Pats Myeloma Beach Party Invite and Interview w/ Dr. Noopur Raje

Its time for Pats Myeloma Beach Party! Hundreds of myeloma patients and caregivers will join Pat Killingsworth this year on Fernandina Beach, Friday afternoon and evening, March 20th, all day on Saturday, March 21st and Sunday for a farewell program and brunch. Dr. Noopur Raje will be at the party this year and talk to the myeloma crowd. Tune in to hear more details on various activities at the party learn more about the Myeloma Crowd Care Foundation, that are dedicated to donating 100% of the money that they raise through crowd funding to sponsor a pair of important, underfunded clinical trials; one to help smoldering myeloma patients and the other to help late stage patients live longer.

Full Transcript:

Priya Menon : – Good evening, everyone. Hello and welcome to Cure Talk. I am Priya Menon, Scientific Media Editor at Cure Talk, joining you from India; and I welcome all of you this evening to a discussion on myeloma. This is our 81st episode, and we have with us our myeloma cure panelists, Pat Killingsworth and Gary Petersen. Joining Pat and Gary on the panel is Jennifer Ohlstrom of Myeloma Crowd. Welcome to the show, everyone. Our myeloma expert on the show is Dr. Noopur Raje. Dr. Raje is Associate Professor of Medicine at Harvard Medical School and the Director of the Multiple Myeloma Program, Medical Oncology, at Massachusetts General Hospital. Hundreds of myeloma patients and caregivers will be joining Pat Killingsworth this year on Fernandina Beach for Pat's Myeloma Beach Party from Friday afternoon on March 20th, all day on Saturday, March 21st, and Sunday. We are going to hear more about Pat's Myeloma Beach Party and the various activities of the party, about Myeloma Crowd Foundation's initiative, and lots about myeloma research. With that, I will now hand over to Pat. Pat, you are on air.

Pat Killingsworth : – Thank you, Priya, and thanks everybody for joining us. I thought we have got to take advantage of having Dr. Raje on the program to ask her some myeloma-related questions, so I figured we would open that way and then do some of the shameless self-promotion toward the end of the broadcast. You know when I started this…, this event, it was just supposed to be a party, but last year we had people come from nine states. We had it in Tampa, I think. We had 65 or so people there and lot of them had a lot of questions and, and I thought if somebody is going to take the time and spend the money to come so far, we should…, we should give them a show and help…, help answer those questions and so that's what, I guess, the event has gotten away from me a little bit, but that's…, that's what we have now. We have three days and some wonderful speakers and some good quality of life type of things that maybe you wouldn't get at one of these normal educational programs that …, that you can…, you can go to, so we are excited about that and I am especially excited about having Dr. Raje join us because I…, I have just always been impressed. She is both a clinician that works with patients and a researcher and she…, besides being an incredibly nice person. I first met her four or five years ago at a…, at a media event up in Boston and I have had a chance to interview her since and I have just always felt she has a good grasp both of…, of myeloma research and also I…, I guess if I was up in Boston and you had room in your schedule, doctor, I would want you to be my myeloma specialist.

Dr. Noopur Raje : – That's very sweet, Pat. I appreciate it. Very kind. Thank you.

Pat Killingsworth : – You are welcome, but let's… So much for the sweet part, let's kick this off with a tough one, right off the bat. So… I have one question and that's… I would just like you to talk a little bit. A couple weeks ago, they had…, HBO had a documentary called Killing Cancer and myeloma was featured in the first 10 minutes of the broadcast and it was the measles virus therapy out of Mayo Clinic that they are working on and they showed Stacy who is like a miracle patient. She was on her…, literally on her death bed,

