Role of Allogeneic Stem Cell Transplant in Myeloma Treatment with Dr. Krishna Komanduri

The role of allogeneic stem-cell transplantation is evolving in the paradigm of myeloma treatment. Despite its therapeutic potential of a myeloma cure, the use of donor stem cell transplantation is highly debated in the medical field due to the safety risks and rate of relapse. We are talking to Dr. Krishna Komanduri to better understand allogeneic transplants, optimal timing, and how to manage graft-versus-myeloma effect for improved efficacy and safety.

Full Transcript: Priya Menon : Good afternoon and welcome to CureTalks. I am Priya Menon, Scientific Media Editor of CureTalks, joining you from India. This is CureTalks' 94th episode, and we are talking of role of allogeneic stem cell transplants in myeloma treatment. My co-host for the day is myeloma survivor and editor of myelomasurvival.com, Gary Petersen; and supporting Gary on the panel are our myeloma survivors and advocates, Jack Aiello and Matt Goldman. The role of allogeneic stem cell transplantation is evolving in the paradigm of myeloma treatment. Despite its therapeutic potential of a myeloma cure, the use of donor stem cell transplant or allogeneic transplant is highly debated in the medical field due to the safety, risks, and rate of relapse. Today, we are talking to Dr. Krishna Komanduri, Medical Director of the hematopoietic stem cell transplant program at the University of Miami Sylvester Cancer Center, to better understand allogeneic transplants, optimal timing, and how to manage graft-versus-myeloma effect for improved efficacy and safety. Welcome to CureTalks, everyone! 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. Komanduri, you can mail it to priya@trialx.com or press 1 on your keypads and let us know so that we can bring you on air to ask your question. With that, its over to Gary. Gary, you are on air. **Gary Petersen :** Well, thank you so much, Priya, again for always bringing us such a wonderful forum for understanding and bringing the latest and greatest information as far as myeloma treatment is concerned; and, doctor, thank you so much for coming as well. Dr. Komanduri is Medical Director for Adult Stem Cell Transplant Program and Professor of Medicine for microbiology and immunology at the University of Miami; and I think one of the very unique parts of his background is the fact that he came from MD Anderson and I think one of the things that I think is so important is how University of Miami has established a myeloma program and brought world class treatment for myeloma to South Florida because up until they brought you and Dr. Nimer to South Florida, I don't think there was really anything of value for the myeloma patients. I mean in…, in the broadest sense, not world class anyway, South of Tampa or, so, you know, thank you so much for what you do and Dr. Nimer as well when they brought Dr. Nimer from Memorial Sloan Kettering, but when they brought you there, they put out a news release and it said University of Miami Leonard M. Miller School of Medicine has hired a top tier innovative position and researcher from the University of Texas MD Anderson Cancer Center, which we all know happens to be probably the best in the world or one of the best in the world, to lead the adult stem cell transplant program at the University of Miami Sylvester Comprehensive Cancer Center. Dr. Krishna Komanduri, MD, will be the Director of the UM Sylvester Stem Cell Transplant Program and Associate Director of Translational Research at Miami Transplant Institution at the Jackson Memorial Hospital. There is a lot more that says, well, and also about your extensive publications, but I won't go into that at this point, but I do want to thank you so much for bringing to South Florida an excellent myeloma treatment and.., and research program. So, welcome to the program, doctor! **Dr. Krishna Komanduri:** Thank you, Gary; thank you, Priya; and thank you to the other advocates and… and to the listeners on the line.**Gary Petersen :** I…, I got to tell you that I am not and never have been a real proponent of allogeneic transplants and the reason has been, as many have stated before, that it has a high treatment-related mortality and I know that you've come to Miami and your program has probably some of the better treatment-related mortality at 70%, but still that leaves 30%. So, I just wanted to let you know that that's kind of where my head has always been at and, you know, and as a result I am not necessarily the biggest advocate of allo transplants, but I know that one of the people that are on this

particular Cure panel, Jack Aiello, is…, is very much so because he is still alive because of it, but, doctor, would you please explain in layman's terms and I ask you that because I read a large segment of…, of a description of your background and what you are working on and I have got to to tell you it…, it sent my…, my head spinning, you know because of the complexity of the whole thing. So, if you could, if you could please dumb it down for us, I would really appreciate it because, you know, you obviously have a tremendous understanding of transplantation, allo transplantation, and graft versus host, and all the things associated with it. So, in layman's term, what is an allogeneic…, allogeneic transplant and how does it differ from an autologous transplant?

Dr. Krishna Komanduri: So, I will be happy to do that and I'll…, I'll say it first that you…, you know that…, that you are a bit of a skeptic with respect to the role of allogeneic transplantation and I think that that's actually appropriate. We…, we… I'll…, I'll…, I'll describe again what…, what this really is, but I'll just say it at the outset that that I think in myeloma we have a less-defined role for allogeneic transplantation than we do in other diseases, like acute myeloid leukemia which is the primary disease for which allogeneic transplant is performed, where the indications are actually very clear and that this is, you know, quite safe, reasonable, and standard of care option, but in myeloma and I think that…, that…, that we will spend this hour talking about that, that in myeloma, you know, there are greater risks, there are clear benefits for a subset of patients, but…, but the…, the data are more murky and I think its important that we thoughtfully have that discussion and I think that's where we'll focus today. So, I think that…, that…., that, you know, that skepticism is not necessarily out of place and I'd like to, you know, I think we'll explore today both the positive and the negative aspects of…, of this approach versus the other approaches and…, and I think one.., one reason that…, that things are more murky is because myeloma in general is a very positive field. There are so many other things that have been developed, both with respect to the…, the role of autologous transplant and the role of emerging therapy including the.., the standard therapies now including IMiD-based therapy like lenalidomide, bortezomib, and…, and other novel agents that are in the developmental pipeline.

