Med Table Talk™ LIVE
Bridging the Gap to Reach Treatment Goals in DLBCL

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Sanjay Juneja, MD: All right, welcome everybody. On behalf of the Medical Learning Institute and the Medical College of Wisconsin and 2023 Tandem Meetings, we appreciate you being here and attending this symposium and for this talk specifically, "Bridging the Gap to Reach Treatment Goals in Diffuse Large B-cell Lymphoma."

So I'm Sanjay Juneja. I am a community hematologist and oncologist in Baton Rouge, Louisiana. I'm super excited to be here to talk on behalf of community oncology alongside Dr. Sanjay Sharma, who is also a practicing hematologist/oncologist in California. So I guess we'll start there if you don't mind giving us a brief, you know, summary.

Sanjay Sharma, MD: Yeah, sure. So I'm Dr. Sanjay Sharma, like the better Sanjay said, I practice in Orange County, California. I'm a generalist. I do both hematology and oncology, large community practice, Orange County, LA. It's a very large city in terms of all the support and all the tertiary facilities that we have and excited to be here and hope we can help you out.

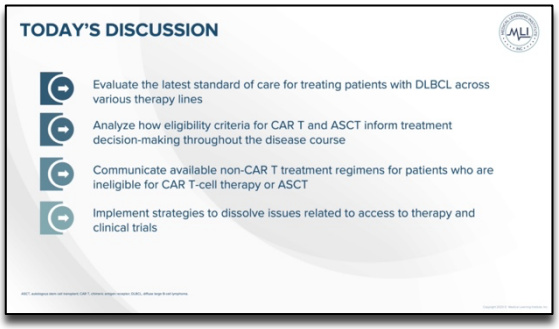
Dr. Juneja: So Sanjay's our, I guess, part of the community oncology side; and then I'm sure a lot of you are familiar with, you know, first, Dr. Flowers. You want to introduce yourself, and we appreciate you being here.

Christopher Flowers, MD, MS: Sure thanks, Sanjay. I'm Dr. Christopher Flowers. I'm a Professor and Chair of the Department of Lymphoma/Myeloma at the University of Texas MD Anderson Cancer Center. And relevant to this talk, our department in lymphoma and myeloma is the group that cares for the CAR T-cells for both of those patient populations.

Dr. Juneja: Awesome. And I'm sure everyone's familiar as well, Dr. Sergio Giralt.

Sergio Giralt, MD: Well, it's great to be here with the Sanjays and with Chris. So I'm Sergio Giralt. I'm the Deputy Division Head of the Division of Hem Malignancies at Memorial Sloan Kettering Cancer Center and a member of the adult BMT service and the cell therapy service there where we take care- We've actually separated the CAR T-cells and the immune effector cells or, into a freestanding service to take care of those patients.

Dr. Juneja: And as a bonus addition, Dr. Rayne Rouce, who's a pediatric hematologist and oncologist, Texas Children's Cancer Center. She'll be in the video form attending this *Table Talk*, and she's actually a member of the Leukemia and Bone Marrow Transplant Programs at the Children's Center in Texas.

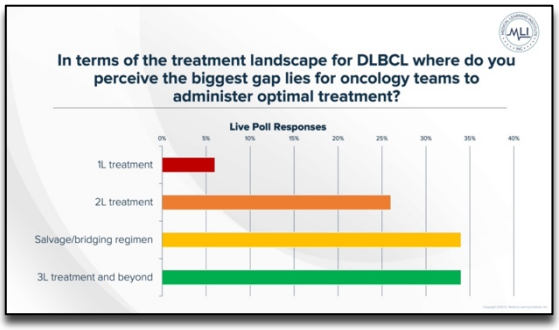


TODAY'S DISCUSSION

So in today's discussion, we're going to take a more, kind of, again, candid and conversational approach about, like, the treatment options in DLBCL but also how cellular therapists and community physicians, you know, there's a lot of room to be able to help that communication and that smooth transition on facilitating that care where, you know, obviously, cellular therapy would be really the, the good next step.

So, we'll do those, and we'll basically just talk about the barriers and what are some of the ways, and that's where we'd love y'alls feedback as well on, like, what are you seeing that may be something that's impairing or kind of slowing down that transition; or what's making it difficult for people to get, you know, on board? And, and, hopefully, we're going to address those again so that we can all take it back to our locations and, and provide, you know, amazing therapy that's being basically found but, but difficult to deliver in a lot of community oncology groups.

Dr. Sharma: Yeah. So I mean, the idea behind this *Table Talk* is that you're supposed to be at the table with us; and since we all can't fit, we're going to do it through a polling mechanism. So now I want you to think about your practice, your experience, your friends, families, loved ones.



POLLING QUESTION

"In terms of the treatment of diffuse large B-cell lymphoma, where do you perceive the biggest gap lies for oncology teams to administer these optimal treatments?"

Dr. Flowers: So, where do you see the biggest gaps in, in first-line diffuse large B-cell lymphoma? Maybe we'll start with you, Sanjay Sharma.

Dr. Sharma: Yeah, yeah. So the, as board certified oncologists, I mean lymphoma is something that we all definitely know and understand. Recognizing the treatments that we can use I think is akin to us; it's natural to us. If not, it's something you can look up in the NCCN. But I think recognizing what is potentially going to happen in the next, recognizing which of the six patients you're seeing, which one is more likely going to progress, which one is going to do better, which one is going to do worse, which ones that I'm going to need your guys' help on.

Dr. Flowers: Yeah. And what about you, Sanjay? What, what, what do you see as the biggest challenges?

Dr. Juneja: Yeah, I agree. I think, like, starting the first-line regimen is, is, hopefully, very comfortable for the community. Where it would be really ideal would be to have basically kind of more of a heads-up or insight where community oncologists know that, okay, this may be challenging down the line and, and having that kind of established relationship early.

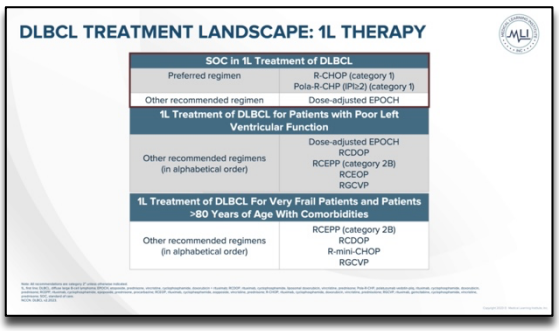
So, you know, as a community oncologist, if somebody's progressing or didn't have an ideal response in the first line or they have, like, kind of a short remission and something's popping up, the most stressful thing is coordinating to get 'em to the CAR T, you know, center. And not just get 'em there, right, but the, but, but the conversations, the insurance, the technicalities. And then I start to stress about how, you know, what if this disease starts to get out of control? What do I bridge with it? I wish I knew which cellular therapists would be seeing him so I, they can basically tell me what would they like me to kind of hold off the disease, and what's the timeline on getting 'em in.

