UltraCAR-T Therapy - Scope & Possibilities in Multiple Myeloma Management

Ongoing clinical trials are investigating the safety and efficacy of a new type of CAR T (Chimeric antigen receptor T-cells) therapy called UltraCAR-T therapy for myeloid malignancies. Unlike current CAR T cells, which utilize viruses to attach the CAR to the T cells, UltraCAR-T uses a non-viral gene delivery system and has a rapid turnaround compared to traditional CAR-T cells manufacturing process. We are talking to Dr. David Sallman, a hematologist in the Malignant Hematology Program at Moffitt Cancer Center to learn more about the new type of CAR-T cells, their action, side effects and scope of their use in treating multiple myeloma.

Full Transcript:

Priya Menon: Hello everyone and welcome to Cure talks. I'm Priya Menon and today we're discussing UltraCAR-T-cell therapy and explore the scope and possibilities of using this therapy in management of multiple myeloma. Joining me on Cure talks today is myeloma panel of Gary Peterson, Jack Aiello and Yelak Biru. The featured expert we have with us is Dr. David Sallman from the Department of Malignant Haematology Moffitt Cancer. Dr. Sallman's research interests focus on the development of novel targeted therapeutic strategies for patients with myelodysplastic syndromes and acute myeloid leukemia. Welcome to Cure Talks Dr. Sallman, thank you for taking this time to join us today.

Dr. David Sallman: Sure. Thank you for the introduction.

Priya Menon: We have a lot of questions registered. In fact, a lot of audience questions too, and I'm going to just jump, right in. Dr. Sallman, we spoke to Dr. Carl June on this platform, back in 2017 and there has been a lot of research on CART-T therapy and the use in cancer since then. Can you just start with what is UltraCAR-T-cell therapy and how is it different from the traditional CAR-T-cell therapy?

Dr. David Sallman: Yes, may be just to take a quick step back, just to set the basis for what we're trying to treat. So, for b-cell lymphomas, multiple myeloma, of course, CAR-T has really been a paradigm shifting therapy for patients that have relapse refractory disease. I think similarly and I think even at higher concern for patients that have acute myeloid leukaemia is we have very limited treatment options once they sort of fail standard therapy. For elderly AML as an example, where hypomethylating agent with ___ is the standard, you still have a median survival of 14 months and essentially all patients, ultimately relapse. And if you don't have a targetable mutation which is really only about 30%, may have a terminal mutation then there's actually no approved standard therapy or even therapy, that's near approval in that setting. So, we're really hoping that we can have sort of a novel CAR-T approach to give our patients, hope both in the elderly setting, which I just mentioned, but still many younger patients, ultimately fail standard of care therapies and the challenges when we're saying how poor some of these patients do, we're talking a median overall survival of less than six months across the board. When we have a relapsed/refractory, AML patient that has sort of failed standard of care treatment. And so, one of the challenges with traditional CAR-T therapy can be the processing time. So, three-to-four-week, sort of time period, where your patients are ready, have a survival, very short-lived, it have lots of issues related to their cytopenias, such as infectious complications with others, trying to have an approach that can sort of give the therapy at right time is important. So, what UltraCAR-T is, it actually allows for autologous therapy. So, we're still using patient cells, but we can basically go from taking this cell out or apheresis and infusion into patient within two days. So, it is a sort of rapid as you could hope for from that perspective. We presented sort of our trial and progress data at Ash. But what's nice is we've not had any manufacturing failure issues and we're continuing to go on to dose escalation. So, I think the ability to rapidly dose patients with this platform as here and again, this is allowing

us to use an autologous platform. I know I'm a little bit long-winded and I'll take a break in a second, but I think the other main approach to sort of rapid dosing of patients is sort of a using somebody else's cells or an allergenic or off-the-shelf approach. The challenges that could be there is that patients may reject these cells quite rapidly and so there may be issues with persistence and expansion which ultimately correlates with efficacy at least in the b-cell both at ALLO and b-cell Lymphoma. And so potentially having a rapid but autologous product may be able to give you both the quick turnaround time, but ideally potentially better issues from its expansion and persistent perspective.

