Beating Leukemia with Groundbreaking CAR-T Cell Therapy

Dr. Stephan A. Grupp made history when he treated the first child with CAR T cell therapy, Emily Whitehead, who is now more than five years cancer-free. In CAR-T cell therapy, a patient's own genetically altered immune cells fight cancer.

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We learnt about the CAR-T cell research journey and FDA approval in our discussion with Dr. Carl June of University of Pennsylvania in the first episode of our CAR-T talk series.

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In this episode, we are talking to Dr. Stephan A. Grupp who carried out the early pediatric trials and the global Novartis trial at CHOP leading to the FDA approval.

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The discussion would focus on required preparations, recovery phase and where this treatment can be availed.

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We will also be joined by Tom Whitehead, father of Emily Whitehead who will share his experience with the trial and progress of Emily post CAR-T cell therapy.

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Full Transcript:

Priya Menon: Good afternoon and welcome to Cure Talks. I'm Priya Menon, your host and today we are discussing how leukemia was beaten with groundbreaking CAR – T cell therapy, and our guest today is none other than Dr Stephan A Grupp , CAR – T cell expert and director of Cancer Immunotherapy and Cell Therapy Transplant section at Children's Hospital of Philadelphia and University of Pennsylvania. We also have Tom Whitehead, father of Emily Whitehead, the first pediatric patient who was administered CAR – T cell therapy, with us on Cure Talks. On the panel are Gary Peterson and Jack Aiello, cancer advocate and Myeloma survivors. So a very warm welcome to all. We will be addressing questions from the audience towards the end of the discussion. You can send in your questions to Priya@trialx.com or you can also post your questions in the comments section. So beginning with the discussion, Dr. Grupp, it's such a pleasure to have you here on Cure Talks and you have saved Emily and the children who are enrolled in the CAR – T

trial and I believe Emily's almost six years in remission. Dr Grupp do you think we are at the edge of a breakthrough in cancer treatment and probable cure?

Dr Stephan A Grupp: Well, thanks for having me on and that's of course a really important question, are we looking at a cure here? And I think that you have to break that question down and think of it in pieces. And so, everybody's heard a lot about immunotherapy as a new way to treat cancer and immunotherapy is actually a whole lot of different things. This particular kind of immunotherapy called CAR – T cell therapy has been used in patients with blood cancer and specifically, with the most experience in the most common kind of a cancer that kids get, which is called acute lymphoblastic leukemia, which is a kind of blood cancer. And so for that group of patients, we have seen some amazing results even in patients who have no other treatment options and no real hope for any kind of disease control, not to mention a cure. And with patients who are a number of years after that therapy remaining in remission, we are starting to hope that maybe that's a cure for some of those patients, but the broad question is whether this is a cure or not. I think that there are a lot of different kinds of cancer, that most cancers are not blood cancers and this really changes the whole face of cancer care, if, we start to see these kinds of dramatic results in patients who have other kinds of cancers like, pardon me for it, like for example, lung cancer or breast cancer or pancreas cancer and so that we haven't seen yet. So is it a cure? It may very well be for patients with a very specific kind of cancer. Is it something that's going to change the whole field of cancer therapy? That's the work of the next five years.

Priya Menon: Absolutely. This certainly has given terminal patients a last chance, and I believe you have made many, many parents very very thankful Dr. Grupp. Tom, great to have you with us. I know you're driving down from New York City after attending the Time Gala, so the thanks for joining us and, I want to congratulate you, I believe it is going to be almost six years, cancer free on 10th May this year. So how do you feel?

Tom Whitehead: Well, we feel very blessed to have Emily back to normal again when you see her with her friends now. If you didn't know what happened to her, you can't tell, she looks normal. And to parents, that's what a cure looks like. So to have her now six years past the treatment and back to normal, the only medicine that she's on right now is Hizentra the immunoglobulin replacement, which we do every two weeks. So it's really just twice a month that she has to get medicine and other than that she's healthy and happy and, we couldn't be happier as far as our family goes. It was a miracle.

Priya Menon: Oh yes. I totally identify with that. I myself have two children. I can understand how you are feeling, it must be really uplifting. You and your wife started a foundation, the Emily Whitehead Foundation for childhood cancer and I believe you recently donated $250,000 to Children's Hospital of Philadelphia. So I would like you to talk a little bit about your foundation and activities for our audience.

Tom Whitehead: Yeah, thank you. So, January of 2015 we decided to start the Emily Whitehead Foundation. We did notice a lot of people were using Emily's story to raise money and a lot of that money wasn't going back to pediatrics. So our goal is to keep the attention on pediatrics and the focus on pediatrics and helped fund it because it's so underfunded and we've been very fortunate to have some really amazing volunteers help us and to have a given now Dr Grupp $350,000 total and we're also part of another grant of $250,000 that's going there to a Dr Barrett. It's pretty amazing for us. And again, we want to specifically focus on the pediatric immunotherapy and make sure they have the funding to move it forward so other families can have the same outcome that we did.