So, you're deciding all of that usually in a, you know, very short period of time; and I fear that a lot of oncologists sort of say, "Well, we gotta act fast" and just go straight to the second line. So I think in an ideal world, you know, and you have to be delicate with the psychology of it because you don't want to discourage a patient saying, "Hey, but if you relapse, we're going to go ahead and send you for this really kind of intense new novel thing." You know, there's a brittleness about it as well. So having that smooth transition, teaching oncologists on how, like, this is not because we want you to relapse, but we just want to be prepared and ready and maybe get some recommendations already on what to use because you all know the mutation so well. I think all of that would really help the comfort level of community oncologists to reach out to the nearest, you know, cellular specialist.

Dr. Giralt: Chris, talking about what Sanjay just said, what do you think is the minimum that a community oncologist should request from their pathologist, for example? What, should they be saying, "Look, I need you to look for mutations TP53?" And are there any new imaging techniques that they can be using to be able to monitor the patient throughout their journey and to decide, you know, this person is not going to go the right way? And to Sanjay's afterwards, I think would it be helpful for you to already have that communication or that connection with a cell therapist like Chris?

Dr. Flowers: Yeah. Really great question, Sergio. I think, you know, some of the things that we see that are important for the decision-making for diffuse large B-cell lymphoma is at the minimum knowing the, the ABC and GCB subtyping of the lymphoma. All those, those have not been readily used within the context of making decisions about therapy yet, I think it is still at least, in general, useful to know where that, where that exists. Likewise, knowing *TP53* status, knowing *MYC* and *BCL2* and *BCL6* status in terms of whether you're dealing with a double hit or triple hit lymphoma by FISH studies, I think, is particularly critical in making decision-making as those points go forward.

I think some of the challenges that we see, particularly as patients move through that standard first line therapy, is how to help to stratify patients and make decisions about what to do next. As of yet, PET/CT scan still remains the standard of care at the end of therapy for evaluating patients and for helping you to, to know what to do next. We hope to see some new data actually that come out of this year's ASCO meeting that may give us a little bit more information about cell-free DNA within the setting of first-line diffuse large B-cell lymphoma and perhaps even later lines. And as many of us have seen, that's an emerging modality for evaluating diffuse large B-cell lymphoma that is really growing over time.



DLBCL TREAMTENT LANDSCAPE: 1L THERAPY

Dr. Giralt: So I think it's important to let's look at the treatment landscape. So first-line therapy the, you know, the standard is R-CHOP. We saw in the *New England Journal of Medicine,* per a paper that Dr. Gilles Salles was the first author on, that pola-R-CHP is actually superior to R-CHOP in regards to progression-free survival or no overall survival.
Quickly, Chris, do you think pola-R-CHP will become the next, the next R-CHOP?

Dr. Flowers: Yeah. Well, so I think it's important to note now, and this is actually new as of January, that the NCCN guidelines recommend that as a Category 1 recommendation for any patients who have an IPI score of 2 or greater. You know, that's really a big proportion of patients with, with diffuse large B-cell lymphoma; and I think that's another important clinical factor to bear in mind when we start therapies for patients.

Dr. Giralt: So currently, this is not on the label, but we're expecting that that label is going to change. That's going to become available very soon. And then dose-adjusted EPOCH is also something, I think, that's used frequently, particularly for doublet lymphoma and other high-risk lymphomas, right?

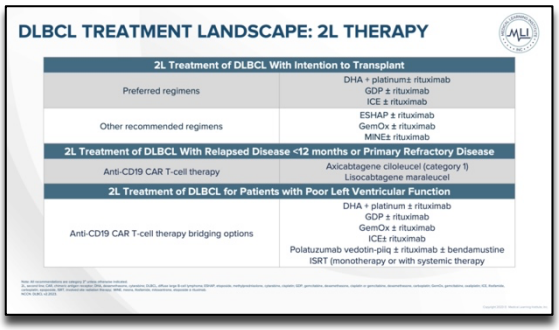
Now where it gets much more complicated is what do we do for treatments with patients with poor left ventricular function? So, there are dose-adjusted EPOCH, and then there's the, the anthracycline-sparing regimens that you see there in alphabetical order.

And then we have what do we do with the very frail patients and patients who are greater than 80 years of age with comorbidities? And, again, you have the mini-CHOP, RGCVP. Where do we stand with pola-R-CHP in those frail patients? Is there any data for them?

Dr. Flowers: Yeah, so that's being explored. So, the initial trials allowed patients, even up to the age of 80, so there are some patients who were treated on that randomized trial of R-CHOP versus pola-R-CHP who fell into that IPI 2 or greater category. It really looks like all patients who were eligible for that trial out of that was an improved outcome for that. But I think for those oldest old, we still do need to try and find other regimens that may be options for some of them who are very frail.

Dr. Giralt: So, unfortunately, currently with R-CHOP and a little bit better with pola-R-CHP, you know, 30 to 40% of the patients will fail to respond or, actually the treatment will fail them, let's say. The patients don't fail; the treatment failed the patient.

These and then second-line chemoimmunotherapy followed by consolidative autologous transplant has, up to recently, been the standard of care for patients with diffuse large B-cell lymphoma. However, most patients are ineligible for autologous transplant due to age, comorbidities, or failure to respond appropriately to chemoimmunotherapy.



DLBCL TREAMENT LANDSCAPE: 2L THERAPY:

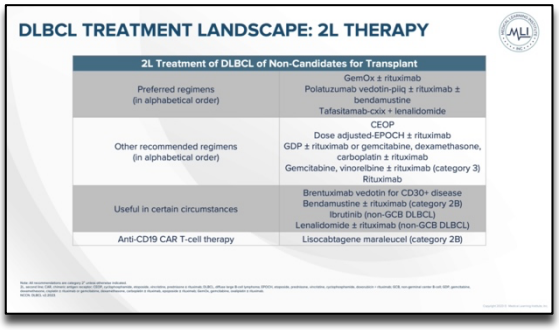
So what do we do in that second line? Again, this is a summary of the NCCN guidelines. So the preferred regimens have usually been platinum-based regimens or gemcitabine-based regimens with rituximab. Then there's the ara-C platinum combinations, the GemOx combinations. And, Chris, I'm correct that none of these have really been compared head to head, and when they've been compared head to head, it's really the same, right?

