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INTEGRATED TEAM APPROACH

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EGFR+ mNSCLC WILL FIND THE BACK ROADS

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

Staying ahead of *EGFR*+ mNSCLC is important

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

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

Burden of *EGFR*+ mNSCLC mutations limits survival

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

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

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

Acquired resistance drives disease progression[8]

up to 50%

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

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

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

References: 1. Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with *EGFR* mutations. *J Clin Oncol*. 2013;31(27):3327-3334. **2.** Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239-246. **3.** Wu Y-L, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(11):1454-1466. **4.** Park K, Tan E-H, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with *EGFR*-mutation-positive non-small-cell lung cancer (LUX-Lung7): a phase 2B, open-label, randomised, controlled trial. *Lancet Oncol*. 2016;17(5):577-589. **5.** Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated *EGFR*-mutated non-small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125. **6.** Saito H, Fukuhara T, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-squamous non-small-cell lung cancer (NEJ026): an interim analysis of an open label, randomised, multicentre, phase 3 trial. *Lancet Oncol*. 2019;20(5):625-636. **7.** Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, *EGFR*-mutated, advanced, non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol*. 2019;20(12):1655-1669. **8.** Passaro A, Jänne PA, Mok T, Peters S. Overcoming therapy resistance in *EGFR*-mutant lung cancer. *Nat Cancer*. 2021;2(4):377-391. **9.** Nieva J, Kari PS, Okhuoya P, et al. A real-world (rw) observational study of long-term survival (LTS) and treatment patterns after first-line (1L) osimertinib in patients (pts) with epidermal growth factor receptor (EGFR) mutation-positive (m) advanced non-small-cell lung cancer (abstract). *Ann Oncol*. 2023. Abstract 1344P. **10.** Lee JY, Mai V, Garcia M, et al. Treatment patterns and outcomes of first-line osimertinib-treated advanced *EGFR*-mutated NSCLC patients: a real-world study (abstract). Presented at: IASLC 2022 World Lung Conference on Lung Cancer; August 6-9, 2022; Vienna, Austria. Abstract EP08.02-082. **11.** Girard N, Leighl NB, Ohe Y, et al. Mortality among *EGFR*-mutated advanced NSCLC patients after starting first-line osimertinib treatment: a real-world, US attrition analysis. Poster presented at: the European Lung Cancer Congress; March 29-April 1, 2023; Copenhagen, Denmark. **12.** Bazhenova L, Minchom A, Viteri S, et al. Comparative clinical outcomes for patients with advanced NSCLC harboring *EGFR* exon 20 insertion mutations and common *EGFR* mutations. *Lung Cancer*. 2021;162:154-161. **13.** Leonetti A, Sharma S, Minari R, et al. Resistance mechanisms to osimertinib in *EGFR*-mutated non-small-cell lung cancer. *Br J Cancer*. 2019;121(9):725-737. **14.** Yu HA, Kerr K, Rolfo CD, et al. Detection of MET amplification (MET amp) in patients with *EGFR* mutant (m) NSCLC after first-line (1L) osimertinib (abstract). 2023 American Society of Clinical Oncology Annual Meeting. June 2-6, 2023; Chicago, IL. Abstract 9074. **15.** Ramalingam SS, Zhang N, Yu J, et al. Real-world landscape of *EGFR* C797X mutation as a resistance mechanism to osimertinib in non-small-cell lung cancer (abstract). *J Thorac Oncol*. 2022;17(9S):S670S68. Abstract MA07.13. **16.** Besse B, Baik CS, Marmarelis ME, et al. Predictive biomarkers for treatment with amivantamab plus lazertinib among *EGFR*-mutated NSCLC in the post-osimertinib setting: analysis of tissue IHC and ctDNA NGS (abstract). 2023 American Society of Clinical Oncology Annual Meeting. June 2-6, 2023; Chicago, IL. Abstract 9013.

In September 2024, MJH Life Sciences will celebrate its 25th anniversary. The company, initially founded by my father, Mike Hennessy Sr, was created with the shared goal of improving health care.

Looking back over the years, the innovation and developments have far exceeded anything we could have expected. In oncology, we have covered major approvals across all disease types that have helped to push the needle forward. Throughout the years, advancements in cancer treatment have covered personalized therapies, the introduction of CAR T-cell therapy, liquid biopsies, and, most recently, the use of artificial intelligence to help predict outcomes.

This issue of *ONCOLOGY* focuses on one of our brand descriptions: multidisciplinary care. Our main manuscript this month, written by Carl He, MD, discusses the multidisciplinary team approach, ways to positively implement this, and how to overcome any barriers. Additionally, Laura Bucher-Bailey, PharmD, discusses the use of tisotumab vedotin-tftv (Tivdak) and gives her take on implementing this treatment into clinical practice for patients with cervical cancer. For pharmacists and clinicians alike, this interview brings great value to deciding which treatment to use and how it may affect patients.

Finally, Nausheen Ahmed, MD, lead author on the study investigating toxicity linked with CAR T-cell therapy, spoke about how the Risk Evaluation and Mitigation Strategy mandate should be updated. In her study on patients with lymphoma, post- CAR T-cell therapy, she found on-average patients needed less hospital stays than what the mandate required, and this was leading to financial toxicity for patients. Every step of the way, *ONCOLOGY* has covered the latest developments to bring our audience the highest-quality information on ways to improve cancer care. These advancements are a testament to the dedication and hard work of researchers, clinicians, and health care professionals worldwide.

As we look to the next 25 years, we hope to continue to bring timely, multidisciplinary, and engaging content for all *ONCOLOGY* readers. Thank you all for your contributions and continuous support throughout our journey. ■

Warm regards,

Mike Hennessy Jr
President and CEO
MJH Life Sciences®

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CONTENTS

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2024 Statistics May Impact Next Decade of Cancer Treatment

Estimates published in *CA: A Cancer Journal for Clinicians* project that more than 2 million people in the United States will receive a new cancer diagnosis in 2024. Of them, 600,000 will die from cancer or complications, according to the annual report on cancer trends by the American Cancer Society.[1] Over the past 30 years, the risk of dying from cancer has steadily declined, due to smoking cessation, early detection, and treatment advancements. However, at the same time, cancer incidence is on the rise for certain types of cancers.

In 2024, for the first time, new cases of cancer in the US are expected to cross the 2 million mark. The top 10 most common cancers are breast, prostate, endometrial, pancreatic, kidney, melanoma, lung, colorectal, bladder, and non-Hodgkin lymphoma. Although some cancers are not increasing overall, there are subgroups of these cancers that *are*, including colorectal cancer in patients 55 years or older, liver cancer in women, human papillomavirus (HPV)–associated oral cancers, and cervical cancers in women aged 30 to 44 years. Early detection in a higher percentage of the population would certainly improve these diagnoses for some of these cancers, such as HPV-associated cervical cancers or colorectal, for example. Many of the cancers that are increasing are also associated with obesity, such as endometrial, liver, colon, and breast cancers. The data also point to racial disparities in early detection; in addition, overall cancer death rates are 19% higher in Black men than in White men, largely due to the number of deaths from prostate cancer. Hispanic patients have one of the highest rates of HPV-associated cervical cancer; it is 35% higher in Hispanic women than White women.

Julie M. Vose, MD, MBA,
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What can we do as hematology/oncology physicians to improve these statistics? Most patients come to us after receiving a diagnosis, not before. However, through the efforts of our cancer centers and professional societies, we can advocate for early detection, community education for screening and prevention of primary or secondary cancers, follow-up of cancer survivors for new cancers, and funding for screening tests for underserved populations. In addition to improving education regarding the need for cancer screening, some of the studies that have shown the greatest improvements in screening were among the subset of interventions that addressed transportation to screening appointments, language interpretation, and affordability.[2-4] It is in the best interest of our patients and society to either prevent cancers or diagnose them earlier in the course of the disease when treatments are less intense and outcomes are improved.

By improving our commitment to education, screening, and early detection, we can use our resources wisely to improve prevention as well as offer successful treatments and preventive measures for all malignancies. ■

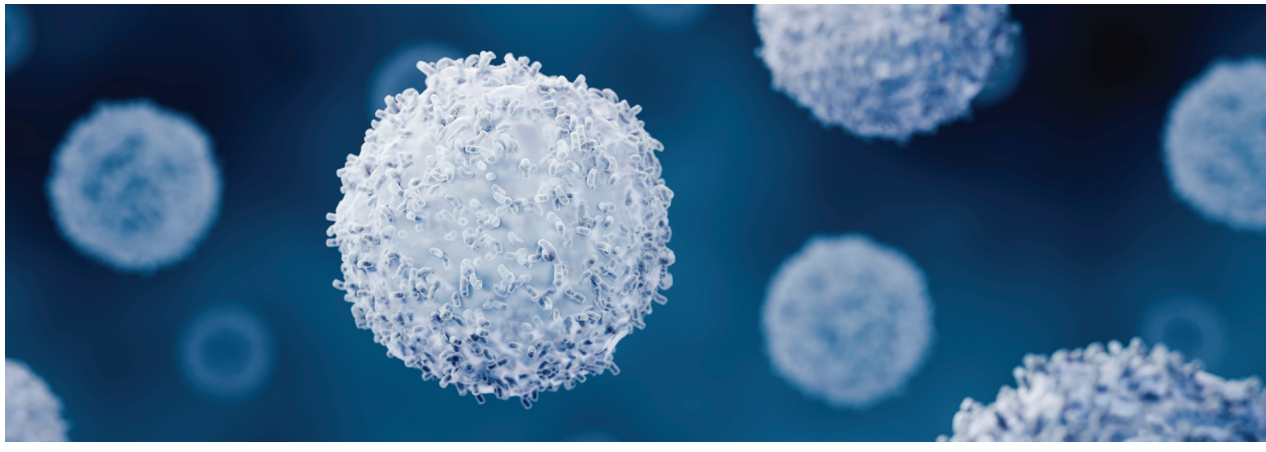
REFERENCES

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin.* 2024;74(1):12-49. doi:10.3322/caac.21820

2. Moralez EA, Rao SP, Livaudais JC, Thompson B. Improving knowledge and screening for colorectal cancer among Hispanics: overcoming barriers through a PROMOTORA-led home based educational intervention. *J Cancer Educ.* 2012;27(3):533-539. doi:10.1007/s13187-012-0357-9

3. Mojica CM, Almatkyzy G, Morales-Campos D. A cancer education-plus-navigation intervention implemented within a federally qualified health center and community-based settings. *J Cancer Educ.* 2021;36(1):152-159. doi:10.1007/s13187-019-01611-5

4. Alcaraz KI, Wiedt TL, Daniels EC, Yabroff KR, Guerra CE, Wender RC. Understanding and addressing social determinants to advance cancer health equity in the United States: a blueprint for practice, research, and policy. *CA Cancer J Clin*. 2020;70(1):31-46. doi:10.3322/caac.21586



Reconsidering REMS Mandate May Improve CAR T-Cell Therapy Accessibilit

Nausheen Ahmed, MD, Associate Professor, Division of Hematologic Malignancies and Cellular Therapeutics at the University of Kansas Medical Center, Kansas City, KS

Investigators of a study recently published in *Blood Advances* assessed toxicity onset and duration in patients receiving chimeric antigen receptor (CAR) T-cell therapy to test the viability of FDA Risk Evaluation and Mitigation Strategy (REMS) mandates.[1]

CancerNetwork spoke with the study's lead author, Nausheen Ahmed, MD, an associate professor in the Division of Hematologic Malignancies and Cellular Therapeutics at the University of Kansas Medical Center in Kansas City. She shared post–CAR T-cell therapy toxicity findings and discussed their implications regarding patient accessibility and a potential revision to FDA guidelines.

