL], which is the most common lymphoma. Epcoritamab and glofitamab have been studied in the frontline setting in that patient population, and epcoritamab has been studied in mantle cell lymphoma. There's also a study looking at this drug in Richter transformation, [which comprises patients with] chronic lymphocytic leukemia who develops a large cell lymphoma transformation. There are multiple non-Hodgkin lymphoma subsets that have been explored with epcoritamab and the bispecifics in general because of their combined ability with other agents. I would anticipate we'll likely see them combined with other drugs with earlier lines of therapy than what the current FDA approvals will say at this current time. ■

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AI Use May Improve Treatment Outcomes in Prostate Cancer

James B. Yu, MD, MHS, FASTRO, Assistant Professor Adjunct, Department of Radiation Oncology, Smilow Cancer Hospital at Saint Francis Hospital, Hartford, CT

Julian C. Hong, MD, MS, Assistant Professor, Department of Radiation Oncology, University of California, San Francisco, San Francisco, CA

To read the Hot Topics article, scan the QR code here.

A Hot Topics article published in the May issue of *ONCOLOGY* explored artificial intelligence (AI) use in prostate cancer and its effects on treatment and patient care outcomes.[1]

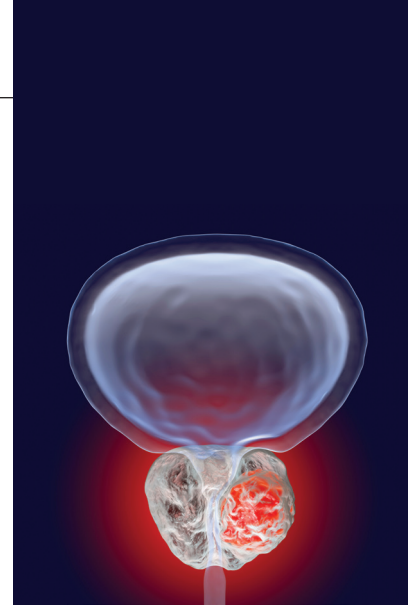
CancerNetwork® spoke with James B. Yu, MD, MHS, FASTRO, assistant professor adjunct, Department of Radiation Oncology, Smilow Cancer Hospital at Saint Francis Hospital, and Julian C. Hong, MD, MS, assistant professor, Department of Radiation Oncology, University of California, San Francisco, who were authors of the article. They shared their expertise on advances in AI use to better conduct diagnostic imaging, predict clinical outcomes, evaluate histopathology, and plan treatment.

The researchers highlighted a mirroring of innovations seen in the application of AI to prostate cancer to those happening in medicine. Image analysis and computer advances have been applied to classify prostate pathology and imaging, as well as prediction of outcomes. AI tools may improve practice efficiency in radiation oncology as well as patient-facing tools.

Q / How has the use of AI in the prostate cancer field evolved regarding image classification and analysis? What data support these advances?

Hong / The question was specifically about image classification and analysis, and that's been one of the major areas where AI has made the first steps in cancer care—in medicine—and a big part of that is related to the analog developments in AI more broadly. Most of this comes from huge advances in computer vision: training computers to distinguish between a dog and a cat. These same types of approaches are being applied in medical areas—in prostate cancer and, more broadly, in cancer in general. The main image classification areas that come up are things like pathology, radiology, and then on the radiation side, radiation planning. Those are probably the big areas computer vision has been contributing to. A lot of the data are being used and trained are coming from academic centers. There have been bigger efforts toward pooling more data, which for all AI applications is a major problem—not just having enough data, but also having biased data. Different fields in medicine are ahead in different things. For instance, for computer vision and bias, dermatology has been very much ahead of the game because one of the natural questions is, "Can you identify a skin cancer from a picture?" As a consequence, there have been studies showing that the data that these algorithms are trained on are often in fair-skinned individuals. They're a biased data set, so data quality and fairness are also important.

Yu / The most visible use of AI for prostate cancer is this ArteraAI multimodal AI platform, which was built and validated using largely National Clinical Trials Network data, or NCTN data, from the NRG. It highlights the importance of federal funding for research and an unintended but very nice result of all this federal funding. [No one] 30 years ago, when RTOG 9408 was being initiated, would anticipate that we would use these slides for this AI histopathology feature classification system that will be built into a prognostic tool. It's a neat proof of concept that federal funding of research is important and can lead to a myriad of benefits for society. That's also an issue for imaging data. The federal government



constantly has to decide whether to continue to store all of these data. Are we going to continue to support these data repositories? Hopefully, the answer is yes, and they'll look at applications like this in the future and say, "We don't know if it's [going to] pay off now, but in the future, there's a very good chance it will."

Q / How have these algorithms become equipped to predict relevant clinical outcomes in prostate cancer?

Hong / The broader realm of AI is trying to have computers do some form of reproducing informal intelligence with a machine, which is more based on the traditional, original definition. Then machine learning is typically considered like a subset of AI specifically geared toward learning from prior data. As far as trying to predict clinical outcomes in prostate cancer, it's still a work in progress. That's across the board, probably one of the more long-standing things.

