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COMMENTARY

Bispecific Monoclonal Antibodies in Multiple Myeloma: Data from ASH 2022: A Podcast

Ola Landgren · Omar Nadeem

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ABSTRACT

The introduction of novel immunotherapies has transformed the treatment landscape in multiple myeloma (MM). The addition of these agents has significantly improved patient outcomes; however, MM remains largely incurable, with heavily pretreated patients suffering from shorter survival times. To address this unmet need, the focus has shifted toward novel mode of action therapies, such as bispecific antibodies (BsAb), which simultaneously bind to immune effector cells and myeloma cells. Currently, there are several T cell–redirecting BsAb being developed that target BCMA, GPRC5D, and FcRH5. These BsAb show impressive clinical activity for the relapsed/refractory population targeted and will likely become an essential part of MM treatment protocols in the future. In this podcast, the authors summarize and highlight some of the T cell–redirecting BsAb currently in development for the treatment of relapsed/refractory MM with a focus on the data reported at the oral session for BsAb at the American Society of Hematology's 2022 meeting from clinical phase 1 and 2 studies. The six presentations reported the latest safety and efficacy data for the BsAb: talquetamab, elranatamab, teclistamab, forimtamig, and alnuctamab.

PLAIN LANGUAGE SUMMARY

Multiple myeloma is a type of bone marrow cancer. It affects a type of white blood cell known as a plasma cell. Although multiple myeloma cannot be cured with current therapies, it can often be controlled with treatment. In some people with multiple myeloma, the treatment does not work at all, or it works at first but the cancer comes back. This is known as refractory or relapsed multiple myeloma. New types of treatment are needed for these people.

Researchers are studying a type of antibody made in a laboratory called a bispecific antibody. They are a new type of treatment for multiple myeloma that work in a different way to existing treatments. This means they may help people who earlier treatments did not work well for. Bispecific antibodies use the body's immune system to kill cancer cells. They work by attaching to two different types of proteins:

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O. Landgren (✉)
Sylvester Comprehensive Cancer Center, Miami, FL, USA
e-mail: col15@miami.edu

O. Nadeem
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

one found on plasma cells, and another on a type of white blood cell called a T cell.

At the American Society of Hematology's 2022 meeting, researchers presented results from clinical trials studying five different bispecific antibodies: talquetamab, elranatamab, teclistamab, forimtamig, and alnuctamab. In this podcast, two healthcare professionals summarize the most common side effects people had while taking these new medicines, and how manageable they were. They also discuss how effective these bispecific antibodies were at treating refractory or relapsed multiple myeloma.

Keywords: Multiple myeloma; Bispecific antibodies; Clinical trial; Podcast

DIGITAL FEATURES

This article is published with digital features, including a podcast audio file, to facilitate understanding of the article. To view digital features for this article, please go to https://doi.org/10.6084/m9.figshare.22782896.

INTRODUCTION

Ola Landgren (OL): Hello and welcome to this *Advances in Therapy* podcast. The purpose of this podcast sponsored by Pfizer is to highlight on some of the T cell–redirecting bispecific antibodies (BsAb) currently in development for the treatment of relapsed refractory multiple myeloma (RRMM). Speaking today is Dr. Omar Nadeem, Clinical Director of the Myeloma Institute Effector Cell Therapy Program at the Dana Farber Cancer Institute. And I'm Dr. Ola Landgren. I'm chief of the Myeloma Division and leader of the Translational and Clinical Oncology Program at the Sylvester Comprehensive Cancer Center at University of Miami. In this podcast, we will be focusing on the data presented in the Bispecific Monoclonal Antibodies in Myeloma oral session at the American Society of Hematology, or ASH 2022, meeting from clinical phase 1 and 2 studies. Omar, could you please tell us why the BsAb are of interest to the myeloma community?

Omar Nadeem (ON): Yeah. Thanks, Ola. So, as we know, these novel immunotherapies have really transformed the landscape of MM therapy. We're seeing a lot of advances in therapy, and patients are doing much better, but unfortunately, the disease still remains incurable and patients become refractory to a lot of their conventional therapies [1]. So, because of that, we've now shifted toward these immunotherapies in patients with heavily pretreated and RRMM, and BsAb are of tremendous interest and they're being studied across many different targets. So, we have B cell maturation antigen (BCMA), G protein-coupled receptor family C group 5 member D (GPRC5D), and FcRH5 [2, 3]. These are all targets now that the bispecifics are studying, and they show some impressive results and likely will become an essential part of myeloma therapy in the future. So, today we will highlight six presentations that were oral abstract presentations at the ASH annual meeting, and we'll review their safety and efficacy for the current bispecifics that are in development. So, Ola, would you like to get us started and talk about the first presentation, which was from the MonumenTAL-1 study?

