Myeloma - ASCO 2014 Updates with Mayo Clinic's Dr. Shaji Kumar

The American Society of Clinical Oncology (ASCO) met in Chicago this year. Dr. Shaji Kumar of Mayo Clinic walks us through the exciting myeloma research that was shared at the meeting of the worlds largest gathering of oncologist, researchers and health professionals.

Full Transcript:

Priya : Hello everyone and welcome to the Cure Panel Talk Show on Multiple Myeloma

I am Priya Menon, Scientific Media Editor at Cure Panel joining you from India and I welcome all of you this evening to a discussion on multiple myeloma.

This is Cure Panel's 64th episode and on our myeloma broadcast today we are discussing Myeloma Updates from ASCO 2014.

My co-host for the show today is myeloma survivor and editor of myelomasurvival.com, Gary Petersen. On the panel are Cure Panelists, Pat Killingsworth, Jack Aiello, Nick van Dyk and Cynthia Chmielewski.

We have a very eminent expert with us today, Dr. Shaji Kumar. Welcome to the show Dr. Kumar. It's a pleasure to have you with us once again.

Before, I hand over to Gary to introduce the expert and begin with the show…I would like to mention to the audience that if you have a question for Dr. Kumar please press 1 on your keypad and we will bring you on-air to ask your question or you can email me priya@trialx.com with your question.

Gary will now introduce us to our expert. Gary you are live on air!

Gary : Gary: Priya thank you so much and I haven't said it enough, I hope can tell you how important you are to the whole effort we have informing he myeloma patient community, and I appreciate all of your efforts.

Dr. Kumar, this is the second year that you have been with us and I must admit that you are one of the remarkable members of what I consider the Mayo myeloma dream team. And you know there is very few institutions in the world that has assembled such a great team at a fight against this deadly disease multiple

myeloma.

We certainly do appreciate all of your efforts. I won't get into your extensive bio because you have an unbelievably great bio and many publications and all the rest, but just the fact that, you are a member of the fantastic team is remarkable itself. So thank you so much for being here and we would like to get going with your presentation of 2014 ASCO.

Dr.Kumar: Thanks Gary, that was really kind of you. It's all team work right. So it needs everyone involved in there, including all the patients. So, just kind of getting into the ASCO 2014, clearly, ASCO represents, but not as many new data of the ASH meeting typically have, since it encompasses all cancers including hematological cancers. But it clearly shows, some of the highlights of what is happening in the myeloma world. So, I think, you know, if you would go through, there were almost I think close to 100 abstracts including talks and posters that were related to multiple myeloma. So I am just kind of going to go and break them ahead into several groups depending upon what category they belong to. I think the most exciting one of things and I know some of those things are going to come in the questions later on – I think its the monoclonal antibody is clearly one of the most promising things that we have seen, both at the last years ASH and also again at ASCO this year go we have more data. So, its different monoclonal antibodies that are being developed almost in parallel here, responsible of the Sanofee monoclonal antibody. And there were 2 presentations from each of those drugs. One alone and one in combination with Revlimid. And while the study is fairly early on, I think the results that we are seeing so far are very encouraging. As a single agent these drugs have resulted in a partial response in almost a third of patients or better, in a group of patients who have seen a variety of different treatments before. And in combination with Revlimid it appears that we are seeing from Synergy, and the response rates were even higher when they were used in combination with Revlimid. And this kind of ties on with what we believe is one of the strongest mechanisms of action of Revlimid which is its ability to enhance immune system. [00:05:20] So at least even theoretically the combination of those two should make the antibodies work much better. Because these antibodies do, kind of, harness the immune system to some extent in its activity. So, I think the next year or two is going to be pretty exciting from this particular class of drugs. We are going to start seeing lot of these different combinations. We are going to start seeing them in the relapse patient population, patients with newly diagnosed myeloma, [00:05:50] and potentially, also in some of those maintenance settings. So, I think the monoclonal antibodies is clearly on the top of the list for things that we need to be watching out for in the next few years.

And the clinical trials – as a quite a few of them that are being planned, and many of them would start accruing patients in the next few months to a year. And I would encourage all patients to consider participating in some of those trials.

So the second big thing that was presented was the Panorama Trial or the Panobinostat. So that is again, you know, the team of all the new drugs that is coming along in myeloma. This is again, its a pill. We have, kind of, seen that class of drugs before the Vorinostat trial, and we really did not see a significant advantage of adding Vorinostat to Bortezomib. But the data that was presented to by Dr. Richardson at ASCO looking at the combination of Panobinostat with Bortezomib or Velcade Vs. Velcade alone, clearly showed that addition of Panobinostat to the Velcade improved the response rates and also improved the progression free survival in patients. So, I think, you know, that is quite exciting in the sense, this another class of drug which clearly demonstrates an improvement in progression free survival. And I think we will come to some of those nuances of the PFS – what are the implications of the PFS – progression free survival improvement in the

