

Experts Discuss Choosing Bispecifics and Sequencing Options in Multiple Myeloma

During the 2024 International Myeloma Society conference, teams from Cleveland, Ohio, and New York, New York, met to debate the latest advances in multiple myeloma. Each round focused on the use of bispecifics, chimeric antigen receptor (CAR) T-cell therapy, and how to choose appropriate sequencing. Read on to see which team was crowned the winner.

Moderator



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Judges



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Team Cleveland



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Team NYC



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At the 2024 International Myeloma Society Annual Meeting, experts in multiple myeloma gathered to debate current treatment options in the space. The teams competed in 3 key areas: recent trial updates, patient cases, and sequencing options.

What Is Face-Off?

An educational program designed as a competition for teams to present to and against each other.

How Does It Work?

There are 3 rounds: data presentations, patient cases, and hot topics. During each round, both teams will have the chance to present and defend their ideas but also challenge the other team. The judges will determine who is worthy of the top prize.

Round 1: Data Presentation

Team NYC on TRIMM-2 Data

Presented by Donna D. Catamero, NP

The phase 1b TRIMM-2 trial (NCT04108195) assessed talquetamab-

tgvs (Talvey), daratumumab with hyaluronidase-fihj (Darzalex Faspro), and pomalidomide (Pomalyst) in patients with relapsed/refractory multiple myeloma.¹ Patients were given either 0.4 mg/kg of weekly talquetamab or 0.8 mg/kg biweekly talquetamab with a step-up dose and subcutaneous daratumumab and pomalidomide.

For patients who were given the 0.4 mg/kg dose, the objective response rate (ORR) was 100%, with 56% of patients having a complete response (CR) or better. For those given the 0.8 mg/kg dose, the ORR was 76% and 56% had a CR or better. The median duration of response was 26.4 months and the median PFS (progression-free survival) was 20.3 months.

In the weekly and biweekly arms, neutropenia was reported in 83.3% of patients and 79.7% of patients, respectively. The rate of grade 3/4 infections was 16.7% and 37.3%. Additional treatment-related adverse effects included oral toxicities (100% vs 84.7%), skin (88.9% vs 67.8%), nail (83.3% vs 55.9%), and weight decrease (66.7% vs 49.2%) in the weekly and biweekly arms, respectively.

Team Cleveland on the Efficacy of a Triplet

Faiman / It's exciting in terms of the response rate. These patients have limited therapeutic options, but the excitement is dampened by the infections. Grade 5 AEs [adverse effects] were significantly higher than you'd see in other single-agent talquetamab trials. That gives us pause. Also, if you want to use these 3 drugs together, it heightens the importance of supportive care. IVIG [intravenous immunoglobulin], antibiotics, close assessments. It still can be given successfully as a triplet, but I look forward to the data

maturing.

Atrash / I have a few points to make here. Infections are 70% to 75%. The same thing for dyskinesia. It's in the 75% range. I would argue that everybody who had a response ended up with complications. To me, practically, it's 100% because those who don't respond will get off treatment. That's concerning. It's very important to give supportive care for infections, as well as to follow up on the [oral] AEs.

Rodriguez / One thing to keep in mind with combination therapy is that we're trying to find ways of making the bispecific more effective. The daratumumab plus IMiD [immunomodulatory drug] is trying to help mediate the immune system, not necessarily provide cytotoxicity, but mediate the immune system so that those who do have a proper immune system and are responding continue to have that response throughout the whole therapy. That's something that's very interesting in this combination therapy, that we are seeing an improvement in the overall responses, but the median PFS and the duration of response are also extended in those who did respond, which makes us believe that this combination is doing some type of immune modulation in these patients. The infection rate is higher, and unfortunately, these studies were designed where the pomalidomide dose is 4 mg, which is the one that was FDA approved, and then it got reduced to 2 mg. We know that we need the minimum possible for immune modulation. Maybe tweaking the dose to 1 mg or just doing it intermittently might help reduce the infection rate but still provide this immune modulation that is required.