TALQUETAMAB, A GPRC5D × CD3 BSAB, IN PATIENTS WITH RRMM: PHASE 1/2 RESULTS FROM MONUMENTAL-1 [4]

OL: I will certainly do that, yeah. The MonumenTAL-1 study is an ongoing phase 1/2 study of the drug talquetamab, and this is for patients in RRMM. Talquetamab is the first-in-class bispecific antibody that targets both GPRC5D on the myeloma cells and CD3 on the T cells. This particular study was presented for the first time and highlighted on safety and also efficacy of the subcutaneous (SC) talquetamab at the recommended phase 2 doses in patients that were naïve to T cell–redirected therapy. There were two cohorts. The first cohort was 0.4 mg/kg once weekly (QW) in two step-up doses in a total of 143 patients. The second cohort was

0.8 mg/kg every other week (Q2W) with three step-up doses. And the sample size here was 145 patients. There are a lot of details that I don't have the time to fully go through and cover, but I think some high points are that these patients are heavily pretreated. They were triple-class exposed. About 70% of the patients were penta-drug exposed; 93% and 92% were refractory to anti-CD38–targeted therapy respectively for these two cohorts, and about 13% and 10% were also refractory to belantamab mafodotin, respectively, for the two cohorts.

Speaking a little bit about the safety profile, similar to what has been seen with other BsAb across the board for different targets, the most common any-grade hematologic adverse events (AEs) that were present in $\geq$ 20% of patients were anemia and neutropenia, lymphopenia, and also thrombocytopenia, and these ranged around 30% or 40% or so. The most common any-grade non-hematologic AEs that were found in $\geq$ 40% of the patients were cytokine release syndrome (CRS). That was found in around 80% and 70%, respectively, for the two cohorts. There were also skin-related events and nail-related events. The skin were around 50–60%, and the nail-related were around 50%, or 40–50%, and there was also impact on the patient's taste in around 50% of the patients. A lot of focus for these types of drugs clinically have been around CRS, and the CRS events were grade 1/2. In the vast, vast majority of cases it was only about 1–2% that were grade 3 and higher. The median time of onset for CRS was ranging from 1 to 8 days but the average was around 2 days, and patients with more than one CRS event was about 30% of patients, also similar to what has been seen with many of the other BsAb. The duration of the CRS was around 2 days, but it also had a broad range from only 1 day up to… the longest was reported up to 2, 3, or even up to around 4 weeks for some individual cases. This could be treated successfully with tocilizumab and also steroids, and this is similar to what we have seen for other of these bispecifics. Another side-effect profile aspect here is similar to the other bispecifics. These are the immune effector cell–associated neurotoxicity syndrome (ICANS) that were reported at a rate of about 10% in the patients. Most of them were grade 1/2, and again, it was only around 2% that were grade 3. The median time of onset was similar to CRS, around 2 days. Median duration was 2 days, and this was concurrent with CRS in somewhere between 60% and 70% or so of the patients. The ICANS resolved in the majority of the patients. There was already infections noted in these patients, and that happened in around 50–60%, and there were even grade 3/4 infections in around 10–20%. There were some of the infections being labeled as opportunistic infections. These were single-number percentages, around 4% or so. Patients also became hypogammaglobulinemic, and around 10–15% of patients received intravenous immunoglobulins (IVIG) for the two cohorts. The discontinuation due to AE was low… around 5% or 6% for the two cohorts. So, I've tried to cover some of the high points that were clinically important. So, Omar, is this a novel safety profile for the myeloma community? What do you think?

ON: I think there are some things unique about this particular bispecific, namely due to the target GPRC5D. We see some similarities with other BCMA bispecifics such as CRS at generally similar rates. And thankfully, we're not seeing as high a grade of CRS as we've seen, let's say, with some of the chimeric antigen receptor T cell (CAR-T) products. So, I think across the board with bispecifics that seems to be a little bit lower. What's interesting about this target is that it does have some unique toxicity profile, particularly as it relates to dysgeusia, nail bed changes, and skin changes, which is really a hallmark of this particular target. So, it'll be important to see as time goes on how impactful these are when it comes to quality of life for patients. But overall, I think this is something to note. But importantly, only a low single-digit percentage of patients actually discontinued because of these AEs. So, that should hopefully bode well as more and more patients are treated. The other factor here is the infections. This is something we've seen with the BCMA bispecifics at pretty high rates, but if you look in this particular abstract, the rates of grade 3 or 4 infections were actually lower. So, I think that's a bit reassuring, so it's starting to maybe give us some signals that these

bispecifics are different, and it may have to do with the target.

OL: I would agree with that. So, the high response rate for single drug in heavily pretreated patients, I think that's quite impressive. It's what we have seen for many of the other drugs, as well across the board for the bispecifics. We see pretty high response rates, and it was actually around 70% or so in the patients here, 62% overall, and it was 70% of patients with prior CAR–T cell therapy. And they also had information on patients that had been treated with prior BsAb, and that was around 44%. So, what do you think about that, Omar?

