ASH 2020 Updates: CAR T Cell Therapies in Multiple Myeloma

We kickstart the new year with a discussion on CAR T cells in myeloma treatment with a focus on the CT053, a CAR T-cell therapy targeting the BCMA protein and granted orphan drug status by the U.S. Food and Drug Administration (FDA) for the treatment of multiple myeloma.

CAR T- cell therapy harnesses a patient's own immune cells to fight cancer. These therapies consist of collecting a patient's T-cells — a type of immune cell with the ability to fight cancers — and genetically modifying them in the lab to produce a chimeric antigen receptor, or CAR, that targets a specific cancer protein.

American Society of Hematology (ASH) 2020 meeting saw CAR T cell therapies for myeloma presented and discussed at length. The Myeloma panel of Gary Petersen, Jack Aiello, and Cynthia Chmielewski is talking to Dr. Shaji Kumar of Mayo Clinic about CT053 and other CART therapies in the pipeline for myeloma treatment.

Full Transcript:

Priya Menon: Hello everyone and welcome to cure talks. I'm Priya Menon and today we are discussing Car T Cell therapies and multiple myeloma with Dr. Shaji Kumar, Professor of Medicine at Mayo Clinic. Mayo has a lot of Car T-cell programs and Dr. Kumar is one of the Doctors working with a focus on myeloma. Joining us on the myeloma panel of patient experts are Gary Peterson, Jack Aiello and Cynthia Chmielewski. Thank you for being here. We will be taking in a few questions at the end of the discussion based on the availability of time. So, please add your questions in the comment section of the page or you can also email them to me priya@trialx.com. Getting started with the discussion Dr. Kumar, thank you for today. I want to start with something which is on everybody's mind and I would like to address it first before we dive into the Car T therapies of covid-19 and the vaccine rollout. It would be great if you could comment on the Covid vaccines and what you are telling your patients.

Dr. Shaji Kumar: Yeah, thanks Priya. I think obviously that's on the top of everyone's mind trying to think how to stay out of the way of that infection and when everything gets back to normal. So, I think the good news is we have vaccines and not so good news is we just don't have enough of it yet, but hopefully that will change in the near future. So, at least in the U.S. practice currently, we have two vaccines that are approved both the Moderna's vaccine and the Pfizer Biotech vaccine and both of them appear to be quite comparable in terms of their efficacy. The Pfizer vaccine needs a little bit more colder storage facilities and is given 21 days apart. The Moderna's vaccine is given 28 days apart and appears to be a little bit more stable at higher temperatures. Now, both of them have the same technology behind it, which has not been widely employed for creating the accents in the past. But clearly, it's the technology that is quite fascinating and it's become now with these vaccines mainstream and hopefully will allow us to create vaccines in the future too. So, the big question that comes up is first of all, should myeloma patients get the vaccine and the simple answer is yes, everybody should get the vaccine including the myeloma patients particularly. Now, the second question that always comes up is, is it going to be as effective in the myeloma patients as for normal people, normal individuals and the answer is we don't really have good data on that. Nobody has done systematically a steady look at the immune responses following vaccination. I suspect we will see more of those coming out in the next few months. Until we have more definitive data, the ___ should just work on the assumption that at the minimum it will be better than not getting a vaccine even if it isn't a 95% effective as it is in the normal

individuals, it still is going to be valuable in one potential preventing the infection and even if it doesn't prevent the infection can decrease the severity of infections if someone gets it. So, then the question is when should someone take it right, especially in the context of the different treatments we use for myeloma. So, if someone has let's say smoldering myeloma or active myeloma who is not on any treatment, there's no difference in anyone else. If somebody just had a stem cell transplant or had a Cellular therapy, the recommendations widely have been given three months from the chemotherapy associated with the particular therapy. So again, conditioning therapy for the transplant, or the lympho-depletion therapy that was given prior to the Car T-cell therapy. So, wait for 3 months. Now, how hard and fast is the three months, there's no data to say it has to be three months right, just basing that on our experience post-transplant looking at the history of the risk of infections in general. So, if someone has the opportunity to get a vaccine let's say 60 days from the transplant. I would be okay with them getting it knowing that they're going to get a booster dose 28 to 30 days after that. So, now what about people who are getting other treatments, right? If somebody's on let's say lenalidomide maintenance, I think it should be just fine. Now the big question we have we don't know very well would be the people who are getting cytotoxic chemotherapy or people who are on the monoclonal antibodies both of which we know can depreciate your immune system. In those settings, in the absence of clear data, I think what we should just try for is, when you get access to the vaccine take it because, given the scarcity, we don't want to pass up on the opportunity to get back soon because of delays. If you're able to get a few days before and after the vaccine without getting any institutions, I think It would be great. But I wouldn't traumatically change the schedule based on the vaccination dose itself because as we have seen from all the data we have, the biggest risk for the patient is myeloma that is not under control. So, I don't think we should compromise on the myeloma care to facilitate the vaccine. So, again nothing is Ironclad. Everything has to be in the context of the individual patients. Now finally, I think there are other vaccines that are going to come online. The J&J vaccine looks like the data is good. So, we will get a better sense in the next few weeks. The advantage of that is it's more stable, easy to transport, it's a single dose. So, that's a huge advantage. Then outside of the US, the AstraZeneca vaccine is also approved and is being used across the world. It is again two doses, much more easy to transport and so forth and does not use the mRNA technology. I think there are opportunities or options, but definitely the key thing is getting vaccinated.

