CAR Therapy for Myeloma Treatment with Dr. Craig Hofmeister

CS1-CAR is a new and radically different approach in cancer treatment that harnesses the power of the patients immune system to rid itself of cancer. Initial clinical trials of a similar therapy used in treating Acute Lymphocytic Leukemia showed extraordinary success 88% of patients achieved complete remission.

CureTalk panelists are talking to Dr.

Craig Hofmeister to help us understand this new therapy and how myeloma patients will benefit.

Full Transcript:

Priya Menon : Good evening, everyone. Hello and welcome to Cure Talk. I am Priya Menon, Scientific Media Editor at Cure Talk, joining you from India; and I welcome all of you this evening to a discussion on multiple myeloma on Cure Talk's 85th episode. My co-host for the talk is myeloma advocate and editor of myelomasurvival.com, Gary Petersen; and supporting Gary is our esteemed myeloma panel of advocates, Pat Killingsworth and Jack Aiello. We are truly excited to have amongst us a very distinguished expert, Dr. Craig Hofmeister. Dr. Hofmeister is Assistant Professor of Medicine at the Ohio State University Comprehensive Cancer Center and is currently working on a breakthrough myeloma treatment therapy. Welcome to Cure Talk, Dr. Hofmeister.

Dr. Craig Hofmeister : – Thank you so much.

Priya Menon : – I would like to remind our audience that we will be addressing questions sent in via email towards the end of the discussion. If you have a question for our expert, you can let us know by pressing 1 on your keypad or mail them to priya@trialx.com. With that, I now hand over to Gary to begin with the discussion. Gary, you are on air.

Gary Petersen : – Well, thank you very much, Priya, and as always, thank you for bringing this great educational format for all myeloma patients. Dr. Hofmeister is an Associate Professor of Medicine at the Ohio State University and is the lead of the section of plasma cell dyscrasia and one might ask or one might google, what is dyscrasia or what happens to be plasma cell…, plasma cell dyscrasias are produced as a result of abnormal proliferation of a monoclonal population of plasma cells that may or may not secrete detectable levels of monoclonal immunoglobulin or immunoglobulin fragments, paraprotein or M protein. Neither is it either MGUS, multiple myeloma, solitary plasmacytomas of the bone, extramedullary

plasmacytomas, Waldenström's disease, primary amyloidosis, light chain deposition disease, paraproteinemia, and heavy chain disease; and thank goodness, you just called it dyscrasia, but in addition to this research…, his research interests, he is attending physician in lymphoma, myeloma, and bone marrow transplant service. He is an ad hoc reviewer of publications including Blood, Journal of Clinical Oncology, Clinical Cancer Research, and the British Journal of Hematology in addition to others. He is the recipient of the Image MMORE Award and Business First Forty Under 40 Award in Ohio, the Ohio State University College of Medicine. So, thank you very much, doctor, and we certainly do appreciate you being here. Could you tell us T cells are a type of…, are a type of white blood cell and…, and…, and our listeners may not necessarily know what a CAR T cell is for use in cancer treatment and could you please give us a definition of what is a CAR T cell and a history of its use in cancer treatment…, in the cancer treatment armamentarium, if you would?

Dr. Craig Hofmeister : – Absolutely! So, a CAR T cell is not automotive. There is no transportation involved here. CAR, like many acronyms in medicine, stands for chimeric antigen receptor and the idea here is the T cells are part of your immune system and your immune system lives in your bone marrow in your blood and those two areas are really connected. So, in your immune systems, T cells and B cells are both different types of white blood cells and your blood is made up of white cells, red cells, and platelets. Now, T cells have T cell receptors on their surface and that helps them recognize what is…, belongs in the body and what doesn't belong in the body and the idea is that T cells use this T cell receptor as well as other receptors to figure out if there is potentially a foreign invader in your body, bacteria, fungus, all sorts of things that might come in and attack it and kill it and that's what the T cell receptor does, in general, quite well, but cancer is crafty and cancer essentially creates on its cell surface and around it a protective layer so that your own T cells don't recognize these cancer cells as foreign. So, to get around this, you can, through genetic modification, force a T cell to put up a chimeric T cell, somewhat synthetic T cell on its surface, forcing that T cell to recognize a particular antigen or a particular protein on the cell surface of whatever cell you are looking for and for us its all myeloma cells. So, a CAR T cell is a genetically engineered T cell that targets towards at least one but potentially more than one target on a myeloma cell and CAR T cells have a difficult history. This has been in investigation in clinical trials and in laboratories for decades: and there's a lot being modified, how the T cells are forced…, how the T cells are created, how to make a T cell and genetically modify it, not to mention the targets that these T cells look for. Now, over time, we have had many…, a lot of CAR T cells that were in clinical trials that did not really have much effect and over the years modifications have occurred to make these CAR T cells more effective and most recently, these CAR T cells have been used effectively in other blood cancers, specifically ALL, acute lymphoblastic leukemia, and CLL, chronic lymphocytic leukemia; and ALL and CLL have had some fabulous results and there's also been a number of great results in a type of aggressive lymphoma called diffuse large B cell lymphoma which is a type of non-Hodgkin's lymphoma and there are many, many clinical trials using CAR T cells currently in process or actually ongoing in accruing patients, a number of cancers, but certainly a number of them looking at ALL, CLL, and lymphoma.

