MSKCC Expert Dr. Ola Landgren on Can High Risk Disease Progress Cure Myeloma ?

Is high risk disease progress, the key to a cure for all myeloma patients? And what can researchers do to get new therapies to work for more than 30% of relapsed patients? Multiple myeloma has many different treatment options and the path patients' follow is different depending on response. In fact in some cases a disease that starts out as low risk may one day progress to high risk. That is why the treatments for these higher risk diseases is so important. A new therapy would need to show efficacy across different lines of therapy. CureTalks' myeloma panel is talking to Dr. Ola Landgren on high risk disease, progress, and cure.

Full Transcript:

Priya Menon : Good evening, everyone. Welcome to CureTalks' 91st episode. I am Priya Menon, Scientific Media Editor at CureTalks, joining you from India. Multiple myeloma is a popular talk on…, topic on CureTalks, and today we have Dr. Ola Landgren with us to talk about his research and views on whether high-risk disease process is the key to a myeloma cure. Dr. Ola Landgren is Chief of Myeloma Service at Memorial Sloan Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College. My co-host of the evening is Gary Petersen. Gary is Editor of myelomasurvival.com. Our myeloma panel consists of myeloma survivors and advocates, Pat Killingsworth, Jack Aiello, and Cynthia Chmielewski. I extend a warm welcome to everyone. Today's topic for discussion, as I mentioned, is high-risk disease progress – Is this the key to a cure for all myeloma patients and what can researchers do to get new therapies to work for more than 30% of relapsed patients. Multiple myeloma has many different treatment options, and the path patients follow is different depending on response. In fact, in some cases, the disease that starts out as low risk may one day progress to high risk and that's the reason why the treatments for these higher risk diseases are so very important. A new therapy would now need to show efficacy across different lines of therapy, and we are going to learn more about high-risk disease progress in the coming hour. Before I hand over to Gary, I would like to remind our listeners that towards the end of the talk, we will be answering questions sent in via email and those posted on our website, curetalks.com. Over to you, Gary.

Gary Petersen : Thank you very much, Priya, and again for all that you do for the myeloma patient community. Dr. Ola Landgren is the Chief of the Myeloma Service in the Division of Hematology/Oncology at Memorial Sloan Kettering Cancer Center, one of the best in the…, in the world, perhaps, and the Professor of Medicine at Weill Cornell Medical College. Previously, Dr. Landgren was the Chief of the Multiple Myeloma Section at the National Cancer Institute in the Cancer…, Center for Cancer Research. Dr. Landgren received his MD and PhD at the Karolinska Institute in Stockholm, Sweden. Dr. Landgren is a board-certified hematology oncologist whose research focuses on the development of novel treatment strategies in advance disease monitoring by new minimal residual disease, MRD, assays as well as biological studies focusing on disease and host biology. Dr. Landgren studies the mechanism and markers of progression from MGUS and smoldering myeloma, the symptomatic multiple myeloma, and identification of high-risk precursor patients who might be candidates for earlier treatment and we found, I think and those people believe now, that the earlier you treat it, the better off you are. I have a strong interest in the development…, or he has a strong interest in the development of early treatment clinical trials targeting high-risk smoldering myeloma. He is one of the pioneers in the development of minimal residual disease testing in myeloma and use of trials at Memorial Sloan Kettering; and he is a member of the IMF working group and he is also on the scientific board of the MCRI, Myeloma Crowd Research Initiative, and has too many publications that may end up without using up this entire hour. In addition, he is fluent in German, Swedish, and English. Thank you for your boundless efforts to…, in keeping us alive, doctor. Welcome aboard, doctor.

Dr. Ola Landgren : Yes, I heard. I guess I look pretty good on paper, but I am just a simple guy.

Gary Petersen : Hey, no. You are pretty good-looking guy too, but what I would like to ask is first, thank you so much for all you do for the myeloma patient community and, you know, for all the hard work that you do, you know, keeping us all alive. We certainly appreciate that and one of the things that came up is, you know, there is much of a dichotomy about what high risk is. You know, some people say, well, its…, its based on FISH, other people say its based on 70-gene profile. I heard that, well, any time you relapse, you are at high risk; and when you are refractory, you are at high risk; if you have co-morbidies like kidney damage, you are at high risk. So, it seems like, you know…, you know, could you please explain what high-risk disease is and…, and why without a cure…, why without a cure low-risk disease will one day either morph or maybe morph into high-risk disease and become incurable?