Dr. Flowers: Yeah. Really, the, the, the only major comparisons have been looking at the, the R-DHAP regimens versus R-ICE. There was really no clear benefit for one regimen over the other; and there's, so as a result, there's no preferred second-line regimen. Really, what I say is the preferred regimen in the second line is the regimen you as a community practitioner feel most comfortable with in delivering.

Dr. Giralt: And we agree that and this area is something that we actually need better salvage regimens because none of these are actually very good in the context of rituximab failures. The one thing we do know is that for patients with early relapse or primary refractory, you know, CD19-directed CAR T therapy seems to be based on randomized trial, the treatment of choice.

And then we should think about what happens with patients, you know, in, after that, and we should talk a little bit about the bridging to CAR T. You know, we all know that you can't, it's not, you know, Sanjays can't call us up and says, "We want CAR T," that there is a timepoint. What do you think are probably the best bridging strategies for CAR T therapy according to, you know, you want to make sure that you don't eliminate the possibility of CAR T because you gave a bridging therapy that was more, too toxic but you wanted to give 'em a chance to respond?

Dr. Flowers: Yeah. The, there's been a fair amount of variability in that. I think one of the challenges that we had very early on with the data that we have in that setting is that it looked like giving bridging therapy was worse, but it perhaps is more likely; and we'll see some of the data there, that it was more that patients who needed bridging therapy had particularly worse outcomes. There are some potential options there like radiation that seems to be quite provocative, but we'll talk much more about bridging therapy in the later part of the discussion.



DLBCL TREATMENT LANDSCAPE: 2L THERAPY

Dr. Giralt: Okay. So let's keep on talking about, you know, what happens with the patients who are not candidate for transplants? You see up there I think polatuzumab becomes very reasonable options, very well tolerated, can be combined with rituximab. There is the use of brentuximab in patients who are CD30-positive, bendamustine, and then, you know, the double Rs, lenalidomide and rituximab, has also been frequently used.

So, I think, you know, there is a variety, and I think is what you just said. For the community oncologist is, you know, what is it that I feel more comfortable with? So, for some patients, lenalidomide-rituximab is, is, and particularly for the frail patient because it's oral with a regimen that they can come in once a week.

So it really is, you know, for the individual patient, particularly if you're thinking about bridging to CAR T, the two things that I think we need to keep in mind is, one, you want to prevent severe toxicity and, two, you want to give them a chance to be able to respond.

Dr. Flowers: You know, one of the things that I'd be interested in hearing from the two Sanjays is when you see that laundry list of potential options, which of those do you see as kind of the go-to regimens?

Dr. Sharma: I mean, I think you said it, Chris, in terms of comfortability, right? So what are, what are you used to? What is your, you know, there's some inpatient regimens on there, so what is your team used to, what is your hospital used to, and what is your, your comfort level? And then recognizing the, the comorbidity of the patient.
And I'm actually going to throw in there, also at the same time, is part of this whole relationship that you're seeing at, at the table is what you're bringing to the patient in terms of recognizing that you're getting expertise across different levels. So they're not just seeing Dr. Sharma, who may know the patient and the family intimately well, but they're seeing my version of Dr. Flowers of my version of Sergio in the same room. And then as that treatment paradigm gets made, it's, it's smooth.

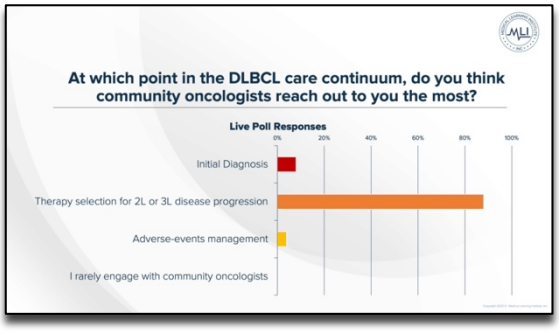
So for me, if I'm using R-squared or if I'm using RICE, I got a plan. Like, your version in my community knows, okay, hey, second cycle or third cycle is going to be such and such, and it's a natural one-team player. So that's how I look at it, my comfortabilities and, and, and how are my experience with the drugs.

Dr. Flowers: Yeah.

Dr. Juneja: Yeah. And the only thing I'd add to that is, like, I try to keep the myelosuppression in mind, so I try to go with agents that are ideally things that are the, the most frequent interval. So I explain. I'm like, "I w-, I could do a Q3 week, but I would like to do, like, len or something where when we start getting, dipping into those problems, I can just hold it." So anything that, where I have a little more kind of pliability in, in reductions or delays is just to temper it until it gets, you know, to transplant or something.

Dr. Flowers: And, so when we look at the population-based studies looking at R-CHOP in the first line, approximately 40% of patients will have R-CHOP fail them and will relapse with their therapy.

Dr. Sharma: Okay. This leads us to polling question number 2. "At which point in the diffuse large B-cell care continuum do you think community oncologists should reach out to you the most?" And I'm just going to go back and stress Chris's last slide where it said, "40% failure." When you're see a patient, a first-line patient who has diffuse large B-cell lymphoma, at least the, the tone that I'm using with the patient, I said, "Hey, you're going to be fine; this is curable," but recognizing that 40% are going to fail.



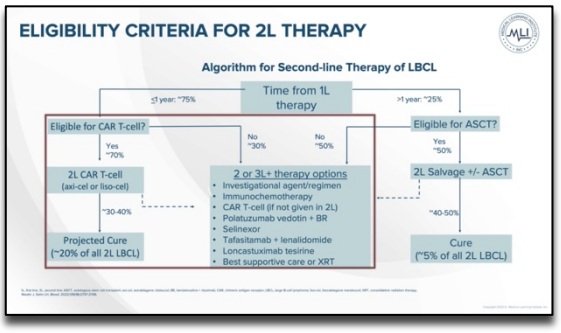
<u>POLLING QUESTION</u>
So knowing that, at which point does this table come into your world in the patient's room? So would that be (A) initial diagnosis, (B) therapy selection for second line or third line after the disease progresses, (C) helping with adverse events, or (D) I rarely engage with the community oncologists?

Dr. Flowers: Sergio, how do you reflect on that? You know, where do you think that we should be engaging with our community oncologists in that setting?

