ASH 2014 Myeloma Updates with Dr. Parameswaran Hari

We bring you myeloma updates from the upcoming 56th Annual ASH (American Society of Hematologists) Meeting and Exposition. Tune in to learn what was exciting and what looks promising in the field of hematology from our myeloma expert Dr.

Hari and our panel of myeloma survivors /advocates.

Full Transcript:

Priya Menon – Hello, everyone, and welcome to Cure Talk for a discussion on multiple myeloma. I am Priya Menon, Scientific Media Editor at Cure Talk, joining you from India and I extend a warm welcome to all of you this evening. This is Cure Talk's 74th episode. We are excited to inform our audience the launch of our new website. Please do visit us at www.curetalks.com and do send in your feedbacks to priya@trialx.com. On our myeloma broadcast today, we are discussing ASH 2014 myeloma updates. My co-host for the show is myeloma survivor and editor of myelomasurvival.com, Gary Petersen. On the panel are myeloma advocates and survivors, Pat Killingsworth, Cynthia Chmielewski, and Jack Aiello. We have with us today Dr. Parameswaran Hari from Medical College of Wisconsin. Welcome to the show, Dr. Hari. It's a pleasure to have you with us once again.

Dr.Parameswaran Hari – Hi! Thank you, Priya.

Priya Menon – Gary Petersen will introduce us to our expert and begin with the discussion. Before I hand over to Gary, I would like to tell all listeners that we will be addressing questions towards the end of the show and if you want to ask a question to our panel, you can press one on your keypad and we will bring you on air to ask your question. Alternately, you can email me with your question at priya@trialx.com. With that, its over to Gary. Gary, you are on air.

Gary Petersen – Thank you very much, Priya, and I have visited your new website and it is very good. People should go see Cure Talk's brand new website, but today I am here to talk with Dr. Parameswaran Hari about the ASH 2014 and on the panel not only was Dr. Hari there, which I had an opportunity first time to meet him, I was so pleased to do that, but all of the other members of this panel, Cindy, Jack, and Pat were there as well. So, it should be a relatively informed group. Dr. Hari is an MD, an MRCP, and an MS and what that MRCP, I had to google it, is a membership of the Royal Colleges of Physicians of the United Kingdom and MS is a Master of Surgery, at least I believe it is. Dr. Hari currently practices at Froedtert and the Medical College of Wisconsin, specializing in hematology, oncology, and hematologic malignancies. Since 2004, he has been serving as the Director of the Adult Blood and Marrow Transplant Program at Froedtert, and he is also the Section Head of Hematology Malignancies and Transplantation. He is a Scientific Director for the CIBMTR, which is a group of hospitals which number about 500, that report all of, and have an organization that reports on stem cell transplants, both autologous

and the other one (laughter) auto and allo, I will just leave it at that, and works with those plasma cell disorders and adult solid tumor working committee. He is also 2014 Multiple Myeloma Survivorship Conference Chairman.

Gary Petersen – He received his education in, his MD at Jawaharlal Institute of Post Graduate Medicine in India, which is one of the three top medical schools in India and like the Harvard, Mayo, or Dana, you know, one of our better ones as well. He then completed his fellowship in internal medicine and hematology at the Royal College of Physicians and Royal College of Pathologists in United Kingdom and in the medical oncology and transplantation at the Medical College of Wisconsin. He has many peer reviewed publications. He is also multilingual. He speaks five different languages. The Medical College of Wisconsin happens to be and Dr. Parameswaran Hari's program happens to. He provided me with the survival statistics for www.myelomasurvival.com and his three-year survival is 93.8% versus the SEER data of 55.6% and this is one of the two best performances for myeloma survival in the entire world. So, I think its a remarkable performance and its such a find for a center that is not that well known outside of Wisconsin. They have myeloma patient population of over a thousand and I think Milwaukee's little myeloma treasure is no longer their little secret and as a matter of fact, you know, I think that, you know, it deserves to be in the same language and senses with UAMS, Dana Farber, Mayo Clinic, etc. So, with that I want to try something here. Its one of the languages Dr. Hari knows. Kulu kuna patula tuta vera ver karuma, (laughter) which is supposed to mean "Welcome to Cure Panel" in Tamil. (Laughter) Wasn't even close, was it, Doctor?

Dr. Parameswaran Hari – No, I kind of figured it. (Inaudible) Yeah.

(Laughter)

Gary Petersen – Better in English, huh?

Dr. Parameswaran Hari – Yeah. Yeah.

Gary Petersen – Well, welcome to the program, Dr. Hari.

Dr. Parameswaran Hari – Thank you, Gary.

Gary Petersen – I tried. I even practiced.

Dr. Parameswaran Hari – Oh, thank you so much.

(Laughter)

Dr. Parameswaran Hari – You take… Yeah, I appreciate all the efforts you take on behalf of everyone who is dealing with myeloma, just the effort to go to my history is remarkable there, yeah.

(Laughter)

Gary Petersen – Well, welcome, and I know that you went to ASH and based on your observations, I would like to ask you what you believe the state of myeloma is, kind of state of union but for myeloma and you might break that down into four different categories and, you know, if you forget any of the categories as we go through it, just let me know and I will repeat it. You know, the first one is for all those existing newly diagnosed patients that are looking for first-line therapies and what was represented at ASH that would be exciting for those. The second one would be existing approved drugs for relapsed, refractory myeloma patients for both high and low risk, you know, using like Kyprolis and Pomalyst, and then new drugs which will be approved in the near future for newly diagnosed and the relapsed and refractory multiple myeloma patients such as SAR and daratumumab and then finally any research which you might see on the horizon which may be helpful for either measurement, early diagnosis, early intervention, or

possibly new pathways. So, you know, if you could kind of follow that outline. You have the chair, Dr. Hari, and thank you so much. It was a pleasure getting to meet you.

Dr. Parameswaran Hari – Oh, thank you, Gary. Thanks, everyone. Thank you to all the people listening and thank you, Priya, for this opportunity. So, the first… So, we will talk about the state of myeloma in maybe the four buckets that Gary so nicely summarized. So, first of all, let's think about newly diagnosed myeloma. So, the outcome for patients with newly diagnosed myeloma is getting better and better, but as we all know, myeloma is not one disease. It is probably multiple different diseases with varying risk profiles. So, from the two of the largest studies that were done with people who had initial diagnosis and then treatment with what we call novel agents, which means including lenalidomide or Revlimid and bortezomib or Velcade, then followed by transplant, followed by maintenance. That's the standard approach for patients who are transplant eligible. So, for that type of approach, we think the first remission usually lasts four years or so for most people and that's the state of things as they stand. So, there are many ways of making this number go better. The people who do not benefit that much from this type of approach are the people who have high-risk disease. Now, high risk is defined by a combination of cytogenetics or you know the genetic markers on the myeloma cells. There are many ways of doing that now, but the most common way still remains something called FISH test. There are other techniques also. For people with high-risk genetics, people who are of older age, people who have kidney failure that prohibits intense treatment, all of those people the outcomes have not kept up with the other standard-risk patients. So, there are many ways of making this better.