Dr. Krishna Komanduri: So…, so, let me answer your question first. What is an autologous and what is an allogeneic transplant? So, I think to start off answering that question, I would like to really start at the most basic part of that and…, and, you know, that is what the bone marrow does. So, the bone marrow and again I apologize because many of you will know this very, very well, but the bone marrow is really a factory for blood cells and…, and to really to live each day, we need red blood cells that carry oxygen to our tissues. We need platelets. Platelets are actually fractions of cells that are produced in the bone marrow that help to clot the blood. So, if I cut myself shaving, the platelets will go and plug the initial hole and start the clotting process and then we…, we have a number of white blood cells that are produced in the bone marrow and those white blood cells include neutrophils. Neutrophils are cells that…, that keep our bacteria, which we have billions of bacteria in our body in check and may live typically only about a week or so and then there are the longer-acting white blood cells, longer-lived white blood cells that include the lymphocytes and may include B cells and T cells and these cells live for decades and protect us from viral infections and other infection, not typically the bacterial infection and indeed these different white blood cells can in some cases become cancerous and indeed multiple myeloma is a cancer of plasma cells which are cells that normally would produce antibodies that protect us from infection but in myeloma patients have become cancerous and then build up in the bone marrow from levels that would normally be very small levels to increasing levels as the disease progresses. A small number of the cells in the bone marrow, some of the white blood cells, typically less than 1 in 100 cells are what we call progenitor cells or stem cells and these cells give rise to really all of those different blood cell types. So, they…, they ultimately can differentiate into white blood cells. They can become red blood cells or they can become platelets and if we take those cells out, those cells are like the seeds of…, of a…, of a plant, in that…, that one cell can actually give rise to multiple different cell types. So, a seed can grow into an oak tree and…, and it has obviously leaves and bark and…, and roots that are quite different from each other and the progenitor cells can be transplanted. So, when patients come to me first for autologous transplant, they often have the misconception that we are curing the disease by somehow transplanting cells, that is, that the transplant itself is curing the disease, but indeed what we are doing and many of you who have experienced this or…, or considering it will already know that, but in myeloma what we are doing is often I think explained to me by an analogy related to the garden. So, if we have weeds in the garden and we have a prize plant next to the

weeds and we try to…, to use weed killer, for example, to get rid of those weeds, we may end up poisoning the plant that we are trying to save. In other words, if we let the weeds grow, the weeds will eventually outgrow the healthy cells and indeed when myeloma eventually progresses, the healthy blood cells aren't produced in normal levels and this is one of the primary reasons that myeloma can be fatal if its untreated. So, if we try and again treat the you know, the weeds with the healthy plant in place, we may end up poisoning the good cells and so the analogy extended to myeloma and autologous transplant is if we give chemotherapy, especially at high doses, we can poison the healthy blood stem cells.

Dr. Krishna Komanduri: So, in myeloma and autologous transplantation, by taking out the…, the healthy blood stem cells, that is by collecting them and these days we collect them through the peripheral blood, we can save them outside the body and then we can give high doses of chemotherapy. So, the analogy with the garden, if we take out the healthy plant and give high doses of weed killer, we now don't have to worry about poisoning the plant. We can let the rain wash away the weed killer and then when the weed killer is gone, we can transplant back the…, the plant that came from the garden, but you can imagine in other diseases, the bone marrow itself may be not functional. There are…, there are marrow failure diseases where the bone marrow can…, the healthy stem cells can no longer be removed and transplanted because they have been destroyed in the context of the disease process or in diseases like acute leukemia or in myeloma, it may be impossible to get sufficient numbers of healthy cells because the…, the bone marrow is now filled with malignant cells and so donor transplants were first done for diseases where it wasn't thought to be possible to take healthy blood stem cells from the bone marrow and instead if you imagine again taking the…, the garden analogy, that if you now wipe out the weed killer but you have no good stem cells left, you now go to the garden store and get new cells, that are new plants, from somebody else and then re-plant them. Doing a donor transplant means that we are getting those progenitor or stem cells from another individual. Now, the catch is that…, that donor transplantation requires immunologic matching because when we transplant cells from another individual, especially when we…, either when we get those cells from the bone marrow or from the peripheral blood, we are also transplanting immune cells from that donor that recognizes foreign tissues and foreign things. The immune system of the donor, of course, is supposed to protect the patient, that's the donor, from viral infections and…, and from foreign invaders like bacteria and other…, other pathogens and if we transplant those cells into the recipient, we are basically putting the immune cells in environment that's completely foreign, even if well matched, and so in the donor transplant setting or the allogeneic transplant setting, we have the immune effects that come into play.

Dr. Krishna Komanduri: So, when we do an autologous transplant and we transplant a patient's own stem cells back, they are, of course, in their own environment and there are…, there is no immunologic reaction, but when we transplant cells from a donor, we can have the donor cells attack the recipient and we'll talk about this more, but that can have both good effects and bad effects and…, and the…, the…, the…, the good effect can be that the immune system cells can actually eliminate cancer cells that aren't susceptible to chemotherapy. So, we have what's called, a graft versus malignancy effect or in…, in the case of myeloma, graft versus myeloma effect, but we can also have a graft versus host disease effect, that is the healthy cells of the donor attacks the recipient seeing it as foreign until it becomes comfortable in the recipient's body, which can take typically six to eight months and that actually requires recipients of donor transplants or allogeneic transplants to get immunosuppressive drugs to basically keep the donor immune system calm until it finally becomes comfortable in the recipient, which eventually happens, you know, when the donor cells become tolerant or comfortable in the recipient and then the immune system can then be unleashed by tapering off the immunosuppressive drugs. So, the…, the two, I would say, fundamental differences between autologous and allogeneic transplant are, first the patient is not the source of the stem cells, but rather we have to find a compatible donor and the second thing is the…, the difference between the donor and the recipient lead to these immunologic differences, which can both mediate good effects, that is, anti-cancer effects but also potential toxicity.

