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Dr. Carl June's CAR-T Cell Journey and the Cancer Treatment Revolution

FDA approval of the breakthrough CAR-T cell therapy for cancer brings the first approved gene therapy treatment to the United States. It reprograms the body's own immune system to recognize and kill cancer cells. The therapy initially called CAR-T cell immunotherapy and now named Kymriah by Novartis, is approved to treat children and young adults with a recurrent form of the blood cancer called acute lymphoblastic leukemia (ALL). Dr. Carl June of University of Pennsylvania, is one of the pioneers of CAR-T cell research and leads the team responsible for the historic FDA approval. We are discussing Dr. Junes CAR-T cell journey to understand nuances of the new therapy. The discussion will also bring to focus the opportunity that these engineered immune cells present to cancer treatment and possible use in treatment of other cancers.

Full Transcript:

Priya Menon: Good afternoon and welcome to CureTalks. This is Priya Menon, your host, joining you from India and today we are discussing CAR-T cell therapy treatment for cancer. As we all know, FDA has approved the first gene therapy treatment in the US and our guest for today is the man who led the team behind it all, Dr. Carl June, a pioneer and specialist in T cell biology and lymphocyte activation at University of Pennsylvania. The new therapy uses body's genetically engineered immune system to find and kill cancer cells. In the coming hour we will be discussing the nuances of this therapy. On today's panel we have patient advocates Gary Petersen, Jack Aiello and Mike Scott from our CureTalks community.

I will just brief you on the format that we will be following today. I will start with a few questions and then Gary will begin the patient panel discussion with Jack and Mike. Towards the end of the talk, we will be taking in questions from the audience. The dial-in to ask your question LIVE is 718-664-6574. I repeat 718-664-6574. This number has been posted on Curetalks.com webpage as well, and we will be repeating this number before we begin the QA. You can also post your question in the comment section of the curetalks page or email me priya@trialx.com with the same. I once again welcome everyone to today's episode of CureTalks.

Moving on to the discussion, Dr. June it's such a pleasure to have you here. Welcome. To start off, can you talk about how your research with CAR-T cells began? And whether your background as a Navy physician has had anything to do with it?

Dr. Carl June: Well thank you very much Priya. So I began to study, as a physician in Oncology, in the early 1980's, and at that point, the new emerging therapy was bone marrow transplant. And in the early days of transplant, they thought that it would work because they could give, what are called super lethal doses of chemotherapy, so intense that it could kill you unless you are rescued with bone marrow from a donor usually, a brother or a sister. And, in fact that was the first time that sometimes leukemia could be cured and it was only later when they did a set of identical twins, and they gave them a set of same chemotherapy, as they gave transplants who had a donor as a brother or sister. What they found out was that it only worked with increased survival, if you did not have an identical twin as a donor, so what that means now in

retrospect is that, the differences in the immune system between the brother or sister who was the donor, are with lead to long term remissions in leukemia. And if you had no differences meaning an identical twin, it wasn't as good at all. The only benefit you got was the high dose chemotherapy.

So, the problem back in the early 1980's is that the procedure often had very severe side effect called graft vs host disease, where the immune system of the brother or sister would attack the recipient patient. So I began working on how to get around that and I ended up being..you know..could we do the same benefits of a bone marrow transplant, but not have to do the transplant, and actually use your own immune system as the weapon. And over about 25 or 30 years that has now culminated in FDA approved therapy called CAR-T cells.

So I started off because of that, learning how to grow T cells was the key, from the patient. And then I was in the Navy because of the reason, we wanted that bone marrow transplants, what has been recently shown, we had radiation casualties that could happen for instance, in Chernobyl or the Fukushima reactor accidents in Japan. What you die from that radiation exposure is bone marrow failure and it can be treated with a bone marrow transplant. So in 1980's the navy paid for my education so that I could learn how to do bone marrow transplants, and then we if had an issue, say, with a navy reactor on a submarine, we would have a potential way to treat the sailors. And so that is how I started on the initial research, but then when I began, later after in the later …almost early 1990's, what happened was that we had the collapse of the cold war, and really the reactors and so on became a low priority issue. The only research that I could do in the navy was HIV and malaria, which are infectious diseases.

So the first use we had of getting T cells to patients were actually patients who had HIV and AIDS. So, we showed that we could take the T-cells out from a patient who had AIDS, grow them up in a lab with technology we had developed and then give it back to the same patient, and their T cell counts got much better. So the immune system started to work where it has been failing. So that was throughout the 1990's and then, I left retired from the navy and went to the University of Pennsylvania in 1999, and we began using the same approach, in patients who had leukemia. And so we used all the technologies we had used in HIV and then transferred that to cancer patients and that's lead to now …our first patient treated in 2010, and now FDA approval just in August of 2017. So in the nutshell, that is how it happened.

Priya Menon: Yes, so you just mentioned having talked …having worked with HIV and engineering the T cells. Can you talk about your work with HIV and why HIV was ideal for this engineering…of the genes?

