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NON-SMALL CELL LUNG CANCER | ORIGINAL RESEARCH

Clinical Trial Eligibility and Outcomes in Patients With Metastatic NSCLC Treated Outside Clinical Trials

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Assessing 2024 Oncology Advances and Looking Ahead

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The field of oncology continues to evolve rapidly, with transformative advances in 2024 offering novel diagnostic and therapeutic options. Below are some of the most impactful advances from 2024, which span various cancer types, therapeutic approaches, and treatment settings.

First, we have seen new and improved liquid biopsy assays with high sensitivity for the detection and sequencing of circulating tumor DNA (ctDNA). These improvements in ctDNA detection and profiling have short- and long-term impacts. In the short term, higher sensitivity assays can identify more patients who may benefit from precision oncology treatment approaches. Longer-term impact is anticipated from ongoing clinical trials that incorporate highly sensitive assays to test strategies for escalating or de-escalating cancer treatment based on ctDNA dynamics. Second, another area of rapid advancement is the use of artificial intelligence (AI) and machine learning for early detection, diagnosis, and even treatment. Diagnostic tools, such as mammography and cross-sectional imaging, are increasingly driven by AI because of progress in machine learning algorithms. In the treatment setting, AI-based tools are increasingly incorporated into precision oncology clinical trials for the matching of candidate tumors with targeted therapeutics. Another key priority that has significantly advanced in the past year is quality of life and patient-reported outcomes. Results of several studies now demonstrate that early incorporation of whole-person care—including diet, exercise, and integrative therapies—significantly improves overall quality of life and specific parameters such as fatigue and pain. To have a public health impact, the growing evidence supporting lifestyle interventions in oncology needs to be leveraged for policy-making and reimbursement to optimize accessibility.

In the past year, several notable advancements were made in medical therapies that increase tumor response, decrease recurrence risk, and improve survival. For example, in early-stage breast cancer with an elevated risk of recurrence, the CDK4/6 inhibitor ribociclib (Kisqali) received FDA approval based on results from the adjuvant phase 3 NATALEE trial (NCT03701334).[1] The indication for adjuvant ribociclib includes patients with high-risk N0 breast cancer, a notable advance for patients who have discordant risk stratification by anatomic staging vs histologic and/or genomic assessment.

Another CDK4/6 inhibitor, abemaciclib (Verzenio), was approved for adjuvant use in 2023. Longer-term follow-up data from the phase 3 monarchE trial (NCT03155997), which were presented in 2024, demonstrated that invasive disease-free survival benefit could be maintained in patients with high-risk early-stage breast cancer.[2]

Data supporting the use of novel antibody-drug conjugates (ADCs) and extended use of approved ADCs across various cancer types and treatment settings were released in 2024. For example, new data were presented supporting earlier use of trastuzumab deruxtecan (T-DXd; Enhertu) in hormone receptor–positive, HER2-low metastatic breast cancer and for HER2 ultralow tumors. In 2024, T-DXd was also approved for use in gastric or gastroesophageal junction adenocarcinoma with HER2 overexpression and accelerated approval for unresectable or metastatic HER2-positive tumors.[3]

Other important drug approvals in 2024 were seen in immunotherapy and molecular therapeutics. For example, the ADC tisotumab vedotin-tftv (Tivdak) received full approval in 2024 for the treatment of recurrent or metastatic cervical cancer. The full approval was based on data confirming an overall survival benefit in the phase 3 innovaTV 301 trial (NCT04697628).[4] Immunotherapy in primary advanced or recurrent endometrial cancer treatment was expanded in 2024 to include the use of PD-1 inhibitors pembrolizumab (Keytruda) or dostarlimab-gxly (Jemperli) with carboplatin and paclitaxel followed by single-agent immunotherapy (agnostic to mismatch repair or microsatellite instability status). Immunotherapy for lung cancer was also advanced, including approval for durvalumab (Imfinzi) plus chemotherapy for resectable non–small cell lung cancer (NSCLC).[5]

Impactful molecular therapeutics also approved in 2024 included lazertinib (Leclaza) plus amivantamab-vmjw (Rybrevant) for the first-line treatment of locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 *L858R* substitution mutations based on results from the phase 3 MARIPOSA trial (NCT04487080).[6] Other important molecular therapy approvals in 2024 include selpercatinib (Retevmo) for *RET*-mutated medullary thyroid cancer and repotrectinib (Augtyro) for *NTRK* gene fusion–positive solid tumors. Finally, intriguing preliminary data emerged in 2024 supporting the hypothesis that metabolic interventions, such as glucagon-like peptide 1 agonists, have anticancer potential.

The rapid pace of discovery and innovation in oncology accelerated in 2024. Results from ongoing or planned trials addressing toxicity management (including financial toxicity), optimal therapeutic sequencing, access, and disparities mitigation are eagerly anticipated. ■

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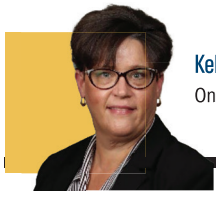
Approaching End-of-Life Discussions With Directness and Compassion



Kelley A. Rone, DNP, RN, AGNP-c, Advanced Practice Nurse in Gastrointestinal Oncology at the Mayo Clinic in Phoenix, AZ

Having an end-of-life discussion with a patient can be uncomfortable. Kelley A. Rone, DNP, RN, AGNP-c, specializes in speaking with compassion while helping the patient understand what is happening.

Rone, an advanced practice nurse in gastrointestinal (GI) oncology at Mayo Clinic in Phoenix, Arizona, talked with CancerNetwork about these discussions and how she is trying to help the entire multidisciplinary team become adept at having these conversations.

She is often one of the first medical team members to mention the possibility of death to a patient, which can create a disconnect with patients in understanding that their treatments may be doing more harm than good. She hopes that, over time, end-of-life discussions will become more integrated into the multidisciplinary approach.

The conversation also focused on combating burnout, discussing opioid use to help manage pain, and facing the challenges she has with these conversations every day.

"Sometimes [patients] just don't want to hear that, and they don't want to believe. We just have to try as best we can to make people understand that they're probably not going to survive their cancer," Rone said.

Q / What is your role on the multidisciplinary care team?

Rone / In our practice, the advanced practice providers—myself and other nurse practitioners—work in conjunction with the medical oncologists. Our team consists of 5 medical oncologists, 2 nurse practitioners, and a variety of nursing staff and medical assistants who help navigate the process of our patients' [care]. My main role and the role of the other nurse practitioner is symptom management. The oncologist will see the patient initially and then [order] scans to review how their cancer is responding, and then the other nurse practitioner and I will see patients in between to manage symptoms, make dose adjustments, and manage all the things that come along with [patients] who are getting treatment for a malignancy.

Q / One of your specialties as a nurse practitioner is having end-of-life discussions with patients and educating oncologists. How do you approach those end-of-life discussions with patients, and what do they entail?

Rone / That is, of course, difficult. Most patients don't want to talk about the fact that they may pass away from their cancer. Approximately 90% of the patients I see in our practice have metastatic disease, and in most cases, those patients will eventually pass away from their cancer. What we try to do is have ongoing discussions with patients. We try to do it from the beginning, but not everybody is ready to have that level of conversation initially. We try to weave that conversation into the ongoing visits that we have with our patients, talking about how they're currently on treatment, but their cancer is for sure not going to be curable. Then, we have to manage it as long as we can.

We will often tell our patients that their cancer needs to be viewed more as a chronic condition, something like blood pressure, diabetes, or high cholesterol. Nobody expects to be cured of those diseases; they just have to be managed with medication. Of course, cancer is not the same as hypertension or diabetes because it's always changing. We have to try to be one step ahead of it, but eventually, we will reach the end of the treatments that are available to our patients. I will discuss with patients, "Your cancer is progressing; you're not doing very well." They're having pain, or they can't eat. If [patients] start ending up in the hospital all the time, I will often say to them, "We may be causing more harm by continuing to treat you

because you're having these [symptoms] every time we give you a treatment; you develop fevers, diarrhea, pain, nausea, and then end up in the hospital."

I'll have a discussion with the patient at that point and say, "If the goal here is for you to live as long as possible and enjoy the life you have, then we should probably stop treating your cancer because the treatment is giving you more difficulties than benefits. It's time to stop. If you stop your treatment, you might live a little bit longer and enjoy the time you have left." It's difficult. One of the things that I struggle with is that when I have these ongoing discussions with patients, I think they [initially] understand it. They're planning their lives and doing things that they enjoy. Then, somewhere along the way, maybe they reach the end of their treatment course, and I'll say, "OK, there's nothing left. You should probably go to hospice," and they're shocked.

Sometimes I feel like we've failed our patients, even though I feel like we've been having that conversation all along. They haven't been understanding it. That is one of the things that I struggle with because you don't necessarily want to be abrupt and so frank as to say you're going to die of your cancer, although I have done that. Sometimes [patients] just don't want to hear that, and they don't want to believe. We just have to try as best we can to make people understand that they're probably not going to survive their cancer.

Q / What unique skills and knowledge do APNs bring to end-of-life care, and how does that differentiate them from other health care providers?

Rone / As nurses—I don't know if physician assistants feel the same way that nurses do—we are taught to take care of patients from the beginning of life to the end of life. We are a little more comfortable, especially those of us who work in oncology, with the concept of death. Being comfortable talking about it is probably the biggest step that allows us to have that conversation. I believe in the concept of a good death because I've seen bad deaths. I would hope that all the people I take care of have a good death vs a bad death. We can't always get there, so you have to be comfortable with the concept of death. As Americans, we're not comfortable talking about it. We think we're going to live forever, and we ignore that. That's the eventuality that all of us are going to reach. [For] some of us, [it happens] sooner than we thought. You have to be comfortable with the idea that we're all dying of something.

Q / As patients are nearing the end of life, what are some pain or symptom management strategies that you use?

Rone / It depends on what their symptom is. One of the most difficult things to manage is fatigue. A lot of our patients are just tired. We talk a lot about how patients need to eat enough. Many of our patients have nausea or pain when they eat, so they don't eat enough. We work around how to get in more calories and how to group their activities. If they are more energetic in the morning, [they should] do the things they need to do in the morning so they can rest in the afternoon. Many patients have pain, and a lot of people are very concerned about becoming addicted to opioid pain medications.

We start the education about pain management early in the process. We ease patients into the fact that they are probably going to need something stronger than acetaminophen [Tylenol] at some point in time, and you have to make it OK. There are a lot of things in the news about the opioid crisis, and you have to explain to [patients] that this is the result of people prescribing things inappropriately and that for a patient with cancer—someone who has a tumor somewhere in their abdomen or in their leg that is causing them pain and won't go away—they are going to need something that's a little bit stronger. We start educating patients about that early on.

You know the patients who are going to need more pain medicine; some of our patients go through their entire cancer journey without having any pain…. [Many] of the patients I see have GI issues. I see patients who have pancreas cancer, and those patients will develop gastric outlet obstructions, so those patients will often have to get something like a venting [gastrostomy] tube. You have to educate, educate, and educate patients about the things that might happen to them. You don't lay it all out for them all at one time. A lot of patients will start asking questions: "What's going to happen at the end? What's going to be the thing that that takes my life?" You can't predict that, but you can lay out some scenarios for patients.

Q / Is there anything else you want to highlight about the stigma around opioids and pain management and how patients are sometimes averse to wanting to use them in a controlled situation?

Rone / It's sometimes quite difficult because I'll see patients, and you can tell that they are struggling. I'll ask them, "What [can you do] if you want the quality of your life to be better? Here at the end, you should probably do that; take a narcotic, and we can do it safely." Sometimes we just have to start small and work our way up to what they need.

Q / How can clinicians or other members of the multidisciplinary team become more comfortable with initiating conversations with patients about end-of-life care? Should they always defer to you or someone in your role, or should they take the initiative?

Rone / We should all have the conversation. This is just my opinion: I think with the way our physicians are educated, they don't spend a lot of time focusing on the fact that their treatment might fail. Maybe one of the difficulties is that a lot of physicians feel like, "Well, we should keep doing what we're doing." [This is] especially [true for] younger patients. We're seeing more and more younger patients, and often the physicians will want to keep treating somebody because they're young. Why do we need to [keep] younger people [on treatment] just because they're young? If this scenario was occurring in someone who's 78 vs 38 years old, would you do the same thing for them?

Most of the oncologists that I work with are reasonably comfortable talking about this, but sometimes it's much more difficult for them based on the patient's situation. I don't know if you can make people OK with talking about death. Oncologists who are newer in the role may struggle with it a little bit more. As they become more seasoned, they become better at it. Some of the oncologists…are just not good at talking about death. With those oncologists, I [might say], "You should probably not have that conversation with the patient. I'll take care of it." If the patient is hearing it from all of us, that [the treatment] is not working, or this may not work at some point, then it's much more easily accepted.

> "You learn to have an appreciation for the good things and not dwell so much on the bad things."

Q / What is the most challenging part of having these conversations?

Rone / It's the patients who are angry that are the most difficult; a lot of times patients will direct that anger at you. You have to learn that it's not you that they're mad at; they're mad at their cancer, but you're the one sitting in front of them.