Gary Petersen : Well, thank you, doctor. I appreciate that and I am sure all the listeners do as well. Now, usually the allo is not a first line treatment, I understand, for myeloma, mainly due to the high first-year death rates of 30% to 50%, I know your's is about 30%, which is some of the best, but what has changed, if anything, to alter this mindset of it not being a first line treatment for myeloma?

Dr. Krishna Komanduri: Let me come back to the…, the…, the first line treatment for myeloma. I think that's obviously a critical question for many of your listeners. So, let me talk about that death rate. So, you…, you quoted again typically one-year survival rates at our center of about 70% and that's…, that's, you know, maybe a little bit better than expected for our risk population, but I want to point out that of those patients again, the majority of the patients that receive allogeneic or donor transplants in the United States and at our center are not myeloma patients. Very few myeloma patients receive allogeneic transplants compared to other diseases, especially the leukemia including acute myeloid leukemia. When we look at that…, that, for example, at our center, the 30%, you know, death rate, its important to note that only about half of that is actually related to treatment-related complications and the other half is actually due to disease relapse. So, the…, the important number, I think, you know, as we think about myeloma is what is the…, the likelihood of dying due to complications of the treatment and…, and you are actually right, you know, in…, in stating historical rates of…, of death due to treatment, that is, you know, complications related to the role of donor transplant that were in the range of 30% to 50% in the early days of transplant. So, I finished my training in oncology a little less than 20 years ago and…, and at that point, the rates of death due to the treatment itself were actually in the 30% to 50% rate. We would typically quote patients who had a brother or sister transplant, a one year rate of dying due to complications of the transplant of 30% to 40% and it might be higher in the unrelated donor setting and indeed, it was known early on that myeloma patients probably partially due to the nature of their disease and the fact that the bone marrow was involved, the age of myeloma recipients which on average at diagnosis is typically 65% to 70% and also the effects of the prior treatments that myeloma patients were getting at that time, that…, that myeloma patients had a higher rate of dying due to donor transplants than patients with acute leukemia, for example, but I think its important and I want to just quote the rates of…, of actual death due to transplant in more recent studies.

Dr. Krishna Komanduri: So, Amrita Krishnan who is at City Of Hope Cancer Center led a Multiple Bone Marrow Transplant Clinical Trials Network study where they performed transplant as first line therapy using modern approaches where low…, lower doses of chemotherapy than the…, the therapy that we use to prepare the patient for transplant 20 years ago were…, were…, were used and in…, in that study, the non-relapsed mortality, that is the likelihood of dying due to the treatment as opposed to due to the disease was about 22% in patients at three years, in high-risk patients and in lower-risk patients, it was actually 11% at three years. Other studies have…, have looked at…, at the rates of complication-related death. Dr. _____[00:20:30]_____ in San Antonio did an analysis for the International Bone Marrow Transplant Registry and showed that in the first three years after transplant, that patients who had autologous transplant and then relapsed and then had an allogeneic transplant following relapse had an 11% rate of dying due to complication and again, a more recent European multi-center study that was published, again in 2012, demonstrated that the rate of…, of…, this was published by Patriarca in the Biology Of Blood Marrow Transplant, showed that the rate of dying due to complications of donor transplant was run 22% at two years. So, I don't want to trivialize this because 10% to 20% rates of…, of…, of death due to complication is not trivial and these days an autologous transplant showed very low rate of dying early after transplant, typically at most centers 1% to 2% and our…, our rates are…, are well below 1% if you look at our…, our results over the last several years. So, 10% to 20% is significantly higher, but we also have to remember that allogeneic transplant is typically done usually after failure of autologous transplant and often in multiply relapsed patients. So, its difficult I think to compare, you know, its not an apples to apples comparison, but the reason for…, for that risk is because of, you know, the rates of…, of graft versus host disease and other complication.

Dr. Krishna Komanduri: One of the things that has changed over the, you know, the…, the…, the 20 years that I have been in the field is that we recognize now, as I talk to you about, that the immune system can actually help to cure patients' cancers. So, it can kill off the cells that are resistant to chemotherapy. So, one of the surprising things is that we now use much lower doses of chemotherapy prior to donor transplant than we used 15 or 20 years ago. Fifteen or twenty years ago, we thought that we needed to use very intensive chemotherapy because we didn't understand actually that the immune system was playing a role in preventing relapse. So, we often used a radiation-containing regimen or combinations of powerful chemotherapy agents. We now often use, what we call, reduced intensity conditioning, which means that we use kinder, gentler chemotherapy that…, that still wipes out the recipient's blood cells but does it in a way

that's not likely to be toxic to the lungs and the liver and other organs. So, while we still have complications typically due to graft versus host disease, the complications due to organ toxicities of high-dose chemotherapy are not necessarily a thing of the past but are dramatically reduced and are relatively low, but its true that this higher rate of dying early that is due to the treatment has prevented it from becoming an excellent first line therapy and indeed the studies that earlier on suggested that…, that in initially diagnosed patients that the combination of an autologous followed by an allogeneic transplant was better, were found not to be confirmed in large trials. The trial that I talked about by Amrita Krishnan, which was a trial of several hundred patients who after an autologous transplant were then randomized if they had a donor to a sibling transplant or donor transplant or in some cases, patients were given a second autologous transplant showed that there was no benefit to the allogeneic transplant in addition to the autologous transplant and the reason for the lack of additional benefit is by lower relapse rate was that increased risk of dying. So, it has not been shown as an upfront therapy to be better than autologous transplant patient, either alone or in tandem, and you are right, I think, to be skeptical at allogeneic transplant in general for most patients as an upfront therapy because of that, but again I…, I do think that the mortality rates are much lower than you quoted because of these improvements in the way that we do transplants relative to the initial approach.