Decipher Prostate, a genomic risk classifier, was built off a model years ago and has been commercially available for years. Even with how long Decipher has been around, we're still looking for, robust, high-quality evidence for how we use it. We're trying to incorporate AI and machine learning into more trials to make these types of predictions because, at the end of the day, we're trying to deliver better care and improve outcomes for patients. It takes trials to figure those things out, so it's a little bit of a work in progress. There's [nothing] out there right now that has those high-level, randomized data, but we're getting there.

Yu / The way I approach this question is [by taking] the words machine learning out and [asking] the question again: "Have our algorithms become equipped to predict clinical outcomes in prostate cancer?" Because if an algorithm that was created without some fancy machine learning tool works, it's just as good as a machine learning algorithm. We see a lot of papers on machine learning algorithms that are based on clinical data, which is just as good as a multivariate logistic regression. The machine learning algorithms based on pure clinical data aren't any better, to be quite honest, but it's going back to what Dr Hong was talking about with the image detection/image processing feature recognition. That's where prostate cancer algorithms are starting to shine. The questions that they're helping to answer are rudimentary at present: "Do these patients need hormone therapy on top of radiation? What's the risk of the cancer coming back?" They're not that much better than existing clinical algorithms. Maybe in the future, they'll be substantively better.

Hong / Those are 2 key important points there. One is AI tools need to be compared with something simple. AI models, and machine learning, tend to overfit on data, which is that they fit too closely to what they're trained on, and that can cause a lot of issues that you don't first see. They should always be compared with something simpler so that we can understand what's going on behind the scenes. Things are very rudimentary right now. We're jumping around a bit, but there are opportunities for AI to help us do better. In computational health, in our field, that's where we should be trying to push things because it's natural that machine learning or AI can model certain things out, that's to be expected. It's about where do we go from here? How do we push things to improve outcomes, improve treatments, reduce physician burnout? There are a lot of opportunities that are important next steps.

Q / What AI tools have assisted with assessing prostate cancer histopathology?

Hong / [ArteraAI] is probably one of the more high-profile systems that's out there, and that uses multimodal data in the sense that it uses some clinical data and combines them with computer vision approaches on histopathology slides. It's going to be an interesting landscape to watch because it's one of the clear applications of computer vision up front. A lot of people are working on that problem. Some of the more recent ArteraAI work is application-centric: "Should a patient get androgen deprivation therapy or not?" It's a rapidly evolving landscape. There'll be a lot of exciting things. It's all relative, but probably one of the more mature areas, if you will, as far as AI tools, and at the end of the day, they just need to be validated and evaluated on studies.

Yu / The next area would be using the same feature recognition tools and applying them to other cancers. Sure, it's much harder than that, but you take the same network and see it extracted from a glioma specimen or anything that needs subclassification and apply it to be a ready application.

Hong / This goes back to the [idea that] data are important, the clinical problem is important, and the context of those 2 things together is important. That will decide the future of how well these things work and how we can help implement them. ■

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LEUKEMIA

Navigating a Paradigm Shift
Venetoclax Treatment Redefines Landscape of Acute Myeloid Leukemia

ABSTRACT Acute myeloid leukemia (AML) is a heterogeneous disease characterized by the accumulation of malignant myeloid progenitor hematopoietic cells in the bone marrow and peripheral blood. Recent studies have shown promising results with the use of small molecule inhibitors and targeted therapy in the treatment of patients with AML. One such molecule is venetoclax, which has been approved in AML by the FDA in combination with hypomethylating agents or low-dose cytarabine. We thoroughly searched electronic literature related to venetoclax and its role in AML, using databases such as MEDLINE, PubMed, Google Scholar, and PsychInfo, through April 2024. We applied population, intervention, comparison, and outcome criteria, specifically focusing on studies with a population using venetoclax from review articles and clinical trials. All selected studies were required to be in English, and any study that did not involve the use of venetoclax was excluded. A meticulous literature review was conducted to consolidate the current knowledge and new combination therapies on AML. In our review article, we focused on the latest advances in the treatment of patients with AML. Based on the literature, we recommend that physicians prioritize the use of venetoclax in the management of this deadly disease because it has been shown to significantly impact the course of the disease.