Priya Menon: Thank you Dr. Sallman. I think I'm going to let Gary start and lead this panel discussion now. Gary, all yours.

Gary Peterson: Okay, well thank you Priya and Dr. Sallman thank you so much for giving us your time on this. We're all very much interested in CAR-T. It's pretty much taken second or center stage for all treatments in benign __ in which Dr. June championed as well as now going to BCMA and being used in the myeloma setting and for you AML, which really doesn't have many treatment options available in the past, all new drugs that we had in AML and in myeloma and other blood Cancers as well have had overall survival and progression-free survival that were in months and not in weeks. And as a result, there wasn't any breakthroughs at all, but in CART-T therapy those have gone progression-free survival and overall survival have gone all the way too many months and now years or both. And as a result, it's very exciting and given what, Carl June said during that program, that Priya had just mentioned, she had mentioned that during that time that CAR-T he thought was going to be cure. And that it was just a matter of finding the right target or the right combination of targets. And that cure was where he thought the whole thing was going to be. So right now, that's great information, that's nice to know but even with those great successes there include a lot of challenges like costs, we're talking a half a million dollars insurance coverage. Insurance seems the block at every time we patients want to try to get something big, you put a five hundred-thousand-dollar price tag on it, that's even worse and also things like you said three to six weeks to manufacture and has side effects like cytokine release syndrome. Now you're tackling AML and like you said there were very few treatments for refractory and relapsed AML and as a matter of fact of life expectancy is just a few months, when you get to that point for AML. So, I applaud you and all that you do to take on such a very difficult subject. And I think you were, frankly, quite amazing and thank you for that. Probably the most important question I have for you and that is does UltraCAR-T work and does this treatment have efficacy and finally is it durable and how are your results today?

Dr. David Sallman: Yeah. So, great questions. I wish I had excellent answers to all of them. I think everybody looks to the b-cell, the CD19 and BCMA and positive diseases, those are really optimal targets. I think the challenge in AML is we already know there will never be a perfect single antigen optimal target. Meaning there's not one marker that's expressed on all Leukaemia stem cells, or ___ blast that we can target. If we had that we would already be as far along as where they're at and CD19 positive disease. We have a good sense of markers that are worthwhile to target, the two kind of leading candidates of targeting right now have been CD33, and CD123. The pros are they are expressed on a high percentage of __ blast with maybe a little bit more heterogeneous expression on cubic stem cells, but they are not uniformly expressed. One negative of targeting them is they do have some expression of normal stem cells, and that's really right now in concepts that are targeting 33 or 123 really, these patients are required to have a backup allogenic stem cell transplant donor because at least in mice modeling, a lot of this work was done ___ group and a couple of other labs just showed a similarly that you could induce a ___ or sort of the lack of ability to produce blood again. So, that somewhat limits our current clinical trial patient whether or not that happens in patients is a little bit unknown. So, I think there's kind of several lines of research going on that are important. One is what is the actual activity when you target CD33 or, or CD123, the answer is, as of today we don't know. I do think over the next 12 months or so, so maybe by ASH of next year, ideally with our trial and with several other trials, both targeting 33 and 123 will have the answer once we've gotten through our dose escalation, what is the activity or not, we're targeting one of these antigens. I think let's say we don't have activity the ultimate issue maybe you need to target more than one antigen. So, for example in China there is a compound targeting CD33 and CL-1. And they actually had quite a bit of activity in the limited cohort they had seven of nine patients presented at AHA last year that had sort of MRD negative complete