Dr. Carl June: Yeah so, you know, one thing about this is, it shows that if you can work in different fields, seemingly disparate fields, like in infection and cancer. You can sometimes have lessons or low hanging fruit, that applies in one field to help solve the problem in another field. So, in the cancer field the problem was how to make T cells attack your own cancer, but not attack your body. And we didn't have an efficient way to genetically alter those T-cells. And it turns out that HIV is evolved to do exactly that. I mean, it infects people, it goes in their immune system, into T cells. But, the natural HIV virus, as people know, destroys T cells eventually, and so the number of investigators over the years developed HIV and modified it so that it would be a tool to insert genes into T-cells rather than kill them.

So what they did was basically, got the virus of the genes, and material that would allow the virus to kill T cell, but retain the ability to insert new genes into T cells. And so we were the group to first test that in humans. In 2006, we treated patients who had late stage HIV with their own T cells – but then, using this modified form of HIV which we called Lentivirus – to insert a new gene into their T cells and that's what we ended up using in cancer patients because it works with very high efficiency and has been very safe in hundreds of patients. We never had a side effect from this virus.

Priya Menon: That's great. So this is a very common question that we have come across as to how this new therapy is different from the standard chemotherapy?

Dr. Carl June: Yeah. It is radically different, you know. One thing, I mean the therapies that we have had until just recently have, I mean other that surgery, and we can cut it out that, usually it is either surgery or radiation or a combination. And both of those are non-specific therapies, and they work by killing cells but they also kill normal cells, which leads to the side effects. And with immune therapy it is precisely targeted at just the cancer cells, there are not those off-target effects. Off target effects are when the therapy is killing cells but its not helping you get better. So chemotherapy has many side effects and symptoms such as nausea and vomiting, to very severe issues which can involve liver failure, heart failure, bloody diarrhea and so on. Those are off target effects and they actually don't help you get better from the tumor.

On target effect is – side effects related to actually when you are killing the tumor. So those happen, you know, when the patient is actually benefitting from the therapy. And the first one we found with our CAR-T cells, and CAR- by the way stands for – Chimeric Antigen Receptor – and basically that means, it is a T cell that's been modified. The word chimera is used because its from greek word – "Chimeric Beast" – which is a fusion of 2 different animals in the greek mythology. So what we have is a chimeric T cell. The T cell that is a fusion of 2 cells in the natural immune system – which is the B cell. B cells normally make antibodies, which we use in our defence against viruses and infections. The T cells normally just kill cells, but does not make antibodies. So a CAR-T cell takes the best world really, of a T cell and a B cell. The T cell can be a killer cell of tumor cells, but also has now – antibodies in it. Then that is how we can direct it to kill tumor cells.

The first on target effect we found from CAR-T cells is very high fever. In our first adults, we have a fever of 106 degrees, that would last for several days, and there is no infection. We now call this cytokine release syndrome or CRS. It only happens in patients who are getting better. The fever happens when the tumor is killing, I mean when the CAR-T cells are killing the tumor cells. It is a violent reaction. It can last up to a week. We now have ways to manage it. We learnt a lot about CRS. As I mentioned it has high fever, usually higher in children than in adults, probably because children's immune system is more robust. We have also learned that if we treat patients earlier, when they don't have as much tumor, there is less CRS.

So our first patient, the first 3 that were reported, that were treated in 2010 were adults. By the scan that were done they had between 5-7 lbs of tumor each. When their tumor got ablated by the CAR-T cells, it was violent. They had fevers which lasted – in one case – 2 weeks, until the tumor was all gone. The patients recovered and they were completely fine. There was no long term side effects from that. So that's an on target side effect is Cytokine Release Syndrome. It can be severe in patients with high tumor loads. Up to 1/3rd of the patients go to ICU, but the fatality rate from this is less than 1%. In the trial that Novartis did to get the FDA approval of CAR-T cells for leukemia for patients between age 3-25, 48% of the patients had Cytokine Release Syndrome, but there was no fatalities.

Priya Menon: Thank you Dr. June. before I hand it over to Gary to start with the patient discussion, can you share some eureka moments that were part of this journey…..this T cell therapy journey.

Dr. Carl June: Yeah. You know we started off first, with just, you know, could we, you know, what we were doing really is kind of CAR-T cell therapy – it is a new form of transfusion medicine. So, the first successful transfusions in animals were blood cells. For that to happen, they had to develop the typing of the blood system – so called ABO antigens – to find out who could be a blood donor and so on. Now what we are doing really is T cells – you know, because CAR-T cells are formal blood cells. We are doing T cell infusions. So, our first "eureka" was when we actually treated those AIDS patients, we made CAR-T cells for HIV and we gave them a single dose of CAR-T cells. We saw immediately, their T cell counts went up, in many cases they doubled and went to normal levels. That was an evidence that the CAR-T cells could go into the patients and stay, and actually survive, start dividing. So, that was what we were hoping for, and it worked better than we thought it would.

