Understanding ASCENT Clinical Trial for High Risk Smoldering Myeloma Patients

This is the first of a 3 part series of talk on high risk smoldering myeloma and its treatments. Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell disorder. There have been major advances in the diagnosis, prognosis, and management of SMM in the last few years. High risk SMM patients carry a high risk to progression to multiple myeloma. High risk SMM has been recognised as the optimal phase to test early treatment strategies. The upcoming ASCENT trial aims to prevent progression to active myeloma by 30-50% in the high risk to progression SMM patients. We are talking to Dr. Shaji Kumar Principal Investigator of the trial and Mayo Clinic expert about the nuances of the ASCENT trial.

Full Transcript:

Priya Menon – Good evening and welcome to CureTalks. I am Priya Menon, Scientific Media Editor of CureTalks, joining you from India; and today, we are talking about multiple myeloma. This is CureTalks' 109th episode. On the myeloma panel, we have myeloma survivors and advocates, Cynthia Chmielewski and Yelak Biru and Jack Aiello. Our co-host of myeloma talks, Gary Petersen, is not able to join us today. So, my co-host for the day is myeloma survivor and advocate, Jack Aiello.

Priya Menon – Smoldering multiple myeloma is an asymptomatic clonal plasma cell disorder. There have been major advances in the diagnosis, prognosis, and management of smoldering myeloma in the last few years. High-risk SMM patients carry a high risk to progression to multiple myeloma. High-risk smoldering myeloma has been recognized as the optimal phase to test early treatment strategies. The upcoming ASCENT trial aims to prevent progression to active myeloma by 30% to 50% in the high risk to progression smoldering patients. We are talking to Dr. Shaji Kumar, Principal Investigator of the trial and Mayo Clinic expert, about the nuances of the ASCENT trial. Before I hand over to Jack, I would like to remind our listeners that we will be addressing questions sent in towards the end of the show. If you would like to ask a question live, please press 1 on your keypad and let us know. You may also email them to priya@trialx.com or post them on the CureTalks' website. With that, its over to Jack.

Jack Aiello – Thank you, Priya, and thanks for making these programs available to myeloma patients. As you noted, I am serving for Gary Petersen who usually moderates these programs. He is unavailable, and I also appreciate what he does and hope I can do him justice. I will introduce Dr. Shaji Kumar with a little bit of background. I have known Dr. Kumar for several years now, but I know he got his medical degrees at the All India Institutes of Medical Sciences and primarily has done his research and practice at the Mayo Institute in Rochester for the last nearly 20 years. Dr. Kumar, thanks so much for joining us.

Dr Shaji K Kumar – Thanks, Jack. Thanks for having me.

Jack Aiello – So, I'll begin by asking you some questions. We all understand the design of the ASCENT trial because, as Priya mentioned, there are some very lofty goals in that trial, that its a trial for high-risk smoldering myeloma patients. So, that means its not for MGUS, its not for myeloma patients, not for other smoldering patients. Can you, though, for us define high-risk smoldering myeloma because I know that's different than high risk as defined for myeloma patients?

Dr Shaji K Kumar – Right. Jack, you are absolutely correct and I think the…, this particular clinical trial, like a few other ones that are currently being designed around the world, really represent a paradigm shift in how we think about this disease. So, for the longest time, almost three or four decades since we have known this disease and have started on treatment, we always thought, yes, this is incurable disease, so we don't do any treatment until its really starting to do something bad. We didn't want to give side effects to people where…, where none existed, I mean we don't want to give symptoms to people that didn't exist already. So,

the traditional approach to smoldering multiple myeloma has been to just wait and watch. Now, the problem with smoldering multiple myeloma all along has been that it is a very mixed bag of diagnosis. We all know the vast majority of patients with MGUS do very well. Three quarters of them live their whole life without having anything that needs to be done for them for the monoclonal gammopathy.