later part of the panelist session. [00:07:39] The other kind of concept, that I want to – that had several abstracts that kind of belong to that team was the duration of treatment and I know it is one of the most hotly debated topics in myeloma today. How long of treatment is ideal? Today, I think you know, there is some very early results of couple of trials looking at Revlimid, kind of given us maintenance treatment after non-Revlimid kind of treatments in the initial part of myeloma therapy. I think these trials are very early on to say anything about. However, there was Thalidomide Prednisone maintenance trial that was originally published several years ago now from the Australian group. And where they actually looked at an updated follow up, 2 more years of follow up in those patient population. And they were able to show that the improvement in the progression free survival was still present, when you gave Thal-Pred maintenance after stem cell transplant. However, I think a note of caution when you interpret all this data, is the fact that they actually show no improvement in the overall survival is anything, the curves was starting to come together. So, I think that, we are not going to see any improvement in the overall survival in that maintenance patient population, even if we continue to follow them. So, one of those things we always talk about is although we see a big PFS improvement today and the overall survival improvement will come later. That may be true for some but it is not necessarily given fact and this trial didn't – goes ways to highlight that.

Gary: Dr. RajKumar, just one point of note. Did that include dexamethasone with the Revlimid or was it just Revlimid by itself.

Dr. Kumar : So, this is Thalidomide plus Prednisone, not revlimid. This is the Australian trial. So, this is the only one we have a median for all. It is almost like 6.1 years now, but all the Revlimid maintenance trial, we still have relatively, you know, around 4-5 years follow up with this point.

Gary: Yeah. That is the one I guess I was wondering whether it included Dexamethasone or not.

Dr. Kumar : No, it just included prednisone. So that is the only one.

Gary : Ok Thank you.

Dr. Kumar : So, The other thing, I think we will again come to it in a panelist session was this whole concept about the PFS2, and so I am gonna leave that alone for right now and talk about it later. Few of the ones that I wanted to highlight – One is the results of the champion trial. That is a trial that is looking at once a week of Carfilzomib, instead of, or Kyprolis, instead of 2 times a week. Now, we all know from the results that Kyprolis is a relatively, an active medication, and can lead to disease control in a significant proportion of patients who have failed on different therapies in the past. So one of the biggest concern has been the need to go into the clinic 2 times a week to get injections. So, this trial actually explores the possibility of doing just once a week, but giving it at a higher dose. And they have in the current study, they have gone on to doses as high as 70mg/m2 which is almost 2.5 times what is the current dose on the label, when it is given once a week, and seems to be relatively safe. And they are seeing results in terms of myeloma control similar to what they have seen with the two times a week. So I think it is very early result and obviously we had to be confirmed in some kind of a randomised trials, but I think it certainly increases a possibility that sometime in future we may be able to get away with just one injection a week instead of two injections a week. It is kind

of similar to what was done with the Velcade going from 2 times a week to one time a week, and going with you know different ways of administering it.

The another trial that is a precursor to a phase III trial, that is looking at a combination of Pomalidomide, Velcade and Dexamethasone. Now this again is the initial part of the trial that Dr. Richardson presented suggesting that yes those drugs can be combined safely and we do see significant anti-myeloma effect from this drug combination. So that is another combination to be keeping an eye out for.

Now there were two studies, which were not clinical trials, but more of looking at experience over time of the combination of Velcade, Cyclophosphamide and Dexamethasone or CyBorD as it is commonly known. So both of them were, these studies came from – one from Canada, one from the Mayo Clinic Scottsdale, both again highlighted that this is a very effective combination something to be kept in mind when patients have disease that is relapsed.

There was another study from Dr. Seigel that looked at the combination of the Carfilzomib, Linalidomide, Dexamethasone and adding Vorinostat to that. So again adding that new class of drugs, what is called the HDac inhibitors, or the histone deacetylase inhibitors. This is the same class of drug as the Panabinostat. So Vorinostat, Panabinostat and other drugs that are currently in development all belong to this class. So this is again, kind of very early on, but kind of suggesting that we are continuing to try to push the envelop, trying to see how can we actually combine these different classes of medications to further improve the outcomes. [00:13:34]

There was another study that was presented by – some data that we had analysed using the SEER data base – looking at patients with plasma cell Leukemia. Now this is a relatively rare group of patients, specially when you are talking about initial diagnosis, and tends to have very aggressive disease course. And when they look at the SEER data base over a 30 years period, what we were able to see was – there is clear improvement in survival even in patients with the aggressive plasma cell Leukemia. Certainly not to the same extent as what we have seen with myeloma but still, overtime these patients are also doing better suggesting that the various medications and combinations we are using now a days, clearly seems to be of benefit.