Gary Petersen : Okay. How…, how does this prior research apply to myeloma treatment?

Dr. Craig Hofmeister : So, most of the work has looked at other blood cancers and been successful and what we would like to do is be part of a new…, another wave of CAR T cell trials, looking at diseases other than CLL and ALL. For us, myeloma is the focus. Now, there are two clinical trials, CAR T trials currently accruing in…, currently accruing myeloma patients, one's at University of Pennsylvania, looking for myeloma patients who express a target called CD19 and most…, and many myeloma cells express CD19 at a very low level and that low level may be quite enough. There is another CAR T trial currently enrolling at the NCI, National Cancer Institute, for patients whose myeloma expresses a target called BCMA, B-cell maturation antigen, and so they are looking for myeloma, BCMA-positive myeloma patients and that is a…, a good proportion of myeloma patients for a CAR T cell trial there. I believe there is a third CAR T trial, looking for NKGD2A antigen on the cell surface of myeloma cells and also on the cell surface of patients with AML, acute myeloblastic leukemia or acute myelogenous leukemia, and that's, I think, going to be open at Dana-Farber, but I don't know if that started accruing patients yet. So, it won't be long before we have three active trials accruing myeloma patients for CAR T-cells and we would like to join this group and we

hope to have a clinical trial open next year for CAR T cells targeting a CS1 antigen, which is… CS1 is the protein otherwise known as SLAMF7, if that doesn't roll of your tongue, that is on the cell surface of the majority of myeloma patients that we have tested so far.

Gary Petersen : Okay. Now, you mentioned this research on CS1 gene and it being the target. So, does this…, and…, and does this mean…, you know, and I understand, you know, what you are…, what you are doing at least in…, in the broadest terms, but I understand there is this target and off target issue and…, and how has that been addressed in…, you know, the other cancers and how is it being addressed in.., in…, in myeloma as well?

Dr. Craig Hofmeister : So, you know, this is following a target, CS1, that's what we are trying to engineer T cells to target on myeloma patients and there is actually an antibody targeting CS1 that's being used in clinical trials and is not currently FDA approved but is being tested in a clinical trial in combination with a common drug Revlimid and dexamethasone plus or minus this drug, elotuzumab, and that drug has made it through phase I, II, and currently phase III testing and so we are hoping that that gives us some evidence of safety, but just because there is an antibody and its just a naked antibody, just targets it but is not attached to a cell or anything and that's essentially how antibodies work. They blanket cells with these antibodies and hopes that just because the antibodies are on the outer surface of these cells that causes your body to chew up the cells, that…, we hope that elotuzumab experience showing it to be safe in patients with myeloma will kind of pave the way and demonstrates that we hope it will be safe for these CAR T-cells targeting CS1. Now, CAR T cells are not naked antibodies. This is a T cell and so, even low levels of expression of CS1 could get us into trouble if there is low-level expression of CS1 on important organs that we don't honestly know about or have not tested or there's cross reactivity with other proteins. Thus far, in the tests that we have that we have no evidence of this, but certainly that's a big concern. So, we call that on-target, off-tumor side effects. We certainly don't want to have that and, but we are wary of that as other CAR T cell trials in the past have had on-target, off-tumor effects, which have led to significant toxicity…, significant side effects for patients. So, we want to avoid that. We are working to try to address that as best we can before this goes into clinical trial and patients are exposed. Interestingly, you had to worry that if there is this elotuzumab out there and that this is used in myeloma patients, that now if every myeloma patient starts getting exposed to the CS1 antibody, maybe at the time that that antibody is no longer effective, that… , that means the patient's myeloma cells won't express CS1. We don't know that yet, so that's another concern and I guess that…., that's dealing with the fact that a drug could cause a proportion of myeloma patients to not express CS1 in the future, making our CAR T cell trial or our CAR T cells ineffective. We don't know if that's the case, but that's a theoretical concern.

Gary Petersen : That happened, didn't it, with, you know, the leukemia trial, but some of those that work was the CD19..and that the leukemia cancer then quit expressing CD19, but it was…, it was still there.