Dr. Ola Landgren : Oh, you are asking a lot of very good questions. I am not sure I know all the answers, but I'll try to do my best. I think, first of all, I would like to emphasize the fact that when we talk about multiple myeloma, we are for sure not talking about one disease; and also, I would like to emphasize the fact that even we being one single patient, although we can set the diagnosis of multiple myeloma, there are multiple types of multiple myeloma going on already at diagnosis in each and every patient. I think that's very important to keep in mind because when we give therapy, there will be differences in responses, in the duration of the responses, and the long-term outcomes across individuals and also within that same individual, there will be different responses across these different subtypes of myeloms, subclones of myeloma within the given patient in relation to a particular therapy. So, if we try to make that very practical what I just said, when we deliver the same therapy to every patient, if that were to be done, some people will have it good, someone will have a poor response and duration of that response and we will then call it high risk or standard-risk disease. In my opinion, in the era of having an established curative therapy, there will not be any high-risk disease. Its always going to be in the light of how any given disease is treated; and if you look back 10 years ago, 20 years ago, there would be more hallmarks of multiple myeloma, clinical hallmarks that would be counted to the category of being high risk and as time is moving forward, that changes because if you develop a better therapy today than you had yesterday, there could be some subtypes of disease that now would respond to this new therapy which did not respond as well to the therapy we had before. So, what I am trying to outline here is that these are not written in stone inherent high risk versus standard risk features. These are always in light of how they are being treated, and they also are in light of what else is going on in their bodies. There are different subclones that will probably also yield back. The last thing I want to say as the turning point on this very topic is that when you treat the given patient with the given therapy, if that disease responds well and you would use whatever tools you use to call it high risk or standard risk, in the event, god forbid, the disease now comes back later and it has a different dynamic, its more…, behaving more aggressively, if you were to apply those same tests again and you would label it as high risk, it may be that those clones were there from the very beginning and in fact there is scientific evidence to suggest that that probably is the case for the most part, but this is more a matter of the distribution of these different subsets of disease being shuffled around.

So, when you start off, you treat and you get rid of and you suppress those subsets of disease that are more prone to respond to therapy. So, when the clinical presentation comes back, it is those subclones that did not go away to the same degree in the beginning, in the first place, that are now in majority. So, the balance of these different subsets of disease have been shuffled around and you are simply dealing with a new balance of subclones. So, I think these are like fundamental principles of…, of the…., how very dynamic these dimensions are. There is no high risk and standard risk and that's it. That's not how it works.

Gary Petersen : So, would you say that high-risk disease or at least the markers, you know, that we would say we had one of the high-risk markers, whatever it might be and that it may not respond poorly, it might respond well and…, and actually the patient might do well.

Dr. Ola Landgren : Oh, well, so… As I tried to outline, across individuals, if we apply a certain set of markers, then we can spend more time talking about what those markers are that people like to use, but as we are moving into the future and we monitor individuals, we will see that certain hallmarks of…, of the disease do respond more or less to given therapy, but then there could be subsets of such features that are not so dominant. So, when you work up and give an individual, you may not see those markers because

there are other cells that are more dominant. Disease…, the…, the disease has different subclones. So, there could be subclones that don't have those hallmarks, but as you treat you may bring down those subsets of disease that don't have the hallmarks of what you call high risk. In the event that the disease comes back later, now these subsets of cells that have these hallmarks may be a majority and you may interpret that as the disease has changed, but its just a balance between these different subsets of disease that have been shuffled around, but if you have therapy that was tailored and designed to kill off these cells that are biologically in a certain way, then you would no longer call that high risk. We simply have a therapy that would kill off cells that have a certain hallmark, and you would now on a clinical note judge those as being standard risk. So, high risk is only, in my opinion, a reflection of the fact that the standard therapy does not do a good job.

Gary Petersen : Okay. So, its… Basically, its just very difficult to define and the definition changes with time.

Dr. Ola Landgren : Oh, if you think about it, its the marriage between biology and therapy. If there is a good match and the therapy depletes the disease, that's what we call standard risk. If that marriage doesn't work, then we call it high risk and given that there are many biologies going on in parallel in the same patient, when you deliver therapy, if there are subsets of the cells of…, of disease that have very bad match to the therapy that's being given, that will be viewed as high risk, but in fact its the match between the therapy and the biology that is not there.

Gary Petersen : So, in the end, we are all high risk because in the end we don't…, no longer respond to therapy.

Dr. Ola Landgren : Well, so, what I am trying to say is like how it works biologically, but you could also take a very practical approach and say, for someone whose diagnosis has a lot of those cells, where very few therapies actually work, are those individuals more of a high risk? Is that the correct statement? Yeah, I think that is the correct statement because you are now dealing with features of disease that can pose more challenge and there are fewer good options right away. So, on the clinical note, absolutely, you could say that there are individuals who have a high risk and there are individuals that have a lower risk, but what you just said to me, I also think its right that there are subsets of disease in each and every person that could be higher or it could be lower in the light of a given therapy.

Gary Petersen : Okay. Thank you so much, doctor. Now, is progress in high-risk disease important to the advancement of cure for all myeloma?