Dr. Giralt: So I think this is really a continuum. We should be engaging with the community oncologists even before they'll, they see it as, you know, as part of the continuum. We need to have- The better relationship we have, the better chances we have of getting patients into cell therapies. And this is actually one thing that, you know, when people ask me, "What do you think is one of the best strategies to try to increase access to cell therapies and reduce barriers?" is working together with the community oncologists, working together closely. So, we've had patients with, you know, first-line treatment that we've been called because said, "Look, Mrs. Smith has lymphoma. She is high risk, but she has all these other social barriers that we will encounter in the event that she relapses. Is there anything you can do to be able to start more proactively working with that?" And, remember, the Sanjays, they have access to social workers; but they don't have a dedicated social worker many times. So many times what we say, "Look, why don't we get her consulted early. We'll get the social worker involved, and that way she can be e-," we're hoping to never, she'll never need CAR T or she'll never need an autologous transplant.

But I think in that regards, it's creating a continuum. Otherwise is what the Sanjays have said, it's, look, I identify a patient. If they're really not high risk, we'll continue with R-CHOP. If they are very high risk, I'll start putting the flags up. If they're not like Mrs. Smith with a problem, we'll just call when we need them, but I do think that having that good relationship with all your community oncologists makes a huge difference.

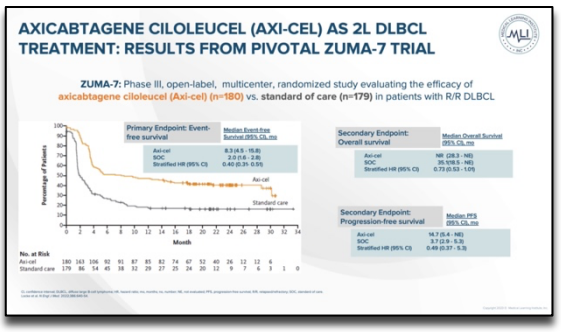
Dr. Flowers: Yeah, I completely agree with you there. You know now, particularly as we're starting to see data from randomized trials like the ones led by my colleague, Sattva Neelapu, and trials that are moving to the randomized setting in the first line for those higher-risk patients, we really do s-, need to start engaging our community oncologists sooner.



ELIGIBILITY CRITERIA FOR 2L THERAPY:

Dr. Flowers: Well, let's jump into the data on the next couple slides. So you heard about this algorithm from, from Dr. Giralt. So this is an algorithm that was just recently published by Laurie Sehn and Jason Westin in *Blood* describing, based on the randomized controlled trials that I'll describe, what to do in the second-line therapy for large B-cell lymphoma.

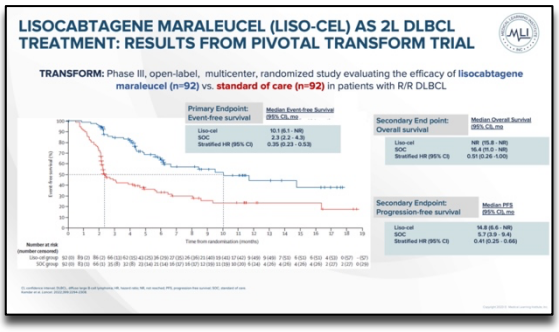
So this really is based upon the time from relapse from first-line therapy. So for those patients who have an early relapse, which is approximately 75% of those patients who relapse within one year of their first-line therapy, then we should proceed on to autologous, proceed on to CAR T-cell therapy for those patients based on the data that I'll show you. But for those patients who have a later relapse, then autologous stem cell transplant is something to consider.



AXICABTAGENE CILOLEUCEL (AXI-CEL) AS 2L DLBCL TREATMENT: RESULTS FROM PIVOTAL ZUMA-7 TRIAL

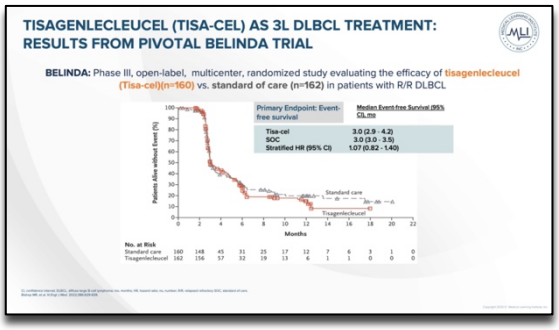
And so this next slide shows the results from the first randomized control trial that I'll describe axicabtagene ciloleucel, or axi-cel, where patients were randomized to axi-cel, 180 patients in that arm shown in the orange curves versus standard of care where

patients received salvage therapy followed by autologous stem cell transplantation for those patients who responded to salvage. And you can see here that there was clearly a benefit in terms of progression-free survival for those groups that r-, received axicabtagene ciloleucel and a benefit in terms of event-free survival.



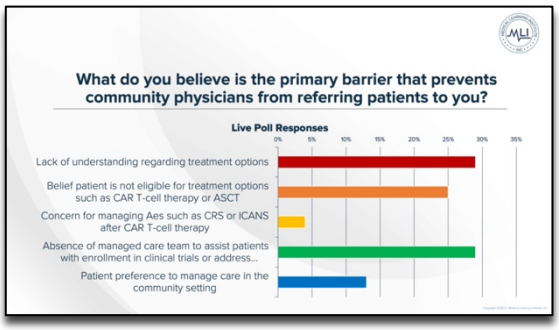
LISOCABTAGENE MARALEUCEL (LIS-CEL) AS 2L DLBCL TREATMENT: RESULTS FROM PIVOTAL TRANSFORM TRIAL:

So the second trial that was also a positive trial looked at liso-cel or lisocabtagene maraleucel in second-line diffuse large B-cell lymphoma, really an identical setup to the randomization for this trial. And you can see here, again, in terms of the primary endpoint of event-free survival that this trial met its primary endpoint showing a benefit for liso-cel over autologous stem cell transplant following salvage therapy.



TISAGENLECLEUCEL (TISA-CEL) AS DLBCL TREATMENT: RESULTS FROM PIVOTAL BELINDA TRIAL

The third trial that used the study design was the BELINDA trial. This looked at tisagenlecleucel. Here there was no distinct benefit for receiving CAR T-cell in this setting.