Gary Petersen : Yeah, I was looking at the information from Be The Match, which a lot of people provide information and your…, you know, your's were, you know, some of the…, I think they started at like probably 50% and going all the way to like 23%, so a 30% is pretty significantly…, pretty…, pretty good. There weren't many that were at that rate.

Dr. Krishna Komanduri: But, remember, that…, that's the rate of dying during the first year of all causes, not…, and again many of those patients have high-risk leukemia for example and have a very, you know, likelihood of…, that many of those deaths are due to the disease itself, in other words, not due to the treatment. So…

Gary Petersen : I understand, but I didn't…, I didn't see that before. Thank God! Yeah. So, there is a potential cure, I think most people will agree with that, you know, and…, and the death rate is the thing that prevents a lot of people from even trying it, but it does, in fact, even though you have an allo transplant, there is a possibility for relapse. So, what is the relapse rate for an allo and what, if anything, has been done to reduce this relapse rate?

Dr. Krishna Komanduri: That's a very good question and I think that…, that again one of the reasons that its…, its…, its, I think, healthy to be a bit skeptical about myeloma is that the relapse rates are higher than, for example, with acute leukemia, which is again the dominant reason that allogeneic transplants are done in the United States. If we look at acute myeloid leukemia, for example, only about 25% of patients who have transplants will relapse at any point after the transplant or for myeloma, you know, again it varies according to the risk of the patient population and how many lines of therapy that they have had and again, in allogeneic transplants that if patients tend to be on the higher risk end of the spectrum because they, you know, often aren't subjected to the upfront risk without, you know, being again in…, in a…, in a difficult position, but the relapse rates have…, have been and again in Amrita Krishnan's study, you know, she noted that…, that relapse rates in allogeneic transplants were…, for patients who had an autologous followed by an allogeneic transplant upfront were around 46% in low-risk patients and around 38% in higher-risk patients. So, this is definitely higher than what we would expect for again a similar patient population with acute myeloid leukemia, for example, and one of the reasons that…, that allogeneic transplantation upfront is not a standard therapy where in acute myeloid leukemia it is absolutely standard and has been definitely shown to be the appropriate thing for most patients who have a standard to high risk disease. So, again, obviously…, you know, so those were the…, the rough numbers. It…, it will vary, you know, according to patient population, of course, like results in any other trials. If you take a patient population that's upfront and low risk, the…, the…, the relapse rates will be lower than patients of course, who had…, who failed multiple therapies.

Gary Petersen : Well, thank you, doctor, for that. I appreciate that. I really didn't know what that was. So, yeah, your input certainly helped me to understand that much better. Now, could you… Yeah, one of the

things that I have heard is that you can, you know, I have a great response with…, with an allo for your disease, but you can still have what's called graft versus host disease and that can make your life pretty miserable. So, why does this happen and…, and what can be done to minimize it if anything and…, and then again you mentioned before, what you really want is graft…, graft versus tumor and that's what in fact provides the cure potential, but…, but you can have a pretty miserable life, I understand, if you have some…, some graft versus host disease and, you know, what percentage of patients get this and…, and…, and…, and what kind of experience do you…, do you see that they have?

Dr. Krishna Komanduri: That's a very good question. Its a critical area and actually the focus of…, of my…, my laboratory research. So, to explain this, in a…, in a way that I think your listeners will understand. So, most people are…, are, you know, think of rejection, for example, in…, in the solid organ transplant setting and its easy to understand that if, for example, if you give me your kidney, that my immune system is likely to reject your kidney. Okay? So, in other words, that's…, that's the process of transplant rejection, but in a donor transplant, if you think about what's happening is, we are actually transplanting a whole entire immune system. So, the immune system of the donor is healthy and its recognizing everything in the recipient potentially as foreign and there are certain organ systems like the skin and the liver and the intestines that tend to be particularly susceptible to the immunologic reaction where the donor immune system realizes its in a foreign place and starts to attack everything around it. Now, again, I did explain in…, in that…, that…, that is associated with a good effect which is called the graft versus malignancy or in this case the graft versus myeloma effect, but to do a transplant at all from a donor, we actually have to put the brakes on the donor immune system by giving immunosuppressive drugs, just like the solid organ transplant recipient has to be given drugs to prevent the…, the recipient from rejecting the donor kidney in that case, but…, but in the donor transplant setting, we actually give immunosuppressive drugs typically for at least three to four months and then we can usually taper them off from six to eight months, but a subset of patients despite the donor being given drugs to…, to, you know, damp down the immune system or to put the brakes on the immune system, the donor immune system will still find a way to recognize, you know, the foreignness of the recipient and attack the recipient. Now, of course, that…, that…, that depends on how closely matched the donor and the recipient are. Brothers and sisters have a 1 in 4 chance of matching and brother-sister transplants have a lower rate of graft versus host disease. Unrelated donors are slightly more likely obviously to cause graft versus host disease in the recipient because they are…, they are, you know, despite having good matching, they are less, you know, closely matched than…., than brothers or sisters. Now, graft versus host disease has two flavors, without getting into…, too…, too many specifics, but it comes in an acute form which happens typically in the first three months after transplant and then there is a chronic form which can happen between three months and…, and…, and even years after transplant. The acute form happens in brother or sister recipients typically 20% to 30% of the time and…, in a…, in a…, in a higher fraction of unrelated donor recipients, but the chronic form of graft versus host disease happens in…, in probably about 40% of…, of brother or sister recipients and…, and as many as 50% or more of…, of unrelated donor recipient. Now, its true that in many patients, grafts versus host disease can happen and then it can actually be treated with more aggressive immunosuppression and…, and it goes away. Unfortunately, a subset of patients will have graft versus host disease that impairs quality of life and again we hope that that's associated with a good effect, that is, freedom from relapse, but in some patients unfortunately, graft versus host disease can be a significant impairment. So, they are now trading a myeloma life or a a malignancy life with malignancy with, you know, life with basically a chronic immunologic or inflammatory condition and in some cases the…, the quality of life impairment can be severe, but fortunately that's a small fraction of patients. If you look at patients in general, for example, with acute leukemia where you have much higher numbers, about 80% of patients are off immunosuppression completely by about two years out after transplant. So, in other words, the vast majority of patients are living without graft versus host disease. A subset of patients will have graft versus host disease and I sometimes tell people this may be like diabetes, and you may be cured of your disease but like, you know, like my father who has been a diabetic for…, for decades and yet a healthy person, can forget he is a diabetic and may have an immunologic consequence or problem that has to take…, for which, you know, he has to take medication, but…, but, you know, that…, that individual can live a high quality of life. Obviously, a subset of patients will have impairment of quality of life, but it is this…, this need to balance the bad effects of graft versus host disease with the good effects of graft versus malignancy that's really a focus and many of us are trying to find better ways of doing this and there are attempts.