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by the accumulation of malignant myeloid progenitor hematopoietic cells in the bone marrow and peripheral blood. It primarily affects older people, with a median age at diagnosis of 68 years. Men are 1.5 times more commonly affected than females with an overall incidence of 4 per 100,000 per year.[1] Currently, patients with newly diagnosed AML are treated with the standard regimen, which consists of cytarabine and an anthracycline followed by consolidation therapy with cytarabine or stem cell transplantation, depending on patient and disease characteristics.[2] However, older patients and patients with comorbidities cannot tolerate intensive induction chemotherapy and are offered only supportive and palliative treatment. As a result, the long-term cure rates of AML in the older population have historically been as low as 5% to 20%.[3]

Recent studies have shown promising results with the use of small molecule inhibitors and targeted therapy in the treatment of AML. One such molecule is venetoclax, which was initially

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approved by the FDA for the treatment of chronic lymphocytic leukemia (CLL) in 2016. It since has been approved in combination with hypomethylating agents (HMA) or low-dose cytarabine (LDAC) for AML in patients who are previously untreated, are older, or cannot tolerate intensive chemotherapy. More recently venetoclax was approved for refractory multiple myeloma. It has also shown encouraging results for other hematological malignancies, especially lymphomas.[4-8]

Methodology

Our team conducted a thorough search for electronic literature related to venetoclax in multiple databases, including MEDLINE, PubMed, Google Scholar, and PsychInfo, through April 2024. We used keywords such as venetoclax and AML to find relevant studies. The first author carried out independent research, while the first and second authors evaluated the titles, abstracts, and reference lists according to specific eligibility criteria. To be included, the articles had to meet specific population, intervention, comparison, and outcome criteria, such as results of a study having a population treated with venetoclax, results of a clinical trial or randomized clinical trial including venetoclax, or a review article on venetoclax. Additionally, all the selected articles were published in English, and we excluded studies that did not include venetoclax. The **Figure** illustrates the PRISMA flow diagram of the study selection.

Results

A total of 58 original articles about venetoclax were identified. The main focus of this article was to review venetoclax use in AML in different chemotherapeutic combinations. Chemotherapy drugs such as azacitidine and decitabine in combination with venetoclax show high safety profiles and are well tolerated in older patients with untreated AML. This combination is effective in high-risk groups such as patients 75 years or older, and, patients taking it have a lower incidence of gastrointestinal symptoms such as nausea, diarrhea, and low appetite.[9]

The phase 3 VIALE-A trial (NCT02993523) was designed to assess the effectiveness and safety of the azacitidine-venetoclax combination.[10] Azacitidine at 75 mg/m^2 and venetoclax at 400 mg were given in combination daily from days 1 to 7 in patients with a new diagnosis of AML. According to the investigators, 433 patients, with a median age of 76 years and from 134 sites in 27 countries, were randomly assigned; 431 were included in the intention-to-treat population. Participants in the venetoclax/azacitidine group had a median overall survival of 14.7 months (95% CI, 12.1-18.7), whereas those in the azacitidine/placebo arm had a median survival of 9.6 (95% CI, 7.5-12.7) months. The HR for death was 0.66 (95% CI, 0.52-0.85; $P < .001$). Most notably, the combination produced quicker reactions than azacitidine only.[11]

According to results from the study conducted by Kwag et al, decitabine in combination with venetoclax significantly improved the