Dr Shaji K Kumar – On the other hand, we know that about 20% to 25% of the patients will eventually double up myeloma and once they get active myeloma or symptomatic myeloma, that means they are starting to have symptoms from it or they have some damage to the body from the…, from the plasma cells or their myeloma cells. Now, the smoldering kind of…, is kind of sitting on the fence between these two; and even though we talk about smoldering myeloma as a diagnosis, over the years we have understood that this is really not a true diagnosis, rather it is a mix of patients with either myeloma or already is…, is more of…, more like MGUS, but we just don't have a good test for given patients to say which side or which direction those cells are leaning towards. So, over time what we have looked at is to try and see who are the people who are at high risk of going on to get myeloma.

Dr Shaji K Kumar – We already know from the studies that Dr. Kyle had done decade ago that patients, there are about…, about half of the patients with smoldering diagnosis will get myeloma in the first five years after that initial recognition of smoldering myeloma. You could argue that these patients have already kind of…, are sitting on the other side of the fence almost in terms of the evolution to myeloma. Another 15% to 16% will get myeloma in the next five years; and beyond that, the remaining patients who have not had a diagnosis of active myeloma behave more like MGUS patients. So, these patients have a 1% risk of progression to myeloma. So, in a way, just watching over time tells us who really is an MGUS versus who really is already leaning towards myeloma.

Dr Shaji K Kumar – Now, what we have… Now, the treatments for myeloma have really changed over the past decade and now we have safer drugs. We have combinations that can potentially give very high response rate, meaning that we can get the disease under control and we can actually get to what we call the minimal residual disease negative status in patients with myeloma, but then everyone's been asking the question, now we have good treatments, can we identify or carve out groups of patients from within that smoldering group who actually have a very, very high risk of getting to myeloma. So, the exercise that has been ongoing has been to identify patients who have an 80 plus percent risk of getting or transforming to myeloma from within the smoldering myeloma group and we…, we basically give those people the diagnosis of myeloma and we would treat those patients just like myeloma. So, that is the change in the diagnostic criteria for myeloma that happened in the past year and a half.

Dr Shaji K Kumar – Now, the…, the paradigm shift that I was talking about was that whole concept of treating somebody who does not have the symptoms yet and that was with the understanding that these people, there is very, very high risk that their myeloma is going to happen, so we don't want something bad to happen before we start treatment. Now, we are kind of stretching that paradigm a little bit more to encompass a larger group of patients with smoldering myeloma who have a very high risk of getting myeloma but not as high as the people whom we have redefined as myeloma. There are lot of different factors that have been used for defining high risk, smoldering. So, what we want to use for this particular clinical trial is based on the bone marrow plasma cell percentage, the free light chain ratio, and the M spike level which is what we have used historically or traditionally, but the other aspect of the whole series of trials that are being done is to ask the question, if we intervene early, is there a possibility that you could actually cure the disease? Now, we don't have any evidence to prove that, but there is enough evidence that supports the…, the exploration of that question. Now, those evidence comes from different sources.

Dr Shaji K Kumar – We know that patients with smoldering myeloma have less of genetic abnormalities or genome or mutation compared to patients with active myeloma or relapsed myeloma. So, conceptually we are talking about a myeloma cell that is less evolved compared to somebody with active myeloma. The second evidence comes or the second set of data comes from the transplant that we have done for patients with amyloidosis, where we know that the plasma cells are not as evolved as myeloma cells, but most of the symptoms come from the protein itself and we know that when we do stem cell transplant in patients with

amyloid, those plasma cells stay away almost three times as long as what it does in myeloma. There is some evidence to suggest that maybe intervening early is a good thing. Now, the question we would like to answer with these trials is, can we actually kill the disease, that's one question. Even if we don't cure the disease, can we actually kind of reset the switch so that these things don't start acting up for a prolonged period of time, which…, which…, which could also be of significant benefit both from quality of life as well as the cost of care. So, in essence, what we are really trying to do is to take those high-risk patients, give them treatment that we would otherwise give for myeloma but for a defined period of time and see if we can reset the clock or maybe even cure the disease.

Jack Aiello – So, just to confirm, I…, I…, I didn't quite understand what the eligibility criteria are or the definition is of high risk to be used in this trial.