Team Cleveland on CRS Reduction With MajesTEC-1

Presented by Shebli Atrash, MD

The addition of tocilizumab (Actemra) to teclistamab-cqyv (Tecvayli) was assessed in patients with relapsed/refractory multiple myeloma and found to lower the incidence of cytokine release syndrome (CRS). These results were supported by the phase 1/2

MajesTEC-1 trial (NCT03145181; NCT04557098).²

A cohort of 24 patients in the MajesTEC-1 trial led to the results on prophylactic use. The median follow-up was 8.1 months. Patients were given 1.5 mg/kg of teclistamab every week or as a comparable fixed dose following a single dose of tocilizumab and step-up dosing. Of note, 8 mg/kg of tocilizumab was given intravenously within 4 hours of the first teclistamab step-up dose.

In 25.0% of patients, any-grade CRS occurred in those given prophylactic tocilizumab vs 72.1% of those given teclistamab alone. Grade 1 CRS was noted in 8.3% of patients and grade 2 in 16.7% of patients in the prophylactic arm. The median time to CRS onset was 2 days, with CRS lasting for a median of 2 days.

In the prophylactic group, grade 3 infections occurred in 79.2% vs 25.0% who had grade 4. Other common any- and high-grade AEs included neutropenia (62.5% vs 62.5%), anemia (58.3% vs 25.0%), and thrombocytopenia (50.0% vs 25.0%). At 20 days after the final dose of teclistamab, there was a grade 5 pulmonary embolism.

Team NYC Questions Prophylactic Tocilizumab Use

Catamero / Prophylactic tocilizumab is still a barrier with insurance so hopefully with these studies, we can maybe gain access across community settings.

Richard / There are a couple of things to pay attention to. One is that it seemed to reduce the rate of the grade 1 [AEs]. I'm not so sure about the higher-grade CRS, which is the clinically more bothersome one. That's one issue. The other is that the CRS overall grade 1 is about 50%. You're perhaps overtreating a good number of people who are receiving prophylactic tocilizumab who don't have to. A couple of things to bear in mind as we're trying to evaluate this.

Williams / In the real world, reducing grade 1 CRS has a huge benefit to patients. Fewer patients wind up in the hospital. There's less utilization of resources in the outpatient setting, and it gets our health systems a little bit more comfortable with outpatient protocols. Maybe we need to separate the medical implications on a per-patient basis from the system implications of having this resource available to us and potentially increasing access and comfort, especially in community settings.

Team NYC on Supportive Care

Round 2: Patient Cases

Catamero / The community giving those bispecifics in the outpatient setting needs to have a clear pathway because we still saw

- A 58-year-old woman with relapsed multiple myeloma after autologous stem cell transplant is not minimal residual disease (MRD) negative on bispecific therapy.
- Based on her MRD status, what are the best practices for optimizing dosing frequency and therapy duration to maintain remissions?
- How should patient characteristics influence decisions on dosing frequency and therapy discontinuation?

grade 2 CRS. Even with the prophylactic tocilizumab, there needs to be a clear pathway. If someone gets in trouble in the middle of the night, can I get them to an emergency department and expedite them to [treatment]?

Faiman / Also, will they take their dexamethasone if you give it to them?

Catamero / If the community wants to do this, we need to have clear pathways for patients if something happens [during] off-hours.

Chari / Just to remind the community, grade 2 CRS could be hypotension. It's not something to be messing around with.

Rodriguez / I do want to repeat the tocilizumab prophylaxis in outpatient, especially in a community center that's [only open from] 9 to 5. I'm going to say no, don't do outpatient. We are always saying that prophylaxis tocilizumab [is the best choice], but we now have generic tocilizumab as well. That could be an alternative, but not just tocilizumab but also focus on combining it with maybe dexamethasone or some other agents. The talquetamab [trial] had a cohort that did tocilizumab prophylaxis and dexamethasone during the step-up tocilizumab and didn't have any CRS that was greater than grade 1. Grade 1 is just a fever. I don't care if 100% of our patients get CRS, but as long as it's just a grade 1 and guaranteed to stay at grade 1, then that's a regimen that we can give outpatients easily. If the patient develops a fever at home, they can take acetaminophen [Tylenol] or they can take a small dose of dexamethasone. Finding the right combination of the prophylactic tocilizumab or its generic with the right dose of dexamethasone might be the best way to tackle the severity of CRS so that we can get this more easily [to be an] outpatient event. Even in a community center that might be [only open from] 9 to 5.