But, in a really curious twist, the FDA has a rule, in the US, that patients treated with gene transfer technologies…So this is a form of gene therapy, because the cells are genetically modified and in this case, the patients got CAR-T cells for their HIV. Starting 1997, the FDA has a rule that each patient needs to be followed up to 15 years and tested each year to make sure that he has been safe, and there has been no toxic effects from the genetic engineering. Analysed in 2012, of all the patients we had treated back in 1997 and 2000, and there were 40 patients, and we analysed them, because the FDA had a rule that if we could show that the gene transfer was had gone away from the patient, then we would no longer have to have the expense of following the patient every year.

So, we analysed all our patients, from the samples in the freezer, and were astonished to find that, in fact, more than a decade later, they were still engrafted and had these CAR-T cells at very stable levels. No one expected that. In the previous trials, that transfused T cells, they had not ever lasted longer than a week. We found that the half life of these T cells is 10 years in patients of HIV. So it suggested for the first time that you can make a living drug, you can genetically modify someone's T cells and give them back, and it would then be there on patrol for potentially the rest of the patient's life, so that they can act in a way like a vaccine. So that was the first amazing ….

Priya Menon: A living drug…that is very exciting.

Dr. Carl June: Yeah..and then the second major one was really in 2010 when, when we treated the first patients with these CAR-T cells, this one was called CTL019 or CART19 because it targets…its a CAR-T cell against a molecule called CD19 on leukemia cells. When we treated those patients we did not know what would happen. All previous CAR cell trials in patients in cancer had failed and not shown any effects. We had all three patients show remarkable remissions. It was so unexpected that patient 1, who we reported in New England Journal of Medicine in 2011, patient 1 when the bone marrow biopsy came back with no leukemia – I did not believe it – I said, that basically they must have missed it. leukemia is in the bone marrow, usually they biopsy part of the pelvis, so I just said "biopsy the other side" – and so we did the first biopsy on day 28, and it was negative. And then biopsy on day 31 from the other side came back also normal, with no leukemia. So that was astonishing and we had that repeated many other times.

Priya Menon: So exciting, awsome, awsome results. So with that, I will hand it over to Gary now to begin with the patient panel. Yes, Gary you are on air?

Gary Petersen: Yes. Can you hear me, I changed on to my cell phone.

Dr. Carl June: Yes very well.

Gary Petersen: Ok. Fantastic. Dr. June I would like to just tell you how excited I was, and I think most of the people on this call, and anybody who I have talked to, about having you on this program, and its because for a lot of us, especially people with myeloma, like myself – in the end we are going to end up with no new options. You provided us with the next best chance, after all our options are over, and maybe even better than that, if it comes earlier in the course of the disease. But I did want to say, earlier when we had a discussion just briefly, you mentioned something that just struck my heart and that was that you recently had a reunion with 40 children. 40 children who were beyond any help, and those 40 children and their parents with you are all alive and well – and if anything I am sure those parents think of you as a "medical messiha"….and, at the minimum your medicine as "Einstein". So thank you so much for all that you do.

Dr. Carl June: Thank you. That event was….I just can't tell you how grateful I am to be able to see those happen. Most people who work hard on a scientific problem or a medical problem for a long time, often times don't see the benefits that may happen years later, but to see these children and young adults, it was incredible. The good news is, they actually look like from what we can tell, most of them are probably cured. Because we have now sensitive assays for leukemia and we can't find any leukemia in these patients after the CAR-T cells. Now that does not mean they couldn't get leukemia again, but at least, from what we can say now is, it is going to be a rare event. Most of them have gone on now and they have just normal lives. So it is quite remarkable. There is one side effect, it is ongoing, which I should describe, which is in this case I mentioned the CD19 molecule – that is on these leukemia cells. It is also a normal B cells. And so as long a these patients have these CAR-T cells on patrol, their normal T cells also get killed. And it turns out that it causes no side effects as long as one gets Gamma globulin – which is something often get in the people who are going to an area where there are a lot of infectious disease. Gamma globulin is pooled antibodies that the red cross makes, and so that shows the CAR-T cells are still working. Because if we intentionally kill the CAR-T cells the they start making B cells again. And so if future generations of CAR-T cells we want to make them controllable by their physicians and patients, so that we could turn them on or off, and then have the B cells come back.

Gary Petersen: Great. Well, I can imagine, you have made some parents very very thankful, and certainly made you very much aware of what you have done. Anyway, Dr. June I thank you again, and just thanks for giving terminal patients a new last chance. My question is CD19 happens to be antigen that you can attack for for lymphoblastic leukemia. My question is, do you believe, there is target on all cancers, it is just a matter of finding it. I ask that question because if it is a matter of finding, then it is just a matter of time. If it does not exist, then Darn!