Q / How do you combat burnout and maintain your well-being?

Rone / One of the best things about where I work is that we are a very cohesive team. All the people on the GI oncology team, the nurses, nurse practitioners, and medical assistants sit in one big room, and we talk about things and solve problems throughout the day. We spend a lot of time [together]. We have a potluck about once a week because it's somebody's birthday. We also do things outside of work as a group, and so that humanizes what we're doing; it's not so dark all the time.

I've worked in oncology for a long time; you have to have perspective, or you can't continue in this role. This [role] helps you appreciate the finality of life. You don't get upset about [minor] things after you see a 39-year-old patient with metastatic cancer. It's hard to be upset by most things in life when you look at somebody who's going through that and you [say], "My life's not so bad." You learn to have an appreciation for the good things and not dwell so much on the bad things. Are there some days that are harder than others? Absolutely. Do we go down a dark hole at times? Absolutely. But you have to recognize what's happening and find a way to pull yourself out of it.

Q / Is there a gap in knowledge that should be bridged regarding end-of-life discussions?

Rone / We are always learning. When you reach a point where you think you know everything, it's probably time to go do something else. Just in oncology alone, there are so many changes that have been occurring. There's no way to know everything. That's one of the things about oncology in general: you have to pick 1 thing—maybe 2 things—and focus on it. My area of focus is symptom management, and one of the things that has been interesting to note that we've been focusing on lately is molecular profiling. That is such a rapidly evolving field, and a lot of our clinical trials are directed at these specific mutations. That's a very exciting new area in the field that probably has a lot of promise for getting people to more longevity or even cure.

Q / Is there anything else that you'd like to touch upon that we may not have highlighted today?

Rone / One of the things that I have been noticing lately is that with all the information that's available to patients now, whether good or bad, a lot of our patients are very well-educated on their cancer and the latest [advancements]. I have lots of patients who ask about [circulating tumor DNA]. You have to come into a patient's appointment with the fact that you don't necessarily know what kind of Google searches they've been doing. Sometimes you have to educate patients and direct them to better sources of information. It's great when you have a patient who [says], "Well, what about this?" Because that challenges me to learn a little bit more as well. I have patients who come to me and ask, "Did you know about this?" I'll say, "Gosh, no, I didn't know about that." That prompts me to look more into things that maybe I wasn't thinking about. ■

NON–SMALL CELL LUNG CANCER

Clinical Trial Eligibility and Outcomes in Patients With Metastatic NSCLC Treated Outside of Clinical Trials

ABSTRACT

Introduction: There are limited data available regarding patient outcomes in those who would have been ineligible to receive therapy based on the original clinical trial eligibility criteria. We decided to conduct a retrospective study to evaluate outcomes based on clinical trial eligibility in patients with metastatic non–small cell lung cancer (NSCLC).

Methods: A retrospective chart review of all patients with metastatic NSCLC who received first-line systemic therapy at a single academic institution was performed. Each patient's chart was reviewed to determine if they would have qualified for the phase 3 clinical trial that led to the approval of the specific treatment regimen which they received. Data were analyzed to determine if there was a difference in survival time between those who would have been eligible compared with those who were ineligible for the clinical trial of the treatment regimen administered.

Results: There were 170 patients with a diagnosis of metastatic NSCLC who received first-line systemic therapy. Of these, 109 received combined chemotherapy, 25 received immunotherapy, and 36 received targeted therapy. There is a statistically significant difference in the restricted mean survival time between the eligible and ineligible groups in those who received combined chemotherapy (19.9 months vs 13.2 months; $P = .03$), but not in either the immunotherapy group (22.4 months vs 12.9 months; $P = .06$) or the targeted therapy group (57.7 months vs 39.0 months; $P = .14$).

Conclusion: These data support less restrictive clinical trial eligibility criteria for those with metastatic NSCLC. This is especially true regarding both targeted therapy and immunotherapy treatment regimens.

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Over the past few years, there has been a significant increase in the eligibility criteria for medical therapy clinical trials enrolling patients with lung cancer, especially for clinical trials focused on patients with more advanced-stage lung cancer.[1] The number of stringent eligibility criteria involving different organ systems, patient's concurrent drugs, and previous cancer diagnoses have been increasing.[1,2] Many of these eligibility criteria are often reflexively incorporated into clinical trial protocols without definite scientific justification.[1,3] Although some of these criteria are important to ensure patient safety, the increase in eligibility criteria complicates the assessment of potential participants and decreases the applicability of the results of these trials to the general population of patients with cancer.[1]

As investigators in multiple studies have noted, less than 5% of adults with cancer in the United States are enrolled in clinical trials.[2,4-7] One possible cause is the more restrictive eligibility criteria. Eligibility criteria are designed to limit the enrollment to a more homogenous population for easier detection of efficacy while optimizing safety.[1,3] Study populations often do not reflect the general population for whom the treatment might be prescribed.[3] Hence, the majority of patients are treated based on information obtained from a relatively small number of patients.

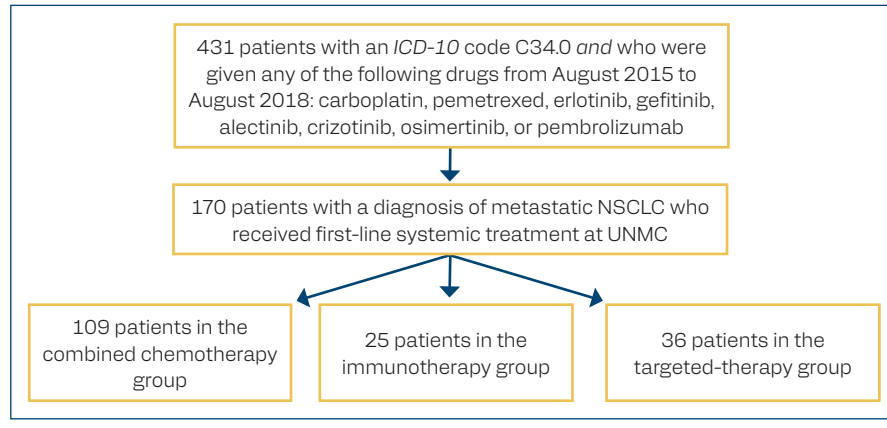
There are limited data available regarding patient outcomes in those who would have been ineligible to receive therapy based on the original clinical trial eligibility criteria. Therefore, we decided to conduct a retrospective real-world study to evaluate outcomes from an academic medical center based on clinical trial eligibility in patients with metastatic non–small cell lung cancer (NSCLC). We hypothesized that real-world survival outcome data would support less restrictive clinical trial eligibility criteria for patients with metastatic NSCLC.

Methods

Data Source and Study Population

Local institutional review board approval was obtained prior to the initiation of this study. A retrospective chart review of all patients with metastatic NSCLC who received first-line systemic therapy at a single academic institution from August 2015 to August 2018 was performed. *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) code C34.0 (malignant neoplasm of main bronchus) was used to search the electronic medical records for patients with metastatic NSCLC. The search criteria also included that the patient needed to receive any of the following drugs: carboplatin, pemetrexed, erlotinib, gefitinib, alectinib, crizotinib, osimertinib, or pembrolizumab. These drugs were selected because they are the mainstay of first-line treatment regimens for metastatic NSCLC. A list of patients who had an *ICD-10* code of C34.0 and had received any of the above-listed drugs was generated.

FIGURE 1. Patient Selection



ICD-10, International Statistical Classification of Diseases, Tenth Revision; NSCLC, non–small cell lung cancer; UNMC, University of Nebraska Medical Center.

Data Collection

The data that were collected on each patient included: date of birth, sex, initial ECOG performance status, date of cancer diagnosis, stage of cancer at diagnosis, histology, molecular mutations, presence or absence of brain metastases (and if present, whether treated with radiation or surgery), first-line treatment regimen, date of the first treatment, second-line treatment regimen (if applicable), date of death or last contact, and cause of death (if applicable). Patients who did not have a histologic diagnosis of NSCLC were excluded. For each first-line treatment regimen, the phase 3 clinical trial that led to the approval of that specific treatment regimen was identified. We selected phase 3 clinical trials instead of phase 2 clinical trials because phase 3 clinical trials typically have less restrictive eligibility criteria. Each patient's chart was reviewed to determine whether they would have qualified for said clinical trial. If a patient would have been ineligible, the reason(s) for ineligibility was documented. Data collection was completed in January 2021, allowing time for the maturation of survival data.

Statistical Analysis

The number of inclusion and exclusion criteria that each patient did not satisfy were recorded. We further stratified those who would have been eligible and ineligible by sex, ECOG performance status,

TABLE 1. Number of Patients Per Treatment Regimen

REGIMEN	FREQUENCY
Afatinib	3
Alectinib	1
Carboplatin/paclitaxel	24
Carboplatin/paclitaxel/pembrolizumab	2
Carboplatin/pemetrexed	75
Carboplatin/pemetrexed/bevacizumab	2
Carboplatin/pemetrexed/pembrolizumab	7
Cisplatin/etoposide	2
Cisplatin/pemetrexed	3
Cisplatin/pemetrexed/bevacizumab	3
Crizotinib	7
Erlotinib	24
Osimertinib	1
Pembrolizumab	16
Total	170

and survival status. We used the Pearson χ^2 test to calculate the *P* value for each subgroup regarding eligibility and ineligibility. Survival time was calculated as the time between treatment initiation and the date of death or last contact.

The primary question in this analysis was to determine whether there was difference in survival time for patients with metastatic NSCLC between those who would have been eligible and those who would have been ineligible for the phase 3 clinical trial that led to the approval of the first-line treatment regimen the patient received. Restricted mean survival time was calculated to identify the variables associated with the difference in survival between those patients who would have been eligible and those who would have been ineligible.[8] The Pearson χ^2 test was used to evaluate the significance of the difference observed between restricted mean survival times for those who would have been eligible and those who would have been ineligible. Kaplan-Meier survival curves were generated for those who would have been eligible and those who would have been ineligible. A log-rank test was used to test the significance of the differences between outcomes. A *P* value of less than .05 was considered statistically significant.

Each patient received first-line treatment for metastatic NSCLC with 1 of 14 regimens. These regimens were classified into 3 different groups: combined chemotherapy, immunotherapy, and targeted therapy. The regimens included in the combined chemotherapy group were carboplatin/pemetrexed,[9] cisplatin/pemetrexed,[10] carboplatin/paclitaxel,[11] cisplatin/pemetrexed/bevacizumab,[12] carboplatin/pemetrexed/bevacizumab,[13] and carboplatin/etoposide[14] regimens. The immunotherapy group included pembrolizumab,[15] carboplatin/pemetrexed/pembrolizumab,[16] and carboplatin/paclitaxel/pembrolizumab.[17] The targeted-therapy cohort included crizotinib,[18] erlotinib,[19] afatinib,[20] alectinib,[21] and osimertinib[22] regimens. Similar analyses as described above were conducted for these individual groups.

Since ECOG performance status was identified to be a common reason for patients being ineligible for clinical trials in our analysis, it was analyzed separately. The majority of phase 3 clinical trial eligibility criteria for the above regimens only included patients with an ECOG performance status of 0 or 1, but there were some clinical trials included in our analysis that allowed the enrollment of patients with an ECOG performance status of 2.[9-22] Patients were classified based on ECOG performance status at treatment initiation into subgroups of ECOG performance status of 0 to 1 or ECOG performance status of 2 to 3. The analyses described above were performed in the ECOG subgroups as well.

Results

A total of 170 patients with metastatic NSCLC received first-line systemic therapy. Of these, 109 received combined chemotherapy, 25 received immunotherapy, and 36 received targeted therapy (**Figure 1**). Table 1 details the number of patients in the study who received each first-line systemic therapy regimen (**Table 1**). The initial ECOG scores were missing in 9 patients, and we were unable to determine eligibility in 7 patients due to missing data. There were 94 women and 76 men in the study, with a median age of 69.6 years. There were 131 individuals with an ECOG performance status of 0 or 1, and 30 individuals had an ECOG performance status of 2 or higher. Of the 170 individuals in this study, 136 had died by the time data collection was completed (**Table 2**).

Of the 163 patients where we had enough data to determine eligibility, there were 105 patients (64.4%) who would have been eligible for the clinical trial of the first-line systemic therapy they received for their metastatic NSCLC and 58 patients (35.6%) would have been ineligible. Of the 58 patients who would have been ineligible for the clinical trials, 38 patients (65.5%) had 1 ineligibility criterion, whereas 20 patients did not fulfill 2 or more criteria for their given clinical trial (Table 2). Higher ECOG performance status and prior malignancy/chemotherapy accounted for approximately 40% of all the ineligibility criteria for ineligible patients. Other causes of ineligibility included prior radiation therapy, renal insufficiency, gastrointestinal disorder, infectious disease, bone marrow dysfunction, central nervous system metastasis, and immunocompromised status (**Table 3**). Sex was not associated with eligibility ($P = .67$). Patients with a lower ECOG performance status were significantly more likely to be eligible ($P < .0001$). When comparing all 3 groups of treatment categories, there was a significant difference in the frequency of eligibility between all groups ($P = .008$).