Dr. Ola Landgren : Yes, absolutely so and I think that its important for many reasons. So, one key reason I think… There are two key reasons that come to my mind right away. One is that for those individuals that are being diagnosed with a disease that is more aggressive, that would fall under the umbrella that we would clinically call high risk, for those individuals, we…, we need better therapies to offer to…, to offer deep and durable responses ideally to develop a cure, but we are not yet there. We are working to try to get there, but at this point the key problem with the…, the clinical hallmarks of…, of disease that is more aggressive is that it may respond to therapy but its little bit more prone to come back and then we have to re-treat it again. So, it becomes little bit of a hassle to deal with that all the time for the individual patient that the disease tends to come back. So, there, that's one of the key areas, I think, for…, for clinical applied research to try to come up with better therapies for those individuals and if I look across the board of all the patients I see, I would say that that is probably maybe 20% to 30% of all patients that are newly diagnosed that come to clinic that would fall into that category, around that number.

Another area I think where high-risk disease discovery work is also very needed is for all the other individuals who do not fall in that category and that will be for the reason you just brought up in…, in your question. That to me, if you could every person potentially carries high risk. I do think for even for individuals who have more standard-risk disease that there probably could be a few cells that would be more of the high risk type. If we could get rid of those, that may be a step in the direction of trying to develop a curative strategy. So, to…, to deplete those last cells that don't go away with standard therapy, to try to

understand how that works and try to get up. It may be that those two goals actually are linked biologically and…, and…, and treatment wise. So, we need to do research in those areas and that could have implications in the opposite direction, so to speak.

Gary Petersen : Okay. Thank you. Along that same line and another following that is, what do you think is currently in the pipeline or on the horizon, either therapies or drugs, which will allow progress towards cure of high-risk myeloma?

Dr. Ola Landgren : Well, I think there are lot of the important efforts going on that I truly think have the potential to…, to make major advancement, not only a few percent but like major…, major steps forward. I think that the… I think the development of cell therapy is important using the chimeric antigen presenting T cells, the CAR T cells, and…, that I think is a very…, very new approach. Basically, what that approach is all about is to identify surface proteins on cells that are myeloma cells and even earlier cells than actual myeloma cells biology wise, but to identify targets in terms of proteins and then take out the individual patient's part of the immune system to take out some of the T cells and re-program them and give them back and then they are now programmed to kill off cells that carry these proteins. So, that's a very sophisticated way of depleting cells and it has been found to be extremely successful, for example, in acute leukemia. There was also evidence in…, in certain lymphomas, and there is ongoing work in myeloma now. The group at the University of Pennsylvania led by Carl June has done very interesting work. There is ongoing work at the NIH. We also have work going at the Memorial Sloan Kettering, and we will probably open up full-fledged cell therapy program with CAR T cells in the coming year. I think that carries a lot of promise for high-risk disease. I think that many of the new drugs that are becoming available probably in the coming 6 to 12 months, they are now being reviewed by the FDA, they have also potential. I think that some of the monoclonal antibodies are very interesting because similarly to the first example I gave you with the chimeric antigen receptor cells, the T cells, the monoclonal antibodies, they go after surface proteins. So, they don't… They are not dependent on certain genetic changes in the cells or they do not work because there are or are not certain genetic changes in the cells. They look for things on the surface of the cells; and from all we know at this point, the high-risk disease looks similar in many aspects on the surface compared to the standard risk. So, these new drugs could be a way to…, to go after those cells that don't necessarily respond to medicines that target the internal features of the genetics of the tumor cells. From what we know right now, high-risk disease has ways to avoid the drugs that are delivered that target the inside. So, treating on the outside, that's a new promising thing, I do think, and I also think that the third important thing in my opinion is the development of sophisticated monitoring tools for response to treatment and maintain deep response, specifically so for minimal residual disease detection. I think that has a lot of promise, and there are lot of efforts going on trying to quantify very low levels and to try to rule out very low levels of detectable disease. I think that we will probably have at our institution, I hope in the coming two years, capacity to measure and rule out very low levels of residual disease even by using just blood or even urine test instead of doing bone marrow tests.

Gary Petersen : How great is that!

Dr. Ola Landgren : And I think that has huge potential, of course. You could see that that could change the whole game. So, that's something we are pushing very, very hard for.

Gary Petersen : To save my butt.

Dr. Ola Landgren : Oh, I think those are probably key things. To use these new approaches with cell-based therapies and to integrate them with new sophisticated monitoring, I think they are…, they are potential game-changing strategies, but, of course, they need to be further investigated and then they need to be validated. So, there is more work to be done, but I…, I am very, very excited about these approaches.

Gary Petersen : Fantastic! It sounds like some really great things are coming up that put us closer than we ever have been to a cure. Now…, now, you are a member of the scientific board of the MCRI, the Myeloma Crowd Research Initiative. Why are you involved in this high-risk initiative and why do you see it will have

any better success at finding high-risk cure than the current processes?