Ahmed highlighted the relatively low occurrences of cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) at 2 weeks after CAR T infusion. Cooperation between a patient's primary care physician and a specialized care center may ensure that physical and financial constraints are reduced for patients without sacrificing access to care. Additionally, the findings supported a more flexible approach, whereby patients undergo a 2-week monitoring period within a certain distance of a specialized care center followed by a collaborative assessment of a patient's individualized needs beyond that period.

Q / What was your rationale for the study?

Ahmed / The rationale for this study started from my background in understanding more about accessibility issues with CAR T. Currently, CAR T-cell therapy is not your regular off-the-shelf drug that, if prescribed, patients just get the next day. It's one of those therapies that have a lot of upfront investment with the patient's time. It does carry some financial and physical burden on the patient from the time of collection of the cells all the way up to the postmonitoring period. Some of my prior work demonstrated that there are groups of patients who are not able to get CAR T or have a lower likelihood of getting CAR T, such as those from lower socioeconomic classes and those who may be from ethnic and racial minority groups, especially African American groups.

I demonstrated that in 2022 in one of my papers,[2] as well as one in 2024, which we recently published in *Transplantation and Cellular Therapy.*[3] We also found that there are some other groups of people, such as those living more than 2 hours from a treatment center, who may not have adequate access to CAR T.

Putting it all together, the question was, "Is there any part of this whole CAR T process that is contributing to the physical and financial burden and is not of much value? Is there anything that we can do to make it easier for the patients without compromising safety or efficacy?" One thought that came to my mind was that there's an FDA REMS mandate [stating that] patients have to relocate to be within 2 hours of the center for up to 4 weeks and they should avoid driving for up to 8 weeks from the day that they get their CAR T-cell therapy. Are those restrictions necessary?

[These mandates] were specifically put in place for monitoring 2 initially unique toxicities of CAR T, which are ICANS and CRS. My study of 475 patients with non-Hodgkin lymphoma [included patients] who received axicabtagene ciloleucel [Yescarta], tisagenlecleucel [Kymriah], or lisocabtagene maraleucel [Breyanzi]. These are the 3 CAR T-cell products they received as the standard of care. We wanted to see whether these toxicities occur up to the 4-week mark [of treatment]. Do they occur beyond that to justify those [REMS] restrictions?

We found that after 2 weeks, the incidence of CRS was 0% and the incidence of ICANS was [approximately] 1%. Our study, based on these data, gives us some grounds to revisit those requirements and see whether we can reduce that time to a 2-week mandatory period, making it more flexible so that patients and their doctors can decide how long the patient needs to be monitored beyond the 2 weeks. This might help [improve] access because patients [currently] have to relocate close to a center. The FDA mandate is 2 hours [within proximity to a center], but a lot of times, our centers have even stricter mandates.

> **"[CAR T-cell therapy] does carry some financial and physical burden on the patient from the time of collection of the cells all the way up to the postmonitoring period."**
> —Nausheen Ahmed, MD

They may say within 30 minutes, 45 minutes, or 60 minutes. If [one goes] to different centers, there will be different requirements. A patient may have to relocate closer to the center and bring a caregiver with them and then not be able to drive for 8 weeks. The study results pretty much demonstrate that these [requirements] need to be revised.

Q / Aside from ICANS and CRS, can you provide a brief general overview of the results of your study?

Ahmed / We also explored causes of death. Although we focused on neurotoxicity and CRS, we wanted to know whether we were missing something or whether patients were dying due to something else that needed to be monitored closely for 4 weeks. We found that within the first 4 weeks, neurotoxicity and infections were the main causes of death. Beyond 4 weeks—we went up to 90 days—the incidence of death did not go down. In fact, there were still patients dying; they were dying of infections, primarily.

That [outcome] was instructive in at least 2 ways. First, there's no magic to day 28. This is a whole continuum of care for the patient. A lot of times, it's the primary referring physician who takes over the care of the patient after the 28 days, and they may not be completely in tune with managing or recognizing these infections or understanding the complications of CAR T-cell therapy. These data inform us that we need to have more of a collaborative approach with our referring doctors in order to improve survival of the patients. The answer is not to keep the patients near the center for 90 days; the answer is more about allowing them to go back to their homes and then to empower, educate, and involve them and collaborate with their community doctors to improve their survival. The level of involvement of the treatment center must be individualized based on the locally available infrastructure and expertise.

Q / What do you propose as the new monitoring guidelines?

Ahmed / We saw that the incidences of CRS and ICANS were as expected, as they usually occurred within the first 2 weeks [of therapy]. [Therefore], monitoring can be [conducted] in an inpatient or outpatient [setting] by the treatment center. It's important in the first 2 weeks that the patient is monitored very closely, which they are right now. Patients are either admitted to the hospital for a period of time, or they're monitored almost on a daily basis with 24/7 access to care bypassing the emergency department for at least 2 weeks. Beyond that, [monitoring] would have to depend on

what's going on with the patient. Are their blood counts very low? Are they at a high risk of infection? It has to involve more [individual-based] decisions on whether the patient can go back, stay home, and be monitored locally. In this day and age, we're still monitoring them very closely, but that can be more flexible and more individualized for each patient.

Q / Are there plans to evaluate other CAR T-cell therapies for adverse effects [AEs] beyond those listed in the study?

Ahmed / Our group has [previously] looked at multiple myeloma and at the 2 CAR T-cell therapies that are available for myeloma, which are idecabtagene vicleucel [ide-cel; Abecma] and ciltacabtagene autoleucel [cilta-cel; Carvykti]. We recently published [findings] in *Transplantation and Cellular Therapy* demonstrating that the chances of CRS or ICANS starting after 2 weeks are extremely low.[4] We also looked at what the causes of death were with the same question in mind for those constructs. We found that infections, again, were predominantly the reason for death, even in the population of patients who had not progressed.

In our multiple myeloma findings, there was also a different AE that was not seen in our lymphoma findings, which is hemophagocytic syndrome. Immunotherapy [may be] associated with hemophagocytic syndrome. There were some deaths from that as well, which is another thing to watch out for with CAR T in general. That's one of the newer AEs that we're becoming more aware of. The onset of that is sometimes a little beyond CRS, but at the same time, if a patient is doing well beyond 2 weeks, there's no reason to keep monitoring [them on site]. They need to be monitored, but it can be done via comanagement with their primary doctors, and it should be more individualized.

Q / How should clinicians utilize and implement the data into their clinical practice?

Ahmed / Right now, we're still bound to the REMS mandates. We wouldn't be able to let patients leave before 4 weeks, and we wouldn't be able to tell them [they can] drive. The next step is seeing what the FDA thinks about these data and whether they think that this is enough evidence for them to reconsider their REMS mandates.

Q / Can you comment on the recent findings that CAR T-cell therapy may lead to secondary malignancies? Would this affect the use of these agents?

Ahmed / My study did not capture second primary malignancies because the follow-up was just up to day 90. Within the first 3 months, there aren't many second malignancies. There are some real-world data coming out [showing] that, even as early as within 2 years [of treatment], there are second primary malignancies. Mostly, those second primary malignancies would be myelodysplasia, leukemia, or skin cancers. The FDA has raised concerns about T-cell malignancies [following] CAR T-cell therapy. That is very rarely seen and is not a major concern. The other second primary malignancies are something that we will be seeing more of as we use more of these therapies.

Would that deter me from using CAR T-cell therapy? I don't think so. We have more choices these days, [such as] bispecifics. Still, the outcomes with CAR T-cell therapy in lymphoma and myeloma are still better than the outcomes with some of these other drugs. [Clinicians] have to think about the efficacy and all those [risks] when considering a therapy. The patients should [also] be informed and know what the risks are.

Q / Is there anything else that you'd like to highlight within your study?

Ahmed / The main take-home message is that we have a [long way to go] in order to improve outcomes for these patients who are receiving CAR T-cell therapy. Specifically, one of the areas where we can make a difference is infection prevention and management. [Considering] the way things have been divided into such blocks of time [before patients] go to the referring physician, there may be a gap in that transition. There has to be more of a hybrid model of care. There has to be more involvement of our referring doctors or community doctors in detecting and managing these infections or working with the specialized center in order to bypass the [emergency department] with other strategies to help these patients. That's going to be important. If there are enough data to say that the patients do not need extra restrictions beyond 2 weeks, which is what [data from] our studies show, then reconsidering the requirements will be one step toward decreasing disparities in access [to CAR T-cell therapy]. There are many other things that can be done at many other levels. This will be one of the things that I will be looking forward to seeing [progress]. ■

References

1. Ahmed N, Wesson W, Lutfi F, et al. Optimizing the post-CAR T monitoring period in recipients of axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel. *Blood Adv*. Published online July 23, 2024. doi:10.1182/bloodadvances.2023012549

2. Ahmed N, Shahzad M, Shippey E, et al. Socioeconomic and racial disparity in chimeric antigen receptor T-cell therapy access. *Transplant Cell Ther.* 2022;28(7):358-364. doi:10.1016/j.jtct.2022.04.008

3. Ahmed N, Sun F, Teigland C, et al. Chimeric antigen receptor T-cell access in patients with relapsed/refractory large B-cell lymphoma: association of access with social determinants of health and travel time to treatment centers. *Transplant Cell Ther.* 2024;30(7):714-725. doi:10.1016/j.jtct.2024.04.017

4. Wesson W, Dima D, Suleman N, et al. Timing of toxicities and non-relapse mortality following CAR T therapy in myeloma. *Transplant Cell Ther.* Published online June 11, 2024. doi:10.1016/j.jtct.2024.06.012

INTEGRATED TEAM APPROACH

Multidisciplinary Team Meetings: Barriers to Implementation in Cancer Care-

ABSTRACT The multidisciplinary team meeting has become a fundamental component of cancer care across most of Europe, North America, and Australia. In certain institutions, it holds a mandatory role in the treatment planning of all patients with cancer. Although the multidisciplinary team meeting has demonstrated improved adherence to clinical protocols in the oncology field and serves as a valuable educational tool for clinicians, it is difficult to truly gauge its impact on clinical outcomes due to the wide heterogeneity in interinstitutional meeting practices and the varied data reporting clinical outcomes. This literature review will provide an overview of the history and contextual role of the multidisciplinary team meeting in cancer management and discuss the barriers to its implementation, offering means to navigate these barriers. This review will also explore the barriers to adherence to treatment recommendations offered by the multidisciplinary team meeting in cancer care, through the lens of the patient and health care provider.