The inclusion criteria were more stringent in the immunotherapy and targeted-therapy groups compared with the combined

TABLE 2. Descriptive Statistics

	MEAN	MEDIAN
Age (years)	69.3	69.6
N = 170		
Sex	Frequency	%
Female	94	55.3
Male	76	44.7
N = 170		
ECOG	Frequency	%
Low (0 or 1)	131	81.4
High (2 or 3)	30	18.6
n = 161		
Eligibility	Frequency	%
Eligible	105	64.4
Ineligible	58	35.6
n = 163		
If ineligible, # of ineligibility criteria	Frequency	%
1	38	65.5
2	14	24.2
3	5	8.6
4	1	1.7
n = 58		
Deceased	Frequency	%
Yes	136	80.0
No	34	20.0
N = 170		

Initial ECOG performance status was missing in 9 patients. We were unable to determine eligibility in 7 patients due to missing data.

TABLE 3. Frequency of Each Ineligibility Criterion

REASON FOR INELIGIBILITY	FREQUENCY
Autoimmune disease	1
Bone marrow dysfunction	5
CNS metastasis	1
Coagulopathy	4
High ECOG performance status	21
Endocrine disorder	3
GI disorder	6
History of malignancy	6
Immunocompromised	1
Infectious disease	2
Prior chemotherapy	8
Prior radiation	15
Psychiatric disorder	2
Renal insufficiency	9
Vascular disease	1
Total	85

CNS, central nervous system; GI, gastrointestinal.

chemotherapy group. Of the patients who received chemotherapy, 72.1% would have been eligible, compared with only 40.0% and 58.8% of patients who would be eligible in the immunotherapy and targeted-therapy groups, respectively.

Concerning outcomes, patients with an ECOG performance status of 0 or 1 who were eligible had a restricted mean survival time of 32.2 months compared with 23.9 months for those who were ineligible. For patients with ECOG performance status of 2 or more, the restricted mean survival time was 24.5 months for those who were eligible and 13.3 months for those who were ineligible. These differences, however, were not statistically significant ($P = .17$ and $P = .10$, respectively) (**Table 4**). Not surprisingly, there was a significant difference, however, in the restricted mean survival time of those with low performance status compared with those with high performance status (23.5 months vs 16.3 months, respectively; $P = .03$).

At the time of data collection, 61.8% of those who would have been eligible had died compared with 75.0% in the ineligible group. Eligibility to the specific clinical trial was not associated with survival status ($P = .163$). There was a significant statistical difference in the restricted mean survival time in those who would have been eligible compared with those who would not have been eligible (31.5 vs 20.9 months; $P = .03$) (Table 3; **Figure 2**).

There was also a statistically significant difference in survival probability between all 3 treatment groups ($P = .0002$) (**Figure 3**). When looking at each treatment group, there is a statistically significant difference in the restricted mean survival time between the eligible and ineligible groups in those who received combined chemotherapy (19.9 months vs 13.2 months; $P = .03$), but not in either the immunotherapy group (22.4 months vs 12.9 months; $P = .06$) or the targeted-therapy group (57.7 months vs 39.0 months; $P = .14$) (Table 4; Figure 2)

TABLE 4. Multivariate Analysis of Factors Affecting Survival

VARIABLE	SURVIVAL (MONTHS)	*P* VALUE
Trial eligibility		.03
Yes	31.5	
No	20.9	
ECOG PS 0 or 1 eligibility		.17
Yes	32.2	
No	23.9	
ECOG PS ≥ 2 eligibility		.10
Yes	24.5	
No	13.3	
Chemotherapy trial eligibility		.03
Yes	19.9	
No	13.2	
Immunotherapy trial eligibility		.06
Yes	22.4	
No	12.9	
Targeted therapy trial eligibility		.14
Yes	57.7	
No	39.0	

PS, performance status.

Pearson χ^2 test for restricted mean survival time for eligibility vs ineligibility for all treatment types and for each treatment grouping. Table 4 also shows the restricted mean survival time for eligibility vs ineligibility for both low and high ECOG performance status patient groupings. A *P* value of less than .05 was considered statistically significant.

Discussion

The primary goal of this study was to gather and analyze data on patients with metastatic NSCLC who received first-line systemic therapy at a single academic institution to obtain real-world data regarding survival in those who would have been eligible and ineligible for the original phase 3 clinical trial that led to therapy approval. We did observe a significant difference in survival time between those who would have been eligible compared with those who would have been ineligible for their original clinical trial.

However, variations emerged when we divided patients by treatments received. Among patients who received a chemotherapy treatment regimen, those who would have been eligible had better survival time compared with those who would not have been eligible. Yet, there were no differences based on eligibility criteria in patients who received either immunotherapy or targeted therapy.

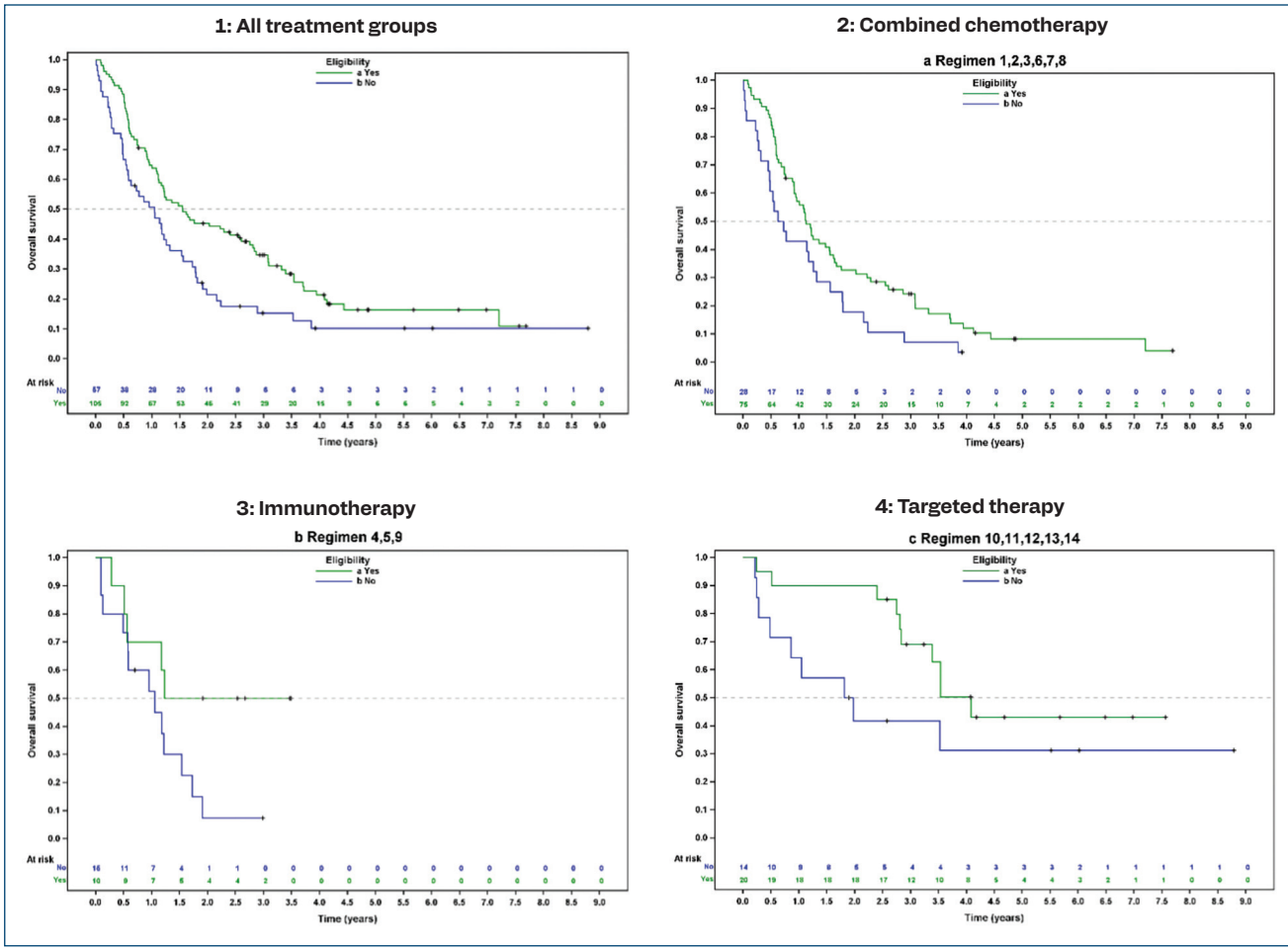
Interestingly, our data also showed a statistically significant difference between the 3 therapy groupings concerning the frequency of who would have been eligible for their original clinical trial. Of the patients in the combined chemotherapy group, 72.1% would have been eligible for their respective clinical trial, whereas this number was significantly lower ($P = .008$) in the immunotherapy group (40.0%) and the targeted-therapy group (58.8%), suggesting that the clinical trials for both immunotherapy and targeted-therapy regimens are likely more restrictive compared with clinical trials for combined chemotherapy regimens. Kim et al previously noted that molecularly driven clinical trials have more eligibility criteria compared with the already restrictive chemotherapy clinical trials for NSCLC.[3] After reviewing the phase 3 clinical trials for all 14 treatment regimens for first-line treatment of NSCLC in our study, we noted that immunotherapy clinical trials and targeted-therapy clinical trials have higher numbers of eligibility criteria compared with chemotherapy clinical trials.[9-22]

Our data suggest that there is no significant difference in clinical outcomes in terms of survival for individuals with metastatic NSCLC who are eligible to participate in both immunotherapy and targeted-therapy clinical trials compared with those individuals who are ineligible to participate. This indicates that reduction of both immunotherapy and targeted-therapy clinical trial eligibility criteria is possible while still having a study population where the investigators can optimize the scientific yield and maximize patient safety. That being said, we do understand that the small numbers of patients in the immunotherapy and targeted-therapy groups make our statistical analysis difficult to interpret.

Many factors may affect the low accrual of patients into cancer clinical trials, including the number of eligibility criteria.[1-7,23-25] Alleviation of eligibility criteria would increase accrual into cancer clinical trials by making the trials more generalizable and helping study completion.[1-7] Less restrictive eligibility criteria could also help with the accrual of patients who are underrepresented in clinical trials.[4-7,23]

Of the patients in our study who would have been ineligible for their respective clinical trials, 65.5% of them were only ineligible based on a single criterion. This suggests that minimal changes to metastatic NSCLC clinical trial eligibility criteria could lead to a marked increase in those who are eligible. Even a slight reduction in the number of eligibility criteria could potentially help with study accrual and generalizability. As previously stated, many of the eligibility criteria for clinical trials are reflexively incorporated into clinical trial protocols.[1,3] These are often carried over from previous trials without scientific justification.[1,3] Laccetti et al previously studied patients with stage IV lung cancer and gathered data on clinical outcomes depending on whether the patients previously had a prior cancer (regardless of stage).[2] They showed that patients with stage IV lung cancer and a prior cancer diagnosis had better all-cause and lung cancer–specific survival compared with those without prior cancer,[2] suggesting that the inclusion of this specific criterion did not affect either the efficacy or safety of the agents studied.