Priya Menon: Thank you. Thank you very much Dr. Kumar because we've had quite a few queries for myeloma patients as to when and whether they should take the vaccine and here Gary has I believe been vaccinated. Jack and Cindy are in line for vaccinations. So yes, thanks for answering that. So, Dr. Kumar my next question is going to be one that will just give us a little summary of the ASH 2020 meeting. I know there were so many new and important developments there. Many of them on Car T therapies, which is the focus of our discussion today and which the panel will be diving in deeply for discussions later. So, could you provide some insights on what you feel the highlights and the major takeaways were from the conference which are Non-Car T?

Dr. Shaji Kumar: Absolutely, Priya. I think this ASH had lots of information in their data, even though none of those necessarily might change how I treat my patients today, but it really gave a very nice glimpse of what's on the horizon, how the myeloma field is going to change over the next five to ten years. And I think it's going to be dramatic based on what we have seen particularly with respect to immunotherapy and we will get to the Car T later on. So, in terms of thinking about the new development, putting it in the context of how we deal with this and their spectrum of disorders, right? So, on one hand, the concept of early intervention for the precursor stages. So, there are increasing numbers of trials that are being done in both smouldering and multiple myeloma phases and I think we have the advantage of having a precursor phase to this disease that lasts for 10 to 15 years of the minimum. And a test that can detect that which is very simple using a blood test. So, we have a good opportunity to identify people with these conditions ahead of the time when they get that myeloma. The second big question is what can we do about that knowledge and I think clearly the trials have shown that at least in the people with the highest risk of progressing to myeloma, some kind of early intervention appears to have some benefit. Now, there is still a lot of clarity that needs to be gained in terms of how can we be absolutely sure that we select the right patient to minimize the risk for the others. What is the best approach because it is a treatment like myeloma or a less intense treatment, or maybe it is different for different patients depending upon certain characteristics that we need

to identify? So, while there was not a lot of data in terms of actual regimens for treating smoldering myeloma, there were a lot of abstracts that looked at the biology of the disease which will help us refine the whole risk stratification system. So, we have the new 20-22 system for smouldering risk stratification developed by Mayo data and then subsequently validated using the international myeloma working group data. Now the question is how do we build on that foundation? And I think genomics, the immune profiling looking at the genetic changes all those will contribute to making that a more specific system so that we don't over treat anybody but at the same time we don't leave somebody untreated who really would have benefited from treatment. So, I think the biology of smoldering myeloma with the new technology that's becoming available is going to get really dissected over the next few years and we will have a better sense of what that's going to be. The next step is looking at the whole concept of risk stratifying multiple myeloma and individualising therapy. That's an area again rapidly evolving. We already said the traditional FISH based high risk stratification which obviously is the most important, but on top of that some of these new mutation profiling and immune profiling will add additional layers of beneficial information to that risk stratification. Then moving from the risk stratification to the treatment of newly diagnosed myeloma. So, we now see the updated data from the Mayo trial using the daratumumab, LenDex, we know that the median even though we still haven't reached the median of progression free survival. It's reasonable to assume that's going to be around five years with that triplet that to me is a big jump ahead. Because in a five-year PFS we have already thought about in the context of a transplant in a transplant eligible patient population. We have not quite reached those numbers in the non-transplant eligible patient population so far. Obviously, we don't want to compare regimens, but this is extremely promising for the non-transplant eligible patient population. And the questions going forward is how do we build upon that regimen? Do we build upon it by adding more drugs, replacing something in that triplet with something else that's new? Now in the transplant eligible patient population, I think the big question now is do we use three drugs, do we use four drugs? Obviously, we saw the updated data from the Griffin trial showing that you can get deeper responses, more patients who are MRD negative prior to stem cell transplant, but the data is still pretty early on to say that we should be giving everybody for drugs because there is a price to be paid both in terms of toxicity and the cost of therapy. So, I think as we get more data from those studies as well as other larger studies, we will be able to identify who, if any, benefits from using it 4 versus 3 or are we better off using that drug in a subsequent treatment later on after transplant. Now talking about transplant there is clearly at least three sets of data which suggested that transplant still plays a role in those patients who are eligible to go through a transplant. And we saw the updated data from the French ___ 2009 trial which showed that even with a 90 month follow-up, the PFS is still about 14 months better with transplant versus no transplant. But it also told us that the transplant did not improve the overall survival as long as these patients accessed transplants at the time of relapses. So, I think that early versus delayed transplant strategy still looks like they are equivalent, providing patients with a choice to delay the transplant, if that's the way they would like to approach this. And finally, we also saw the updated data from the ___ trials again showing the transplant is better than a non-transplant consolidation. Now, that also has to be taken in the context of the data with tandem transplant for high-risk patients, right? So, there are multiple trials which have suggested that maybe there is a benefit for the high-risk patients to get a tandem transplant. I know the jury is still out on it and people have very strong beliefs one way or another but it is something to be kept on the table when we deal with someone with high-risk myeloma because we have not yet made substantial progress in those groups of patients. And there is clearly work that needs to be done for the high-risk myeloma patients. Now, I think the post-transplant maintenance or consolidation, I think the maintenance is fairly straightforward. I think Lenalidomide has become the de facto standard based on clinical trials. We know that the high-risk patients would benefit from getting a proteasome inhibitor plus immunomodulatory drugs. Now where does the daratumumab or any of these newer immunotherapies stand with respect to maintenance, we still don't have good answers for that. Now kind of moving on to the next part, right? Unfortunately, we've still ended up having to deal with relapsed myeloma. So, what do we do for patients with relapsed disease? Obviously, the first relapse is now later and later. Previously with the previous therapist, we used to see the first relapse on an average of two to three years. Now, we have seen the first relapse on the average of 4-5 years from starting the initial therapy, but that first relapse often happens in the context of two different things that are different than what it was 10 years ago. One, patients are often on maintenance therapy, right? So, they are often on low doses of lenalidomide. The second is patients come into that first relapse in much better shape than what they used to 10 years ago when the treatments were a lot more toxic and the treatments were not that effective. So, in a way the first

