A Novel, More Precise, and Effective T-Cell Immunotherapy Approach for Myeloma

A lot of research is being done in immunotherapy for myeloma that is leading to new treatment options for patients. **Dr. Ivan Borrello of John Hopkins** is working on a completely, novel approach. This involves enhancing white blood cells to create a customized immunotherapy for patients. The T-cells from the patient's bone marrow are extracted, enhanced, and expanded in the lab, and are given back to the patient, allowing for a more specific immune response targeting the proteins found on their myeloma cells. The use of bone marrow T cells is more precise than the use of cells from the blood which makes this therapy more effective. Join our myeloma panel talk on this new area of research, as they discuss the difference between CAR-T cells and MILs (marrow infilterating lymphocytes), and how body's natural immune cell growth can be used to fight myeloma.

Full Transcript:

Priya Menon : Hello! Good evening and welcome to CureTalks. I am Priya Menon, Scientific Media Editor at CureTalks, joining you from India; and I welcome everyone here to the 97th episode; and today we are talking about a novel approach for treating myeloma using T cells. My co-host for the talk is myeloma survivor and editor of myelomasurvival.com, Gary Petersen; and supporting Gary on the panel are…, ourmyeloma survivors and advocates, Jack Aiello, Cynthia Chmielewski, Pat Killingsworth, and Jennifer Ahlstrom. A lot of research is being done in immunotherapy for myeloma that is leading to new treatment options for patients; and we are talking to Dr. Ivan Borrello, Associate Professor of Oncology at John Hopkins School of Medicine today. Dr. Ivan Borrello of John Hopkins is working on a completely novel approach. This involves enhancing white blood cells to create a customized immunotherapy for patients. The T cells from the patient's bone marrow are extracted, enhanced, and expanded in the lab and are given back to the patient, allowing for a more specific immune response targeting the proteins found on their myeloma cells. The use of bone marrow T cells is more precise than the use of cells from the blood, which makes this therapy more effective. Join our myeloma panel talk on this new area of research as we discuss the difference between CAR-T cells and marrow-infiltrating lymphocytes and how body's natural immune cell growth can be used to fight myeloma. Before I hand over to Gary to carry on with the discussion, I would like to remind the audience that we will be addressing questions sent in for the panel towards the end of the discussion. If you have a question for Dr. Borrello, you can mail it to priya@trialx.com or press 1 on your keypads and let us know so that we will bring you on air to ask your question. With that, its over to Gary.

Gary Petersen : – Well, thank you, Priya, and thank you again for bringing such a wonderful doctor to the myeloma patient community. Dr. Ivan Borrello is MD and Associate Professor of Oncology and Associate Professor of Cellular and Molecular Medicine for the graduate program and Director of Cellular Therapeutic Center at the John Hopkins School of Medicine. Dr. Borrello's team of researchers has focused on the development of tumor immunotherapy for blood cancers. This approach is breaking new ground and is a pioneering effort by his team. Dr. Borrello has received numerous awards including the American Society of Clinical Oncology Scholarship Award, the John Hopkins University Clinician Scientists Award, and the Kimmel Scholar Award, and Leukemia and Lymphoma Society of American Clinical Translational Scholar Award. I'd go through the rest of his…, his background and all, but it is stellar and I want to leave plenty of time for questions from all the panelists. I did note that I went through his biography on the John Hopkins site, his…, he has a tremendous background and most of his biography happened to be focused on this specific methodology. He spent years and years of research and, you know, putting his shoulder to the…, to the real type of thing to come up with this research. Its not something that's happened overnight and I thank you very much, doctor, for being here with us.

Dr. Ivan Borrello : My pleasure.

Gary Petersen : First and foremost, I would like to have you, if you would, just go through something…, some of the very basics for our…, for our listeners. Our listeners are generally not doctors but are patients and as a result don't necessarily have the background to…. in a lot of what you will be talking about, so if you could spend a short time in explaining what is the difference between immunotherapy and chemotherapy and…, and how your…, your approach differs from immunotherapies that we have heard of recently like daratumumab and elotuzumab, which have recently been approved by the FDA.

Dr. Ivan Borrello : Sure. So, in general, chemotherapy tends to be, at least traditionally, small drugs that target cells that are proliferating, that are growing and this is not necessarily specific to cancer. It kills any cell that happens to be growing. It just turns out in most patients with cancer, and myeloma certainly falls into this category, that cancer cells tend to grow at a slightly higher rate than normal cells and so you get this preferential killing of the cancer cells compared to normal cells. Because its not specific, however, you also get a lot of side effects and that's why with traditional chemotherapy, you know, patients can lose their hair because hair follicles are rapidly growing. They can also develop nausea and diarrhea because the…, the cells of the GI tract are also rapidly growing and once they are killed, they can't absorb water as much and so you can get diarrhea and all the other side effects that I think most people are aware of in terms of chemotherapy either because they have experienced it or they know people that have. Furthermore, what chemotherapy does, being that its a drug, is that it kills and then once the drug is degraded in order to achieve that effect again, you have to give the drug again. What immunotherapy does is its more targeted therapy, so it will only attack often times the…, the cells that it is trying to recognize and for the most part you can think of immunotherapy in two ways. One is, a therapy that is sort of given as a drug through the veins such as an antibody like daratumumab or elotuzumab as you just mentioned, which one has just been approved this week and another one will likely be approved soon or T cell therapy which you give through the veins or there are vaccine approaches which generally work better than pills. It is an injection under the skin of something that recognizes the myeloma and then what that does is ultimately educates the patient's body to develop an immune response against it and so, it can then…, these immune cells can then travel around the body and when they meet the myeloma cell, they can attack it and kill it. This is the same concept by which…, for which vaccines work in a preventive measure against infections such as the flu vaccine, although infection vaccines tend to be more prophylactic. In other words, they are given before the patient actually has that specific disease. So, sort of summarizing, immunotherapy tends to be tumor focused than specific and for the most part, although we will probably get into this later, has a relatively low side effect profile and chemotherapy is much more generalized and tends to attack cells that are rapidly growing.