Dr. Carl June: Yeah. So I have…I think I can explain in terms that people can understand, because it is really simple. So in the case of T cells, they evolved to kill cells that have new DNA in them. So that means a virally infected cell for instance, are the reason we have T cells there. They evolved to protect us against viruses and a virus is an infection of a cell – it could one in your lungs, it would be flu, and sometimes it (the virus) makes the molecule RNA. Other times its DNA. In either case, the T cells can sense that it has altered its DNA or RNA in the cell, and then the T cell would kill it. That is how we get over the flu, how we get over chicken pox, or Mono for instance is the T cells kill those infected cells.

A tumor we now know is a mutation which changes the DNA in the patient's tumor cell, and T cells can sense that and can kill the tumor cells. Because it is in a way very similar to an infection, the problem is usually the tumor cell remain very much like a normal cell from the immune system's point of view. The T cell does not attack it rigorously enough. So that is where the CAR-T technology come into place. We can make a very strong recognition or binding of the T cell to the tumor cell and then it kills, without fail. That is what's really exciting. Now, so there are 2 approaches to solve the problem you brought up. Because right now a big challenge to the field is, for instance, solid tumors, and other tumors, other than CD19 positive bone marrow tumors. And I have several arguments. I am quite confident that that's gonna happen, where we will have successfully engineered T cell therapies for all tumors. So one is that there are many different antigens or molecules…

Gary Petersen: Can I say Yay! and then ….

Dr. Carl June: Yeah! But you have to understand, what I don't know is when, the time scale of this coming out is, and when it comes out, you know, so I can say in mice right now, the principle is already proven, but there are 2 kinds of T-cell therapies. There are CAR-T cells that we talked about- where its antibodies fused into a T cell, and then there are also T cells given, and we have done this at University of Pennsylvania and there are companies doing this, where new T cell receptors are put in. So T cell receptors identify intracellular, you the new proteins, the DNA mutations that I was mentioning, and they can tell inside the cell that has been altered. So they kill in the same way that a CAR-T cell does, but they use a different recognition system than the antibodies system. So we know that T-cells can't kill solid tumors, when they see these mutated antigens through their T cell receptors, that is the basis of so called – TIL therapy – and TIL stands for "Tumor Infiltrating Lymphocytes" – where lymphocytes is a scientific name for T cell.

So TIL therapy has been used for a long time for metastatic melanoma and metastatic melanoma is a tumor where chemotherapy has never been effective and now we have revolution….in that it is a first solid tumor that, where up to 50% of the patients have long term remissions for an immunotherapy – A tumor completely refractory to chemotherapy and has been done with either – so called check-point therapy where antibodies are given to prevent the immune system from shutting off this anti-tumor response. And it is also been done with TIL cell therapy, so that those are adoptively transferred. So the patient's own T cells taken out of the tumor, they are grown up in the lab, and then given back to the patient. So what I think is, is that in every patient there will be combinations of targets that will be the T cell receptor target, or CAR targets.

And there is one more nuance to understand. So right now we have a CAR-T cell that is always on, if you will, like light switch, and its always on and that CAR is always on the surface. If the T cell runs into a cell that has CD19 target it basically shoots before asking. In military terms – there are no questions asked, it just kills. Now it is possible using transistor logic, and engineers would know about so called boolean gates, the

way transitions work. They can do logic, for instance, it can just ask computers to…on initial logic questions, and it can do – AND, OR, NOT games. So, it is possible to make CAR-T cell so it can say, does the target have – two targets – say target A and B. And if it has both of those targets it kills, and you can find 2 targets on every tumor cell, where no 2 targets like that are on normal cells.

So then it can find, that is the really important aspect. On normal cells they may have target A, or Target B, but with the technologies we had you can identify unique combinations that are on the tumor cell and not on any normal cell found on the body. Then they become tumor specific killers. So that is boolean logic gating, we were calling them. Some people call them smart CARs, because they have to..they can be rewired so that they only kill when there is a certain combination of the targets on the tumor cell, and then that's gonna have to be made, so that it is specific and not on normal cells. So that principle has already been shown in petri dishes and mice. It needs to be worked out now in patients with tumors.

And the last part of that equation that makes me optimistic is – so you can always ask, well, can T cells really kill solid tumors like pancreatic cancer and brain cancer, where there has been no real progress for decades and decades. And the answer is if we make CAR-T cells in the lab from a patient and take their tumor cells out from a biopsy. We can show in a petri dish that the CAR-T cells can kill those tumor cells. So the issue is making them so that the CAR-T cells also do not kill the normal cells in a patient as well. And those are the approaches we just discussed.

Gary Petersen: Well, it sounds so exciting. It certainly made me feel a lot better, that there is going to be more solutions to the end game, in what we are confronted with right now if you have myeloma.

Dr. Carl June: Yeah. In the case of myeloma, it is the most common bone marrow malignancy in adults. As you said, it is really not curable. What has happened is that we have got a series of targeted therapies that are much better than the chemotherapy we had in the past. But myelomas has a relentless property where it seems to always come back. It may be that there is something called a myeloma stem cell which is resistant to all known forms of therapies and then that is what leads to another role – recurrences – and so with immune system it may be possible to target both, the myeloma stem cells as well as the, the common myeloma tumor cell that causes all the problems with myeloma.