and they gave her 10 million doses of, apparently of this modified measles virus and she went into almost, instantaneously went into remission and she has been in good shape ever since. I believe she may have…, she might be back on maintenance now, but I mean, my God, it's been almost two years and that's just phenomenal and so the…, you know, they have started a second round or a second cohort of patients, I believe, 14 patients. I mean it takes a… It's not easy to manufacture 10 million doses a patients, it takes…, takes some time and unfortunately I have heard from two of those patients. Two of those patients have commented on my blog, because I wrote about this, you know, how great it was that this new therapy was featured on a program on HBO and fortunately I didn't oversell the cure part and both patients said that they are in the study and neither one responded at all. Apparently, maybe five of the patients had…, had a partial response, but as far as they knew, at least none of the patients they talked to had any…, anything near the type of response that this Stacy out of Minnesota had had and I know this is all confidential type of stuff, but when it's… You know this is a…That's the danger of these days, isn't it, doctor? You have got to promote yourself to get the money and you have got to make a big deal out of…, out of, you know, when you get some good results, but it can come around and bite you in the butt and I think maybe some of these patients had unrealistic expectations going into their…, their trial based on the results that were publicized…, that Mayo Clinic publicized, so I just wondered if you could talk a little bit about maybe that part of the whole thing but first explain how this works and why it might not work for everybody.

Dr. Noopur Raje : Sure. Now that's a great question, Pat, and I… You know, at the outset, obviously there is a lot of excitement with whatever is going on with myeloma. Every week we have something new. You have heard about the ENDEAVOR results this week. We heard about panobinostat last week. So, every week something new comes up. Remember this oncolytic therapy, viral therapy using the measles virus is still in an investigational stage and, you know, one has to tease out the media hype from reality. Certainly, a couple of patients have done really well and Mayo highlighted those in a report which they published in their journal, obviously not fully detailed, but remember when we use these therapies, these are therapies, cellular therapies, and if you think about the concept of this, Pat, and I am… You know, it's hard to say whether this is the way we should be treating everybody or not, but the concept is actually novel. It makes a lot of sense because what you are doing here is viruses typically infect cells in people's bodies and destroy those cells and what Dr. Russell's group is doing out here from the Mayo Clinic is using the measles virus to, in fact, infect myeloma cells and thereby kill these myeloma cells and obviously a process such as this, a cellular therapy such as this, takes a lot and a lot and a lot of work. So, it's fortunate that we have seen partial responses. It's great that we have seen a couple of people who had very good responses as well, but there…, you know, this is something which is not going to work in everybody and that's something for all of us to understand and the reason this will not work in everybody is, you know, what Dr. Russell's group from the Mayo Clinic is doing is using the measles virus, adding a gene to that measles virus, infecting that measles virus, infecting the myeloma cells with the measles virus. Now remember, all of us are exposed to measles. All of us develop antibodies to measles and folks who have high antibody titers to the measles virus, this kind of an approach is not necessarily going to work. So, Mayo, I do know, will be looking at other alternatives also. So, it's not as if every patient is going to respond to this. You have to make sure that you do not have a big antibody burden and then you also have to make sure that whatever virus you are creating with that genetic modulation is able to infect the cells that you want to and in our case, obviously, the enemy cell is the myeloma cell here. So, I think all of these things play into it and, you know, certainly it's…, it's exciting in that it's a new approach, but I will caution everybody it's not end all and I think we are early in understanding of how this kind of an oncolytic viral therapy will, in fact, work and where in the continuum of myeloma will it be incorporated. So, I think we have to think about all of those things, Pat.

Pat Killingsworth : – Sure and I…, and I…, it…, it reminds me and you are right about the lot of work part because I was formerly a Mayo Clinic, Rochester, patient and…, and got to know some of the staff and the team up there and Dr. Dispenzieri, I remember, was originally working on this. She handed it off, I believe, in frustration and obviously the key was the dosing, you know, who would ever think you would have massive dosing like this in order to get the effect that you…, that you are looking for and I just… As a matter of fact, a member of…, of our support group or a neighboring support group was in a trial about 40 years ago and…, and passed away, you know. It didn't work and I think at the time they weren't using anywhere near as much, you know, the dosing was much, much lower and maybe that's the key, but think

about… I know, it just boggles my mind thinking about all of the variables. How do you get the right dosing, I mean, when you are talking about possibly millions of doses, the…, there is an infinite, you know, what might be a good dose for somebody might not be a good dose for somebody else, right, doctor?