ON: Yeah, I think this trial did have a cohort of these patients. Generally speaking, this cohort that had prior T cell redirection, these were younger patients, had a higher prevalence of high-risk cytogenetics; they had more previous lines of therapy, at a median of six. The majority of these patients had prior CAR-T cells, and a handful had a prior bispecific antibody at 35%. And some patients even had belantamab and were refractory to it. And the fact that we're seeing responses at about 62% in this cohort that had prior T cell–redirecting therapy, I think is quite encouraging. It tells us that these therapies do work in that particular scenario, and the numbers are kind of small. If you break it down between the ones that had prior CAR-T cells, it's about 72%, which sort of mirrors what we saw as an overall response rate; but it is lower in the ones that had prior bispecific antibody therapies. So, again, it's difficult to know with these small numbers. Is this going to kind of pan out as we treat more and more patients in sequence with some of these therapies? But it perhaps gives us some clues about what may be the better sequence. Would you rather go from CAR-T cells to bispecific? This may suggest that, but either way you are seeing some responses, which is encouraging.

ELRANATAMAB, A BCMA-TARGETED T CELL ENGAGING BSAB, INDUCES DURABLE CLINICAL AND MOLECULAR RESPONSES FOR PATIENTS WITH RRMM [5]

ON: Next, we'll cover the abstracts that were presented at ASH looking at elranatamab, which is a BCMA-targeted T cell engaging BsAb. And there were two presentations from the MagnetisMM program, which is evaluating this efficacy and safety of elranatamab in patients with MM. So, elranatamab is a humanized bispecific antibody. It targets both BCMA on the myeloma cells and CD3 on the T cells. The first presentation from the MagnetisMM Study was the MagnetisMM-1 Study, which is the ongoing phase 1 first-in-human study evaluating elranatamab in patients with RRMM. This trial has enrolled 55 patients who received SC elranatamab monotherapy at doses starting from 215 up to 1000 μg/kg, given either QW or Q2W. In this particular study, the patient's median age was 64 years old. About a third of patients had high-risk cytogenetics, and patients had a median of five prior lines of therapy, which is quite similar to other trials in this space. These were heavily pretreated patients… 91% of patients were triple-class refractory, and approximately a quarter of patients had prior BCMA-targeted therapy. And this was either with the antibody–drug conjugate (ADC) or with CAR-T cells, and not with the prior bispecific. And 20% of patients enrolled in this study were Black or African American.

So, in terms of safety, we saw again a pretty comparable safety profile to other BCMA bispecifics. We saw some hematologic AE, namely neutropenia at about 75%, but two-thirds of patients had anemia, and then about half the patients had thrombocytopenia. In terms of

non-hematologic AEs, CRS was seen in about 84% of patients, which was the most common AE that was non-hematologic. There were some injection-site reactions in about half the patients, and some fatigue and diarrhea that was also reported. In terms of CRS, most of these events were grades 1 or 2, so about 51% were grade 1 and 36% were grade 2, and approximately half the patients received tocilizumab, and the overall incidence using some of the step-up dosing was about 67%. In terms of infections, so grade 3 or 4 infections occurred in about 21.8% and 5.5%, respectively.

In terms of efficacy, the median follow-up for this study is at 12 months, and the overall response rate was 64%, and 38% of patients had a complete response (CR) or a stringent CR. If you look at the cohort of patients that had prior BCMA-directed therapy with either the CAR-T cells or ADC, the response rate was 54% and there were some CRs and stringent CRs seen even in this population that had prior BCMA therapy. In patients that responded, the median duration of response was 17.1 months. And then in terms of evaluable patients, which was 13 of them that were available for minimal residual disease (MRD), 100% of them had MRD-negativity at a threshold of 10^{-5}. And 62% of these patients had documented MRD-negativity at more than 6 months, and about a third had documented MRD-negativity at more than 12 months, suggesting these may be more durable MRD-negative responses. And if you look at the whole cohort, the median progression-free survival (PFS) is 11.8 months. And in terms of pharmacokinetics, elranatamab demonstrated a dose-dependent increase in exposure, and the 1000 μg/kg every 2-week dose achieved an exposure in range associated with typical antimyeloma therapy. So, Ola, some exciting data here. Is there any correlation between soluble BCMA and responses in patients receiving elranatamab?

OL: Yes, there is; and I think a very brief taking a step back, BCMA, as you and I know equally well, was initially discovered as a biomarker for prognosis in myeloma. And I think in a way it sort of is a very good example of how quickly the field has moved forward from discovery science and how this became a treatment target. So, it was found a long time ago that the cells can shed BCMA, and you can quantify that in the blood; and it can also correlate with the amount of cells you see in the bone marrow if you do biopsies, and also there's a correlation with the amount of protein that these cells make, monoclonal protein or light chain proteins. Do you have anything else you want to add to what I was trying to outline here, Omar?

ON: No, I think you've summarized the history behind BCMA, and then kind of how we're now using some of these biomarkers to help figure out exactly how to optimize delivery of these BCMA-directed therapies, which I think is really going to be important going forward. Going back to the overall findings from the MagnetisMM-1 trial, I think it's important to highlight that the responses look very good. About two-thirds of patients are responding to therapy, again heavily pretreated patients, and then the median PFS that's approaching close to a year is again comparable to what we've seen with some of the available BsAb. But I think it's important to highlight the cohort of patients that had prior BCMA therapy. Although the numbers were small, we did see responses. So, Ola, the authors concluded that the results of this trial support further development of elranatamab in patients with myeloma. Would you like to tell us about the findings of the phase 2 MagnetisMM-3 trial which was also presented at ASH this year?