relapse patients that we see in 2021 are almost like the newly diagnosed myeloma patients from 2010 in terms of their overall well-being, their functional status and the opportunities that are available for treating or controlling that disease. So, what do we do for the patients with myeloma, newly diagnosed who have often refracted in Lenalidomide? So, we need to find regiments that are free of the lenalidomide containing combinations. The good thing is we have lots of different options. So, we have the daratumumab or isatuximab with carfilzomib and we also have carfilzomib with cyclophosphamide, a combination that was presented by the Spanish group. So, we have five different regimens we can use in these patients and obviously there's a lot of other drugs that are coming up in terms of the coming up the ladder. But at least in the first relapse in lenalidomide refractory patients or the ___ refractory patients, we do have good choices of triplets that can control the disease for again like two to three years which again is a substantial improvement from before. And this is going to be an important question because we're going to see some of these patients getting treatment for smouldering also coming in with their first progression, so to speak, who are refracted to Lenalidomide. So, what we learn in this setting is going to be something that could be translated to those patients as well. So, it's an important fund of knowledge that's going to be helpful. Now beyond that first relapses in a second relapses onwards now, we have a whole lot more choices of drugs, we have the newer drugs like Selinexor and Belantamab both of which have been approved. We have data from combinations of Selinexor with Carfilzomib with pomalidomide with Belantamab with the proteasome Inhibitors and immune-modulatory drugs. So, we have the opportunity to use many of these newer drugs in their various competitions. Again, the underlying principle being, can we come up with three drug combinations which include drugs that patients have never seen or only have seen some earlier version and definitely not refractory to that particular class of drug. So clearly, those are all options that we have for the third and the fourth relapse, but I think what is the most fascinating obviously is what's coming through right, which is the immunotherapy. And then again, we think for the longest time we thought the immune system in patients with advanced myeloma just didn't have the ability to react to the tumour cells. Now we have data whether it be talking about Car T cells or the we are talking about by specifics, there is no doubt the T-cells that these patients have are capable of getting rid of the myeloma, but they need some additional help and how do we provide that, the two approaches that I think one is obviously using the Car T cell approach we will talk about but the by specifics I think, the by specifics we saw a bunch of them being presented, majority of them targeted towards BCMA which is the same target as the Car T cell and drugs like Belantamab. So, two by specifics with different targets, the one targeting the FcRH5 and also the GPRC5D, both of them appears to be equally effective as the BCMA targeting by specifics are. So, I think we are going to have a lot of different options. I think the key would be figuring out where these different immunotherapies fit in, both in by itself and in combination with the treatments we currently use.