FIGURE. PRISMA Flow Diagram of the Study Selection

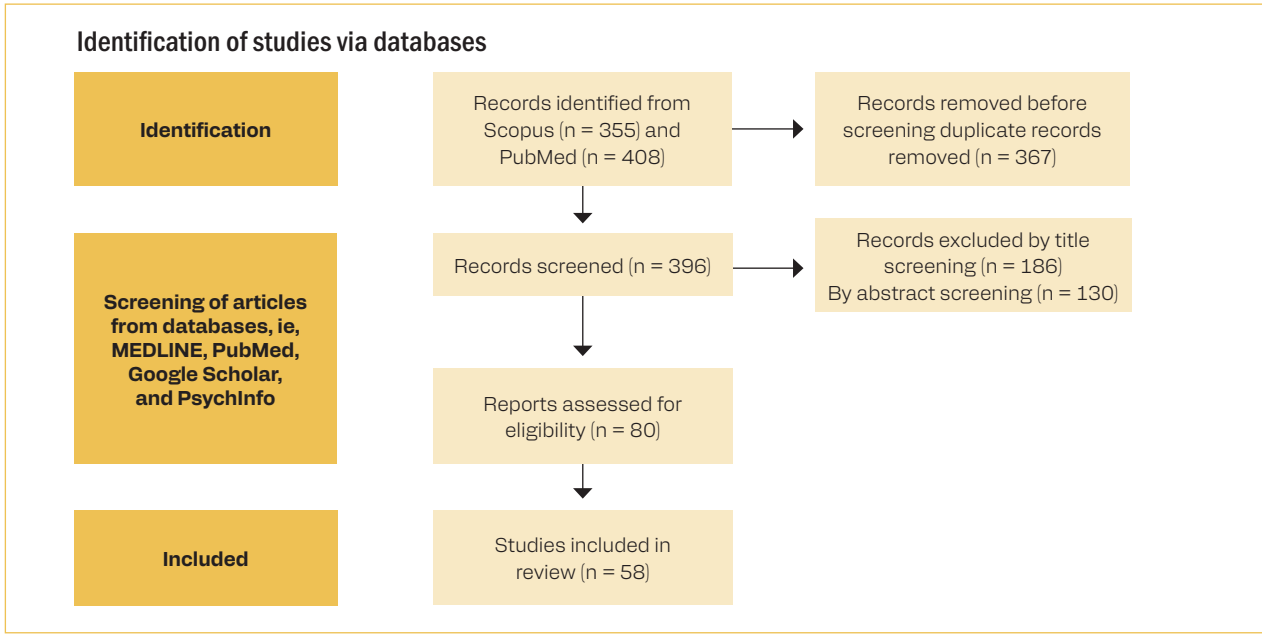

TABLE. Comparison of Therapeutic Agents

STUDIES	COMBINATION	RESULTS
Phase 3 VIALE-A (NCT02993523)[11]	Azacitidine plus venetoclax regimen	The venetoclax/azacitidine group had a median overall survival of 14.7 months.
Kwag et al[12]	Decitabine plus venetoclax regimen	In older patients, the regimen significantly improved the response rates. Patients with AHSCT achieved leukemia-free status.
Bouligny et al[13]	Decitabine plus venetoclax regimen comparison with azacitidine plus venetoclax	Measured tolerability, which showed universal cytopenias across all cell lines are not associated with venetoclax plus decitabine use.

AHSCT, allogeneic hematopoietic stem cell transplant.

response rates and survival outcomes in older patients with newly diagnosed AML compared with decitabine monotherapy. Additionally, 29% of patients who had allogeneic hematopoietic stem cell therapy (HSCT) achieved leukemia-free status with decitabine and venetoclax.[12]

According to Bouligny et al, participants in a retrospective study of decitabine plus venetoclax showed a more serious condition of thrombocytopenia compared with those taking azacitidine plus venetoclax, which depends on periods of transfusion. On the contrary, the degree of severe lymphocytopenia was lower in decitabine plus venetoclax.[13]

Patients with AML generally receive intensive chemotherapy as their primary treatment, which is far more dangerous and toxic, can lead to prolonged hospitalizations, and increases the risk for cardiologic and neurologic deficits. Alternatively, venetoclax with low-dose cytarabine is cost-effective, less toxic, and less hazardous to health than intensive chemotherapy.[14] A comparison of different therapeutic combinations used in 3 studies is presented in the **Table.**

Discussion

Venetoclax and *TP53*-Mediated Apoptosis Pathway

Venetoclax is a selective B-cell lymphoma-2 (BCL2) inhibitor, an important protein in the *TP53*-mediated apoptosis pathway. It has been studied as monotherapy and combined therapy with other agents and has proven its effectiveness.[15] BCL2 proteins play an important role in apoptosis and cell death through the intrinsic mitochondrial apoptotic pathway. Venetoclax produces its effect by binding to the BH3 domain of the BCL2 protein. This interaction leads to the production of proapoptotic proteins, which then leads to cell death. In AML, many cells express BCL2, and hence the use of venetoclax can lead to the death of many leukemic cells, playing an important role in AML therapy because cancer cells have increased survival and abnormal apoptotic processes.[16]

Venetoclax and Drug Resistance

Venetoclax is a groundbreaking cancer treatment that operates by targeting the BCL2 protein, inducing apoptosis (programmed cell death) in cancerous cells. The BCL2 protein plays a crucial role in regulating apoptosis, determining whether a cell survives or undergoes programmed death.[17] Venetoclax, although promising, does not provide a cure for certain types of cancer such as AML or CLL. Furthermore, despite initial positive responses, prolonged exposure often leads to drug resistance, a complex phenomenon not yet fully elucidated.[17-19]

Molecular Factors Influencing Response to Venetoclax-Based Treatment

Genetic alterations and mutations constitute the key molecular factors that can also influence response to venetoclax-based treatment. Some mutations lead to increased positive response, whereas others lead to increased resistance to venetoclax. The use of venetoclax for a longer duration can cause upregulation of antiapoptic proteins such as BCL-XL and MCL-1, leading to resistance. *IDH* and *NPM1* mutations are associated with increased rates of positive response, whereas mutations in *TP53*, *RAS*, and *FLT3* lead to resistance to venetoclax and venetoclax-containing regimens. Using venetoclax together with HMAs can improve the response rate to 93% in patients with *NPM1* and/or *IDH* mutations and also lead to improved rates of relapse-free survival.[20]

Furthermore, patients with *TP53* mutations did not have favorable outcomes with venetoclax-based treatments, but those in other adverse-risk molecular subgroups showed improved clinical outcomes with certain venetoclax-based treatments. These include individuals with signaling mutations such as *PTPN11*, *RAS*, *FLT3-internal tandem duplication*, and *FLT3-tyrosine kinase domain*, and splicing mutations such as *ZRSR2*, *SF3B1*, *U2AF1*, and *SRSF2*.[21] A small retrospective study by Nanaa et al

that enrolled patients with AML and myelodysplastic syndrome with *DDX41* mutations also indicated favorable responses to venetoclax combined with HMAs. Further research is needed to determine whether these mutations can serve as biomarkers for predicting venetoclax sensitivity. Molecular factors that influence response to venetoclax can be due to karyotype, specific mutations, and/or resistance mechanisms. A patient's karyotype, which may be adverse, intermediate, or favorable, affects how their leukemia responds to venetoclax. Studies comparing combination regimens in high-risk cytogenetic acute leukemia subsets with venetoclax vs those without venetoclax showed better remission rates, although overall survival remained the same in older and younger age groups.[22]