Unfortunately, many of the immunosuppressive drugs that can prevent graft versus host disease also increase the risk of infections or increase the risk of relapse and therefore, we kind of, you know, trade one consequence for another. For example, taking out the T cells from a donor graft will, you know, decrease the likelihood of graft versus host disease but will increase the, you know, likelihood of infections in the recipient and…, and most of us think will increase the risk of relapse. So…, so, this is kind of a central question and I think focus of…, of much research to try to find better ways of suppressing the immune system that can allow the good effects of the immune system to happen without the bad effects.

Gary Petersen : Thank you, doctor. I appreciate that. At this point, I would like to open up questions to the panel. Jack Aiello, are you there?

Jack Aiello: Yep. I am on… I am on, Gary.

Gary Petersen : Okay, Jack. Ask your questions.

Jack Aiello: I will do that. Thank you very much for being on the call, doctor. I…, and just to let you know, I am the allo patient that had an allo, but I am not necessarily for it or against it. Its just that when I was diagnosed in '95 and the tandem auto didn't work very long and there weren't many other treatments around then, in '98, the full allo that I went through with TVI was essentially the only salvage therapy had left me and…, and when you talk today about allos, I…, I think not all allos are the same. There is a lot with respect to the condition in the allo. I hear lots with respect to T cell depletion or non-T cell depletion. You hear the terminology of myeloablative versus non-myeloablative, full versus mini versus reduced intensity. So, if a…, if a doctor is proposing an allo to a patient, can you say little bit more about the differences in condition and why one might consider one versus the other?

Dr. Krishna Komanduri: Absolutely and its a very good question, so…, and congratulations to you and…, and I think that…, that your story actually summarizes why allogeneic transplantation has an important place. There are clearly patients who can get standard therapies and have an autologous transplant and be disease free for 8 or 10 years or longer and those patients clearly, I think, shouldn't be thinking about allogeneic transplant, but then there are other patients who have either very high risk disease upfront or have exhausted other therapies, including autologous transplant for which they are likely to face, you know, a myeloma-related death and I think for those patients clearly even if there are risks, allogeneic transplantation which is known to be curative and can be, you know, curative in patients like you. You are 20 years out, that's wonderful! I think that…, that's actually a great lesson. So, you asked the question. So, I…, I explained that in the early days of transplant, we thought that donor transplant really cured patients really just by kind of wiping the plate clean and giving a healthy donor bone marrow. We did not at that point imagine that the donor immune system can actually help to…, to eliminate cancer cells. So, we thought that everything had to be done with the chemotherapy and/or radiation. So, we generally thought the more intensive, the better. So, let's push patients to the brink of death and…, and let's use the most intensive chemotherapy and/or chemotherapy and radiation possible because that will kill the most cancer cells and ironically, when we realized that the immune system actually was doing the work and we realized this between 1990 and 19…, you know, '95 that it became definitively, you know, the case that we realized that…, that the immune system could cure cancers indeed. We said, well, let's use the less intensive chemotherapy because we're indeed probably causing excessive mortality related to organ toxicities like toxicities to the lung or toxicities to the liver and indeed it turns out that those more intensive chemotherapies are all associated in some cases with higher rates of graft versus host disease.

Dr. Krishna Komanduri: So, we started using what we call reduced intensity chemotherapy and we…, we…, we know that in fact in the early days of transplant, when I was starting my career, we didn't transplant anybody over the age of 60 because nobody could tolerate those…, those intensive combinations and that, of course, was a big problem because diseases like acute myeloid leukemia and diseases like myeloma occur most commonly in individuals between the age of 60 and 70 and…, and often over the age of 70. So, if the…, the treatment was so extreme and dire that it couldn't be used, it wasn't of, you know, much value. So, it turns out that reduced…, using lower-intensity chemotherapy and again the terms that you…, you used

reduced intensity really refers to less intensive chemotherapy that's less likely to cause harm in the recipient, but usually chemotherapy that if you give it to the recipient, the…, the recipient's blood cells won't grow back. Okay? And so…, but that means kind of kinder, gentler conditioning chemotherapy. You also asked the question about T cell depletion. Well, normally, we give peripheral blood stem cells and the stem cells from the donor include immune cells that can…., of course, can graft versus host disease. Those lymphocytes and T cells, you know, the T cells which are subset of the white blood cells called lymphocyte that I talked about. Well, certain centers and I think Memorial Sloan Kettering, in particular for your listeners who consider treatment there, is a proponent of removing the T cells from the donor graft. Well, we know from acute leukemia studies that…, that when you take out the T cells from the donor graft, you get more infections in the recipient because it makes sense, you are not transferring the white blood cells that help to protect the recipient from infection, but we know that in the setting of acute leukemia that you get more relapses. Now, the Sloan-Kettering group has been very dogmatic about…, about the benefits of T cell depletion and they cite their data suggesting that their relapse rates don't seem to be, you know, much lower with T cell depletion, but I would say that the prevailing view and certainly the view in general of centers like MD Anderson and others is that that when you take out the T cells and you…, you…, you know, reduce the risk of graft versus host disease, but you pay a price with respect to increased rates of infection and relapse. So, there are…, you know, I think prevailing local customs, right, and…, and I think at…, at Sloan Kettering, its one of the fewer programs in the country, you know, that where you are likely to be recommended to T cell depleted transplant and if you have a transplant there, my view is that you are more likely than to have infection or relapse. Again, you know, there…, the physicians there may disagree.