Keywords: multidisciplinary team meetings, tumor boards, communication, treatment recommendations, treatment adherence

Complex diseases such as cancer require a multidisciplinary approach among health care providers to tailor personalized patient care pathways. The multidisciplinary team meeting (MDTM) is central to this process,[1] providing a space for interdisciplinary health professionals to discuss patient cases and prospectively develop treatment recommendations.[2,3] Multidisciplinary tumor boards, analogous to cancer MDTMs, have occurred in the United States for more than 60 years, historically as an educational tool and later transitioning to focus on patient care aspects in the 1980s.[4] In the United Kingdom (UK), MDTMs were adopted in the 1990s to streamline cancer care coordination[5] following public concerns regarding the widely varied cancer care practices and historically poor survival rates, as noted in the Calman-Hine report of 1995.[2,6]

These reports and the subsequent National Health Service Cancer Plan of 2000[7] encouraged a shift away from introducing new health technologies to cancer care, instead endorsing a multidisciplinary team model approach to care with an emphasis on interdisciplinary interactions among specialists.[8] The MDTM became central to this model and has become the gold standard of cancer management in the UK.[2] Over the past 2 decades, many other European countries and Australia have also adopted the MDTM into cancer care.[4] Today, the MDTM is a staple of cancer care in Europe, North America, and Australia,[4,5,9] where national guidelines including those of the UK, France, the Netherlands, United States, and Australia mandate almost all patients with cancer have their cases discussed before treatment.[10] The functioning of MDTMs, however, varies widely

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among institutions,[5] and this review will address important barriers to the implementation of MDTMs and the adherence to MDTM recommendations in clinical practice.

Search Methodology

Three separate search strategies: (cancer) AND (multidisciplinary meeting)," "(cancer) AND (multidisciplinary team meeting)," and "(multidisciplinary tumor board) OR (multidisciplinary tumor conference)" were performed on the PubMed website in December 2023. The eligibility criteria included original English language articles published between 2003 and 2023 focusing on adult cancer populations. Additional inclusion criteria consisted of articles providing qualitative or quantitative analysis of the barriers to cancer MDTM implementation, proposed improvements to MDTM implementation, barriers to MDTM recommendation adherence, or proposed improvements to MDTM recommendation adherence. Systematic reviews and meta-analyses on the impact of MDTMs on cancer survival outcomes were also incorporated into the inclusion criteria. Articles solely describing MDTMs in pediatric patients or benign tumor types were excluded. All commentaries were excluded.

After the removal of duplicate articles, 3351 articles resulted from the search strategy and were screened by title and abstract for eligibility, with 148 papers selected for full-text screening. After full-text screening, 97 articles met the eligibility criteria, and an additional 20 articles were included through reference extraction. Most of the selected articles were qualitative studies and mixed-method studies. The discussion of cancer MDTM benefits to survival outcomes, barriers to implementation, and barriers to treatment adherence in this review was derived from content within the 117 selected articles.

The MDTM Setting

Most MDTMs occur following a patient's diagnosis,[5,11] often running weekly or fortnightly,[11] lasting 45 to 90 minutes.[12] Participants commonly include the meeting coordinator, chair, surgeons, medical and radiation oncologists, radiologists, pathologists, and cancer nurse specialists. Additional invitees may include relevant medical specialists, palliative care and nuclear medicine specialists, allied health, general practitioners, and students.[3,13] The meeting coordinator is often a cancer nurse specialist, administrative member, or senior physician who receives MDTM referrals and collates patient history and external investigations.[12]

Benefits of MDTMs

The incorporation of the MDTM into cancer care has demonstrated improved adherence to clinical guidelines.[14,15] Findings from a study by Walter et al on lung cancer MDTMs in the authors' institution noted that more than 90% of MDTM treatment recommendations are concordant with national and international guidelines.[16] Although Walter et al did not provide a comparison group of patients whose cases were managed without MDTM input, international rates of guideline adherence have been noted to vary between 35% and 65% in patients with lung cancer,[17] thereby reflecting the value of MDTMs in providing guideline-based care. Similarly, Krause et al demonstrated a high guideline adherence rate (76%) of MDTM treatment recommendations for patients with gastrointestinal cancer at their institution, with the most common cause of guideline deviation explained by the inclusion of patients into clinical trials.[18]

The cancer MDTM also improves diagnostic accuracy.[19] In a study by Newman et al of the MDTM discussions of 149 externally referred breast cancer cases, a review of external imaging by specialist breast radiologists in the MDTM resulted in alterations to 45% of previously interpreted radiologist reports, primarily involving the detection of previously missed lesions.[19] Consequently, 29% of patients received recommendations for additional biopsy or changes to their subsequent imaging plans. In the same cohort, a review of external histology by specialist breast pathologists resulted in pathology interpretation changes in 29% of cases, with 9% of patients receiving changes to their surgical management due to pathologic reinterpretation.[19] The MDTM, particularly with specialist radiologists and pathologists, facilitates a more thorough and expert reevaluation of previous imaging and histology slides to enhance diagnostic precision.[19]

Furthermore, the MDTM provides an opportunity for patients to be identified for clinical trials[20] and enables efficient patient care through early attention to psychosocial needs, coordination of investigations, hospital admissions, and outpatient appointments.[21] For patients, the knowledge that their case has been discussed in an MDTM may provide reassurance that treatment recommendations are well-informed.[22]

The literature largely shows improved survival outcomes when cancer MDTMs are incorporated into patient care.[20,23,24] A systematic review by Kočo et al noted significant overall survival increases in patients with colorectal, lung, or breast cancer with multidisciplinary discussions.[20] Among the articles selected by Kočo et al, Bydder et al compared the overall survival of patients with inoperable non–small cell lung cancer (NSCLC) with and without discussion at an MDTM, noting a statistically significant (log-rank $P = .048$) higher mean survival of 280 days in the cohort discussed in an MDTM compared with 205 days in the cohort not discussed.[25] Furthermore, Ye et al documented a significantly improved overall survival (OS) in patients with colorectal cancer discussed at the MDTMs with log-rank $P = .015$, where patients whose cases underwent management after MDTM implementation demonstrated 1-, 3-, and 5-year survival rates of 95.8%, 87.1%, and 79.1%, respectively, compared with 94.5%, 75.7%, and 62.4% in patients whose cases were not discussed in the MDTM.[26]

Also discussed by the review was a large-scale study by Yang et al comparing survival outcomes in 3681 patients with early-stage breast cancer according to MDTM treatment recommendation

adherence vs nonadherence. After a mean follow-up period of 32.75 months, a significantly higher estimated disease-free survival (93.89% vs 89.69%; $P < .001$) was calculated for the MDTM treatment recommendation–adherent group compared with the nonadherent group, with a significantly higher estimated 3-year OS (98.98% in the MDTM treatment recommendation adherent group vs 97.19% in the nonadherent group, $P < .001$).[27] Pooled meta-analysis data by de Castro et al has also identified a significantly improved OS in patients with NSCLC discussed in the MDTM compared with those without MDTM discussion.[24] A meta-analysis by Algwaiz et al of 5 articles assessing MDTM outcomes in colorectal cancer, head and neck squamous cell carcinoma, colorectal liver metastasis, gastrointestinal cancer, and rectal cancer identified improved 5-year survival rates in the patients whose cases were discussed in MDTMs, with a pooled OR of 0.59 for 5-year death rates.[23]

Despite the commonality of MDTMs, more supporting literature assessing patient outcomes and cost-benefit analyses is needed, ideally stratified to cancer type and meeting processes. There is currently an unequal distribution of cancer types studied concerning patient outcomes following the incorporation of multidisciplinary discussion. Among the most common cancer types, for example, there is a literature gap in prostate cancer outcomes with MDTM incorporation.[20] Although the available literature largely supports MDTMs, some studies have noted negligible improvement in team decision-making[28] and survival outcomes.[29] Creating study designs assessing MDTM outcomes is difficult, due to the heterogeneity of meeting processes and evolving treatments that confound outcomes.[30] Furthermore, randomized controlled trials often cannot be conducted, as the MDTM is now a standard of care across many countries.[31]

The MDTM also confers benefits to health professionals. For staff, it is an educational platform for introducing emerging treatments and clinical trials, and the meeting format can foster good professional relationships.[21,32] Through the establishment of MDTM treatment recommendations, staff may also feel more supported in their management plans.[32]

Barriers to Multidisciplinary Meeting Implementation

Although a well-operating MDTM improves patient care and professional development, a deterioration of decision-making in the MDTM renders it unproductive for implementation in cancer treatment planning, with a systematic review by Lamb et al of 37 studies showing a failure to reach consensus in 27% to 52% of MDTM cases.[33] The following sections will address the barriers to MDTM implementation as summarized in **Table 1**.

Operational Challenges

Time constraints are a common reason for the failure to reach MDTM consensus.[34] It is often not viable for all cases to be discussed in light of the increasing incidence of cancer.[35] Furthermore, centers that incorporate discussion of nonmalignant cases into their cancer MDTMs are subjected to increased caseload pressures.[36] Cases limited by time pressure may not receive adequate consideration of all treatment avenues, and documentation may also be cursory, not capturing the discussion details that led to the consensus.[21] Extensive MDTM caseloads may also result in decision-making fatigue in the latter cases. An observational study by Wihl et al utilized a tumor leadership assessment instrument (ATLAS) to assign objective ratings to case presentations in a series of MDTMs averaging 18 cases each, with findings noting a consistent pattern of case presentation quality decline after case 10.[37]

TABLE 1. Summary of Barriers to MDTM Implementation

1.	Meeting and preparatory time constraints
2.	Inadequate case information
3.	Poor team dynamics and hierarchical meeting structure
4.	Inattention to potential medicolegal ramifications
5.	Information technology issues

MDTM; multidisciplinary team meeting.