Current evidence suggests that there are no dependable laboratory markers available to precisely predict sensitivity or resistance to venetoclax treatment. Venetoclax sensitivity appears to be influenced by various factors, including patient-specific variables, AML subtype, and specific gene mutations. Predicting responsiveness to venetoclax remains challenging.

Role of Venetoclax in AML After HSCT

Relapse after HSCT often occurs within 6 months, partly due to the longer period it takes the graft-vs-leukemia effect to develop to protect against AML relapse.[23] Most clinical trials aim to administer treatment within 2 to 3 months of transplantation. According to Schroeder et al, there are 2 types of post-HSCT maintenance therapy: prophylactic and preemptive treatments.[24] Several options can be considered for post-HSCT maintenance, such as FLT3 inhibitors, which are categorized into first-generation or multitarget agents including sorafenib (Nexavar), midostaurin (Rydapt), and sunitinib (Sutent). Those that are selective are also known as second-generation FLT3 inhibitors: quizartinib (Vanflyta), gilteritinib (Xospata), and crenolanib.[25]

Venetoclax BCL2 inhibitors have recently been under investigation for their potential for use as maintenance therapy in a post-HSCT setting. An ongoing clinical trial is studying the efficacy of venetoclax combined with azacitidine. Moreover, a retrospective trial conducted by Amit et al studied venetoclax monotherapy in one group and donor lymphocyte infusions at increasing doses in another group. Both groups showed early signs of relapse with median survival of 6.1 months.[26-28]

Role of Venetoclax After HMA Failure

Hypomethylating monotherapy targeting AML is generally reserved for patients who are less able to tolerate the more intensive chemotherapy regimens, specifically the antileukemic chemotherapy regimen. HMA provides a much safer option for populations that are medically unfit or older.

However, due to its modest complete remission rates, this regimen is subject to failure. HMA failure is broadly divided into 2 categories. Primary failure is when the HMA regimen fails the patient (ie, the patient is in complete remission or complete remission but has an incomplete count recovery). Secondary failure refers to when a patient has an incomplete remission and an incomplete count recovery.[28,29] In the subset of the AML population, the older regimen constituted a combination of LDAC, HMA, or some form of supportive care. The regimen was found to have fewer adverse effects in the older population. However, despite the safety profile, the complete response rates were not satisfactory, with a median survival of only 1 year.[10,29]

A review article done by Aldoss et al illustrates the potential of venetoclax to be used off-label for patients with AML in whom HMA failed. Twenty-three patients in a prospective cohort were followed up, and a complete response rate of 43% was noted along with a median survival of less than 1 year after the addition of venetoclax to their HMA regimen.[30]

Moreover, according to a retrospective study done by Tenold et al, patients with relapsed/refractory AML were divided into 2 groups. One received HMA monotherapy, and the second group received venetoclax plus HMA regimen. The venetoclax plus HMA group showed improved median overall survival and lower adverse effects compared with the HMA-only group. However, due to the lack of a definitive phase 3 trial and a limited number of patients, these findings are yet to be further investigated.[31]

Conclusion

This review article has included 58 original articles that emphasized the importance of the use of venetoclax in AML. This new emerging drug, when used in combination with other drugs, has transformed the treatment dynamic of acute myeloid leukemia. Venetoclax is a key treatment for AML with minimal adverse effects and can be used across all age groups. Physicians should prioritize the use of venetoclax along with combination drugs to prevent this deadly disease. We aim to bring attention to this promising aspect of venetoclax in the medical literature world.

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GASTROINTESTINAL CANCER

Expert Commentary on the Product Profile of Tislelizumab in Advanced Esophageal Cancer

Krystal Preston, PharmD, BCPS, spoke about the use of tislelizumab-jsgr (Tevimbra) for patients with unresectable or metastatic esophageal squamous cell carcinoma. She highlighted specific adverse effects (AEs) observed with this drug and how it is showing promise in different settings and disease types.