Gary Petersen: Well, that is a good part of the shoot before you ask, isn't it?

Dr. Carl June: Yeah. So we need to target the myeloma stem cell as well as the mature myeloma cell that causes all the bone damage.

Gary Petersen: Ok. One last question. You had talked about the way that you used the HIV virus to introduce this antigen. We hear a lot about CRISPR and how CRISPR is better than existing systems, and is far more accurate. My assumption is that there must be some benefits as far as the cost, and also your ability to make it do what you wanted to do, say, not have too many off-target issues. Could you explain is CRISPR something that you will be using in the future, or not use the HIV, or how does that work into this

whole program.

Dr. Carl June: So, it is just an example of how basic research is lead. Now after cusp of ways where we think we can actually cure diseases, even inherited diseases, which were unthinkable in the past. So called genetic editing is the ability to change the code. Our DNA is about 3 times 10 to the power of 9, or 3 billion different base pairs of this DNA. Sometimes mistakes in just one of the those can lead to even lethal diseases or cause cancer. So you can be have congenital diseases that you can inherit, or you can have acquired ones which happen, for instance, and lead to cancer through mutations after you are born.

So genetic editing offers the ability to repair these, and it can be done in 2 forms. In basic terms, in the lab you can take the cells out, genetically edit them and then return them so that, that could be in bone marrow derived cells like T cells. It happens to be that today the first ever in vivo gene editing was reported by team lead by Sangamo. They used a gene editing technology called Zinc Finger Nucleases. They injected it into a patient who had a congenital disease, to attempt to repair the gene. So too early to know if that is going to work, but in the lab, in mice it does.

So when you actually look down at the different technologies, they alter DNA sequences. We are fortunate to have a number of tools. The first one ever used in patients was the Zinc Finger Nucleases, and we actually did that beginning 2009 in patients with HIV. And we edited their T cells to make them so that the HIV virus could no longer infect their T cells. So that was done in the laboratory, much like our CAR-T cell engineering. This is going to be complementary them. We will not replace technologies like using Lentiviral vectors or HIV to introduce genes. So there is one which is technology which can bring in new genes to the cell. There is another which can change target genes to achieve a benefit in the patient. They are really very complementary.

You mentioned the CRISPR technology which uses an enzyme derived from bacteria called Cas9. It will cut in the DNA and you can target it with amazing precision. It is truly the needle in the haystack. So, of these 3 times 10 to power of 9 or 3 billion different base pairs in our DNA, you can target which on you want to change with this CRISPR Cas9 system. Its real advantage over the previous gene editing technologies like Zinc Finger Nucleases- is that it is more rapid in the laboratory to test many different targets. So it is very flexible. I am quite sure, we are going to see many of these technologies used both in the laboratory – for instance bone marrow cells are altered and then given back to the patients. Or, in certain tissues, they will be injected directly injected, and those areas will be modified as desired by systems like CRISPR Cas9.

Gary Petersen: Very well. Fantastic. By now I am totally convinced that you are a special special person. From now on I am going to start calling you Dr. Carl Einstein June.

Dr. Carl June: No no. You have to understand. I mean immunotherapy had been an idea for more than a 100 years. You know to try to treat cancers. So the ideas are not new. I mean there was a surgeon in New York city in the late 1880s and 1890s injecting bacteria and products from bacteria in the patients tumors, because he thought he could activate the immune system and in fact he did. Some patients were cured when they were deliberately infected with bacteria. We now know in retrospect that that was, it was activating immune system but it never became FDA approved because it was not reproducible enough and was also quite dangerous.

So the idea to use the immune system has been an old one, but we did not have initially the tools that were good enough to make it work. Now we have through all years and years of basic research on the immune system and ways to modify genes. In fact, in the entire human genome sequencing effort has had a major benefit in this cancer immunotherapy. So, these all ideas now are able to actually be done now because we have better tools to get the job done.

Gary Petersen: Well thank you. Jack Aiello, are you online?

Jack Aiello: I am this has been a great discussion. Dr. June it is really nice to meet you over the phone. I have actually met you once before couple years ago at the leukemia Lymphoma Society meeting when you introduced Emily Whitehead and her parents.

Dr. Carl June: Yeah. Thank you jack. Thanks for working with all of us. You know when you have an out of the box therapy, one thing we have learnt is a standard science often does not fund that research, when it is out of the box. I was unable to get initially, funding from National Cancer institute. They funded our development with HIV virus that I described earlier. But when we want to do clinical trials in patients with leukemia, I was unable to get that funding. It was only through the leukemia and Lymphoma society that we were able to start that trial.

