Managing Myeloma

Targeting BCMA in Multiple Myeloma and the Approval of Belantamab Mafodotin

Sagar Lonial, MD, FACP
Chair and Professor
Department of Hematology and Medical Oncology
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

One of the important questions in myeloma is about the importance and rationale for targeting BCMA in multiple myeloma. I think that it's really important to recognize that while we have antibodies that target CD38 or SLAMF7, expression of those proteins is much broader than BCMA. The expression of BCMA is almost exclusively represented on plasma cells. And the expression of BCMA looks pretty similar between newly diagnosed myeloma, relapsed myeloma, and ultimately, refractory myeloma. What we hope is that by having a much more narrow spectrum of expression, that targeting BCMA will have fewer off-target effects than we see with other agents or other monoclonal antibodies in the context of multiple myeloma. Now, we know that because BCMA is such an important target, there are a number of different ways that are being investigated to go after BCMA. For instance, there's a lot of data on different bispecific antibodies or T-cell engagers. Similar to blinatumomab, for instance, in ALL or lymphoma, where you use BCMA and CD3 to try and bring T-cells next to the myeloma cell to attack those, and those are in early development and certainly are encouraging in terms of their activity. There are also CAR T-cells that are being developed that are evaluating BCMA as a target, and there are a number of different types of CAR T-cells with subtle differences between them, but they also seem to have pretty encouraging efficacy and activity as well.

Most recently, however, we did have the first BCMA targeted drug, belantamab mafodotin or belamaf, which is an antibody-drug conjugate. Similar to other agents in this class, such as brentuximab, for instance, it uses an antibody receptor to BCMA and brings to it a chemotherapy moiety called MMAF. MMAF is different from many other antibody-drug conjugates in that it does not have neuropathy as a potential side effect, but it does have some level of ocular toxicity, and we'll talk about that in just a few moments. The data that really supported the FDA approval of belamaf in the context of multiple myeloma was the DREAMM-2 study. The DREAMM-2 study was a randomized phase two study that evaluated two different doses of belamaf. Belamaf was evaluated at 3.4 mg/K and 2.5 mg/K, and it's important to recognize why were those doses chosen. Well, the 3.4 mg/K dose was the MTD that was defined in DREAMM-1. DREAMM-1 had an earlier relapsed patient population, even though it was a phase one study, and in that study, it demonstrated as high as a 50% response rate in earlier lines of therapy. However, when the FDA looked at the package, and because the ocular

toxicity was somewhat new and unique to myeloma patients, they wanted to evaluate a lower dose to see whether a lower dose would be safer in terms of adverse events and maybe the efficacy would be similar. In DREAMM-2, there was a randomization between 2.5 and 3.4. What we learned was that the response rates were almost identical. In the 2.5 mg/K dose, the response rate was about 31% to 32%, slightly higher in the higher dose. But what we did learn was that the adverse events were higher in the 3.4 mg/K dose, and for that reason, the 2.5 mg/K dose of belamaf was chosen going forward.

Now, it's important to recognize that the patient population in this DREAMM-2 study was a triple class refractory patient population. Relapsed and refractory disease following an IMiD, proteasome inhibitor, and CD38 monoclonal antibody. What this really means is that these are a group of patients with a median of six to seven prior lines of therapy who don't really have many other, if any, potential treatment options available. While the response rate was 32%, the median PFS was about three months, the median duration of response, meaning how long those responding patients lasted, was about 11 months. Actually that 11 months is longer than the median DOR for any drug in a triple class refractory myeloma setting. Again, putting it as good if not better than carfilzomib or daratumumab or pomalidomide in a similar heavily pretreated patient population as well. I think that that really does potentially raise the interest level for using belamaf in the context of triple class refractory myeloma, because it clearly has not only efficacy, but also has durability of those responses among the patients that can respond. Again, DOR or duration of response in my view, is a surrogate marker for both efficacy and safety. Because there are other drugs that have a 25% to 30% response rate in triple class refractory myeloma, but the DOR is very short, suggesting that patients simply cannot stay on therapy, even if they're having a response.