EFFICACY AND SAFETY OF ELRANATAMAB IN PATIENTS WITH RRMM NAÏVE TO BCMA-DIRECTED THERAPIES: RESULTS FROM COHORT A OF THE MAGNETISMM-3 STUDY [6]

OL: The MagnetisMM-3 trial is an ongoing, multicenter, phase 2 registrational study evaluating the efficacy and the safety of elranatamab monotherapy in patients with RRMM. Patients that are refractory to at least one proteasome inhibitor; they have to also be refractory to immunomodulatory drug (IMiD), and also anti-CD38–targeted antibodies. They were enrolled

to one of the two independent parallel cohorts. One cohort, called cohort A, focused on patients who were naïve to BCMA-directed therapy; the other cohort, called cohort B, was open for those who had a prior exposure to BCMA-directed therapies. So, in this particular trial, we heard from ASH results being presented from 123 patients with no prior BCMA-directed treatment. So, this was the cohort A, and they received SC dosing, 76 mg QW with elranatamab step-up dose of 12 mg on day 1 and 32 mg on day 4. For patients that received six or more cycles and achieving a partial response or better for at least at 2 months, then the dosing was changed to every other week or to Q2 weeks. The median age for these patients was around 70 years, and most of these patients had an ECOG performance status of 1 or 2. Around a quarter of the patients had what's referred to as high risk by FISH and cytogenetics, and looking at the number of prior lines of therapy, the median was five. So, these are heavily pretreated patients with a high proportion of patients being in the high-risk category, the way we currently define that. Also, looking at prior exposure to treatment, these patients were triple-class exposed, and also 70% or 71% were penta-drug exposed. So again, these are quite sick patients: 79% of the patients were triple-class refractory and 42% were penta-drug refractory, heavily pretreated patients.

Looking a little bit in detail at some of the results that were presented, so the safety to begin with showed that the most common any-grade hematologic AEs in $\geq$ 20% of the patients were similar to what we have seen for other drugs in this class. Anemia in around half the patients, neutropenia in around half the patients, thrombocytopenia in around a third of patients, and also lymphopenia in a quarter to a third of the patients. Similar also to other drugs is the any-grade non-hematologic AE in $\geq$ 40% of patients being CRS. This was found in around 60% of the patients. Among those patients who received the 12/36 mg step-up priming regimen, CRS was reported in around 56% of the patients. They were grade 1 and grade 2, and there were no grade 3 or higher events reported. This CRS event occurred early in the majority, limited to the step-up doses in around 6% of the patients that developed CRS at the third dose. There was only one patient that had grade 1 CRS at later dosing. The median time of onset (similar to what's been found in other trials with other similar agents), around 20 days. Median duration of CRS was around 2 days, similar to what we have seen for other trials. The use of tocilizumab and also steroids was effective, and it happened in about 20% and 10%, respectively. We talked about ICANS before, and they were found in a lower proportion of patients in this trial. It was only 3% of the patients doing the step-up dosing. The median time was similar to CRS, around 2, 2.5 days, and again, the use of the same intervention with the steroids and tocilizumab. There was no patient that permanently discontinued the drug due to CRS or ICANS, and infections were also found similar to what we have heard for other trials for other drugs. Here the infections were around 70%, and about 30–35% were grade 3 and 4. There were opportunistic infections. They saw *Pneumocystis* pneumonia, there was cytomegalovirus (CMV) reactivation, and there was also CMV infection. They were single numbers, so the *Pneumocystis* was around 5%, CMV reactivation around 5%, and CMV infection was 3.3%. Similar to what has been found for the other bispecifics, the rate of hypogammaglobulinemia resulted in the IVIG administration in about 40% of the patients, and 60% of these patients discontinued therapies, and most of the reasons were progressive disease. It was around 35%, and AEs were leading to that in about 10% or so.

Briefly talking about the efficacy, the data cutoff has quite a short median duration of treatment here. From the presentation it was only 5.6 months, so less than 6 months was in 52% of patients, and 6–12 months was found in 33% of patients, and over 12 months was only close to 15% of patients. The median follow-up was 10.4 months, and the confirmed objective response rate that was conducted by an independent centralized review was found to be 61%, and CR or better was around a third of those patients; very good partial response (VGPR) was around 60% of them, or VGPR or better. So VGPR by itself was around a third also, so a third CR and a third VGPR. So quite deep responses; so that's very encouraging. The

clinical benefits that were observed across the different subgroups, and they also looked for MRD-negativity, and that was found in 90% of the patients that were tested for it. But it should be cautioned and said that that was only done in 22 individuals. At the data cutoff, 77% of the objective responses were ongoing, and there were also good results looking at the median duration of response, median PFS, and median overall survival, and they were not reached or not evaluable, so the results are quite strong. So, just talking in conclusion about the MagnetisMM-3 findings and kind of broader clinical impact, I personally think this is a very interesting study design. Patients could be enrolled to two independent cohorts, and I think it addresses really a lot of those clinical questions that people are asking me and I'm asking myself: how does the drug work in those patients who are naïve to BCMA-directed therapy? That's what this cohort A is all about. And I think also for those who are previously exposed to BCMA-directed therapy–that's the cohort B. And I think, in my opinion, I think that's a brilliant way to do a study like that, to try to capture some of those clinically important aspects. What do you think, Omar?