Dr. Krishna Komanduri: The vast majority of programs in the country will give you the cells that are collected from the donor, which include T cells and again will use different types of conditioning that may be more intensive or…, or less intensive. Again, if the disease is less robust at the time of transplant, you can imagine that it becomes safer to use less-intensive chemotherapy. So, somebody who is in a complete remission might not need as much chemotherapy to get the disease in check and then the donor immune…, because the donor immune system has less work to do, but you can imagine if you have a patient with a lot of disease and this has been proven in the setting of acute leukemia, less so in the setting of myeloma that…, that it helps to have some intensity and I often tell people like, you know, its like knocking a bully down before, you know, somebody else can finish him off, that…, that the chemotherapy plays a role in tandem with the immune system. So…, so, the reduced intensity refers to basically the intensity of the chemotherapy which along with the immune system effects are the two things that help to keep the disease in control and can prevent patients from relapsing and indeed can cure patients, a subset of the time like you.

Jack Aiello: Thank you. My other question and I think you already answered that. I just want to make sure I understood the answer. My other question had to do with high-risk patients. So, for example, I am a deletion 17p patient who has failed an auto transplant and most other therapies and I am being recommended to get an allo. Did I understand you to say that unfortunately high-risk patients have also a higher rate of relapse than standard risk patients from an allo transplant?

Dr. Krishna Komanduri: They do. I…, I think that its common sense that, you know**…**bad disease is likely, no matter what treatment you throw at it, to be more likely to relapse. Right? On…, on the other hand, you know, its not always true that the more risky things are going to achieve better outcomes. There are, you know, times when you can't overcome that risk, but you…, you are a perfect example of somebody who at high risk with likely, you know, I mean we don't think of myeloma typically as a curable disease, but with, you know, extraordinarily unlikely to live, you know, for more than a year, let alone 20 years. So, I think that if you look at the modern role, you know, again there were early studies that…, that were single-institution studies that were not randomized that suggested in upfront patients that autologous followed by allogeneic transplant did better than what we would have expected of autologous transplants alone, but then that led to a large randomized study that I talked about that was published in Lancet Oncology and again Dr. Krishnan was the first author, that failed to show a benefit upfront in standard risk patients, but clearly there seemed to be subsets of patients that we know do very poorly in myeloma and…, and they include patients, for example, with plasma cell leukemia who have high amounts of the malignant plasma cells that even circulate in the blood and there are patients who have chromosomal abnormalities and…, and some of the

genetic abnormalities include the deletion of chromosome 13, the deletion of chromosome, you know, 17p, and then other chromosomal abnormalities like translocations of chromosomes 4 and 14 and then there are new modern gene expression profiling signatures that appear to be associated with…, where there are multiple mutations that can be, you know, assessed by modern methods that appear to be associated with, you know, particular resistance to standard approaches and I think that if you look at what most of us would say about the role of allogeneic transplant, one is that we should continue to ask studies to see if there are subsets who either at relapse or upfront if they have very high risk disease may be cured with allogeneic transplant or have better survival with allogeneic transplant than they would with these traditional approaches which we know with these, you know, subsets of patients, you know, respond very poorly.

Dr. Krishna Komanduri: Right now, I have to say its not proven yet that allogeneic transplant is the right thing to do, but I think that we know that there are patients like you who…, I think you would say, it would be virtually impossible to have expected you to be alive 20 years later, given how you presented. Right? So…, so its common sense. Now, the question is, which subsets of patients should take the risk of the…, of the…, of the higher treatment-related mortality even though that treatment-related mortality is much better than it used to be and I think that's the question. So, I think that…, that if you ask me again, not to over simplify, I would say that…, that there is a subset of patients who have failed autologous transplant and, you know, either have failed additional therapy after autologous transplant or had a very short response to autologous transplant that we know historically are likely to do poorly and they should be considered for allogeneic transplant and there's another group of patients, either who have plasma cell leukemia which is a very rare but very, you know, terrible subset and there are patients with these high-risk genetic signatures whether they are chromosomal abnormalities or gene expression signatures, that appear to do very poorly and I think in those patients we need to know whether allogeneic transplantation can achieve better outcome as we suspect it may than the traditional approaches.

Jack Aiello: Thanks very much, Dr. Komanduri, and just to clarify for the listeners, I… In 1995, they didn't even determine if I was high risk or not, so I wasn't saying that I was the deletion 17p candidate.

Dr. Krishna Komanduri: I see. Right. No… I…, I appreciate your clarification because I…, I thought maybe that there were examples for something else that was done afterward because absolutely those…, those…, those techniques were not available at that time.

Jack Aiello: Right. Thank you.

Gary Petersen : Thank you. Matt, you online?

Matt Goldman : Yes, I am, Gary.

Gary Petersen : Your question?

Matt Goldman : Yeah. Thanks for your time, doctor. You…, you kind of touched on a couple of my questions, but you…, you have brought about other questions, so I am going to go off script a little bit. You talked about for the donor, you took the break from the immune system for couple months leading up to the transplant.

Dr. Krishna Komanduri: No, that's actually in the recipient after the cells are infused. We don't do anything to the donor. We just collect cells from the donor, that's right. So, we…, we put… In other words, once the cells are infused in the recipient, the donor's immune system, of course, would attack the recipient, you know, in almost all cases. So, we give the recipient immunosuppressive drugs after the donor's immune system has been infused.