FIGURE 2. Survival Based on Clinical Trial Eligibility



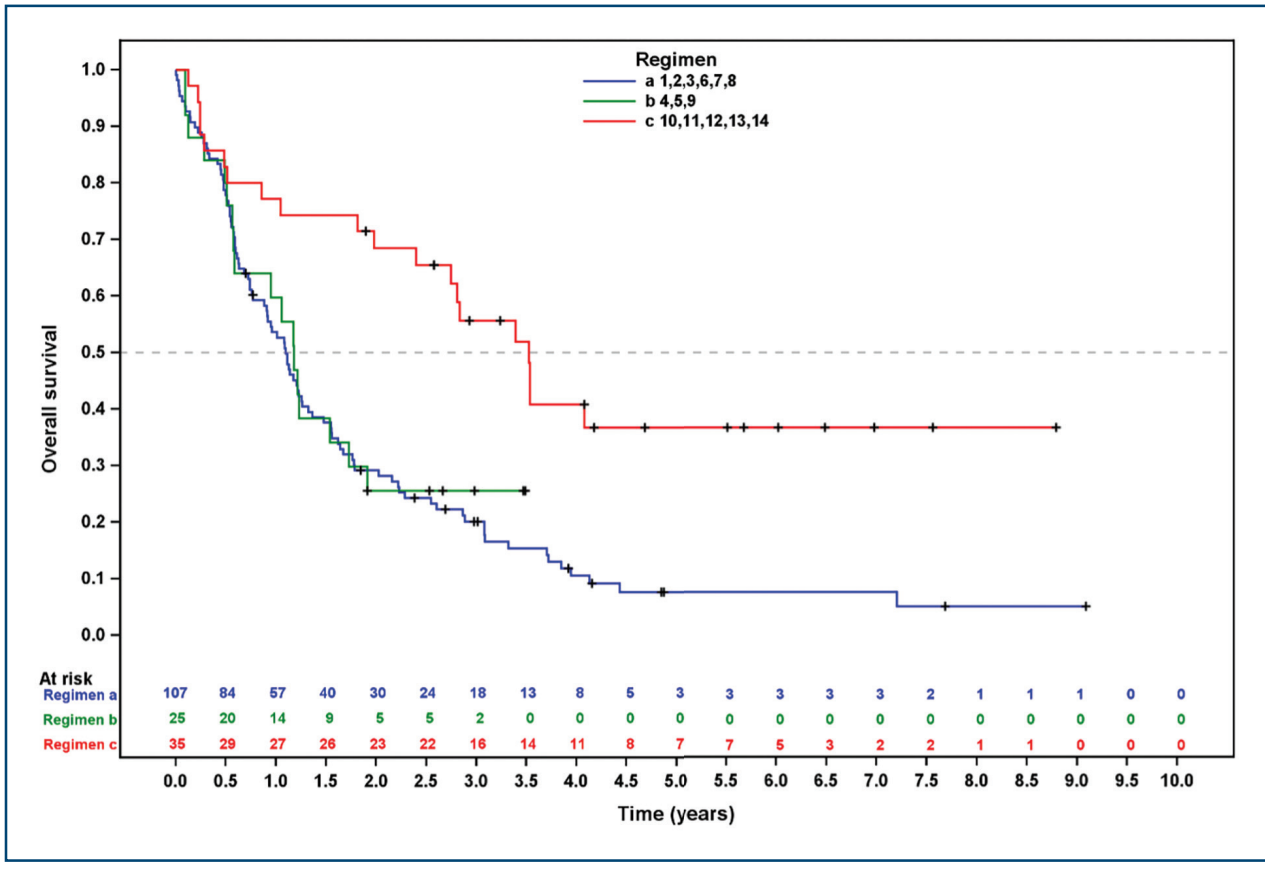
Kaplan-Meier curves showing the difference in overall survival over time in years between those who would have been eligible (green) vs ineligible (blue). (1) All treatment groups ($P = .008$). (2) Combined chemotherapy group only ($P = .03$). (3) Immunotherapy group only ($P = .07$). (4) Targeted therapy group only ($P = .1$).

Prior cancer diagnosis is a common exclusion criterion for metastatic lung cancer phase 3 clinical trials.[2,9-22,24] Laccetti et al showed that 14.7% of patients with advanced lung cancer have a prior cancer diagnosis.[2] They suggested that broadening the inclusion criteria to include those who had a prior cancer diagnosis could help with clinical trial accrual without impacting clinical trial outcomes.[2] Our study did further analysis on ECOG performance status and survival probability. We found that 76.7% of patients with higher ECOG performance status (2 or 3) were ineligible for their respective clinical trials for first-line treatment of metastatic NSCLC. Although studies have shown that patients with high performance status tend to do worse, they form an important subgroup of patients, and these patients must be included in clinical trials in order to identify the best treatment approach for them.[26,27] It is possible that removing ECOG performance status as an eligibility criterion, at least for trials not involving cytotoxic chemotherapy, might have an impact on scientific yield and patient safety, therefore impacting clinical trial outcomes.

There has been recent work in the field of oncology to address low rates of patient participation in clinical trials. The LUNGevity Foundation convened a working group of experts to address the topic of outdated or unnecessary restrictions on lung cancer clinical trials.[28,29] Their work includes an evaluation of how certain criteria have played a role in excluding patients from clinical trials.[28] They have provided scientific justification for reducing certain criteria that routinely exclude patients from lung cancer clinical trials. More recently, they have worked on standardizing eligibility criteria to simplify cancer clinical trials and harmonize trial populations.[29] We believe our study supports their work by providing real-world data on trial eligibility and outcomes in patients with metastatic NSCLC.

There are some limitations to our study. This was a retrospective single-institution analysis. Another limitation was the

FIGURE 3. Survival Comparisons Among All Treatment Groups



Kaplan-Meier curves show the difference in overall survival over time in years between the combined chemotherapy group (blue), the immunotherapy group (green), and the targeted-therapy group (red) ($P = .0002$).

smaller number of patients who received either immunotherapy or targeted-therapy first-line treatment for their metastatic NSCLC. Both immunotherapy and targeted therapy were newer than combined chemotherapy for the treatment of metastatic NSCLC at the time of data collection. Also, both treatment groups require specific targets that can limit the number of patients who receive said treatment.[15-22] As immunotherapy and targeted-therapy treatment regimens become more broadly used for first-line treatment of metastatic NSCLC, repeat analysis can be done to help validate the findings of this study.

Conclusion

In summary, real-world survival outcome data supports less restrictive clinical trial eligibility criteria for patients with metastatic NSCLC. This is especially true regarding both targeted-therapy and immunotherapy treatment regimens, where survival probability and restricted mean survival time were not statistically different in those who would have been eligible compared with those ineligible for their respective phase 3 clinical trial for first-line systemic treatment of metastatic NSCLC. Our data show that both immunotherapy and targeted-therapy eligibility criteria are more restrictive compared with chemotherapy regimens. Less restrictive lung cancer clinical trials can have benefits for both individual patients and the health care system as a whole. Our data show that most patients are only ineligible based on 1 of the many eligibility criteria for a phase 3 cancer clinical trial for metastatic NSCLC. Even a slight relaxation of eligibility criteria could help address the major challenge of patient accrual to cancer clinical trials. ■

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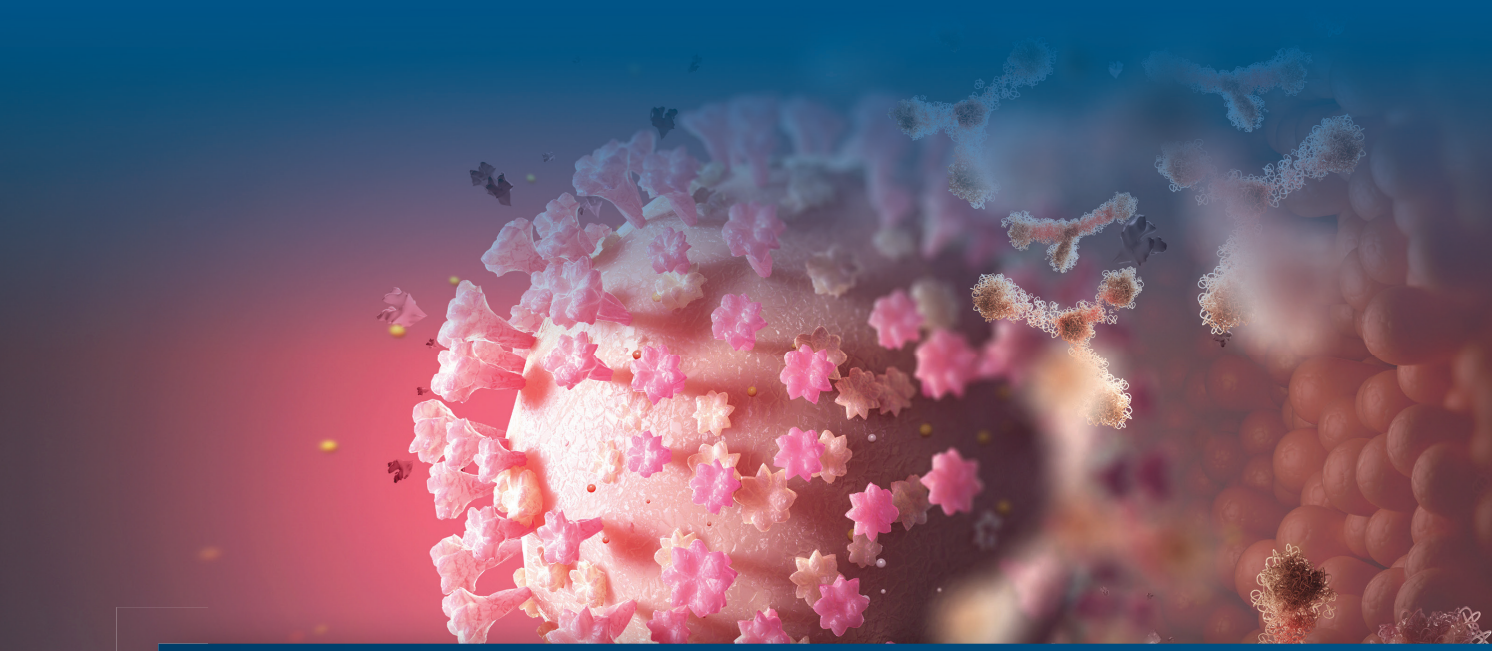

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APPROVAL ALERT

Zolbetuximab's Impact on Gastric/GEJ Adenocarcinoma

John Marshall, MD, sat down with CancerNetwork to review zolbetuximab-clzb, which the FDA recently approved for patients with claudin 18.2 (CLDN18.2)–positive locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. The therapy was approved in combination with fluoropyrimidine- and platinum-containing chemotherapy.[1]

Marshall is the physician executive director of MedStart Washington DC Integrated Hematology-Oncology Division, director of the Ruesch Center for the Cure of Gastrointestinal Cancers, Frederick P. Smith Endowed Chair, and chief medical officer at Georgetown University Lombardi Comprehensive Cancer Center in Washington, DC. He explained that although zolbetuximab is helping to improve an unmet need, there are still many obstacles to overcome in the treatment of patients with gastric/GEJ adenocarcinoma.

Q / How has the FDA approval of zolbetuximab affected patients with locally advanced or unresectable CLDN18.2-positive gastric or gastroesophageal adenocarcinoma?

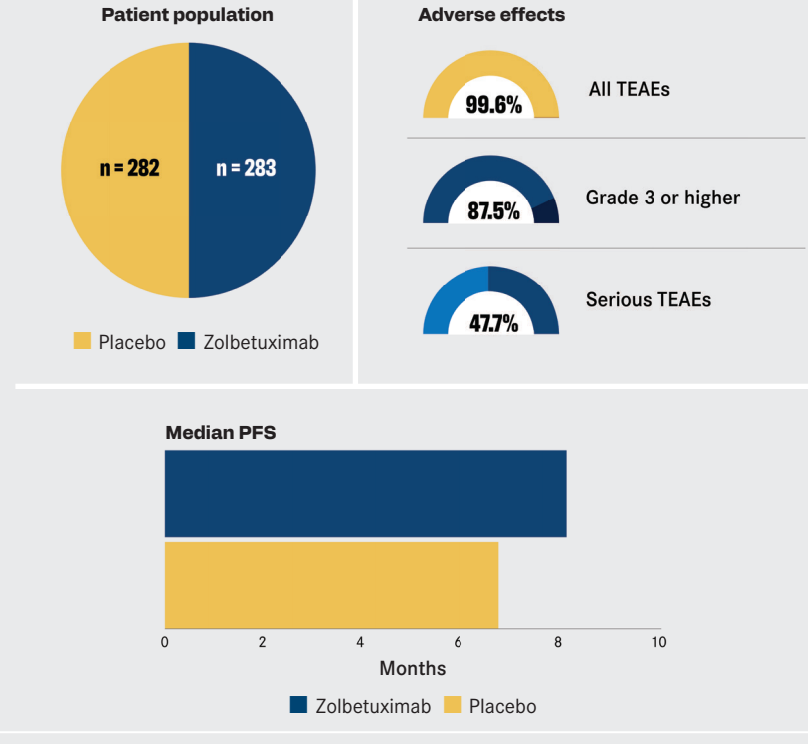
Marshall / In GI [gastrointestinal] cancers, we have been longing for new targets. We have been longing for new therapies. Finally, we are getting one. CLDN18.2 has been out there for a while, and drug development targeting this has been going on for a while. Two big randomized studies now support the benefit [of zolbetuximab] in this patient population. Now we [have] the drug [approval]. We have been delayed by some other issues that have slowed the approvals, but we are excited, and we are all looking forward to incorporating [zolbetuximab] into our treatment paradigm.

Q / What is your impression of the SPOTLIGHT (NCT03504397) and GLOW trial results (NCT03653507)?[2,3]

Marshall / These 2 big phase 3 studies demonstrate [support for the approval] and took patients with gastric and GEJ

STATS AT A GLANCE

SPOTLIGHT Data[2]



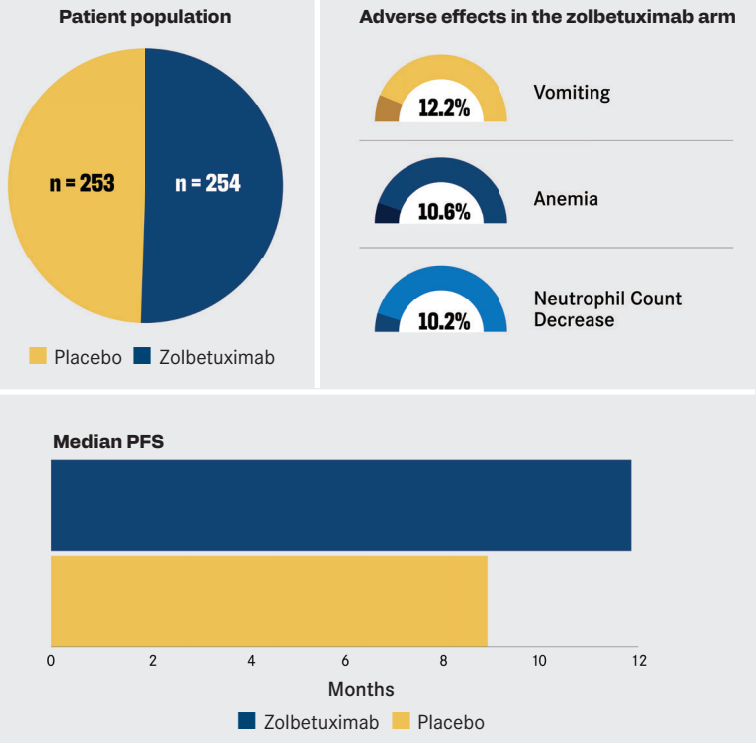
PFS, progression-free survival; TEAE, treatment-emergent adverse effect.

cancers and measured their CLDN18.2 expression. [Approximately] 40% had high enough levels to be involved [in the studies]…. One of the studies was using traditional chemotherapy, and the other [used] capecitabine-based therapy; [these were] essentially the same trial, with 2 different backbones of fluoropyrimidine. Both of them demonstrated an improved progression-free and overall survival [with zolbetuximab]. Based on [the findings], we are hoping to get this approval.