Priya Menon: Thank you, Dr. Kumar. That's very comprehensive, thanks a lot. With that Gary, please start the discussion.

Gary Peterson: Yes. Thank you very much and thank you for that excellent introduction Dr. Kumar. Now one thing I found over the last several months is that all new classes of drugs have been approved in the last 16 years have had dual designations. Meaning that it's an orphan drug designation by the FDA with another one like fast-track breakthroughs etc. They have been given a special preferred status by the FDA. We now have seven such dual designations for myeloma and four of them happen to be Car T. So, it's taken center stage with regard to myeloma treatment. Now, I was there at the presentation that you gave on CT053 and I thought that was pretty impressive and I figured that you must be very well versed on Car T. Now. First thing is can you explain to our audience a lot of which are newly diagnosed and not necessarily nearly as skilled as you are in understanding this disease. That you could put it in a patient friendly format, what is Car T? I know my first thought was that it was the first car made by Ford Motor Company, but that can't be true. So, because it has to do with blood so I figure maybe you could provide me with a little bit more information with regard to Car T.

Dr. Shaji Kumar: Absolutely. No, this a good analogy actually to think about, Model T is what brought the cars with the masses, right? And hopefully these Car T will actually get this treatment approach to all patients of myeloma at some point. So if we start from what exactly is a Car T, so gently when you think about T-cells, whenever they engage or whenever they encounter a tumour cell, the T cell receptors that are naturally

developed or I should say resized or reformed on those T cells are targeted towards the tumour antigens. Now obviously in the myeloma setting we are not getting that natural response against the tumour cells and that's why these T-cells are unable to get rid of the myeloma cells. So, what the Car T does is it basically takes the T Cell receptor and modifies it in such a fashion that it now can target a specific antigen or protein that is on the myeloma cell. Now the vast majority of the Car T cells that have been developed so far have been targeted to PCMA in the setting of myeloma, but other antigens like CD19 in the setting of lymphoma, for example. So, whatever antigen you think is unique to a particular tumour can be used as your target antigen and your T-cell receptor can be made to target/ attract that particular antigen. Now the next step is to get those modified receptors into the T-cells of the patient. So, what we end up doing is collecting the autologous T-cells or patients' own T-cells using apyrases. We collect the T-cells, we transport them using an anti-viral vector and what that virus does is it allows the gene or the genomic region that codes for these modified T Cell receptors and makes/ integrates that into the cell's DNA. So, it essentially becomes a part of these cell's genetic makeup and that is a permanent change that is brought into that T-cell. And once it is integrated into the T Cell genome then T-cells will start making that protein and the protein gets expressed on the T cells and now the T cells are targeted. Now, basically the only antigen it will recognize and get stimulated by would be the PCMA or whatever antigen we are targeting it against. And this is different because there are a variety of ways you can introduce genetic material into a different cell, a lot of them are transient. So, what we call the transient transfection, which does not allow the genetic material to get integrated with the cell's genome. Those ones tend to be transient; they are in the cell. They make a bunch of protein and then that genetic material gets completely wiped out. Here what we want is a permanent change in the T-Cell. So, that's why we use an anti-viral vector. Now the disadvantage of using an anti-viral vector is that theoretically there could be random insertions of this genetic material which can lead to some mutations, theoretically can cause other problems by modifying the genome in unintended fashion. As a result, that is why many of you have noticed that these clinical trials will have you sign you up for up to 15 years of being followed up because that is something the FDA wants to make sure there are no long-term impacts of that. Now we will talk about it later, but there are other technologies that can potentially go around this problem. Now, once we have these T-cells, the autologous T-cells transfected with the anti-viral vector, then they make sure they are all expressing the particular T Cell receptor and there are minimum threshold in terms of the percentage of cells that should have it and then that product is then re-infused into the patients. Now the problem is if we just really Infuse it there's a high probability that it can get destroyed by the or it just may not be able to do its job if there is a completely intact immune system that's already there. So, we use that lympho-depletion chemotherapy ahead of time to get rid of the lymphocytes or at least decrease a lymphocytes that are already there and then this autologous Cart T cells then goes in, it recognizes the tumour cells and it creates what is called as a immunological synapse, which is basically a connection or a tunnel between the T cells and the tumour cells. And then they basically inject a whole bunch of other kinds of chemicals which lead to cell death. And so, it's basically highly targeted, very specific for the tumour cell. It will not care about whatever other cells are around and just specifically kills the tumour cells. Now will it kill all the tumour cells. We don't think it does because of the fact that the majority of the patients still have relapses at some point in time. So obviously the ongoing work is trying to see how can we enhance the efficiency of that or how can we figure out why some tumour cells escape this. Now, the other part about the Car T cell I am sure all of you have heard about is the kind of cytotoxicity that we see with them and that is related to all the chemicals that are released as part of this tumor cell kill because the same chemicals that these T cells are secreting to kind of enhance the immune reaction on kill the myeloma cells also need to kind of a systemic reaction to those which result in the cytokine release syndrome that is often seen in these patients.