Priya Menon: That's great. We hope your foundation is able to have a lot of children out there Tom. Dr Grupp, a lot of debate and discussion surrounding CAR T therapy has been around mostly two aspects, one being the serious side effects and the other being the cost, high cost of treatment. So we like to talk about this one by one. Can you take a little bit about the severe cytokine release syndrome and how for Emily you found a rheumatoid arthritis drug as a remedy?

Dr Grupp: Sure. So I think it's important to understand both the therapy can be helpful and it can also have

side effects. And I think it's important to understand that . I'm going to a step away from that question for just one second and just follow up on Tom's point because I think it's so incredibly important. We here at CHOP are incredibly grateful for the funding support that we've gotten from the Emily Whitehead Foundation, but I think Tom and I both strongly believe that even more important than the funding is the messaging and the messaging is that the first CAR T cell therapy and medical history was approved for children and young adults. And kids led the way, pediatrics lead the way. It's very unusual actually to have a new therapy approved in kids, especially as the first thing. And so we want to make sure that as the immunotherapy revolution continues, that of course the appropriate attention is paid to all of the very serious adult cancers that we hope that we can help and we want to make sure that there's some attention paid to the pediatric side as well. So I just, I wanted to jump in on that because I so strongly agree with Tom in that regard and he is really, his foundation and his family have really been leaders for this point of view. Now, let me go back to the question you asked me, which was about side effects. So this therapy is basically a setup where we collect immune cells called T cells from each individual patient. We then genetically reprogram the cells so that they become cancer fighter cells and then we put the cells back in the patient and in situations where the patient has a relatively small amount of leukemia, the side effects that we see are very mild. A patient may or may not have a fever or they may or not may not spend a short period of time in the hospital. They may stay out of the hospital altogether. They may have a short headache one afternoon, really almost nothing but what we've also learned, and we learned this from Emily's case and from cases since her, is that patients who have a great deal of leukemia in their body can have a different experience.

And so the great news for those patients is that we're also able to put them into remission with CAR T cell therapy. But if you have a patient who has literally pounds of leukemia in their body, the T cells, the engineered the reprogrammed t cells have to grow to a very high level to attack all that cancer. And that's why this works. So if you have a little bit of cancer, your T cells don't have to do very much, but if you have a lot of cancer, then the T cells really have to get revved up to get on top of all that cancer. And it's nearly miraculous to us that we're actually able to see those kinds of responses even in patients with completely uncontrolled disease. Why do patients get sick? Why do they get this thing called cytokine release syndrome? Well, it happens because those T cells are part of your immune system and your immune system gets incredibly revved up in the process of killing all that cancer. And so we really did have to learn how to control that reaction. And the first patient that where we really recognized this reaction that at the time we didn't even have a name for it, but now we call it cytokine release syndrome and when we really understood how severe this could be was in Emily Whitehead's case because she fit that profile. She had very significant amounts of leukemia and the T cells had to really get a very revved up in order to control all of her disease. The reason that it is safe to do this and the reason that Emily, after a definitely a tough time in the intensive care unit at Children's Hospital Philadelphia, the reason that she was able to pull through was what you mentioned. So we were doing all sorts of science in the background trying to figure out why Emily was as sick as she was. We were doing research tests to look at without getting too technical about this, we were looking at all the things that happen when your immune system gets activated, including producing all these inflammatory proteins, which is how the immune system talks to each other. One particular protein was through the roof. It was incredibly high. Turns out oddly enough, it's not even a protein that's made by T cells, it's made by other cells of your immune system and that protein turned out to be the one that was making Emily sick. And the great news is that there just happened to be a drug that was developed for patients with rheumatoid arthritis. And Dr Carl June, who's very involved in developing this therapy. His daughter actually has rheumatoid arthritis and that drug, it's called Tocilizumab, would never have heard of it as a cancer doctor before this. That drug specifically targets the abnormally high level of this inflammatory protein that was making Emily sick. And that observation and her experience getting better very rapidly after we treated this, a toxic side effect with this new medication that had never been used for this purpose ever has, I think not only been transformative for this particular CAR T cell therapy, but it's now the basis of all the toxicity management in CAR T cell trials across the world.

Priya Menon: And I understand that this drug has been approved by the FDA for treating CAR T cell therapy induced CRS?

Dr Grupp: Yes. And that's also a fascinating side story because this is the company that makes the drug is

not the company that makes the CAR T cells, so Novartis makes the CAR T cells and they don't make Tocilizumab, but the Food and Drug Administration recognized that they were going to say, hey, you need to use this drug for this purpose. So they basically use data from the cell therapy trial to provide an extra approval. And that I think is a highly innovative way to go about this. They didn't make the drug company do their own trials to show that it worked. We already had data that it worked. It was very clear data with dramatic responses like we saw in Emily's case. And they were, they were happy to use that data. I think it was a great thing that the FDA did.