Faiman / These are future solutions. Right now, [there isn't] a clear pathway. For the community, I don't think it's ready for prime time.

Atrash / For disclosure, we are doing it as outpatient. We do dexamethasone, not tocilizumab. Tocilizumab is difficult to [get approved by insurance], and the patient goes home with an extra pill of dexamethasone as well. For patients with uncontrolled diabetes, we do it inpatient because they will end up with 2 doses of dexamethasone back-to-back if they have CRS.

Team Cleveland on Bispecific Therapy Implementation

- You are advising an affiliated community center (only open from 9 to 5) on implementing bispecific therapy while addressing challenges such as safe outpatient administration and limited on-call coverage.
- The goal is to optimize patient care within the constraints of a community setting.
- Which bispecifics would be most suitable for implementation in a community?
- How can prophylactic strategies, staff training, and adverse effect management protocols be implemented to ensure safe outpatient administration and effective support?

Faiman / The challenge right now is the risk evaluation and mitigation strategies system suggests that we should keep our patients 48 hours after that initial step-up dose. In my center, we still admit a majority of our patients. The tocilizumab data that we heard [about in other] analyses provides some comfort. Predose of tocilizumab has a long half-life. If they're generally close to that center, you can safely administer that down the road. But not today. I'm still not comfortable not admitting patients, but with further data, we're going to be more comfortable doing that.

Atrash / That's a great discussion. The future for bispecifics is [for it] to be given as outpatient. I hope everybody agrees to that. We just have to figure out the optimal regimen [because] that seems like prophylactic tocilizumab is one way to do it. Also providing local lodging around the step-up dosing or closer to the hospital that is doing step-up dosing is another suitable option. There are the prophylactic strategies; that's where we have to collaborate with our colleagues locally by giving the best supportive care. Infection down the road is what we worry about. Whether it's a growth factor, IVIG Bactrim, or pentamidine, those are important medications to help us avoid infections down the road. We should be very cognizant of opportunistic infections, and if a patient has persistent fevers, ask for help.

Martin / Is there a patient population for whom you wouldn't consider outpatient therapy?

Atrash / Currently, if we have a patient who is, let's say, on hemodialysis or has compromised kidney function with a large disease burden where we expect a lot of CRS there and administration of fluids or the cardiovascular issues might be compromised there. This type of patient might benefit from inpatient management of their CRS, like [patients with cardiovascular] and heart problems, but that's the select population where we have it. We, in our institution, do give it to outpatients.

Team NYC for Sequencing Bispecific Prior to CAR T-Cell Therapy

Round 3: Hot Topics

Presented by Shambavi Richard, MD

Richard / What's very clear from what we have seen thus far from CAR T is that it's not the final answer. We're still not seeing a plateau in the survival curve. I argue that we need to stop thinking of CAR T as a stand-alone drug. Maybe we have to go back to looking at it in the context of how we can improve the overall result from the CAR T. One way to do it, as we have done so frequently in multiple myeloma, is to throw things together, combine it, sequence it, do different things like that. One of the things that we have seen repeatedly and now we have several publications and abstracts that say this: Bridging therapy is extremely important prior to CAR T. It improves the outcomes; it reduces the toxicity. How are we going to practically apply that? Most of the time when we're dealing with CAR T, let's set aside the [patients] who are [in] early lines of therapy. For advanced diseases, they've pretty much blown through all the major drugs that we know of. There are very few options. How are you going to now improve the results of the CAR T? I argue that let's learn from a bunch of things that we have learned so far.