Dr. Craig Hofmeister : Right and its likely that what happened was that there was a different clone or a group of leukemia cells that weren't the majority but was actually a small minority that didn't express CD19 and when all these CAR T-cells came about that killed all the cancer cells that expressed CD19 allowing the CD19-negative cancer cells to take over and obviously the…, the CD19-focused CAR T cells are going to be ineffective. We don't know if that's going to be a big issue in myeloma for CS1, for CD19, or for BCMA, any target currently. [END]

Gary Petersen : Okay. Those…, those pesky little cancer cells that keep on morphing and…

Dr. Craig Hofmeister : …and its a question of really whether its morphing or whether because of the majority of myeloma patients at diagnosis have a number of clones around, so two to six kind of different clones or tribes of myeloma cells at diagnosis. So, those… and its not that they all go away. Its just that at relapse usually one clone takes over, but the other clones really aren't usually gone.

Gary Petersen : Okay. I understand you have already had some really very positive results. Could you explain these results and what the next steps will be in the development of this treatment?

Dr. Craig Hofmeister : So, the positive results so far are…, form the basis for the clinical trial. So, we have tested it in cells from salines. We have tested it against cells that we got from bone marrow aspirates from patients. We have tested it in mouse models that use salines in these mouse models to kind of get a better idea of how it works in an actual animal. Those tests have all been very effective; and when we see the cells die, when we see the mice have myeloma everywhere and then take a picture of them after the CAR T cells go away and then you can't find any myeloma, that's always very reassuring and positive and suggestive that this will be effective in humans, but, you know, how many in-bred mice have we cured of cancer? Lord knows its quite a lot and what we hope to do is try to bring this to patients because in-bred mice really aren't as reflective of a patient's immune system and the complexity of human disease as we would like. Now, we are working on this at the same time, trying to develop newer, more accurate, more reflective mouse models that bring in a lot of the complexity of the human immune system so that we can test it before we expose patients to this and that work's ongoing.

Gary Petersen : Next, you are going to tell me that your mouse models don't come from Victoria's Secret. Is that right?

Dr. Craig Hofmeister : Sadly enough, the…, the…, the…

Gary Petersen : Or you gave me the car joke, so… `

Dr. Craig Hofmeister : Yeah. We…, we…, we don't call them angels either.

Gary Petersen : …the mouse model joke. (Laughter) Okay. All right. And this…, this next one is, I think, quite important and that is, as is the case with many outstanding clinical trial ideas, we understand that your's is not yet totally funded and how can we and the audience help to make this happen?

Dr. Craig Hofmeister : So, the… I appreciate your asking. You know, we never… You never have fund… You can never say you have funding until its done, until the trial is there and everything's, you know, every patient's been treated. So…, and we are still trying to work out the exact cost of each patient, but from other CAR T cell trials, not our's, we know that, in general, CAR T cell trials cost an extraordinary amount per patient, somewhere between a 100,000 and 500,000 dollars to just treat a single patient and that covers obtaining the patient's own T cells, genetically modifying them, expanding those genetically modified cells in a sterile and supportive environment, and then infusing those cells back into the patient and monitoring the patient for side effects and for effectiveness. That's a…, that's a big task and its incredibly expensive and there's a lot of effort to try to show that this will be success for the patient's own T cells and to think about what's the second generation of these trials, the third generation, what can we do to make these even more effective, even safer and with less cost and that's all coming down the pike. If…, if you are reacting to this, thinking, "Ah, this is way too expensive. Why would we even be in support of this?" This is the first wave and the first wave is…, is…, is never perfect and we will continue even as we get this clinical trial up and going to find ways to make the treatment better, safer, and more cost effective. To support this research, our clinical trial specifically…, we are doing everything we can. We are looking to industry partners. We have written scientific grants to a number of funding agencies. We even had a crowd funding campaign through endmyeloma.org. So, anything we can to try to support the research to get it quickly from where it stands now to actual patients accruing, that's…, that's all we are interested in.

Gary Petersen : Okay. Well, thank you, doctor, and what I would like to do now is to open it up to our distinguished panel and if… Pat Killingsworth, are you on the line?

Pat Killingsworth : – I am here, Gary.

Gary Petersen : All right, Pat. Your questions?

Pat Killingsworth : Hi, doctor! I have a couple questions. You know… I know its difficult to get consensus that you are all trying to find the magic acronym plus number if you could call it CS1 or WT1 or whatever and

I understand how difficult it is and I thank you so much for basically giving your life to try to save our's. I mean, its… its… amazing! So, thank you! It seems to me there are two types of safety, though. There is safety as in, is the T cell therapy safe, but then what about the opportunity cost lost and what I mean is so, if fiddling around with the CAR T cells and doing this…, this other stuff and in the meantime there's no maintenance, maybe no Revlimid or pomalidomide or Velcade or Kyprolis or whatever, isn't there a danger from that aspect also?

Dr. Craig Hofmeister : So, I… I guess that your question focuses on are we putting with this therapy, with these patients? Are we putting all our eggs in one basket and expecting these CAR T cells to do everything? Shouldn't we kind of not forget some of the therapy that came before and is ongoing?