Priya Menon: Yes, absolutely. So Tom as Dr Grupp was explaining that Emily had a severe episode of the CRS Cytokine Release Syndrome and I believe she was critically ill at one point, she was put on a ventilator and a coma was induced to keep them alive. How did you and Kari hold up during this time must have been so very difficult. It'd be great if you could share that. What kept you going on?

Tom Whitehead: Yeah. So, we knew before entering the trial that Emily could not survive without it. So keeping the faith that, that was our only chance and it had to work, I never looked at it as any other way than the end result would be that she would survive, but I can tell you that 14 days that she was on the ventilator were brutal. So, we just kept talking in her ear, playing music to her, but at some points it didn't even look like Emily anymore, but she just kept fighting. When we would feel weeks, she would give us a sign and when we could, we relied on faith a lot and we just stayed positive and said there was no other outcome that's going to happen here that she's going to wake up from this and be okay. And, after the 14 day coma she came back to us on her seventh birthday, but absolutely what Dr Grupp said when he came through the door, it was looking very bleak to the point where the PQ team didn't think she could survive. And he suggested that Tocilizumab and once he gave it to her, everything turned around within 12 hours. Things were turning around and, they were telling us in the intensive care unit that they had never seen a child that's sick get better any faster. So, we'd been waiting for what I say was our miracle. And then it finally came with that dose of medicine and Emily turned around and she woke up on her seventh birthday on May 2nd of 2012. And we went home on June first and she's been cancer free ever since.

Priya Menon: So amazing to hear that. Dr Grupp what was the follow-up regimen of the therapy that these patients have to follow? Are there any precautions that children and parents had to keep in mind during recovery and going forward?

Dr Grupp: Well, so I think that, there you can sort of break this up into a getting ready for the therapy, receiving the therapy and then what is the long term look like. And so from a getting ready standpoint, we're working with the doctors at the hospital where the patient is treated to make sure that the patient gets an appropriate amount of leukemia therapy without being so intensively treated that they get sick from their prior therapy and we can never treat them. So that's one precaution that we take. , During the months after the cells go in, we like to keep the patients close by and we're treating patients from all over the country and actually all over the world. And, and so we do ask the families to stay in the Philadelphia area, for three or four weeks after the cells go in. And so during that period we're looking for a cytokine release syndrome that that's our big thing and it's easy to pick up because if you have a fever that's the start. You can just stay with a fever or you can get sicker like Emily did and it depends very much on how uncontrolled your leukemia is. So most of these patients are admitted to the hospital for a short period of time and 20, 30 percent of them actually end up needing ICU level care for a week or less. And so that is that sort of what happens right after you get the cells. Now what's amazing to me, these are kids, underneath their cancer, they're still healthy, and so all you have to do with kids like this, and we saw this with Emily, is leave them alone and you're not giving them treatment after treatment after treatment. You're not keeping them in the hospital all the time for high dose chemotherapy. You're not causing them to get infections because their white cells and immune systems don't work anymore because of the chemotherapy. So they get better so fast after that initial three to four week period where we're watching for potential side effects and there, the precautions are minimal. I mean, we're pushing these kids and of course the parents are pushing harder than we are to get back to school as quick as possible. We want to get them back to their lives. The one long term side effect we absolutely do see, and I don't want to minimize this, is that the kind of leukemia that we're treating is related to normal cells in your body called B cells and B cells produce antibodies and antibodies are

basically what vaccines make for you. And if you don't have normal B cells, you don't make antibodies. You don't have that vaccine like protection and you need to get a medication to replace that, which Emily and a lot of the patients do get. So if they get that medication, I think, and Tom can confirm this for me, I think that basically we don't see a lot of problems associated with that and that's really the only long term side effect that we've seen in these patients.

Priya Menon: So, Tom, as a parent, what are some of the precautions you keep in mind when she is probably outdoor at school or at play?

Tom Whitehead: Well, I think, you know, we look at her now as a normal child, just minus B cells, so cancer parents Kari and I still panic inside if somebody's really sick around her. I mean, but I think anybody that sees somebody that's something contagious is going to try to keep their child away from him, but we don't have to, we don't have to limit whatever she wants to do. She can do, minus being around somebody that's got a severe virus or whatever, but I think any, any parent would do that. So I don't, I can't say that, now we still worry a lot his parents because we don't know what's going to happen tomorrow. But she's a normal child.

Priya Menon: So does she have a favorite game or sport that she likes to play?

Tom Whitehead: Well, she's on her computer quite a bit now playing Sims and she likes to do minecraft, architectural skills for minecraft.

Priya Menon: Okay that's nice to know. Dr Grupp moving on to the cost. As I mentioned right at the beginning, the high cost of CAR T cell treatment has been a shocker for many at $480,000, the affordability of this treatment has come under a lot of fire. So it will be great to just hear your views on this.