It is important to note that there was not a big delta in response rate, which surprised us; there was some delta, but not a big delta. It is doing something to the biology of this patient population. The one thing that will be confusing to us as clinicians is what to do for a patient [whose disease] is PD-L1 positive and CLDN18.2 positive. Do you bring immunotherapy in? Right now, the preliminary data suggest that most of the patients who [have CLDN18.2-positive disease] also have low PD-L1 [expression]. That might help our decision-making as to what targeted therapy to bring to the table, but that will be the biggest decision tree we will have going forward.

STATS AT A GLANCE

GLOW Data[3]



PFS, progression-free survival.

Q / What unmet need would this approval help reduce?

Marshall / Let's not forget our goal here. The unmet need is [enormous]. You can't imagine how much need we have, and each of these therapies is 1 step on a very long staircase. We need [zolbetuximab]. We need to include [zolbetuximab]. It will improve outcomes for a select group of patients, but we need more [options].

Q / How will this regimen be implemented into clinical practice?

Marshall / The next steps are, how do we take this new tool in the toolbox and leverage it to get even more benefit? It's clear that the clinical data will support this. The biggest need will be that doctors need to start testing for [CLDN18.2]. It's not in our routine to test for CLDN, and that's going to be the biggest new thing that's going to happen across the country.

Q / Are there any toxicities with the zolbetuximab regimen that stand out to you?

Marshall / When you combine this drug with chemotherapy, there is an increase in nausea, vomiting, and a little bit of appetite loss. There is a GI effect, and we will learn to manage and dose appropriately to get around that, but it's certainly not an unmanageable toxicity.

Q / What other developments in GI cancers have the potential to change clinical practice?

Marshall / We are increasingly understanding that gastric cancer is more than 1 disease. It is molecularly broken out into different subgroups, and depending on the molecular subgroups, we have different treatment algorithms. We are beginning to gain knowledge that I believe, over time, is going to continue to improve outcomes. As with many of the GI cancers, we still have a long road [ahead] to understand how to better manage this cancer [type]. I am hopeful that with improvements in our understanding of immunotherapy approaches, [and with] more precision medicine targets and therapies, we will see the robust improvements that we need.

The biggest thing that we need to do as clinicians is begin to incorporate CLDN18.2 testing for our patients. We are not incorporating fast enough the molecular testing that is required based on the speed of development. If you have a [patient with] gastric cancer [for whom] you do HER2 testing and microsatellite instability [testing], you also now have to do CLDN18.2 [testing]. ■

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GASTROINTESTINAL CANCER

Efficacy and Safety of Zolbetuximab in Gastric Cancer

ABSTRACT Gastric cancer remains a major global health concern with high incidence and mortality rates, particularly in East Asia. Patients often have poor outcomes due to limited treatment efficacy. Zolbetuximab, a monoclonal antibody targeting claudin 18.2 (CLDN18.2)—overexpressed in 50% to 80% of gastric cancers—demonstrates promise by initiating antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity in CLDN18.2-positive cells. In clinical trials, zolbetuximab with chemotherapy improved progression-free survival (PFS) and overall survival (OS). The FAST trial showed a median OS increase from 8.4 months to 13.2 months (HR, 0.72; $P < .01$). The SPOTLIGHT trial found PFS extended to 11.0 months vs. 8.9 months (HR, 0.73; $P = .0024$) with OS reaching 18.2 months in the zolbetuximab arm. The GLOW trial also confirmed efficacy, with median OS improving from 12.16 months to 14.39 months (HR, 0.771; $P = .0118$). Zolbetuximab's targeted action, combined with manageable adverse effects, positions it as a promising therapy for advanced gastric cancer.

Introduction

Gastric cancer continues to be a significant global health issue, with more than 1 million new cases and approximately 800,000 deaths annually.[1] The largest incidence rates are seen in East Asia, particularly Japan, South Korea, China, and some Eastern European nations. Despite breakthroughs in diagnostic and treatment procedures, patients with advanced-stage stomach cancer continue to have a dismal prognosis. This is primarily due to the limited efficacy of current therapies and the need for more effective treatment options for metastatic and locally advanced disease. Zolbetuximab is a novel therapeutic drug that targets claudin 18.2 (CLDN18.2), a protein overexpressed in many gastric tumors. Zolbetuximab, an anti-CLDN18.2 monoclonal antibody, binds exclusively to cancer cells that express CLDN18.2, causing their destruction by mechanisms such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).[2] This targeted approach represents a promising development in the management of gastric cancer, offering potential benefits over traditional therapies and addressing an urgent need for more effective treatment options in this challenging disease setting.

Mechanism of Action

CLDN18.2 is a tight junction protein in the stomach mucosa that regulates epithelial barrier integrity. CLDN18.2 is aberrantly expressed on tumor cells in gastric cancer, making it a promising therapeutic target. CLDN18.2 is expressed in 50% to 80% of

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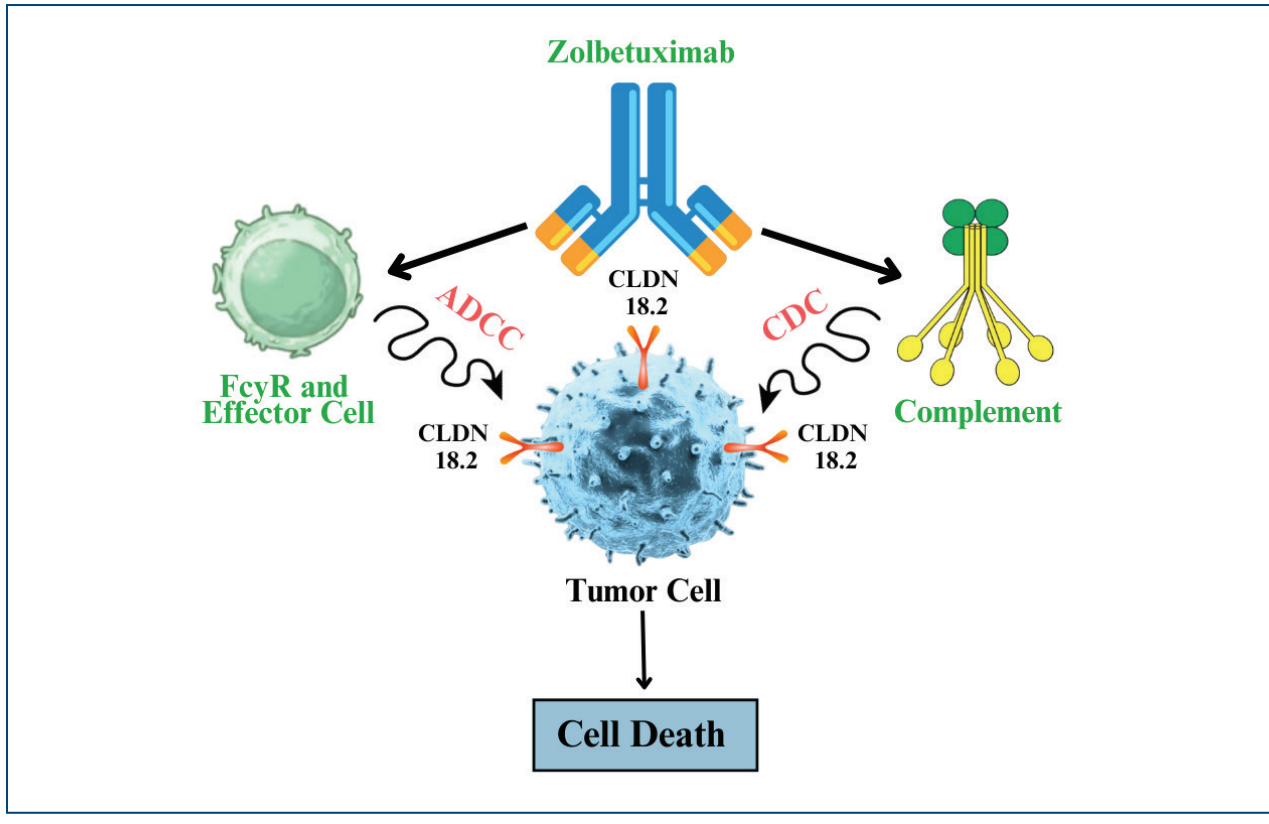
Abdul Baseer Wardak, MBBS, Razia Bahlol Hospital, Kabul, Afghanistan

FIGURE. Mechanism of Action of Zolbetuximab



ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CLDN18.2, claudin 18.2; FcγR, Fcγ receptors.

stomach malignancies, and its limited presence in normal tissues reduces the danger of off-target effects.[2] However, its predominance in tumors suggests a possible path for targeted therapy. Zolbetuximab, when bound to CLDN18.2 on the surface of cancer cells, activates 2 major modes of action that result in cell death. First, immune cells such as natural killer cells recognize and bind to zolbetuximab-coated cancer cells via ADCC. This connection causes immune cells to produce poisonous chemicals that directly destroy cancer cells. Second, zolbetuximab activates the complement system, causing CDC. This mechanism causes the creation of a membrane attack complex on the cancer cell, which disrupts the cell membrane and, eventually, causes cell death. Zolbetuximab is a highly successful targeted therapy for CLDN18.2-positive gastric tumors because of its multiple mechanisms. The **Figure** illustrates zolbetuximab's mechanism of action, where the antibody binds to CLDN18.2 on gastric cancer cells, activating immune effector mechanisms such as ADCC and CDC, resulting in targeted cancer cell destruction.

CLDN18.2's predominance in tumors suggests a possible path for targeted therapy.

Efficacy of Zolbetuximab

Several major clinical trials, including phase 2 FAST (NCT01630083),[3] phase 3 SPOTLIGHT (NCT03504397),[4] and phase 3 GLOW (NCT03653507),[5] have investigated the efficacy of zolbetuximab in individuals with advanced gastric or gastroesophageal junction tumors that express CLDN18.2. The FAST trial investigators focused on zolbetuximab in combination with chemotherapy (epirubicin, oxaliplatin, and capecitabine) vs chemotherapy alone.[3] The results showed significantly improved progression-free survival (PFS; HR, 0.64; 95% CI, 0.49-0.84; $P < .01$) and overall survival (OS; HR, 0.72; 95% CI, 0.62-0.83; $P < .83$) in patients receiving zolbetuximab, with a notable increase in median OS from 8.4 months to 13.2 months in the zolbetuximab arm.

The SPOTLIGHT trial investigators studied the combination of zolbetuximab and chemotherapy (leucovorin calcium, fluorouracil, and oxaliplatin; FOLFOX) in patients with CLDN18.2-positive advanced gastric cancer.[4] The trial's primary goal was met,

demonstrating a significant increase in PFS of 11.0 months (95% CI, 9.70-12.5) in the zolbetuximab arm vs 8.9 months (95% CI, 8.2-10.4) in the chemotherapy arm (HR, 0.73; 95% CI, 0.59-0.91; *P* = .0024). In the zolbetuximab arm, the OS was 18.2 months (95% CI, 16.1-20.6) vs 15.6 months (95% CI, 13.7-16.9) in the chemotherapy arm (HR, 0.78; 95% CI, 0.64-0.95; *P* = .0075).