remission, and it appeared that those responses were durable. Small number that trial is gone slowly but again, that's targeting two antigens. So, what is the benefit of targeting one. Again, where we're early in our dose escalation our hope would be by ideally, I would say over this next year we finish it. So, we got to get to the cell dose. We've not had manufacturing issues; we've not had safety issues in early dose levels but again the major question of what the activity is of these we don't really know. And again, there are major safety issues that are unique in AML that are not present in patients that have multiple myeloma or a lot of the b-cell malignancies. I think, once you've known the targets that are key, so 33 is great and that's easy, we can rapidly go for the current clinical trial and work to try to get an approval of a therapy. If 33 is not enough and you have to target 33 and another marker, then I think what's important is your platforms that you're utilizing able to be rapidly adapted. So, one nice thing with this sort of UltraCAR-T program, it's a non-viral vector-based system. So, it uses a plasmid with the sleeping beauty system. It is rapidly changeable. So, if we needed to target more than one marker, I think we would like to be able to easily do that. The challenge is, once you do that, you have to kind of restart from scratch your dose escalation, your safety, but at least you're utilizing relatively the same technology that from that perspective, should not create differences. So, the problem is as of right now, there are so many unanswered questions that I can't give a single answer to your question, but my hope is that yes, these therapies and potentially with the UltraCAR-T platform will be sort of a novel cellular therapy option for patients, in the future. But again, many of these questions are still unanswered.

Gary Peterson: So, if it was available, would you be able to include CS-1 along with the 33 or 120?

Dr. David Sallman: Yeah, I think the sky is the limit. So, I mean, what's nice is if you target more than one antigen, you can create it, two different ways. So one is, you can try to create it from a safety perspective, meaning that the T-Cell will only kill if it sees both markers. So, you can say, hey, I'm going to require it to be CD-33 and CLL-1, that may be very specific just to the leukaemia cell and spare really any normal cells. And some of this work has been published over recent years where people have done large flow cytometry panels looking at different combinations. So, from a safety perspective, that's great. The challenge is what happens if you have some of your cancer cells, that only express one marker or don't express either marker. And so, this sort of concept of antigen escapes maybe a major issue. From my perspective, I'm really more on the boat of trying to do anything to increase efficacy. Right now, we just need options for our patients, and we have come a long way with managing the side effect profile. So, to me maybe you create the CARs to where it activates, if it sees either marker. Again, that may be a little bit more toxic because it can potentially hit cells that are not the cancer cells. But again, our major issue, I think right now is efficacy. We know, even with CD19 CAR, for example, is these cancer cells, can sometimes lose their CD19 expression. And that's one reason why these patients are progressing later on, in their time course. In AML, we have no idea because we're still learning what is our safety and activity of targeting it. But yes, I think both of these main concepts again, targeting two antigens for more of a safety perspective or targeting two antigens to increase the chance of getting activity and potentially not allowing these cells to escape. I think both of these are really important concepts but sometimes we're getting a little bit ahead of ourselves because again what is the activity which is targeting one.

Gary Peterson: Well, patients' kind of like you guys looking ahead of yourselves.

Dr. David Sallman: I mean there's a couple systems right now. And again, some of this work is at ___and Dr. Mukherjee as well there's a couple companies or biopharma and then ___ been doing this work at UPenn where you actually remove CD33 expression off the normal stem cells. So, the concept would be is you kind of go forward with like it a Allo transplant. You take normal donors stem cells, and you knock out CD33. And then you give the CD33 CAR and so it can't hurt the normal cells and it can only kill the cancer cells. I think it's an interesting approach. Again, whether or not 33 is the answer complicates this, because you may go through a lot of this without having to answer and that sort of platform is not easily changeable because if you needed to knockout multiple markers and that's probably not going to be safe or you're not going to have the ability to do that, but there are other concepts looking to try to improve safety. Again, what I do like about the UltraCAR-T approach, one is the rapid manufacturing, two is it incorporates this membrane-bound IL-15, which really allows these cells, it kind of gives their own food support inside the