PRODUCT PROFILE

DRUG NAME: Tislelizumab-jsgr (Tevimbra)

DATE OF APPROVAL: March 14, 2024[1]

INITIAL INDICATION: For patients with unresectable or metastatic esophageal squamous cell carcinoma after prior systemic therapy not including a PD-L1 inhibitor[2]

DOSAGE: 200 mg every 3 weeks

HOW SUPPLIED: 100 mg/10 mL injection

PIVOTAL CLINICAL TRIAL: Phase 3 RATIONALE-302 (NCT03430843)[3]

DESIGN OF THE PHASE 3 RATIONALE-302 TRIAL

INCLUSION CRITERIA
Histologically confirmed diagnosis of esophageal squamous cell carcinoma, tumor progression on or during first-line treatment, at least 1 measurable value by RECIST v1.1, and an ECOG performance status of 0 or 1

END POINTS
Primary: Overall survival
Secondary: Overall survival in the PD-L1–positive analysis set, objective response rate, overall response rate, and progression-free survival

COMMENTARY

Krystal Preston, PharmD, BCPS
Senior Clinical Oncology Pharmacist at CVS Health
Clinical Pharmacist at the University of Chicago Medicine
President of Chicago Pharmacists Association

Q / What is tislelizumab's mechanism of action?

Preston / This is an anti–PD-1 antibody that binds to the PD-1 receptor and blocks interactions between PD-1 and its ligand PD-L1, releasing the PD-1 pathway–mediated inhibition in the immune response. When we bind the PD-1 receptor with its ligand found on T cells, it inhibits T-cell proliferation and cytokine production. Blocking PD-1 activity has resulted in decreased tumor growth in animal models in different studies.

Q / Are there any specific characteristics that may help identify patients who are most likely to benefit from tislelizumab therapy?

Preston / Currently, tislelizumab is a second-line therapy option that will most likely benefit patients who have advanced or metastatic esophageal squamous cell carcinoma, and patients who have progressed on first-line therapy.

Q / RATIONALE-302 findings demonstrated an improvement in overall survival (OS). How is that significant in the context of treatment options available for unresectable or metastatic esophageal cancer?

Preston / It's very significant. In fact,

more studies have been done beyond RATIONALE-302. In terms of this study, the OS with tislelizumab was statistically significant and showed a clinically meaningful improvement compared with chemotherapy. OS with the tislelizumab group was 8.6 months vs 6.3 months in the chemotherapy group. These results are similar to other anti–PD-1 drugs that are indicated for esophageal squamous cell carcinoma.

However, in a more recent study, the phase 3 RATIONALE-306 trial [NCT03783442], tislelizumab plus chemotherapy demonstrated superiority over chemotherapy plus placebo. The OS was 17.2 months in the tislelizumab plus chemotherapy ground vs 10.6 months in the chemotherapy plus placebo group. That's significant. We use tislelizumab right now in the second-line therapy space. With the most recent data, we see that it has the potential to be a contender in the first-line therapy space similar to other drugs in its class such as pembrolizumab and nivolumab.

Q / What are some of the most common AEs that are observed with tislelizumab, and how do they compare with other treatments for esophageal cancer?

Preston / Usually, first-line therapy for esophageal cancer involves chemotherapy; that's our first-line option. When we get into second-line options, we now have other immunotherapies, and some of those immunotherapies are used first line now as well. In terms of the AEs, tislelizumab is similar to other PD-1 drugs for this particular cancer indication, but it's still less than we see with chemotherapy. We have the standard metabolic effects like decreased sodium [levels], hypothyroidism, and increased serum glucose [levels]. We also see an increase in the liver enzyme [levels], specifically serum alkaline phosphatase. We also see hematological effects such as anemia and decreased platelet count. Other AEs would include gastrointestinal effects like abdominal pain, nausea, and vomiting. Additionally, [we see] fatigue, musculoskeletal pain, and cough. These are standard with the other drugs in this class.

Q / As with other targeted therapies, resistance may develop. What are some known potential resistance mechanisms associated with tislelizumab?

Preston / There are several potential immunotherapy resistance mechanisms that can impede the antitumor activity of these immunotherapy drugs. Some of these mechanisms include antigen deletion, T-cell dysfunction, increased immunity of immunosuppressive cells, and the alteration of ligand expression within tumor cells. Specific to PD-1 immunotherapies, it's important to note that the nonpotential mechanisms of resistance involve the interaction between the Fc region of the drug and the Fcγ receptor on the macrophages of those tumor cells, which would induce phagocytosis. With tislelizumab and the RATIONALE-302 trial, it was noted that this particular anti–PD-1 monoclonal antibody was engineered to minimize binding of that Fc region to the Fcγ receptor. This is crucial when it comes to antitumor activity. The inability of the Fc region on the drug to bind with the Fcγ receptor on the tumor limits antibody-dependent phagocytosis. Therefore, we're eliminating the resistance mechanism.

Q / Where do you see this agent headed?

Preston / Tislelizumab is currently FDA approved for resectable/metastatic esophageal squamous cell carcinoma but only in the second-line setting. Things are looking promising for tislelizumab, which is likely to receive more FDA-approved indications, and it is expected to be approved in the first-line setting in combination with chemotherapy, such as etoposide and carboplatin. This approval will be based on the RATIONALE-306 trial [findings].