Dr. Ola Landgren : I was invited by the founder of this program, Jennifer Ohlstrom and I am…, I was…, I was fascinated by the fact that this is really driven by patient initiative. Its driven by modern, very dynamic thinking in terms of collecting funds. This is like a group effort and also the way the whole process is driven forward. Its…, its very much driven by dedication and energy and focus on getting the work done and I also think that the…, the priority focusing on high-risk disease, I think, that's very much needed. If you look at the past 10 to 15 years of drug development in myeloma, we have shown…, we have seen in many studies that survival has probably tripled for patients diagnosed with myeloma if we compare today with 10 years ago and my projection is that is going to continue to double or triple one more round, but importantly, that's 20 or so percent of patients that have hallmarks of high-risk disease. That group of patients have not really had a lot of benefit from all these new drugs. There are individuals in that group that do have, but on average there is much less benefit in the group. So, its basically the group that was left behind. So, there had to be focus on that group and that's exactly what these funding mechanists decided to focus on. So, I think that's…, that was the absolute right thing to do.

Gary Petersen : Okay. Well, thank you so much for your efforts and with regard to that because, as I said, I think its our next best…, or the best current way to get a cure for all myeloma. So, thank you so much for everything that you are doing with regard to that. At this point, I would like to start and turn this over to questions from panel, if you don't mind. Cindy, would you have…, each of you ask either a question and followup to that question or two questions and we will run through your questions and, Cindy, your questions.

Cynthia Chmielewski : Okay. Thanks a lot for that wonderful introduction, doctor, and my question kind of has to do with the newer therapy, the newer immune therapy. I know there is a lot of question around that, the CAR T cell therapy to the high-risk myeloma, but right now I guess the most aggressive high-dose therapy we have for high-risk myeloma is the allogeneic transplant. Where do you think that's fitting in now with the newer trials going on and I know there is a T cell depleted transplant at Memorial Sloan Kettering. Would that be something that high-risk patient would want to consider?

Dr. Ola Landgren : Yes, you are asking me whether I see a role for allogeneic transplant and…, and for the depleted T cell approach linked with allogeneic transplant, if that has a role now and in the future. Is that the question you are asking me?

Cynthia Chmielewski : Right. Exactly.

Dr. Ola Landgren : Well, I do that think that allogeneic transplant for many years has been abandoned in the field of multiple myeloma because the results were not very promising and also the toxicities and risks were very, very high, but there are a couple of groups that have continued to see how…, how allogeneic transplant transplant could be improved and working with the conditioning approach to the therapy that was given before the cells were transplanted and also how…, how the modulation of the immune system was handled. That has been worked on and there are couple of groups that have really done a lot of work. I do think that there…, there is no data coming out, including you mentioned here of Memorial Sloan Kettering. There are other groups as well, but those data coming out from…, from this new work showing that the risks can be significantly reduced with these additional procedures and…, and…, and tweaks in the…, in the processing and in the management and the deliveries of the T cells.

So, the graft versus host disease that has been a major problem in the past can be majorly reduced and extremely reduced and the risks also by the therapy have been majorly reduced by the conditioning therapy. So, I do think from where we are at this very, very moment until the CAR T cell therapy has been fully evaluated and it unfortunately may not work, but it could very much work and I hope it will work. If it really works, that will become a major player, but at this point that's too early to…, to say. So, its something that needs to be explored and also these other therapies I mentioned have not been fully evaluated in high-risk disease. So, I do think that even where we are right now for someone who has high-risk disease, if other

therapies do not work, I do think that an allogeneic transplant in the setting of modern T cell as reported and modern conditioning done at the top notch center, I do think is very, very reasonable option to consider.

Dr. Ola Landgren : The key question for many patients who…, who are asking this question even when you hear that its much safer and its much better than it used to be, still the question that comes up is, are there any other options I should consider before I do it and what will those options be and if I pick these other options, if they work, that's fantastic, but if they don't work or if they stop working, will I still be a potential candidate for this allogeneic transplant? These are very difficult questions to…, to know for each and every patient ahead of time. So, I think for patients who are on…, on the.., on the verge of not being candidates but they are candidates for the allogeneic transplant, will that be something that that individual is potentially interested in. I think the timing issue is probably even more important than maybe to pursue something else may potentially risk the opportunity to…, to have the allo as that's not something that individual patient chooses to…, to do as a rescue and so to not do it could worse case mean that these will not be something that can be offered due to safety reasons, but for a patient who is in better shape, who…, who wants to explore something else, I…, I see that there are patients that go for other therapies and…, and they try that and they explore that and then if that works, that's very good obviously, but else, coming back to the allogeneic transplant could be an option for that individual patient. So, these are very, very, very difficult situations and usually we spend a lot of time going through the individual patient's biology, looking at prior therapy, response to prior therapy, the duration of that response, the depth of that response, toxicities and organ function in general and being very, very transparent and show all the data and all the pluses and minuses usually is…, is being very clearly demonstrated and…, and discussed between the doctor and the patient and…, and then each an individual patient will have to make the decision what…, what is the right thing for…, for he or she. These are difficult, very difficult questions.