So Finally, just want to highlight a couple of studies that were looking at the quality of life. Now I think that is something that we have for a long time not really looked at. But I think increasingly we are starting to look at that. Because patients with myeloma are living longer and longer, and we certainly need to give a lot of attention to the quality of life aspects. And our goal is obviously to extend life, but also we want to make sure patients have good quality of life. So, to that extent I think, there was an analysis from the first trial. Just as a reminder the first trial is the one which was done by the French group looking at giving Revlimid, long term vs. Revlimid for 18 months Vs. Melphelan, Prednisone and Thalidomide. This was presented last ASH and showed that the Linalidomide Dexamethasone was superior to the Melphelan, Prednisone and Thalidomide in all the patients. So in this particular analysis, what they were able to show was that the patients getting the Lenalidomide, Dexamethasone had better quality of life compared to the ones who were getting Melphalan, Prednisone and Thalidomide. [00:15:42] So, I think, even though the result itself may be along the expected lines, the fact that we are starting to look at that in lot of these clinical trials – certainly highlights the fact that we are all cognizant of the impact of quality of life, or impact of treatment on quality of life. So those I think were kind of the highlights of the meeting. I know it is a lot of different things that they talked about in a short

time period. But I can certainly expand on things as we go along in the later part of the session.

Gary: Alright, well. Thank you so much doctor. One of the things that I saw in yesterday's presentation by Dr. Durie, Presentation with the organization, and his very first slide happen to be your slide which had to do with, I think, you know how survival has gone from I think before 2005 and after 2005. He put another line up there which was after 2010 and I was wondering, did you provide that information for him for 2010, because that looked to me like we are all gonna be living a happy life.

Dr. Kumar : No. I think the data that we have goes up till only 2010. Beyond that we really don't have very long term follow up, or 2011 – Beyond that we really don't have very long term follow up, to make any kind of judgments at this point. But I think, looking at the trend..

Gary: Did you see that graph, by the way, or no?

Dr. Kumar : No I did not.

Gary : Oh OK. So, he extrapolated perhaps?

Dr. Kumar : I suspect that may be the truth. You know may be that is what where we want to be.

Gary : Oh OK. Because that was pretty impressive. I was gonna ask you about that ..I was gonna say, Yay !

Dr. Kumar : Oh, we will get there. It is just a matter of time.

Gary: Ok. You need to see that from..yeah, yeah. You know he showed even the first two graphs were, I think, before 2005 and after 2005 were pretty impressive, I thought for mayo clinic. But when I compare that to what is on the SEER database, obviously mayo clinic is significantly above that. So that difference, you know, and I was wondering, and I don't mean to give you a question that you haven't seen before, but you know, why is there such a big difference between what your results are and what the average SEER facility is? You know, can you explain that?

Dr. Kumar : Yup. Absolutely. Yeah, You know that is to be expected. And the fact is the SEER probably captures, I mean it captures everybody and that is probably closer to the, to the truth if you look at it as a, you know into the community, look in the community. What happens is the, I don't think its just Mayo clinic

data, I am sure if you look at any of the referral institutions, the data is going to be much better than the SEER. Because what happens is many of the older patients elect not to go a referral center, and tend to be treated more in the community. They tend to not have very aggressive therapies. So somebody decided that they don't want any aggressive therapies, they are less likely to search, get a second opinion and move to a different institution. So, I think we obviously have selecting of people who are likely to do better primarily because they were well enough to travel, they were younger enough, that they felt that they want to take an aggressive approach to treatment to the disease. And many of those factors clearly play a role.

Gary: Oh Ok. That is actually sad. But unfortunately sounds like it is true. Not everybody gets the same quality of care that Mayo provides Dana Farber, you know and Myeloma Institute for research and therapy and all the best locations unfortunately.

Dr. Kumar. : Right, and more than just quality of care, even if you were to take all those patients who did not come to Mayo and treated them exactly the same way as we would have treated them at Mayo, still those patients probably won't do as well, because they are probably more older patients, more other problems. And that may be the reason why they elected not to pursue aggressive path.

[00:20:37] Gary: Ok. Alright, another question, you know is that – We are very small population. We are 20,000 newly diagnosed patients of all the people that go to ASCO. Do you feel we are getting adequate coverage at these conferences, that we are getting, you know, getting the progress in, you know the focus that we need at these conferences.

Dr.Kumar : So, I would say, you know, more can never hurt, but having said that for a disease of this size of myeloma, I think we have a lot of exposure, and I think that partly comes from the fact – there is obviously organizations like IMF and MMRF who are always out on the forefront, looking out for the interest of patients. But more importantly I think rapid progress has been made over the few years and that, I think attracts lot of the pharmaceutical industry to that. And then finally, I think, even though it is only 20 K a year, now we are looking at patients living you know 8,9,10 years. So, that people living with myeloma now have far far exceeded that number of 20K. So, I think the newly diagnosed patients or patients diagnosed within the past year is increasingly becoming a smaller proportion of the larger group of patients with myeloma.

Gary: That is a good thing.

Dr. Kumar : Yup. That is a good thing.

Gary : So, where do you think the future for multiple myeloma treatment given your view of ASCO's and Mayo's crystal ball?