Gary Peterson: Thank you very much. The other thing I would like you to discuss is really and not so much about IDA cells and CedA cells or BB 2121 and J&J 4528. Those are going to be covered in depth by Cindy and Jack. So I don't want to steal in here. But you gave a presentation on CT 053 and you were also there when they also talked about PCMA 101 and they seem to have some special characteristics with regard, I think the speed of development of the Car T. They are a quite a bit faster maybe and also seem to have a longer overall survival and a few other things. So I was wondering, if you could talk about those things, but prior to that just tell us why there's so much enthusiasm around Car T to begin with given a cytokine release syndrome and all the hurdles that exist.

Dr. Shaji Kumar: Absolutely Gary. I think the reason why we are all enthusiastic about the Car T cell for two reasons one, it is proof of principle that you can use your own immune system to actually get rid of myeloma. And it's a paradigm change to me because we are worried that we won't be able to do that. Second, obviously the responses that we have seen right. So, we have seen patients who have seen 14 15 lines of therapy and they get to be a minimal residual disease negative, right. I mean we are all quite stunned by some of the images that have been shown of the Pet-Ct that is completely, vividly colourful and then months later has no evidence that there is myeloma and we have with us this particular Car T as well as others we have seen that after you induce the Car T cell, four weeks later, you don't see any myeloma cells in the bone marrow, you go from being packed to completely not there. So, I think those are the traumatic things that we haven't even seen with some of the treatments that we consider standard for today's treatment. So clearly, we cannot compare any of this with anything within the absence of randomized phase 3 trials, but individually based on what we would have expected this how these patients would have been expected to do were clearly seen that they are doing much better than what we have historically seen. So, there is no question these are all highly effective therapies. And I think the big question is who gets it, when do they get it. And what are the toxicities and how do we manage the toxicities and are there things that we need to be thinking about long-term particularly with respect to toxicities. So, with that in the kind of the background I just want, maybe I'll jump into the CT 053 part of it. Now, obviously as you have seen there's a whole host of different Car T cells that are being developed, there's obviously the concern that where are we going to fit all this in and just one work and then the others don't work after that. I mean to me the more the better because, it's just like what we talked about with the vaccines for the Covid, right. And with more vaccines, the better here also the same thing the more number of options you have, I think the better we are. So, with the CT 053, with each of these Car T cells there having minor tweaks, most of them have been done with the aims of one either make it more tightly binding to the antigen or it actually is able to stimulate T-cells efficacy is enhanced by changing the intracellular domains, or we create Car T cells which are less differentiated in terms of their immune navdy. So, that these are actually may be more flexible Car T cells so to speak and then finally can actually make these Car T cells faster than the two to three weeks that we have right now because many of these patients cannot afford to wait for weeks without treatment or without effective treatment. So, the CT 053 is again overall it's very similar, but it certainly seems that the manufacturing time appears to be shorter compared to what it wants some of those first generation, I should say the Model T Car T cells, right? So, now we are moving on to some of the improved versions of the same thing. So, with the CT 053, it's again ___ escalation study, we enrol patients on two different dose levels, 94 percent of the patients did respond to the treatment, some many of these patients were able to have MRD negative. Almost all the patients we saw had bone marrow plasma cells percentage coming down to less than 5% in almost all the patients by the end of four weeks. When you look at the M Spike or look at the sound free light chains dramatically decrease, pretty much normalizing all the defrost coupled cycles. So clearly, it's effective, it seems to be working fairly rapidly consistent with what we have seen with the other Car T cells. And in terms of toxicity, it seems to be fairly comparable. We didn't really see a lot of cytokine release syndrome, most of what we saw and again it is a small study. So, everything has to be taken carefully from that context, there are only like 20 patients, but the grade 3 or more CRS was not seen in any of these patients. There was only one patient who had a grade 3 neurological toxicity. So, all these cytokine releasing syndrome was seen in the first couple of days, lasted for an average of four days where a third of the patients were treated with those tocilizumab and all these cytokine release syndrome was very well controlled with the supportive care management that we have, which also I think highlights another aspect about Car T is that, we talked about why we are so excited, right. In the beginning, we were a little bit worried about these toxicities, but as we get more comfortable with them and we know we can detect them early, treat them early with drugs like tocilizumab. We don't feel as worried about this. So, clearly, we are more comfortable with toxicity and more impressed with their frequency. And that's why I think the Car Ts are continuing to move, kind of to the front of the pack so to speak. Now the responses and the follow-up are relatively short, and we have patients followed up until less than a year in this particular study. So, it's hard to know but there was another study that was presented by the group from China who has opted for two year for with the same product and they were able to show that many of these responses were pretty durable. They don't have the median PSF in their study again in a relatively small number of patients. It was about 18 months and the median duration of the response was about 22 months. Now, granted those patients were not as heavily pre-treated as the ones we put on this study, but it still tells us that you are able to get durable responses with this particular Car T