ON: Yeah, absolutely. I think the patient populations, it's really important to study those cohorts because that's how we're going to be thinking about patients as we move forward anyways. And I think it's good to see the results that we saw in this study. And I think the important thing to note, contrasting this with the previous abstract with elranatamab, is the use of the step-up dosing. And if you look at the data from the original trial, the rates of CRS were almost 84% or so. And then with these step-up dosing strategies that were implemented with this particular trial, we saw the CRS rates clearly go down to 56%, with no grade 3 or greater CRS events reported. So, I think it really does kind of highlight an example of how to safely give these products. And hopefully over time this is going to allow us to treat more and more patients in the outpatient setting and not necessarily require the level of care that they currently do with some of the bispecifics. So, I think it was interesting to see the breakdown between the two presentations with elranatamab.

TECLISTAMAB IN COMBINATION WITH SC DARATUMUMAB AND LENALIDOMIDE IN PATIENTS WITH MM: RESULTS FROM ONE COHORT OF MAJESTEC-2, A PHASE 1B, MULTICOHORT STUDY [7]

OL: I agree with that. And I think it's important to emphasize these various clinical important aspects. It kind of comes down to how we're going to use these drugs in the clinic and how we can improve, and we can think about how to optimize the management of our patients. So, Omar, this presentation discussed so far demonstrates quite promising efficacy of this bispecific antibody. Do you think that there could be combination strategies that still would be needed, or do you think a single drug is going to be good enough?

ON: Yeah, I think we're seeing pretty impressive results with a single-agent therapy across the board with these bispecifics, but the response rates, generally speaking, are two-thirds of patients, so I think we can probably do better and hopefully improve the durability of these responses, notably well beyond what we're seeing so far. I mean, I think the data still have to mature with some of the trials that were presented at this particular meeting, but I think there's definitely room for combinations. And one of those trials that I'm going to go over now looked at combining teclistamab, which is an approved BCMA bispecific agent, with SC daratumumab (dara) and lenalidomide in patients with myeloma. And this is the MagesTEC-2 trial, which is a phase 1B multicohort study, and this is reporting on that cohort of a combination from this particular trial. So, the initial results: again, this trial looked at this combination of teclistamab/dara and lenalidomide in patients that had one to three prior lines of therapy, and these patients must have had a prior proteasome inhibitor and an IMiD. Thirty-two patients have been treated in this study so

far, and they received teclistamab at several doses: 0.72 mg/kg, or at the 1.5 mg/kg QW dosing and then transitioning to 3 mg/kg Q2W, starting with cycle 3. Dara and lenalidomide were given at the typical schedules, 1800 mg of dara and 25 mg of lenalidomide. So, median age was about 65 years. So, there's two cohorts. There's a 0.72 mg/kg cohort for teclistamab, and then a 1.5 mg/kg cohort. Median age was 65 and 60 years, respectively. About 25% and 46% of patients had high-risk cytogenetics, respectively. And then notably, patients in each arm had a median of two prior lines of therapy. So, this is now different than some of the heavily pretreated patient populations that we've covered in the past. About 46% of patients were refractory to lenalidomide in the first cohort, and about 16% were refractory in the second cohort, and about 15–23% of patients between the two cohorts were refractory to prior anti-CD38 monoclonal antibody.

So, now getting into some of the data from this trial. So, in terms of safety, the most common hematologic AE was neutropenia, seen in about 84.4% of patients; and 25% of patients had thrombocytopenia, and similar percentages had anemia. In terms of non-hematologic AEs, CRS was seen in 81% of patients, and then we saw fatigue, diarrhea, and cough in approximately 40–45% of patients. In terms of the CRS, all events were grades 1 and 2. Median time to onset was 2 days, and median duration of CRS was also 2 days. Tocilizumab was given to 40% of patients, and 15% or so of patients had also steroids for management of their CRS. No ICANS events were reported with this particular combination. In terms of grade 3 or 4 AE, this occurred in 90% of patients, and most commonly these were cytopenias and pneumonia. Infections were common, actually seen in 90% of patients. The majority of these were low-grade infections, and about 37% of patients had grade 3 or 4 infections. And if you look at the breakdown of infections, the most common infections in more than 20% of patients were COVID-19 in about 37% of patients, upper respiratory infection in another 31% of patients, and pneumonia in about a quarter of patients. And some of these pneumonia events were pseudomonal pneumonia; and also CMV infections, reported in 6.3% of patients.

In terms of efficacy, median follow-up is 8.4 months, and the overall response rate is 93.5% with over half the patients, 54.8% having a CR or greater, and 90.3% of patients having a VGPR or greater. And responses were seen in those patients that had prior daratumumab and or lenalidomide. And at the time of the data cutoff, 80% of these response-evaluable patients remained progression-free and currently on treatment. So, Ola, this is our first look at combination therapies with bispecifics in an earlier line cohort. So, I'd love to hear your thoughts about what we can learn from the data from these MajesTEC-2 findings, and what kind of clinical impact could this have going forward?