Dr. Parameswaran Hari – So, first of all, you know, how do we make the overall outcomes better? So, recently, about a month ago, there was this study published from Dr. Palumbo's group in Italy where they randomized patients to the option of giving initial therapy with lenalidomide and dexamethasone, patients either got two transplants or they got melphalan and prednisone and Revlimid orally for nine months, then followed by maintenance and half the people got maintenance, half didn't. So, here again, the role of transplant was established as being crucial to prolonging the survival of the patients and especially the progression of free survival. So, we know that even in the modern era with all these drugs, transplant still continues to be one of the backbones of treatment. So, that being said, how can we make the initial therapy better, the first treatments that you get better before transplant? So, the reason for thinking in those lines is at this time the three-drug approach is what we use across the country and the three drugs are going to be proteasome inhibitor, i.e., Velcade, then Revlimid which is an IMiD, and then dexamethasone. So, there was a study called the EVOLUTION study where we did these three drugs versus another three-drug combination with Velcade, cyclophosphamide or Cytoxan, and dexamethasone versus a four-drug combination where we added Cytoxan and Revlimid together to the Velcade, dexamethasone backbone. So, three drugs one way, three drugs another way, and all four drugs together. We found that the four drugs, that particular four-drug combination was no better than the three-drug combination and the three-drug combinations were mutually equal. So, that's how this three-drug approach became standard.

Dr. Parameswaran Hari – So, for the last four to five years, that has spread across the country. At least here in the US, that's the standard approach for younger patients with myeloma who are transplant eligible. Even older patients benefit from it, but they would need some dose adjustments so that, you know, the doses are not at the same level. So, a bunch of new developments have happened in this initial induction phase. One is using newer proteasome inhibitors. So, we have the new proteasome inhibitor, carfilzomib or Kyprolis. So, Dr. Jakubowiak's group did a combination of Kyprolis with lenalidomide and dexamethasone or KRd and they showed similar or even better results compared with the Velcade-Revlimid-dexamethasone combination. So, that's one broadened achievement and these patients had deep molecular responses with MRD negativity to a level that we have not seen with any other induction treatment.

Dr. Parameswaran Hari – Then, Dr. Kumar in a multi-center group, many centers participated including our own, has lead a study where ixazomib, another proteasome inhibitor which is an oral form of boronic acid type of proteasome inhibitor, similar to Velcade, but it's an oral drug you take one day per week. So, one day per week of ixazomib, everyday of Revlimid and then dexamethasone once a week. That combination

also had dramatic initial response rates, but then Dr. Kumar updated the results of the study at ASH this year and he showed what happens if you continued with the treatment, if you continued with the ixazomib orally as maintenance treatment afterwards. So, that was very interesting. Up to 48% of patients, so that means about 50% of patients increased their responses while on this maintenance treatment with ixazomib, which means that the complete response rates went up from about 25% at the end of eight cycles to about 62% while they were on maintenance. So, that's amazing, you know, 62% complete response is a very dramatic good result in this setting. So, that's one thing. So, we can say that the three-drug combinations are getting better and we have new three-drug combinations that might become standard. So, that's number 1 for newly diagnosed disease.

Dr. Parameswaran Hari – Number 2, we are still exploring four-drug combinations. You know, ultimately, most people believe that this approach of using non-cross-resistant drugs, drugs that do not mutually interfere with each other and they augment each other, those type of combinations are going to be the future of myeloma. So, the non-cross-resistant combinations of four drugs are again gaining traction. So, there was a small study, about 22 patients' study, with RVD or Velcade, Revlimid, dexamethasone plus a new drug HDAC inhibitor, H-D-A-C inhibitor called panobinostat added to that combination. So, in that, the results are not mature yet, but again the overall response rate was 95%, suggesting that almost everyone who got this combination responded. This was newly diagnosed patients and the study is still ongoing and the doses are not set yet, so this will be a, you know, like watch-this-space type thing. Then, we have some other combinations that have, that are being explored again, you know, cyclophosphamide, carfilzomib, and dexamethasone or CCD. This has some attraction for people in Europe because with cost being a big issue there, they are unlikely to get two expensive oral medications or two expensive medications to combine. Cyclophosphamide is a cheaper, a very effective drug, has been around for many, many years. So, their combination is cyclophosphamide-carfilzomib-dexamethasone. Then, there is Velcade, pamolidomide, and dexamethasone, a different proteasome inhibitor plus IMiD combination similar to RVd, but again, you know, with. Then, Europeans again presented a combination of carfilzomib or Kyprolis with thalidomide and dexamethasone. So, all of these are excellent new combinations that are being derived and the three drugs. So, in summary, we could say that the more potent the drugs and the less toxic the drugs, the more likely people are able to continue with treatment for longer duration and we can actually get greater responses and deeper responses with the more potent combinations. We hope that this (inaudible). Yeah

Gary Petersen – Umm. Just the Kyprolis and Pomalyst and that… that inhibitor that you had talked about, all of those have yet to be approved, have they or are they, you know, I know Kyprolis and Pomalyst have been approved but only for a relapsed, refractory. Is that correct?

Dr. Parameswaran Hari – That's correct.

Gary Petersen – So, is… Yeah, so people can't really take that as newly diagnosed until they get approved for initial treatment or…

Dr. Parameswaran Hari – Or on a trial. They can take it on a trial. Yeah.

Gary Petersen – Or on a trial?

Dr. Parameswaran Hari – So, there is a national trial right now. Yeah, we can do it on a trial. The national trial of the ECOG, there is a national intergroup trial that's ongoing right now, where newly diagnosed patients are randomized to getting Velcade, Revlimid, and dexamethasone versus Kyprolis, Revlimid, and dexamethasone. That's ongoing right now. So, right now, we have access to that combination. Yeah.

Gary Petersen – Okay, but not your local…?

Dr. Parameswaran Hari – Yeah. It will be 50-50.

Gary Petersen – …hematology-oncology colleges couldn't do it, could they?

Dr. Parameswaran Hari – Well, this is a national trial. So, even community practices should be able to join that trial. I think, you know, its something that everyone should be thinking about. Yeah.

Gary Petersen – – Okay. That was… That was a sort of barge in.