Gary Petersen : In chemotherapy, we would consider drugs like melphalan, Cytoxan, Velcade, and Revlimid.

Dr. Ivan Borrello : Yeah, although traditional…, the typical chemotherapy are actually the melphalan and Cytoxan. Velcade and Revlimid, although I think, you know, in lay terms, we refer to them as chemotherapy, they actually work through slightly different mechanisms and clearly have a much better side effect profile, but…, but I…, but I would say in general terms its probably reasonable to call those chemotherapy as well.

Gary Petersen : Okay, well, thank you very much, doctor. Would you tell the audience what your immunotherapy approach is and how it might vary from the other one that is very much in the news and that's CAR-T cell therapy?

Dr. Ivan Borrello : Sure. So, let me start off with what CAR-T cell therapy is. So, CAR is an acronym that stands for chimeric antigen receptors. So, obviously, CAR is easier to remember and to say and basically what CAR therapy is, is T cells that are engineered to recognize a certain protein that's present on the surface of the tumor cell and…, and then so it recognizes it normally in the form of an antibody and then the…, the part of the…, of this molecule and some of the inside of the cell actually causes the T cell to proliferate when that…, that receptor engages a protein that it can recognize; and for the most part, this approach…, this approach has used blood cells, cells from the blood and…, and for the most part, what this

does is that it…, it engages and recognizes only cells that express this one protein. As you mentioned, CAR-T cell therapy has gotten a lot of press because the results certainly in a certain type of tumor, specifically acute lymphoblastic leukemia or ALL which is one of the most common childhood leukemias, has shown very dramatic results and also with significant toxicities, but one of the problems with that approach is that as these patients relapse, they tend to relapse with a tumor that does not have the protein on the surface that was originally recognized by the CAR-T cell and in technical terms, that's called the development of antigen escape variants. So, its sort of like the same concepts with antibiotics that when you give antibiotics for long time, you ultimately select out a population of bacteria that are resistant to the antibiotic and with CAR-T cells you are selecting out a population of tumor cells that are resistant to the CAR-T cells because they don't have the protein on the surface that the CAR-T cell recognizes.

Dr. Ivan Borrello : In…, and in contrast, the approach that we have taken is an approach that we call MILs which stands for marrow-infiltrating lymphocytes and so the idea is…, well, first of all, a lymphocyte is… T cells are lymphocytes, so they are both…. These are cells that are trained normally in the body to recognize, fight, and kill viruses and also tumor and what we have been able to show is that these cells that come from the bone marrow have a much broader ability to recognize many, many more proteins on the surface of the tumor cells than do cells that are…, are obtained from the blood. So, in some early experiments that we did, we were basically able to show that if we took blood cells and activated them, turned them on in the laboratory and then asked whether they recognized myeloma, there was virtually zero recognition of the myeloma. In contrast, when we did the same thing with MILs, we could see that approximately 70% to 80% of the cells that we were activating and putting in contact with the…, with the marrow…, with myeloma were able to recognize and to kill the…, the myeloma upon encounter. So, from a scientific perspective, the ability to recognize potentially hundreds and thousands of proteins would make the likelihood of developing antigen escape variants significantly lower. The other important thing about MILs is that being that these cells come from the bone marrow and being that in myeloma, the bone marrow is where the disease is, its very…, its much easier for these cells to actually go back to the bone marrow after they are put into the patient than theoretically a cell that's from the blood can do.

Gary Petersen : Okay. Well, thank you very much and isn't there something about myeloma which is in the…, is it the stroma of the bone marrow tends to be more difficult to kill than that in the blood?

Dr. Ivan Borrello : Well… Yeah.

Gary Petersen : And that…, that there is something and as a result, that's why these MILs are a little bit more active?

Dr. Ivan Borrello : So, I think what you are alluding to is that there has been work done by several groups showing that the ability of the myeloma cells to attach to their surface, which specifically they are attaching to the stroma, these…, these cells… The…, this fact that they are attaching inherently gives the myeloma cell the ability to resist killing from either drugs or possibly even immunotherapy. In contrast, when a cell is detached from the bone marrow stroma, then their overall ability to die increases with the same approach. I am not sure that we have actually shown that MILs can overcome this resistance, but what we have been able to show is that we can get very good in trafficking and…, and increase the concentration of these MILs into the bone marrow when…, when its given either in mouse experiments or even in humans.