Jack Aiello: That is what I understand. In the trial that you discussed, we configure the T cells to recognize the CD19, and yet, I also think you gave that treatment to some myeloma patients. And I had heard that some of the myeloma patients responded and yet I never understood why because we don't really have CD19 as a marker on our myeloma cell, I don't think. But I was curious if that is true, did they respond and what is their condition today?

Dr. Carl June: I am going to go back and describe what I think is the stem cell. There is a cancer stem cell, and myeloma cells may be in a way like a chameleon, and change the molecules on their surface at different times during their lifespan. We have data and there is a scientist at Johns Hopkins named William Matsui, who has shown over the years, that there are normal B cells that do have CD19, that appear to be the precursor to the mature myeloma cell. So, as you mentioned we treated the first patients on our trial, just testing our CD19 CAR, with patients with myeloma. She had a complete remission and she is doing very well now 4 years after treatment. She had had 10 different kinds of therapy before that never worked. When we looked at her myeloma, only about 2% of the myeloma cells had CD19, and yet all the myeloma cells went away when we treated it with CD19 CARs. So, we have now done a trial and about 2 out of 10 patients had quite strong responses to the CD19 CAR, but 80% of the patients did not.

There is another molecule that we are testing, and other companies are now testing for myeloma called BCMA – stands for B cell maturation antigen. We are having responses quite routinely in patients using CAR as a target BCMA. So, what I am going to describe now is not yet been published, but we took 10 consecutive patients with myeloma and tested their cells in a petri dish and then put them into an acid, and looked like we eradicate all the myeloma cells. Even the long term so called stem cells. And when we treated

with CD19 CAR, it eradicated about 20% of the myeloma patients – where all the cells were killed, that had long term ability to cause myeloma. With BCMA it was 70%. And then, when we gave a combination of CARs targeting CD19 and BCMA, we had 10 out of 10 eradications in the laboratory. So we are really excited about that and we are just beginning the trial with no one yet treated, but we are going to get them the combination of CD19 and BCMA CARs. So if you will, it will be a cocktail of CARs, and that may become common, I think, where many tumors will be treated with a combination in order to eradicate every single last tumor cell.

Jack Aiello: So that was actually my next question, and that is, is it possible to build a CAR-T to recognise more than one antigen, maybe through the analogic or maybe just through having separate CAR-T development will do that?

Dr. Carl June: Yeah. It is a very exciting area of research. There are number of ways technically to do this. I was mentioning this boolean logic, where you can have a CAR target A or B or C, may be 3 different CARs on the same T cell. So, we now have the technology to do that, and there is a trial that just opened up at stanford, targeting 2 molecules for leukemia. It is targeting CD19 and at the same time CD22. I think we will have the same thing as myeloma, you know, as i just described, using BCMA and CD19, and I think we are just at the surface. We are just scratching the surface of next generation therapies, that will be both, more potent, higher cure rates and then less toxic.

Jack Aiello: And I also hear in the future that this CAR-T technology might be off the shelf and might be replaced by something called BITE technology. Can you share a little bit about that?

Dr. Carl June: Yes. So, those are 2 different concepts. Off the shelf, I mentioned that CAR cell therapy really is a form of transfusion medicine, and instead of red cells or platelets which are routinely transfused, this is T cells. Off the shelf, CAR T cell would when it won't be the patient's own T cells. And if that could happen, it would make the process much simpler. Because right now, it is logistically intense effort, where the manufacturing process is unlike anything of the pharmaceutical industry really, where, it starts with a patient. They donate the T cells in a process called, where the blood is taken out by either, just blood donation or apheresis machine. The cells are then shipped to the manufacturing plant. About 2 weeks later they return back, and are now frozen. Then the CAR T cells are given to the patient by about a 5 minute infusion. So, the cells are just thawed in a water bath, that is the same temperature, as body temperature – 98.6 degree F. When the cells are all thawed out the CAR T cells are just infused over a period of about 5 minutes. So that is how, the current FDA approved CAR T cells are given to patients.

And off the shelf form would be more like a standard pharmaceutical product where it could be made in large batches. What it requires is that is, we have something like we do in the blood cell transfusion where we can have universal donors. So it happens to be that I am an O negative donor, and I can donate blood to anyone. Because of that, about 15%of patients have this blood type of O negative. We do not have that for T cells, unless you have an identical twin. So if you are an identical twin, you are lucky, you got someone else who can be an off the shelf donor for you, but for most people that is not true. We need to be able to genetically modify the donor T cells so that they do not do 2 things. So one is – I mentioned that in bone marrow transplants, you get graft vs host disease. That is where the incoming bone marrow attacks the patient, and T cell would do that, so I would take someone off the street, make CAR T cells, and then infuse them in the patient, the patient would later get graft vs host disease from the infused CAR T cells.