Pat Killingsworth : Well, that's… That's a good… That's a good point. I wasn't going there, but we should go there. Now, I was just thinking that why you are doing, for example, another…, another doctor that we are considering supporting is working and his target is WT1 and so you go through this process and if that doesn't work, you haven't been using the tried and true drugs that have been helping keep a patient's myeloma under control and isn't there a real risk to that?

Dr. Craig Hofmeister : Well, I mean the patients that, you know, are…, are eligible for this trial have in many ways been there, done that. They have seen most or all of the effective therapies and there's not much else that can be safely given. So, these patients that we think of here that are…, that are eligible for a good section of these trials don't have a lot of other options or if they do have other options, its clear from the pace of their disease that the current options are not sustainable. There certainly are clinical trials that… There certainly are experiments ongoing at…, at our center and others that are looking to combine CAR T cells with other therapies to try to make the CAR T cells more effective and to see if they are in essence synergistic or antagonistic in any way and as…, as you would expect, there are experiments ongoing at many centers now looking at multiple CAR T cell targets at the same time. If one is…, might be effective, wouldn't it be better and you increase your chances to have two or even three CAR…, CAR T cell targets? So…

Pat Killingsworth : Sure, I was going to ask about that.

Dr. Craig Hofmeister : Absolutely! All those…, all those scientific experiments are ongoing and all of them, you would imagine the most successful are going to translate to the clinic. So, absolutely! I agree with you, is that we need to be thinking oh, is the target right? Is the…, the way we… If we genetically modify the T cells right, are we, you know, missing something in terms of how we treat the patients to kind of keep them in balance and safe after they have the CAR T cells? This is something we can do along the way to make it easier for the CAR T cells to expand, to kill but yet not hurt the patient in all this expansion. So, most clinical trials ongoing now question at least some aspect of this.

Pat Killingsworth : Sure, it just has to be so difficult, but the patients you are getting are so darn beat up that…, that can't make it…, that can't make it easy either. You are fighting a very trained and likely full by the time you get to where you are doing your trials. So, that has to make things even more difficult. Can you explain? Now, are you doing these in…, are you doing this in conjunction with allogeneic transplantation?

Dr. Craig Hofmeister : So, you know, the vast majority of allogeneic transplants in myeloma that are standard allogeneic transplants, you know, those are usually not very popular or terribly effective in myeloma if unpopularity is related to the fact that its not terribly effective. Certainly, there are some novel strategies to make allogeneic transplant more effective and…, but for our trial and for many…, most…, for the two other CAR T cell trials that…, the three other CAR T cell trials that are either accruing or in…, in…, in…, in production, you know, none of them are necessarily required or linked to an allogeneic transplant and that's…, that's different than CLL and especially the ALL because both of those have had a closer link to transplantation because in those diseases, allogeneic transplant has had a little bit more successful history.

Pat Killingsworth : Sure and so there's no…, there's no auto involved either. This is sort of a free

standing. Well, that… Well, that's nice from a safety standpoint. That's…

Dr. Craig Hofmeister : Absolutely and, you know, the UPENN group, their CAR T trial targeting CD19 in myeloma patients is tied up in an auto transplant and so, you know, that could be, you know, that changes the patient selection. It changes potentially some of the risks and certainly incredibly different from a patient standpoint in terms of expected toxicities, etc. We don't know which will be better and so its…, its an interesting hypothesis to link it there and it may be the best way to do it as that type of immunosuppression from that dose of chemotherapy may be what's needed for expansion of the CAR T cells. We don't know and that's a big question. The UPENN is fabulous in looking at the kinetics of how these cells expand and we will all be looking to try to figure out what's the best environment for these CAR T cells to expand and be effective.

Pat Killingsworth : Great! Thank you. I just have one more…, one more general question. There seems to be no consensus with this. What is your opinion? If in an allo transplant, is graft…, GVHD, graft-versus-host disease necessary, do you think, to…, to…, to slow down or…, or kill myeloma or do you think that it could be done without the GVHD and, of course, then that would make the procedure a lot safer, I am assuming.

Dr. Craig Hofmeister : Yeah, I mean you described quite…, quite concisely the holy grill of allogeneic transplantation, graft versus tumor without graft versus host and there are, you know, 10 interventions we can list off real quick of things that are ongoing in clinical trials to test if that particular intervention gets us closer to an allogeneic transplant that has graft versus tumor without graft versus host. Currently, you know, you would say that the majority of patients who have clear graft versus…, effective graft versus tumor have some evidence of chronic graft-versus-host disease, but this chronic graft-versus-host disease is not like pregnancy. It is not yes or no. It is a huge spectrum of symptoms, side effects, signs, so that a little chronic graft-versus-host disease from a patient's perspective and a physician perspective is drastically different from graft-versus-host disease which is lethal and there is everything in between. So, I think that currently chronic graft-versus-host disease is often linked to effective graft versus tumor and clearly, lot of interventions to try to dissociate those two, so we can get graft versus tumor without GVHD.