Dr Shaji K Kumar – Right. For this particular trial, what we are going to use is a combination of serum M spike that's more than 3 grams and involved to uninvolved free light chain ratio that's more than 8 and a plasma cell percentage that's more than 10.

Jack Aiello – Okay and can you explain the trial design?

Dr Shaji K Kumar – Yeah. So, the way we're going to do this trial, you know, as many of you would know, that the combination of carfilzomib, lenalidomide, and dexamethasone is a very effective combination and there's actually phase 3 trials currently ongoing in myeloma. So, we have taken that combination and added daratumumab to that, and we already know that the daratumumab is quite efficacious in patients with myeloma. So, what we are hoping is, we would give these patients four cycles of treatment with daratumumab, carfilzomib, lenalidomide, dexamethasone and that is what we would call as induction. Then, half of the patients will have the option to go to a stem cell transplant, and this would be the group of patients who are considered eligible and willing to go to a transplant and the patients who are ineligible or don't want to get a transplant will be on the other arm. There is no randomization. This is basically depending upon the…, the indent for transplant. So, half of those patients, which would be 41 patients will get a stem cell transplant. The other 41 patients will get four more cycles of the same combination and then everybody will get four more cycles of consolidation with slightly reduced doses of the same medication and then everybody gets what we call a maintenance treatment for an year, which will include the carfilzomib and the daratumumab in those…, in those patients along with lenalidomide but not dexamethasone. So, the overall treatment would last a total of two years; and then at that point, we will stop treatment and then we will look and see if we have managed to get an MRD-negative state and then we will repeat the testing a year after that to see if the patients are still staying in the MRD-negative state and they will be watched closely after that.

Jack Aiello – And I want to make sure I heard correctly. The maintenance regimen is, do you say its dara plus carfilzomib plus Revlimid for a year?

Dr Shaji K Kumar – That…, that is right, for a year.

Jack Aiello – And when do you expect to start the trial?

Dr Shaji K Kumar – So, the protocol is all ready. So, we need to have some of the…, the agreements in place with the pharmaceutical companies and then we also need to get the FDA IND and then the individual side will have to put it through their own institutional review boards. So, we hope that we can get this trial open by before the end of the year.

Jack Aiello – And are there any somewhat unique either inclusion or exclusion criteria for patients that will want to investigate this trial?

Dr Shaji K Kumar – No. So, the…, the only thing that is, the diagnosis is smoldering and having to meet those three criteria.

Jack Aiello – Right. Okay.

Dr Shaji K Kumar – And patients also need to have adequate kidney function.

Jack Aiello – No previous treatment, I presume?

Dr Shaji K Kumar – Yes, that is correct.

Jack Aiello – Okay and since you are talking about cure, I presume, as you mentioned earlier, minimum residual disease testing is somehow incorporated into this trial. Can you say kind of…, can you talk about when one will have MRD testing?

Dr Shaji K Kumar – Right. So, along the study…, along the clinical trial, there's…, there are going to be some bone marrows that are going to be done in a timed fashion. So, after we finish each of those phases of treatment, like the induction, the consolidation, and the maintenance, and then one year after the end of treatment. So, in all these samples, we will estimate the plasma cell population and see if there is any minimal residual disease left.

Jack Aiello – And if someone is apparently MRD negative at the first time you have taken it and the second time you take it, you would at least consider them cured for the time being?

Dr Shaji K Kumar – If they remain negative, at least a year after the end of the treatment, so we want to make sure that they stay negative despite not getting any treatment at least for a year.

Jack Aiello – And by the end of treatment, you mean a year after maintenance is done?

Dr Shaji K Kumar – Year after the maintenance is done.

Jack Aiello – Got it.

Dr Shaji K Kumar – So, if you are still negative, then we hope that will translate with your…, but obviously that is what the study will tell us.

Jack Aiello – Right. Well, thanks so much for the…, I understand it better now and I know that both Yelak and Cindy have some questions. So, Yelak, if you are on the phone, I will turn it over to you.