Matt Goldman: And…, and how long do you…, do you sort of on average keep the recipient on those…, those immunosuppressive drugs?

Dr. Krishna Komanduri: So, on average, we would typically continue them at full doses for somewhere between two to four months and then we typically would taper them, you know, as often as schedule might be. We continue them at full dose for around three months and then we drop them by about 25% each month over the next three to four months so that…, that, you know, in…, in a good situation where the recipient is not experiencing any graft versus host disease and is doing well, like six to eight months after transplant they are off the drug.

Matt Goldman : And is that similar to what autologous transplant patient will go through in terms of suppressing the immune system and making…?

Dr. Krishna Komanduri: Absolutely not. An autologous transplant is the patient's own cells, so we don't have to suppress the immune system at all and the risks are very low. There is no risk of…, of the…, the patient's own stem cells causing problems and indeed, autologous transplant, really the only risk, the major risk, is the first couple of weeks after the transplant when the blood cells haven't recovered to kind of healthy level. The immune system is more suppressed in all. You know, many cancer patients, including myeloma patients and, you know, autologous transplant patients will have a somewhat high risk of infection, but it dramatically diminishes and the likelihood of having fatal complications is…, is very, very low beyond the first couple of weeks after transplant. So, that's quite different than the donor transplant setting where…, where patients are on immunosuppression for prolonged period of time and if they do have graft versus host disease, that six months can become a year or two or longer in that small subset that has more serious graft versus host disease. So…, so, its that the…, the need for immunosuppressive drugs in the donor transplant setting that makes it a much more, you know, risky and cautious proposal and requires much, you know, more complexity of care and expertise.

Matt Goldman : And so, again, for the donor there is…, there is no risk or choice enough to worry about?

Dr. Krishna Komanduri: Really, I think very, very limited risk of, you know, discomfort. Again, we have to wait, sometimes collect the cells from the blood and we have to, you know, achieve…, get IV access sometimes in a subset of patients who have small veins. In…, in…, in some patients, not so many these days, we do operative bone marrow harvest, but the vast majority of patients, almost all…, all brothers and sisters and, you know, these days the majority of unrelated donors have cells collected from the peripheral blood. There is some minor, I would say, discomfort and some minor risk, but, you know, very, very low risk. No one should really think about it and…, and, you know, there are, you know, thousands of…, of unrelated donors each year who donate for patients who are not part of their family and…, and safely recover and typically back to work within days.

Matt Goldman : And the related donor or donor could be a donor more than once, I would imagine, right?

Dr. Krishna Komanduri: They could, though again, we, you know, that you…, you wouldn't often do a transplant more than once because again, you know, typically, you know, this is not something that's frequently done, you know. There are…, there are less than, you know, there are… The number of allogeneic transplants for myeloma in…, in the country, you know, are probably in the hundreds as opposed to, you know, maybe 8,000 that are done for overall, you know, for mostly for leukemia and other diseases. So, we could do a transplant with a donor twice, but it would be extraordinarily unusual.

Matt Goldman : So, you haven't done an allo if the same patient has _____[00:50:11]_____?

Dr. Krishna Komanduri: No, we will. You know there are patients who, for example, will lose, you know, rarely the donor graft kind of is lost because there is an infection in the recipient and the blood cells drop and we might re-transplant from the donor. There are patients who, you know, appear to be cured, again like, you know, in situations like…, like where, you know, Jack had, but, you know, but then would experience a very late relapse, not necessarily an early relapse, but…, but if somebody relapsed maybe five years later, we might consider another allogeneic transplant. So, you know, those of us who have been transplanted for a long time have certainly seen circumstances where we have to do allogeneic transplant and on occasion

from the same donor, but its…, its not common for myeloma or other diseases.

Matt Goldman : Okay. And then, I think my last question is, for…, for myeloma patients that are kindney infected, is an allo transplant something that might totally just demolish those kidneys?

Dr. Krishna Komanduri: Yeah. So, it's a very…, very good question. The…, the primary immunosuppressive drugs are a class of drugs called calcineurin inhibitors and they include tacrolimus and cyclosporine and these drugs unfortunately cause abnormal kidney function in even healthy individuals and so, there is definitely higher risk in patients who have baseline kidney function abnormalities and typically patients who have a creatinine and, you know, those individuals who have experienced kidney problems will know what that number is. Above the level of 2 are usually not considered for donor transplant because of…, of typically the risk of the immunosuppressive drugs causing further kidney problems because what you don't want to do is to do a donor transplant and then have that be complicated by kidney failure because that increased the risk of deaths and causes other problems. So, you are absolutely right, that I think that patients who… Again, its fine if patients have… You know many patients with myeloma will have kidney problems, but then when treated that kidney function will improve dramatically and that's actually not a contraindication, but ongoing kidney problems, especially at the time of transplant are a concern.

Matt Goldman : Okay. That's all I have. Thank you.

Gary Petersen : Okay. Thanks, Matt. Really appreciate that. Priya, could you bring on line some callers?

Priya Menon : Thank you, Gary. Dr. Komanduri, we have a list of questions, I think I have shared with you. I believe you have…, may have answered quite a few of them, but let's just go through the rest for our listeners. The first one is from our listener who asks, do you need to be in complete remission to do a full allo as part of a first line therapy?