Dr. Parameswaran Hari – No, no, no. That's okay. You know, please feel free to stop me in the middle. And then the second thing, you know…, the second group that Gary wanted me to talk about. So, that was the first line therapy is getting better and when you get first line therapy is getting better, everybody benefits. You get more people into complete response, the responses last longer, you get people into deep molecular responses. The relapse rates go down. So, you know, the benefits of initial therapy cannot be overstated and that's your best shot at dealing with this, you know, once relapse starts out, therapies are generally less effective than they are at the beginning. So, we really need to work on getting these initial therapies really, really the strongest we can get them with the least toxicity. Now, the second group that we wanted to talk about are existing approved drugs for relapsed, refractory myeloma. As you all know, the last two drugs to get approved were Kyprolis and Pomalyst and these two got approved within the last 18 months or so. So, the single-agent response rates are not that exciting to these drugs. So, what we are trying to do is to use these drugs in rational combinations. So, the big study that was presented at ASH, although it was almost…, it came out as a publication around the same time too. It happened at the presentation and the publication happened simultaneously and lot of people had access to both, so was the randomized study of carfilzomib, Revlimid, dexamethasone versus just Revlimid and dexamethasone for relapsed disease. So, that was presented by Dr. Stewart from the Mayo Clinic in Scottsdale and this was again an international effort across the world. So, they randomized patients who were in, what we call, early relapse, meaning they have not relapsed, they were not relapsed and refractory. Patients had to be still expected to be sensitive to Revlimid. So, half the people got just Revlimid and dexamethasone. The other people got Revlimid, dexamethasone plus Kyprolis. And they had a standard treatment with Kyprolis in addition to Rev-dex for about a year and then they had reduced intensity of Kyprolis every other week for about six months and then they stayed on Revlimid maintenance after that. And this is a very effective study. This combination proved to be much better than just Revlimid-dexamethasone. People who got Rev-dex had an average of 17 months before they progressed to needing another treatment, whereas people who got the Kyprolis combination had 26 months. They had a nine-month progression-free survival advantage and deeper responses and a trend that could be significant for a longer survival, overall survival. So, its not fully significant yet, but its kind of on the border there. So, this was really the major study that was reported in myeloma at ASH and this was called the ASPIRE study. So, this study is already published. So, if you want you could actually look it up at the New England Journal of Medicine from about two weeks ago.

Dr. Parameswaran Hari – So, the other combinations in with these drugs are, you know if you stick with the ones that I just mentioned, i.e., Velcade with Pomalyst. There is a study going on where Velcade-Pomalyst-dexamethasone is compared with Velcade-dexamethasone. There is a combination of carfilzomib, pomalidomide, and dexamethasone or KPd, which has shown outstanding response rate in multiply relapsed patients and again, I am sure you all know that the Panobinostat which was an HDAC inhibitor that is not yet approved, went before the FDA and at this time its still not approved. So, relapsed, refractory myeloma, the combinations of existing drugs are the way that people will be using this. What is important about the ASPIRE study is that, you know, there was a belief that you could just use one or two drugs and then we wait for those drugs to fail, then go to a second drug, like that. We are increasingly seeing this trend where combinations are turning out to be better than two-drug…., three-drug combinations are getting better than two-drug combinations. The advantage of using the combination is that you get more people into a complete response quickly and then that translates into a longer time from relapse. So, I am firm believer in using ideal combinations whenever possible, obviously sometimes insurance, sometimes the toxicity, those can be a hindrance, but we need to get quick deep responses in myeloma whenever we treat it. So, you know, strike hard when you are striking is kind of one of that philosophy and I think that is interesting that both the Thal-Dex versus Velcade-Thal-Dex study and the Rev-Dex versus Velcade-Rev-Dex study, both of those studies have showed that the three drugs are better than the two drugs, especially in terms of preventing progression.

Dr. Parameswaran Hari – So, that's the state of the art in relapsed, refractory myeloma is going more and more towards combinations and new drugs. So, what are the new drugs that are going to be approved in the near future or going to be looking really promising for the next two… I am sure you have all heard about the antibodies. There are two big antibodies that are gaining all the attention right now and there are a couple of others that are coming right behind. So, the two big ones are daratumumab which is an anti-CD38 antibody. CD38 is a marker present on the surface of plasma cells. So, this antibody, when you inject it into patients, it can go and find out wherever CD38 is on the surface and that means it will pick out all the myeloma cells attached to that, those cells only and kill those cells selectively. So, it is targeted. It has very little collateral damage. So, it is generally better than chemotherapy and most antibodies have this problem that when you give it to patients IV, the patients get a reaction and since its happening in a doctor's office or in a hospital, you actually have good control over that situation and over time the body gets used to it and the reactions tend to go away. This is common for all antibodies, including Rituxan which is kind of the most famous antibody in oncology, which is CD20 antibody used in lymphoma. So, we have always been looking for the Rituxan equivalent in myeloma and we might be getting there now.

Dr. Parameswaran Hari – Another CD38 antibody that's being trialled is the SAR650984 or people call it SAR, but if you said SAR, you know, there are several drugs made by that company Sanofi which go by that acronym, so its SAR650984 is the one in myeloma Its again an anti-CD38 antibody. There are technical differences between the two antibodies, the daratumumab and SAR, and they are actually both being tried in relapsed, refractory disease with very promising single-agent response rates, but we knew about the single-agent responses from the previous data already. However, at this ASH, we have data in combination with Revlimid and dexamethasone. So, there is a study from Denmark where they showed a combination of daratumumab with Revlimid and dexamethasone. They had almost, I think, 45 patients and essentially everyone in phase 1 responded and of the people in the phase 2 part, almost 87% responded to the three-drug combination and including a lot of patients, almost 50 had a very good partial response or more. This is just unbelievable, the amount of…, the responses that we are seeing with a combination at this stage, you know. For relapsed myeloma, getting 50% VGPR is very, very good and there are some other technical issues with the antibodies, you know. It turns out that if you have antibodies-based treatments, sometimes the way we do serum protein electrophoresis and immunofixation may underestimate or overestimate the number of people who are actually in a remission, so there are technical issues with calculating remissions and that's because this is an antibody that you give to people. So, the IFE test may also need to be modified in this situation. Similarly, the combination of SAR650984 with Revlimid is also being explored. So, this was a study from UCSF, again a phase 1b study. Again, I think 84% of patients who, you know, something like 30 patients who came on that, almost 60% had a very good response. So, this is, you know, very exciting news. Again, interestingly, if you note, it is not single agents. Its the combination that's being explored. I am sure that these combinations will get approved and then they will probably move into the frontline setting, probably within the next three to four years. So, we are looking at an exciting phase, a new phase, of new classes of drugs that might be available. Finally, you know, the fourth thing that Gary asked me to talk about are things that may be helpful for measurement, early diagnosis, intervention, etc. So, we have several different pathways that are branching off at the same time. So, we have redefined myeloma definition. So, we are asking, telling… We are redefining who has myeloma. So, people who we used to call high-risk smoldering myeloma, where they were going to get myeloma within a few months or weeks, we have moved a bunch of those people into actual myeloma. So, the new criteria for myeloma includes anybody with more than 60% plasma cells. They are considered myeloma, whether they have bone disease and calcium, anemia, renal problems, etc. Next, people with a very high light chain ratio, they are also…, that are considered a myeloma-defining feature. People with one or more focal lesions on MRI scans and PET scans, they are also considered myeloma. So, we have actually moved some of the people who we used to consider smoldering myeloma into myeloma so that we are going to benefit those people by early treatment.