One is target switching. We know that multiple myeloma is very clonally heterogeneous. If that's the case, how then are we going to improve the results and reduce the selective clonal pressure by combining 2 different targets? One of the things that many people are looking at is using talquetamab or GPRC5D bispecific as a bridge to CAR T. In fact, on the phase 3 KarMMA-3 trial [NCT03651128], about the impact of optimal bridging therapy prior to [CAR T],³ we know the KarMMA-3 results had a median PFS of about 13.8 months. What was found is that when you've teased out the patients who responded to the bispecific, that median PFS went up to over 20 months. If you ever had patients who had stable disease, that was still about 15 months better than the overall group. The ones who pulled those numbers back were the ones who were not responding to optimal bridging therapy.

There's another [trial] now, an analysis for the phase 3 CARTITUDE-4 trial [NCT04181827].⁴ They used to cut off 25%. If you got a disease and had a response that was at least 25%, those patients did much better in terms of the outcome compared with the others. We have seen this over and over... We're going to see what the outcome of all of that is, but I think my hypothesis is that it is going to tell us something.

Faiman / That was great, but I have to remind you of one thing. You can't give a bispecific unless you're [in] the third or more lines of therapy. CARTITUDE-4 showed us that you can give a CAR T-cell therapy in earlier lines, and that was a far more improved PFS and overall survival than any of the other regimens. Giving CAR T in earlier lines of therapy so you're not having that attrition—you're not losing that ability to give that CAR to that person, and then in later lines of therapy, you have that long journey to get that patient [prepared for us] to harvest the T cells, get the approval of the insurance. If you're a community [physician], refer your patient to a CAR T center as early as possible, get that CAR T as soon as you can. We also saw from other studies that you can still have a CAR T. We were just talking in that prior study you could have a CAR T, and it didn't affect your response when we had the combination study.

Martin / If you look at the CARTITUDE-4 vs the CARTITUDE-1 PFS curve, they overlap. It doesn't seem like there's going to be much better [results] from doing it earlier rather than later. What would you rather do? Would you rather do the CAR T earlier, or the CAR T later? What would you do?

Team Cleveland on Sequencing CAR T-Cell Therapy Before Bispecifics

Presented by Louis Williams, MD

Williams / There are 2 things. There's an argument for bridging, but I don't know that that was the question. When we talk about sequencing, using bispecifics until progression is what I think about. Two things that concern me are antigen loss and T-cell exhaustion. [If you] look at CAR-directed therapies vs the bispecifics, the percentages of patients who exhibit antigen loss are much higher in the case of continuous treatment, and we know from correlative studies that when you look at coinhibitory marker expression, *LAG-3* [lymphocyte activation gene], PD-1 expression, and T cells are much higher when people are exposed in the long term to these therapies. In reality, if we're not trying to beat each other up here, there's probably a role for bridging using bispecifics and bridging context if you can get them. Using the therapies to their point of progression is a separate question. That needs closer evaluation. We've seen in the CARTITUDE-2 cohort C that the response rate drops from somewhere around 90% to 60% once you use those bispecifics, and we have our biggest and best gun, which is probably ciltacabtagene autoleucel [Carvykti] at this point. I'm hesitant to do that.

Atrash / Since team NYC made the case for bridging therapy, not for sequencing therapy, I think they agree with us, basically. I would say if team [NYC is] not worried about the toxicity from lymphodepleting chemotherapy early on and the high doses of alkylating therapy with cyclophosphamide or the immune

suppression from fludarabine, which seems they are not, then CAR T should be first. We make the case here. Also, if we look at the real-world data that was published from the immune therapy [conference], we see a big drop for patients who get CAR T after bispecific immune therapy.

Richard / We should stop thinking about either/or because the fact is, we ultimately want to improve the response, so we're talking about 2 completely different things. We have learned over and over again if you wait for one drug and you wait and you wait until they no longer respond, then you go to the next drug. That is not the way to ultimately cure these illnesses. What we want to do is use them intelligently, use them in ways that are not going to beat up the microenvironment, not going to beat up the T cells, but then after you've got a little bit of that response, go directly onto CAR T. We're talking entirely 2 different things. All the studies that said that response rates are worse after bispecifics are after you've run the T cells down with the bispecifics over and over, and then now you're trying to do another T-cell-directed therapy. This is a no-brainer. ■



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