patient. And so instead of having again, to grow a higher cell number, , outside of the patient, these cells will actually proliferate in the patient and probably safer from that perspective as well. And then of course, three, which we sort of mentioned already, is sort of the ability to adapt it if we ultimately need to target more than one antigen. But if we had could have a 30% remission rate in this group that would be an extreme home run. I don't think we necessarily have to shoot for the 70% response rates that have been seen in the sort of CD19 and BCMA world. I think we really just ideally start with something, now, the higher, the better and I think to your question, the beginning, the durability matters because patients are going through a lot. A lot of times they still require several weeks remission with all CAR-Ts, you typically have to be close to the center of month afterwards. So, we really want these responses to last for. What's nice also, with this technology is that it does bring up the ability to repeat dose much easier. And so, let's say we had a response but then it lasted only six months, or 12 months or something could be than just re-dose at the right time. And then, I think one of the biggest concepts, and this is really where things are moving in the CD19 world is you're treating patients at the right time. So, you don't necessarily want 90%, blast, when you're giving a cellular therapy. I think one of the most intriguing data were from Dr. Parks New England, Journal of Medicine in B-cell Allo, and really the durable outcomes for patients that had less than 5% lymphoblast. And so, treating the patient at the so-called MRD level, maybe really where these therapies are best utilized and what's nice is those technologies are already commercially available. So, we can sometimes to detect down to one in a million cells that they're still leukaemia, maybe that's the time to give a CAR-T, it will definitely be safer and can we eradicate that MRD with the goal of ideally for cure of our patient. I think that is the long hope again we're in our infancy period though right now.

Gary Peterson: You said, it's a kind of a follow-up on something you said earlier that, if you target, two different antigens that it has to have both of them before it will engage, is that what you said?

Dr. David Sallman: That is one of the two approaches. So, that is done more from a safety perspective because if you require dual, it will really only be expressed on the leukaemia cell, it's extremely unlikely to be expressed on normal cells. The challenge would be so that the tumour could potentially escape if it was negative for one or both of them.

Gary Peterson: And how about sequencing?

Dr. David Sallman: Yeah. I think that's a good question. I mean, the challenge is right to get the answer of any single antigen and whether or not it works or not takes us several years to answer that question often. And so, we want to ideally come up with new options for patients sooner. So yeah, sequencing is and like for example they're doing that CD19, followed by CD22 or you try to do them both. These things are being done in b-cell malignancies where there are more options, that's a great question, is it better to target them all at one time or sequence them. But I think the challenge is by the time you get each individual answer, like the field is going to be moving too rapidly. So, I think that is likely not a challenge unless we had multiple approved therapies and then that question will come back. Okay, could we sequence these. I think it's the same issue. I think until there's another, not CD19 but another approved CAR-T targeting a different antigen, the question of sequencing versus doing it at the same time would still be an open question.

Gary Peterson: Okay. Well thank you so much. What you've done is you've kind of wiped out most of my questions, but I appreciate that, and I guess all those issues that I mentioned before that come on the UltraCAR-T system states that it's a low-cost, next day infusion, Hospital based system which can be reapplied with the same or different antigens as target. This just sounds too good to be true. So, you think this is fact or is this science fiction?

Dr. David Sallman: I think everything that you stated could be fact, I think there are so many unanswered questions to truly make, its fact, but everything that you stated is possible, these are still highly complex therapies. And I think, yes, they all can be decentralized meaning that each Center of Excellence could potentially be utilizing this. But I don't think this will ever sort of roll out to the community. So, I think the answer is potentially yes, but it's probably going to be very specific based on each Centre of Excellence and not something that you can just do anywhere just given the complexity of managing a very, very sick group of

patients. But I think it's giving us a lot of different hopeful next steps for ideally coming up with a new therapy for our patients.

Gary Peterson: Well, thank you. At this point, then I'd like to go on to the questions from Jack Aiello and Jack has been living with myeloma for like 25 years. He's an anomaly, we do know him understand that he really is an anomaly. So, Jack?

Jack Aiello: Yes, thanks for that introduction, Gary. Dr. Sallman, it is really interesting to me and I did, as you're aware ask some myeloma related questions, but can we kind of turn them into questions that still kind of benefit myeloma patients. The most interesting thing to me is the speed of the manufacturing process. Is there any reason that the same process couldn't be used to target BCMA instead of CD33 or 123?

Dr. David Sallman: Yeah. I don't see any reason why that could not be done. And so yeah, could you use the same platform to incorporate BCMA from a technological perspective. I don't see any challenge with doing that.

Jack Aiello: So, __ cell, for example, was just approved for myeloma and requires an infusion of 450 million cells. Does your process generate the number of cells required within the two days or you depend on cell expansion in the patient to occur to get up to that required minimum dose if you will?