Dr. Parameswaran Hari – Second issue is monitoring. So, we have… I am sure you have all heard about minimal residual disease monitoring and minimal residual disease is something that is very interesting nowadays because we are getting more and more people into complete remissions. When we say somebody is in a complete remission, we mean that we cannot detect. We looked very hard and we could

not detect any disease in this, but when we talk minimal residual disease, we are asking the question how hard did you look? Can you look even harder? So, basically, if you are in complete remission by whatever we conventionally define as, then we apply much stronger techniques like flow cytometry or next gen sequencing and look even harder, we might be able to find more disease. So, we can find disease to the level of one cell in out of 10,000, one cell out of 100,000, if its myeloma cell, we can pick it out. And it turns out that people who are minimal residual disease negative in their bone marrow tend to do better than the people who are minimal residual disease positive which king of stands to reason. But then the second part of that question is can you convert people who are MRD positive into MRD negative and thus improve the survival of patients? So, you know, we thought they were in a CR and they were going to do well, but they didn't do well because they had minimal residual disease, so can we change that by additional treatment, either maintenance, consolidation, additional transplant, etc.? So, this is an exciting field and that is…, you are going to hear more about it, but right now it is being used not uniformly, mostly academic centers tend to use it. So, those are some of the big things that were in discussion at ASH. So, I think… Gary, any questions about this?

Gary Petersen – Umm…. Just, you know, new pathways meaning, you know, other drugs other than the ones that do CD38?

Dr. Parameswaran Hari – Oh, new, new… Oh, yeah. Of course, there are several new drugs and new pathways. So, we talked about the antibodies. So, we talked… There are a bunch of new, what we call, small molecules. So, the most exciting one was this molecule that's already approved for a disease called CLL and mantle cell lymphoma. This is called Ibrutinib or Imbruvica. Its already approved and its approved in those two diseases. There was a study presented by my friend, Dr. Vij from Washington University, where they used Ibrutinib with Dexamethasone for patients with relapsed myeloma and he had promising response rates in that setting. Interestingly, most drugs that work in mantle cell lymphoma were in myeloma too and the reverse is also kind of true. So, in this study, I think it was about 69 patients included in that study. They had a median of almost four treatments before that. So, they were all relapsed patients and the combination achieved a minor response or meaning like at least 25% decline in paraprotein, in 20% and another 25% did stop the progression of disease. So, the median progression-free survival was about six months in that and so it suggests that there is some activity and there might be scope of using that activity further in combinations. Now, then the second group or, you know, there was a study on this other proteasome inhibitor called Oprozomib which again is a same pathway but a newer drug in that pathway, similar to Carfilzomib but oral. Next, we have a group of drugs known as cyclin-dependent kinase inhibitor of CDK drugs that again has been in use for a little bit but now may be becoming main stream in the future. More interestingly, there is a new class being explored called export protein inhibitors or XP1 inhibitors. This class of drug seems to be particularly effective for people who have a 17p deletion. Now, as you all know, 17p deletion is a very powerful, bad prognostic factor in myeloma and in any other disease for that matter. So, this drug inhibits the export of toxic proteins out of the cell's nucleus, so these proteins that make the cell die accumulate in the nucleus of the cell and kills it off. So, this drug is being… Its called Selinexor and its being explored in myeloma and in other diseases that was also data presented at ASH. There is a new HDAC6 inhibitor called Rocilinostat or Rocilinostat which was again presented. So, the hope is that instead of using pan-HDAC inhibitor which hit across all HDAC enzymes in the body, this drug is a more targeted drug and it hits hits only HDAC6 which is active in myeloma. So, we have several different pathways that are being explored newly and again, you know, some of them are early, very early testing.

Gary Petersen – Fantastic! Well, thank you very much, doctor, and this excellent presentation is one of the reasons that you are one of my great eight of myeloma specialists in the world. Pat Killingsworth, are you… Are you online?….

Pat Killingsworth – – I am, Gary.

Gary Petersen – All right, Pat. Your… Your… Your question for Dr. Hari?

Pat Killingsworth – Sure. Hello, doctor. I was pleased to get a chance to meet you at the poster session in

ASH. I was with Gary.

Dr. Parameswaran Hari – I had seen. I remember about that. Yeah. Pleased to meet you too. I have heard a lot about you.

Pat Killingsworth – Thank you and I was… I had the pleasure to sit next to somebody else you might know, Dr. Michael Thompson from down in your neck of the woods.

Dr. Parameswaran Hari – Oh, yeah. Of course, yeah, yeah.

Pat Killingsworth – And we started talking about total therapy a little bit. When I… I was diagnosed in 2007 and total therapy was still sort of a mystical. University of Arkansas Medical Center thing that, you know, there wasn't a lot of data supporting it outside of Arkansas and it was never presented to me as any kind of option, I started at the Mayo Clinic. But now almost eight years out, I am in my third relapse and Pomalidomide is working for me, thank goodness, but I am…, you know, I am constantly medicated and starting to run out of options and I have good friends like Gary right here on the line and a dozen others who are drug free, 3, 4, or 5, 6 years out from their total therapy experience. They are all low-risk patients as was I at the time and I am starting to think with the emphasis on heavily hitting myeloma hard upfront, and now as more data possibly supporting total therapy that it might be an option that a newly diagnosed patient should explore. And I guess I just wondered when I was talking to Dr. Thompson, the reason I brought that up is he mentioned selection bias, the fact that only certain patients can make it to Arkansas in order to be treated, and…, but you know, that just seems… At this point, that just seems to ring a little Harvard at me and I am not a… You know, I don't know if Arkansas bias or total therapy bias, but as an outsider looking in, I just can't believe its only selection bias, that they are allowing all of my friends to be running around, having practically normal lives without using maintenance therapy at this point in their life. Could you… Could you comment about that and if you agree with that its the selection bias thing, I mean I want your honest opinion. I am not trying to color your answer, but I…

Dr. Parameswaran Hari – Sure, yeah. Yeah.

Pat Killingsworth – Go ahead, I am sorry.

Dr. Parameswaran Hari – Yeah. No, no, no. Absolutely. I see the question. So, let me… So, to put things in perspective, you know, total therapy went through like three or four versions. It was total therapy 1, 2, 3, and then total therapy light and there's this couple different versions of total therapy going on, all of them have been tested exclusively at Arkansas, University of Arkansas Medical Center under Dr. Barlogie, and he has reported outstanding survival in patients who went through that program. That's for sure. There is no question about that and so, what Dr. Thompson and others would tell you about total therapy is that it has never been studied in a randomized fashion. So, the gold standard of medical, you know, when we… So, the reason why total therapy is not adopted from Arkansas to other centers like Mayo and these other centers that you mentioned is because it has never been studied in a randomized fashion. So, why do we know that carfilzomib-Rev-dex is truly better than Revlimid-dex? Because we had… You know, if we had a 100 patients and that we had almost 700 patients in that study, one person got carfilzomib-Rev-dex, the other person got Revlimid-dex and it was randomized. So, you could predict who was going to get what and at the end of the study you looked at all the people who got carfilzomib-Rev-dex and the people who got Rev-dex and then you looked how many high-risk people were there, how many people had 17p deletion, how many people had… What were their ages, were they comparable, so the two groups were comparabale and then the people… So, between two comparable groups that had identical myeloma, broadly one group had carfilzomib-Rev-dex, the other group had Rev-dex only and the people who got those three drugs lived longer or had a longer progression-free survival. So, we now…, you know, that's a scientific method. You have to do a randomized study. So, the reason why total therapy is not more popular is because it was never done in a randomized fashion where half the people got total therapy and the other half got, say, less therapy such as like, you know, induction, transplant, just maintenance. So, we don't know if total therapy is better than anybody, anything else that we do. So, we know, we… Everyone… You know, I

have people who are 20 years out, doing great; people who are 10 years out and have never, you know, had any treatment after six months. So, this, you know, every center has that, but do we know this is because my treatment is better than total therapy or total therapy is better than my treatment? We don't know that. So, unless we do a randomized study, we cannot say that for sure, but it is clear that…

Pat Killingsworth – Doctor, are there any… Isn't that something that should be done? Do you know of any ongoing or has it even been started and if not, why not? It seems like a logical thing to do.