So we have to remove that with genetic editing. The ability of off the shelf cells to cause graft vs host disease. And then, the other problem happens is that the patient themselves will reject the incoming CAR T cell, and that is called host vs graft. So it is the other way round the patient's immune system. And, so then, these off the shelf T cells need to also not have that happen. There are trials now testing these off the shelf cells. Very early stage trials are being done in London at the Great Ormond Street Hospital, for infants with leukemia. And in New York city there is a collaboration between 2 biotechs and pharma – Cellectis, Servier, and Pfizer are working on making off the shelf T cells for patients with leukemia.

So I think, in the end, we will have standard oncology – what we call induction chemotherapy and then maintenance therapy often times. I think, we may well have 2 kinds of CAR T cells in the future. One that is the kind that can last for the rest of your lives in your body, and that would be your own cells manufactured. And there will probably be I think an off the shelf form of CAR T cell, that could be at any community hospital and given right away. And then later probably for a long term. I don't think the of the shelf T cells are likely to last life long in a patient, unlike, when you use your own T cells. So I think we will have both forms of induction and consolidation with these kinds of engineered T cells.

Priya Menon: Thank you Jack. We are just running a bit overtime here. So, Mike you are on air, please asak your questions and then we can just open it up for the audience.

Mike Scott: Hi Dr. June. I am not going to ask you any questions because I want to make sure we have time for people who are on the phone to ask you questions. But I did want to tell you a very brief story. In 1983, I met a man called Berry Marshal, and on the way to a meeting in Belgium just after he had shown that a bacteria caused ulcers. I published that paper, I told him at that time, he would get a nobel prize. And I am telling you now, i hope you and your team get a nobel prize after this work.

Dr. Carl June: Well. Thank You. I did notice…..

Mike Scott: I know how rare it is, that something like this happens.

Dr. Carl June: Yeah. I have been very blessed. I have amazing team that I work with. Many of the people I am working with, I am working with for more than 20 years. But I notice you work for Prostate Cancer. And I want to just say that we have just treated our 2nd patient for patients who had metastatic hormone resistant prostate cancer with CAR T cells.

Mike Scott: Excellent!

Dr. Carl June: Yeah. It is a trial sponsored by the Prostate Cancer Foundation. It is at a very early stage – a

pilot trial to understand if we have a safe target and if we can make any headway in these patients right now who have no options.

Mike Scott: I did hear a presentation you gave a few years ago at the Prostate Cancer Foundation meeting in washington. So I have been optimistic ever since.

Dr. Carl June: Yeah. So it is finally happening. So we are excited about that but you know, we just don't know how long the road is going to be in patients with solid tumor. It is a complex problem.

Mike Scott: I really want to give people on the line the chance to ask questions, so I will waive my right to ask any others.

Dr. Carl June: Ok.

Priya Menon: Thank you so much Mike. We are opening up the discussion for the audience and I am repeating the number to dial in if you have a question for Dr. June please use 718-664-6574 to dial-in. Press 1 on your phone keypads and we will bring you on-air to ask your questions. We already have quite a few listeners dialled in Dr. June. I will just bring first one on line. Hi Dana, please ask your question.

Dana: Thanks Priya. Hi Dr. June. I am checking in a little bit late, so I have a few questions which you may have already answered so please feel free to say, already answered, and I will listen to the transcript when it comes out. I did want to make a comment that I was excited to hear about combo CAR T trial about myeloma – CD19 and BCMA. This was one of my questions. I was going to ask you, which was the most promising target for myeloma – was it BCMA or CD19. And the CD19 did confuse me because most myeloma is CD19 negative. But I did hear you say it, and I am going to listen to that again. So thank you for that.

If a patient responds to CAR T, but begins to lose response and show signs of relapse, would they get a CAR T cell boost similar to what is done with allo?

Dr. Carl June: Yes. In short there are a number of strategies, both in the lab and then just starting to look at that, if boosting CAR T cells, either by reinfusing and maybe we need to have maintenance infusion and that has been explored in some early stage trials. There is this trial in seattle where they are vaccinating patients to boost up the CAR T cells. So they are vaccinating with CD19 antigen, and then that would be a way then, without having to reinfuse the CAR T cells where potentially, one could maintain the effect in those patients who lose effective CAR T cell engraftment.

Dana: Ok. And do you eventually, this is for myeloma patients, because I am a smouldering myeloma patient. Do you eventually envision using CAR T early on in the disease, newly diagnosed myeloma patients,

even smouldering myeloma before the disease seems to take traction.

Dr. Carl June: So I hope that. We would love to be able to move it up to the benign, the so called MGUS. That would be more cost effective and that trial is going to begin in leukemia where children….right now the standard of care for leukemia is 2-3 years of chemo and or radiation. And the trial is going to begin where there is going to be people with poor prognostic, you know, newly diagnosed leukemia is going to be randomised to repeat standard care or CAR T cells. So, we first need to get FDA approval of CAR T cells for advanced myeloma. And then I think those conversations will happen in trials to test it, more and more upfront rather than as a salvage.

Dana: Would patients need to be treatment naive to be able to benefit from something like that. I would presume it in smouldering and MGUS stage we already are. Let's say for a newly diagnosed myeloma patient?