Dr. David Sallman: Yeah, it's a good question. So, we have dosed now in sort of the one times ten to the six although we do have a potential dose plan up to 1 times 10 of the 8. So, we think actually, most likely we could make the number of cells required without requiring the actual proliferation in the patient. But you have to investigate that in each patient population and how is relapse/refractory, what's your baseline lymphocyte count. But potentially, we could easily dose that number of cells with just in that rapid turnaround process but there would be some things to answer that question definitively in the setting of treating myeloma patients.

Jack Aiello: You mentioned that your patients required to have an Allo donor available in case things don't go well. For myeloma Allos aren't down very much because myeloma patients have very poor outcomes just getting through the transplant. So, does that mean there's a difference in terms of your procedure?

Dr. David Sallman: Yeah, so that would have been a risk. So, for example, if we did UltraCAR-T targeting BCMA, there would be no need for requiring a backup donor. The only reason we require is because the markers we are targeting an AML, unfortunately are expressed on normal amount of poetic stem cells. So BCMA is not and that's what's been, it's nothing to take away but in B cells when your Plasma cells are still B-cells. It's a biological difference that they're able to exploit. Unfortunately, in myeloid leukaemia, there is no perfect marker that's really expressed, only on the cancer cell and what's nice even if you target 19 or BCMA and you wipe out B cells people from an immune system perspective, have still appeared to do very well without severe complications from that. So, it's really a target difference, which is why that's required. But if we were targeting BCMA, there would be no reason to require a backup donor.

Jack Aiello: Got it. I got to say, I mean I think your platform is awfully important, create some breakthrough for myeloma. They're trying to come up with a Allo CAR-T off the shelf. That as you mentioned, there can be risks associated with that. And if we can get down the minimize the time of a couple days to generate CAR-T cells and re-infuse them, that just sounds like a bandwagon that all the designers should jump up on.

Dr. David Sallman: Yeah, I think there is a lot of off-the-shelf approaches but again if they're ultimately not having the level of efficacy similar to the Autologous products are made from the patients and this may be a way to both do the rapid in a manufacturing parts, but still allowing the Autologous and inability to not get rejected right away. What's being required in the off-the-shelf Allo products is typically more intensive lymphodepletion, so for example, several technologies use Elotuzumab because the product has been modified to not have CD52 but that may increase risk of infections and complications just from the lymphodepletion. So, that's not something that would be required with an Autologous platform. Just sort of the standard through their being cyclophosphamide that all patients are getting.

Jack Aiello: Thanks very much. I look forward to following the progress of UltraCAR-T and I'll turn it over to you Yelak.

Yelak Biru: All right, good morning. I want to go back to Gary's and Priya's CAR-T one on one question and ask why does it take such a long time for practitioners to _____ traditional CAR-Ts to be engineered and infused back to the patient?

Dr. David Sallman: Yes, I think, typically with the viral vector-based systems, once you have the transfection, you have to sort of grow the cells up to get to the level that's going to be efficacious and so that takes a significant amount of time again in that three-to-four-week period with this sort of transfection system using what's called an ultra operator, if that's not required.

Gary Peterson: Dr. Sallman, you're saying the persistence of CAR-T as has been seen by Dr. Nora that's DISISDS ovarian cancer also using the UltraCAR-T therapy and that's at Seattle Cancer Alliance. Are you saying the same Persistence of CAR-T?

Dr. David Sallman: Yes. And the only data we have is this patient we presented at ASH atleast at the six-month timeframe, we were still able to detect the PRG and copy so we could say at least six months we don't have follow-up longer and then I think that was a patient that was actually without lympho-leukemic chemo therapy which to us was actually quite surprising to have some level of persistence out that far and probably more related to the membrane bound IL-15. So again, that's an N of 1, which we don't should never make any conclusion or definitive answer. But the answer is we have at least seen persistence in a patient at a relatively low dose level without ___. So, potentially with future dose levels, especially when we get to like let's say our expansion dose level will be and likely ____ should increase the ability for persistence in expansion, then we'll have that answer. But already the answer is at least yes in N of 1.