Navigating around time pressures is challenging. Focusing only on complex cases may provide a more effective context for discussion.[5] Complex cases tend to receive more MDTM input and treatment modifications. For example, an analysis by Ryan et al noted a management change in 50% of complex cases (as defined by the preoperative management of rectal cancer, disease recurrence, metastatic disease, or malignant polyps) discussed in colorectal MDTMs compared with 3.4% in routine cases.[38] Findings from an observational study by Munro et al demonstrated a significant 5-year survival benefit for patients with advanced colorectal cancer discussed in the MDTM but not for those with early-stage disease.[39] Rare tumor types such as Merkel cell carcinoma or sarcoma may also benefit from a multidisciplinary team discussion due to complex management.[29] Beyond disease status, patient comorbidities, psychosocial factors, and logistical considerations also affect the complexity of the case and warrant multidisciplinary team discussion.[40] Of note, although the MDTM may be appropriate for advanced disease, patients with very poor prognoses may be excluded from MDTMs[41,42] because they are unlikely to get significant benefits from treatment.[39,42] Per caseload, case complexity, and available meeting time, each institution is advised to develop a protocol to decide which patients require MDTMs.[13]

Furthermore, preparation for MDTMs is time intensive, involving the collation of patient history and external investigations, in addition to logistical preparations. The increasing caseload over recent decades has not been met with a proportional increase in resource availability,[43] and staff members who

spend time beyond their regular clinical duties to prepare for the meetings should be appropriately compensated.

There is emerging software that can be used to facilitate more efficient workflow in the preparation and presentation of cancer MDTM cases. For example, the NAVIFY Tumor Board is an oncology informatics software that integrates patient data from various platforms without requiring manual collation of clinical data.[44] It has demonstrated a reduction in preparation time for cancer MDTMs with increased subsequent cost-effectiveness in early studies.[45,46] NAVIFY, however, may encounter difficulties in retrieving radiology and pathology images, which are often stored within their own information systems. Furthermore, the software cannot autonomously extract pertinent images or delineate specific regions of interest within these images; that must be done manually by radiologists and pathologists.[44]

In the MDTM itself, there are computerized clinical decision-support systems (CDSSs) that can be used to improve meeting efficiency. Examples include the OncoDoc2,[47] CancerLinQ,[48] and Watson for Oncology (WFO)[49] software systems. OncoDoc2 is a breast cancer CDSS that analyzes patient data to create guideline-based treatment recommendations.[47] CancerLinQ is a CDSS that utilizes rapid learning knowledge derived from electronic patient databases to deliver real-time clinical decision support.[48] WFO is an artificial intelligence–based breast cancer CDSS that integrates knowledge from medical texts and patient cases to guide clinical decision-making.[49] Computerized CDSSs ultimately improve MDTM efficiency by streamlining the decision-making process while providing treatment advice in concordance with guidelines. Computerized CDSSs, however, have drawbacks. A series of interviews conducted with MDTM participants revealed that many were unfamiliar with computerized CDSSs, with many concerned that CDSSs limit the opportunity to deviate from guideline-based treatment advice.[50] Furthermore, rapid learning CDSSs, particularly those incorporating patient data into their learning algorithms, may encounter legal issues relating to intellectual property rights and patient privacy, which may pose barriers to data sharing and widespread implementation into clinical practice.[48]

Another barrier to the implementation of the MDTM as a useful treatment planning resource is lack of complete case information,[51] another common reason for the failure to reach MDTM consensus.[32] At times, patients' cases are discussed in the MDTM before being medically reviewed, resulting in limited information to influence treatment planning.[32] Patients with investigations conducted at external sites must have their investigations and reports transferred to the MDTM site, and patients must reliably present for additional investigations that are required before the scheduled MDTM. Radiologists and pathologists also require adequate time to interpret their findings while balancing their external commitments.[5] As such, it is commonplace for MDTM referral deadlines to exist before meetings. However, this poses a limitation whereby new patients who narrowly miss the deadline are moved to the subsequent MDTM, which can delay the time to treatment.

Interpersonal Challenges

There often exists an implicit hierarchy in the MDTM, which can limit equal member participation. The MDTM is often led by doctors, and studies have noted less decision-making capacity for nurses.[33,43,52] Focus group interviews by Rosell et al with registered nurses unveiled significant barriers to nursing staff contribution in MDTMs.[53] These included the nurses' feelings of undervaluation in MDTMs, ambiguity surrounding their roles, and barriers to attendance, such as meetings being scheduled around the physicians' availabilities.[53] Results from a survey of lung cancer nurse specialists in the UK revealed only 51.7% expressed a willingness to challenge other MDTM members, whereas 19.1% found the MDTM to be an uncomfortable or intimidating experience.[54] Furthermore, an observational study by Wallace et al noted only 58 of nearly 1500 MDTM case discussions received any input from a clinical nurse specialist.[55] When actively involved, nurses tend to involve psychosocial aspects and patient preferences in MDTM discussions, which are important parameters in treatment planning.[43] Indeed, study results have identified a general deficit in the discussion of psychosocial aspects of patient care in MDTM formats, where medicalized discussions frequently predominate over patient-centered considerations.[56] Meetings are often chaired by surgical personnel,[43] and having a rotating leadership[43] or ascribing the chairing role to the clinical nurse specialist has been suggested to be a successful means of flattening the hierarchy and increasing nursing input in MDTMs.[57]

Discussion quality may also be poor if differing perspectives are not expressed due to time pressures or inferred hierarchy.[58] An Australian survey of doctors on the MDTM format noted that although 85% had disagreements with treatment recommendations, 71% did not dissent,[59] which therefore limited open communication and consequently promoted groupthink. As such, it may be useful to employ observational instruments to assess MDTM communication dynamics for better quality monitoring.[43]

Furthermore, although the MDTM is often intended as an educational tool for residents, barriers such as time pressure, team hierarchy, and lack of familiarity with meeting regulations may prevent residents from actively engaging, thus limiting the educational value for them. To enhance residents' proficiency in communication and collaboration during MDTM sessions, incorporating MDTM simulation training could be useful.[60] The simulation environment would allow for pauses at any point for residents to evaluate their behavioral and communication skills, whereas the fast pace of the real MDTM does not afford this opportunity.

Logistical Challenges

MDTMs cannot operate sustainably when there is poor awareness of physician medicolegal responsibilities. There are limited articles addressing the medicolegal aspects of cancer MDTMs worldwide, although there are some Australian articles dedicated to this topic. An Australian National Forum produced a consensus recommendation requiring informed consent to be obtained before MDTM discussion in Australia.[61] Nevertheless, results of a survey across 51 Australian hospitals and various cancer categories by Wilcoxon et al noted that half of all patients had not consented before the MDTM discussion of their cases.[62] Results of a survey by Rankin et al in 2016 across 7 hospitals found that verbal consent was the primary means of patient consent and was infrequently documented in medical records.[63] Irrespective of the country, it is recommended that all patients consent in either verbal or written form, with documentation of consent kept in the medical records.[61,63] The Australian National Forum also advised a duty of care to be conferred upon all physicians participating in the MDTM, except nonparticipating meeting members.[61] However, results of an Australian survey of doctors across 18 MDTMs noted that only 48% believed in individual liability for MDTM treatment decisions, with 73% indicating their interest in further education about their legal responsibilities in MDTMs.[64] It is important for physicians to be aware of the professional liability they bear for their contributions within the MDTM. Regarding MDTM documentation, meeting members should be formally identified along with their contributions to the treatment plan.[59] Given the significant legal responsibilities of participating doctors in the MDTM, precise documentation of discussion is important. An audit in the UK revealed a high accuracy (97.1%) in the recording of MDTM treatment recommendations, which was largely attributed to the presence of a post-MDTM review process conducted by the MDTM coordinates and secretarial staff after each meeting.[65] The scribe needs to possess a medical background and be well-versed in their understanding of the investigations and management processes related to the respective oncology field. Furthermore, the scribe should be encouraged to seek clarification during the meeting in cases of ambiguity and have their documentation reviewed by the MDTM chair shortly afterward.

The virtual MDTM format has become increasingly popular since the COVID-19 pandemic.[66] Although the virtual platform eliminates the necessity of physical travel and geographical barriers for members, its smooth operation hinges greatly on robust information technology (IT) infrastructure because IT issues can delay or cancel meetings.[11] Institutions considering using virtual MDTMs should invest in a reliable IT setup and ensure readily available IT support during the meetings.

Barriers to MDTM Treatment Recommendation Adherence: Patient and Health Care Provider Perspectives

MDTMs coordinate holistic care, and the literature largely favors MDTMs concerning patient survival outcomes,[20,23,24] diagnostic precision, and adherence to practice guidelines,[67] where adherence is associated with improved survival.[68-70] Patient and health care professional adherence to MDTM treatment recommendations is generally high.[31] However, the notion that MDTM treatment recommendations should always be adhered to contains nuances for exploration. The following sections will address the barriers to MDTM recommendation adherence in clinical practice through the lens of the patient and the health care professional, as summarized in **Table 2**.

TABLE 2. Barriers to MDTM Recommendation Adherence

PATIENT PERSPECTIVES
1. Fear of treatment toxicity
2. Personal preferences for care goals
3. Psychological, social, and cultural influences
HEALTH CARE PROFESSIONAL PERSPECTIVES
1. New or overlooked clinical findings not previously discussed
2. Underestimation of procedural feasibility
3. Underestimation of patient suitability for aggressive treatment

Patient Perspectives

It is important to consider reasons for nonadherence to MDTM recommendations from the patient's standpoint. For example, patient fear of treatment toxicity can be a deterrent to recommendation adherence. Fear of treatment toxicity was a prominent reason for nonadherence to MDTM recommendations in a retrospective analysis by Samarasinghe et al of patients with breast cancer.[31] Yang et al noted a high rate of nonadherence to chemotherapy when recommended by MDTMs in patients with breast cancer, due to fear of chemotherapy adverse effects. Patients with the luminal A disease subtype showed greater adherence to MDTM recommendations, as chemotherapy was less often recommended as a treatment modality in these patients.[27] Clinicians should ultimately gauge the validity of patient concerns regarding treatment toxicities and educate patients on the likelihood and severity of such toxicities in addition to ways of managing toxicities, which will better inform patient decisions.

Patient preferences may also result in nonadherence to MDTM recommendations. This was noted to be the most common cause for deviation from MDTM recommendations findings from a study by Hollunder et al of 3 multidisciplinary tumor boards[71] and by

Cao et al findings from a retrospective cohort study of patients with hepatocellular carcinoma (HCC), where the vast majority of patient nonadherence to MDTM recommendations occurred due to their disagreements with MDTM-suggested goals of care in that of curative vs palliative intent.[72] Patient preferences may also be influenced by sociocultural contexts. Results of a retrospective analysis of MDTM recommendation adherence in patients with early breast cancer identified patients' social status, psychological conditions, and caregiver status as discussion points often excluded from the MDTM. These considerations would subsequently surface in outpatient visits, potentially prompting management adjustments toward a lower intensity of care.[73] Furthermore, inconvenience can deter patients from engaging with MDTM recommendations. For example, patients invited to clinical trials through the MDTM are often expected to present for more rigorous follow-up, for which they may not have the resources and/or time to accommodate.[31] As noted by Samarasinghe et al, patient pursuit of alternative therapies was a common reason for nonadherence to MDTM recommendations.[31] Although certain patients place great value on alternative therapies due to cultural beliefs, it should be acknowledged that most alternative therapies have limited medical evidence. Such patients should be educated about this in a culturally sensitive manner.