Gary Petersen : Okay. Well, thank you. You use this therapy after autologous…, autologous stem cell transplant. Why not a standalone therapy? Patients really do not like transplants.

Dr. Ivan Borrello : Sure. No, absolutely. So, we…, I can say that our ultimate goal would be to develop this in…, in the absence of a transplant. However, there is one feature of T cell therapy that…, that warrants mention and that is…, that if you think about many organs in our body, they have a finite size and the easiest example of this is the liver that if somebody chops out half of the…, of a patient's liver, that liver will ultimately grow back to its normal size and the same thing is true with lymphocytes, that if you think about now lymphocytes as filling up a glass, the amount of lymphocytes that are in the body are enough to fill up

that glass. So, what T-cell therapy needs is a way to increase the number of tumor-specific cells that can actually fight the…, the cancer and so one way of artificially doing this…, of artificially doing this is not only to grow up the cells in the laboratory which we can increase by anywhere from 50 to 200 fold but also to allow the body to then allow these cells to further expand and one way of doing that is by emptying the glass. So, if we empty the glass by 50%, then we can get 50%, hopefully 50% expansion of these T cells even after we put them in and if we completely empty the glass, then we can hopefully get a 100 fold or 100% expansion of these lymphocytes after we put them in. So, that's basically what transplant does. It empties the glass. So, in addition to fighting myeloma, it also creates what's called technically lymphoid space that then allows for these T cells to further expand in the body in addition to having expanded in the blood…., in the bags of the laboratory. Now, do we need a transplant? Likely not. A lot of CAR-T cell therapy right now is being done not in the context of a transplant but in the context of chemotherapy that nevertheless empties the glass by…, by basically killing a lot of the lymphocytes and so we are slowly moving in that direction of trying to see whether we can achieve similar things without requiring a transplant, but considering how transplant is a mainstay, a therapy for many patients with myeloma, this was at least an easy place to start.

Gary Petersen : Does it also reduce the tumor burden and that is helpful?

Dr. Ivan Borrello : The…, the transplant?

Gary Petersen : Yes. Yes.

Dr. Ivan Borrello : Yeah, well, yeah, the…, I mean the transplant…., I mean clearly the transplant, you know, certainly has a…, a known clinical benefit. So, it does reduce the tumor, but…, but really what the chemotherapy in the transplant does from immunotherapeutic standpoint is that it might actually allow the immune cells to better recognize the tumor because of the way the chemotherapy can kill myeloma cells.

Gary Petersen : Okay. You have been pursuing this approach for years and I think you started on lymphoma, I believe. Do you have any seasoned data which shows you are on the right track?

Dr. Ivan Borrello : So, our first clinical trial that we did was started in 2007 and that trial was very different from where we are right now, but what we were able to show from that trial was that patients that got at least a 90% reduction in their disease burden showed a benefit from the overall approach compared to patients that got less than a 90% reduction in their disease and we published this data. I think it came out in May of this year and what we are seeing is that there is a significant tale in terms of the overall survival of these patients and I think what we'll do is probably try to update that data in the next year or two, but that tale of overall survival is better than what we would have expected sort of historically, although we don't technically have controls with that. We are now actually conducting a randomized trial, so this would really give us the better head-to-head comparison that will hopefully be maturing in the next one to two years.

Gary Petersen : Very well. Thank you. I can tell you that I am very, very excited about your work, but I do not see why it has not gotten the attention of some of the CAR-T cell work because it doesn't have the…, you know, some of the side effects and why you are just not flooded with money from drug companies and everywhere so you can expedite your work. What…, what gives?

Dr. Ivan Borrello : Yeah and that's a good question. You know, I…, I think part of it is that we haven't published as much on this as a lot of other people have and I think, you know, the other big aspect of this is that there is…, the…, the thing that I think has made CAR-T cells up, you know, in…, in the front pages of a lot of news is that there is a wow phenomenon. I mean, there are patients in whom you give these cells and with a matter of weeks, their disease is gone. I think, you know, our approach is much more of a marathon than it is of a sprint and I don't think marathon runners get as much publicity often times as sprinters do.

Gary Petersen : Okay. You know, the other…. I know that you are getting some, I think the LLS is doing some work with you, but is…, is this something that ultimately can be patented and…, and companies would be just, you know, clamoring to support you if you show great results?

Dr. Ivan Borrello : So, we have…. Yeah, so we have patented various aspects of this and there has been interest in…, in licensing this technology to various companies and, you know, I am actually very excited about the interest I have been seeing over the past several months and hopeful that we will eventually see this going into a company form and we could rapidly expand our research and hopefully look at this, not just in myeloma which is, you know, the…, the disease that I also see clinically and that's why its the first disease that we have tested this end, but we are also beginning to explore the use of this in a variety of other disease settings as well.

Gary Petersen : All right. So, those are…, those are my questions and so I would like to open it up to the panel for them to get some time with you. First stop, Jack Aiello, are you online?

Jack Aiello : – I am. Thanks for having me. Let me clarify one thing you asked in your very first question, Gary, when you indicated…, where you said daratumumab and elotuzumab have recently been approved by the FDA, I am sure you are aware daratumumab has, elotuzumab has not yet although they applied for a new drug application. My question to Dr. Borrello, are MILs still engineered to attack a particular antigen like CD38 or are they just expanded, you…, you killed more of them?