Dr. Kumar : So, I think we are certainly, you know, bottom line is – we are continuing to improve treatments. I think the people will continue to live longer with this disease. We certainly have new classes of drugs. So I think, the next kind of the wave is going to be these monoclonal antibodies and they are going to be combined with all the other things that we know worked very well. And the wave after that is probably going to be more of the targeted therapies and then of course some of the biological therapies like the viral therapy and the immunological therapy like the T cell therapies will also – I think they are all kind of coming to age at this point. But, the goal eventually is obviously to get patients to live a normal life span. Even though we may not necessarily get to a 100% eradication of the disease if we can keep things under control with good quality of life and a relatively normal life span, I think we have achieved the goal that we want to. So, I think the future would be like you know deciding, who needs what therapy. So right now, we only had like 4-5 drugs so we were treating everybody the same way. Now as we increase the number of available drugs I think, we have to start looking at which group of patients is gonna to get the maximum benefit from a given type of treatment. So, I think individualizing and personalizing the treatment right from the beginning is what is going to be the future.

Gary: Ok. Well, thank you so much. Let me go over the questions right now if you don't mind.

Dr. Kumar : Yeah. Certainly

Gary : Ok. Pat are you online.

Pat : I am here Gary can you hear me.

Gary: You bet. Pat your question?

Pat: Well, I want to throw Dr. Kumar a curveball right out of the gate here. I was gonna ask about Panabinostat and I am sure you will touch on that again doctor, but I hear from a number of myeloma patients from all over the world, and this is just a anecdotal observation, but for some reason there seems to be, or my impression is there seems to be an almost and overnight explosion of allo-transplants. More and more I am seeing doctors propose them and more and more I am seeing patients accept the risk and challenges. And like I said, I know it is just a anecdotal observation, but I wondered if, and I don't see lot of studies about them, and I understand that they are considered too risky for most main stream patients, but I know a number of high risk patients – they go ahead and they take the risk and they have a donor transplant and they seem to do pretty well. It is difficult and it is a challenging role, but a number of them – and even in a salvage therapy role, they seem..I have several friends who have lived – now approaching two years longer than they were projected to because they underwent a salvage allo. So, I just wanted to get your thoughts on all of that is Allo making a comeback? Is my impression correct or is it just a coincidence?

Dr. Kumar : No, I think there are several reasons for that. One, you know, the allogenic stem cell transplant, we know from long term experience from the bone marrow transplant registry is certainly something that

works in a small proportion of patients and gives you very long term survival. Now, it had gotten quite a bit of bad rep, I think primarily for two reasons. One – we were taking patients way late in their disease stage when they had nothing left to be treated with and those patients – it is hard for the allogenic transplant to really give some much benefit. The second reason was – we used to use high dose chemotherapy or the myelo-ablative allogenic stem cell transplant in the beginning, and there was lot of treatment related deaths, because of the side effects from the high doses of chemotherapy and so forth. Now, both those things have changed overtime, so I think now there is a better appreciation of who actually has high risk disease upfront, because of the increased availability of FISH and all those kind of studies. And so, the younger patients of the high risk disease, we talk about allogenic transplant much more early in the course of the disease.

Second thing is, I think we have gotten a better handle on managing the complications of managing an allogenic transplant. Either by managing the complications or by using the reduced intensity conditioning regimens. So, the proportion of patients dyeing within the first year from complications have a gone from like a whopping 40% down to more in the region of 10% or so. [00:27:26] So, I think that has made the whole modality little bit more acceptable.

The third thing is – there has been several large phase 3 trials that have been done, looking at allogenic stem cell transplant, specially the one with the CPN, which also, not only increase the awareness, but also increase the possibility of patients going on trials and getting allogenic transplants. [00:27:45] And I think finally, we have patients who actually do very well with their first line therapy or even the second line therapy. And they are still in very good shape -coming into when you.. thinking about what do we do the third line or what do we do the second line for this high risk patients. So, I think we all have better – patients are going into the allogenic transplant in a much better shape than they used to in the past. So, I think overall, it all points to the results being, you know looking better. We have started to hear more about these patients, but you know at the end of the day – I think, we really need to show – in a face to face comparison that there is a group of patients in home, we can use allogenic transplant and give results better than what would otherwise be.

Pat: Sure, so would you consider – isn't a patient who has relapsed multiple times, don't they in effect become high risk patients?

Dr. Kumar : They do. Yes. And I think, a lot of it depends on, you know, what is the duration? So, if you have a patient you are getting the fourth treatment two years after diagnosis – that is really high risk. Whereas, if you are talking about somebody who is getting their fourth therapy 10 years after the diagnosis, that person is not necessarily that high risk at this point.[00:29:03] You know it has got a more indolent kind of a behavior in biology. So here to take into context, what all drugs that person has got become resistant to and also in what period of time.

Pat: The thing that, I am not sure concern is the right word – but you know these therapies are all over the map. That is a lot of responsibility to put on a patient. You know they will email me and they will say- well, what do you think? You know, I mean, one doctor won't even use them for a myeloma patient; another is pretty quick to jump in. Some are using many allo's some are using – I mean it is just all over the map, and it would be nice to pin things down, narrow things down a little bit.

Dr. Kumar: Absolutely. I am totally with you on that point. I think, you know, the good thing is we have lot of options. The bad thing is we still haven't defined what option is good for who. And the data, you know the only data that you can always kind of, hang your hat on definitively, are kind of the randomized data. And especially in the transplant setting, that is not really there. And so I think, you know the important thing is to have a very frank conversation about what it entails and that is often the most difficult part about allogenic transplant. You still kind of convey what a bad graft vs. host disease can be, and what it could mean for quality of life.