cell. So, I think it looks exciting this trial is moving ahead with the larger Phase 2 with their ability in the end and at some point, in time. Also, a phase 3 trial just like what is being done for Car T cells. Gary, I think you wanted me to talk about the PBC MA-1, but I'll just stop here to see if there are any questions before I move on to that one. Shall I jump onto that?

Gary Peterson: Yes, please.

Dr. Shaji Kumar: So, we had talked about before, right. So, using the anti-viral vector has some disadvantages and again potential disadvantages of genetic changes. So, what the PBCA May 101 is doing is a different approach. It is a transposon based approach, different technique to getting the T-Cells transfected with these T Cell receptors and they feel that they may be able to get a more earlier, more naive immune cells to be transfected potentially leading to long-lived immunity against the tumour. So, that is what is being there are a couple of exciting things about the BCMA product compared to the ones we have been talking about so far. In addition, they also have what they call a safety switch built into it. So, if the Car T does lead to too many side effects, there is a potential for us to be able to turn off those Car T cells inside, even after it is infused. So, there is an added layer of efficacy with the PBC MA product that is not available with the other Car T cells. Now, the data that was presented at ASH, it had a whole bunch of different approaches in terms of additional treatments given along with the Car T, like couple of the arms had lenalidomide one of them had rituximab and some of them had reinfusion of the Car T cells. So, they are looking at a whole bunch of different approaches, all of which are important questions for the field, but I think the only takeaway message right now is that it appears that the PBC MA is certainly effective. We did see some responses including deep responses at the higher dose levels and we did not really see a lot in terms of cytokine release syndrome or neurotoxicity suggesting that this is a safe product. But I think, hopefully we will get more data. These trials are crewing more patients.

Gary Peterson: Well, thank you so much. We will then go on to Jack. Jack's your questions, please.

Jack Aiello: Dr. Kumar, thanks so much for being available for this. It's always so much information that you're able to provide, it's pretty incredible. So, this year in 2021 will likely see the FDA approving a couple of the different Car T treatments that go by the names IDA cell and CedA cell and yet we also know there still be Clinical trials for different Car Ts. So, given if all of these are available to patients, how will you and how will the patient decide which Car T to shoot for?

Dr. Shaji Kumar: That's a very important question, Jack. I mean it's a good problem to have obviously and hopefully we'll be there by the end of the year. My preference would be that if you can get on a clinical trial that's always should be the default option partly because we are continuing to improve upon this car T cells, right? So, we are asking questions that can make them better. Can we figure out where to use them? So, I think that would be my default option if you cannot get on a clinical trial in which this is the case in many patients, because of very strict entry criteria for these clinical trials. Then I think we need to consider using one of these approved Car T cells. But it also depends on the comfort level of the other patients, if they don't feel comfortable getting on a trial where we don't fully understand how effective a particular agent is that is totally understandable. Finally, I think even with lymphoma it's taken years to really kind of cut through all the red tape associated with the reimbursement issues. So, I suspect it is not going to be any different for myeloma either even though we may have the products approved by the end of the year. It might be another year or two before we totally figure out all the funding agencies how they're going to reimburse for these products.

Jack Aiello: Great answer. You also mentioned earlier that most of the Car Ts and most of the by specifics that are in trial targeted BCMA antigen, as such if you're treated with one of these and then you possibly relapse would you still be comfortable considering another BCMA targeted treatment? Do you have to wait for a while? Would you go to one of those Car Ts or bites that targeted different antigen? How do you advise on that?

Dr. Shaji Kumar: Jack, that's going to be an important question coming up for the future as we have more

of these drugs available with BCMA. So, if you look at the BCMA target, right, there are three classes of drugs. There's the antibody, the ADC like the Belantamab, there are the Car T cells and there are others by specifics. Now there is little in terms of actual data to say that one works after the other but theoretically you could argue that something like an ADC which works through an entirely different mechanism. There's no reason why we can't use a T-cell based therapy after someone relapses on the Belantamab because even at the time of relapses from the Belantamab, the myeloma cells still express the BCMA antigen. But a more difficult question would be if we have kind of schlock the T cells already with one of these treatments, will the other one still be able to recapitulate some of these effects from the T cells. I don't know the answer to that, I think that needs to be studied. Theoretically, I think they should work because they're different approaches. But practically I think we really need to have the data. But it may not be a problem that we may have to continue to face for long, too long. We already saw two differences by specifics that were presented at ASH, the talquetamab and teclistamab. Both of which are targeted to known BCMA antigens and I anticipate that those choices are only going to continue to expand so we may not have to really deal with this question ever. Even though it seems like the most important question.