Dr. Ivan Borrello : Yeah, so that's a very good question. So, the therapy that we are currently using, they are not engineered and I think, you know, that is potentially one area that…, that may be very attractive, I think, to…, to industry because its a lot less labor intensive and a lot less expensive to develop this approach than it is to engineering a kind of T cell and so the idea is that because it represents such a broad range of proteins that are present on…, on the tumor cells, that we can potentially get away with not having engineered that. Now, having said that, in my lab, we are also beginning to look at approaches of modifying the…, the…, the T cells with…, with genes that are recognizing certain proteins to turn them into better cells to see whether that approach may offer some benefits and I think, you know, one could theoretically hypothesize that there may be different settings which you would want to use, either gene modified or non-gene-modified T cells depending upon where you want to give this therapy.

Jack Aiello : Are they susceptible to the cytokine storms I have read about like the CAR-T cells?

Dr. Ivan Borrello : No, we… We are not saying cytokine storms. So, in the current randomized trial that we have, basically the approach is that everybody is getting a stem cell transplant with melphalan which is the standard transplant that myeloma patients get and then the patients that are randomized to the MILs arm are getting these cells infused on base three and four after the stem cells are infused and we do…, here at Hopkins, we do our transplants as outpatients and patients ultimately get hospitalized if there's any complications. The most common complication that one sees with transplants is the development of fevers and I can tell you that what we are seeing is a significantly higher rate of hospitalization in the patients that are getting the MILs compared to patients that aren't and the reason for this is fevers and the diarrhea, but all of these things are rate limiting and basically go away on their own and we have not had to actively treat anybody for the cytokine storm. So, when I talk to my patients I say that if one looks at the kinds of toxicities that CAR-T cells are giving and if you want to set it up to 10, we are probably seeing about a 3 or a 4. So, we are seeing something, but its not the kind of thing that patients are ending up in the intensive care units or requiring active intervention.

Jack Aiello : How are MILs physically extracted and then given back to you?

Dr. Ivan Borrello : So, MILs, again they are called marrow-infiltrating lymphocytes, so we get them from the marrow. So, what we do is we… Patients undergo a bone marrow aspiration which is the…, the typical bone marrows that most patients get. The difference is that an average bone marrow gets about 10 to 20 mLs of bone marrow. We are collecting 200 mLs of bone marrow and before anybody cringes, the way we do this is patient…, all patients are getting what we call conscious sedation. So, they are getting pain medications as well as sedative, you know, a sedating medication just like they would if they were getting a colonoscopy and…, and the…, the sedative meditation is also slightly amnestic. So, in other words, patients forget what's happening and I can tell you that the average procedure takes about 10 to 15 minutes, the time in the bone

marrow, and most patients, the only thing that they complain about is a little bit of soreness at the sides of the harvest and the…, no actual pain because of the medications that they are given. So, its a very powerful procedure.

Jack Aiello : How is it given back to you?

Dr. Ivan Borrello : Oh, sorry. So, then these cells are…, are taken out. They are put in a bag, then taken to the lab and then they are growing and they are given back through the IV. So….you know, it goes into…, it goes into the patient's veins and eventually finds its way into the bone marrow, just like stem cells are.

Jack Aiello : Well, that sounds exciting. Those are my questions, I know more will be answered and I really appreciate what you are doing.

Dr. Ivan Borrello : My pleasure.

Gary Petersen : Yeah. Thanks, Jack! Cynthi… Cindy Chmielewski, are you there?

Cynthia Chmielewski : Yeah, I _____[00:28:12]_____ I am sure you could hear her, I am trying for quiet. This is so exciting, all right, this MIL therapy and I have some questions, excuse me if you answered them a little earlier. I…, I kind only… I thought it was at 6:30, not 6 o'clock, so… My first question is, we are talking about some clinical trials _____[00:28:35]_____ and I was wondering if they are just being offered at John Hopkins or if there are other sites and what would this time commitment mean be…, mean being away from home to pursue clinical trials and what kind of followup after the initial stem cell transplant and the MILs infusion will they get?

Dr. Ivan Borrello : Yeah, but… So, those are all very good questions. I can tell you that right now this trial is only being offered here, but I am hopeful it…, it…, it will be a multi-center trial and the other two sites that are going to be opening at are Moffitt in Tampa, Florida, and Mayo, Jacksonville, also in Florida. So, for some reason, we ended up getting Florida contingent and I…, we just got approval from the various regulatory agencies to open the study there. So, I am hopeful that at the latest by January they should be open there. We are also talking possibly to some other sites to…, to see what their interest would be in in moving forward. In terms of the time commitment, what generally happens is if a patient is coming from out of town, the…, the bone marrow harvest to collect the MILs generally occurs about six weeks before the transplant procedure starts. So, for example, for my patients that are here, they would get their bone marrow harvested and the reason why it takes six weeks is because we have to make sure that we have not contaminated the product. So, the first thing that's done is after the bone marrow is collected, we send it off to a microbiology lab and that testing lasts two weeks and if after that two-week time frame, the product is clean, then we can expand it and the expansion is normally between 7 and 10 days and then we have to send off the product, the expanded product off to the microbiology lab to make sure that that hasn't been contaminated. So, you can see that there's four weeks of basically sterility testing and a little over one week of…, of growing the cells and so that's where we come up with this six-week time frame. During that period of time, the patients start their pre-transplant workup to make sure that they are otherwise healthy enough to undergo transplant and then they get the transplant and the transplant, you know, time commitment would be the same, I think, wherever anybody was. They…, they would… So, if somebody were coming from out of town, they would stay here through the time that their cells come back up, which is normally around three to four weeks after the transplant and then the study, because this is a study, the study time points in which we monitor further disease and immune responses are at 2 months, 6 months, and 12 months. So, those would be other visits that would be required for patients if they were to come from out of town and then we are monitoring disease response quarterly, but that doesn't have to be here. It could be just getting those from the patient's physician sent to us every three months until the patients are relapsing.