Dr Grupp: Well, you know, that's, that's a very important consideration. So, obviously I'm a pediatrician at a hospital in Philadelphia. I'm not a drug company person, but what the discussion about the price of CAR T cells has really brought forward in my own personal mind is medicine in America is incredibly expensive. Being in the hospital is expensive, cancer drugs are expensive. The cost of this particular therapy Kymriah or it has another name which is nearly unpronounceable, which is tisagenlecleucel – the cost of that is very comparable to a lot of the brand new cancer drugs that are available these days. And the reason why it is a little bit more striking for sure, is that instead of being a therapy that you get every month and it costs you $20,000 a month, but you could be on it for years, this is a therapy you just get once. Emily got these cells once. And so the concept that for at least some of the patients, not all of them by any means, but because a big fraction of the patients, this can be one and done. This is a one time therapy. I mean literally, although the side effects can be significant as we've talked about, the administration of this therapy takes two minutes, you walk into the door with a syringe that you infuse it into the patient in a very short period of time and that has the potential to be the last treatment the patient ever gets. And so from our perspective, we worry about excess, we want to know will insurance companies pay for this? And in our experience, having given more commercial CAR T cell product, and then any other hospital in the country right now is that insurers do pay for this. So that's extremely important if we, if we can't get an insurance company to pay for it, then we can't give it to the patient and that's a significant problem. So we want to make sure that the kids can actually get this. And then the issue of why medications in America are as expensive as they are. Broadly speaking, that that's a societal question I'm not really prepared to have a good answer for. But do I feel like in this particular instance, this therapy offers significant value to patients, not just a marginal increase in potential months of life, but a potentially being a cure for a reasonable fraction of patients? I think it does offer a significant value.

Priya Menon: Well, thank you for sharing that, Dr. Grupp, we'll have a couple of questions are on the therapy and the trial as such and then we'll hand it over to the panel for some questions. So Tom, I'll start with you , we want to know where did you first hear of the CAR T trial and what prompted you to make the final decision to enroll Emily in an experimental drug trial?

Tom Whitehead: So we actually found the trial on our own. My wife Kari, works in research at the Penn State University, so she used her research skills to look at any available possible options and it really made us happy that there was something available that's only four hours from her house. I know at one point I told Emily if I have to crawl to the North Pole to get you better, I'll do that. But we, we did not get support from our local hospital on going through an experimental trial, but we did it on her own and we trusted our instincts, his parents, and transferred Emily down into Dr. Grupp's care was the best decision we've ever made. So, when we, by the time we had transferred down our options were take Emily home on hospice or go down, transfer down to children's Hospital Philadelphia and try her as a first patient in a phase one trial. And we weren't ready to stop fighting and Emily wasn't ready to stop fighting, so hospice wasn't an option for us and I can tell you as a parent that deciding to join this trial for me was easier than trying to give Emily full body radiation to go to a bone marrow transplant because that scared me more than this trial did, worrying about doing permanent damage to her learning ability and everything with the radiation and I think we were almost going to bone marrow transplant and in the end the CAR T treatment costs much less for our insurance than the T cell treatment did. So that was the life and death decision.

Priya Menon: Yes. Dr Grupp, I know you talked a bit about how and what the therapy entails, but as we're talking about children here, so do the trials for children have any specific considerations that you have to make?

Dr Grupp: Oh yeah, there are definitely significant considerations that we have to make. The most important one is that, when we set up a clinical trial for kids, for especially a new medicine that's not been tried before, we really have to ask the question, do we think it might help if we feel like that they call this prospect for benefit? Did they, do they feel like this might actually be helpful? There's no guarantee of success in anything that you do in life. But is there a reasonable chance that the child who is in front of you will benefit from the therapy that you're offering them. And if you can basically convinced the Food and Drug Administration and the Ethics Review Board at your hospital that you have data that shows that there might be a hope for that individual child, then that's really when you can include patients in research. And obviously for patients who have much less serious conditions, that's a pretty high bar to get over. But in patients who have cancer and no other treatment options, the bar becomes a little bit lower because as Tom pointed out, for many of the patients that we treat, it's either this or care intended to make the patient comfortable in the last few weeks of their life. And so that's a very stark decision that said, from my perspective, I know I'm a pediatric oncology researcher. I've been doing this for a long time, but facing a family like the Whiteheads and saying this is a brand new therapy. It's only been tried in, in a small handful of adults. Nobody has ever really treated cancer with something like this exactly like this before. It's never been tried in the child before. It's never been tried in a patient with this kind of leukemia before. I mean, that's a lot of nevers. And so while we were very hopeful that it might provide some benefit for Emily and could not have done that without that, the courage involved, for the family to get involved in this kind of research I think is also extremely important. So yes, we have a special requirement in pediatrics that we feel like the research is worth doing.

Priya Menon: Yes. I have one last question before I hand it over to Gary Peterson. CAR T cell is a living drug and it's supposed to remain in the body for months and years fighting cancer so apparently, in some patients the T cells go away quickly. Dr Grubb do we know why this happens and if the CAR T cells go away from the body will the cancer recur?