Gary Petersen – Excellent! Excellent question.

Dr. Parameswaran Hari – Right. So, the thing is, you know, we would.. So, the other people who wouldn't, you know, so… So, total therapy as it is practiced in Arkansas involves a lot of cumulative chemotherapy and a lot of chemotherapy, multiple transplants, all that. And most of us believe that we are able to mimic the same treatments, you know. So, what has happened? So, which part of total therapy has the rest of the world adopted? We have adopted the approach of strong induction, transplants, post transplant treatment, maintenance because in total therapy 1 did not have maintenance. Total therapy 2 had thalidomide maintenance versus no maintenance, so its randomization at that point and then total therapy 3 I believe had Velcade-based maintenance and even the total therapies that are being used now have some form of additional treatment after you get transplanted. So, we have all adopted from that. Dr. Barlogie taught us that if you are going to treat myeloma, you need continuous treatment for a long period of time and till, you know, so…This everyone else has taken off, you know, So the largest study that was done here nationally across the country was initial treatment, one transplant followed by Revlimid maintenance versus two transplants followed by Revlimid maintenance versus one transplant followed by consolidation with Velcade-Revlimid-dexamethasone followed by maintenance. That is the type of total therapy that we do. We don't use, you know, more chemotherapy like, you know, so the people who are getting treatment in Arkansas get more chemo treatments.

Pat Killingsworth – Sure. They are getting VDT PACE

Dr. Parameswaran Hari – VDT-PACE and things like that.

Pat Killingsworth – Probably something that they found in the back of some storeroom they are tossing that into. And the tandem transplant… It drives me nuts too, the tandem transplants. I know the date is not good for tandem models, but in the context of total therapy, all of a sudden tandems start to look a lot better. So, once again…

Dr. Parameswaran Hari – No, don't write off tandem transplants.

Pat Killingsworth – It would be nice to compare total therapy in its…

Dr. Parameswaran Hari – Well, everybody is moving away from chemo, Pat. That's what's happening. So, you know, VDT-PACE is kind of a treatment of last resort for the rest of the world and that's what's happening. So, I use VDT-PACE probably two or three times a month. That's almost always in people who have extremely high-risk myeloma that is not responding to anything else or people have something like plasma cell leukemia where they have really high-risk myeloma.

Pat Killingsworth – Doctor, I get it. I understand exactly what you are saying and I think a lot of our listeners do too that I get hammered constantly and I am, you know…

Dr. Parameswaran Hari – No, I am not saying total therapy is bad.

Pat Killingsworth – About the total therapy thing, it would just be nice to know.

Dr. Parameswaran Hari – Yeah, absolutely. Total therapy is definitely, the people who took total therapy,

you know, did not have anything to lose and they didn't lose anything by taking it. They had outstanding results and like I said, as a single-center result, those results are unmatched. They are fantastic results, and we have all adopted from that. We have taken bits and pieces of that. We have not taken it whole, you know, en masse mainly because it was not done in a randomized fashion you know. And, you know, you have to, so, the rest of the world to buy in we have to use it in a, you know, we have to have a randomized control. So, when Dr. Thompson said it was selection bias, he meant they didn't have a randomized trial.

Pat Killingsworth – He mentioned it, he did mention the randomized part too. It was very… It was very helpful. Well, great! And I am not going to sit here and beat you up. I am not… I haven't been drinking the total therapy Kool-Aid, but it just seems like from an outside adviser that they have had some pretty good success.

Dr. Parameswaran Hari – They have had very good success. Nobody is arguing that. Yeah, exactly. Yeah.

Gary Petersen – If you look at the selection bias, I think the thing is that, you know, and I have heard it from other people too is that if you can make it to Mayo, Rochester, you know, obviously (a) you've got money and (b) you are not one of those that got diagnosed late and died in the first two months.

Dr. Parameswaran Hari – So, let me tell you in Milwaukee if you get myeloma and you cannot make it anywhere else, you know, that's the… When I started here, the patients who came here were the people who, you know, like if you had money and, you know, before the reputation builds up, people who you get are the people who don't want to go anywhere else and, you know, now I get people who can travel. I get people from other states who come here because they have the ability to travel. They have done their research. They already know a lot about the disease and they can have an informed conversation, but I also get people who live here and who don't know anything. They could be having leukemia or myeloma or whatever, they don't care. They just end up here because they are sick and then, you know, we have to take good care of them. But if you are a tertiary center situated in a far of city, almost all of the people who show up to you are people who have the ability to travel, who have heard about you, and who have made the investment to travel and be there. So, that's a… That's a little… There's a little bit of selection bias going on that way. So, you get the best of the best patients.

Pat Killingsworth – Well, doctor, keep up the great work. We appreciate what you do so much.

Gary Petersen – Pat, Dr. Hari has got the opposite of that selection bias.

Dr. Parameswaran Hari – Right.

Pat Killingsworth – Yeah. That makes the numbers even more impressive, Gary.

Gary Petersen – Yeah. So, he is… You know, he is on the other extreme, right? He gets… He gets… You're haggard searching for what…, whatever and his survival rates are some of the best in the world. You know, so go figure. And also, Dr. Hari, I believe you have for younger patients you do induction, transplant auto, then auto, then allo, and then maintenance. Right?