POLLING QUESTION

Dr. Sharma: Okay, so "What do you guys believe, what do you folks believe is a primary b-, barrier that prevents the community physicians from referring to patients, like you guys?" Is it (A) a lack of understanding regarding treatment options, meaning did you guys just understand what these two guys were talking about regarding CAR T, transplants, third lines? (B) belief that the patient is not eligible for treatment options such as CAR T therapy and auto stem cell transplant, which was also discussed about, amongst these two guys in terms of patients up to the 80s getting CAR T; (C) concerns for managing AE such as cytokine release syndrome or ICANS after CAR T-cell therapy. How many of you guys want that phone call when you're on call from the ER telling the patient is confused and having febrile and what to do with it? Does the ID doctor get called in and they get an LP? What's going on? Do they need steroids? Do you really want to deal with that? (D) absence of a managed care team to assist patients with enrollment in clinical trials or address insurance coverage issues. Who else is on your team? With what other resources does that patient have to get that patient the appropriate evidence-based treatment is what (D) is talking about; and (E) patient preference to managed care in the community setting. What does the patient really think about you and your system and what else is out there?

Dr. Giralt: So Sanjays, both of you, what is your current workflow regarding referring to cellular therapists? And I think one of the things that's very important to note and I think the co-, the audience here is full of cellular therapists, The Leukemia & Lymphoma Society is a great resource for our patients who are potential candidates for CAR T to help them, one, understand the treatment, and they do have access to resources that you may not

have in your practice but they can have to help patients go in, you know, one, understand and, two, to help them manage what we know is a difficult journey from, you know, your community practice to what, the cell therapy service. And we, the cell therapists, are trying to do everything possible to make that transition as easy as we can. But what's the current workflow in your offices now?

Dr. Juneja: One thing that I, is important to highlight, and it's not sobering I think, you know, I hope you all find it almost terrific, is that even Sanjay Sharma, Dr. Sharma and I are like two very different community oncology, like, subtypes.

So you'll be, just remember that in America today, I mean, they're, you're at the mercy in a lot of, like, community oncology practices in the country of, of the pathologists in the, in the room. Like sometimes there's not even reflexes to see if it's double or triple. That's not the case in, in Baton Rouge, fortunately, but, but that is existing every single day. Like, they don't even know how to refle-, to reflex that. And then let alone to then, like, if your oncologist, if you said you, "Did you order molecular and R-CHOP?" they're like, "What?" I mean, "Why?"

Like so that's where I think what we touched on earlier really, like, if you can engage, you're doing this, like, big service for all of those patients and likely many that they're seeing just, just with that one reach out. So that's very important. And then with that reach out, I think the workflow becomes a lot easier.

So I have the fortune of, you know, having a couple of BMT physicians that I'll text; and, you know, when you see that 40% rate, right, of failure after all DLBCLs, when I have my 30-year-olds and 40-year-olds – I had two just last month – and they had really high-risk disease, triple hit, *TP53*, that's where I'm like do I even want to risk the myelosuppression and injury to the bone marrow or make them get a trial because they're young and, and, and they have a high chance of failure?

So, I think we all agree in this room, like, the earlier the better; but how do you expect your community oncologist to know or think about those things? And then that conversation then facilitates, okay, think about it, which is the most common answer; they don't know, right, and then the second thing is, well, this is how you do it. So, like, you know, somebody can call and let your navigator or your triage nurse know. And suddenly you have just opened the gates for not just that individual but everyone they treat. But without that, there's no door open, and I think that's, by far, the biggest, I think, facilitator on making sure these patients get captured.

Dr. Giralt: Sanjay, in Orange County does it feel that same way or not?

Dr. Sharma: Yeah. So, the way I think about it and, yeah, my practice is different than d-, Dr. Juneja's. I'm in a big metropolitan cities, and I have lots of tertiary centers – City of Hope, Cedars-Sinai, UCLA, San Diego. So, although a lot of times it's confusing which one I can use based on insurance companies and the contracts, and but that's a different issue.
But I mean, I always picture myself, and I want all of you guys to picture yourself regarding, having that patient in the room for you, you know, telling them the diagnosis. Lymphoma is a diagnosis that we give. This is not a type of d-, cancer that someone else does, that makes the diagnosis, the primary care doctor, a surgeon, the pulmonologist, whatever, and then they come to us with the diagnosis. We're making the diagnosis. We are managing expectations. We are leading. We're talking about the patient (A) how dangerous is your cancer, (B) how do you manage this cancer.

So, I stress again, and, and like Dr. Juneja, there's a, 40% of these patients are going to fail, so you do need to have a plan. So, for example, for my practice, my practice, I try not to be the most important person in the room. I consider myself the educator. I have my nurse navigator with me, my palliative care team, my social worker, etc. and, quite frankly, in the community world, you also are marketing yourself and your, and your system. So who else is in on that team with you? And, again, for me, oftentimes I don't know. Is insurance going to tell me Cedars-Sinai or City of Hope or whomever it may be?

But I strongly feel, and I asked you guys this earlier, what is like the MD Anderson and Sloan Kettering in terms of systemic wide, way of creating those relationships? But that's what you also need in, in, in the same room in, in, in addition to my palliative care social worker, etc., etc. And I am making this more of a vision as opposed to a solution, but that's, like, where operations come in.

Dr. Giralt: So, Sanjay, you know, what do you think the perceived barriers between referring physicians with therapists are?

Dr. Sharma: Providing patient education. The community burden of treating emergency. Like I said before, a patient comes in with cytokine release syndrome, does your ER doctor know what to do, do the hospitalists know what to do, and do you want to get woken up at, to figure it out? Assisting patients with logistics, insurance, transportation, etc., language barriers also. Community physician knowledge, how much do we know? How much are you going to gather from these meetings that you go to and what you read? And how to access service.

Dr. Juneja: And then a very popular one, which I, I hope isn't, in part, just kind of a copout answer because I think it's been really, like, met with kind of, like, disillusionment or realizing it's, it's not as, you know, early on when we heard about a CRS, "Oh my gosh!" But it's the fear of treatment-related toxicities, as Dr. Sharma touched on with the previous polling question.

And for that, I'm super excited to have Dr. Rouce ask us or to answer that kind of, like, concern. So Dr. Rouce, thanks for being here. When you are returning your patient back to their referring community physician, what is the communication process on, like, okay, I did the thing I needed to do. You know, here's, here, here it is? What, what, what's involved in that process?

Rayne Rouce, MD: So that's a really good question, Dr. Juneja, and I think one thing that has become obvious is that CAR T-cell therapy can appear extremely complicated, especially to referring physicians who have not been a part of the day-to-day care of the patient in the immediate post-CAR-T period. So, it's really important to establish open lines of communication; and initially, you may need to communicate a bit more frequently as things come up, but along the way it actually becomes a lot easier.