Dr Grupp: So, there are lots of pieces to this. So, let me try to take that apart a little bit. So the answer is that with this particular CAR T cell therapy, the recipe seems to be that the vast majority of the patients keep their T cells for months and years. I mean, Emily still has those engineered reprogrammed T cells in her body and a lot of the patients who were this, were four or five, six even seven years out do, and so that's a large number of patients, but there are patients who, 20 % or less who lose their, their cells within a few months instead of keeping them for many years and then there are other kinds of CAR T cell therapy that don't last nearly as long that lasts four or five, six weeks and then the cells are gone. And so we're just now figuring out lots of things. So the first question is, can you give the cells again if the effect wanes and you want to protect the patient for a little bit longer and the answer is yes, you can. And we've done that in patients who

have lost the cells quicker than we would like. So you can totally repeat the treatment safely in these patients, when you repeat the treatment under these circumstances, they don't have leukemia. You're just trying to protect them and they are. The side effects are nearly zero. It's, it's a whole different experience for these patients, so repeating the treatment is not, it doesn't have significant risks associated with it at all. And then the other question you asked me is how come Emily has her cells for all these years and other patients might only have it for a few months and that's an area of really intensive research. We want to understand why T cells behave the way they do. Remember that this is not a drug where everybody gets the exact same thing. We're making this "drug" or this treatment out of the patient's very own T cells and we're starting with the T cells that they have and so what are the characteristics of these T cells that make them last longer and go the distance? Some people have marathon T cells and some people have sprint T cells and they go away a lot quicker and and that that actually is one of the major areas of research focus in my own personal lab and especially Dr Barrett who has been supported by the Emily Whitehead Foundation as well, is looking at these questions of why do T cells behave the way they do, but the short answer is we don't know. We have a lot to learn because it's a brand new field of medicine.

Priya Menon: Well, thank you for that Doctor I now hand it over to Gary Petersen, Gary you are on air.

Gary Petersen: Well, thank you Priya, I appreciate it. And obviously for all of us and I'm sure for Tom, this looks like a miracle and possibly so for not only you and your family and daughter, but for many other people as well. So thank you so much for being part of that clinical trial. And, Dr Grupp, thank you so much for all that you've done as well. I understand that CAR T cell therapy focuses on at least for leukemia CD19 and has some off target impacts and that the B cells as a result of the patient needs a transfusion. And you said it was a, I think, some immunoglobulin. Can anything be done to correct this? Are there any other targets that just yet which could eliminate the off target effect?

Dr Grupp: Great question, yeah so first off for other kinds of cancer, the target is going to be totally different. And so we wouldn't see this side effect except in B cell type cancers and that's leukemia and lymphoma. And so when you get away from this kind of disease, we're not going to see that side effect. There are two ways to get around this and one way is you can use a short acting form of the CAR T cell. So the other CAR T cell product that was also approved in 2017 a couple of months after the Kymriah was approved and that is made by a different company, it has a name that's called the Yescarta and that only lasts for a few weeks. And so there's no issue with long term B cell aplasia. But the issue for me is that this long lasting property of the cells that we use is really what's allowing us not to take these patients to bone marrow transplant. That's actually what I do as a doc. I'm a bone marrow transplant doc and I'm so excited that there are patients like Emily, where we can just use this therapy and not transplant. So that long lasting effect. Now, what can I do about it? Well, you could engineer, we haven't done this, but you could engineer a switch in the T cells so that you could turn them off and remove if you engineer, if you remove the reprogrammed or engineered T cells than the natural B cells would come back and this need would go away. And so the reality is that we probably could erase these T cells from the patients. And after a few years, one of our central questions is, is that a good idea or not? And I would love Tom for you to comment because this is an area that we talk about at every visit, what you think about the prospect of erasing the T cells.

Tom Whitehead: Yeah. So Dr Grupp would ask us quite often and we've always told them that we have a normal child and what we went through to get them in there as parents, we would never make the decision to go back in there and erase them. And we said, when Emily gets older and becomes an adult after she's 18, if she would decide that it's time that it's been long enough and she would want to make that call, then that would have to be her own decision because we just won't ever do it as parents. She lives a normal life and other than that medicine that she gets every other week, we have a normal child. Yeah. It's pretty amazing. And we saw a lot of parents, that we're in at the same time fighting just as hard as we were and they lost their child and they would give anything just for one more day with their children. So, we know how fortunate we are. And, I've had talks with Dr June too and his research and he said maybe eventually they're going to have a switch that they can turn the T cells off with a medicine and turn them back on if needed. So they wouldn't have to completely eliminate them. But that again, that's coming in the future with more funding.

Gary Petersen: Well, that sounds great. One other question Dr Grupp, a recent long term follow up at Memorial Sloan Kettering Cancer Center, I believe they've been doing some research and they found that the cytokine release syndrome occurs in 26 % of patients, including one patient who died at the rate of severe neurotoxicity and that was at 42 %. So this, there was a CR in 83% of patients, but the median overall survival was just 12.9 months. So, and the median EFS event free survival was 6.1 months. So the median follow up time was 25 months. Is this your experience as well? And if this is a far cry from a cure, but what improvements do you see over a this, and is yours different in some way?