Dr. Parameswaran Hari – That's true. Yeah. So, that's the something that… Yeah. So, yeah. So, Pat, I think Pat has that question too. So, when are allo transplants an appropriate option for myeloma patients? So, yeah. So, our program, there is a little… You know, so what we do uniquely is we do a lot more allo transplants than most patients and that's because we believe that patients with what we call, ultra high-risk multiple myeloma, which means patients who present with kidney failure, patients who have…, and high-risk markers. People who have progression, you know, they get Velcade-Revlimid-dex and they are actually progressing on that treatment. If they have plasma cell leukemia, if they have an auto transplant, good initial treatment, auto transplant and then within a year if their myeloma has progressed, those are patients who we don't think can be saved by our current technologies, medical technologies, If we, you

know, especially when a person who is younger, meaning anybody below the age of 60, then we have been pushing up the age actually. I am doing a lot of Allos in people between 60 and 65 too nowadays. We believe an Allo transplant might be the option for them. The big problem with Allo transplants in myeloma used to be high mortality. In 1993, that was 21 years ago, there was a trial going on in the US when Allo was compared against auto and chemotherapy and the Allo arm had to be shut down because of almost prohibitive mortality. In the first month, they managed to kill 30% of patients going through it. You know, transplants have come a long way since then. Our own mortality at our center for allo transplants for myeloma is below 5%. Its very, very low. It is still higher than for auto transplants, but it is, you know, its not, you know, the 30% or 40% that people think about. That is very old numbers and even nationally the numbers have come down closer to 10% than, you know, those high numbers. At ASH, this was a, There was a, You know, So, just to put things in perspective, in the US, we hardly do about a 100 allo transplants for myeloma a year. In Europe, they do about 700. So, its seven times more popular in Europe and the number of myeloma patients are broadly similar across the two countries. So, there was a study from Germany that was presented at this time's ASH where they looked at allo transplants in patients who had high risk markers, especially those who had 13q deletion, and it suggested that after… This was very, very followup, almost eight years of followup, People who got the auto transplants followed by allo had a longer progression-free survival and it didn't matter whether they had a sibling match or if they had an unrelated donor. So, that was actually a good result for people who had high risk markers and at this time we are restricting this allo transplant approach to people who have only high risk markers or people who relapse very quickly following an auto transplant. And I think this still has an option. It is more a poor man's immune therapy right now, you know, our immune therapies in myeloma are going to get better in the next 10 to 15 years, I think, you know especially with CAR T-cells and many other technologies that are coming along, vaccination approaches. So, ultimately you have to teach your immune system to live with the myeloma or control it and that's why, you know, we all know that people who have MGUS which is very, very early myeloma or, you know, a pre-myeloma condition, they can live forever, you know. They… The vast majority don't ever go to myeloma. That's because their immune systems can keep myeloma under check. So, the allo transplant gives you a new immune system from the donor and that is why it works sometimes, but it doesn't work in everybody. We still have a lot of progress to make in that, but if we can get rid of the mortality associated with allo transplant and make it safer, more people can undergo that. That's been my philosophy in using it for especially younger people with very, very bad disease.

Pat Killingsworth – Thank you, doctor. Gary, you better get some of our other…

Gary Petersen – We are on to Jack. Yeah. Jack, you online?

Jack Aiello – – I… I am and I have a… That was fascinating, the comment about the low mortality rate with allos. Can I just ask a followup to that, though?

Dr. Parameswaran Hari – Sure.

Jack Aiello – Are these… Are these minis or fulls? Are they T cell depleted or non-T cell depleted? What makes the mortality so low?

Dr. Parameswaran Hari – So… We… So, I do either fulls or kind of in between. We don't do minis anymore. So, we did a mini study between 2002 and 2007 where we did really, really mini transplants and those patients, we had very low mortality. That's how we learned to get rid of the mortality, but then we found that relapse rates were still high and not as low as they are now. So, what we did was we amplified the conditioning regimen to somewhere in between mini and full intensity for patients who are older, and if you are really young, I do full intensity transplant. They are not T depleted because I want the T cells in them to fight the myeloma. There are two approaches – You can actually T deplete and do the transplant and then give the T cells later as what we call donor leukocytes, we don't do that. We do donor leukocytes if patients relapse after allo, but then we also use maintenance approaches to boost the immunity afterwards. So, we did a study with Revlimid and we have a new study that's being planned, which should come online nationally within the next few, actually within the next three or four months, we will have

the national study of allo for high-risk myeloma open.

Jack Aiello – Well, that's really impressive! I am… I have to adjust my comments when I talk to people about allos.

Dr. Parameswaran Hari – Right. I, believe you are an allo survivor.

Jack Aiello – I am. Yeah. So, I am really glad to hear because when I got mine back in 1998, there was a 40% mortality rate.

Dr. Parameswaran Hari – Right. Exactly. Yeah. Exactly. That has gone away and… So, did you ever relapse following the allo or…?

Gary Petersen – But it has not gone away for everybody, has it? Doctor, I am sorry. It hasn't gone away for everybody because I look at the information on, you know, be the match or one of those things that shows all the allo transplants and there are still places that are having 30% to 40% one year.

Dr. Parameswaran Hari – Yeah, but that's for leukemia and everything else, you see. So, there are…

Gary Petersen – Oh, Okay.

Dr. Parameswaran Hari – Yeah. Yeah. So, you know, its not, you know… Very few places do enough myeloma allo transplants. There is probably… I told you about 85 to 90 transplants being done for myeloma in the country, and almost all of them are at like seven or eight centers. That's it. So, everybody does, if a little bit. We happen to be one of the bigger places, yeah, for this.

Jack Aiello – So, the question I was going to ask and I will still ask is that for the last couple to three years I have heard that one day we are really going to be able to say there are eight or nine different myelomas.

Dr. Parameswaran Hari – Yes.

Jack Aiello – Ultimately, the goal is to understand what treatment works for which myeloma. And I wanted to know how, I assume you don't know what those eight or nine are now and I assume that's not by FISH or cytogenetics and high risk. I don't know if its…, we are going to find them up with respect to genomic analysis or gene expression profiling or markers that we look at flow cytometry and such. What's your guess on how we are going to be able to determine those eight or nine different myelomas?

Dr. Parameswaran Hari – So, these eight or nine different myelomas, we have a glimpse of what they are now. So, so… It is not just one thing. You are right. So, right now we just put them in two buckets – high risk and low risk and we define high risk a certain way and low risk a certain way and that's going to change over time because, you know, so what… Translocational chromosomes 4 and 14 used to be a very high risk marker, but we found out that that is an exquisitely Velcade sensitive or proteasome inhibitor-sensitive myeloma. So, patients who get this myeloma, if you get diagnosed correctly and you know that your doctor knows that you have it, they use a Velcade-based approach. They used Velcade in maintenance and those patients now tend to do just as well as patients who don't have 4;14. So, we have converted what was a high risk marker by knowing more about that marker and knowing how to treat it, we have converted them to a standard risk or an intermediate risk now. So, this is going to happen. So, this eight or nine different types of myeloma… Maybe, let's say, there are six different kinds of myeloma and we will be treating them differently.

Dr. Parameswaran Hari – So, lymphoma is a classic example. We had one lymphoma, you know, 30 years ago. Now we have 45 different kinds of lymphoma and there are subclassifications of lymphoma. So, a combination of things such as flow cytometry, the genetics of the myeloma itself, what genes are expressed, what is the driver mutation that causes it, what are the acquired abnormalities that come on top of

it? Those are the things that define each type of myeloma and that definition is going to get refined as time goes on. Right now, we would… I would broadly place people into people who have translocations which are good, such as translocation 11;14, that's one group; people who have trisomies, those people tend to be very sensitive to IMiDs like Revlimid, thalidomide, pomalidomide, that would be one group; people who have 17p deleted disease would be another group; people who have high-risk translocations like 4;14, 14;20, 14;16 would go in another group; and then people who have chromosome 1 amplifications would be another group. So, those are the, you know, some of the…, one way you can think about, but that's just a crude method and like I said, not everyone's FISH test is positive, so there are some people who are unclassifiable by that technique, so we will have to do more, you know, reliable techniques to classify these people, and that's only going to get better with time, but more importantly if we classified people rightly we can choose the right drugs for them and that is what's going to make a difference in the lives of people.