Pat Killingsworth : Sure. Interesting! Well, I want… Before you describe exactly what you are trying to do and… and…, and…, and your next step, why don't I turn things over to Jack? Jack, are you there?

Jack Aiello : – I am here. You can hear me okay?

Pat Killingsworth : Yeah, I hear you great. Thanks, Gary.

Gary Petersen : You bet! Jack, you are up.

Jack Aiello : Dr. Hofmeister, I appreciate being able to meet you over the phone and I am really encouraged by your explaining this very complex issue to us. I was fortunate enough a couple and a half months ago to hear Dr. Carl June at the University of Pennsylvania speak on this subject and he off the side did mention that, as you said, they tried these CAR T cells modified CD19 on a few myeloma patients and he further indicated, to his surprise, some of them showed some response and he wasn't sure why because as you indicated CD19 is not much of a marker on myeloma cells and I was wondering if we understand more about why there was a response now and do you know what's the response that, durable response even if its only a few months?

Dr. Craig Hofmeister : So, I…, I don't have an update on durability. He did describe this data at the American Cyto-Hematology meeting in December 2014. I have not heard an update since then and, you know, CD19… You know, Carl June is a…, is a…, is a wonderful scientist and he is right to be questioning and be a little bit surprised that you would see a response because its not thought to be a characteristic marker myeloma, but even a small density of this target on the cell surface may be enough for these CAR T cells to have activity and to be effective anti-tumor agents if the target is present even rarely on the cell surface. Now, the…, the question is durability, just as you say. Do the cells… Are we able to create,

genetically engineer CAR T cells so that they persist in myeloma because we don't necessarily know that they will persist in myeloma as well or as long as they did in ALL or CLL and the next question is, just because you are able to kill all the myeloma cells that even have rare expression of CD19, does that just mean that we nip off some of the clones but that resistant clones that are CD19 negative won't creep up and to my knowledge, those questions are not yet answered from the UPENN group. We know that from the NCI group, for their BCMA CAR T trial that there are some patients who don't express BCMA. Their myeloma… The predominant clone that…, that presents in those relapsed patients didn't have BCMA, so they couldn't enroll on the trial. We don't know what percentage of relapsed myeloma patients are BCMA negative. So, we are interested to see how effective that would be and, you know, its literally on the tip of your tongue and brain, that, oh, wow, wouldn't it be great if we could do two CAR T trial targets at the same time or three? You know, you… I just find my brain heading there super quick, but I think that because the risks are so significant we have to keep plodding along bit by bit to be sure that we don't all jump on the bandwagon of the therapy, that's too dangerous.

Jack Aiello : With your decision to yield the CS1 CAR T cell, you are doing that because more myeloma cells express CS1 and that's the reason elotuzumab monoclonal antibody for CS1 has been developed as well. Correct?

Dr. Craig Hofmeister : Yes, its our…, its our hypothesis that the majority of relapsed myeloma patients have CS1 on the cell surface of myeloma and its our hypothesis as well that we think its less likely that we will have CS1-negative myeloma cells in patients than the other targets that we test.

Jack Aiello : I was going to ask, do you ever envision elotuzumab, the monoclonal antibody, and the CS1 CAR T cell being used as part of the same treatment, but maybe that doesn't make sense if you believe that all of your myeloma cells in the relapsed patient already has CS1 present.

Dr. Craig Hofmeister : And, you know, its… I think you could…, you could conceive that an antibody targeting the same thing would compete for the same targets, I guess, even though these antibodies are going to wash out whereas ideally the CAR T cells won't. What we think about is, well, are there ways to make the target more…, more dense on the cell surface of myeloma cells. So, could we give a patient a drug that increases their expression of the target, CS1, or could we give the patient a drug that when the CAR T cells have…, are based essentially in this drug, that they are more effective killers or even on the other side that if they are based in this drug, they kill but they don't kill so rapidly because that has also been a source of significant side effects for patients who have CAR T cells expand too quickly, in patients when the CAR T cells get in there and all they see is target. Sometimes its like a bomb going off and sometimes you want that to be muted.

Jack Aiello : And you mentioned earlier the idea of, what.., trading a CAR T cell that not only targets CS1 but would also target CD38 and…, and the other antigens that are being looked at via flow, there are six or eight others, I mean, and you think that possible to trade a CAR T cell like that?

Dr. Craig Hofmeister : Yes.

Jack Aiello : …and I guess the last question. I got this again from Dr. June. He envisions a time where he might almost think about CAR T cells like blood banks where he could have these CAR T cells on a shelf being given to a patient as opposed to have to be harvested and re-engineered from that to the patient. Do you vision that as possible?