Pat: thank you doctor. Very helpful. Appreciate it.

Gary: Pat, thank you. As always you come up with some great out of the pocket kind of questions. Jack are you there?

Jack: I am. can you hear me Ok?

Gary: Absolutely. Your question?

Jack: Dr. Kumar, we as patients look forward one day to the possible shot, and the doctor says – yeah! this will take care or at least put you in remission for a very long time. So, with that in mind the measles virotherapy created lots of excitement from Mayo and Dr. Russel a few weeks ago. If I understand it and I guess that is what I am asking for clarification, it appears, if it end up being a treatment, that it will only be effective if the patient has minimal measles antibodies, which if you have had that measles vaccine or a measles disease, you probably have lots of antibodies, so as such, do you see this ever being a viable initial treatment for the newly diagnosed myeloma patient who most likely has measles antibodies?

Dr. Kumar : Right. So I think, one of the biggest kind of the hurdles for the future of this therapy of course is you know, it is very exciting, despite it is kind of the proof of the principle at this point and it is just, you know, couple of patients in whom we have seen the response, so what does it mean for the myeloma in general. I think we need to have more patients treated, before we know – One – whom does it really help; and is it a consistent phenomenon or is it a random thing. And if even if we see that the clinical trials show that there is a proportion of patients who really benefit, then comes the question who are those patients and how do we identify them ahead of time. So, one of the things that we know already, is that the patients who have very high titers of measles antibody, typically get these measles virus eliminated right away, so that the viral therapy really would not have much of a benefit. So, I think you are absolutely right on the mark in the sense that vast majority of patients with newly diagnosed multiple myeloma would have measles antibody in the circulation. So I think right at this point, given the limit of information we have, it seems to be something that we may, at least in the initial stages look at it in the relapse setting.

Now having said that, obviously there are, you know, we will have to explore options of – one- Can we actually do something before giving the measles virus therapy to suppress the measles antibodies. So, who knows, I mean we have not done the studies. May be in newly diagnosed patients, after some kind of intense therapy for a few months, their anti-measles titres may go down substantially enough that we can actually treat them with the measles, as kind of a call it a consolidation or something, the tail end of the additional therapy. So that is one thing. May be at some point we can modify the measles virus to some extent that these antibodies don't really recognize them anymore. So, all those possibilities exist, but I think, that is ways down the lane. Right now, I think the goal is to better define what proportion of patients would it be effective, and what, who are those patients and how can we identify them prospectively.

Jack: Thank you very much.

Gary: Thank You Jack. Nick Van Dyk are you there.

Nick: I am here can you hear me?

Gary: you bet. Your question.

Nick: So, first doctor, thanks for joining us and of course for all the hard work that you and your colleagues at Mayo done, on behalf of all of us. I ask a variant of this curability question pretty regularly, but there is more data than the last time I asked it, so I am gonna ask it again. In April, there was a retrospective Italian study that showed that after 10 years of remission post Melphalan, very few patients relapsed and in other words, this suggests a cure. And In the same month, a Spanish study looking at deep sequencing for minimal residual disease, and it took patients who were all in complete remission, but had different levels of MRD, and tracked them. And the patients that had minimal or no MRD at 7-8 years, none of them, not a single one lost remission over over 4-5 years. Not a single patient experienced disease recurrence, so that points again towards a cure. Of course Barlogie and some of his diaspora have been saying for years that some subset of patients are curable with aggressive therapy. Now obviously, does not work for everybody, there are some people that have challenging disease biology. Lot of people are not eligible for transplant, and there is no easy cure regardless, but acknowledging that some patients are cured, I would think, it be useful for directing the goal of research, it wasn't a few years ago that complete remission was not even considered that be end all of markers, and now it is. So, of course, if it is curable, it also impacts the realities of survivors dealing with health and life disability insurance. At this point do we reach the stage where a newly diagnosed patients should be told that in some cases it may be curable?

Dr. Kumar : So, I think we have drawn for a long time right? There are some patients who have survived years out from their diagnosis and we had some of those patients even at the times when they were just using the Melphlan, Prednisone. Obviously from Dr. Barlogie's group there has been a lot of data suggesting, that, may be a substantially more proportion of patients could get to that flat region of the line. So, we certainly are curing a proportion of patients. The question is – we don't have a good sense of how much that proportion has changed over time. Obviously, the new therapies are only been around for the past 10 years or so. So, you know, it may take another 5-10 years to conclusively show that the so called cured patient proportion have increased. Now the biggest problem that we face is, you know, there are all different types of therapies and we find a few patients at the end of the treatment, who have done very well. But, it

does not tell us whether we should be using treatment A or treatment B or treatment C. And the second thing is we still don't have a good way of identifying these people ahead of time. If we could identify them ahead of time, and decide that they need a particular therapy, then we can tell the patients – yes, there is an X percentage chance you are gonna be cured of this disease. Until that time, I think all we can say this, you know, we know that some patients potentially get cured, but we cannot tell you what is going to happen to you. You know it is kind of saying that you could win the lottery. But we can't predict it. [00:37:25] So, I think, you know, kind of, we are very very excited to see that, that the proportion of patients with long term remissions. And the question is – may be these new studies like the MRD testing might help us identify those patients at 5 years instead of, at 15 years from diagnosis. So, may be in a few years, we might know from the studies that if you are MRD negative for two years in continuum, you know, two years continuously, or three years continuously, that could reflect long term cure.