Yelak Biru – Sure. Thank you. Thanks, Dr. Kumar, for taking the time to talk about this important Black Swan Research Initiative-based trial with the myeloma community. I actually have three questions, which are bundled as two so the moderator will let me get away with it. (Laughter) My first question is, you mentioned that the three things that are used as inclusion and you did mention FISH or gene expression profiling as part of the inclusion or exclusion criteria. Can you explain why and then as a followup to that and this is submitted by several of the questions that were submitted, what is the rationale for not choosing to randomize those patients that are transplant eligible and achieve MRD negativity after the first four cycles of the dara-KRd regimen?

Dr Shaji K Kumar – Right. So, in terms of the… So, we want to keep the trial as simple as possible and we wanted to go with something that, you know, we have validated extensively in thousands of patients in terms of risk factors for progression. While both FISH and gene expression profiling have been shown in smaller studies to be prognostic or predictive of progression, it is not something that has been studied extensively and again, I mean the gene expression profiling especially and I think using just commonly available test makes it much more easy and also makes it more comparable to what is being done elsewhere. If you remember, this is a small study. Right? Its not going to give us a definitive information. It will give us information that might still need to be confirmed by other randomized trials, but at the same time what is happening around the world is that multiple of these phase 2 small clinical trials exploring the question of the

cure possibility and they are all looking at, you know, the traditional ways of risk stratifying patients so we can at least compare the results among the studies. So, there are multiple reasons why we are not using the…, the gene expression profiling. In terms of the randomization, you know, I think eventually we will have to come to that question as to whether, you know, we would randomize patients right from the beginning or we would randomize patients based on the MRD test results later on, but I think that is the next question that we need to ask. So, that this study will tell us in few years that maybe, you know, most of the patients get to be MRD negative or half of the patients continue to be MRD negative after a year or after four years of treatment, then the next question would be, you know, does everybody need the same treatment or can some people get away with less of treatment? So, I think that those…, those kind of questions will need to be asked eventually but probably not at this point.

Yelak Biru – Okay and…, and then the followup questions I have for you are, how were the dosage in the cycle amounts chosen for this trial?

Dr Shaji K Kumar – Right. So, that's a good question. The…, you know, there is obviously this particular…, I mean the combinations have been studied. Right? So, we know what combination of carfilzomib, lenalidomide, dexamethasone is safe in patients with…, with myeloma and is well tolerated. When we look at the data from Dr. Jakubowiak as well as what we know from the ECOG trials and also from what has been published by the other groups, like also in the ASPIRE trial and we use the standard dose of daratumumab because it doesn't have any real overlapping toxicity between these…, between these drugs. Now, the four cycles of induction before transplant have been fairly standard. So, I think by saying that the usual convention, we can also compare what has been happening in other areas, for example in myeloma. So, if you take for example the French trials or even the…, the BMT CTN trial that completed accrual, what they have done is, the four cycles of induction and transplant or some other form of consolidation and then maintenance after that. So…, so, we have kind of tried to structure the…, the length of the different segments of therapy similar to what we have historically been doing in myeloma.

Yelak Buri – Cindy?

Cynthia Chmielewski – Okay.

Jack Aiello – Thanks, Yelak, and I did count. You had three questions. So, Cindy, I know you have a…, have a fourth, but, Cindy, if you have a third, you are welcome to ask it as well.

Cynthia Chmielewski – Okay. Thank you so much. I guess my first question will stick along with the ASCENT trial and it says that I have heard that the goal of secure rate would be between 30% to 50% for…, for people in the high-risk multiple…., smoldering multiple myeloma category and I…, I guess I…, I'll put my two questions in here at the same time. How did you reach the 30% to 50% cure rate? Would those patients be the ones that if you did a gene expression profile or a FISH study that they would be considered more on the low risk or intermediate risk? Even though those testing isn't being done as inclusion or exclusion to criteria, will that be done as part of the data that you are collecting during this study and just curious how you got those numbers and how might this be possible?

