Advancing RRMM Care Through Communities of Practice: Educating Community-Based Hematologic/Oncologic Teams on the Use of BCMA-Directed BsAbs—A Project ECHO® Initiative

Community of Practice: **Session 2 Questions**

During the Community of Practice session that took place on April 23, 2026, Dr. Ajay Nooka addressed questions from the participants. Below are the questions asked during the discussion and Dr. Nooka's responses (based on the transcript).

QUESTION 1: There are now 3 BCMA-directed bispecific antibodies, and 1 GPRC5D-targeting bispecific antibody available. Which do you give, and how do you determine the sequence for patients who have received 4 prior lines of therapy, including an IMiD combination and CD38 antibody?

Faculty response: The caveat and the underlying principle of our use of these bispecifics is if using one before the other, it should not have any impact on the subsequent lines of therapy. The data support using the BCMA-directed bispecific first, and the GPRC5D-targeting bispecific is given to patients after exposure to BCMA. There are no data on the opposite way, where the GPRC5D is exposed first then followed by a BCMA-directed bispecific antibody. However, that does not mean that the opposite way is not feasible if a patient has a contraindication to receiving a BCMA-directed bispecific antibody. For example, for a patient with a latent TB infection, my first choice would be to go with the GPRC5D bispecific antibody. When the patient progresses, one option can then be to go with a BCMA-directed bispecific antibody. The only caveat is that I prefer to not use a T-cell–redirecting therapy followed by another T-cell–redirecting therapy and would like a sandwich in between, such as a non–T-cell–redirecting therapy. This could be an IMiD combination or selinexor, which I would consider to be a breather to give these T cells time so that they can reinvigorate and are ready to work with the next bispecific antibody. To summarize, the opposite sequence is possible; when a patient has a contraindication to one bispecific antibody, use the other one first.

QUESTION 2: Can you sequence a BCMA-directed bispecific antibody followed by another BCMA-directed bispecific antibody?

Faculty response: There are data from a pooled analysis from the MagnetisMM trials of patients who received a prior BCMA therapy and then received subsequent elranatamab, a BCMA-directed bispecific antibody. The patients who received prior BCMA CAR T-cell therapy followed by elranatamab had a median PFS of close to 10 months. For patients who received a prior antibody drug conjugate, or prior BCMA-directed bispecific antibody teclistamab, they had a median PFS of close to 5 months. In summary, this can be practical and feasible; there are smaller cohorts in these studies that show the use of the bispecific antibodies after prior exposure to another one.

QUESTION 3: Would you advise using a bispecific that has an alternate target, such as talquetamab versus teclistamab?

Faculty response: The first option is to give teclistamab/elranatamab/linvoseltamab first, followed by a non–T-cell–redirecting therapy as a sandwich, then talquetamab, which is the more conventional approach from the clinical trials. Alternatively, talquetamab can be given first, followed by the sandwich non–T-cell–redirecting therapy, and then teclistamab/elranatamab/linvoseltamab, but there are currently no clinical trials showing one way is better than the other. The third option is to combine both teclistamab and talquetamab. The forest plots from the different trials, such as Majestic-1, MagnetisMM-3, and LinkerMM-1, showed the benefits varied among study participants. For comparison, as single agents, daratumumab, belantamab, and selinexor gave ~30% response rates in this space. The bispecific antibodies as single-agent therapies yielded response rates of ~60% to 70% in these studies. However, patients with a heavy tumor burden (with bone marrow plasma cell burden ≥ 50%), or those with extramedullary disease, tended to have a 30% to 40% response rate. I would make a case for combination treatment with teclistamab and talquetamab for these patients, where the combination yielded a response rate of 70% to 80%. The NCCN guidelines currently recommend this combination only for specific patients based on the results from the RedirecTT-1 study showing

efficacy for patients with relapsed/refractory multiple myeloma and extramedullary disease (Kumar S, et al. *N Engl J Med.* 2026;394:51-61). In summary, this decision is patient driven. You need to choose which regimen the patient is more likely to benefit from. If there is no reason to give two bispecific antibodies to a patient, then I would avoid that, but I would consider combining both therapies for the patient example given above.

QUESTION 4: How do you help patients tolerate quadruplet (quad) therapy?