Nick: That is a remarkably evenhanded answer. Thank you.

Gary: Alright, thank you Nick. Cindy are you there. You are last this time, but you are gonna be first next time. But you are always first with me.

Cindy: Thanks, So, I guess, My question is that, I guess, debate keeps on going on that continuous therapy vs. a fixed duration therapy. I guess Dr. Palumbo's in his retrospective study found out that a certain group of people who had continuous therapy had not only significantly longer Progression Free Survival (PFS) but Overall Survival (OS). My question is should we as patients consider staying on continuous therapy if we can tolerate it, if the quality of life is not affected? Also, I think, his study was with newly diagnosed myeloma patients. Would this see something in the relapse refractory setting? And something that we talked about earlier, he was talking about Progression Free Survival 2 (PFS2). Could you talk about a little bit, what that is and why is it so significant as a marker? I think I heard in one of the other teleconferences that Progression Free Survival 2 (PFS2) might be indicator in drug approval in Europe. I guess this is first time may be a couple months ago I heard that term, so could you touch upon a little bit.

Dr. Kumar : Sure. So let's take the whole PFS 2 thing first, and then we will talk about the fixed vs. continuous therapy. So, the PFS-2 is a, the progression Free Survival 2 is basically the time that, time from the diagnosis for the newly diagnosed patients to the time when the disease comes back or the patient dies of something that maybe unrelated to the disease. So, just as kind of an explanation of different terminologies, and they can get confusing. So, overall survival is the time from, again just from the time from start of therapy to the time to the individual passes away. The time to progression is the time that is taken from the start of therapy to the time when the myeloma actually relapses. PFS or the progression Free Survival is a composite of the two because it includes patients who die of unrelated reasons as well as the patients who progress. So, somebody with myeloma was on therapy and dies of heart attack, they would show up in the progression Free Survival, but they will not show up in the time to progression, if the myeloma was still in remission at the time when they died, so that is just a background for these different terminologies. So, the progression Free Survival 2 is the total time from the start of the therapy to the time when they went on a second type of therapy and then the myeloma came back. So, if you were to look at two treatments A and B, you can look at a scenario where everybody got started on treatment A, and let's say after sometime if myeloma came back and they got started on treatment B and the myeloma responded and then it came back again. So, the time from the beginning of therapy to that second time point when they fail the treatment B, is what is called PFS 2. And the PFS, typically the PFS that we describe typically is the one from the start of therapy A to the end of therapy A or the progression after A. This should not be confused with the second PFS, which is actually the time from beginning of B to the myeloma coming back. So, the reason why the European agencies have also been looking at the PFS 2, and again, I don't think

they are looking at approving drugs just based on the PFS 2, but again looking at other things as well. The whole question of – what happens if the initial therapy were to significantly impact the ability to use the second therapy. If that was the case then it would, the PFS2 would capture both the beneficial effect of the initial treatment and also the long term adverse effects of the initial treatment. And that is the reason where the PFS2 might be of benefit. So, for example if you were to take, let us say a drug that has lots of side effects, and…forget about drugs with lots of side effects. Let's take a drug which you give for 4 years vs. you give it for 2 years. So, if that drug has a cumulative effect on the bone marrow and if in that 4 years your bone marrow is badly beaten up, compared to if you just got for 2 years, then whatever treatment you get after 4 years, might not work very well. Whereas the other group of patients where you gave a shorter duration of therapy, the drug might work very well. And so the second PFS will be significantly longer. So the PFS 2 then actually helps kind of capture that part of the long term effect of the drug. And that is the reason why they are looking at that, in addition to the other traditional end points that have been used. So, I don't know, is that more confusing or more clear.

Cynthia: I am starting to get it. I think I will need to hear it a few more times, you know. I am just starting to understand what it means.

Dr. Kumar : Going back to the question of continuous therapy vs. fixed therapy. Now Polumbo's data was pretty interesting. You know he kind of pooled patients who got very different kinds of treatments in the non-transplant eligible patient population, and basically looked at people who got a fixed a fixed duration of treatment and who got a continuous therapy long term. [00:44:25] Now, he was able to show that overall survival seem to better in the continuous therapy vs. fixed therapy. I think it raises as lot of very interesting hypothesis. But I don't think it is the answer to that question. Primarily because of 2 reasons. One is – we don't know, how many people were in that fixed duration of treatment were able to get the same drug back, that the continuous therapy patients had access to. So, for example it included patients who got Revlimid. So, we want to make sure the patients who are at relapse, also got Revlimid or had access to it. So, that is one problem.