Gary Peterson: Recent administration, those patients in cohort-1 of your study which have been given lower doses, so they can check safety and tolerability have they been re-dosed with the same dose or maybe increased dose?

Dr. David Sallman: Yeah, so far, no patient has been re-dosed. The technology definitely gives the ability to do that. It really comes down to sort of a safety and sort of in discussion with FDA and so the trials have to be written, very specifically, each patient followed extremely closely to ensure that we're learning what we need to learn. And so, in general, patients are not allowed re-dosing. I think how I see it as once we get to the dose that we think is both safe and ideally effective and let's say, a patient has a response, potentially you can go back to the FDA on a single patient case and say hey I'd like to re-dose this patient that has been done with other cellular therapies or perhaps once we know our dose we may be able to build in criteria and so if the patient has no toxicity, has no evidence of persistent cells could be then re-dose on a case-by-case basis that has been done with some other therapies including CAR-T trials that I've been involved with. But immediate answers right now we're too early to be able to do that but I think realistically once we get to an expansion dose, I think there will be possibilities and from a technological perspective, easy enough to do.

Gary Peterson: I think you might have touched on a little bit, these AML patients have very short time, like three months to live. One of the patients, whose dose was enrolled directly from hospice meaning, they were touring a lot of chance to spend much time alive and was given days and weeks to live, that was reported that seven months later, is the patient still alive, are all patients enrolled at cohort still alive and how many re-dosed?

Dr. David Sallman: Yeah, a lot of that you have just given that the trial is still in dose escalation. I can't speak specifically of, but I do think, we were excited just by that one case because as you pointed out typically a patient with relapse AML, especially, let's say a patient that's enrolled on hospice has a very, very limited amounts of time, and even though that patient did not have an objective response, the patient did have last clearance and had a quality of life during that amount of time. But I do think, looking at quality

of life, looking at the durability of these responses over time is really important and even above just objective responses is can there be some clinical benefit cleaned from these cases.

Gary Peterson: Well, that's kind of Lazarus Syndrome.

Dr. David Sallman: Yeah, I hope so.

Yelak Biru: I don't know if this question was already asked but, if it is not, are there any concerns with quality of distribution at manufacturing? Now that this is going to be either at the hospital or nearby facility done a centralized place. Can you address that?

Dr. David Sallman: Yeah, so I think it's a really good question whoever asked that because obviously with this is sort of a unique system. Everything has typically been centralized to single manufacturing source so I think those questions will have to be answered. I would say what's likely going to happen is there's relatively limited number of true centres of excellence for cellular therapy and likely these types of therapies will be done there. But I don't see any reason because all this would go to the sort of extreme quality runs before patients are dosed that it should be similar. But I think there will have to be before the therapy was approved, you're very definitive proof that there are not any technological differences among centres, but I don't really see why there would be. Again, I don't see this personally, it's not that we have a thousand centres that are then giving UltraCAR-T. But, again, the centres of excellence across the U.S. and the world again there's no reason why they couldn't again develop this technology in house ensure with tech run that everything meets all the batch specifics and then we can prove that there's some level of uniformity from there.

Yelak Biru: What are the side effects of CAR-T in the traditional CAR-Ts in the cytokine release syndrome. Are they overall normal CAR-Ts?

Dr. David Sallman: Yeah. So far, our therapy has been well tolerated. We have seen cytokine release syndrome but, at least in our early dose levels have not had any dose limiting toxicities or severe or refractory cytokine release syndrome. I think we've benefit in a setting that we've learned so much from all of the investigators who are taking care of the b-cell, lymphomas and leukaemias' in myeloma. So, we now give dose in much lower thresholds than we used to, steroids when we need to. We've not really appeared, and I would say really in my myeloid experience neurotoxicity has appeared to be significantly less. So, is there something unique or different or maybe we're just not far enough along in our dose escalation but we clearly have seen cytokine release syndrome in CAR-T therapies but, to my knowledge, even with other therapies, the neurotoxicity appeared to be close to zero or much less. Is that something different in the target, or it's different in the dose levels, I think we will see. But I think we know a lot more on how to manage CRS in general. We have algorithms at each expert center, when a patient needs grade 1 for X hours or grade two you kind of do this or that, and we still need to learn and keep an open mind that with AML-CAR that maybe we have to have a somewhat unique approach, but I think we've learned so much that we're better capable of managing those toxicities.