Cynthia Chmielewski : Okay, great! Do you know if there is a transplant house nearby that patients could stay at for that time…

Dr. Ivan Borrello : There are.

Cynthia Chmielewski : …or they could be staying in a hotel or…

Dr. Ivan Borrello : Well, no, so Hopkins… So, I mean, we get a lot of patients from a lot of different places and so there is sort of hospital housing literally right across the street, but I mean, obviously, there's no guarantee that that will be available and then there are a variety of housing opportunities available throughout the city. Generally, patients get significant discounts if they stayed at John Hopkins and in some cases, I think and don't quote me necessarily unless, but insurance companies might actually…, may actually pay for them because its certainly a lot cheaper than a…, a night in the hospital is, so…

Cynthia Chmielewski : Okay. That sounds good. Okay. Are they trials for newly diagnosed myeloma patients, relapsed refractory or both?

Dr. Ivan Borrello : So, these are… So, yeah… So, these are trials for anybody… The current trial, the way its written, is for anybody that has never received a transplant. Now, most patients get transplanted sort of as part of their upfront therapy, but if for whatever reason, they didn't get a transplant initially and relapsed and otherwise meet the criteria for the trial that they would be eligible for the trial even at relapse as long as they have not had a transplant.

Cynthia Chmielewski : So, besides the transplant as an exclusion criteria, are there other inclusion criteria, inclusion criteria. What were some of the others?

Dr. Ivan Borrello : Criteria…., yes. The…, the other major… The other major exclusion criteria are…, would be the absence of autoimmune disease. Because we are giving immunotherapy, you know, we don't want to make patient's underlying autoimmune disease worse. So, if patients have lupus or multiple sclerosis or scleroderma, those kinds that are actively being treated, those would be exclusion criteria and other than that, they basically…, patients basically need to be healthy enough and to meet the criteria for transplant and so the other exclusion criteria are basically transplant criteria.

Cynthia Chmielewski : Okay. So, if there are nonsecretors, that would be okay as long as you could measure things in their bone marrow or light chain?

Dr. Ivan Borrello : I'm sorry, I didn't… I didn't hear your question.

Cynthia Chmielewski : For nonsecretors….

Dr. Ivan Borrello : Oh, non… Oh, so that is an exclusion. I'm sorry. So, the patients also have to have at least a history of a measurable disease. So, patients that are nonsecretory myeloma unfortunately are not included in the study.

Cynthia Chmielewski : Okay and is there a minimum M spike you have to have at 1.0 or…?

Dr. Ivan Borrello : Nope. Nope. They just have to have had a history of an M spike. So, if a patient had a…, a myeloma, let's say with an M spike of 1 and going to complete remission but otherwise meets the criteria and the criteria for the current trial is that they have to have high-risk myeloma. Then, in that case, they would be eligible for the study even if they…, even if they come to us in complete remission.

Cynthia Chmielewski : Okay. High risk by the M spike criteria or…

Dr. Ivan Borrello : No, its high risk by FISH. So, we are looking at…, at a 1q amplification, a (4;14) translocation, a (14;16) translocation, a 17p deletion, or if they have high risk based on the gene expression profiling and the one that we are currently using is the one that was developed in Arkansas, called the MyPRS.

Cynthia Chmielewski : Okay and, finally, after the transplant and they are back at home, is there any maintenance therapy as part of the trial?

Dr. Ivan Borrello : There is. Patients are going on Revlimid as maintenance therapy… ..starting at around two months.

Cynthia Chmielewski : Okay and that's the part of the trial..with Revlimid. How about for patients who stopped responding to Revlimid prior to the trial, they will still use Revlimid as maintenance?

Dr. Ivan Borrello : Yes. The reason we are giving Revlimid, well, its two fold. One, I am sure, many of the people listening are aware of the randomized data that was generated by both the French as well as by American studies showing that patients treated with Revlimid maintenance had a longer progression-free survival compared to patients that weren't. So, in other words, it took longer for the disease to come back, so actually that study was 48 versus 24 months. So, that's one reason and I think from…, in many places throughout the world, not all but many, Revlimid maintenance has now become the standard of care, but the other important reason why we are doing this is because Revlimid is actually a drug that augments immune response. So, the idea would be that by giving this therapy, we can increase the overall efficacy of these MILs for a much longer period of time.