The second problem is the way that that analysis was done. It was the landmark analysis meaning that – we kind of assumed or we just looked at people who survived the first one year and then looked at the difference. And we already know that, from a statistical perspective, when you kind of remove that one year from that whole graph. It reduces the power or, in this situation it actually kind of skews the power or the ability for that particular analysis to show a particular outcome. But I think the more, you know – if this is the same question that is kind of being asked in the setting of maintenance trials too. So, there are several trials that have looked at maintenance, either in the post transplant settings or in the without transplant. And the vast majority of them, even though they show a progression free survival, have not yet shown an overall survival advantage, except for the US trial, with the Rvelimid maintenance. And also one of the Spanish trials, that looked at continuous therapy in the older patients. So, I think we still need to kind of wait and see what these trials which have been designed specifically to ask this question shows, before we make any conclusions. But it certainly, pushes that, at least highlight that as a very interesting or intriguing question that needs to be answered.

[00:46:40] Cynthia: It is hard as patients to make that decision right now I guess, you know, whether you should continue on therapy or whether we should take a therapy for it. So, it is always hard.

[00:46:53] Dr: It is always hard. And you know, the thing is, you know it always gonna to boil back down to the quality of life as well. So, we have to kind of see how much of benefit are we getting by taking two years of treatment, vs. say three years of treatment, in terms of long term outcome. But at the same time what is

the price have you paid for the side effects of the treatment also. So I think it has to be a composite or accumulative effect of both things.

Cynthia : Kind of like a see-saw, you have to wait on both sides. Thank you so much.

Gary: Thank you Cindy. I really appreciate that.

Doctor, I have a question, and we will go on to the question from our listeners. And that has to do with a study not too long ago, by Dr.Richardson from Dana Farber, and also Dr.Lionel of Ambry university. And they had gone to a number of – and for us who have myeloma, you know, were obviously considered, you know, very much, you know wanna consider, what happens when we become refractory or have relapsed. So, in the RR area, they said that- in the evaluation of a number of studies that VRD had a 69% overall response rate (ORR). And RCD had an 81% response rate. And then Velcade and Doxorubicin had 63%; Thalidimide,PL Doxorubincin, Dex) – 76%. So all of those obviously were quite good and they are basically full line therapies. And then the most recent one that have come up are the ones for KPD(Kyprolis, Pomalyst, Dexamethasone) – 70% and KRd(carfilzomib, lenalidomide, and low-dose dexamethasone) – 69%. And if you look at that, and I don't quite understand, but 70 and 69 are really no better than the older line treatments. So, Are you disappointed with that, or am I looking at this in totally incorrect way?

Dr. Kumar : I am not at all disappointed. Because you have to remember that the more recent studies would include patients who have already gone through some of those newer treatments that we studies a few years ago. If you look at the Velcade, Revlimid, Dexemethasone trial, that started putting patients on sometime in 2005 or 2006. So, at that time, a vast majority of the patients had a transplant. All of them had seen Thalidomide, many of them had seen Mephalan type medications, but they had not seen some of the newer drugs at that time already. Now, when you look at the more recent trials, these are patients who have already seen Velcade, Revlimid, Transplant, Thalidomide, Pomalidomide. So, increasingly the newer and newer studies are looking at patients who have already exhausted a lot more options than what was available at that time. So, I am sure if you were to take the same type of patients who went into the Velcade, Revlimid Dex study, if you can find them and gave them these newer therapies, I suspect we are gonna see responses similar to that.

Gary: So its just a matter of timing basically.

Dr. Kumar : It is a matter of what all they have seen before they came into this treatment.

Gary : Fantastic. That makes all the more sense to me. At this point we would like to take some of the viewer, and listener. Not viewer but listener questions. So priya, has anybody got some questions for the doctor?

Priya: Thank you Gary. We have Dana, who just dialled in. I think she has a question for Dr.Kumar. Dana you are on air, please ask your question.

Dana: Thank you Priya and Panel members. Hello Dr. Kumar. Thanks for taking my call. I am a smoldering and asymptomatic smoldering myeloma patient. I would like to ask you – What do I need to know going forward. Should all smoldering patients consider early treatment intervention to possibly delay progression or hopefully even cure the disease? If we treat well, we are in a lower disease burden state which may be less, heterogenesis. I am not pronouncing it right. I am sorry, you know what I mean though right? So, I would like to know, what guidance could you give me.