Yelak Biru: Okay. In CAR-T in general, I think there is a requirement for CD40 depletion. Why is that? And I think I heard you mention that in the UltraCAR-T you use Cytoxan for that and is that a requirement in the UltraCAR-Ts as well?

Dr. David Sallman: The standard sort of lympho-depletion is some combination of the drugs, Fludarabine and cyclophosphamide ranging from anywhere between two days and four days and those things both across approved and not approved. The reason why you need it is that each patient has their own T cells, and their T cells unfortunately can reject these T cells even though they are Autologous. And so, you're depleting their host T cells to allow these cells to best expand and persist. So, every approved CAR-T therapy has some level of lympho-depletion with the combination of Fludarabine and cyclophosphamide. Again, what total number of days and total dose, I think people are still seeing that there's a difference, it appears there doesn't really appear to be a difference, it's just important that you give it. In mildly CAR, we

have tried to not give it, so for example, even in our current trial we have two cohorts, one gets no lympho-depletion and they're basically one dose level above the cohort that get lympho-depletion. The thought is that maybe with membrane-bound IL-15, could this overcome the need of the lympho-depletion, I've no idea if that is true or not true. And my kind of gut tells me that probably lympho-depletion will be ultimately required. But we are actually testing with and without, I think a lot of this speaks to efficacy. Again, we've not had any approved therapy without lympho-depletion. So, just common sense being likely, it will be required.

Yelak Biru: Well, and I think my mind is prepared question is around CAR manufacturers in the CAR-T or myeloma for example, there are many CAR-T manufacturers, what is product portfolio for UltraCAR-Ts? I know that one company Precigen that is being used now but are there others?

Dr. David Sallman: Yeah, I don't know of another company that has a like the same type of platform sort of this rapid autologous turn around. Again, there are lots of off-the-shelf Allo companies involved in this space. We talked about some of those issues. There are also other approaches. So, for example, like NK therapies there was just a recent presentation by FATE where they have sort of like the most potent NK cell you can have, and they did report responses early on in their dose escalation phase of their trial and heavily relapsed refractory patients. So, I don't know if there's a similar platform but there are other cellular therapies, not even just traditional CAR-T. There are TCRs, there are NK therapies, there are Gamma Delta T cells, all of this is early on. And again, the bar is low, I think we were looking at we can have a 20-30 percent complete remission rate that lasts for six months and everybody is extremely excited. Obviously our goal will be to improve that, and our goal is to Dr. June's point to ideally cure these patients. But really, we're just very early on. But from the rapid autologous turnaround platform, I think this one is currently quite unique. Again, with all the challenges for AML directed CAR that we've kind of mentioned earlier.

Yelak Biru: Gary, if you want to go back to the audience's questions.

Gary Peterson: Okay, thank you. Thanks for coming back there, Yelak. We appreciate that.

Yelak Biru: I wouldn't miss your talk, Gary.

Gary Peterson: You take care. AML patients enrolled might see their AML cancer reduced or even cured but they might develop other cancers. JPMorgan Helen, I guess she is the CEO of Precigen. Helen Sabzevari mentioned that Precigen will be in 2022 launching a library approach, which I would like you to discuss at all. Whereby, the Ultra___ can produce multiple CAR-Ts targeting different cancers on a mix, pick-mix and re-dose basis as needed. The AML patient enrolled in cohort 1 might not make it to 2022. Is this library approach going to be used earlier on a compassionate use basis for these enrolled patients who would otherwise die?