Dr Shaji K Kumar – Sure. No, I think…., I think its a very good question. The… We don't really know, you know, we think that we are curing probably some patients with myeloma because we know we have patients, you know, obviously, we all know patients who are 10 and 15 years out from the diagnosis or even 20 years out from the diagnosis doing well and many of them don't have any evidence of myeloma and so obviously we are already curing some people and the best estimate, I would say, based on all the modelling that I think would be probably doing that or somewhere between 10% and 20% of patients currently, so we wanted to look at, you know, something more than that and is there anything magical about the 50%? No, I think part of it is just kind of justifying number of people you need to study to give an estimate that is reasonably confident, for that reason that we can be reasonably confident…., be confident about. So, that's…

Cynthia Chmielewski – Okay.

Dr Shaji K Kumar – …where the 30% to 50% comes from.

Cynthia Chmielewski – Okay and I…, I know that there have been some other trials for the high-risk smoldering multiple myeloma population. Can you talk a little bit about what those trials are and if we have seen any outcomes of these trials just yet?

Dr Shaji K Kumar – Absolutely no. I think, you know, this is…, this is increasingly becoming an area of intense investigation. So, I would say the…., you know, there have been some trials in the past that have used thalidomide for example, but the…, the results have been quite mixed because of the fact again there can be significant neuropathy with thalidomide…

Cynthia Chmielewski – Okay.

Dr Shaji K Kumar – …but I think we have really…, I mean the area has really taken on with the introduction of these new drugs like lenalidomide. So, the Spanish group did the trial where they randomized patients to lenalidomide-dexamethasone (AUDIO BREAK) risk of progression and they were able to show that not only did the use of lenalidomide-dexamethasone decrease the risk of progression as we would anticipate, it also made the patients live longer. Now, these were the results that were published couple years ago and there was an update that was published last month, again showing the same thing, that the improvement in the overall survival is…, is significant and continues to be that way. One of the interesting things in that study was that, again one of the concerns we have had was, if we used that drug for smoldering, what happens when they really need another treatment? Is it going to compromise their subsequent treatment? And when we look at the data from the long-term results, its clear that using the lenalidomide early to delay the progression of myeloma does not compromise the responses they have from the subsequent treatment. So, I think that is very good, strong evidence, but obviously its only one clinical trial and obviously we also used a combination of lenalidomide and dexamethasone and we would like to know how much is Revlimid alone doing it. So, there is the ECOG clinical trial that is currently randomizing patients to lenalidomide alone versus just observation and that trial is nearing the accrual goal and that will tell us, do we really need dexamethasone in this particular setting or can we get away with just using Revlimid alone.

Dr Shaji K Kumar – In the opposite direction, obviously, you…, there have been a handful of patients who were studied by Dr. Landgren's group, looking at the same combination of carfilzomib-lenalidomide-dexamethasone and again demonstrating that a vast majority of these patients were able to go into an MRD-negative state. Now, there is a trial called CESAR trial that is being done by the Spanish group, which is kind of a very similar design of the ASCENT trial, but that one does not have the daratumumab combination in there. So, there are multiple groups doing these small trials, looking at different combinations is what stands out.

Cynthia Chmielewski – Okay. How is the MRD-negative state being tested? What tests are we using for that?

Dr Shaji K Kumar – Right. So, right now, we have two tests for which we have sufficient data to say that those both of them are useful. So, we have the flow cytometry-based assessment and we also have what we call the next-generation sequencing. Both of them have been studied quite a bit and both are good methods. In fact, the new response criteria that's going to be coming out tomorrow in Lancet Oncology defines MRD with either of the methodology as long as they have the sensitivity of being able to detect at least 1 in 100,000 myeloma cells. So, for the particular trial…, this particular trial, we are going to be doing both because we believe especially in this patient population, both the methodologies can be complementary and they might actually give us information that could be…, that could…., that could help us better understand the nature of the cells that are left behind after treatment.

Cynthia Chmielewski – Okay. Thank you so much and thanks for giving us a sneak peak of what's coming out tomorrow.

Dr Shaji K Kumar – Okay

Jack Aiello – Thanks, Cindy. Dr. Kumar, just following up on that question, will there be also bone imaging tests as part of that MRD process?