Dr. Krishna Komanduri: So, the answer is no, but we know that allogeneic transplant because… So, the immune system is better at finishing, you know, the…, the job when the disease is relatively responsive. Okay? So, I would say that…, that in most cases, and if you look at the…, the…, you know, the…, the…, the trials that they normally would require at least a partial response or a very good partial response that is more than 50% or 90% reduction. So, the answer is that the patients typically don't have to be in a complete response and…, and I want to specifically plug. You know, there is a large study of allogeneic transplant and one of the things you have heard me say more than once is that I think that allogeneic transplant should be done ideally in an academic center in the context of a clinical trial. There's actually a very large clinical trial that's being done in the…., through the Bone Marrow Transplant Clinical Trials Network and will be available at many academic centers around the country that looks specifically at…, at the value of allogeneic transplant for the groups of patients that we talked about, either very high-risk patients upfront or patients who had a short remission after an autologous transplant. So, these are the patients that we think, you know, should be, you know, it would be reasonable to subject them to the risk of allogeneic transplant because we know that they are likely to do poorly otherwise and if they can be cured and if you look at the criteria for that trial, the BMT CTN study, again it…, it does require one of these high-risk types and…, and typically requires responsive disease but not a complete response.

Priya Menon : Thank you, doctor. The next question is, is there an age limit for a patient who is doing well after relapse on Velcade maintenance to go on for an allo?

Dr. Krishna Komanduri: So, that's a good question. Again, so at our center and I think many centers, we really don't think twice about doing allogeneic transplant, again in appropriate patients at least to the age of 65 and routinely we are doing transplants up to the age of 70. Above the age of 70, we get very cautious with respect to making sure patients are in particularly good health. We all know individuals who are healthy, who at the age of 73 are…, are, you know, going to the gym multiple times a week and then we know people who are bed bound at the age of 73. So, not every 73-year-old is…, is at, you know, equivalent, you know, risk, but…, but…, but I would say in general, in most centers up to the age of 65 or 70 is…, is again not a

contraindication. The BMT CTN study that I talked to you about specifically includes patients only under the age of 65, so that has an upper limit of 65, but…, but that's…, that's true and certainly one of the groups of patients that we would consider upfront treatment are patients who are very young and unfortunately there are patients who, you know, are diagnosed with myeloma in their 30s or their 40s and we know that that those patients are much more likely to die of their myeloma than…, than patient who is obviously 75 at the time of diagnosis.

Priya Menon : Uhmm… Yeah. Thank you, doctor. The next question is, recently radiolabeled antibodies are of particular interest for conditioning regimen for allogeneic transplant. Could you explain to us how they are going to be helpful?

Dr. Krishna Komanduri: So, that's a great question. You know, there are… I talked to you about one of the reasons that…., that bad things happen after transplant and that historically the high doses of radiation and chemotherapy which can affect organs like the liver or the lung. The idea with radiolabeled antibodies is, the antibodies are ironically produced by plasma cells, you know, healthy plasma cells, but they can, you know, be engineered such that they can be like smart bombs basically. They can go and…, and they recognize a specific protein on the body and they are now antibodies that are in clinical trials and some of these were developed at the University of Washington which is at the Fred Hutchinson Cancer Center, which is the pioneering center, which can basically home to the bone marrow without affecting nearly as much. You know, there are some stray antibodies that are radiolabeled that can end up in the liver or the lung, but the idea is that…, that more of those cells end up in the bone marrow and therefore can get rid of, you know, cause damage, you know, to the cancer cells in the bone marrow with doing less harm to ordinary tissue. So, in…, in animal model system, this appears to be promising, but…, but I would caution that we don't have human clinical trials despite the fact that this is a promising intellectual, you know, strategy that seems appealing that…, that…, that this is really going to work because, you know, one problem is you could infuse these cells and although you…, you think that they are going to end up in the bone marrow, they end up kind of trafficking through the lungs for example and causing some bystander damage well they are there. So, this is an interesting strategy that is now starting to enter clinical trials but isn't ready for prime time and and hasn't been shown to be better than the standard way that we give chemotherapy, which as I told you, are much safer than the way we used to give chemotherapy at higher doses 20 years ago and…, and, therefore, you know, there is less of a need to develop targeted strategies because we think that just by reducing the intensity of conditioning that we have made transplant much safer.

Priya Menon : Thank you, doctor. We have time for just one more question. What does your research show concerning early versus late transplant?

Dr. Krishna Komanduri: So, I think the early versus late transplant is the best question in the setting of autologous transplant. You know, we know that…, that studies 20 years ago demonstrated that autologous transplant should be the standard of care for, we think, most patients with myeloma, but yet we know if we look at the number of myeloma patients out there that many are not getting early transplants and many are only getting transplanted later on. There is a large study that…, that the Dana Farber and the French are doing that…, and we are hoping that there will be some preliminary results reported at the hematology meeting in December, looking at…, at results of a new randomized study in patients who have gotten novel agents, new agents like Revlimid and…, and Velcade, looking at early versus late transplant and we think we will have some more information about that. In the context of allogeneic transplant, which of course, has been our focus today, I would say that that allogeneic transplant should probably really be considered in the early setting only for patients who have truly high risk disease, either by those chromosomal markers or by the presence of plasma cells, leukemia, or adverse gene expression profiling results. The majority of allogeneic transplants are performed for patients who have relapsed post autologous transplant, then again…, and that's partially because we…, we know that applying allogeneic transplant upfront to everybody probably, you know, subject some patients to harm, who, you know, would do well with, you know, standard autologous transplantation. So, I think for allo transplant setting again, like the.., the criteria for that BMTCTN study would be really upfront really only for the patients with highest risk disease and then in other patients who have failed autologous transplantation and perhaps other lines of therapy.

Priya Menon : Thank you, Dr. Komanduri, for sharing all this information with us. I think this is some of the most simplest and clearest explanations of auto and allo that I have heard so far on the show. So, thank you very much. Gary, Jack, and Matt, thank you so much for your participation as always; and today's talk will be made available on CureTalks' website along with its transcript. Please visit curetalks.com for details of upcoming talks. Thank you, everyone.

Dr. Krishna Komanduri: Thank you.

Gary Petersen : Thank you very much, doctor.

Dr. Krishna Komanduri: It's really a pleasure.