Cynthia Chmielewski : Yeah. Its a very difficult decision, I.., I guess, its very individualized depending on…, on the patient and what stage of disease and what the features are. So, thank you, and my second question… I hear a lot of talking about…, about continuous therapy versus a fixed duration of therapy. Would you recommend a continuous therapy for a high-risk patient for someone just to stay on therapy until they progress or if…, if they achieved a complete response for them to get off of therapy and how do you envision MRD testing in the future to help make this decision?

Dr. Ola Landgren : This is also very…, very good and very difficult question. So, at this moment, there are couple of things that have been addressed in studies that we know the answer to and there are couple of questions we can ask, but we don't know the answers. So, let's try to do this in a very rational fashion here. So, what has been shown across the board in more than 20 published studies independent of what technology and what assay has been used, if a patient reaches minimal residual disease negativity versus reaching a complete response with MRD positivity, statistically speaking progression free and overall survival is longer in individuals that are MRD negative. There is also data showing that MRD negativity, you can have different measures of sensitivity, that for every step in the more sensitive direction, we use log. So, its a 10-fold or 100-fold or 1,000-fold, etc. fold more sensitive assay, but every 10-fold improvement, that translates into longer survival. So, deeper responses seem to be preferable if that's possible to achieve. Of course, it has to be light on toxicity. If someone cannot really reach it, then you just keep on pounding with therapy. It may still not respond, but you just add a little toxicity. So, it has to be done in the light of…, of all other aspects. I think we assume that its possible to reach it with reasonable therapy. That would, of course, be the preferable outcome. Now, for high-risk disease, there are studies showing that if you reach a certain level of depth of MRD negativity, if you have standard risk or high risk, there is data to suggest that the duration of that maintained MRD negativity is shorter if you don't have any maintenance therapy. There also is some data. Now, the information is much more sparse because there are very few studies that have really looked into this in a systematic fashion, but there is data to suggest that even in maintenance therapy, that probably is a true statement that the high-risk biology still has little bit more of a tendency of coming back versus the standard risk over time. Now, what's not known is whether you adjust the therapy, if you could quantify the MRD negativity if it turns MRD positive, if you were to increase the therapy, the intensity to bring it down to MRD negativity again and then continue monitoring. So, these are things where we don't know the answer. So, these are kind of the principles. So, based on this, my interpretation and my

recommendations that are based on data and my experience, so there are many pieces of data that we simply don't have the answers to specific questions. You have to just use your clinical judgment. So, my interpretation and my recommendation on average would probably be to keep some maintenance approach or both actually standard risk and for high-risk disease and that will be based on the fact that there are studies showing if you stop the maintenance therapy, that the disease has a shorter time to returning. Now, it has to be given in the light of toxicities. So, I would probably do maintenance for both those two groups as my default and there could be deviations from that for individual reasons.

Gary Petersen : Thanks a lot, Cindy, for those questions. I appreciate it.

Cynthia Chmielewski : Thank you, doctor.

Dr. Ola Landgren : You're welcome!

Gary Petersen : Pat, are you online with your question?

Pat Killingsworth : I am here, Gary.

Gary Petersen : All right.

Pat Killingsworth : – Doctor, could you…, could you explain how the exciting new T cell therapies work? I know that the myeloma crowd, our…, our group is going to support two…, two research programs that both use different types of T cell therapies. Could you just take a moment and explain how that works and I know some of them are used in with a transplant and some aren't and could you just shed some light on that for us?

Dr. Ola Landgren : Yeah. So, the principles are such that you…., you…, you can characterize cells throughout the body and you can look either on the inside, you can look at the genetic signatures of cells, and you can also look on the outside of cells and you can characterize their protein repertoire if you want. They have proteins on their surface and if you look on the inside, if you are looking healthy throughout the body, most of the cells in the body look very, very, very similar genetically. Its because the…, the DNA in our bodies is very…, very similar. It comes from both mother…, mother and father and most cells independent of origin have the same genetic contents. When a disease of…, of a malignant type develops such as multiple myeloma, that's an outgrowth of, in this case, plasma cells that belongs to the immune system, the white cell category. They also have very similar genetic content to all the cells in the body and they are, of course, very closely related to the normal plasma cells in the body, but they have certain genetic changes inside that make them exist. We don't really understand what goes wrong, but something goes wrong and then all of a sudden they are there. To try to direct therapy after these these genetic changes is…, is very difficult because they don't look exactly the same or the myeloma cells, so instead people look at the surface of the cells and then if you look for…, for markers on the surface of these cells, what you want to make sure is that you don't have the same proteins on the surface of other cells. You could theoretically have that in any other organ throughout the body – the lungs, the kidneys, the liver, the eye, the skin, the bone, everywhere. So, lot of work first has to be done to determine what proteins do myeloma cells express on their surface that are unique to them and you don't find elsewhere. A lot of work has been done and its not 100% clear which is the perfect protein to go after and the reason I spent some time talking about this is because this is the huge part of the research, which of the proteins shall you pick as your targets. It may sound easy, but its very difficult and to make it very simple, there could be proteins that are not expressed on every myeloma cell or there could be proteins expressed on every myeloma cell, but it could also be on other tissues and there could be proteins that if you go after them, then the cells may be down regulated, so they stop expressing them temporarily, so then this therapy wouldn't work.