Faculty response: Moving from doublets to triplets to quadruplets has markedly improved depth of response for patients from ~10% to 20% complete response (CR) with doublets, ~40% to 50% CR with triplets, and ~90% very good partial response (VGPR) with appropriately used quadruplets. The regimen components are synergistic, and quad therapy with dose reductions is often preferable to giving a 3-drug regimen at full doses. Effective quad-based induction (often followed by transplant and maintenance, when appropriate) is linked to very prolonged disease control with modeled PFS estimates of 15 to 17 years in some settings. The overall goal is to achieve the deepest remission possible while continuing to incorporate new advances over time.

QUESTION 5: How would you use the new data presented at ASH for teclistamab and daratumumab for patients who were previously nonrefractory to daratumumab? How would you combine this, especially when quad therapy is very effective?

Faculty response: First, we need to think about the drug-development pathway across 3 sequential buckets: newly diagnosed, early relapse, and late relapse. Agents typically get approved in late relapse first, then move to earlier lines of treatment as safety and efficacy allow (daratumumab is an example). Teclistamab was first approved in late-line therapy with about a 60% response rate, with infection risk that can be mitigated using "guardrails" (see Questions 6 and 7). The combination of teclistamab and daratumumab has been evaluated in the early relapse (bucket 2) setting in the MajesTEC-3 randomized trial with good outcomes—3-year PFS of ~83%, with a large reduction in risk of progression and death. These data suggest bispecific-based combinations are likely to change treatment in early relapse and drive broader community adoption, rather than replacing frontline quad therapy immediately. Bispecifics are now being explored even earlier, including frontline cohorts, where they are tolerable even in frail/transplant-ineligible patients. Additionally, questions remain about how long to continue bispecifics, such as is there an opportunity to hold off, give for a finite period, and see how long the response lasts?

QUESTION 6: Infections are a common reason for discontinuing bispecific therapies. How can the risk of infection be managed? If bispecific treatment is stopped for an infection, when do you restart?

Faculty response: Bispecifics are highly effective, but they carry a significant infection risk, requiring proactive management. Key preventive strategies include antimicrobial prophylaxis, monthly IVIG administration, vaccination (ideally before starting therapy), and baseline viral screening and ongoing monitoring. During bispecific therapy, hold treatment if infection is suspected and use antibiotics and growth factor support to maintain therapy safely. Bispecific therapy can be safely resumed after completion of the antibiotic course and confirmation that the patient is clinically recovered and noninfectious, with appropriate antimicrobial prophylaxis in place.

QUESTION 7: Can you explain the need for IVIG when using bispecific therapy? Do you need IVIG for GPRC5D bispecifics? Do you give the IVIG irrespective of the patient's baseline IgG level or do you wait for the IgG level to be less than 400 mg/dL?

Faculty response: Early trials for bispecific therapies showed that severe (grade ≥ 3) infections requiring hospitalization occurred in ~60% of patients. This infection risk was higher than with other myeloma therapies and was a major concern for patients. Giving IVIG prophylactically has reduced this infection risk because BCMA-targeted bispecifics cause B-cell aplasia and hypogammaglobulinemia, increasing infection susceptibility. IVIG is used to replace immunoglobulins and restore immune protection. Routine monthly IVIG has been shown to reduce severe infection rates from ~60% to < 20% in clinical trials. In our practice, we have seen severe infection rates of ~10% to 15%. IVIG should be given monthly and continued after stopping the BCMA-directed bispecific for 4 months posttreatment.

At our center, we give monthly IVIG to patients regardless of the bispecific (BCMA or GPRC5D). The severe infection risk (grade ≥ 3) in the clinical trials for the GPRC5D bispecific was ~15%. When we give IVIG, that risk comes down to

almost 0%.

At our center, we give IVIG irrespective of the patients' IgG levels. There might be some pushback from the insurance companies, which can be handled with a phone call to tell them this is a BCMA bispecific antibody where 60% of the patients are going to be hospitalized for severe infection without IVIG. The reason why we do not follow a tiered approach is that about 70% of the myelomas are IgG myelomas so it will be challenging to separate which is the myeloma protein versus which is the real IgG.

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