Measures can be used to better incorporate patient perspectives into the MDTM. These include providing a pre-MDTM patient questionnaire to elicit insights into their sociocultural background and treatment preferences and integrating their responses into MDTM treatment planning. Furthermore, institutions can endorse training of MDTM members in shared decision-making and patient-centered care.[74] When the patient's preference for treatment is unknown, the MDTM should list multiple treatment options. This approach enables more flexibility to account for the patient's potential preferences.[75] A patient representative, such as a nurse or general practitioner, should be encouraged to participate in the MDTM to convey information about the patient's psychosocial background and preferences. Patient attendance at the MDTM also has been suggested as a useful way for patients to self-advocate for treatment preferences; however, there are limited studies on this.[21,29] Although patient participation largely amounted to positive patient and health care professional experiences in findings from a pilot study by Choy et al,[76] Butow et al noted strong physician apprehension toward the inclusion of patients in their MDTMs. These physicians expressed concerns of inducing patient anxiety and the need to use lay language that limits professional dialogue, thereby slowing meeting progression.[77] As such, the decision regarding patient participation in case discussions should be at the discretion of the institution.

Health Care Professional Perspectives

When MDTMs lack important clinical information, are subjected to time pressure or IT issues, or are missing core team members, the resultant treatment consensus may be misinformed and unsuitable for patients.[43] Information realized after the MDTM, such as new or unexpected clinical findings, may prompt the primary treating physician to alter the treatment plan. For example, patients recommended for surgery by the MDTM consensus may later be deemed unfit for surgery, so an anesthetist's presence in the MDTM to discuss fitness for surgery may be of benefit.[43]

MDTMs can misjudge the feasibility of certain procedures. As noted by Cao et al, some patients with HCC in their study were unable to undertake MDTM-recommended surgery or ablation because of tumor locations that were later found to be too difficult for surgical or ablative access.[72] Although patients should consent to and commence treatment soon after the MDTM, a lack of resources and staffing may result in treatment delays, and as acknowledged by Cao et al, tumors such as those in HCC can rapidly progress between the time of the MDTM and the time of initial treatment, so patients may no longer be appropriate for the recommended treatment.[72] Similarly, poor judgment of patient conditioning in the MDTM can force a deviation from MDTM recommendations if aggressive therapy is not appropriate for the patient due to deconditioning or comorbidity profiles.[78]

Conclusion

The multidisciplinary meeting confers important value to the landscape of cancer care, serving to optimize treatment planning and patient outcomes. A successful MDTM hinges upon several factors, including adequate time allocation, comprehensiveness of clinical data, effective team collaboration, and well-organized logistics. Focusing on complex cases can improve meeting efficiency, and setting referral deadlines will ensure adequate time for comprehensive data gathering. Introducing workflow and decision-making software can also improve meeting efficiency. Such software has recently come to adopt rapid learning and artificial intelligence technology, for which there is further scope for interventional studies to assess their accuracy and efficacy. Regarding team dynamics, a flattened hierarchy should be embraced across all MDTMs to optimize multidisciplinarity. To improve adherence to MDTM recommendations, care teams should address sociocultural considerations and patient fears and preferences for treatment. Similarly, physicians should ensure an accurate presentation of clinical details of the patient and their disease profile to allow for feasible recommendations to result. Due to the variations in MDTM practices across institutions, audits within institutions are advised to assess MDTM quality with stratification to cancer type concerning clinical outcomes, member satisfaction, and adherence to MDTM recommendations. ■

FOR REFERENCES VISIT
cancernetwork.com/9.24_Multi-D

GYNECOLOGIC CANCER

Expert Commentary on the Product Profile of Tisotumab Vedotin in Cervical Cancer

Laura Bucher-Bailey, PharmD, discussed the approval of tisotumab vedotin-tftv (Tivdak) for patients with recurrent or metastatic cervical cancer who have had progression after chemotherapy. Bailey discussed the benefit the treatment brings to patients and how it compares with other options in the space when addressing adverse effects (AEs).

PRODUCT PROFILE

DRUG NAME: Tisotumab vedotin-tftv (Tivdak)

DATE OF APPROVAL: April 29, 2024[1]

INITIAL INDICATION: Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy[2]

DOSAGE AND ADMINISTRATION: 2 mg/kg with a maximum of 200 mg for patients 100 kg or more

HOW SUPPLIED: Intravenously for 30 minutes every 3 weeks

PIVOTAL CLINICAL TRIAL: Phase 3 innovaTV 301 (NCT04697628)[3]

DESIGN OF THE PHASE 3 innovaTV 301 TRIAL

PRIMARY END POINT: Overall survival

SECONDARY END POINT: Progression-free survival, confirmed objective response rate, duration of response

INCLUSION CRITERIA: Patients who had experienced disease progression during or after treatment with a standard of care systemic chemotherapy doublet or platinum-based therapy; received 1 or 2 prior lines of systemic therapy for recurrent and/or metastatic cervical cancer; had an ECOG performance status of 0 or 1; and had a life expectancy of at least 3 months.

COMMENTARY

Laura Bucher-Bailey, PharmD
Clinical Oncology Pharmacist
Riverside Cancer Institute, Kankakee, IL

Q / What is the mechanism of action of tisotumab vedotin?

Bailey / It is an antibody-drug conjugate. It's made up of 3 components. It has the tisotumab, a cleavable linker, and then MMAE. Tisotumab is an antibody that looks for tissue factor antigens on the surface of cells. The MMAE is a microtubule-disrupting agent, so it prevents cells from dividing, which leads to apoptosis.

Q / Which patients are most likely to benefit from this treatment?

Bailey / It's indicated for adults with recurrent metastatic cervical cancer. It's approved for second-line treatment, so they would have had to have progressed on first-line treatment. There are 2 other preferred agents as second-line [options]. Pembrolizumab [Keytruda] is preferred for patients with certain tumor markers, and then tisotumab and cemiplimab-rwlc [Libtayo] are also second-line options. In our practice, what I've been seeing is they're using it more as third- or fourth-line therapy after patients progress on the first line. Then they've been using pembrolizumab. Now we're seeing tisotumab being considered.

Q / The innovaTV 301 trial demonstrated an improvement in overall survival [OS]. How significant is this improvement in the context of other treatment options in the space?

Bailey / An improvement in OS is what we're looking for. You want patients to survive a little longer. The treatment options for patients who have recurrent cervical cancer are not super effective. It's always nice to have new options with new mechanisms of action. The leading OS from the trial [was] an 11.5-month OS in patients who received tisotumab vs 9.5 months [who received chemotherapy]. That's 2 more months of OS, and that difference is a 30% lower risk of death in the patients who received tisotumab. Anytime you increase OS, that's a step in the right direction.

Q / What are some of the most common AEs associated with tisotumab, and how do they compare with other treatments in the space?

Bailey / The most common AEs are ocular toxicities, peripheral neuropathy, and hemorrhage. Some patients also experience pneumonitis and cutaneous reactions but to a lesser degree. Immunotherapy, in general, is associated with an increased risk of immune-mediated AEs. The other second-line options also have pneumonitis and other immune-mediated AEs associated with them. So that's similar.

For tisotumab, the big thing to point out is that there is a black box warning regarding ocular toxicity, and there are also ocular care requirements. Prior to initiating treatment, the patient needs to be examined by an ophthalmologist. They will be prescribed 3 types of eye drops: a corticosteroid, a vasoconstrictor, and lubricating eye drops. They have to bring those with them to treatment. They need to start before treatment and then…they need to place cold packs on their eyes throughout the duration of treatment. They're not allowed to wear contact lenses throughout the duration of treatment. For some patients, that might be a consideration. The other second-line options of pembrolizumab and cemiplimab don't have the same ocular toxicity. That's a big difference between tisotumab and the other second-line agents.

Q / What are some of the potential resistant mechanisms associated with this treatment?

Bailey / With immunotherapy, resistance does tend to develop. With an antibody-drug conjugate, specifically, you can develop resistance to the antibody portion or the payload portion. If the issue is antibody-related, but they still want to get the MMAE into the cell, they can change what they're targeting on the cell surface to still get the payload into the cell. If the problem is the opposite, then the cell is either kicking the MMAE out or changing the way it processes it. But the cell is still taking up the antibody; the antibody is still recognizing the antigen on the outside of the cell. They can change the payload and get a new microtubule-disrupting agent inside. It's so cool that we can find antigens on the cells of tumors, target those, and then get something inside that will be super effective but won't affect cells globally. Then you don't have all those AEs that you see with the more traditional chemotherapy, [such as] nausea, vomiting, mouth sores, and hair loss. It's amazing that we're figuring these things out.

Q / Where do you see this agent headed?

Bailey / There are some trials right now looking at tisotumab with other solid tumors, [such as in] metastatic/recurrent, pancreatic and colorectal cancer, other solid tumors that have tissue factor protein on the cell surface. Anytime you have a new mechanism of action, a new opportunity to use a new class of drugs in a patient who has recurrent disease, it's always an improvement.

When I was looking at the subgroup analysis, I thought that it was very interesting that the patients who had received bevacizumab [Avastin] prior to tisotumab did better with tisotumab than investigator's choice chemotherapy, but for patients who did not receive bevacizumab, there was no difference between the patients who got tisotumab [vs] investigator's choice chemotherapy. The investigator does mention in the results that there's no biological reason for the differing outcomes of subsequent therapy in patients who have received bevacizumab previously vs those who have not. That's super interesting and something to look into.

Q / Is there anything else you'd like to highlight?

Bailey / The dose of tisotumab is 2 mg/kg up to a maximum of 200 mg. Any patient [weighing more than] 100 kg would still just get 200 mg. It's 30 minutes every 3 weeks, just like the other 2 second-line options. This agent does require the cold packs and all the eye drops, and the package insert has a nice outline of dosage adjustments for patients experiencing AEs. Also, the use of tisotumab with any strong CYP3/4 inhibitors will increase the patient's exposure to MMAE. That also increases the patient's risk of AEs, and then you should avoid the use of tisotumab in patients with moderate to severe hepatic impairment. [The trial] did see that patients with mild to moderate hepatic impairment had, about a 37% increased exposure to MMAE, so they didn't even use it. They didn't use it in patients with moderate or severe hepatic impairment. It's recommended that you avoid use in those patients. ■

FOR REFERENCES VISIT
cancernetwork.com/8.24_Tisotumab

KEY PRESENTATIONS FROM THE

Kidney Cancer Research Summit

ONCOLOGY reviews key presentations from the 2024 Kidney Cancer Research Summit. Highlights from the conference include advances in survival and the use of artificial intelligence to predict treatment outcomes. CN

Nivolumab Combo May Show Long-Term Benefits in Advanced RCC

Combining nivolumab (Opdivo) with ipilimumab (Yervoy) may potentially improve long-term outcomes in patients with advanced renal cell carcinoma (RCC) regardless of their International Metastatic RCC Database Consortium risk, according to findings from the phase 3 CheckMate 214 trial (NCT02231749).