Dr. So there are I think few different aspects to the answer. One is, I think is a blanket statement. All patients with smoldering multiple myeloma should not go on treatment at this point outside of a clinical trial. Because first of all, some of those patients will be used to call a high risk smoldering multiple myeloma. With new definitions of myeloma they are going to be grouped as myeloma rather than smoldering multiple myeloma, so obviously that group of patients would need treatment, just like we would treat newly diagnosed patients. But you bring up very important point. Can we cure the disease if we intervene early? I think that is a research question and there are clinical trials that are looking at intense therapy in the high risk smoldering multiple myeloma patients. Similar to what we use for smoldering myeloma to see if that is actually a possibility. [00:53:00] Now if you were to look at the answer to that question from the perspective of the results of the Spanish trial which look at the Revlimid-Dex treatment in patients with high risk smoldering – a good proportion of those patients – so called high risk smoldering multiple myeloma, would actually end up being called myeloma with a refined definition. The second is – that the trial still does not tell us – you know – it is again a relatively small study and the question is – Do we need to take everybody or can we just wait and watch and see a particular type of change or look at the tempo and then intervene early. So, I think there are still lot of questions that have not been answered, and how much of it is effective from Revlimid vs. Dexamethasone. I mean Revlimid alone vs. the combination. So, I think at this point I would look at smoldering myeloma patients as 3 groups. One – who meet the definition of the newly diagnosed myeloma – based on the new definition who should all be treated; Patients with high risk myeloma, who should all be treated in the context of a clinical trial participation; and patients with standard risk or low risk myeloma who should just continue to be observed.

Dana: Thank you doctor. For the sub group of smoldering patients that are being redefined as early myeloma, hence treatable myeloma, what criteria do they need to meet?

Dr. Kumar : So, the three new things that have been added was – If you have a bone marrow with more than 60% plasma cells; If you have a free light chain ratio that is more than hundred; and if you have a PET scan or MRI actually showing lesions – then these patients would be considered as having symptomatic myeloma. Even though they may not have the typical CRAB – high Ca, the renal problems, the anemia or the bone disease.

Dana: Is there a threshold of lesions to meet?

Dr. Kumar: Yes. If you see 2 or more lesions then you should consider treating them as myeloma.

Dana: 2 or more. Very good. Thank you so very much for taking my questions. Appreciate it.

Priya: Thank You Dana. Listeners if you have a question for Dr. Kumar, you can please press 1 on your keypads and I can bring you live on air to ask your question.

We have a question Dr. Kumar from one of our listeners and it says – What options would you suggest for pancytopenia remaining one year after an auto SCT, and the patient is in a stringent complete response confirmed by a bone marrow biopsy, which did not show MDS or other bone marrow, and cytogenic abnormalities? Also, for a standard risk patient, who has pancytopenia one year after an auto SCT, and who is in SCR, would you suggest watchful surveillance over any maintenance use of either lenalidomide, bortezomib, or other maintenance therapy?

Dr. Kumar: Right. So, I think the question is how severe is the pancytopenia. If the pancytopenia is not severe then I would say, just continue to watch, specially since the disease is in remission. If there is a significant pancytopenia that the person is needing transition, then he certainly should consider, if they have stem cells stored away, considering reusing them. You know the maintenance therapy yes or no would depend more on the underlying disease. If its one of the high risk myeloma then I think, certainly should be considered, but again would be limited by what the blood counts are doing, in terms of would they be able to tolerate the treatment.

Priya: Thank you doctor. If any of the panelists have any questions, please go ahead and ask them. We have just a couple of minutes more before we wrap up for today.

Cynthia: Hello. This is Cindy. I have a question on how is the new flow cytometry measuring MRD. I am not so much concerned about the MRD at this point, but I think I heard rumblings that Flow cytometry test also may be give a signature of the person who will go back to the MGUS stage and may not get into complete remission, but return to precursor MGUS myeloma. IS that true? If it is, will that test be available commercially soon?

Dr. Kumar: Right. So, I think you heard right. Before cytometry, testing that we do, does give us multiple pieces of information. One obviously is whether there is MRD or not. But it also can give us a profile of how much of a normal plasma cells have come back which is also an important predictor of how long the response might last. And it also can give us some profile as to whether some patients have starting to develop this myelodysplastic type of changes. So, here are multiple pieces of information that the flow cytometry can provide and obviously we need more studies to see, what is the relevance or the implications of some of the findings.

Cynthia: OK. Now is that inside of a clinical trial now?

Dr. Kumar: Right. So, I think the flow cytometry is just kind of being, at least way its developed by the Spanish group- is kind of being rolled out across multiple institutions and we are hoping that over the next few years it will definitely be incorporated into all clinical trials, but also eventually be incorporated into routine practice as well.

Cynthia: So, I should ask for it next time I go for an evaluation to have that test done? Is that a blood test or something done..?

Dr. Kumar :It is a bone marrow test right now. Yes.

Cynthia: So it is a bone marrow biopsy for

Dr. Kumar: Bone marrow aspiration for that right.

Cynthia: Ok

Priya: Thank you Cindy, Thank you so much. I kept interrupting you, so I could not hear you clearly. Thank you so much Cindy. We have almost, I think one hour has just flown by. Dr. Kumar Thank you so very much for joining us today. It is always a pleasure to have you here with us on Cure Panel. I thank the wonderful panel – Gary, Pat, Jack, Nick and Cindy – you people are the best. Please join us again through our next myeloma broadcast on 8th July, 6 PMET, and we are having Dr. Rodger Tiedmann as our expert speaker. Please visit curepanel.carefeed.net for details of upcoming shows and you can always mail me priya@trialx.com. The link of today's show will be shared with all participants. Thank you and have a great weekend.