Dr. David Sallman: I think I very clearly know unfortunately to that question. I think there are kinds of logistics in coming up with these therapies for our patients and of course and I think rightfully so we have to prove safety. I think this kind of speaks to the future, because I think three to five years from now and I know that's 2022 but realistically longer than that. At some point we're going to know what the truly best antigens are to target and again with this library type of approach can we target A and B and that's the best one for all or does this have to be very personalized. So again, one of our issues is there is no perfect marker in AML. And so potentially each patient needs their own CAR-T approach and with a viral vector based that would likely be an impossibility. But if you could create it to where we've proven safety with CARs A B C D, E and F maybe you have a three or four, I mean, that would still be a huge number. And then you have your patient enrolled and you choose the CAR based on their screening flow cytometry of their bone marrow blast. So, you get their bone marrow, and you say, hey this one has the highest expression of marker A and D, I'm going to choose that or marker whatever. So, I think that adaptability and personalization, which may ultimately truly be required for an AML patient, has the ability here. Of course, we'd love to say, hey BCMA for all or CD19 for all, that's not realistic. Again, we may have to take a step back and say, hey, we're going for our thirty percent response rate, but if we really want to individualize it, having a library approach would be amazing. I think that the red tape and the logistics and the challenges is you have to prove safety of all of

these different approaches or if you're going to sequence them or combine them. But at least with this, it would one allow you to adapt it if you are, hey, marker A and D are the best find, we can do that immediately. But if we really have to personalize it, we could do that in the setting of a trial, it would be a first in every trial, but there is that potential. Again, I think some of this is hope, but I do think there is that opportunity there.

Gary Peterson: So, there be like a BCMA, CD19, CD38 like you pick?

Dr. David Sallman: Yeah, it could be like you pick an option. I think the challenges in the field is once you have an effective therapy, everybody wants to somehow duplicate it, but I think thinking about it and moving to the next step. Again, when you understand well, why do patients with BCMA carve progress. Are they BCMA negative or what is their resistance factors and could you then give some other CAR-T targeting something else or can you rescue the CAR-T cells that are there? I think there's a lot of unanswered questions and I think what's nice is we do have the technologies to answer a lot of these questions in the setting of the current clinical trial to get in AML we just lack a lot of anything from a data perspective, but that is the hope that you can real-world personalize this therapy to a much greater perspective.

Gary Peterson: Great. Now, are you saying evidence is CAR persistence initial cohorts which were given a low dose contributing to some level of efficacy?

Dr. David Sallman: Yeah, I mean as far as public data just have the one patient, the answer is ___ blasts continue to go down over time with persistence at least at six months. But I would look forward to our future presentations, I think those are key questions. What is the safety, what is the activity from a PK translational perspective? How durable are these cells over time, I think are really critical questions that I hope to be able to present these data and not just in future.

Gary Peterson: Okay, you own a Tesla? Don't you?

Dr. David Sallman: I wish. I looked at them before.

Gary Peterson: Because I got to tell you, you're an early adopter. If you lived in the 50s, you'd be saying sure they're going to put a man on the moon.

Dr. David Sallman: Yeah, in an AML clinical trial research we have to be very optimistic. It doesn't take a lot of patience to do well with any of these therapies, for us, for the fields to get extremely important. Again, when you have three, six, nine patients, you want to be careful how can pick where these patients, how durable are their responses etc. But I think in the future again, when you start to see cohort to 20, 30 patients, with reproducible responses with any of these therapies and that's what I would really be getting excited because that's just never been shown to date in the relapsed/refractory group, and that's really at minimum. Now, if you see something better, then that's even more of a home run. But I think you have to be optimistic in this field.

Gary Peterson: I love people like you who look at the most difficult problems that can exist in the field that they're in and choose to go head-on.

Dr. David Sallman: Thank you.

Gary Peterson: Thank you so much. Priya, do we have any other questions from the audience?

Priya Menon: No, nothing related to the subject that we're discussing. I think we can wrap up for today. Dr. Sallman, thank you so much. That was a great session and a lot of information was shared. Gary, Jack and Yelak, thanks for joining. Your questions were absolutely great and please visit curetalks.com for details of our upcoming shows. And this show will be uploaded right away onto the website.

Gary Peterson: As always thank you again Priya for putting this together and Yelak and Jack for being such great participants.