Cynthia Chmielewski : Okay, great! They are my questions. Back to you, Gary.

Gary Petersen : Thanks, Cindy. Pat Killingsworth, you online?

Pat Killingsworth : – I am. Can you hear me, Gary?

Gary Petersen : Yeah, sure can.

Pat Killingsworth : Great! Thanks for joining us, doctor. I guess I just have…, I just have one question. So, what if someone participates in the study, what is considered a goal, what…, what would be a good outcome and what percentage of patients would you anticipate would achieve that outcome?

Dr. Ivan Borrello : So, the…, being that this is a randomized trial where we have two arms to the study, one either gets the MILs with the transplant while the other one doesn't, what we are comparing and the primary endpoint of the study is looking at progression-free survival, which is the medical term to basically state how long it takes for the disease to come back. So, what we are hoping is that when everything is said and done that there are more patients that are disease-free on the arm that got MILs compared to the arm that didn't get the MILs. So, that's the primary endpoint of the study. We are also in the process of opening sort of two substudies after that and…, and specifically and I…, and I would like to spend some time talking about that because I think its important for the listeners. As I mentioned, primary…, the primary endpoint is progression-free survival. So, technically, once we reach that…, that metric, the patients can then go on to whatever therapy they…, they choose. So, for the patients…, but what I will be telling the patients is that the patients that were randomized to getting a standard transplant, they are eligible to get their MILs at the time of relapse. So, really, everybody can get the MILs, but the MILs given at the time of relapse are…, are given in the nontransplant setting. So, what we are doing is we are giving some high doses of chemotherapy but not enough to require the stem cells in combination with the MILs. We are in the process of modifying that…, that…, that arm of the study to also include anti-PD-1, which is an antibody that has shown significant success in…, in many diseases including melanoma, the skin cancer, certain types of lung cancer. It was just approved, I think, today for kidney cancer and there will be data presented at our annual ASH meeting, The American Society of Hematology, next week showing that in combination with Revlimid, this anti-PD-1 has about a 70% response rate. So, the idea would be to see whether MILs plus anti-PD-1 with Revlimid can show an even more dramatic response. So, that's…, that's another thing that the patients that are in the study would be eligible for and for the patients that are on the arm that got MILs with the transplant, they would then be eligible to get PD-1 with Revlimid at the time of relapse as well.

Pat Killingsworth : So, is that…, is that…, is that, like you said, 24 and 48? Is that 48 months out? Is that the…, is that the…

Dr. Ivan Borrello : Well, so…, because we are…, because we are targeting a high-risk patient population, that time frame is actually going to be shortened. The average time for relapse for the population that we are targeting is somewhere around a year and a half, somewhere between 16 and 20 months. So, that's the median time for…, for relapse for these patients. So, the idea would be that either before that time or after that time, whenever they relapse, that we would be giving them the sort of therapy that I just mentioned.

Pat Killingsworth : Sure because once a…, once a high-risk patient relapses, it tends to…, everything tends to be accelerated, I understand that.

Dr. Ivan Borrello : Correct.

Pat Killingsworth : Thank you.

Gary Petersen : And, thank you, Pat. Now, I'd… Is Jenny Ahlstrom on the call? Jenny, are you there?

Jennifer Ahlstrom : Yeah, I am here. Can you hear me?

Gary Petersen : Yeah, sure can and Jenny is a special guest tonight. She had worked with Dr. Borrello on the Myeloma Crowd Research Initiative to find high-risk projects that were the best that were at least not funded as…, as of yet and…, and Dr. Borrello is one of those and…, and we have an opportunity now to have Jenny ask some questions. So, Jenny, fire away.

Jennifer Ahlstrom : Okay. Well, Dr. Borrello, thanks for joining this show. Its a real treat to be able to hear more about these projects and I do want to say that just part of the process, we are just patients who want a cure and for the Myeloma Crowd Research Initiative, we gathered a group of top myeloma experts and then some very highly educated patients including this group, our panelists, and said what should we go after and…, and the doctors said, hands down, high-risk myeloma because these patients are not having good outcome. So, we…, we did that and out of 36 proposals, Dr. Borrello's proposal was one of two proposals that were selected as the most exciting. So, we are very, very excited about what you are doing. My questions would be, the first, when you think about CAR-T cell and you think they are…, you are pulling them out, you are engineering them to go after the certain protein, I remember in the…, in the show that we did, you said you pulled them out, you grow them in the presence of the tumor cells. How does that work? How do they know what to go after because you are…, you are…, what you are saying is that it could go after potentially hundreds of targets that that particular patient might have. Its going to be completely different than the patient sitting next to them and the infusioner. So, how does that… How do your T cells know what to go after, I guess that's my first question.