Dr Grupp: So, yes it is, and no, that's not our experience. There are patients whose disease does come back after this kind of therapy and one of the reasons that sometimes comes back is that the leukemia which is really evil at doing stuff like this learns to hide that target that you mentioned, which is CD19. And so in that situation you can have awesome CAR T cells on the hunt, but they don't see the cancer anymore because the CD19 is gone. And so that is the problem that we see in some patients. Our long term experience is considerably better than the numbers that you just mentioned. 50 to 60 percent of our patients remain in remission one, two years out. That does, that seems to be sustained beyond that. But then the number of patients, as we go further and further back in time, we've treated smaller and smaller numbers of patients, including when you want to go to six years, there's only one human being on the planet with ALL about six years and that's Emily. So 100 % of one patient. That doesn't really mean much from a statistical point of view. And so the reality from our standpoint is that the long lasting characteristic of the cells has allowed us to avoid transplant and it does keep in remission in patients in remission for a long enough period of time that we are hopeful that the potential of cure. But, that is 50 to 60 % of the patients. It is not 100 % of the patients. And so I just want to be clear about that. So we feel like the therapy has legs and that we're able to keep a reasonable number of the patients. And then you ask the question, how do you improve that? Well, my answer to that would be if the some leukemia learns to hide, maybe what we need is a second target. And so we're actively working on clinical trials and this is actually a major area that we're using the Emily Whitehead foundation support to go after this. We're actively pursuing a second target, not to treat patients when their disease comes back, although that's how we would use it right now. But in the future to prevent that from ever happening. And we think that having two targets has the potential to bring that long-term disease control rate up from 50 to 60 % to closer to 80 %, which is, which is a number that still isn't good enough, but is way better than what we have right now.

Gary Petersen: Well, yeah. Exactly. And even a median overall survival of 12.9 months really beats anything that's really out there for late stage Myeloma for example. And I would imagine that similar for leukemia, I mean new drugs are approved for two or three months improvement. So thank you very much doctor. And, obviously you're doing something right that other people have you got to figure out. So hopefully that will go and become common knowledge at some point in time for you. Priya, that's it for me.

Priya Menon: Thank you. Thank you Gary. Jack please go ahead with your questions.

Jack Aiello: Good morning, at least here in California. I really appreciate this phone call. I've learned an awful lot. I've been fortunate enough to meet the Whiteheads, a wonderful family a few years ago in DC at one of the Leukemia and Lymphoma Society Foundation meetings. So, thank you for all that you've done. Dr Grupp, I have a question with respect to the cytokine release syndrome. Does it vary or is it better or worse considering the disease is being treated or is this strictly related to the amount of cancer in that patient?

Dr Grupp: Yeah, that's a great question. And so this was a surprise to me. I had a definite prediction and I was definitely wrong. I was thinking that it's all about your disease burden and not the kind of cancer you have, but it's not true. So it turns out that leukemia, like Emily had, is one disease that we treat with this but lymphoma, which is a different kind of cancer, a very related, but it works differently in your body – lymphoma has a lower rate of this severe cytokine release syndrome and without, again, I don't want to over technical to this, but the thing is that leukemia is a disease where there are single cells floating all over your body in your blood and your bone marrow sometimes in the spinal fluid. And when you put it in the T cells, they find the cancer right away and that's where that severe cytokine release syndrome comes from as a

whole bunch of T cells killing a whole bunch of cancer in a very short period of time. Lymphoma is organized into balls of cancer in almost like a solid tumor. And there the T cells have to work their way in and they don't have access to all of the cancer, the minute, that you infuse the T cells and that's slower ramp up, means that patients don't get sick. So it seems to be very dependent on the kind of disease.

Jack Aiello: And you've answered most of my other questions. So, the one thing we hear about it every so often with respect to CAR T is that it may become a procedure where instead of taking T cells from the patient that T cells or re-engineered CAR T cells can be produced off the shelf. Do you envision it happening and can you say a little bit about that?

Dr Grupp: Absolutely. So the off the shelf concept is under active development right now. I myself have treated a patient with an off the shelf CAR T cell product and will be working on another clinical trial where we're going to be trying these cells. And so the hope is, pardon me, the hope is that if you didn't have to make this product for every patient, it would be less expensive to make basically take cells from a normal donor and make them into a dozen or a couple dozen products. And that would reduce the cost. And so if that turns out to be the case, that would be great because that would obviously simplify they manufacturing problem. In this case, we have to collect cells from each individual patients. We have to send it to the facility, the Novartis facility where they make the cells and then they send it back or we send them to our local facility as well. And so the issue though is that these cells are from another person and the potential is for your body to say, hey, those cells don't belong there and your own personal immune system reject those incoming cells. And then you wouldn't have that long lasting capability. So if they can figure out a recipe where these cells last, where they have legs, where they are marathon cells that we were talking about, then this is a real additional step forward that might reduce costs and make the whole process a little bit simpler. If on the other hand, the cells don't last very long, then then it's not going to be as an exciting a potential replacement. So right now we don't have the sense of equivalence, but this is a hot topic. People are working very hard on it. There's a lot of interest in CAR T cells, which means this is a lot of investment in the area from a drug company standpoint. And so these are questions that are going to be answered in the next few years for sure.