Dr. Carl June: So, you know, we first have to use FDA approved drugs, before we go to experimental settings. But I think, all we know about immunology, says, that the earlier it is used, it works better. Because the tumor is less complex and because immune system is more intact and so the CAR T cells work better, than after many rounds of treatment with all the steroids and chemotherapy in myeloma. So, it is a matter of how fast can we do this clinically and ethically. We first need to show that these are small number of patients so far, but trials are very good in advance myeloma of CAR T cells. And then how we would we move that upfront. Myeloma teams will be doing those trials, it is just going to take longer than we would wish. Because when you treat people in early stage disease, it takes a lot longer to prove it works. It was really easy in our leukemia trials, because those patients really had only weeks to live, so it did not take very long to show that it worked. As we move earlier up front in myeloma where, as you know, there can be very long term survival, it is going to take more than a decade to get there.

Priya Menon: Thank you Dana. The next caller on our line is Williams. Williams you are unmuted please ask your questions. Williams please ask your questions. Ok let's move on to the next caller. Richard you are unmuted please ask your question. Richard Davis we have unmuted you please ask your question now.

Richard Davis: Yeah. Hello Dr. June. This is a question going back to your comments on prostate cancer. In layman's terms how does this CAR T technology differ from the proven Sipuleucel T technology that has been approved in prostate cancer in 2 or 3 years. I recognize one difference is that the Sip T uses the patient's own cells but what else do you have similar and what else is different?

Dr. Carl June: So they are very different Richard. So the Provenge or Sipuleucel T is a vaccine and it is made of cells that are used to vaccinate which are dendritic cells. Dendritic cells are what start and immune response, and so in this case it is the patient's own cells that are collected by apheresis, the same way we collect cells for CAR T cells therapy. Then they are modified in the lab over about 4 days and given back to the patient, for the vaccine that is Provenge. Now CAR T cells it is using…it does not….you know.. for a vaccine you have to have the patient develop and immune response, and then later they are protected. That is why right now we should be getting flu vaccines to protect us in January if you live in the US…you know..for when you will have flu epidemics. So takes time for the immune response to occur.

With CAR T cells it is called active immunotherapy. They start working the minute they are infused. And you do not have to wait. T cells live for years and years, I mentioned more than a 10 years half life with our initial CAR T cell trials. Dendritic cells only live 3-4 days, and then what they need is to then trigger a long lasting immune response in the patient. So they are probably complementary therapies, I mean they are very different approaches – one being a vaccine approach and one being active therapy. So that is the main difference – using different cells – dendritic cells in one case versus T cells in the other that has long life.

Priya Menon: We have got a lot of questions on our site. I would like to cover something that we have not already discussed Dr. June. Is this treatment offered for 55 years or older?

Dr. Carl June: Yes. There is immunotherapy can work in very old patients, in fact where chemotherapy use is not given. One of the first 3 patients we treated, one was 77 at a time. It came out in the press about an year and half ago, Jimmy Carter, age 90-91 got melanoma that spread to his brain. he was treated with immunotherapy, not with CAR T cells, but with check-point therapy, and what is said out in the press is that he has had a remarkable response. So anyway, 55 and older is very common in our trials.

Priya Menon: Just one couple of questions and the we can wrap up. I think we are almost at the end of the time. When is this treatment becoming available for AML?

Dr. Carl June: Well that is a great question. AML is – the standard for treatment for AML has not changed since I was in medical school in the 1970s. So there are trials now, there is one beginning at the National Cancer Institute in Bethesda, in 2018, to where the CAR T cell trial targeting CD33. There is another one targeting CD123 for AML, which has opened in City of Hope in Los Angeles, and will be open at University of Pennsylvania. We also have a trial targeting CD33 for AML at the University of Pennsylvania in 2018.

Priya Menon: Thank you doctor. The last question – I have stage 4 colon cancer. Is it something that can treat this?

Dr. Carl June: So the answer is – in a long term – yes. Presently there are a very few trials for colon cancer now and they require the use of T cell receptors rather than CARs. And I described some of that earlier. And if the boolean gating, making the so called smart CARs that I described earlier can be done then, CAR T cell could also be used for colon cancer. But at this point all the CAR T cells targets tested so far, would also cause colitis, and target the normal colon.

Priya Menon: Thank you doctor. CAR T cell therapy as we all heard is a game changer in cancer treatment and offers hope to people, but probably the cure is around the corner. So we have heard how the new therapy works and we wish Dr. June and his team all the very best in continuing with CAR T cell research. And hopefully we will have a new breakthrough soon. Thank you very much Dr. June for your time and it has been an exhaustively informative session for all of us here. Gary, Jack and Mike thank you for your participation and the great questions. And A big thank you to the wonderful audience.

The talk will be available on CureTalks website, along with its transcript, question answers and summaries. Please visit curetalks.com for details on upcoming talks.

Thank you everyone, have a great evening!