Jack Aiello – Thank you.

Gary Petersen – Thank you, Jack. Cindy, you online?

Cynthia Chmielewski – – I am here. Can you hear me?

Gary Petersen – – So nice to speak to you, Cindy. Yes.

Cynthia Chmielewski – – Okay.

Gary Petersen – – Your question.

Cynthia Chmielewski – Thank you, Dr. Hari, for everything. Its a very inviting conversation tonight. Sorry, I didn't get to meet you at ASH this year, but maybe I will next year.

Dr. Parameswaran Hari – Maybe next year. Yeah.

Cynthia Chmielewski – My question revolves around MRD. We hear… I guess that's kind of a hot topic myeloma now, and I am hearing that maybe in some of the clinical trials now we are starting to use MRD as an end point, but I am also hearing there are different ways to measure MRD.

Dr. Parameswaran Hari – Yes.

Cynthia Chmielewski – Can you explain the different ways? I have heard about flow, maybe Next-Generation sequencing, the heavy-light, I even heard MRD negative from type of imaging test and are these tests clinically available now? If they are, should I be asking my doctor to do MRD testing on me? If yes, when should it be done? If I am negative now, will I always be negative? Just the last question about MRD, so if you could just talk a little bit about that topic?

Dr. Parameswaran Hari – Sure. So, you asked a very tough question. Its a matter of debate actually. So, like I said, if you have… You know, MRD is just a way of measuring very, very low levels of disease. So when we say somebody is in a complete remission, it means that we have looked very hard to find out if they had myeloma and we found no myeloma. So, when we say somebody is MRD negative, it is basically a way of saying we looked even harder than we normally look and we found they are negative. And it stands to reason just, you know, just as people who are in complete remission tend to do better than people who do not get to a complete remission. Similarly, people who are MRD negative, they tend to do better than people who are MRD positive. So, whichever the way of looking, if you are negative by that way of looking, you tend to do better than the people who are positive. So, that's very obvious, right? There are… So, there are two different places that you look for. Number one is in the bone marrow. So, the problem… The advantage of the bone marrow is that's where the action is for the vast majority of people. So, you do a bone marrow biopsy and look for plasma cells. That is the myeloma cell, so and if you can… You know, normally if you say if you have 5% or less plasma cells, you call it a complete remission. If you are 0% plasma cells, you call it

a stringent complete remission. So, that's, you know… So, MRD in the bone marrow is really only useful for people who are in a stringent complete remission, where you didn't find anything by your normal way of looking. Then, you know… So, in the normal way of looking, we count 500 cells and if you didn't find any plasma cells in those cells, then you say okay, I looked for 500 cells and I didn't find any. That's great! If you do MRD, the most common technique of using it which is very widely across the country is flow cytometry. That means, you take a tube of bone marrow, you put it in a liquid bone marrow, you separate out the cells, and you flow them around in a tube and there are sensors which pick up certain colors from these cells. Actually, you have to coat them with antibodies before and then you flow it in a tube and it picks up the colors. You shine a light. The reflection tells you which cells are plasma cells. So, you can flow like a 100,000 cells. You can flow a million cells across the tube very quickly, and then you can count how many plasma cells and that technique is sensitive to the tune of 1 in 10,000. So, if you have 1 plasma cell among 10,000, that's sensitive. So, you know, obviously a person cannot sit around a microscope and count 10,000 cells. So, this is more sensitive. The next technique that came along is for something called the ASO-PCR which is sensitive to the technique of about 1 in 100,000. So, its even little bit more sensitive. but it is… The problem with that technique is you are actually, you need to know what is the signature of myeloma in that particular person. So, you have to have a tissue from diagnosis, then you have to follow the person long time and its more cumbersome. It takes five or six days to do it and its individual specific. So, in each people there is a lot of work they have to do on that particular person's myeloma. So, its not widely applicable. The latest technique that came along is what we call Next-Generation sequencing and as you all know, genetics advances mean that sequencing costs have come down dramatically and so it may become the technique of the future. Its not right now the technique of the future. We can do it right now. There are companies that will do it for you for about 2,000 dollars and they promise that they will not charge the patients. So, sometimes I do send in some of my patients. Especially when we did, like, when we are trying to really cure the person or we are trying to get to nothing in their marrow. So, this is sensitive to the tune of almost one in a million cells. So, if you have a million… So, its like counting a million cells in the bone marrow and saying there was not even one plasma cell in one million cells. So, that turns out that if you are MRD negative, your chances of relapse are lower or when you relapse, you relapse…, you tend to relapse much later than people who are MRD positive. So…, but at this time we have not gone to any level of MRD at which we can say this person because he is MRD negative at Next-Generation sequencing, he is never going to relapse. We have not gone to that level. So, eventually, in the future, we might get to a level of technique where we say, okay, this person is so negative that he is not going to relapse, so he doesn't need any more treatment at this point. So, that will be one use of having an MRD. You know, we can come to a level where we can say it is so sensitive… My technique is so sensitive that people who are negative by that technique, they are not going to relapse, then that will be very useful for patients, but we are not there yet, but I am hoping that we will be there in the future.

Dr. Parameswaran Hari – The second advantage is if you do the same treatment to say 10 individuals and you find that, you know, this particular treatment gets eight of those people MRD negative, another treatment would in a similar group of people, another treatment gets only four of these people MRD negative, you can compare treatments. You can say which treatment is going to get you more MRD-negative patients, that is a surrogate for long-term benefit. So, that's why all of the clinical trials now, they have to have MRD done. Otherwise, you know, we don't, you know, we say how many people did you really get MRD negative? That means, you know, you have an early signal as to which treatment is going to be long term more effective.

Dr. Parameswaran Hari – But, there people who argue that MRD is not all that it is touted up to be, and this is the reason for that, you know, so we know that you can live with myeloma, right? If you have… There are many people who never get into a complete remission, so then they don't even… The question of MRD doesn't even arise in them. They have a little bit of M protein left after all the treatment they had, but then and they are also going to have a 10-year remission or an 8-year remission or even never come out of relapse. They are almost going back into a smoldering myeloma state. Its as if their immune system is actually taking care of that little myeloma that is left behind. So, if you are going to live with that little myeloma, you don't even need to get into a complete remission. So, the people who are, you know, who are saying, okay, MRD is a hype. It is not all that's hyped up to be, but it is true that you can actually be okay even if you have MRD positivity. So, I wouldn't rush into judgment on MRD. Eventually if you are going to

cure everybody with myeloma, we need to have treatments that will give us MRD negative. So, that is the ultimate test of getting rid of every single myeloma cell in the person's body. That will be proven by MRD only, but it is not necessary to be MRD negative in every person for them to have a long life. I hope that's….