So, I just want to remind here that most of the complications that occur after CAR T-cells that are expected, that are ones that we're very accustomed to managing are going to occur in the more immediate post-CAR T-cell period. And so I say that because it's very easy to be intimidated by having to take care of immediate toxicities of CAR T when in reality that's usually not what is taking place by the referring physician.

So, we actually have very clear guidelines about how we manage patients post-CAR T, and it's important for the CAR T site and the physician and medical team to share that information with the referring physician but ensure that there are open lines of communication for any expected or unexpected complications that may come up.

So, it really is an ongoing relationship; and a lot of times you feel like friends and like you know each other very well by the end of the process because we all want what's in our patient's best interest, and we understand that having a shared care model where the referring provider, who usually that person's primary oncologist feels comfortable in having an ongoing discussion.

So one thing I think is really important to remember is that as cell therapists, we're very accustomed to managing CRS and ICANS, and it's almost become second nature. We have algorithms for identification. We have algorithms for management, and referring community oncologists are becoming more familiar but usually have not managed these patients acutely. And while we recognize that these signs and symptoms of syndromes are a lot less likely to happen further out from therapy, it is important to ensure that the referring oncologist knows enough about CRS and ICANS to watch for things that may come up so we can actually reassure them that that's less likely.

It's almost important to ensure that they understand these more longer term algorithms that we have, and really we start to assess these patients the same way we would for the patient who has had a bone marrow transplant or who's had some other therapy. We know that there are specific things we may need to follow long term. We know that there are specific labs we may need to get. We know there are specific therapies that they may need. And because we've been doing this for a while now, we actually have that information. We just have to ensure we can share it with the referring providers but also continue to be a resource as needed.

Dr. Flowers: I mean, I think one of those ones that is a big one that comes up from time to time, and I face this all the time in talking to clinicians about CAR T and when they're, they're considering it is that CAR T oftentimes is considered to be a last resort therapy that patients are referred to. And that really sh-, you know, based on the data that I showed, should not be something that community practitioners think about it in that way.
I think the other component of that, that some of our, our referring physicians worry about are the AEs and the toxicities that Dr. Rouce present to us being AEs that the community docs will have to manage at home. And, in general, the AEs are all managed prior to those patients are sent back to the community, and the kinds of long-term follow-up and management typically is around cytopenias and may not be nearly as extensive as the kinds of things that happen at the CAR T center.

I think as Sergio mentioned earlier, you know, that close communication and tightknit practice really makes it easy that when patients do need to come back to a CAR T center that that can happen as well.
Can you give me kind of some of the, the ways that you've been able to co-manage patients in that setting—

Dr. Juneja: Yeah.

Dr. Flowers: -with docs in your community?

Dr. Juneja: I mean, hopefully, once, hopefully, everyone has a relationship already with their community oncologist, right. So, like, fortunately, you know, or hopefully, again, you, you've sent a referral for autotransplants for myeloma and for even allos, you know, unfortunately for leukemia. So that relationship, again, goes back to what I was saying earlier. Once it's established, it's, I, I think of it as more of the same. Like, I, maybe I'm spoiled but, you know, I think it's, it's kind of inherent in, in BMT specialists. You all are very comprehensive and you have the algorithms and, and, and are very, you know, make us feel very prepared and, and edified. It's not, like, "Okay, here." Like, and I think if a community oncologist suggests that, I just don't know that that's the majority of the cases.

So for that reason, I just think of it as a, you know, a continuity of, of what's already been taking place or, you know, "Do the vaccines now, you know, at this time." And, and sometimes I'm like, "Oh, I know." But it's just, it's thoughtful and that same thing applies to, you know, as therapies get more novel, it's just what we look for, what's the percentage, and what do we do? And then, of course, being able to just text y'all and know.

Dr. Giralt: And am I, are we correct in assuming because we both have, we have, like, this little cheat sheet that we give the patient to give to you both when you're—

Dr. Juneja: Yeah.

Dr. Giralt: -going out in the community of what to do in the case of neutropenia, what to do in the case of thrombocytopenia, vaccine eligibility. Hypogammagobul-, hypogammaglobulinemia has become a big one. And, you know, we're still, initially the reflex was to replace with gamma globulin. I think now we're both going back to the choosing wisely that you only replace in the setting of, you know, recurrence and pulmonary infections or the case of a serious infection. Are those things helpful for you or—?

Dr. Sharma: Yeah, for sure.

Dr. Juneja: Yeah.

Dr. Sharma: Yeah.

Dr. Juneja: And that's what I mean. It's like it's the same algorithms that y'all provided us for, you know, regardless of the setting where we have to have a relationship, you know, for further treatment.

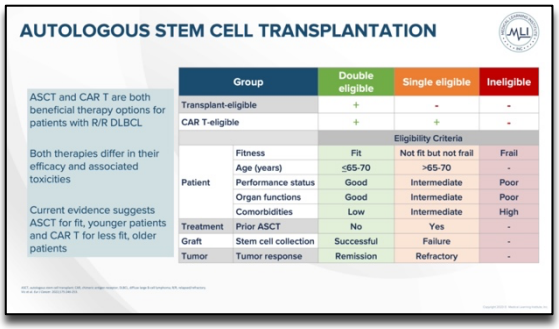
Dr. Giralt: So, you know, one of the things that I get, which is fine, I mean I carry both hats; I do transplants and I do cell therapy. And they always ask me, "So which, what do you go?" I mean, and I'm going to be provocative here a little bit, so, and because it just happened recently. We had a patient who relapsed 10 months after CHOP and got R-ICE. Nobody was expecting them to have a dramatic response. And after one cycle of R-ICE, this patient's achieved a PET-negative complete remission.

And when we presented in consensus conference, I actually said, "Why not do an autologous transplant on that patient because actually the data from the CIBMTR shows that those patients would actually have had long-term disease control with an autologous transplant?" My CAR T colleagues would say, "Yeah, but the axi-cel." And what I've always remembered, look, the randomized trials were really not CAR T versus transplant. It was really CAR T versus R-ICE, and R-ICE is not necessarily very good. So, Chris, where do you stand on that?

Dr. Flowers: Yeah. So that's a really challenging discussion to have with a patient and to have with your colleagues. And I think there're a number of options for a patient like that.

You know, until I moved to MD Anderson, for 17 years I was also in transplant, auto and allo setting as well, when I was at Emory. And so I, I think from the patient care standpoint, yes, those are patients based on the CIBMTR data that you would expect to fare well and, historically, the kind of patient that we would have been excited about taking to autotransplant in that setting, and we know that CAR T is option potentially for that patient in the third line that can potentially provide meaningful benefits.