Dr. Craig Hofmeister : Absolutely! That's…, that's probably about those clinical trials are probably less than 12 months away.

Jack Aiello : Well, that's exciting and I will stop asking questions and I really appreciate the work you are doing.

Dr. Craig Hofmeister : Thank you so much.

Gary Petersen : And thank you, Jack. Priya, would you…, you would like to bring on the listeners at this point? Anybody…

Priya Menon : Yes, Gary. There is a caller on line. Person calling in from 394-5741, please ask your question. You are on air. (Pause)… Person calling in from 394-5741, you are on air. Please ask your question.

Caller : Yes, can you hear me?

Gary Petersen : Yes.

Caller : Yes. My…., my question has to do with basically the nature of the…, the trials, and also whether or not the therapy is eventually planned to be a one-time therapy. Normally… I presume these are phase I trials. Normally, phase I trials are designed to find a proper dosage, but I am gathering from what you are saying that in this case, this may be an attempt to determine whether or not the modified CAR T cells will stick around long enough to continue to do the job. Is that basically what…, what part of the goal is for these trials and also is it hoped that eventually there will just be one of these 500,000-dollar therapies necessary to treat a patient?

Dr. Craig Hofmeister : Well, I think that…, that of the at least 64 active CAR T cell trials that I see here for a variety of diseases, when I go on clinicaltrials.org, clinicaltrials.gov, they are questioning almost everything, single dose more than one dose, different doses of cells in patients, different lymphodepletion strategies, in essence different chemotherapy. There is not a question that I think is too…, too small for us to consider and i think that the cost of these trials and interventions when they actually become available for outside of a clinical trial, you know, envisioning that world so its not 500,000 dollars a dose, is not hard to see. You know, if you only do it once and you are thinking…, comparing it to a myeloma patient who may get 10 years of therapy, well clearly a one-time 5000,000-dollar charge is called savings, but again the idea of a 500,000-dollar one-time treatment is…, is not the real exciting to anyone who has bought a copy of Quicken Online. So, I think we are all looking for single treatments that are going to be even less expensive and things that…, that we just talked about, having essentially a bank of CAR T cells available for specific tumors would certainly be much less than, you know, personalizing or genetically engineering every patient's T cells, that would be much less expensive and that's clearly where the field is going or at least experimenting, but its effectiveness is unknown.

Caller : Thank you.

Priya Menon : Gary, I think we can go on to the long list of questions that we have received via email.

Dr. Craig Hofmeister : Okay.

Gary Petersen : All right and that's exactly what we will do. Okay, doctor, let's go down the list. We have got a number of them here and the first of which is, somebody would like to understand and this is really specific to them and…, and we might as well start off with it then. I think its the only one this way. I would like to understand what the increase in light chain has to do with my myeloma. I have gone from a low three-digit to a high four-digit number.

Dr. Craig Hofmeister : So, I think that, you know, light chains and monoclonal proteins are really the protein products of myeloma cells and we use them as an indirect measure of the number of myeloma cells in the patient. So, if a particular patient…, patient's myeloma makes a set of light chain, a proportion of light chains and that amount of light chains in the blood changes, you would expect that there would be an increase in the number of myeloma cells in that patient and therefore, you…, you would conclude that the patient's myeloma is not in good control and that's a dangerous spot because when the patient's myeloma is not in

control, they are at an increased risk for fractures, anemia, and kidney failure and those are all bad things. So, I…, I think an increase in your light chain suggests your myeloma is not in control and we need to do some different therapy to get it back under control.

Gary Petersen : Okay. Thank you for that. I am sure she or whoever that was appreciates that. What… The next question is, are there any contraindications to this therapy, which is when you are talking about the CAR T cells or any drug interactions that you suspect could occur and one should be aware of?

Dr. Craig Hofmeister : So, the things I think about are… The contraindications are that if you have a CAR T trial towards a particular target and the patient's myeloma or at least the predominant clone, does not express that target. Well, that would be something that you and I would be unexcited about. So, that would be a contraindication to therapy because you would expect it wouldn't work. As far as drug interactions, if you thought about it for a second, you can think well, you know, if we have a… If patient is taking medications that prevent their white cells from expanding, that essentially are immunosuppressants and this comes about is if a patient is taking immunosuppressants to decrease their risk or decrease the manifestations of graft-versus-host disease, those often are immunosuppressants and you don't want immunosuppressants when you give a CAR T cell therapy. You want the CAR T cells to be able to expand whenever they see the target and if you are taking medications like Prograf, Cytoxan, or CellCept or any of a variety of drugs that are immunosuppressive, we theorize, although we don't know, that that might make the CAR T cells less likely to expand and therefore be less effective.

Gary Petersen : Oh, thank you. How long would it take for this therapy to be administered and in what form, injections or oral? Would you take a little or would you talk a little about the dosage in which this would be effective?