Dr. Ola Landgren : So, there are lot of possibilities here and…, and there is so much research that needs to be done to fully understand this and there are lot of unknowns here, but the basic principle is that you look for these proteins on the surface of the myeloma cells and then we know that the immune system has a lot of

subsets of cells that are designed to go after structures that enter the body and the outgrowths of these malignant cells, the bad plasma cells, they do express markers that I am talking about your proteins that you could…, you could tell other person's immune system that these are not supposed to be there, please can you take them away? So, you hook up the individual, a person, with a device and then you suck out T cells that are in the body and then you expose these T cells to something called vectors that make these T cells develop structures on their surface that are the counterpart of these proteins that you now have identified on the myeloma cells. So, if you give these lymphocytes back, these T cells back, in the blood stream, when they enter the blood stream they will go into the blood and they will find these proteins that they are designed to identify and when they bind there, then they will trigger a cascade of immunological events and you basically will have the immune system eradicating the cell that this T cell now has attacked if you want. So, in order to do this, if you just take all these T cells and give them back, the first thing that will happen is that the body will say, hey, wait a second. Even if these T cells are my own, they don't look normal. So, the body will try to destroy these CAR T cells. So, you need to suppress the immune system a little bit in order to do that.

Dr. Ola Landgren : So, you…, you can then do an autologous stem cell transplant first and then you give the T cells or you can do chemotherapy and then give back the T cells. So, you basically deliver these T cells in the setting of little bit of a suppressed immune state. You don't want to have complete suppression because then you…, then you won't have the effect and even if you suppress it, you want it to recover, so these immune effects then can…, can take place and take out the bad cells, so to speak. So, I tried to outline here that there are couple of areas of development. One is to pick the right protein and you may have to have T cells that go…, CAR T cells that go after more than one and this is not really known, but the field is going in the direction of having more than one maybe and also…, is also under development is what is the perfect type of therapy to deliver these cells and different groups have done different things. Some groups, they did autologous stem cell transplant, other groups they do the chemotherapy and there are different opinions about this. So, these are like the basic principles.

Pat Killingsworth : That's probably the best explanation I have ever heard. That helps a lot and no, none of it sounds simple to me. I…, I have this image of someone sitting there with a microscope trying to change the… (laughter) …change these T cells before they were put back in the body. So, that…, that helped a lot and so obviously, there are lot of speed bumps here. How close do you think we are to…, to having these therapies that are…, that are really…, that you can count on that are really going to work?

Dr. Ola Landgren : Are we talking about CAR T cells?

Pat Killingsworth : Right. Right.

Dr. Ola Landgren : Well, so there are currently two trials that have been opened and the first trial that opened, opened at the National Cancer Institute in Bethesda and this was by Jim Kochenderfer that came out of Steve Rosenberg group who… Steve Rosenberg is probably one of the biggest cancer immunologists at all times. He has done a lot. So, Jim did work in Dr. Rosenberg's laboratory and he looked for these proteins that I was talking about and he identified a protein called BCMA that's expressed on the myeloma cells and Jim showed that in mouse models that they could deliver these CAR T cells and they could have very good eradication of these myeloma cells in the mouse model. So, that led Jim to…, Jim Kochenderfer to develop the clinical trial and he has opened at NCI, I think, 6 to 12 months ago, at least think they are still doing a phase I trial. So, they are trying to identify how higher the dose of these CAR T cells they need to give in order to have…, have effect. Then, at this point, to my knowledge, this study is still ongoing and the exact dose has not yet been determined. We…, they basically have not finalized the study and its ongoing and they are trying to increase the dose to see if they can find the optimal dose to have response…., responses. The second study that was developed was developed at the University of Pennsylvania by Dr. Carl June who is also one of the big leaders in the world for cancer immunology. Carl June, he did a study using CAR T cells for lymphoma couple of years ago and now he decided to take his lymphoma CAR T cells. So, he was on purpose not looking for proteins that were expressed on the surface of myeloma cells. So, he did a completely different thing. So, he said, why does myeloma exist. He said

myeloma cells are what's called very late stage B cells and they cannot proliferate. They cannot get…, they cannot get more of them. They have to come from somewhere else. I think he said that they are probably originating from B cells, earlier stage of the B cells. He said, I am going to take one of these CAR T cells that I developed the lymphoma and give that to patients with myeloma and see if I can actually see responses there and he presented this at ASCO and the European Hematology Association meeting in June in this year and there were only three patients that were initially treated and the first patient had, I don't remember the order of them, but there were three patients.