Across the intent-to-treat population, the median overall survival (OS) was 52.7 months (95% CI, 45.8-64.5) in patients who received nivolumab/ipilimumab (n=550) compared with 37.8 months (95% CI, 31.9-43.8) in those who received sunitinib (Sutent; n=546; HR, 0.72; 95% CI, 0.62-0.83). Additionally, the median progression-free survival (PFS) was 12.4 months (95% CI, 9.9-16.8) vs 12.3 months (95% CI, 9.8-15.2) in each respective arm (HR, 0.88; 95% CI, 0.75-1.03).

Data highlighted an objective response rate (ORR) of 39% (95% CI, 35%-44%) with the nivolumab combination compared with 33% (95% CI, 29%-37%) with sunitinib. In each respective arm, 12% vs 3% of patients had complete responses (CRs) and 27% vs 29% had partial responses. Additionally, the median duration of response (DOR) was 76.2 months (95% CI, 59.1-not evaluable [NE]) vs 25.1 months (95% CI, 19.8-33.2) in each respective arm (HR, 0.52; 95% CI, 0.38-0.72).

Among patients with favorable-risk disease, the median OS was 77.9 months (95% CI, 64.6-91.6) in those who received nivolumab/ipilimumab (n=125) vs 66.7 months (95% CI, 56.0-79.9) in those who received sunitinib (n=124; HR, 0.82; 95% CI, 0.60-1.13). The OS rates in each arm were 85.1% vs 88.4% at 24 months, 52.3% vs 46.4% at 72 months, and 42.8% vs 34.4% at 90 months, respectively.

Treatment yielded a median PFS of 12.4 months (95% CI, 10.3-18.0) and 28.9 months (95% CI, 23.2-42.8) in the nivolumab/ipilimumab and sunitinib arms, respectively (HR, 1.76; 95% CI, 1.25-2.48). Additionally, the PFS rates were 36.5% vs 58.5% at 24 months, 17.0% vs 17.0% at 72 months, and 12.7% vs 17.0% at 90 months in each respective arm.

The ORR across the favorable-risk population was 30% (95% CI, 22%-38%) with the nivolumab combination vs 52% (95% CI, 43%-61%) with sunitinib, and the CR rates were 13% vs 6% in each arm. Data showed a median DOR of 61.5 months (95% CI, 27.8-NE) vs 33.2 months (95% CI, 24.8-51.4) in each respective arm (HR, 0.70; 95% CI, 0.36-1.34). Additionally, 68% vs 66%, 37% vs 14%, and 37% vs 14% of patients in each arm had ongoing responses at 24 months, 72 months, and 90 months, respectively.

Abemaciclib May Show Synergistic Effect in Trials of Kidney Cancer Combination

Bradley A. McGregor, MD, discusses results from a phase 1b study (NCT04627064) assessing the efficacy of abemaciclib monotherapy in heavily treated patients with metastatic clear cell renal carcinoma.

To watch the full video, visit
cancernetwork.com/KCRS24_McGregor

For full article and references visit
cancernetwork.com/KCRS24_CheckMate214

Multimodal AI Approach May Predict Outcomes in Renal Cell Carcinoma

A multimodal artificial intelligence (AI) approach may help identify important elements for predicting outcomes in renal cell carcinoma (RCC). Specifically, investigators found that segmentation and partial volumetric analysis showed an improved chance of predicting postoperative kidney function. The presentation also highlighted that if this function could be quantified, personalization of RCC treatment might occur.

Investigators had 2 aims for researching this multimodal AI approach. The first was to develop an accurate and noninvasive AI tool to evaluate patient information, laboratory tests, and characteristics. These capabilities may allow investigators to differentiate between benign or indolent kidney masses and identify potentially aggressive tumors in the preoperative setting. The second aim was to establish an AI tool using preexisting data to estimate postoperative kidney function through nephron-sparing surgery or total nephrectomy.

Initially, the goal was to evaluate approximately 1000 to 1500 patients. However, with additional technologies such as pathology and the radiology pipeline, investigators plan to evaluate approximately 3000 patients. An additional 300 to 400 patients are being evaluated in a subset population for gene expression.

Investigators also recently submitted data regarding the age of patients. The hypothesis first focused on what it meant if the AI model incorrectly diagnosed a patient's age based on their CT scans. Results found that if the AI model thought the patient was younger than they were, they would be discharged earlier from the hospital than those who were predicted to be older than their actual age.

This was also observed in survival. If the AI tool predicted an age that did not correlate with the patient's actual age, it was predictive of better or worse outcomes. Investigators believes there are additional data to be extrapolated from these results because there hasn't been a way to truly analyze these outcomes before the development of this AI tool.

For full article and references visit
cancernetwork.com/KCRS24_CheckMate214

Real-World Data Showcase Survival Outcomes After Immunotherapy/TKI Regimens in RCC

Patients with metastatic renal cell carcinoma (RCC) preferred tyrosine kinase inhibitors (TKIs) with or without immunotherapy-based treatments, according to results of a poster presented at the 2024 Kidney Cancer Research Summit. Investigators also highlighted that there was no difference in overall survival (OS) between the different immunotherapy- and TKI-based treatment regimens.

In the first-line setting, the most common postimmunotherapy treatments were axitinib (Inlyta) plus pembrolizumab (Keytruda; n = 212), ipilimumab (Yervoy) plus nivolumab (Opdivo; n = 156), immunotherapy monotherapy (n = 34), cabozantinib (Cabometyx) plus nivolumab (n = 19), and lenvatinib (Lenvima) plus pembrolizumab (n = 12).

In the second line, the most common postimmunotherapy treatments were cabozantinib (n = 197), cabozantinib plus nivolumab (n = 53), other second-line options (n = 46), axitinib or pazopanib (Votrient) or sunitinib (Sutent; n = 42), ipilimumab plus nivolumab (n = 40), axitinib plus pembrolizumab (n = 24), everolimus (Afinitor) plus lenvatinib (n = 15), and lenvatinib plus pembrolizumab (n = 12).

In the third-line setting, 56 patients died, and 88 had ongoing treatment. Additional therapies included other third-line options (n = 133), axitinib plus pazopanib and sunitinib (n = 38), cabozantinib (n = 38), ipilimumab plus nivolumab (n = 10), everolimus (n = 10), lenvatinib plus pembrolizumab (n = 6), and nivolumab alone (n = 4).

For full article and references visit
cancernetwork.com/KCRS24_RCC

Ubamatamab and Anti–PD-1 ICI May Bolster Immune Response in Kidney Cancer

Ubamatamab in combination with an anti–PD-1 immune checkpoint inhibitor may enhance the immune response in patients with MUC16-expressing SMARCB1-deficient renal medullary carcinoma and epithelioid sarcoma, according to Pavlos Msaouel, MD, PhD.

To watch the full video, visit
cancernetwork.com/KCRS24_Msaouel

Manageable AEs Noted in Belzutifan for Advanced RCC

Safety remained manageable when belzutifan (Welireg) was used for patients with previously treated advanced clear cell renal cell carcinoma (RCC).

Results showed that of the 576 patients included in the analysis, 99.3% had at least 1 all-cause adverse effect (AE), and 61.6% experienced at least 1 AE that was grade 3 to 5 in severity. Serious AEs occurred in 41.0% of patients. AEs led to dose modifications in exactly half of patients, and this included reductions, interruptions, or discontinuations. The treatment discontinuation rate due to AEs was 6.4%. Nineteen patients (3.3%) experienced an any-cause AE that led to death.

All-grade and grade 3 to 5 treatment-related AEs were reported in 91.3% and 37.7% of patients, respectively. One death, due to multiple organ dysfunction syndrome, was reported to be related to belzutifan therapy.

Because of its unique mechanism of action and a historically distinct AE profile, investigators sought to evaluate belzutifan's safety profile across 4 clinical trials: phase 1 LITESPARK-001 (NCT02974738), phase 3 LITESPARK-005 (NCT04195750), phase 2 LITESPARK-013 (NCT04489771), and the von Hippel-Lindau disease–associated RCC cohort in the phase 2 LITESPARK-004 study (NCT03401788). Patients eligible to be included in the study had received at least 1 dose of belzutifan at 120 mg orally once daily across the 4 studies.

Investigators analyzed the severity of AEs per the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 or 5.0.

For full article and references visit cancernetwork.com/KCRS24_LITESPARK

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Determining Administration of BCMA, T-Cell Engagers in R/R Multiple Myeloma


Joseph Mikhael, MD, MEd, FRCPC, FACP


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Natalie Callander, MD


Joshua Richter, MD

The assessment of updated clinical trial data, optimal dosing strategies, and integration of bispecific antibodies into current relapsed/refractory multiple myeloma treatment paradigms were the focus of conversation during a *Frontline Forum*. Experts in multiple myeloma gathered to discuss these points of interest and experiences they have had in the clinic.

The panel was led by **Joseph Mikhael, MD, MEd, FRCPC, FACP**, professor in the Division of Applied Cancer Research and Drug Discovery at the Translational Genomics Research Institute, an affiliate of City of Hope, in Phoenix, Arizona. He is also the chief medical officer of the International Myeloma Foundation.

He was joined by **Muhamed Baljevic, MD**, associate professor of medicine in the Division of Hematology-Oncology, director of the Plasma Cell Disorders Research of Vanderbilt-Ingram Cancer Center (VICC), director of the Vanderbilt Amyloidosis Multidisciplinary Program, and cochair of the VICC Protocol Review and Monitoring Program in Nashville, Tennessee; **C. Ola Landgren, MD, PhD**, professor of medicine, chief of the Division of Myeloma, director of the Sylvester Myeloma Institute, coleader of Translational and Clinical Oncology Program, and Paul J. DiMare Endowed Chair in Immunotherapy at the University of Miami Miller School of Medicine in Florida; **Cesar Rodriguez Valdes, MD**, associate professor of medicine at the Icahn School of Medicine at Mount Sinai, and clinical director of Multiple Myeloma at Mount Sinai Hospital in New York, New York; **Saad Z. Usmani, MD, MBA, FACP, FASCO**, chief of the Myeloma Service at Memorial Sloan Kettering (MSK) Cancer Center in New York, New York; **Natalie Callander, MD**, professor in the Division of Hematology, Medical Oncology, and Palliative Care at the University of Wisconsin School of Medicine and Public Health in Madison; and **Joshua Richter, MD**, associate professor of medicine in the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai, director of Multiple Myeloma at the Blavatnik Family-Chelsea Medical Center at Mount Sinai and editorial advisor board member for *ONCOLOGY*.