Dr. Craig Hofmeister : So, the… Basically, you need to get a certain amount of T cells from the patient. You need to genetically modify them and then you need to expand them. Some patients don't have a lot of T cells. Older patients have more difficulty having them be successfully genetically modified and expanded and that's an…, that's an issue for patients where the average age of diagnosis is 70. The T cells that are genetically modified, we don't know exactly what dose to give and we don't even know if it matters because if they are going to expand, well, you are essentially giving a…, a drug that increases in dose whenever it sees a target. So, we don't even know if the initial cell dose is important, but certainly their T cells are infused, you know, pretty rapidly, through an IV line and then a proportion of them go from their blood stream into their bone marrow and usually that's a target-rich environment.

Gary Petersen : Okay. The next one is pretty important as well. What is the timeline that you are looking for this therapy to be practically being administered to patients as a treatment?

Dr. Craig Hofmeister : So, I imagine, you know, for a clinical trial, we are looking to have this start up in the summer of 2016, but I think this question is really when do you think this stuff is going to get FDA approved to do in any old cancer center and I think its a number of years away. To be able to find intervention that's both safe, reliable, and I think we are a number of years away from FDA approval in myeloma.

Gary Petersen : Number being 2, 5, 10…?

Dr. Craig Hofmeister : I wish I had some sort of granularity on that and I don't. You know, this is a rapidly changing field where five years ago we weren't talking about this in myeloma and certainly we are talking about it, you know, occurring it for autologous CAR T cells, potentially allogeneic, you know, all this is …, is new and in a rapidly changing field.

Gary Petersen : Okay and obviously at Ohio State, but are there other centers that will also be able to have access to this treatment?

Dr. Craig Hofmeister : Certainly, there are other centers doing it now, right? University of Pennsylvania; Dana-Farber; the NCI, National Cancer Institute, are doing these trials that have eligibility in myeloma. I know of other trials that are going to be opening up, kind of across the world, in London, France, and other spots in the US. So…

Gary Petersen : Are these CS1 trials, though?

Dr. Craig Hofmeister : The CS1 trial for myeloma is likely to start out at Ohio State and probably won't be…, won't be in other centers.

Gary Petersen : And then after what length of this therapy do you expect to see improvements in a patient's condition?

Dr. Craig Hofmeister : Well, the expansion of these CAR T cells usually occurs in most diseases in the first two weeks. So, I certainly want to see a response but around two to four weeks after the initial infusion and if we don't see a response in four weeks, you would think that the likelihood of response is very low.

Gary Petersen : Okay. One of the papers on this technology mentions that treatment of patients with CAR T cells can cause cytokine storms, which is…, which is the setting of allogeneic transplant may induce graft-versus-host disease. Could you please explain what cytokine storm is and what in the CAR T cell triggers this reaction?

Dr. Craig Hofmeister : So, every time that you infuse these CAR T cells into a patient in the proper environment, in a target-rich environment, these T cells expand. They see a target and where there was one T cell seeing a target, then there's two and where two cells see a target, then there's four and you can imagine with those type…, with that type of mathematics, its not long for your 500,000 genetically modified CAR T cells to quickly turn into 5 million and 5 billion T cells. Well, as this happens, T cells that are in such a target-rich environment, these are cells that by their nature when they are surrounded by what they think of as foreign become aggravated and their job, in general, is to kill all the foreign cells and they are now genetically modified to see the patient's myeloma cells as foreign or the patient's cancer cells as foreign, thus far, and when this happened in the past, lot of aggravated CAR T cells being rapidly produced, some of the things that they use, these T cells to kill the cells around them are called cytokines and so, they tend to leak the cytokines into the marrow and into the blood, but with such a rapid expansion, these cytokines are chemicals, leak into the blood and can cause the patient to be incredibly sick and this can occur with allergic reaction. This can occur in a number of spots where you have all these particular type of chemicals shoot up in the blood and these patients can become incredibly sick, develop what looks to be a pneumonia. Dialysis may be required due to kidney failure. They can lose all their blood pressure and require ICU admissions. These patients are sick and when these…, these lines of testing and these CAR T cells trials were at the beginning, this is pretty mysterious, but it wasn't long before people figured out what was going on and in parallel there is a group of drugs that are anticytokine therapies. They target these chemicals specifically. Interleukin-6 is a target for a lot of these drugs and when they lower interleukin-6 levels after giving these drugs, patients get quickly better. So, what we hope to do is monitor patients for the cytokine storms and if they occur, to have this supportive therapy administered early before patients become sick. This will allow the CAR T cells to still expand and do their job but not have such rapid expansion that it puts the patient vulnerable and causes them to be sick.

Gary Petersen : Very, very interesting! Thank you so much. Does the risk of becoming a non-secretor increase as patients survive longer and how should this affect monitoring, you know, the labs, PET scans, etc.?