Dr. Ivan Borrello : Yeah, so, I don't know the answer to that question, other than to say that, you know, that was a concern when we first started doing our first clinical trial of that, because we are growing the cells within the bone marrow environment. So, we are not taking these cells out. We are growing them within all the components of the bone marrow that are there and, you know, even a myeloma patient has normal bone marrow elements because otherwise it wouldn't have blood counts. The concern was that we would potentially be activating these cells and cause, for example, the patients to not have any platelets or not have any red cells or anything like that. The one thing that I can say to you is that when we…, when we have now treated probably close to about 80 or 90 patients, that we do not see any delay in engraftment. So, in other words, the amount of time that it normally takes for the white cells or the hemoglobin or the platelets to come up or not are not delayed in patients getting MILs compared to those that don't and that may be due to the fact that these T cells, these MILs that are there, specifically recognize abnormal components that are present on the tumor cells and that if you think about how our immune system has been developed, its really developed to recognize what's called in immunological terms, self from non-self. So, that's the reason why we don't normally react against our eyes or our lungs or our heart or anything else and when we do, its…, its

a disease, its called autoimmune disease and so that, I think, is the major explanation that the…, the MILs are recognizing something foreign or something not right with these plasma cells and so when we are able to turn them on and this whole process of growing the cells actually does two things, one, it wakes them up and, two, it expands them. That…, that we are able to turn them on and to increase the percentage of the cells that are actually recognizing the tumor cells themselves and to do this in a way that is safe as…, as demonstrated by the absence of toxicity.

Jennifer Ahlstrom : Okay. That's great! And, second question is, are you planning on having this available for relapsed refractory patients who have already had a transplant because, no, I have friends who are going to their second or third transplant and in my mind, I wouldn't want to do a standard transplant. I wouldn't want to do a standard transplant but something really promising and exciting like this project.

Dr. Ivan Borrello : Yeah, so, right now, as I mentioned earlier, for the patients that get transplanted without MILs, we are basically giving them these cells in the absence of a transplant. I think if this looks promising, then I could certainly envision a subsequent trial being just in the transplant setting and not in…, sorry, in the…, in the relapsed setting and not involving transplant. So, that would certainly be our intention.

Jennifer Ahlstrom : Oh, okay. So, you wouldn't have to go to another transplant……necessarily, but you could skip a potentially heavy dose of chemo and then you get them afterward?

Dr. Ivan Borrello : Correct.

Jennifer Ahlstrom : And with your phase 2 study that you are running right now, when do you anticipate having some of those results that can and knowing kind of what your next step is?

Dr. Ivan Borrello : Right. So, we have… This trial is a…, is a 90-patient trial and to date we have enrolled roughly half of the patients and I am hoping that for ASH of next year, so again ASH is in December, that we will at least have data that we can present, that would be representative of a little over half of the patients and at that point to begin to get an idea of how to move in the next direction.

Jennifer Ahlstrom : Okay. Great! Well, I would like patients who are listening to know that if they like to help fund your research, that they can do that. We… Our goal in picking these two projects is to help you get 250,000 dollars to move your research forward so you could do it much faster and because of the process, you know, sometimes pharma companies get funding and will do their own drug development, but you are really working on that and trying to make it…, give it a go with other foundation funding and…, and probably institutional functioning and…, and your own street smart. So, we would love to help support you and if other patients want to do that, they can do that on the Myeloma Crowd site.

Dr. Ivan Borrello : Well, I… I want to thank you for —[00:48:28] — being selected and…, and…, and for all your support in this, true, I mean these are rather expensive therapies and there are not a lot of sources of funding. So, clearly, that…, that is a very limiting step also in terms of moving forward.

Jennifer Ahlstrom : Yeah. Its…, its clear I think that its tough for investigators to do research if they want to do just because there is limited funding and and if there are patients who want _____[00:48:50]_____ I think its a great thing to do is to get involved and help raise funds for things that look completely promising like this. So, Gary, I didn't have any other questions.

Gary Petersen : Okay. Well, Jenny, thank you so much and…, and…, and what we would like to do now is go to some of the questions from our listeners. Priya!

Priya Menon : Thank you, Gary. Dr. Borrello, we have a few questions from our listeners. Some of them, I think, we have already covered. Yeah. One of our listeners wants to know, how long are the MILs active in the body, in the patient's body?

Dr. Ivan Borrello : That…, that's a very good question. The short answer is, I don't know with certainty because these cells are not in any way marked, G marked, but I can tell you from our first study, when the last time when…, the latest time that we looked at was at a year following transplant. We were still able to see myeloma-specific MILs in the bone marrow and the patients that had more of them, in other words the patients with the greatest anti-myeloma response immunologically were the ones that had the…, the best clinical outcomes. So, at least out to one year we could detect these cells, potentially even further.

Priya Menon : Yeah. I think we did touch upon a little bit about side effects, but just a new question that's come in, asking what about the side effects of this treatment?

Dr. Ivan Borrello : Not many. We are seeing a slight increase in fevers, a little bit of diarrhea, but all of this has been very limiting. We have… We have not had to specifically treat anybody for any of the side effects that we have experienced.

Priya Menon : Okay. We have one of our panelists' questions unanswered, Matt Goldman, who is also a cancer…, myeloma survivor, was supposed to join us but could not. He wanted to ask, what do expanded and enhanced T cells actually mean?

Dr. Ivan Borrello : So, what enhanced means… So, let me… Let's start off with a basic concept in immunology and that is that normally what happens in cancer patients is that the tumors secrete a…, a series of proteins that ultimately paralyze the immune system and this process in…, in…, in technical terms is called the development of tumor-associated energy. So…, so, we say that these T cells are energetic. So, what we're doing is taking them out of the body and…, and…, and turning them on so they go from a drunken state to an awake state and that's the process of enhancement and then the expansion is that we actually increase their numbers, so they go from, let's say, a hundred million cells to ten billion cells and so we are hoping that a combination of waking them up and giving more of them will increase the likelihood of achieving a measurable anti-tumor effect.