OL: I think these results are very interesting in many ways, although I think it should also be mentioned that the study is not very large and it's also not a very long follow-up. So, this is not a definitive answer to all the questions we have, but I think it's a very important study in many ways. For example, it shows that we can combine these BsAb with existing drugs that we already have. We obviously don't have all the drugs included here, but the examples we have show that this seems to work out well, and I think that's quite reassuring. It also seemed to me that the AE profile of the drug is not drastically different from what we have seen in single drug use, and I also think that it indicates that we have improved the efficacy. There are higher rates of overall response, there are more deeper responses than we would see with the use of single drugs. So, I think it builds on similar experience we have with other already FDA-approved drugs, with other mechanisms of action that you can get good efficacy and good tolerability from drugs, and when you start combining them that you can build on that, and you can build combination therapy regimens. So, I think a lot of work going forward for all these different antibodies, in my opinion, will be to find different combinations in different settings and to figure out the dosing schedules and the duration of combinations in relation to maybe a single drug.

RG6234, A GPRC5D × CD3 T CELL ENGAGING BSAB, IS HIGHLY ACTIVE IN PATIENTS WITH RRMM: UPDATED INTRAVENOUS (IV) AND FIRST SC RESULTS FROM A PHASE I DOSE-ESCALATION STUDY [8]

OL: So, I would like to talk a little bit about RG6234, which is another GPRC5D CD3-targeted T cell engager bispecific antibody. And this has been found to be highly active in patients with RRMM, and there was updated IV and first SC results from a phase 1 dose-escalation study presented at this ASH. So, to just briefly touch on it, this was a phase 1 dose-escalation and dose-expansion study that was focusing on evaluating the safety and the clinical activity of the drug, as I mentioned both as IV and SC, focusing on patients with RRMM. Patients received prior IMiD and proteasome inhibitor, and previous BCMA therapy was allowed in this study. So, the authors presented updated IV and initial SC data from this dose-escalation cohort. Among the patients that received the IV, there were 51 of them and there were SC in 57. The median age was around 60 or so years, and around 50% of the patients were reportedly high-risk cytogenetics, a little bit higher than some of the other studies have reported. But also, we know that there are different ways of determining high risk, so if you add certain markers maybe the patient population is or is not that different, so it's hard to determine that really. Nevertheless, the patient had received a median of five and four prior lines of therapy for the IV and SC dosing, respectively. Eighty to 90% of the patients were triple-class exposed, and around 65% of the patients were penta-drug exposed. Looking at the triple-class refractory component, that ranged from 60% to 70% for the two cohorts, and the patients that were penta-drug refractory were around 40% in the two cohorts. A little bit more than 20% of the patients had prior BCMA therapy and that included either prior ADC, CAR-T cells, and also prior bispecific antibody. So, that's an interesting aspect to think about when we look at the data. The study is not that large, so again it's not a definitive study.

The most common any-grade hematologic AEs in $\geq$ 20% of the patients were anemia, and that was true for both the IV and the SC arm, around 30–50%; thrombocytopenia, about a quarter to a third of the patients; and neutropenia, about 20–25%. The most common any-grade non-hematologic AE in $\geq$ 40% of patients again was CRS, similar to what we have seen for the other drugs for the most part. That was found in about 80%, and then we have impact on the taste in about 50% of the patients. The overall AEs were consistent with the target class and the mechanism of action class, and that would be skin we talked about for previous GPRC5D-targeted drug we talked about. We had the mucosa, we talked about the hair and the nail changes, and then we had also the hematologic and the infection. In both the arms, most of the CRS events were grade 1 and 2, and there were only single digits for grade 3 or higher, around 2% for the two groups of patients. The median time also here is shorter. It's only 5 h for the IV, and it was 24 h for the SC cohort. ICANS were reported only in one patient in the SC arm, and it was grade 3 or higher. There were no events reported for the IV arm. Infections were found in about 60% and 45% of the patients, respectively, and around 20–25% for grade 3 or 4. The most common in this study was COVID. The AEs that led to discontinuation were around 5–10% for the two cohorts.

To briefly touch on the efficacy here, after a medium follow-up of 11 and 8 months, respectively, for the IV and the SC arms (and I remind you we are talking about 49 and 55 patients, respectively), the overall response rate was 70% and 63%, respectively. The CR rate was about a third or a quarter or a third of the patients, and VGPR or better was around 60% of patients. They evaluated 14 of the patients for MRD, and this was set to 10^{-5} and that was found in 71% of patients. The median duration of response was 10.8 and 12.5 months, respectively, for the two cohorts. So, Omar, what do you think we can learn from these findings in a wider clinical perspective?