It is also expected to be approved in the first-line [setting for] advanced gastric and gastroesophageal cancer, and that has the Prescription Drug User Fee Act date of December 2024. There are other disease states where tislelizumab is being studied as well, including hepatocellular carcinoma. The National Comprehensive Cancer Care Network guidelines have already approved it to be used as first-line therapy for hepatocellular carcinoma and for patients who are ineligible for resection transplant or local regional therapy. Tislelizumab is also being studied in urothelial carcinoma, Hodgkin lymphoma, and so many other types of cancer.

Q / Is there anything else you would like to highlight today?

Preston / Tislelizumab was approved in March as a second-line option for esophageal squamous cell carcinoma. It has the potential to gain approvals and treat some of the same cancers as its competitors, such as nivolumab [Opdivo] and pembrolizumab [Keytruda]. Based on its premier drug design that helps it to evade resistance mechanisms and with the new promising data, tislelizumab is a strong contender and is a premier cancer therapy option. This may even supersede the other drugs in this class in the future. There is a lot more to come with tislelizumab. ■

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Quadruplet Therapy May Be the New Frontline SOC in Multiple Myeloma

 Rafael Fonseca, MD

 Peter Voorhees, MD

 Luciano Costa, MD, PhD

 Hans Lee, MD

 Binod Dhakal, MD

 Shaji Kumar, MD

During the 2024 European Hematology Association (EHA) Congress, experts in the field of multiple myeloma sat down to discuss the effect of earlier lines of therapy on the disease.

The panel was led by **Rafael Fonseca, MD**, director for innovation and transformational relationships at Mayo Clinic in Arizona. He was joined by **Luciano Costa, MD, PhD**, professor at the University of Alabama at Birmingham, Heersink School of Medicine; **Binod Dhakal, MD**, associate professor at the Medical College of Wisconsin; **Peter Voorhees, MD**, professor and director of outreach services at Levine Cancer Institute, Atrium Health; **Hans Lee, MD**, associate professor in the Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center; and **Shaji Kumar, MD**, a hematologist from Mayo Clinic.

The conversation focused on frontline therapy, CAR T-cell therapy, and updated trial results. Additionally, the panelists could cover any data that emerged from EHA or the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting.

Earlier-Line Options for Newly Diagnosed Multiple Myeloma

The PERSEUS Trial

The panel discussed the phase 3 PERSEUS trial (NCT03710603), which assessed the use of daratumumab (Darzalex) plus bortezomib (Velcade), lenalidomide (Revlimid), and dexamethasone (D-VRd) vs VRd for patients with transplant-eligible newly diagnosed multiple myeloma.[1]

Updated data found the minimal residual disease (MRD) rate at 10^{-6} was 34.4% and at 10^{-5} it was 57.5% for the end of consolidation in the D-VRd arm vs 16.1% and 32.5% in the VRd arm. Additional results were assessed up to 12 months were 43.9% and 65.1% vs 20.9% and 38.7%; up to 24 months it was 57.7% and 72.1% vs 27.4% vs 44.9%; and up to 36 months it was 63.9% and 74.6% vs 30.8% and 46.9% in the D-VRd and VRd arms, respectively.

While presenting these data, Fonseca noted that when a patient enters MRD, it becomes a major marker for good long-term outcomes. When the floor was opened to comments, the panel chimed in about the use of MRD and quadruplets in the space.

"We're at a point now where induction therapy is so good that using MRD negativity at 10^{-5} is going to become increasingly difficult because there's going to be such a high percentage of patients who achieve it. There's no question that [quadruplet therapies] are the preferred standard for patients who are fit or transplant eligible."

Costa noted that MRD plays a large role in determining outcomes. He believes that as trials develop and initial efficacy data emerge, the standard of care (SOC) may change, and it will help clinicians to adapt.

Fonseca asked Dhakal which patient populations, if any, should be treated with a triplet regimen vs a quadruplet.

"That is an important question for patients who are older than 80 years," Dhakal said. "In my clinical practice, if I have to choose a regimen for a patient who is older than 80 years, unless they are ultra-high risk, I would be more inclined to choose just DRd-based regimens." He tries to avoid bortezomib as it comes with increased neuropathy.

Lee believes that quadruplet therapies are superior to triplets but would prefer to think of the question as who is more eligible for a quadruplet vs a triplet. "If they're eligible to receive 4 drugs, they should receive 4 drugs whether they're transplant eligible or ineligible. If they're triplet eligible, the favored regimen would be the DRd regimen because it's so well tolerated."

Lee wondered if adding daratumumab to lenalidomide maintenance as seen in PERSEUS and the phase 2 GRIFFIN trial (NCT02874742) yielded positive efficacy.[2] He believes the results observed especially from PERSEUS with the MRD data show a benefit to the population.

Kumar thinks of the daratumumab plus lenalidomide maintenance therapy as a package and continues with it after transplant. He believes there is knowledge missing on how to effectively use this treatment.