Additionally, the GLOW trial investigators focused on zolbetuximab plus capecitabine and oxaliplatin as first-line treatment for CLDN18.2-positive gastric cancer.[5] The investigators found higher response rates and survival improvements than with chemotherapy alone. PFS in the zolbetuximab arm was 8.21 months vs 6.80 months in the placebo arm (HR, 0.687; 95% CI, 0.544-0.866; *P* = .0007) Notably, the median OS in each arm was 14.39 months vs 12.16 months, respectively (HR, 0.771; 95% CI, 0.615-0.965; *P* = .0118). Zolbetuximab excelled over existing therapies in terms of PFS and OS. The ability to preferentially target CLDN18.2-positive tumors decreases off-target damage, making it an intriguing addition to the therapy landscape for advanced gastric cancer.[3]

Safety of Zolbetuximab

Zolbetuximab had a manageable safety profile in the FAST, SPOTLIGHT, and GLOW trials. Common adverse effects (AEs) included nausea, vomiting, fatigue, and gastrointestinal discomfort. Other AEs such as anemia, neutropenia, and infusion-related reactions also were noted, although they were manageable. AEs were managed with antiemetic medications for gastrointestinal issues and growth factors such as granulocyte colony-stimulating factor for neutropenia. Infusion-related reactions were treated with premedication, including antihistamines and corticosteroids, alongside slower infusion rates. Compared with standard therapies, zolbetuximab's targeted mechanism allows for reduced off-target toxicity, making AE management relatively straightforward.[4]

Conclusion

The FAST, SPOTLIGHT, and GLOW trial results indicated that the success of zolbetuximab is dependent on the selection of patients with CLDN18.2-positive cancers. Testing for CLDN18.2 expression is required before prescribing zolbetuximab, ensuring that the treatment is reserved for patients with high CLDN18.2 expression, maximizing efficacy while preventing unnecessary treatment in others. Zolbetuximab is expected to become part of standard gastric cancer treatments, especially in combination with chemotherapy regimens such as FOLFOX, because of its ability to improve PFS and OS. It may also be used, likely in first- or second-line treatments, with other targeted therapies or immunotherapies, particularly for patients who are CLDN18.2 positive and HER2 negative.[5]

Future development of zolbetuximab will likely focus on exploring its use in combination with other therapies, such as immunotherapies or novel targeted agents, to enhance its efficacy. Ongoing trials should aim to expand its applicability beyond first-line treatments, possibly extending to other cancers expressing CLDN18.2. Additionally, further research is needed to investigate biomarker-driven strategies to optimize patient selection and treatment outcomes. Zolbetuximab is a promising advancement in the treatment of patients with CLDN18.2-positive gastric cancer, providing a targeted approach that has demonstrated considerable improvements in clinical trials. As it becomes integrated into standard treatment protocols, it may provide a novel therapeutic option for patients with advanced gastric cancer, especially those with few therapy options. ■

Zolbetuximab is a promising advancement in the treatment of patients with CLDN18.2-positive gastric cancer, providing a targeted approach that has demonstrated considerable improvements in clinical trials.

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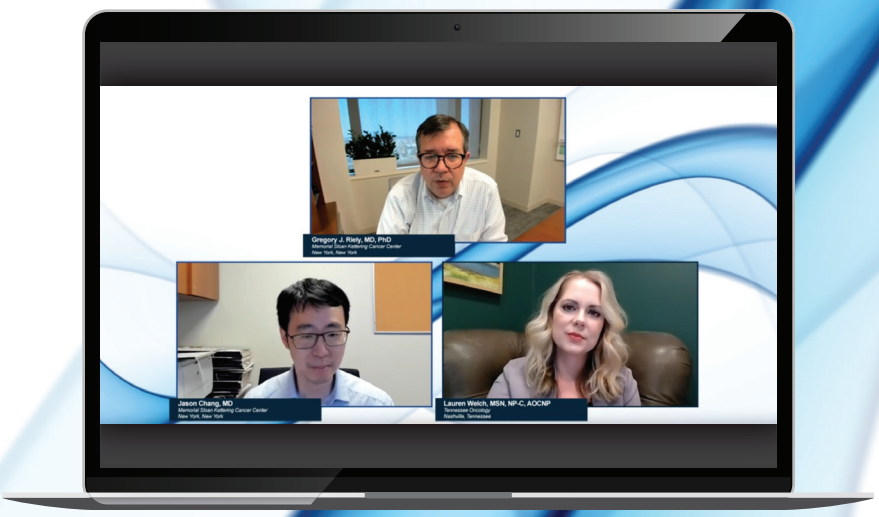

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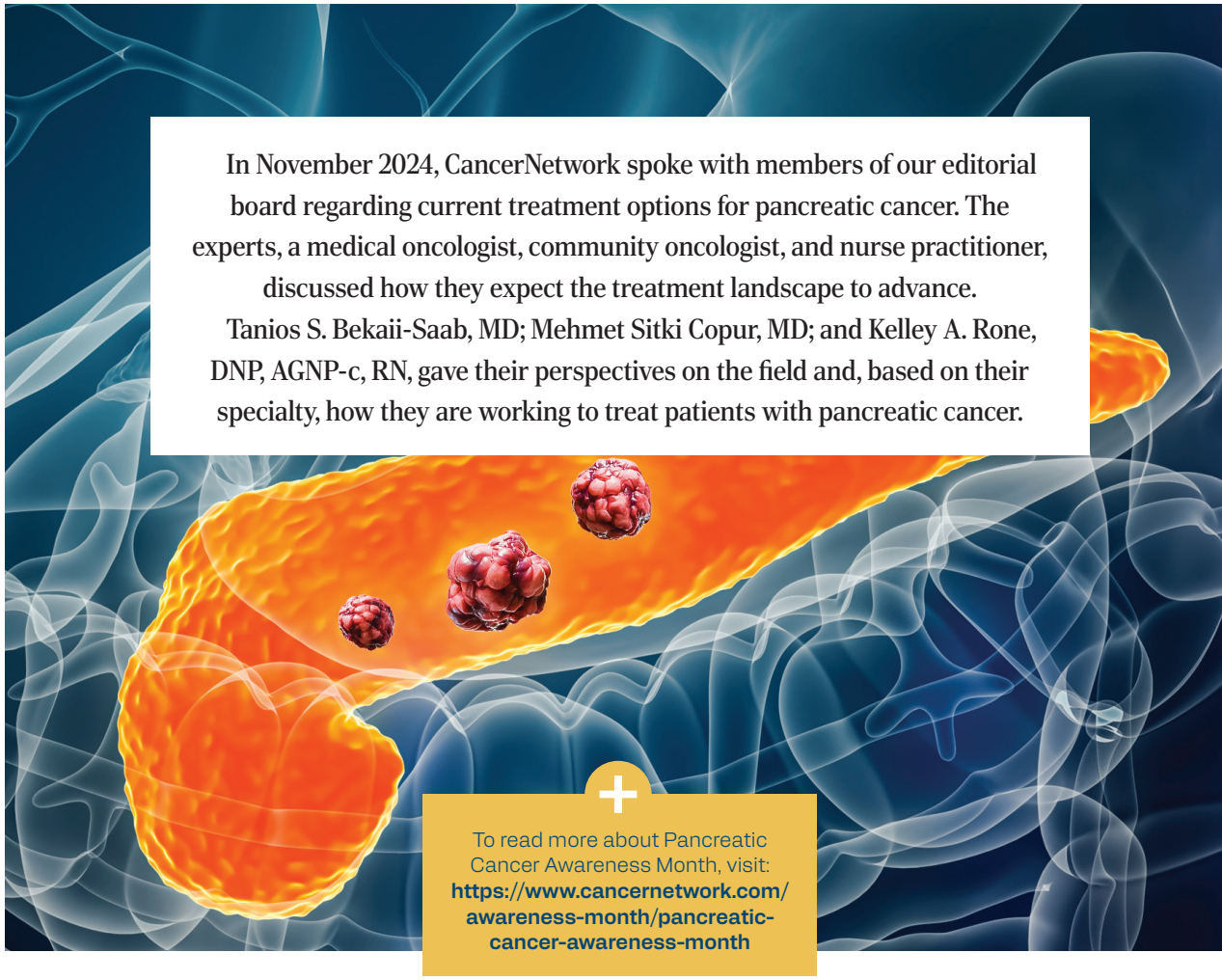
Experts' Perspectives on Pancreatic Cancer Treatment



In November 2024, CancerNetwork spoke with members of our editorial board regarding current treatment options for pancreatic cancer. The experts, a medical oncologist, community oncologist, and nurse practitioner, discussed how they expect the treatment landscape to advance. Tanios S. Bekaii-Saab, MD; Mehmet Sitki Copur, MD; and Kelley A. Rone, DNP, AGNP-c, RN, gave their perspectives on the field and, based on their specialty, how they are working to treat patients with pancreatic cancer.

To read more about Pancreatic Cancer Awareness Month, visit: **https://www.cancernetwork.com/awareness-month/pancreatic-cancer-awareness-month**

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Tanios S. Bekaii-Saab, MD
David F. and Margaret T. Grohne Professor of Novel Therapeutics for Cancer Research, Chair and Consultant in the Division of Hematology and Medical Oncology at Mayo Clinic in Arizona, and Co-Leader of Advanced Clinical and Translational Science at Mayo Clinic Cancer Center in Phoenix, AZ

Bekaii-Saab on the Emerging Field

If I have any message for my colleagues, my patients, and all patients with pancreatic cancer, it's that [we can almost see] the light at the end of the tunnel. We're seeing it clearer now. We have a lot more to offer our patients. We're working very hard on bringing all these agents comprehensively into clinical trials and the clinic. I have never been more optimistic. I'm always the eternal optimist, but I'm even more optimistic today that we're going to move the needle for our patients with pancreatic cancer and continue to enhance that likelihood of living longer, having a better quality of life, or even increasing the level of a cure for this cancer.

In the end, many of these agents that are very active in the later stages of the disease need to start trickling back to earlier [disease] stages. We've done great work with chemotherapy and surgical resections, and improved surgical techniques have moved a lot of patients with early-stage cancer into a cure. But [it is] not enough, and we now must think about how we can bring these targeted agents to earlier lines of therapy to enhance even further the likelihood of cure for these patients. [There is] plenty of work ahead of us. Certainly, the future looks bright. We're chipping away, one drug at a time. We can now remove that whole concept of nihilism in pancreatic cancer and look quite optimistically at the future. Finally, we're going to get there.

Mehmet Sitki Copur, MD, FACP
Medical Oncologist at Mary Lanning Healthcare and Adjunct Faculty Professor at the University of Nebraska Medical Center Department of Internal Medicine Division of Hematology/Oncology in Omaha

Copur on Treating as a Community Oncologist

As far as the physicians who practice in the community setting, not necessarily academic, one big thing I would recommend is multidisciplinary involvement. It is the very first big principle. When you see a patient, the first thing is to make sure the surgical oncologist, medical oncologist, radiation oncologist, the pathologist, and your basic science people, even if you are in the community, [are involved]. The next very important thing is genetic counseling [approval from] insurance companies. Make sure you make a referral to a genetic counselor, which would complement your next-generation sequencing on the tumor tissue. The genetic counselor will order germline mutation testing. If I order it as a physician, they may not approve it, but if a genetic counselor sees and orders it, that goes through.

Then you have connections with your academic colleagues. Even though I'm in a community-based setting, I have The Clinical Trials Network, I'm a member of Alliance [for Clinical Trials] through the University of Nebraska and Buffett [Cancer Center], so I make sure clinical trials are first. As soon as you see a new patient, check if there is a clinical trial. If you follow the prior recommendations I gave, like the multidisciplinary team, next-generation sequencing, and germline testing with genetic counseling, it opens the door for clinical trials out there. All you need to do is check them out, and…make sure that you are not missing a great clinical trial [for your patient]. Let's say they didn't qualify up front; after they go through [various lines of therapy], certainly they will be eligible for a clinical trial. Most people miss this because they think clinical trials are later in the line, and if you look at the NCCN [National Comprehensive Cancer Network] guidelines, the best way to treat any patient is in a clinical trial first.

Kelley A. Rone, DNP, AGNP-c, RN
Advanced Practice Nurse of Gastrointestinal Oncology at Mayo Clinic in Phoenix, AZ

Rone on Educating Patients

We need to start with education. [Not many] people think about [pancreatic] cancer as something that they will ever get. Most people think about the more common types of cancer: colon, breast, and prostate. Education about modifiable vs nonmodifiable [risk factors] is the starting place. Once people know what those are—[which are] the usual things, such as you should not smoke because that increases your risk by 2 [times] vs nonsmokers, so you double the risk if you are a smoker.

Obesity is also a risk if you have diabetes. [Many] people do not realize that when you are newly diagnosed with diabetes, that increases your risk of developing pancreatic cancer. We do not know much about [the connection yet], but it is something that people should be aware of. Certainly, for people who have chronic pancreatitis, those people are also at a greater risk of developing pancreatic cancer. If someone is having recurrent pancreatitis, one of their providers should say to them, "Hey, we have to get this better controlled, or you are at risk [for pancreatic cancer]."

Modifying the behaviors that cause you to develop pancreatitis, like excessive drinking, [can help.] Patients should be aware that pancreatitis increases their risk. There is some information on exposure to chemicals. If you work in a workplace that exposes you to chemicals, sometimes that is difficult to control, but maybe you could have a discussion with your employer: "How do we protect ourselves from these chemicals?" For people who have nonmodifiable risks, such as genetic syndromes that predispose you, those people should be screened in a different way, and they need to be aware of how the screening should proceed. ■

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3 Things You Should Know About Immunotherapy in DLBCL

RELEASE DATE: December 1, 2024
EXPIRATION DATE: December 1, 2025

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:
- Assess recent pivotal trial data investigating targeted agents in patients with DLBCL across multiple lines of care.
- Select appropriate treatment strategies for patients with relapsed/refractory DLBCL considering efficacy, safety, and patient-specific factors to optimize patient outcomes.
- Discuss mechanisms of treatment resistance/lack of response in patients with DLBCL and how they can affect treatment sequencing in DLBCL.