Jack Aiello: Good and then lastly although I can ask more. If a Car T patient continues to do well clinically, I know that they are still being measured for the amount of re-engineered Car T cells that are still being seen in that patient. If the amount of Car T cells decreases, is that necessarily a prognosticator that the patient will in fact relapse?

Dr. Shaji Kumar: No, not necessarily. I mean most of these Car T cells tend to disappear by six months at this point in time, at least disappear to the extent that we can detect them. I don't think it means patients don't have those T-cells around anymore, some were hiding. So, till now there has not been very good correlation in terms of defined time period between the becoming undetectable and the myeloma coming back. It's all over the spectrum, but we do know that people who don't mount that initial response, they are more likely to get a response in the first place and relapse soon.

Jack Aiello: Okay, good. Thanks so much, Dr. Kumar and I'll hand it over to Cindy.

Cynthia Chmielewski: Thank you. Thank you, Jack. And thank you Dr. Kumar. Yeah, I had tons of questions I could ask too but I'll stick to my three, maybe sneak in the fourth one, I don't know. But there was one that came to my mind when you were talking before and I'm wondering is there like a sweet spot as how many myeloma cells that you need to have in your bone marrow for a Car T Cell to be effective? Is there like too few T cells and I mean too few myeloma cells and the T cells will have anything to recognize and too many or too great of cytokine release syndrome?

Dr. Shaji Kumar: That is the million-dollar question considering it's about a million dollar for each of these therapies. You need enough of the tumour cells to mount an antigen response, right. So, I think as we start to move into the earlier lines of therapy, we don't know the answer to that question, if there is a minimum number of myeloma cells that need to be there. But in the setting of other diseases like lymphoma, there it appears that even with the lower tumour burden, they do develop an adequate response. I'm hoping and expecting that the data would be similar even for the myeloma setting. And it is going to be important because especially if you're going to move this in the upfront setting as a way to get rid of remaining disease after conventional therapy, we really want to find out if there's a threshold that right. And that is one thing in terms of the actual numbers and second is we also know that the myeloma cells can do become more and more heterogeneous as they go through relapses and having a wide spectrum of antigens, does that have something to do with a more robust immune response compared to a diagnosis where they tend to be more homogeneous. We don't know that either.

Cynthia Chmielewski: Okay, thank you about that. And I guess Car T Cell therapies hinged on T cells and I've been learning that there are many different types of T cells and that they're not all the same. Is there a subset that might be better to be used for Car T-cell therapy? And also, could you address I keep on hearing that some people may not be eligible because their T- cells are exhausted. So, how do you measure your viability and if T cells get exhausted should you harvest them and store them like you said stores

themselves? See I snuck a lot of questions in the water.

Dr. Shaji Kumar: Yeah, I know. So, with respect to the T cells, there is a minimum amount of T cells that you need to collect from the apyrases sessions, and there's clearly some individuals who may not be able to collect the adequate. There's a failure in terms of the manufacturing process because we just don't have good quality adequate numbers of T cells. There is no real measure that we can do before we do the apyrase system to see if that is going to work out or not. Typically, right now, it's a question of collecting, trying to make them and you fail at making those T- cells. Now, how can we get around that, right. So, I think a couple of things, one is obviously as you mentioned when patients get their transplant in the beginning, we collect some T cells and store them away. That's an exciting thought. Would it be the same thing for even smouldering myeloma patients, should we collect some T cells from those high risk smouldering myeloma and store them away for future? I don't have a right answer for that question because of the logistics and the cost involved with many of these things. The second is, I don't know if you're going to be talking about the allergenic T cells but that's another approach where we can take normal volunteer T cells and convert them or change and modify them to be used. And we saw data at ASH from the ALLO 715 which is the first allergenic Car T cell to be used for myeloma, and we did see responses and we did not see any graft-versus-host disease suggesting that it is also a potentially a safe and effective way to approach and might be the way to do that for some of these patients where we are unable to make their own autologous T-cells. Cindy, I think that maybe there was one more question buried in there which I forgot.

Cynthia Chmielewski: Yeah. I was just wondering if there's a specific type of T cell.

Dr. Shaji Kumar: Yeah. So, I think one of the approaches has been to use kind of the earliest stages of T cells, right. More than memory phenotype cells with the hope that those T cells will live longer and are able to provide an anti-tumour immunity over an extended period of time then what we're doing right now. So, there are studies looking at that, whether it be the PBC MA1 or there are other Car T cells also targeting that approach. So, I think it's again a theoretical possibility, we don't have the data yet to say that those approaches will lead to a more durable response.