ON: Yeah, it's nice to see another GPRC5D bispecific antibody in development. I think there's a lot of similarities to what we saw with the data that you presented with talquetamab. You're seeing the similar on-target, off-tumor effects that we're seeing with the dysgeusia and some of the specific AEs related to the target as we've covered. There's two formulations being developed, IV and SC. I think the fact that the step-up dosing schedule is a bit different for this particular product, where they're getting it on days 1 and 8 and CRS is happening almost immediately, may have some impact in terms of how we give these therapies in practice, which is a bit different than the traditional step-up dosing schedule that's seen across some of the other bispecifics. But clearly the agent is active, and we look forward to seeing some updates as we get longer follow-up for this particular product to see how it develops further and compares with other BsAb in this space.

ALNUCTAMAB (ALNUC; BMS-986349; CC-93269), A BCMA × CD3 T CELL ENGAGER, IN PATIENTS WITH RRMM: RESULTS FROM A PHASE 1 FIRST-IN-HUMAN CLINICAL STUDY [9]

OL: I would agree with that. So, Omar, you're going to talk a little bit about another drug that targets BCMA and CD3. It's a T cell engager. Why don't you tell us a little bit about that presentation?

ON: So, the next abstract we'll cover is with alnuctamab, which is a BCMA and CD3 T cell engager, and this is in patients with RRMM. This is results from the phase 1 first-in-human clinical study. So, alnuctamab is a humanized 2 + 1 bispecific antibody that again binds BCMA on the myeloma cells and CD3 on the T cells. Previously, we saw preliminary activity of this agent IV in the phase 1 open-label, dose-finding study. So, in this particular presentation, they reported the initial results in patients treated with SC dosing and also the long-term results from the original IV trial. Across the board in this study, patients must have had three or more prior lines of therapy including an IMiD, proteasome inhibitor, and a CD38 monoclonal antibody. And notably, no prior BCMA-directed therapy was allowed in this particular trial. So, first going over the long-term results of the IV arm.

So, 70 patients received IV alnuctamab at doses ranging from 0.5 to 10 mg with or without step-up dosing. Safety profile was considered manageable, but limited the ability to use higher IV target doses. CRS was reported in three-quarters of patients at 76%, including four grade 3 and one grade 5 CRS event. Median follow-up was 8 months. The overall response rate for the entire cohort was 39%, and median duration of response was 33.6 months, with the median PFS of 3.1 months. I think it's important to know that these were several cohorts seen in this sort of original IV trial, so you're seeing a bit of discrepancy with some of the numbers here. But in terms of responders, we did see some durable responses going out all the way to almost 3 years, which is interesting. And then for the non-responders, the median duration response was very short. It was actually less than 2 months. So, Ola, this was the IV portion of this particular trial that I just went over. And the presentation at ASH also focused on the SC administration of this agent to see if this would help manage some of those CRS and the high-grade CRS events that they saw with the IV formulation and to improve that dose convenience. So, would you like to go over the SC data for this particular product?

OL: Yes, I certainly will. So, the SC part, or the SC arm here, focused on 68 patients that got the SC version of the drug and it was given in 10–60 mg QW with the step-up priming doses on day 1 and day 4 and the target dose on day 8 of cycle 1. The dosing switched to Q2W from cycle 4 and then it switched to Q4W from cycle 7. The median age here is around 64 years, and based on FISH and cytogenetics, about a quarter of the patients were high risk. Patients in this trial had received a median of four prior lines of therapy. All the patients were triple-class exposed and 63% penta-drug exposed. The triple-class refractory component was 63%, and 28% for penta-drug refractory, consistent with the other trials—quite sick patients.

The SC version of the drug improved the safety profile compared to the IV that you just went over here, Omar, and most of the any-grade hematologic AEs in $\geq$ 20% of patients were anemia, found in about 40%; neutropenia, also around 40%; and thrombocytopenia, in about a quarter of the patients. The most any-grade non-hematologic AE seen in $\geq$ 40% of patients was CRS. That was found in 53% of patients. All the CRS events were grade 1 and 2, and the proportion of patients that had two or more CRS events was 21%. Median time was about 3 days, duration, median 2 days, and similar to what has been used for the other trial, for the other drugs, tocilizumab and steroids given in around 50% and 25–30% of patients was given effectively. ICANS were reported in only two patients, and they were both grade 1, and the duration here was only 3 or 5 days. The infections that were reported was about 34% of patients, and close to 10% were grade 3 and 4. Most common was COVID and also rhinovirus was found in a few cases. There were none of these patients that discontinued the drug due to AEs.

And briefly, efficacy for the SC arm shows that the median follow-up was about 4 months in 55 patients who were evaluable for efficacy in the SC arm. The overall response rate was found to be 53% for all the doses. So, less than 30 mg target dose, then it was 41%; and 30 mg, which was the target dose, was 65%. So, the overall result of 53% was partly diluted by these less than 30 mg target dose. The VGPR or better was found in 40% of patients, and among the 29 patients who did respond, the MRD-negativity was found in 80%, but that was only tested in 20 of those patients so the denominator does not include all the patients. The median duration of response was not yet reached, and 90% of them were still ongoing responders at the time of the data cutoff. So, what do you think about this finding and the wider clinical impact?