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Cytotoxic T cells play a vital role in the body's immune defense against tumors. However, their effectiveness can be limited by factors such as the immunosuppressive nature of the tumor microenvironment and the scarcity of T cells that naturally recognize tumor-specific neoantigens. Here are 3 things you should know about immunotherapy in diffuse large B-cell lymphoma (DLBCL).

1 CAR T-cell therapy enhances the immune response to DLBCL.

Chimeric antigen receptor (CAR) T-cell therapy aims to enhance the antitumor capabilities of the adaptive immune system by collecting a patient's T cells and modifying them genetically to express a receptor that specifically targets an antigen expressed on the patient's tumor cells (**Figure 1**).

CD19-targeting CAR T-cell therapy consisting of either axicabtagene ciloleucel (axi-cel) or lisocabtagene maraleucel (liso-cel) is the recommended second-line therapy for patients with DLBCL who are not sensitive to chemotherapy, meaning that their disease is refractory to treatment or that it relapses within the first 12 months of first-line chemotherapy.[1] Liso-cel is also a second-line therapy option for patients who do not intend to proceed to hematopoietic stem cell transplant (HSCT) based on results from the phase 2 PILOT study (NCT03483103).[2] In this clinical trial, investigators administered liso-cel to 61 patients aged at least 70 years whose disease relapsed after first-line therapy who met at least 1 prespecified criterion for transplantation not intended. The overall response rate was 80% (95% CI, 68%-89%); a complete response (CR) was noted in 54% of patients. Median event-free survival (EFS) was 7.23 months (95% CI, 3.22-22.60 months). Median overall survival (OS) was not reached (NR) (95% CI, 17.28 months to NR). The most common treatment-emergent adverse events (TEAEs) of grade 3 or 4 were neutropenia (48%), leukopenia (21%), and thrombocytopenia (20%). Cytokine release syndrome (CRS) is an AE of special interest with CAR T-cell therapy; it occurred in 38% of patients in this study, including 1 grade 3 case. Neurological events, including 3 grade 3 cases, also occurred in 31% of patients.

Axi-cel was tested in the open-label, phase 2 ALYCANTE trial (NCT04531046) as second-line therapy in 62 patients aged at least 65 years with relapsed/refractory (R/R) LBCL who are ineligible for HSCT.[3] The objective response rate (ORR) was 90%, including 79% of patients who had a CR. Median EFS was 12.3 months (95% CI, 7.2 months to NR). Median progression-free survival (PFS) was 11.8 months (95% CI, 8.4 months to NR). Both median OS and duration of response were not reached. Some 95.2% of patients experienced AEs of grade 3 or greater including neutropenia (66.1%), anemia (38.7%), and thrombocytopenia (38.7%). CRS was reported in 93.5% of patients, including grade 3 or 4 CRS in 8.1% of patients. Immune effector cell-associated neurotoxicity (ICANS) was reported in 51.6% of patients, including grade 3 or 4 ICANS in 14.5% of patients.

FIGURE 1. Overview of CAR T-Cell Therapy

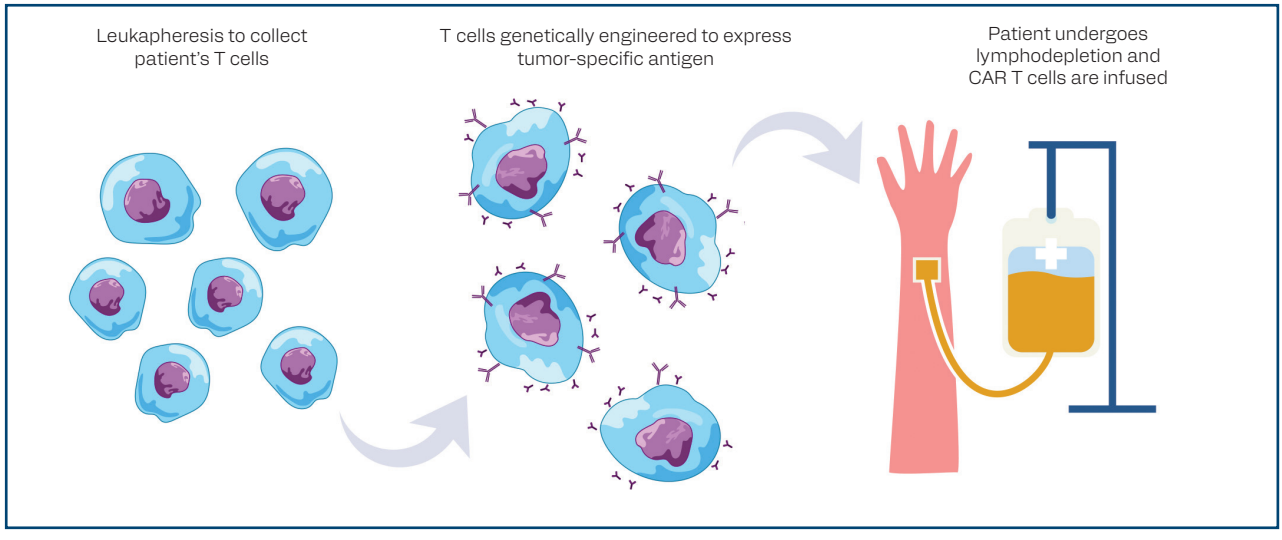
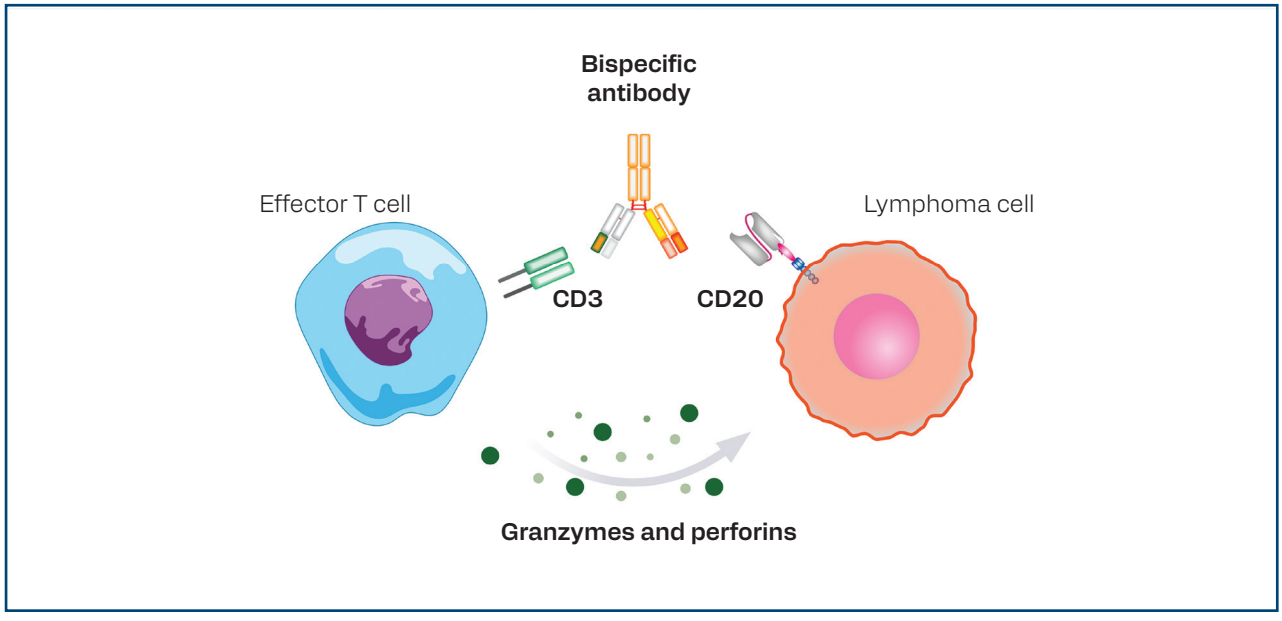


FIGURE 2. **CD3xCD20 Bispecific Antibodies**



2 Bispecific antibodies provide an off-the-shelf immune enhancement option in the R/R disease setting.

For patients whose disease progressed during or after at least 2 lines of systemic treatment, which can include HSCT or CAR T-cell therapy, use of the CD3×CD20 bispecific antibodies (BsAbs) epcoritamab or glofitamab can be an option (**Figure 2**).[1]

In the single-arm, pivotal EPCORE NHL-1 trial (NCT03625037), 157 patients with R/R LBCL, including 139 patients with DLBCL, were given epcoritamab as a third- or later-line therapy.[4] At a median follow-up of 20 months (range, 0.3-28.2 months), the ORR in patients with DLBCL was 61.9%, including CR in 39.6%. The median duration of CR was 20.8 months. CR was achieved at a median of 2.7 months from the start of treatment; however, 8 patients converted from a partial response to a CR after 36 weeks or more of follow-up. Median OS was 18.5 months (95% CI, 11.7 months to NR). TEAEs occurring in more than 20% of patients were CRS (51%), neutropenia (24%), pyrexia (24%), fatigue (23%), nausea (22%), and diarrhea (21%). In patients who experienced CRS, 94% of the events were grade 1 or 2 with the remainder being grade 3. All cases of CRS occurred after the first full dose of epcoritamab. ICANS occurred in 10 patients; 9 patients experience grade 1 or 2 events, 1 patient had a grade 5 event with confounding factors. Two fatal TEAEs (COVID-19 and ICANS) were attributed to epcoritamab therapy.

Glofitamab is another CD3×CD20 BsAb approved for use as a third-line or later treatment for patients with R/R DLBCL based on the results of a pivotal phase 2 trial (NCT03075696).[5] Of 154 patients with R/R LBCL who had received at least 2 prior therapies, investigator-assessed ORR was 59%, including CR in 38%. The median duration of CR was 24.1 months (95% CI, 19.8 months to not estimated). The 18-month OS rate was 41% (95% CI, 32.1%-49.3%). CRS was reported in 64% of patients; these included grade 1 (48%), grade 2 (12%), grade 3 (3%), and grade 4 (1%) events. The most common grade 3 or 4 AE was neutropenia (27%).[6] No treatment-emergent deaths were attributed to glofitamab.

3 Antibody-drug conjugates and other targeted therapies offer increased options in downstream therapy.

In addition to CAR T-cell therapy and bispecific antibodies, the DLBCL armamentarium includes a variety of treatments beyond chemotherapy for patients who have progressed on first-line therapy (**Table**).[1] Brentuximab vedotin recently joined the list of second-line options after its use demonstrated improved ORR, CR, OS, and PFS when combined with lenalidomide and rituximab vs lenalidomide and rituximab alone in the ECHELON-3 trial (NCT04404283).[7]

TABLE. Selected Treatments in the Second Line or Greater[1]

THERAPY	MECHANISM OF ACTION	INDICATION
Polatuzumab vedotin	Antibody-drug conjugate	Bridging therapy during CAR T or second line for patients who have no intention to proceed to transplant
Tafasitamab (combined with lenalidomide)	Anti-CD19 monoclonal antibody	Second line for patients who have no intention to proceed to transplant
Brentuximab vedotin	Antibody-drug conjugate	Second line for patients with CD30+ who have no intention to proceed to transplant
Loncastuximab tesirine	Antibody-drug conjugate	Third line and beyond
Selinexor	Inhibitor of nuclear export	Third line and beyond including patients with prior transplant or CAR T

CAR T, chimeric antigen receptor T-cell therapy.

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1 **Relapse that occurs how long after chemoimmunotherapy is considered to be *chemosensitive*?**
A. At least 3 months
B. At least 6 months
C. At least 9 months
D. At least 12 months

2 **A 65-year-old male has been diagnosed with nongerminal center DLBCL with high CD20 expression. He has refractory disease following treatment with R-CHOP and is not a candidate for high-dose chemotherapy followed by autologous stem cell transplantation (ASCT), nor is he a candidate for CAR T-cell therapy.**
Which of the following is an appropriate treatment for this patient at this time?
A. R-CHOP
B. Bendamustine plus rituximab
C. Tafasitamab plus lenalidomide
D. R-ICE (rituximab, ifosfamide, carboplatin, etoposide)

3 **In the randomized, phase 3 ECHELON-3 trial, addition of brentuximab vedotin to lenalidomide-rituximab led to which of the following compared with placebo-lenalidomide-rituximab?**
A. Significantly improved OS
B. Significantly worse OS
C. No significant difference in OS

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Follow-Up VISIT from PER®

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Disclosures
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Disclosures
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Consultant: Alexion Pharmaceuticals, Apellis-Sobi, Novartis; *Speaker:* Alexion Pharmaceuticals.