And so I think you have to have all of those discussions with the patient wi-, in line with the randomized data that I showed earlier to, to describe what, what the potential options are. And either of those can, can be made as reasonable options based on a, an informed patient.



AUTOLOGOUS STEM CELL TRANSPLANT

Dr. Giralt: And I think where we both will agree, and I think the Sanjays will help us in this, is that we always get the conversation from, you know, that, particularly when CAR T started, older patients, frail patients. And I think there's now good data that patients who are over the age of 70 who would not be candidates for autologous transplants because of bad DLCO, bad ejection fraction, or will not say poor performance status but less than stellar performance status, those patients, again, actually benefit from CAR T-cell therapy, right?

Dr. Flowers: Oh absolutely. So I just rotated off the CAR T-cell service about two weeks ago, and we had at least four 80-year-old or older patients on our CAR T service. And so those patients over the age of 70 really are the kinds of patients that in that setting can potentially benefit.

Dr. Giralt: And for you, the Sanjays, we know that there, is that a barrier? I mean can we help you with the older patient who I mean many times says, "What do you mean, CAR T?" I mean how can we help you to get that message because these are patients who can potentially benefit. We forget a 78-year-old has a 10-year life expectancy and this disease is going to take that away.

Dr. Sharma: So as, as you guys were having the communication about and you were talking about at your, at your meeting where you had a, a complete response to R-ICE transplant versus CAR T, I am absolutely picturing that next visit. And it kind of reminds you of the myeloma days, transplant versus no transplant, the patient comes back to you, "Okay, what do I do?"

Because I've just given this patient R-CHOP. I'd just given all this. I've known 'em for months and months, and they come back to me in terms of what is my comorbidities? Am I going to survive this? They talked about death.

So absolutely. Yeah, we absolutely have to be informed and understand your input because your input is going to greatly influence us. That statement, even though it was at MD Anderson and you guys are aggressive, that statement that you had four people who were, you know, 80 years old that did it gives us that comfortability, "Oh yeah, Chris has got you."

You know, we're good. We're in this together.

Dr. Flowers: So, what kinds of communication processes do you have with patients about initiating bridging therapy and the ways that you'll be able to manage that in a community physician? We start with you.

Dr. Juneja: I mean I think it's, it's, it's a good thing, but then it's also a problem, which is when you start having that, that thought process, obviously, you know or, or the ideal community oncologist knows that you would help with that decision process, right? I mean, for me it's I send to the BMT and cellular department and, and specialty.

The reason I say it's a problem is I think there's a big association still when you have BMT and cellular, you know, specialty or specialists that they kind of liken them together in their candidacy of, like, oh they could never handle a transplant; and somehow cellular is being, like, lumped into that category.

So I think the communication on explaining that, hey, there's this thing and it's a new thing and that you don't have to necessarily have an ECOG of 0 and be under 7-, you know, 75, whatever, 65. That, that, that message needs to be very clear. And then at that point, at least with autos and, and cellular therapies and stuff, Sanjay Sharma was exactly right. They come back and they say, a lot of times they want to know, "Well in your experience, how do you think I'll do?"

Well, there's very little experience for us to be able to guide in this setting when it comes to CAR T therapy. And it makes people nervous. And, like, 'cause they're like, "I have a remission now or I have decent control or, or it's working," and generally people buck away from things that are unfamiliar.

But all that to say that's where, like, I think the facilitation of just getting to the specialist and, and really kind of hyping that specialist up to the patient. Like, that's where I say, like, "I trust them." And I don't want to, I can't say that unless I know them. So, like, those relationships are so important, I think, to foster because what you all as specialists offer I mean have huge consequences on how these families, like, you know, how this process goes.

And I think, ultimately, there needs to be some room, even if it's asynchronous, for as things evolve where specialists have an asynchronous portion of their week that's billable or what, I don't know, but to be able to address and field these things. These once-a-week tumor boards, like, you know, ours is just packed with every kind of cancer type and—

Dr. Giralt: Yeah.

Dr. Juneja: -and there needs to be support in some manner.

Dr. Sharma: Yeah.

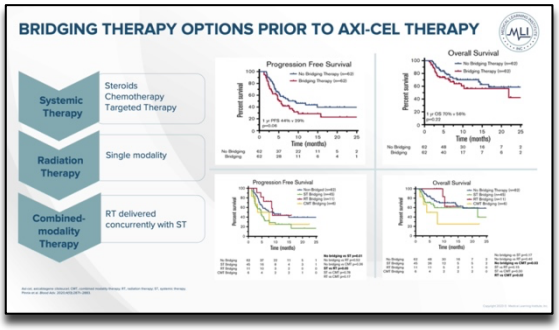
Dr. Giralt: Chris, you know, it's interesting, and optimal bridging therapy is a conversation you're going to have with us, but antibody drug conjugates and bispecifics, at least in the context of myeloma, particularly the bi-, the sequencing of bispecific and CAR and the use of antibody drug conjugates that are targeting the same antigen that a CAR T, go over what do you think should they be used or should we go through the standard systemic therapy? And-

Dr. Flowers: Yeah.

Dr. Giralt: -what's your approach to bridging?

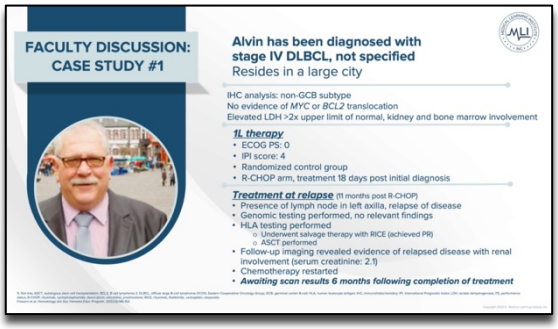
Dr. Flowers: Yeah. Really a fantastic question. You know, when, when we think about CD19-directed therapy prior to CD19-directed CAR, in general, that is something that I try to avoid. You know, there have been some significant concerns about that initially, but it's approximately 25% of those individuals who fail CD19 CAR who have loss of CD-19 as the primary problem. So it's possible to use, but it's something that I, I tend to avoid.

You know, we teased you a little bit earlier about bridging options that was something we were going to discuss there. I think there are a number of those. Early on in the management of CAR T-cell therapy, we were concerned about giving steroids as a, as a form of bridging therapy, but I think that is an option that we now or have much more comfort with, particularly when those steroids are relatively short-lived in terms of the duration of therapy.