Dr. Ola Landgren : One of the patients had no effect and unfortunately had the disease coming back right away. The other one had, I think, little bit of an effect, but it didn't last, but then there was another patient who I think had a very good response and it seemed to be very durable. So, at this point, they are now trying to dig deeper into this individual who had this very good response and I think its…, I think that's a very interesting observation because he is not only addressing the issue of CAR T cells, he is also addressing the way of going after the disease, not going after the plasma cells directly. So, I think that's a very interesting approach. Lastly… So, there needs to be much more work done for both these two studies. They are very, very early. Its based on one patient at the University of Pennsylvania, one is simply only one. So, its way too little to…, to know for sure. What we are doing here at Memorial Sloan Kettering is that we are working on multiple targets that go both after myeloma cells and B cells and we are developing strategies where we have integration of these two models and we think that we will probably open our first study around the summer of 2016. So, we…, our program is heading very, very fast forward and…, and we…, we believe that both these models are important and we are not using the same targets that these two studies have done, but we…, we have identified targets we think are maybe better, but that remains to be proven.

Pat Killingsworth : Thank you, doctor. That's…, that's really helpful. Gary!

Gary Petersen : Yes. Thank you, Pat. Doctor, you know, we are running over a little bit. Would you have a little extra time for some questions from not only Jack but some of our listeners as well? (Pause) Doctor! Do you have a little extra time?

Dr. Ola Landgren : Yeah. I can do a few more minutes, but then I unfortunately have to wrap up. I have to prepare for a talk. I am going to Europe tomorrow.

Gary Petersen : Okay. Well, thank you so much for the little extra time. We really do appreciate it. We know how…, how you are stretched for time. Jack, your question please.

Jack Aiello : Sure. Dr. Landgren, thanks for being available to us. Your research is really exciting, but if I am a patient today and my doctor says I have this high-risk factor they call deletion 17p, does initial induction treatment of that patient differ from a non-high-risk patient?

Dr. Ola Landgren : So, now we are talking a little bit about how do we define high risk in the clinical setting of 2015. So, myeloma, as I said, has very many different types of disease within the given patients and across patients. If we apply these very superficial tests that we have been using for many years such as cytogenetics and FISH, we can capture 17p deletions in probably 10% of individuals that are being newly diagnosed. It has been found in several studies that that disease could be more active and could be harder to get full control over. So, it would, in the clinician's mind and I agree with that, impose that a more effective therapy should be given and the standard approach typically would be to use a three-drug combination with therapy. Usually, a proteasome inhibitor is included in combination with steroids and either it could be a immunomodulatory drug or cyclophosphamide. Those are probably the combinations that many or most centers in the United States would use. It should be mentioned that most individuals who have this deletion 17p, that there is a… Actually, all patients who have this, there is a gradient of the penetrans of these deletions. So, these deletions could be present in every cell or it could be present in a small subset of the myeloma cells. There are several studies showing that if only a small proportion of the cells have this deletion that the…, the impact of that deletion may not be there. It may be very similar to not even having it. There is little bit of a controversy there. There are some studies showing if you have less than 30% and

some studies say even if less than 70% of the cells have it, that that would be the same as not having it. So, its…, its not entirely, entirely clear. Its controversial, but I do think that most centers would recommend a three-drug combination for individuals who do have it, but again having it may or may not carry the same weight depending on…, on these reasons.

Jack Aiello : And…, and would you prefer that same three-drug regimen for a patient that doesn't have those factors?

Dr. Ola Landgren : So, that's the other question and I am glad you asked that. So, I do believe that until there is an established curative therapy, I personally think that there is…, until there is data to show the opposite, I think that the best therapy should be given to every single patient and I will not cut back on therapy until there is a cure, unless there is toxicity. So, there are several studies showing that for patients who had the standard risk that would be not, for example, having this deletion or other such findings that if patients who do not have it are receiving the three-drug combination, then their outcome is better versus if they only get two-drug. So, in my opinion, every patient should be offered a three-drug combination unless there are contraindications or other reason. That would be my default and there is no data to support the use of two-drug, that is pure opinion-based treatment strategy. So, this whole business with what's called risk-adapted therapy, I…, I don't believe in that and there is no hard data to back that up.

Jack Aiello : Thank you very much.

Gary Petersen : Thank you, Jack. Appreciate it. Ummm…. Priya, could you check online to see if we have any questions and, doctor, after you have answered a question whenever you find that you have to leave, just let us know and we will wrap it up. Okay?

Dr. Ola Landgren : I think I can take one more question and then unfortunately I do think I have to…., to return. I have to finish my slides.

Gary Petersen : Okay.

Priya Menon : Thank you, Gary. Yeah. Listeners who have a question for Dr. Landgren, you can please press 1 on your keypads and we can bring you live on air. Dr. Landgren can take only one question. We are already over time. Yes, the person calling in from (408) 8329-005, you may please ask your question.

Caller : Yes. My name is Srihari. The question I had was, is there… If a patient gets to very good, like almost even an MRD negative kind of a response, I see…, I think you just mentioned that continuing maintenance might be appropriate. Is there any data about using, say, some more consolidation after slightly different triplet from…, from the induction regimen which might help with ensuring probably a deeper response that is much more durable?