Dr Shaji K Kumar – Yeah. So, as part of the MRD definition, its not really bone imaging, we are recommending getting a PET scan….

Jack Aiello – Yeah.

Dr Shaji K Kumar – …as part of the MRD-negative assessment. If the MCB PET scan is negative as well, then we would call it the imaging plus MRD negative.

Jack Aiello – Good. And then, I have one last question before turning it over back to Priya. As you mentioned, there is…, there is a lot of interest these days in smoldering patients and will earlier treatment result in longer term survival. You have been recently appointed as co-chairman or elected as co-chairman to the NCI Myeloma Steering Committee. Can you share what will be various cooperative groups like SWOG and Alliance in this country play in kind of bridging that gap between the different approaches being explored for smoldering?

Dr Shaji K Kumar – Absolutely and…, and…, and, you know, being…, being on the committee, you know lot of the discussion that goes on and in those the goal for the NCI Steering Committee, which again for others on the call, is the committee that actually looks at all the different trial ideas that are brought up by the cooperative groups, which again is the ECOG, the SWOG, and the Alliance. So, what has been…, and some of the discussions have been around, you know, for example, let's take the ECOG clinical trial, E3A06, right. So, we had the Spanish trial that looked at lenalidomide-dexamethasone. So, we obviously…, the ECOG trial is filling in the gap of trying to understand, is the dexamethasone needed or can we just do the…, the Revlimid…., the lenalidomide alone. Similarly, there are new concepts that are coming through the cooperative group mechanism that are going to look at some of the…, the…, the monoclonal antibody-based approaches, maybe not as intense an approach as what we are looking at in the…, in the ASCENT trial. So, the ASCENT trial is looking, can we really push the envelope and cure the disease and the trials that are being designed in the corporative group are going to take the in-between approach. Between the lenalidomide and the really intense approach, middle of the road, can be maybe use less intense therapy maybe for a longer period of time and still achieve the same goal. So, I think between what is being designed by, you know, the academic institutions and what is being designed by the pharmaceutical companies, the cooperative group really provides a platform to explore the middle of the road.

Jack Aiello – Well, thanks so much. Priya, I…, I don't know if you have callers on the phone. I certainly…, I know you certainly have caller questions. So, do you want to proceed with those?

Priya Menon – Yes. Thank you, Jack. Yes, we do have lot of caller questions and, callers, if you want to ask a question live, please press 1 on your keypads and let us know and we can bring you on air to ask your questions directly to Dr. Kumar. Dr. Kumar, we have a long list of questions. Some of them, I think, we just touched briefly upon, but I would still like to ask them again because these have come from a Facebook group on…, on smoldering myeloma and they are like very excited about this trial and most of them are looking forward to actually interacting with you too on this group. I can send you the link so that you can just like take a look. I don't know, this is run by…, I mean the moderator of that group is Dana Holmes. So, she is unable to join us today. So, we have this whole list of questions sent from the group and so, I'll just go over them. Beginning with the third one on your list, Dr. Kumar.. After the first four cycles of KRd, daratumumab, will both arms to be tested for MRD-negative status. I think Jack just touched upon this, but if those in the transplant arm are MRD negative, will they still receive a transplant? In the non-transplant arm, if they are MRD positive after eight cycles, will they be offered a transplant?

Dr Shaji K Kumar – So, these are really great questions. I mean, I think this is, you know, what we are really

trying to understand even in…, even for myeloma, do we actually change treatment based on the fact that somebody is MRD negative or positive and we actually don't know very…, for sure that if somebody who is MRD negative, if we stop the treatment right then and there, are they going to do equally well or better than the rest and vice versa. The problem is, lot of these myeloma patients who have high-risk myeloma, they tend to get to a good response very fast. Unfortunately, many of those myeloma also tend to grow back fast. So, that's why…., what we would like to do with this study is to give a defined, a very well-defined package of treatment, irrespective of what happens in between and then see how that would affect the long-term outcome. Once we can prove that that is the beneficial approach, then the next step would be to see if we can modify things based on what happens in between.