What are some of the issues or adverse events that one needs to know about or be comfortable with if you're using belamaf? There are two adverse events that occur relatively frequently. One of them is keratopathy or ocular toxicity. We'll talk about that in just a second. The other is hematologic toxicity, so thrombocytopenia, neutropenia, and anemia. And those are similar for any other antibody-drug conjugate. They're similar for almost any treatment that we use in the context of myeloma, particularly in refractory myeloma where we know patients often have compromised counts and have resistant disease going into the initial treatment. But what about ocular toxicity? Well, the first point to make about ocular toxicity is that this is really measured by an ophthalmologist or an optometrist. It's an eye care specialist that you really need to partner with in order to get these exams done. Finding the ocular toxicity, which is microcysts within the cornea, is very easy. I think we heard an ophthalmologist at ODAC describe it as something that a first-year optometry student could find. It's not a complicated finding, it's not a difficult finding to be able to make. At our center, we tend to partner with ophthalmology, but it doesn't have to be ophthalmology, it could be an optometrist that can do the slit lamp exam to really look at the cornea and give you an estimation for the extent of the keratopathy. Now, it's important to realize that while keratopathy is graded

1 through 4, and 70% of patients who get belamaf have keratopathy at all, grades 1 through 4, keratopathy itself is purely an ophthalmologic exam finding. It isn't always correlated with clinical symptoms. Of the 70% that do have keratopathy, only 50% had symptoms, and those typically include dry eyes or itchy eyes that can be addressed with lubricating eye drops, and that is part of what's recommended in the package insert. Only 20% of the 70% actually end up having changes in visual acuity. It's really a relatively small number of patients that have major issues with keratopathy that results in clinical symptomatology despite the fact that a significant fraction of patients may have keratopathy at all as measured by an ophthalmologist.

I think the keys here are partnering with an eye care professional, they need to have an exam before each dose of drug is administered, you need to look at that exam and understand and put it all together as recommended by the package insert to determine whether or not a patient is due for their next dose of belamaf. Now, one of the things that is commonly done in DREAMM-2 and should be commonly done in routine practice with belamaf is dose holding or dose attenuation. What I can tell you is that in DREAMM-2 when doses were held and missed, that most patients actually had stabilization of their disease or improvement in their disease status despite the fact that belamaf was not given, and that has something to do with the very long half-life of belamaf. In some patients, it may be longer than others, and that's what allows you to do dose holding or dose attenuation to try and maximize the benefit of belamaf, and you don't necessarily lose control of the disease by holding the treatment. Just as an example to give you a sense of reversibility, the reversibility on keratopathy, meaning resolution of keratopathy, takes roughly 60 to 80 days, but again that's the ophthalmologic finding. When you look at resolution or reversibility of changes in visual acuity, the median time is 22 days. Missing a dose of therapy and coming back in three weeks doesn’t result in loss of control of disease, and allows most patients to be able to resume with improvement in their visual acuity symptoms, if they develop them at all. I think, again, partnership with an eye care professional is really important. We found one or two ophthalmologists that we work with very closely. They get them in either the day of the dosing or the day before the dosing. We use that information and make a decision on whether or not to treat them. In this context, belamaf, which is given every three weeks, is relatively straightforward and easy compared to other drugs in the refractory myeloma setting. Yes, there's an extra visit with an ophthalmologist, but there are not visits once or twice a week for fluids or antiemetics or count checks or all those other things. I would likely recommend count checks once a week, just so you can make sure you know what's going on with the blood counts during that first cycle of therapy. But beyond that, there is not a huge amount of supportive care that's required, and that makes belamaf a pretty attractive treatment option for patients in the refractory myeloma setting. Thank you very much for your attention.

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Reference:

ClinicalTrials.gov. A Study to Investigate the Efficacy and Safety of Two Doses of GSK2857916 in Participants With Multiple Myeloma Who Have Failed Prior Treatment With an Anti-CD38 Antibody. https://clinicaltrials.gov/ct2/show/NCT03525678