Gary Petersen – – Fantastic! Thank you so much.

Cynthia Chmielewski – – That sounds good. Just one followup question.

Gary Petersen – – We need to… Yeah. We are over right now, Cindy, if…

Cynthia Chmielewski – -Okay. No problem.

Dr. Parameswaran Hari – Yeah. You can email me if you have a question.

Cynthia Chmielewski – – Okay, I will email you.

Gary Petersen – – I was going to ask Dr. Hari, if you had a few extra minutes…

Dr. Parameswaran Hari – Sure.

Gary Petersen – …to take calls from our viewers, that would be great.

Dr. Parameswaran Hari – I do. Yeah. Yeah.

Gary Petersen – Okay and, Cindy, did you still want to ask that question?

Cynthia Chmielewski – – Well, if you have a caller…, calls coming in, go ahead and answer the calls.

Gary Petersen – Okay and if there is time left over, we will..we will have you come back in. All right. Priya, could… You call for some callers?

Priya Menon – Ah, yes. Callers, if you have a question for Dr. Hari, please press one on your keypads and we can bring you live on air to ask your question. Dr. Hari, we had received some submitted questions and there is just one which came by email right now. It says can you seek any new information about genomic profiling progress reported at the ASH?

Dr. Parameswaran Hari – Ahh… So, genomic profiling… I did not actually see a lot more of genomic profiling. There is a group, The Multiple Myeloma Research Foundation has a genomic profiling approach known as CoMMpass program and they did report some of the mutations that are important for patients with multiple myeloma. This was actually started a while ago and they have already had some high-profile publications. So, at this time, you know, we don't have any actionable items from that, but you know, the interim analysis for that study was actually, you know, presented at ASH. That was the only thing and I think it was presented last year. I don't remember anything from this year, but there are some mutations like NRAS, KRAS, BRAF mutations that were found in myeloma patients and especially the recurrent fusion gene that was very significant was the classic 4;14 translocation gene. So, that was another finding, but I am sorry. I don't remember anything that was like actionable intelligence from there, unfortunately. Maybe its just me, you know its such a big meeting, you don't get to everything sometimes.

Priya Menon – Yes. We have another question asking consolidation of the auto stem cell transplant is showing promise for patients of all risk levels. The data is often for newly diagnosed patients. What is the data and the experience indicating for previously treated patients, that is, patients who delayed the auto transplants and had consolidation with it?

Dr. Parameswaran Hari – So, it is… The question is if patients had auto transplant after prior treatment and,

you know, then they relapse, what are the data. Right?

Priya Menon – Yeah.

Dr. Parameswaran Hari – Okay. So, these are patients who have delayed transplants or, you know, so there are two ways in which you can have an auto transplant at relapse. One is, you never had an auto transplant upfront. You had initial chemotherapy, induction treatment and you were going along and then you relapsed at some point and then you are having an auto transplant at that point. So, it turns out that auto transplants are equally effective at that stage. In fact, overall survival data would indicate that early transplant versus late transplant has similar outcomes overall for the patient. Unfortunately, the most recent study that came out was Dr. Palumbo's study from Italy where the approach was initial transplant in half the patients and the other half the plan was to do a delayed transplant, but only about two-thirds of the patients who were planning to have a delayed transplant actually ended up getting a transplant. So, that was one problem. So, if you think your transplant is going to be happening later on in life, you know, two or three years into the disease, sometimes you don't even get to it because of something else happening, you know, life happens. You know, you may get a complication, you may get some other illness which precludes transplantation, so people didn't get it and then in this particular study though, the people who got early transplant actually did better. So, there is some advantage that if you are able to have a transplant, current data suggests that you should try to do it sooner and that is also my personal bias; however, if you are able to get a second transplant later, you know, the data are that you tend to have a good long overall survival, and the other group who gets a delayed transplant are the people who had an auto transplant at the beginning, then they relapsed later on, so then you do a second auto transplant at relapse. For that group, we call that a salvage second transplant and there is a lot of interest in doing this now. Many people believe that when people relapse, we should approach it as we approach initial disease, newly diagnosed disease so you get good induction treatment at relapse, you get them into a good remission and do a transplant and do different drugs as maintenance. And that is going to be tested in randomized trials very soon. We had several meetings about this within the last six months or so and I think we will have some trials going on about that. So, I think there is some value to using a transplant-based approach especially in people who had benefited from a transplant upfront.

Priya Menon – Thank you, Dr. Hari. Cindy, I think we can just squeeze in your question and then wind up for today.

Cynthia Chmielewski – – Okay. Umm… My question was just to ask with the MRD again. I was talking to I guess one of the companies that do MRD testing, Sequenta. They do the ClonoSIGHT testing and they were mentioning something that their test is a two-part test. In the first part of the test, they need to have a sample of your bone tissues from initial diagnosis. Could you explain something about that?

Dr. Parameswaran Hari – Correct.

Cynthia Chmielewski – And are there samples like… When my sample since I was diagnosed seven or six years ago will be kept somewhere that they could access it, but could you explain what that means?

Dr. Parameswaran Hari – Yeah. So, there is… So, the… So, what you say is very true. So, when you do a genetic test, your myeloma has a particular genetic signature. Okay? So, the genetic signature of your myeloma is unique to you as a patient. So, if they are going to do… If you are going to look at a million cells' DNA and find out that signature, then that's when they call you MRD positive. So, they need to know what the signature is. So, they need tissue from when you had myeloma for sure. If you are in a complete remission right now and you are, you know, if you are truly MRD negative, they don't know what to look for. So, it is for them to figure out what to look for. So, many a time, you know, the lab which did your original bone marrow biopsy will have some tissue left behind from that. You know, they can even do it off the slides that you have, you know. The good hing about DNA is, you know, they can test for small amounts even in very little tissue. You know, they can do it from mummies in Egypt, right? So, they can, you know…, they can take little bit of blood or tissue is all you need. So, if you have a bone marrow slide from when you

were diagnosed, you have a little paraffin block from when you were diagnosed, that should be enough. The other option is to, you know, if you have any time you relapse or something, you send them that tissue whenever you get that tissue. When you have known myeloma, you send the tissue to them and then they have that signature which they can follow for ever.

Cynthia Chmielewski – Okay. Thank you so much.

Priya Menon – Thank you, Dr. Hari. I think that was a whole lot of information that you shared with us today. And it was absolutely great listening to you. Thank you very much for your time. Gary, Pat, Cindy, and Jack, thank you all. The link for today's broadcast will be shared with all our participants. Please visit curetalk.com to register for upcoming shows. Until then, thank you.

Dr. Parameswaran Hari – Thank you very much. Bye, bye.

Gary Petersen – Thank you. Thank you so much, Dr. Hari. Remarkable job.

Dr. Parameswaran Hari – Yeah. Thanks, Priya. Thanks, everybody. Bye, bye.