Priya Menon – Thank you, doctor. We have, like, received two questions on, I think, inclusion criteria or the definition of high-risk smoldering myeloma. So, will you…, they are asking will you be incorporating the high-risk smoldering definitions recently published by Dr. Rajkumar on…., on behalf of the IMF, IMWG, which includes abnormal cytogenetics or would you be sticking to the old defining parameters like BMB percentage and M spike?

Dr Shaji K Kumar – So, for this particular study, we decided to stick here with what has been very well validated, not really because its been validated and has been used for a long time, but also it makes us…, makes it easy for us to compare with the other data sets or other clinical trials, but we will be doing the GEP 70 type of…, or the gene expression profiling type of studies on the samples from the clinical trial. So, we will be able to look back and…, and see how those things influence the outcome.

Priya Menon – Yes and Cindy was just asking about the 30%…, 30% to 50% in cure rate, so the question is, is this prediction across all disease prognostic risk types, that is low, standard, and cytogenetic profiles?

Dr Shaji K Kumar – Yeah, I mean, you know, we don't really know if the…, we…, we anticipate that maybe this intense an approach would negate the influence of those kind of risk factors, but we don't know that for sure. I think the clinical trial will let us…, will tell us if he finds equal end outcomes among the different subgroups of myeloma based on the cytogenetic profile.

Priya Menon – Yeah. The next question is, I think, from a non-resident American, he says, which myeloma centers will participate in this trial other than Mayo Clinic in Rochester and will it be in the US only, how many patients will be recruited?

Dr Shaji K Kumar – So, this trial is going to be only in the US, but we anticipate that there may be about a dozen or more centers that will participate in the trial. We do not have a final list as of yet. We plan to enrol a total of 82 patients, 41 of them getting the transplant and 41 not getting transplant.

Priya Menon – Okay. Thank you. The next one is, I am interested in the screening process and testing during trial regarding carfilzomib toxicity for patients with and without cardiac history.

Dr Shaji K Kumar – So, there is obviously someone who has very clear heart failure or significant heart damage will not be able to go on the clinical trial, but we will be watching patients closely in the…, by using echocardiogram as well as some blood tets like the cardiac enzymes to make sure there is no evidence of cardiac toxicity.

Priya Menon – Thank you, doctor. Next one…, next question is, should any patient progress to active disease during or after the ASCENT trial. I, is this considered a first relapse excluding patients from participating in newly diagnosed multiple myeloma clinical trials?

Dr Shaji K Kumar – Given the fact that we are going to be using treatments as comparable to what is being done in myeloma, I suspect that is…, that is…, that would be the case, but again a lot of its going to depend upon how those newly diagnosed myeloma trial criteria is…., is written up.

Priya Menon – Okay. I think that's the complete list. There were a couple of other questions, doctor. For what I researched so far, amplification 1q21 appears at a progressive stage leading to SMM or multiple myeloma. If so, does having abnormalities of amp1Q21, deletion 13, trisomy 7 and 9 put the patient at higher risk of progression if he or she is currently MGUS?

Dr Shaji K Kumar – Right. So, the…, the value of these prognostic factors in patients with MGUS is less known compared to the smoldering patients, but in the smoldering patients we know there have been studies which have shown that the 4;14 translocation, the 17p deletion can increase the risk of progression. In MGUS, you know, again this is very small data set. When we have looked at these patients, it certainly appears that maybe the patients who have these trisomies are at a higher risk than what we would have anticipated and that could…, and we don't know the…, the reasons behind it. It could also be a reflection of the fact that these patients indicate diagnosed as myeloma early, earlier, but then they do much better than the rest of the patients after the diagnosis. So, the total time that we are talking about might be very comparable, but…, but again, I think this is very, very preliminary data.

Priya Menon – Yeah. The last one, doctor, is the SET arm randomized or based upon SET eligibility, that is, fit, frail, or fit-frail status and comorbidities?

Dr Shaji K Kumar – So, there is no randomization. Patients can elect to… If patients are eligible for a stem cell transplant, meaning age wise and other comorbidities, they can decide whether they want to join the transplant group or the non-transplant group. If the patients are ineligible to go through the stem cell transplant, they only can enrol in the non-transplant group, which is not a randomization, because the patient choice for selection.