Discovering the Ideal Talquetamab Dose

The panelists started by going through the data of important trials in multiple myeloma (**Table**[1-3]). Regarding the MonumenTAL-1 trial, Richter commented that although there was a high response rate, duration of response and progression-free survival were significantly less. He noted that additional work is needed on this trial because although the response was high, it was not durable.

"It's showing that every other week [dosing] is much more beneficial overall. I don't think it's changing our practice. All of us are already using [talquetamab] every other week, where it just reaffirms the fact that we're on the right path," Rodriquez said.

Baljevic said he believes talquetamab would be the preferred therapy for patients who have not been able to maintain adequate absolute neutrophil and absolute lymphocyte counts. He has also observed a difference in intravenous immunoglobulin (IVIG) replacement between bispecific antibodies and GPRC5D treatments.

Landgren wondered how this treatment would work with monthly dosing or perhaps in combination with another drug. Additionally, the weekly dosing was showing increased toxicities, which he noted was not viable for patients.

Callender said she recently had a patient who did not respond well to the step-up dose portion with talquetamab. Because of this and other experiences, she believes they'll use the treatment more spaced out than the label recommends.

Mikhael asked Callender to elaborate on her approach and what responses she's observed.

"[I dose-reduce] after cycle 1 very quickly. The response rates are fast; at least, that's been my experience. I don't know that you're getting more benefit by just slamming patients [with doses once a week]; you're just going to see more toxicity. I'm sure everybody else at this table is doing this too. This became our preferred bridge with a short talquetamab course, particularly if they've been through a lot of other [lines of therapy]. You get a lot of benefits and skip a lot of the toxicity," she said.

Another hot topic was treatment administration in an inpatient or outpatient setting. Richter admits patients for the first initial dose or so. If cytokine release syndrome (CRS) occurs, tocilizumab (Actemra) is administered, and the patients can go home within 24 hours.

Rodriguez, who works with Richter, noted that tocilizumab is administered at the first fever. Patients are also discharged with dexamethasone so if more symptoms arise, clinicians can instruct them to begin that course of treatment before coming in for an evaluation.

At Landgren's institution, tocilizumab prophylaxis is given prior to the first treatment with a bispecific antibody. He conducted a study on the use of this with teclistamab and found the rate of CRS decreased from 75% to between 12% and 15%. Prophylaxis was also implemented with talquetamab and elranatamab.[4]

With talquetamab, a major issue has been taste-related adverse effects (AEs). Richter and Rodriguez have tried giving patients mouthwashes, supportive care measures, and even Oreo cookies to help tamp down these taste AEs but they have not had much success. The one thing that does seem to work is using lemon juice to stimulate the tongue's taste receptors that are sensitive to sour tastes.

Rodriguez has tried giving patients dexamethasone plus nystatin 3 times a day from the first step-up dose of talquetamab. He believes this helps prevent oral inflammation and dysgeusia. He also recommended referencing *Flavorama*, a book written by a chef and biochemist that delves into how to enhance flavors.

Callender said that she believes dose holds rather than reductions are leading to a reduction in these taste AEs.

Improved Responses With Real-World Teclistamab Use

The conversation then transitioned to the use of teclistamab in the MajesTEC-1 study. "I've observed that the infection rates in the real world have been better than in studies because the prophylaxis approaches have, at least in my institution, been more organized and intense than what studies have mandated over time," Baljevic said.

In terms of prophylaxis, he gives 10 g of IVIG to all patients. The results of this were presented at the 2023 American Society of Hematology Annual Meeting.[5] Of the study's 30 participants, 60% received GPRC5D therapies. There was not an increase in infections with this dosing. For those who did not respond well, 20 g of IVIG was administered to initiate a response.

Callender said she typically gives teclistamab to older patients but cautioned that they are more susceptible to infections.

Usmani noted that teclistamab de-escalation typically occurs after the third cycle. He arrived at this conclusion based on the time to best response and the discontinuation of patients who had a sustained response before a biochemical relapse.

At MSK, there is an outpatient administration model that includes any patient living 1 commutable hour from any MSK facility. Upon the first fever after treatment, patients are given acetaminophen (Tylenol). At the second fever, they are given dexamethasone, told to come in for an evaluation, and given tocilizumab in the clinic. Patients can be monitored for up to 6 hours if they're still febrile; if they're fine, they can go home.

Richter equates the early use of tocilizumab with helping prevent later flare-ups of infections.

"If you're concerned about high-grade CRS in the older patients who are coming in with higher disease burden, you have to be selective. If we're already saying that one-size-fits-all is not right for myeloma, we also

TABLE. Top Trials in Multiple Myeloma[1-3]

TRIAL NAME	DRUG	EFFICACY	SAFETY
Phase 1/2 MonumenTAL-1 (NCT03399799)	Talquetamab-tgvs (Talvey) at 0.4 mg/kg every week or 0.8 mg/kg every 2 weeks	ORR: 74.1% vs 69.5% DOR: 9.5 months vs 17.5 months PFS: 7.5 months vs 11.2 months	CRS: 79.0% vs 94.7% Taste-related: 72.0% vs 71.4% Nonrash skin-related: 56.6% vs 73.4%
Phase 1/2 MajesTEC-1 trial (NCT03145181; NCT04557098)	Teclistamab-cqyv (Tecvayli)	Median DOR: 24.0 months 30-month DOR rate: 45.0% Median PFS: 11.4 months 30-month PFS rate: 30.1%	TEAEs of any grade vs grade 3/4: 100% vs 94.5% Infection: 78.8% vs 55.2% Neutropenia: 71.5% vs 65.5%
Phase 2 MagnetisMM-3 trial (NCT04649359)	Elranatamab-bcmm (Elrexfio)	ORR: 61% CR: 35.0% VGPR: 56.1%	TEAEs of any grade vs grade 3/4 Anemia: 48.8% vs 37.4% Neutropenia 48.8% vs 48.8% CRS: 57.7% vs 0.0%

CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; ORR, overall response rate; PFS, progression-free survival; TEAEs, treatment-emergent adverse effects; VGPR, very good partial response.

have to be a little bit careful about how we say, 'Tocilizumab for all.' Maybe [it would work for] the patients with CAR [chimeric antigen receptor] T-cell therapy, where the proposition of CRS is very different. You're concerned about mostly grade 2, grade 3 going to grade 4. With bispecific antibodies, it's a little different," Usmani said.

Regarding outpatient administration, Rodriguez noted that it's feasible in academic centers, but the community setting may not be ready for it. Landgren agreed and said that this is why his institution had not gone to outpatient administration so quickly. Until the University of Miami was ready with a dedicated myeloma service, they could not trust that patients presenting to the emergency department with a fever would be treated for CRS and not an infectious disease.

Of note, Mikhael said that he has helped to create a curriculum to teach hospital internists how to properly diagnose CRS or immune effector cell–associated neurotoxicity syndrome.

Finding a Space for Elranatamab Treatment

A majority of the panel said they had not yet worked with elranatamab. Landgren has been able to use all 3 treatments at his institution, but because of financial calculations, he would stick with either teclistamab or elranatamab, the B-cell maturation antigens (BCMAs).

Baljevic, who has experience with elranatamab, has not seen a difference when using this treatment compared with teclistamab or talquetamab. He noted that the formulary team could not justify adding it, but there had been experience administering it in studies.

Usmani echoed Baljevic's sentiment saying he has experience with both elranatamab and teclistamab and has not seen a difference in terms of efficacy. Both are on the formulary at MSK, so it's the principal investigator's choice on which to use for their patients.

He did note that he and his colleagues gravitate a bit more toward teclistamab. Sometimes insurance influences the use of one vs the other and whether it can be administered as inpatient or outpatient, he said.

"The only difference is with fixed-dose vs weight-based dosing. There we've seen some interesting safety issues with patients [receiving] elranatamab where we are seeing some funky neurologic adverse effects, which were originally reported, but then we haven't heard a lot about," Usmani said.

Panelist Perspectives on Combining Treatments

Mikhael asked how the panel felt about combining talquetamab plus daratumumab (Darzalex).[6] He wanted to know the rationale behind it: Was it because they have the same manufacturer or was there a biological reason?

Richter said he is not a fan of this combination specifically because it's a BCMA plus CD38. He prefers 2 mg of low dose pomalidomide (Pomalyst) plus talquetamab. Rodriguez agreed, especially because of the different AEs experienced with the combination. Usmani has been researching immune profiling and combining immunomodulatory drugs (IMIDs) with novel checkpoints.

"There's some synergy with bispecifics and IMIDs, again with an effect on T-cell [therapy], that just seems natural. Based on our experience, less is more for the IMID with these combos because you do have to be careful with them," Callender said. ■

References

1. Rasche L, Schinke C, Touzeau C, et al. Long-term efficacy and safety results from the phase 1/2 MonumenTAL-1 study of talquetamab, a GPRC5DxCD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma. Presented at 2024 European Hematology Association; June 13-16, 2024; Madrid, Spain. Abstract P915.

2. Garfall AL, Nooka AJ, van de Donk NWCJ, et al. Long-term follow-up from the phase 1/2 MajesTEC-1 trial of teclistamab in patients with relapsed/refractory multiple myeloma. *J Clin Oncol.* 2024;42(suppl 16):7540. doi:10.1200/JCO.2024.42.16_suppl.7540

3. Tomasson M, Iida S, Niesvizky R, et al. Long-term efficacy and safety of elranatamab monotherapy in the phase 2 Magnetismm-3 trial in relapsed or refractory multiple myeloma (RRMM). *Blood.* 2023;142(suppl 1):3385. doi:10.1182/blood-2023-182130

4. Kowalski A, Lykon J, Diamond B, et al. Emerging strategies for the prevention of immune toxicities associated with T cell-engaging cancer therapies. *Blood Cancer Discov.* 2024;5(2):90-94. doi:10.1158/2643-3230.BCD-23-0228

5. Marneni N, Dholaria B, Sengsayadeth D, et al. Flat dose intravenous immunoglobulin primary infection prophylaxis in multiple myeloma patients on bispecific antibody therapy: Vanderbilt experience. *Blood.* 2023;142(suppl 1):3778. doi:10.1182/blood-2023-190749

6. Dholaria BR, Weisel K, Mateos MV, et al. Talquetamab (tal) + daratumumab (dara) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): updated TRIMM-2 results. *J Clin Oncol.* 2023;41(suppl 16):8003. doi:10.1200/JCO.2023.41.16_suppl.8003

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Pancreatic cancers have the dubious distinction of having the lowest survival rates of any major cancer, with an overall 5-year relative survival of only 13%.[1] The majority of pancreatic cancers are detected after they have already spread, with 29% of cases involving regional lymph nodes and 51% of patients receiving a diagnosis of metastatic cancer. Pancreatic ductal adenocarcinoma (PDAC) accounts for 90% of pancreatic cancers.[2] PDAC is particularly resistant to chemotherapy owing to the broad heterogeneity of mutations and dense stromal environment found in these tumors.