Dr. Ola Landgren : So, I had a hard time hearing the very last few sentences you said. I think I heard you said that if you reach MRD negativity and then I couldn't really hear.

Caller : Yes. Is there any data about probably instead of just maintenance therapy for really extended periods of time, say a triplet-based consolidation just for a few months or so, few cycles, after slightly different regimen from probably the induction regimen? In the literature, I found very little information about consolidation other than probably the STaMINA trial and probably one VCD kind of information.

Dr. Ola Landgren : So, you… Oh, you are asking me about additional consolidation or you are asking me about the…maintenance?

Caller : Consolidation in lieu of probably really extended maintenance. The prospect of, you know, unlimited maintenance when probably something little more short term is quite attractive and I am wondering if that's a premise which is even valid.

Dr. Ola Landgren : Well, so there are so many different studies looking at different things and they have a lot of…, there are lot of differences how these different studies are designed. So, some of the studies that use little bit less powerful therapy and then they have high-dose melphalan with stem cell support, autologous stem cell transplant. Some of those studies have added additional chemotherapy or…, or triple-drug therapy after the transplant and found that that could further deepen the response. Now, if you look at patients who have received very powerful therapy, it actually seems that four cycles are not necessarily the number of cycles that will take the individual patient to the deepest response. In fact, there is some data suggesting that it could even be up to six cycles on average. Now, some patients would have two cycles, some three, four, five on average before they reach very deep response MRD negativity. Why do four cycles usually…, why does that show up? Why is that like a common number? I do think that 15 years ago we had old VAD therapy with chemotherapy and one of the drugs, Adriamycin or doxorubicin, that was part of that regimen, is cardiotoxic and we did never give more than four cycles because that was toxic for the heart, but when that therapy was replaced by newer therapies, what happened was that the number of cycles remained the same, this is just how the logic happened, I mean just happened like that. So, instead of giving four cycles of VAD, people gave four cycles of RVD, but if you instead look at the…, the depth of the response, if you just gave more cycles, we did a study when I worked at the NIH where we looked at the number of cycles in relation to MRD being achieved and we saw that the average time was six cycles. So, if you forget about the history and you just look at the response, I think that four on average is probably too little, but there are patients again that reach MRD negativity already after two cycles. I am not saying that every patient needs that. So, given that, I think for studies that give four cycles, give high dose and then give additional therapy. In my opinion, that is not consolidation. Its just like there is disease left behind and you just give more therapy and you can call it whatever you want. If you give it upfront or you give it and do transplant and give more, its just more therapy. So, I think that, in my opinion, is why you see these different patterns.

Dr. Ola Landgren : Now, in an individual who has received a certain degree of response but then you put the patient on maintenance, even if therapy is little bit detectable disease, if you are MRD positive. So, thus, maintenance continues to suppress the disease and the answer is actually yes. I have seen patients being on maintenance for like 1-1/2 years and then MRD negativity can be measured and I simply think that in many patients the low dose of…, of therapy works as an extended dosing. So, in my mind, I have kind of stopped using the terminologies with induction therapy and consolidation therapy and maintenance therapy. I think of it more as combination therapy because you combine drugs and then I think of it as extended therapy which I think the lower intensity is. So, I think, like you have more combinations and then you have the extended and ideally, of course, you would like to stop therapy. What I am doing right now in my clinical research program, I am leading a study. I am going to…, going to open very, very soon. We treated patients when I was at the NCI. We…, we had programs we developed with combination therapy and then we treated with maintenance for two years. We will now offer to continue on this new study that we are opening for another three years of…, of extended dosing or what people call maintenance and we will continue to monitor for MRD negativity and my plan is for individuals who have stayed MRD negative for five years, my plan will be when that happens, will be in another three years, to see if we can develop a new study and I will start working on that probably next year or so, to offer people to go off or to stay on therapy with continued MRD negativity, MRD measurements to see if the MRD negativity can be maintained without therapy. This… That would be the next logical question to see if you can go off therapy and I don't know the answer to that and I don't know if five years is right or wrong, but you have to…, you have to start somewhere. So, that's my next step in terms of seeing if we can start peeling back on therapy and…, and I don't know the answer at this point. So, these are like my…, my rationale approaches to pursue these questions.

Priya Menon : Thank you, Dr. Landgren. It has been a pleasure to listen to you. Thank you for the time and I thank the myeloma panel, Gary, Pat, Jack, and Cindy. Thanks for joining us. This talk will be made available on CureTalks along with the transcript. Please visit curetalks.com for details on upcoming talks. Thank you, everyone.

Dr. Ola Landgren : Thank you so much for having me.

Jack Aiello : Thank you.

Gary Petersen : Thank you, Dr. Landgren. You made some very comprehensive answers to some very difficult questions, and we certainly appreciate that.

Dr. Ola Landgren : Thank you very much, everybody. Enjoy the evening and take care!