Priya Menon – Thank you very much, doctor. Jack and the panelists, in the end, like, if you have any questions, we have time to go over them with Dr. Kumar.

Jack Aiello – Yelak or Cindy?

Cynthia Chmielewski – Yeah, this is Cindy. I guess if not for the ASCENT trial but for those patients that are on the phone and new to this whole idea of myeloma and smoldering myeloma, could you tell us what the difference between MGUS and smoldering myeloma is and at what point does an MGUS patient move over to become a smoldering patient?

Dr Shaji K Kumar – A lot of the difference between MGUS and smoldering relates to the amount of the myeloma cells, for one. So, when somebody's M spike goes above 3 grams or their bone marrow plasma cell percentage goes above 10%, then they go…, move from MGUS to smoldering myeloma. There is also probably some biological difference in the cells between myeloma and MGUS and probably what is happening in the smoldering patients is just a mix of those more malignant plasma cells with the less malignant plasma cells. So, its a continuum. So, in the MGUS its predominantly the non-malignant plasma cells and eventually the…, you know, the malignant cells overtake and replace most of those non-malignant or non-cancerous plasma cells and that's when you start showing evidence of myeloma.

Cynthia Chmielewski – Okay. Thank you.

Jack Aiello – Yelak, any questions?

Yelak Biru – I…, I think the only question I have is, carfilzomib versus Velcade or ixazomib. Why was carfilzomib chosen over the other two PIs?

Dr Shaji K Kumar – Right. So, the reason for choosing the carfilzomib was based on, you know, the phase 2 studies that have shown that carfilzomib-lenalidomide-dexamethasone combination gives a very high rate of response, especially the complete response and MRD negative from the phase 2 studies. So, we thought we will use the regimen that seems to be…., again, you know, it…, it has not been studied head to head with

bortezomib-len-dex or at least we don't know the results of it. So, we found with the data from the smaller trials which suggests that that combination may be particularly effective.

Yelak Buri – Thanks, Jack. I…, I don't have anymore questions.

Jack Aiello – So, Dr. Kumar, I guess I would note for patients listening or will listen to this subsequently. This is an aggressive trial in terms of the treatment protocol – four drugs over a two-year time frame, but that said, for us myeloma patients, who have been battling it for many years and on continuous treatment, maintenance treatment and such, if…., if smoldering patients really are cured after a couple years of treatment and don't progress to myeloma, its…, its a pretty exciting opportunity and I hope that the trial goes well.

Dr Shaji K Kumar – You know, it certainly is… I mean that would certainly change the way we think about…, think about this disease and maybe even other diseases where currently we just continue to watch.

Jack Aiello – Yeah. Yeah and watching and waiting is a horrible thing.

Dr Shaji K Kumar – It is, I mean its always a balance between, you know, the…., what side effects you could give somebody from this, though some of them cannot…, may not be trivial. At the same time, you know, I am…, I am, obviously it must be very difficult thing for people to just keep…, you know, go on with that sword hanging over their head.

Jack Aiello – Yeah, correct. So, Yelak and Cindy, thanks so much for your questions. Priya, thanks so much…., so much for coordinating the call and…., and…, and reading off the other patient questions, but most of all, Dr. Kumar, thanks for making your time available and educating all of us in terms of the ASCENT trial and we…, we'll look forward to it, actually getting out there and hearing somebody else in the future.

Dr Shaji K Kumar – Sounds good. Thank you so much for having me.

Jack Aiello – Bye. Bye.

Cynthia Chmielewski – Bye, bye, doctor. Thank you. Bye.

Priya Menon – Please visit curetalks.com for details of upcoming shows. Talk…, this talk and its transcript will be made available on Curetalks' website. Dr. Kumar, thank you for your time and sharing all this information with us. Thank you, everyone.

Yelak Biru – Yeah, bye.

Dr Shaji K Kumar – Bye.

Priya Menon – Bye, bye.