Head-to-Head Trials of First-Line Chemotherapy

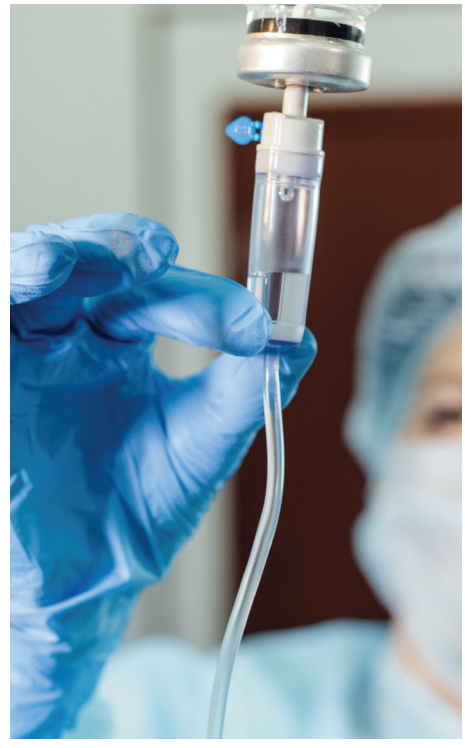
Both modified FOLFIRINOX (mFFX) and gemcitabine plus nab-paclitaxel (GnP) are preferred first-line regimens for PDAC, according to National Comprehensive Cancer Network (NCCN) guidelines.[3] The randomized phase 2 PASS-01 trial (NCT04469556) compared these regimens head-to-head in 140 patients with de novo metastatic PDAC (mPDAC).[4] Patients given GnP experienced a numerically but not statistically longer progression-free survival (PFS) than did those given FOLFIRINOX (5.5 vs 4.0 months, respectively; *P*=.14). Median overall survival (OS) was 9.7 months with GnP and 8.4 months with mFFX (*P* = .04). Partial response (PR) was achieved in 29% of patients receiving GnP and 24% of patients receiving mFFX. Serious adverse events (AEs) were reported in 3% of patients receiving GnP and 13% of patients receiving mFFX.

The phase 3 NAPOLI 3 trial (NCT04083235) compared NALIRIFOX vs GnP in 770 patients with metastatic PDAC.[5] Median OS with NALIRIFOX therapy was 11.1 months (95% CI, 10.0-12.1 months) vs 9.2 months (95% CI, 8.3-10.6 months) with GnP (HR, 0.83; 95% CI, 0.70-0.99; *P*=.036). The 12-month OS was 45.6% (95% CI, 40.5%-50.5%) in the NALIRIFOX arm and 39.5% (95% CI, 34.6%-44.4%) in the GnP arm. The 18-month OS was 26.2% (95% CI, 20.9%-31.7%) with NALIRIFOX and 19.3% (95% CI, 14.8%-24.2%) with GnP. Median PFS with NALIRIFOX was 7.4 months vs 5.6 months with GnP (HR, 0.69; 95% CI, 0.58-0.83; *P*=.0001). Treatment-emergent AEs (TEAEs) were reported in 369 (99.7%) of 370 patients who received NALIRIFOX and 376 (99.2%) of 379 patients who received GnP. The most common TEAEs of grade 3 or 4 with NALIRIFOX and GnP, respectively, were diarrhea (20.3% vs 4.5%), nausea (11.9% vs 2.6%), hypokalemia (15.1% vs 4.0%), anemia (10.5% vs 17.4%), and neutropenia (14.1% vs 24.5%). Treatment-related AEs (TRAEs) leading to death occurred in 2% of patients in the NALIRIFOX group and 2% of patients in the GnP group.

Targeted Therapies in Early-Phase Trials

The phase 1b/2 OPTIMIZE-1 trial (NCT04888312) evaluated whether adding the anti-CD40 antibody mitazalimab to mFFX would improve outcomes for 70 patients with newly diagnosed PDAC.[6] Objective responses were confirmed in 23 of 57 patients (40.4%) evaluated for efficacy (1-sided 90% CI; ≥ 32 of 57 patients),

including 1 complete response. Median OS was 14.3 months, median PFS was 7.4 months, and median duration of response (DOR) was 12.5 months.[7] The most commonly reported AEs of grade 3 or greater were consistent with the mFFX safety profile: neutropenia (25.7%), anemia (11.4%), hypokalemia (15.7%), and thrombocytopenia (11.4%). The most common serious AEs reported were vomiting (5%), decreased appetite (6%), diarrhea (4%), and cholangitis (4%).[6] None were considered related to mitazalimab.



The phase 1/1b ARC-8 clinical trial (NCT04104672) investigated the benefit of the CD73 inhibitor quemliclustat.[8] CD73 is overexpressed in 40% to 60% of PDAC and is associated with poor outcomes. ARC-8 combined quemliclustat with GnP with and without the anti–PD-1 antibody zimberelimab in 122 patients with untreated mPDAC. Outcomes were better in the arm without zimberelimab. In the quemliclustat plus GnP arm, the objective response rate (ORR) was 41% (95% CI, 24%-61%), the median PFS was 8.8 months (95% CI, 6.4-12.6 months), and the median OS was 19.4 months (95% CI, 12.1-23.0 months). AEs of grade 3 or greater were reported in 85% of trial participants, with the most common being decreased neutrophil count (31%) and anemia (25%). A total of 23% of patients discontinued the study due to AEs.

For patients with core homologous repair deficiency (HRD) such as germline *BRCA1/2* mutations, maintenance olaparib therapy has been shown to improve PFS.[9] The phase 2 POLAR study (NCT04666740) investigated whether the benefit of this PARP inhibitor combined with pembrolizumab as maintenance therapy could be extended to 30 patients with non–core HRD mutations (cohort B) and exceptional platinum responders (cohort C).[10] The ORR was 0% in cohort B and 13.5% in cohort C. The disease control rate (DCR) was 60% in cohort B and 46.5% in cohort C. The median PFS was 4 months (95% CI, 4-not reached [NR]) in cohort B and 3.3 months (95% CI, 1.9-5.4) in cohort C. Median OS was not reached (95% CI, 12-NR) in cohort B and 11 months (95% CI, 9.1-NR) in cohort C. TRAEs grade 3 and higher were diarrhea (7%), hyperglycemia (7%), anemia (14%), and increased lipase (7%).

Breaking the *KRAS* Barrier

KRAS mutations occur in approximately 90% of pancreatic cancers, including *KRAS* G12C mutations in approximately 2%.[11] Adagrasib is an irreversible inhibitor of *KRAS* G12C that was evaluated for efficacy as monotherapy in patients with unresectable or metastatic solid tumors harboring this mutation in the phase 1/2 KRYSTAL-1 trial (NCT03785249). In the 21-patient PDAC cohort, ORR was 33.3%, DCR was 81.0%, median PFS was 5.4 months (95% CI, 3.9-8.2 months), and median OS was 8.0 months (95% CI, 5.2-11.8 months). In all 63 patients in this basket trial, the most common TRAEs were nausea (49.2%), diarrhea (47.6%), fatigue (41.3%), and vomiting (39.7%). Grade 3 TRAEs were reported in 25.4% of patients; grade 4 TRAEs were reported in 1.6%. In the phase 1/2 LOXO-RAS-20001 study (NCT04956640) in patients with solid tumors harboring *KRAS* G12C mutations, LY3537982 yielded an ORR of 42% in the 12-patient pancreatic cancer cohort.[12]

The ORR was also 42% in 7 patients with pancreatic cancer, including 3 PRs in a phase 1 basket trial of divarasib monotherapy in advanced or metastatic solid tumors harboring a *KRAS* G12C mutation.[13] In the overall population of 137 patients, grade 3 TRAEs were reported in 11% of patients, most commonly diarrhea, increased alanine aminotransferase (ALT) level, and increased aspartate aminotransferase (AST) level. One grade 4 event of anaphylaxis was reported.

Glecirasib produced a confirmed ORR of 46.4%, including 13 PRs and a DCR of 96.4% in 28 patients with PDAC harboring a *KRAS* G12C mutation in a phase 1/2 clinical trial (NCT05002270).[14] Median DOR was 4.1 months, and median PFS was 5.5 months (95% CI, 1.2-13.1 months). The most common TRAEs were anemia (52.1%), increased blood bilirubin (39.6%), decreased white blood cell count (18.8%), increased AST (18.8%), diarrhea (16.7%), increased ALT (14.6%), asthenia (14.6%), hypertriglyceridemia (10.4%), and nausea (10.4%). Grade 3 or 4 TRAEs were reported in 25% of patients.

According to NCCN guidelines, germline testing, as well as somatic tumor profiling to look for actionable molecular findings, should be considered for all patients with pancreatic cancer.[3] With the advent and advancement of next-generation sequencing technology, molecularly informed treatment selection and sequencing is at the forefront of the field. ■

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https://www.gotoper.com/mxf24pancreatic-references

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

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

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

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

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

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

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

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

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

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

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

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

07/23 cp-352216v2

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

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

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

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

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

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

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

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

Interference with Serological Testing

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Interference with Determination of Complete Response

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

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

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

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

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

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

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

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

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

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

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

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

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

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

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

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

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

Herpes Zoster Virus Reactivation

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

Infections

Grade 3 or 4 infections were reported as follows:

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

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

Fatal infections (Grade 5) were reported as follows:

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

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

Hepatitis B Virus (HBV) Reactivation

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

Other Clinical Trials Experience

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

Nervous System disorders: Syncope

Immunogenicity

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

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

Postmarketing Experience

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

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

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

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

Neutropenia

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

Thrombocytopenia

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

Embryo-Fetal Toxicity

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

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

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

Hereditary Fructose Intolerance (HFI)

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

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

For patent information: www.janssenpatents.com

cp-271933v4

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

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

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

Local Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Embryo-Fetal Toxicity

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

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

Interference with Serological Testing

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

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

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity

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

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

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

Postmarketing Experience

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

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

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Data

Animal Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

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

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

Manufactured by:
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For patent information: www.janssenpatents.com

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