Priya Menon : He wants to know if the T cells are tainted by the myeloma?

Dr. Ivan Borrello : I am sorry, what was the question?

Priya Menon : Whether the T cells are tainted by the myeloma?

Dr. Ivan Borrello : Oh, well, in the body they are and…, and…..so this process of activation and then expansion in the lab hopes to reverse that process, yes.

Priya Menon : Okay. Gary, the panelists, if they have any more questions, they can actually ask Dr. Borrello. We have a few minutes more.

Gary Petersen : Okay. Any of the panelists?

Jack Aiello : I am good.

Gary Petersen : Okay.

Priya Menon : The listeners, if you have a question for Dr. Borrello, please press 1 on your keypads and we can bring you live. Yes, we have a caller on line. Caller calling in from (907)209-9890, please ask your question.

Caller : Yes. Thank you very much. I…, I kind of lost track of…, of the timeline. I wondered if you could just briefly go through your research goals in terms of now you are doing first transplants only and you are talking about being able to do this for refractory patients at some point that are already through the…, the transplants. Do you have a stance of how long it will take your research to get to the point where you are

ready to treat refractory patients without another transplant?

Dr. Ivan Borrello : Yeah. So, in the current trial, as I mentioned earlier, its randomized and so the patients that get transplants without the MILs are then…, they will be getting the MILs in the absence of a transplant and so, but the eligibility for the whole process requires a transplant, but what I am hopeful is that at the end of the study we will see that…, that even the patients that get the MILs without the transplant are achieving a benefit and that we could then open up another study. As to the timeline for that, a lot of it depends, one, on how quickly this trial accrues and I am hopeful that by the end…, by…, by this time next year we will be close to that time frame and…, and, two, what the overall efficacy is of this approach in the non-transplant setting, but I would say assuming that both of those things are positive, I would hope that by the end of next year at this time, we will begin planning for our…, our non-transplant trial and would be starting that basically in some time in 2017.

Caller : Great and that, do you think that that trial a year from now could involve multi-centers or…, or will it be limited to your own center for the time being?

Dr. Ivan Borrello : I would… I would hope that it would involve multi-centers.

Caller : Great! Thank you very much. That's all I have.

Dr. Ivan Borrello : You are welcome.

Priya Menon : Yeah. Yeah. Dr. Borrello, one last question. Just came in, so its just been posted on our website. Listener wants to ask, if this MILs treatment will ultimately be curative for high-risk patients? Will subsequent booster infusions lead at least to a functional cure?

Dr. Ivan Borrello : Well, I would hope so. I mean, my…, my hope is that what we will be able to show is that we could significantly impact the disease with…, with this approach and then I think one question would be whether patients that have shown evidence of achieving a benefit from this would benefit from multiple infusions afterwards? So, that certainly would be one of the goals of this study.

Priya Menon : Thank you. Gary, you had a question?

Gary Petersen : Yes. Doctor, one of the things that has come up in recent literature anyway is that if you can…, can somehow find the disease early, you know, during its MGUS or smoldering phase, when it hasn't had time to multiply and have more clones and more resistant clones, that this kind of therapy might in fact be used as kind of a prophylactic and…, and that you could…, you can kind of nip…, nip the disease in the bud with this because you got low disease burden and your immune system has yet to be totally compromised.

Dr. Ivan Borrello : That…, that's true and so, I mean, clearly if…, if we are seeing evidence of…, of benefit, I think one of the…, one of the dramatic differences and that hopefully would work to our advantage in this case over CAR-T cells is that this is a much more benign therapy and so one can certainly envision delivering such a therapy in…, in a much earlier part of the disease setting, i.e., in the smoldering myeloma stage, where toxicity is not an issue because we already know what the toxicity profile is of this approach. So…, so absolutely…

Gary Petersen : Okay. Well, actually, like I said, I just don't understand myself why, you know, it…, it takes societies like The Lymphoma Society and now MCRI, Myeloma Crowd Research Initiative, to…, to provide funding when to me, you know, this…, you know, there should be people just storming to your door, you know, because, you know, you patent this process in, I mean, you know, there's just a lot of money to be made and that's from my business background, but apparently people are starting to see that and…, and I think that is probably one of the reasons that, you know, you haven't seen that, you know, the…, you know, the immunotherapy in general has been slow to start because its not a pill, its not something that you…, you are going to find a lot of pharma companies going after, but, you know, that's just a little bit of my own

personal belief.

Dr. Ivan Borrello : I…, I would agree with you, but…

Priya Menon : Thank you, Gary. Dr. Borrello, thank you so very much. This is very exciting research; and hopefully, I am sure it will break through myeloma treatment going forward. Gary and Jack, Pat, Cindy, and Jenny, thank you very much for your participation; and today's talk will be made available along with its transcript on the CureTalks' website. Please visit curetalks.com for details of our upcoming talks. Thank you, everyone. Have a good day.

Dr. Ivan Borrello : Thank you.