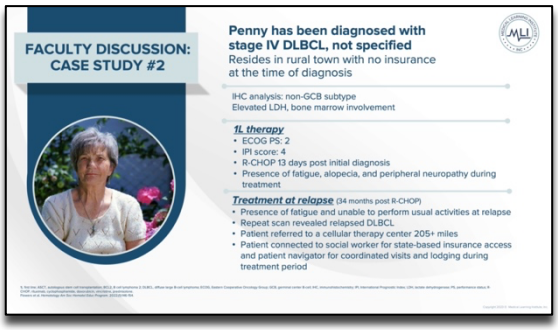
BRIDGING THERAPY OPTIONS PRIOR TO AXI-CEL THERAPY:

Other modalities like radiation therapy can be delivered as a single modality therapy, and there're really nice and provocative data from my colleague Chelsea Pinnix that are shown there in the curve at the, the bottom looking at those patients who had radiation alone as their bridging therapy. Some of that could be related to what I described earlier that's shown as the curve at the top that likely those patients who required bridging therapy, as opposed to those who did not require bridging therapy, are those ones that tend to fare worse. But there also are some biological hypotheses associated with antigen release and abscopal effect that we see with radiation therapy that may be ways to proceed.



FACULTY DISCUSSION: CASE STUDY #1

So we have another handful of cases to, to run through. So our first is a gentleman who had Stage IV diffuse large B-cell lymphoma, resides in a large city, and with first-line therapy, you could see his ECOG performance status and his IPI score of 5, so fell into that high-risk category. He got R-CHOP therapy that he received 18 days after his diagnosis, so a diagnosis treatment interval of 18 days. And relapsed 11 months after R-CHOP. He had presence of a lymph node and follow-up imaging indicated relapse disease and is awaiting CT scans following completion of therapy after chemotherapy in that setting.



FACULTY DISCUSSION: CASE STUDY #2

So our next patient is Penny who was diagnosed also with Stage IV diffuse large B-cell lymphoma, not otherwise specified. She lives in a rural region of the country. Does not have insurance at the time of diagnosis. Her immunohistochemistry showed evidence of non-GCB subtype. Had a high LDH, so another poor risk prognostic factor. You can see her IPI score was also poor, and she received R-CHOP 13 days after diagnosis, so with a shorter diagnosis-to-treatment interval. With therapy, she did have some neuropathy and fatigue. And then relapsed 34 months after her R-CHOP and then went on to referral to a cellular therapy center and was connected to a social worker in preparation for care there.

So which patient do you think would be most appropriate for CAR T-cell therapy in this setting? Alvin, Penny, or both, or neither?

Dr. Sharma: So, I'll say in terms of the, the, just purely the cancer, I would say both Alvin and Penny, but socioeconomically there's significant barriers. Alvin is going to have the easiest time, and Penny is going to have the most difficult time, for sure.

Dr. Giralt: And I think as they're aware, that patient advocacy groups like Leukemia & Lymphoma Society can help Penny with different resources to be able to help her access, you know, but like, and, for one, is to help with out-of-pocket expenses. So there are places that, you know, Penny's physicians can look into to try to help her get into the cell therapy program.

Dr. Flowers: Yeah. I, I think those are critical. We talked a little bit about many of these points, but we mentioned the diagnosis-to-treatment interval. We know for those patients who have a shortened diagnosis-to-treatment interval, less than 14 days, those are patients that tend to have worse outcomes with the standard R-CHOP therapy. And you mentioned many of the barriers that we see for rural patients that have worse outcomes and limited access to care. But I think it's important to note that all of those barriers can be overcome with the, with significant interventions, but it will take effort to be able to overcome those.

Dr. Giralt: And going back to the first thing we talked about initially is that's where early communication and close communication with the cell therapy programs can help these patients.

Dr. Sharma: Dr. Rouce, how do you typically engage with community physi-, physicians to address barriers and managing cares for diffuse large B-cell lymphoma?

Dr. Rouce: So that's a really good question, and I think it's a question that comes up more frequently than we would like. As cell therapists and as transplanters and physicians and healthcare workers who have access to these very exciting and often potentially life-saving therapies, the harsh reality is is that there are patients that people may deem more suitable for therapy not because of a clinical characteristic or a disease characteristic but because of something within their social circumstance or life situation that may make one therapy more challenging than others.

I think one of the most important things that I try to ensure that I impress to referring physicians is please don't let a barrier stop you from referring someone for cellular therapies, including CAR T-cell therapies because we recognize these barriers, there usually are quite extensive resources set up to try to mitigate these barriers, and we really always want to do what's in the patient's best interest.

So I often find that referring providers may say, "Well, I was considering CAR T, but they live alone, they don't have a great social network, the nearest site is very far, I'm not sure how they would manage." It's important to think about those things, and that's a part of taking care of the entire patient, but it's also important to not let those things truly serve as roadblocks or obstacles but instead to reach out and see if there are ways that we can mitigate these factors, of course, involving the patient, the referring physician, and the cell therapy site. So we don't have to know the answer to all the questions or how to solve all of the problems, but it's important to recognize that we should strive to not let these factors truly be barriers and allow some people to have access to the therapy while some don't. And this is something that we all have to work on together as a field.

Dr. Juneja: All right, that was very riveting. Appreciate Dr. Rouce tuning in, and I hope that everyone feels that, you know, we've kind of recognized or uncovered, one, the need, right, to make sure that people are referred, but also what are some of the ways we can, like, you know, I, if, is it comfort that an oncologist needs, a community oncologist to send? Is it, is it the awareness, education? It sounds like it's a lot of both.

I personally feel very strongly that it's just that one reach, even if it's from you or someone on your team to, I mean just, just float it because I do think community oncologists as things get more complicated in every cancer

type, like any kind of assistance or just knowledge that someone's available to help quarterback some of the more complicated cases, it goes a very long way now more than ever. But what, what do you all think? I mean what are the big takeaways really that—

Dr. Giralt: The two things is, one, communication between the cell therapist and the community oncologist.

Dr. Juneja: Right.

Dr. Giralt: And two, educating the patients. I think, as you've heard, I mean there are a lot of preconceived biases from patients – "I'm too old for this. It's too far. It's too hard." That, that's where you come in, and we can give you the material to help you make that conversation happen.

Dr. Juneja: Well, thank you all again, like, sincerely for being here, participating in the symposium. Hope we could, you know, provide something that's valuable just based on our observations for you to take back to where you're practicing. I personally just appreciate everything you're doing and, and the attention and care you put into, you know, very complicated process.