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3 Things You Should Know About Hemolytic Anemias

RELEASE DATE: December 1, 2024
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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:
- Analyze data for current and emerging therapeutic strategies for PNH, aHUS, and wAIHA
- Determine the implication of recent approvals as well as emerging data for investigational approaches for PNH, aHUS, and wAIHA

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Hemolytic anemias are a collection of rare but severe diseases including paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS), which occur in less than 1 person per 100,000, and warm autoimmune hemolytic anemia (wAIHA), which occurs in up to 3 people per 100,000.[1-3] Here are 3 things you should know about hemolytic anemias.

1 Anti-C5 targeted therapy is a mainstay of PNH and aHUS treatment

In both PNH and aHUS, overactivity in the alternative complement cascade can lead to anemia, kidney damage, and other systemic dysregulation.[4,5] Several drugs have been developed targeting proteins of the alternative complement cascade to treat symptoms of PNH and aHUS (**Figure**). The C5 inhibitors eculizumab and ravulizumab were compared head-to-head in the 301 and 302 trials (NCT02946463 and NCT03056040, respectively).[6,7] Ravulizumab demonstrated noninferiority to standard-of-care eculizumab in terms of transfusion avoidance, least-square mean (LSM) percent change in lactate dehydrogenase (LDH) levels, change in FACIT-Fatigue score, percentage of patients experiencing breakthrough hemolysis, and hemoglobin (Hgb) stabilization.

Crovalimab is the most recently approved therapy for PNH based on results from the phase 3, single-arm COMMODORE 3 trial (NCT04654468) in 51 complement inhibitor-naive patients with PNH who received at least 4 transfusions of packed red blood cells in the 12 months prior to screening.[8] The estimated mean proportion of patients with hemolysis control from week 5 through week 25 was 78.7% (95% CI, 67.8%-86.6%). The proportion of patients with transfusion avoidance from baseline through week 25 was 51.0% vs 0% within 24 weeks of prescreening ($P < .0001$). No treatment discontinuations were due to adverse events (AEs).

Investigations into novel C5-targeting agents include a phase 2 trial (NCT04811716) of the combination of an anti-C5 monoclonal antibody, pozelimab, and cemdisiran, an small interfering RNA that suppresses C5 production in the liver.[9] During the 28-week open-label treatment period, 83.3% of the 24 trial participants maintained control of LDH (LDH levels were no greater than 1.5 times the upper limit of normal [ULN]) at all time points. Additionally, 75% of participants were considered to have stabilized Hgb, (no blood transfusions required and Hgb levels of at least 2 g/dL were maintained). Breakthrough hemolysis requiring a blood transfusion occurred in 2 patients. No severe treatment-emergent AE (TEAEs) were considered to be treatment-related.

FIGURE. Alternative Complement Cascade and Inhibitors

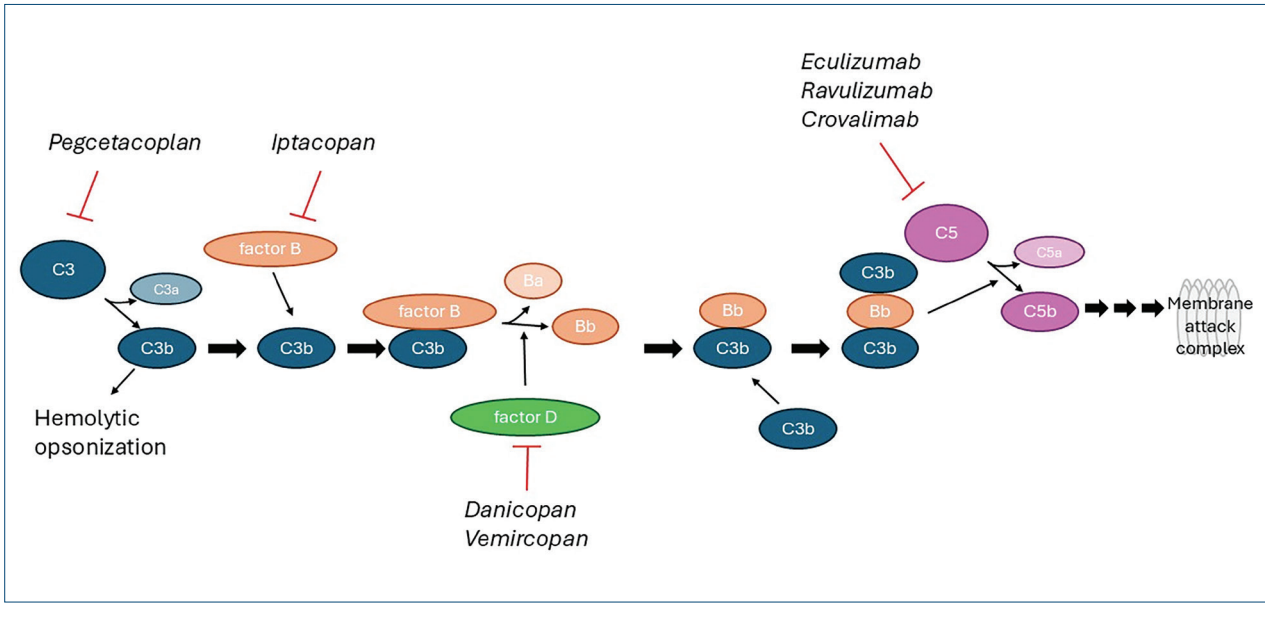

TABLE. Novel Therapies in Clinical Trials for the Treatment of wAIHA

DRUG / TRIAL ID / PHASE	MECHANISM OF ACTION	PATIENT CHARACTERISTICS	PRIMARY END POINT
Rilzabrutinib[17] NCT05002777 Phase 2	BTK inhibitor	wAIHA with no sustained response with corticosteroids	Proportion of patients with ≥ 2 g/dL increase of Hgb over baseline by 24 weeks
Povetacicept[18] RUBY-4 NCT05757570 Phase 1b	BAFF/APRIL inhibitor	ITP, wAIHA, CAD; prior to concurrent treatment with corticosteroids allowed	Safety and tolerability
Nipocalimab[19] ENERGY NCT04119050 Phase 2/3	FcRn-targeting monoclonal antibody	wAIHA with insufficient response to prior treatment	Percentage of patients achieving durable improvement in Hgb

APRIL, a proliferation-inducing ligand; BAFF, B cell-activating factor; BTK, Bruton tyrosine kinase; CAD, cold agglutinin disease; FcRn, neonatal Fc receptor; Hgb, hemoglobin; ITP, immune thrombocytopenia; wAIHA, warn autoimmune hemolytic anemia.

2 Additional PNH and aHUS treatments target upstream components of the alternative complement cascade

Pegcetacoplan is a C3 inhibitor (Figure) approved for use in PNH. In the phase 3 PRINCE trial (NCT04085601) in complement inhibitor-naive patients with PNH, pegcetacoplan demonstrated improved Hgb stabilization from baseline to week 26 in 85.7% of 35 patients vs 0% of 18 control patients receiving supportive care (difference, 73.1%; 95% CI, 57.2%-89.0%; $P < .0001$).[10] Pegcetacoplan also improved change from baseline LDH with an LSM change of –1870.5 U/L vs –400.1 U/L in the control arm (difference, –1470.4 U/L; 95% CI, –2113.4 to –827.3 U/L; $P < .0001$). Treatment with pegcetacoplan did not contribute to any serious AEs.

Iptacopan is a first-in-class oral factor B inhibitor (Figure) that demonstrated improved Hgb levels in patients with PNH in a pair of phase 3 trials.[11] In the APPLY-PNH study (NCT04558918), patients who had received prior eculizumab or ravulizumab were randomly assigned to continue with anti-C5 therapy or switch to iptacopan. The APPOINT-PNH study (NCT04820530) evaluated patients who had not received complement-inhibitor therapy and had LDH levels that were at least 1.5 times the ULN. In the 2 trials, 85% and 94% of patients receiving iptacopan experienced an increase in Hgb levels of at least 2 g/dL from baseline, respectively, vs 0% of patients in the APPLY-PNH study who continued with anti-C5 therapy. The most common AE reported among patients receiving iptacopan in these trials was headache.

Danicopan is a selective factor D inhibitor (Figure) evaluated as an add-on therapy to ravulizumab or eculizumab in the phase 3 ALPHA trial (NCT04469465).[12] A total of 73 patients with PNH who had been on ravulizumab or eculizumab for at least 6 months were randomly assigned (2:1) to add danicopan or placebo to their regimen. At 12 weeks, add-on danicopan increased Hgb from baseline by a LSM difference of 2.94 g/dL (95% CI, 2.52-3.36 g/dL) vs 0.50 g/dL (95% CI, –0.13 to 1.12 g/dL). No serious AEs were attributed to danicopan.

3 Novel targets are under investigation in wAIHA

Standard of care for patients with wAIHA involves successive use of corticosteroids, rituximab, and splenectomy.[13] Fostamatinib is an oral spleen tyrosine kinase (Syk) inhibitor approved for the treatment of chronic immune thrombocytopenia and is under investigation for the treatment of wAIHA in the phase 3 FORWARD trial (NCT03764618).[14] A total of 90 patients with wAIHA who had experienced insufficient response to at least 1 prior treatment were randomly assigned (1:1) to receive fostamatinib or placebo. At 24 weeks, after censoring for Hgb values impacted by steroid rescue during screening and excluding 2 patients deemed unlikely to have wAIHA, 33.3% of patients in the fostamatinib arm achieved a durable Hgb response of at least 10 g/dL vs 14.0% of patients in the placebo arm ($P = .0395$).

Sovleplenib (HMPL-523) is another Syk inhibitor under investigation in patients in China with wAIHA in a phase 2/3 study (NCT05535933).[15] A total of 21 patients who had received at least 1 prior therapy were randomly assigned (3:1) to receive sovleplenib

or placebo. At 8 weeks, the overall Hgb response rate was 43.8% in the sovleplenib arm vs 0% in the placebo arm.

A retrospective study queried whether the anti-CD38 monoclonal antibody daratumumab could suppress the secretion of wAIHA-inducing autoantibodies from CD38+ plasma cells.[16] In 12 patients with steroid and/or rituximab-refractory wAIHA, overall response was 50% with a median duration of response of 5.5 months (range, 2-12 months). Blood samples were prospectively collected from 2 patients and showed complete CD38+ T-cell depletion.

Additional early-phase trials of novel therapies are outlined in the **Table**.[17-19] Rilzabrutinib is approved for the treatment of immune thrombocytopenia, where it inhibits the activation of B cells to prohibit the production of autoimmune antibodies.[17] The cytokine antagonist povetacicept suppresses autoimmune antibody production by plasma cells.[18] Nipocalimab blocks IgG recirculation, causing a reduction in serum IgG by approximately 90%.[19]

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1 Which of the following therapeutic agents for the management of paroxysmal nocturnal hemoglobinuria (PNH) targets and inhibits factor B in the alternative pathway of the complement cascade?

A. Crovalimab
B. Danicopan
C. Eculizumab
D. Iptacopan

2 Which of the following novel drug targets is inhibited by the investigational agent nipocalimab for the treatment of warm autoimmune hemolytic anemia?

A. BTK
B. FcRn
C. SYK
D. pIgR

3 Which of the following statements best describes the outcomes of the phase 3 COMMODORE 2 study of crovalimab vs eculizumab with respect to hemolysis control, transfusion avoidance, and breakthrough hemolysis events in C5 inhibitor treatment-naive patients with PNH?

A. Crovalimab was inferior to eculizumab.
B. Crovalimab was noninferior to eculizumab.
C. Crovalimab was superior to eculizumab.
D. The study was insufficiently powered for efficacy analysis.

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

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

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

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

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

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

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

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

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

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

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

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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IMPORTANT SAFETY INFORMATION (CONTINUED)

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

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

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

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

Systemic Reactions

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

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

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

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

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

Local Reactions

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

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

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

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

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

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

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

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

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

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

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

DARZALEX®: ADVERSE REACTIONS

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

DARZALEX *FASPRO*®: ADVERSE REACTIONS

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

INDICATIONS

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

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

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

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

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

cp-248517v3

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

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

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

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

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

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

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

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

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

Interference with Serological Testing

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Interference with Determination of Complete Response

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

Embryo-Fetal Toxicity

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

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

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

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

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

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

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

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

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

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

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

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

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

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

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

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

Herpes Zoster Virus Reactivation

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

Infections

Grade 3 or 4 infections were reported as follows:

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

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

Fatal infections (Grade 5) were reported as follows:

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

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

Hepatitis B Virus (HBV) Reactivation

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

Other Clinical Trials Experience

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

Nervous System disorders: Syncope

Immunogenicity

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

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

Postmarketing Experience

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

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

DARZALEX® (daratumumab) injection

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

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

Neutropenia

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

Thrombocytopenia

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

Embryo-Fetal Toxicity

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

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

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

Hereditary Fructose Intolerance (HFI)

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

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

For patent information: www.janssenpatents.com

cp-271933v4

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

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

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

Local Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

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

Neutropenia

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

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

Thrombocytopenia

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

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

Embryo-Fetal Toxicity

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

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

Interference with Serological Testing

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

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

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

Immunogenicity

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

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

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

Postmarketing Experience

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

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

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

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

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

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

Lactation

Risk Summary

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

Data

Animal Data

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

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

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

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For patent information: www.janssenpatents.com

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