The CASSIOPEIA Trial

The next trial of discussion was the phase 3 CASSIOPEIA trial (NCT02541383). The trial assessed bortezomib, thalidomide (Thalomid), and dexamethasone (VTd) with or without daratumumab (D-VTd) maintenance or observation for patients with transplant-eligible, newly diagnosed multiple myeloma.

Topline efficacy results included a median progression-free survival (PFS) from first randomization regardless of second randomization of 83.7 months (95% CI, 70.2-not estimable) in the D-VTd group vs 52.8 months (95% CI, 47.5-58.7) in the VTd group (HR, 0.61; 95% CI, 0.52-0.72; P <.0001). The median overall survival from first randomization despite second randomization was not reached in either group, with 72-month rates of 86.5% (95% CI, 83.5%-89.3%) in the D-VTd group and 77.7% (95% CI, 73.9%-81.0%) in the VTd group.

A subgroup analysis was conducted to analyze the PFS of D-VTd maintenance vs D-VTd plus observation. The PFS was significantly longer in the maintenance group vs observation (HR, 0.76; 95% CI, 0.58-1.00; P = .048).

Looking at these data, Fonseca said he struggles with using maintenance and determining the amount of benefit a patient gets from it. Dhakal hypothesized based on the data presented that daratumumab maintenance will "win" as longer follow-up occurs. Following this treatment plan is also similar to what was discussed with PERSEUS.

"We've struggled with this question at our institution, and most of my colleagues use single-agent lenalidomide maintenance after induction and transplant therapy. The CASSIOPEIA data are starting to make me want to go back to the group and reevaluate how we approach this. In this analysis, the D-VTd followed by daratumumab was not compared with the VTd followed by daratumumab, where the PFS curves are similar, even with long-term follow-up," said Voorhees.

Voorhees concluded that while these data were beneficial, it was not a home run.

CAR T-Cell Therapy Options

Quadruplet therapies are a big topic in the conversation about the use of CAR T-cell therapy. The phase 3 CARTITUDE-4 trial (NCT04181827) assessed ciltacabtagene autoleucel (cilta-cel; Carvykti) vs SOC for patients with functional high-risk multiple myeloma.[3]

In patients with 1 prior line of therapy and functional high-risk multiple myeloma, the overall response rate was 87.5% in the cilta-cel arm vs 79.5% in the SOC arm. The OR for a complete response or better was 3.3 (95% CI, 1.3-8.4; P = .0102).

The overall MRD negativity at the 10^{-5} threshold was 65.0% in the cilta-cel arm vs 10.3% in the SOC arm (OR, 16.3; 95% CI, 4.8-55.1; P <.0001).

Kumar often hesitates to use CAR T-cell therapy during a first relapse. Adding CAR T-cell therapy comes with increased toxicity, and Kumar sometimes does not want to interrupt the first or second progression-free interval with that.

"This is a very good clinical dilemma that I have in the clinic. If somebody is daratumumab naive, are you OK with giving these patients CAR T-cell therapy in the second line? Looking at the data, at face value, it looks solid, right? Because 25% of the patients there are exposed or refractory in CARTITUDE-4, and 75% are daratumumab naive, and they still did very well," said Dhakal.

Voorhees uses cilta-cel depending on his patients as he worries about secondary malignancies and neurotoxicities. If a patient is standard risk, he prefers to look at other options. He believes the term functional high-risk needs a better definition so patients can be treated more accurately.

Lee believes more decisions can be made when additional CARTITUDE-4 data come out, and those who are functional high-risk should be prioritized for use with cilta-cel.

Kumar commented on the best time to sequence CAR T-cell therapy. "You have to start thinking about what we are going to give in the first-line therapy and second-line therapy that least impacts the ability of CAR T to give the maximum benefit. We don't have much data at this point, but I think as we start dosing more and more patients in the first and second line, we'll get a better sense of whether certain regimens used in the first and second line impact the outcome of the CAR T later."

Looking Toward the Future

As the discussion ended, the panelists were asked how they hope to see the field evolve. Kumar wants to maximize the intensity of treatment in the up-front setting, specifically looking at quadruplets plus transplant. For those in the first relapse, CAR T-cell therapy can be considered, but in second relapse and beyond, the patient should be consulted, as it may impact their quality of life.

Dhakal highlighted that quadruplet regimens have cemented their positions in the newly diagnosed setting. He is still hesitant about the use of maintenance therapy, but the data with doublet maintenance seem promising. He is also keeping an eye on the B-cell maturation antigen setting, as it is an emerging field.

Costa agreed that more data and trials are needed for the maintenance setting so providers can provide clear and concrete answers to their patients.

For patients with standard-risk multiple myeloma, Voorhees believes the progress made there has been "phenomenal"; however, for those with ultra-high risk, a new regimen is essential.

Lee is looking forward to subset analyses for patients aged 65 to 75 years, as this is a gray area for data and how to treat the population.

Fonseca concluded that education in the community needs to be improved so that all patients are getting the same level of care. ■

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

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

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

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

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

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

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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For patent information: www.janssenpatents.com

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