Jack Aiello: Thank you very much. Dr. Grupp and I'm so excited for your success and your family's success Tom and that's it from me.

Priya Menon: Thank you. Jack. Ok, we will open it up for some Q & A from the listeners. Those of you who want to send in a question, please email them to priya@trialx.com or you can also post the questions on the page that you're listening to this talk now in the comments section. Dr Grupp, we have received quite a few questions via email and some on the page as well. So I will quickly go through them. I will read them out so that you can answer them as best possible. Phil wants to know if CAR T cell therapy be considered for frontline treatment?

Dr Grupp: Oh, I love that question. So, right now the FDA approved therapies available for patients for whom either chemotherapy doesn't work at all, which is called refractory or where the disease is going to come back, not just once but twice. So two relapses. And we love the idea of being able to use this treatment earlier and save kids a lot of intensive chemotherapy. And so the children's oncology group, which is the national clinical trials group for cancer in the United States is starting a protocol this year that's going to pick patients very early in their treatment who have not experienced a relapse but who we know have characteristics that say this is really bad ALL , bad leukemia and we're going to try CAR T cells, within a few months of diagnosis in these patients. And so that's pretty upfront and it'll be awhile before we have an answer on that clinical trial, but we're starting that research right now.

Priya Menon: Thank you doctor. The next question is from Amy, she wants to know what happens if the cancer cells mutate to not express the antigen anymore, that the T cells are targeted towards, would kind of be able to function?

Dr Grupp: Yes. So it does. So the answer that was, that's what I was talking about before, that the thing

that the T Cell C is a particular target called CD19, if CD19 sometimes goes away, which leukemia sometimes does, then you need an alternative target and we have developed an alternative target and that's one of the things that the Whitehead foundation is helping us with. So that is our limitation. That is the thing that I believe is keeping us from an 80 % success rate. Long term, short term, we're over 90 %, but the parents aren't coming to us for short term. They're coming to us for longterm. And the way to get the long term, 80 % is to have that second target. So I think Amy's question is spot on.

Priya Menon: Yeah, thank you doctor, I think you have answered the question on whether the booster will be given if patients relapse. But we have a question from Nick who asks, what about children who have not relapsed? Would they need to take a booster dose sometime in future to maintain that cancer free state?

Dr Grupp: Yeah. So, if the patient has their disease come back, but it is still CD19 positive, which is to say it's still has the target, we could use these cells to get them back into remission and we have, but the question that's being asked here is really about a true booster situation. So we have a well patient with no leukemia that we can detect, but a fear that the leukemia might come back because the T cells have disappeared and we, even though that's a small minority of our patients, we have absolutely done the booster approach, and it's hard to say whether it works or not, right? Because you don't, you're not actually treating leukemia that you can see, but it certainly is something that has not caused any harm.

Priya Menon: Thank you Dr. Kenny wants to know, if there is an advisory board of researchers which will guide a patient cancer support group to which immunotherapy platform is best matched with their particular tumor etiology? For example, CAR-T therapy vs ACT vs Crispr.

Dr Grupp: That's a tough question. The trouble is that there's so much innovation going on in the field right now that the usual benchmarks that we use as docs is long term disease control and for that to happen, you need to have been doing it for a number of years. I mean, we're six years out for the first patient we ever treated. That's pretty, pretty early in some ways. And so the reality is that the picking the right therapy when they're five different options is a challenge and that's where your oncologist I think is a great help. And then, as Tom mentioned Kari doing her research on this and also seeing what makes sense from a clinical trial perspective. All of these new therapies that are available at largely at large medical centers on clinical trials. And so this is a real opportunity for families of children or for adults with cancer to say, Hey, I'm willing to try something that's new. I want to see if there is some possibility for better outcomes in the way I'm going to access that is a clinical trial, but there's no magic formula for three or four competing therapies that are very early in their development because we don't have that comparative data.

Priya Menon: Thank you. Doctor. We have a question come in from Australia, Katie writes, our one year old child has ALL, MLL and had got blood transplant recently. If she relapses, can you provide CAR T treatment for her? Please be noted that your trial is for 3-yr old children only due to the limited availability of expanded T cells in younger children. What CAR T options do you have for younger infants like our daughter?

Dr Grupp: Well, what I'll start off by saying is that I hope that this particular patient stays in remission forever. And nothing I would say it is intended to provide medical advice for an individual patient because I don't know any of the details. But I can answer the question in a general way. And that I would say two things about that. First off, it is absolutely true that patients who are two years and younger, we have a lot more difficult time making CAR T cells from patients than we do for patients who are older and it really what ends up happening. There's been a lot of work done on this at CHOP and Dr Barrett is really leading this research and what we've learned is that the very intensive chemotherapy that babies get for ALL really messes with their T cells and even though the T cells grow back and are present in the patient's body at reasonable numbers, they don't work right. And this is very much an issue for babies. Now in a patient, this is where it gets kind of complicated and interesting. When a patient has undergone a bone marrow transplant, then they don't have the baby T cells anymore. They have the T cells that have never received chemotherapy and in that situation we're perfectly capable of making a CAR T cell product in a patient, in that situation. But of course, the hope is that the transplant is successful and there's no need for CAR T cell therapy. The patient just remains in remission. That's what we all hope for.