Dr. Craig Hofmeister : So, being a non-secretor, some patients at diagnosis are non-secretors and some patients do become non-secretors, but, you know, in…, in my experience its the minority of patients and following non-secretory myeloma is difficult because no one particularly wants to do a bone marrow biopsy every clinic visit and a bone marrow biopsy in myeloma only tells you what's going on on that side of your

pelvic bone, which is not necessarily indicative of what's going on in the entire patient. Sometimes patients with myeloma bone disease who are non-secretors, you can follow via CAT scan, MRIs, and PET scans, but a lot of times PET scans are not particularly helpful here either because it only detects the most aggressive myeloma and somewhere between 20% and 40% of patients with myeloma bone disease have PET-negative disease. So, following non-secretory myeloma is a challenge, especially since many clinicians often follow myeloma patients simply by blood tests. I think that…

Gary Petersen : And when you said… Yeah.

Dr. Craig Hofmeister : Go ahead.

Gary Petersen : When you said the…, the PET scans, that was a…, that's news to me, the 20% of bone disease is not identified through a PET scan, so how is it identified if at all?

Dr. Craig Hofmeister : So, you can see it on CAT scan, you can see it on x-ray. X-ray obviously is probably the most insensitive way because it requires cortical destruction. The outer part of the bone has to be destroyed before it shows up on x-ray. Cross-sectional imaging like CTs and MRIs are much more sensitive and PET scan can be even more sensitive than CTs and MRIs, but it can occasionally be less sensitive because it requires that the myeloma cells that are non-secretory are metabolically active enough to pick up the dye used in the PET scan. So, non-secretory disease generally requires that patients be followed reliably by either the same physician or excellent documentation to state, hey listen, this patient doesn't secrete, so don't bother doing the myeloma labs all that often or depending on them. Make sure you depend on cross-sectional imaging like CTs and MRIs and occasionally PET scans to follow their disease as that's most likely to be accurate.

Gary Petersen : All the non people who are not non-secretors, didn't the PET scan work for them? Its just these non-secretors that its an issue?

Dr. Craig Hofmeister : No, no. It can be… PET scans may be insensitive in both secretory and non-secretory disease. PET scans are insensitive in patients whose myeloma doesn't pick up the dye quickly and that may not have anything to do with whether there is secretory or non-secretory disease.

Gary Petersen : That's… To me but that's interesting. Thanks. I appreciate that. I have one last question and that is…, is that…, that a person says that they want to pose a question to you…, that they feel is off subject and they think its off subject because there is a fine line between immunity and autoimmunity. Dr. Hofmeister mentioned on previous Cure Talk call that he had observed that myeloma patients with autoimmune disease experience an increase to their autoimmunity, while their myeloma is improving with treatment. Could you expand upon that observation as well as any other learnings about myeloma and autoimmune disease?

Dr. Craig Hofmeister : Sure. So, autoimmune diseases are well known. Rheumatoid arthritis, psoriasis, lupus, connective tissue diseases, all these are when your body is attacking itself really and that doesn't necessarily mean that these patients who have an autoimmune disease are protected against developing myeloma. In fact, they can, but myeloma in and of itself is very immunosuppressive. So, if your myeloma flares, usually the patient's autoimmune disease simmers down. So, we are often found to say that having active rheumatoid arthritis and active myeloma cannot happen at the same time in the same patient and what we have seen is patients who have an autoimmune disease or maybe they don't and they develop myeloma and then after treatment their myeloma goes into a deep remission and then their autoimmune disease flares and then as their myeloma becomes more active, their…, their autoimmune disease simmers down and sometimes you get this back and forth. This doesn't occur that often, right?

Gary Petersen : Talk about basically being between a rock and a hard place.

Dr. Craig Hofmeister : Right and, you know, it requires somebody to have an autoimmune disease and

myeloma, but they do occur in the same patient population but usually not in the same population at the same time.

Gary Petersen : Okay. That's quite interesting. Well, those are all of the questions that we had for your, doctor, and as always, you have been a wealth of knowledge and we really appreciate all of the things that you are doing, especially with this CAR T cell study because it looks so good and…, and…, and your results to date have been very good. Priya, do you have anybody else online that would like to ask a question or would you like to..?

Priya Menon : Thank you so much, Gary. I think we have almost come to the end of the hour. Dr. Hofmeister, it was great listening to you. Thank you so very much for having taken time out to share this information about the new therapy with our audience. Gary, Pat, and Jack, as mentioned, thank you so much for your participation; and today's talk and the transcript will be made available on Cure Talk's website. Please visit www.curetalk.com for details on our upcoming talks. Thank you, everyone.

Gary Petersen : Thank you, Priya. Thank you, doctor.

Pat Killingsworth : – Yes. Thank you and nice to talk with everybody.

Dr. Craig Hofmeister : Thank you. Bye, bye.