ON: Yeah, this is an interesting product. It's got like a 2 + 1 design. So, it's kind of trying to mirror, I think, some of the CAR products where you kind of had perhaps two binding domains and leading to deeper and more durable responses. I think it's too early to tell if it's achieving that based on the data so far. I mean, you definitely see responses at the higher doses, comparable to what we've seen with other BCMA bispecifics, but I think longer follow-up will tell us if those are any more durable than what we've seen with some of the agents we've already covered today. I think it's important to highlight that a lot of these agents are starting to move to SC and more convenient dosing structures, and that's important from a patient experience perspective but hopefully will be also important from a toxicity perspective, particularly as it relates to infection. So again, it's highlighting the activity going on in this space with these bispecifics, and I think they're all trying to really find that optimal balance of efficacy and safety.

CONCLUDING REMARKS

OL: I would agree with that. I think there's a lot of excitement overall. I think we clearly see that all these different examples we are giving today provide very effective clinical outcomes in terms of response rates, though quite high rates of deeper responses. And I think we have evidence from all these different drugs we are talking about on the applicability of feasible dosing schedules and also combinations. We have some data, but there is a lot of work ahead of us. We need to figure out exactly how to use these drugs in the clinic once these drugs become approved. What combinations? How are we going to step up and go down in doses? What are the optimal dosing intervals? So, we have a lot of work ahead of us.

ON: Yeah, I couldn't agree more. I think it's an exciting time, and as soon as we think we have something figured out we get all new classes of drugs and more things to figure out. So, it's exciting to be in this field, and most importantly, exciting for patients.

OL: One last thought that I would like to bring up is that I think this discussion we have had today, it's to me very clear that we are now entering the era of immunotherapy. I almost feel the myeloma field has passed two eras and is now coming to the third era. In my mind, we started off in the field long before you and I

were even born or started working in the palliative era, and you and I have spent our entire time together with many others, and everyone who's listening here in the chemotherapy era. But we are now heading right into the immunotherapy era in my mind. And I think the immunotherapy era comes with probably the message to many patients, in my opinion, being diagnosed today, having the same lifespan as a person of the same age and gender without myeloma. For now, with the unfortunate need to continue to be in therapy and being tested... because we don't yet have an established cure; but I do think these drugs are actually bringing to the table a lifespan that is very similar, if not the same, as a person with the same age in general. Not for every patient, but I do think for many patients, which I think is a huge thing. What do you think about that?

ON: I couldn't agree more. I mean, I think it's amazing that in all those decades with progress, but the last 10 years or so, I think the progress has just exponentially improved. And I think we're just at the tip of the iceberg. I think we're just going to optimize these therapies between these immunotherapies even further with these new targets, with newer approaches to kind of improve durability, and hopefully we can finally cure patients with some of these immunotherapies. And I think this has potential, and now we just have to figure out the right approach, and individualized therapy, as you pointed out earlier.

OL: This was a really interesting discussion. I really enjoyed it. Thank you very much, Omar, for doing this together.

ON: Thank you so much for having me.

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REFERENCES

1. Rodriguez-Otero P, San-Miguel JF. Cellular therapy for multiple myeloma: what's now and what's next. Hematol Am Soc Hematol Educ Progr. 2022;2022:180–9.

2. Cipkar C, Chen C, Trudel S. Antibodies and bispecifics for multiple myeloma: effective effector therapy. Hematol Am Soc Hematol Educ Progr. 2022;2022:163–72.

3. Kazandjian D, Kowalski A, Landgren O. T cell redirecting bispecific antibodies for multiple myeloma: emerging therapeutic strategies in a changing treatment landscape. Leuk Lymphoma. 2022;63:3032–43.

4. Chari A, Touzeau C, Schinke C, et al. Talquetamab, a G protein-coupled receptor family C group 5 member D x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM): Phase 1/2 results from MonumenTAL-1. Blood. 2022;140:384–7.

5. Raje N, Bahlis NJ, Costello C, et al. Elranatamab, a BCMA targeted T-cell engaging bispecific antibody, induces durable clinical and molecular responses for patients with relapsed or refractory multiple myeloma. Blood. 2022;140:388–90.

6. Bahlis NJ, Tomasson MH, Mohty M, et al. Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma naïve to B-cell maturation antigen (BCMA)-directed therapies: results from cohort A of the Magnetismm-3 study. Blood. 2022;140:391–3.

7. Searle E, Quach H, Wong SW, et al. Teclistamab in combination with subcutaneous daratumumab and lenalidomide in patients with multiple myeloma: results from one cohort of MajesTEC-2, a phase 1b, multicohort study. Blood. 2022;140:394–6.

8. Carlo-Stella C, Mazza R, Manier S, et al. RG6234, a GPRC5DxCD3 T-cell engaging bispecific antibody, is highly active in patients (pts) with relapsed/refractory multiple myeloma (RRMM): updated intravenous (IV) and first subcutaneous (sc) results from a phase I dose-escalation study. Blood. 2022;140:397–9.

9. Wong SW, Bar N, Paris L, et al. Alnuctamab (ALNUC; BMS-986349; CC-93269), a B-cell maturation antigen (BCMA) × CD3 T-cell engager (TCE), in patients (pts) with relapsed/refractory multiple myeloma (RRMM): results from a phase 1 first-in-human clinical study. Blood. 2022;140:400–2.