Cynthia Chmielewski: Thank you. Yeah, my next question is, although Car T-cell therapy is amazing in myeloma population, it's not that we don't see the long-lasting results that we see in some of the other indications. Can you talk about maybe some of the trials that are underway, or studies are underway to see ways to improve the efficacy and sustainability of Car T-cell therapy?

Dr. Shaji Kumar: Absolutely, Cindy. If we talk about the data from the BB 2121, for example, we saw the median progression-free survival was just under a year, but the concern there has been that it's such a late stage the myeloma is so rapidly growing but we just don't have enough. Even when they get them down to very low levels,they still grow back up. So, different ways of getting around and making it more effective, right. One is to use it in the earliest setting, there are phase 3 trials that are looking at the time of early relapses randomizing patients the Car T versus the triplets like the ones we talked about earlier today. There are also other trials that are looking at high risk patients, even as part of their initial therapy. Either with the transplant or without a stem cell transplant and all those trials will give us a good sense of, can we improve the efficacy by doing it earlier. Then we are also trying to change the efficacy and durability by using these different approaches in terms of what type of T-cells we include in that population. I mean, there is some suggestion that early approach is better, more durable because there was data from the Chinese studies where the patients were not that extensively pre-treated where you have the progression free survival that is in excess of two years. So, it seems reasonable to assume that will be the case as we move in the earlier.

Cynthia Chmielewski: How about those targets? Is that something that may increase efficacy?

Dr. Shaji Kumar: Yes. So, there are two different approaches. So, obviously we can make Car T cells that could do one or more of the antigens against or else we can also use sequential T cells, Car T cells and that has been done with a couple of studies. One from China where they did BCMA as well as a CD 19 based Car T cells to see if that would increase the efficacy. And the hypothesis there is that maybe some of those

myeloma stem cells, so to speak or early myeloma cells might be CD19 positive and so by getting rid of the more mature tumour cells and the more immature Tumour cells we can get a more durable response. Whether that pans out, I guess we'll have to wait and see.

Cynthia Chmielewski: Alright. Thank you so much. Gary, I don't have any more at this point.

Gary Peterson: Yeah, I know your third one was actually a four-part question, Cindy. Anyways, Priya, do we have questions from the audience?

Priya Menon: Yeah. We have a couple of questions. Dr. Kumar, what next if the Car T-cell therapy does not work?

Dr. Shaji Kumar: Well, the good thing is we have so many other options right, for other treatments. So, let's say if the Car T cell either didn't work or worked and then stopped working, we can certainly look at other treatments. We have the more traditional types of treatments. There is always the by specifics that are coming along and one of the very interesting findings from the presentation from DB 21-21 at ASH was that even though the progression-free survival was under a year, the overall survival for that cohort of patients was about three years. Now, one could argue that this is because it was a highly selected group of patients because of the clinical trial eligibility, but it also brings up the question that can we reset the disease to some extent by making those myeloma cells down to that MRD negative stage before it grows back up or do they become more responsive to the treatments that they were not responding to before. I think that is an interesting concept. I think we just need a larger body of data to say that's true.

Priya Menon: Thank you, Dr. Kumar. Next question is will Car T-cell therapy replace stem cell transplant in the future?

Dr. Shaji Kumar: Well, I think it might. I don't see that happening in the next 4-5 years. This is because of the extent of the studies that needs to be done. But I think the proof of concept is going to be in the high-risk patient population where it's being studied, right. So, I think especially in those populations if we can show that the Car T cells actually are giving you more durable responses than what is currently achievable with the stem cell transplant. I think that sets the stage for definitely displacing the transplant from that point of care. Whether we will stop using transplant completely for myeloma ever. I don't think that happening in the next 10 years or so because until they have a cure for the disease, I don't think you're going to be throwing anything out the window.

Priya Menon: Thank you, Doctor. One more question, can you speak specifically to relapsed and refractory myeloma patients who have undergone many lines of treatment and how Car T will or won't be an option for them?

Dr. Shaji Kumar: So, I think for the people who have had multiple lines of therapy. I think those are the ones who would definitely have access to the Car T when it gets approved because again, we don't know what the final nable would look like, but I suspect it's going to be for patients who have exhausted the currently approved treatments. So yeah, I think for those patients Car T would be the appropriate approach or any other immune therapies.

Priya Menon: Thank you, Dr. Kumar. I think we've been discussing in detail about Car T-cell therapy in myeloma. Thank you so much for all the information shared. Gary, Jack and Cindy, thanks for joining us today. This talk and transcript will be available on curetalks.com. So, stay tuned for more talks on curetalks.com. Everyone have a nice day and stay safe.

Thank you.