Priya Menon: Thank you. Doctor. We have a question from an anonymous person who writes in… any recent advances in the use of CAR-T for T-cell lymphomas?

Dr Grupp: That is a really challenging question. So, what I would say about that. So, so all the diseases we've been talking about using CAR T cell therapy for is leukemia or lymphoma, that's a B cell origin. And now the question is about leukemia or lymphoma that is of T cell origin. And so here's this odd circumstance that we're in, we have CAR T cells which are made from your own normal T cells and we have a cancer which just arrived from T cells. And the problem is we don't have without some very fancy genetic manipulation, which we're trying to figure out right now, there's no good way to keep the CAR T cells from killing each other because they're also T cells at the same time that they're trying to kill the cancer. And so that problem of the CAR T cells killing each other because they're using a T cell tag is a real challenge in the field right now. T cell leukemia and lymphoma when it relapses, is very hard to treat. I've had a wonderful parent who has been pushing for many years for us to make the kind of advances in T cell therapy that we've made in B cell directed therapy. And, I think that there's hope for this in the future. But, there's some targets that we think that may not have killed the CAR T cells at the same time that we kill the cancer T cells. But it is a challenge in terms of getting the T cells not to recognize each other.

Priya Menon: Thank you Dr Grupp. Neil writes in asking if you can share your perspective on the Car T program at Novartis, versus the program at Glaxo and Legend Pharmaceuticals? Any other players in this space that you could highlight for us?

Dr Grupp: So for full disclosure, the product that I have or the CAR T cell approach that I have been working personally to investigate for the past decade is the one that was licensed to Novartis, which is called Kymriah. The other major product that's available right now is that Yescarta product, the difference between the two is that one tends to last longer, which is the one that we've been working with Kymriah and one tends to go away very quickly, which is the Yescarta product. Now in leukemia patients there is a clear advantage to keeping the cells longer. So I think it's really important in lymphoma patients, it may be that just having these cells for a six to eight to 10 weeks maybe long enough and there may not be as obvious a difference. So it's a little bit hard to tell the answer to that right now. And so I think the platforms differ, the diseases differ and the applicability differs. And then of course I have the most experience with the product that lasts the longest. Now there are lots of other companies that are developing a whole group of different approaches. And so, the answer to this question is in two years is going to be completely different I think.

Priya Menon: Thank you. Dr Grupp. We have one last question from Mike and this is on multiple Myeloma. How is this therapy being conducted to address multiple Myeloma? Are they targeting BCMA, CD38, or CD19 or a combination of these targets or all of them?

Dr Grupp: So, a lot of all of that. So I'm a pediatrician, I don't treat patients with Myeloma, but I have been very excited by the results that I've seen with a specific target, which is the first one mentioned, by that person, which is BCMA. And BCMA is a great target for Myeloma and we're definitely seeing significant short term results in patients with bad myeloma with BCMA. And so, we don't have enough follow up to say if these are long lived responses, which just doesn't mean that I don't think they are, it just means we haven't followed the patients long enough because it's brand new. But for me as a researcher in the CAR T cell field to see something other than CD19 working this well is incredibly exciting. CD38 is being approached by a drug, but it's also being approached by CAR T cells. And I bet in the next year or two we're going to see some data on CD38. Again, I could get super technical this CD19 shouldn't work in Myeloma because of the way that Myeloma works, but it does occasionally work. And when it works, it works amazingly well. But it would be probably working in a very small minority of cases. So for me right now, the most interesting shot on goal in Myeloma, which is a disease where there are a lot of therapeutic options, but no cures at all is really the BCMA CAR.

Priya Menon: Thank you Dr Grupp. We have a comment to that is just come in on our page and this is for you and the team at CHOP. The parent says, thank you Dr Grupp and the team at CHOP our daughter is 3 months post CAR T at CHOP and thriving! Our family is so grateful to all of you!

Dr Grupp: Well thank you very much for that. And it's our fondest hope for each of our patients that those responses just go on.

Priya Menon: Dr Grupp, this has been a great discussion. CAR T cell therapy is a breakthrough treatment for cancer. And thank you so much for your time and sharing all this information with us. We almost at the end of an hour. And thank you for all the great work that you're doing saving so many lives. Tom, thank you so much. Wishing Emily and your family the very best. Gary and Jack thanks for the great questions. I also want to thank University of Pennsylvania and Children's Hospital of Philadelphia and the wonderful audience. This talk will be made available on curetalks.com. Please visit our website for details on upcoming talks. Thank you everyone. Have a great evening.