Dr. Noopur Raje : – That's…, that's exactly right, you know, and that's part of the reason why clinical trials are so, so important. So, what is being done is it's being studied in the context of a clinical trial. When we talk about millions of… It's millions of, you know, the dose of viral load has to be in millions, Pat. So, that's something, you know, as with any drug, this is a little more difficult because this is more designer specific, but even with the drug, when we first start out, we start out with a very low dose and then we keep upping the dose to figure out what the optimal dose level is. So, this is kind of similar to that and they have to reach to these dose levels where they ended up with responses in a couple of people and then when they have opened it up to a broader group of people, they have obviously not seen the same results. So, we have to go back to the drawing board and see what is wrong. Is this an antibody issue? Is it ability of this virus to infect the myeloma cells in this case? So, all of these different factors, which might play into how people respond, have to be taken into account and that's why I really think, you know, we all have to take a step back, appreciate the good results but wait for the signs to kind of dictate itself and kind of educate us along the way and, you know, certainly hopeful but I don't think everybody… It's not the end-all answer for everybody, Pat, and that's something which is very important for all of us to understand.

Pat Killingsworth : Sure and there would probably…, probably never…, never be one fits-all therapy, I am guessing, but, yeah, it's great, it's amazing what you are all doing to…, to try to help keep us alive, I know. I appreciate it and…, and speaking of great, we have Gary Petersen with us. So, Gary, how about….. How about asking Dr. Raje a few questions? (Pause) Or, is Gary… Gary, are you there?

Gary Petersen : – Pat, can you hear me?

Pat Killingsworth : – I can hear you now.

Gary Petersen : – Okay. Great! Having met you once, doctor, I can say that with you we certainly have a great resource for multiple myeloma. I consider you part of the young guns of multiple myeloma.

Dr. Noopur Raje : – (Laughter) I appreciate you saying that, Gary. Thank you.

Gary Petersen : – Okay. There's you and there's Dr. Ghobrial and a number of the people on our scientific board that I just am totally just humbled just to be considered in the same group as you guys. You guys are… Like I said, there is all those…, like Dr. Kyle and all the folks that came before you, but then there's this whole new group of highly skilled, ultimately intelligent, and…, and…, and energetic individuals that are part of this and you are definitely one of those. So, thank you so much for your participation.

Pat Killingsworth : I think we are… I think we are embarrassing her probably.

Dr. Noopur Raje : – Ha ha ha. I think…

Gary Petersen : – No. I hope… I hope, but it's all true.

Dr. Noopur Raje : – No, now we need to live up to all of these words, Pat.

Gary Petersen : – This party and multiple myeloma walk are both part of a program to educate patients, raise awareness, and help to fund research and you are, like I said, one of the remarkably skilled new guns, young gun in the myeloma profession with more than a full plate. I mean you can keep yourself busy all the time without adding anything new to your plate. So, why did you choose to be part of this new Multiple Myeloma Crowd Funding Initiative?

Dr. Noopur Raje : – So, you know, what was very striking to me, Gary, about the Myeloma Crowd

Research Funding Initiative was…, you know, this is a novel way of doing research, raising money for research and really incorporating not just the research expertise and the academic expertise but mostly, you know, in… It's a nice collaboration between the myeloma specialists and patients and getting a patient perspective on to this whole what should be funded, what should not be funded, because sometimes when we are doing our research, we kind of, you know, can get lost and I think all of us are doing this for one very simple reason. We want to make this better for myeloma patients the world over. We want people to live longer and we want to cure patients and so getting that patient perspective piece into this Myeloma Crowd Research Initiative was actually critical. When Jenny called me and asked me if I would be willing to be a part of this, I told her, "Oh, God! Jenny, this is going to be an honor for me,"because ultimately, you know, whatever I do, even the work we do in the lab, Gary, I think are central. At least my central focus has always been, is this going to be helpful to my patients and if the answer is yes, it's a no brainer, right? You have to do it. So, you know, that's what helps guide what we do with research and, you know, getting this initiative in place was just a very cutting edge, new way of thinking about research, new way of thinking about raising funds for research, and new way of having kind of a peer review process where initially you are doing a scientific review and then you are presenting it to the larger myeloma community, which includes patient advocacy as well to really understand and make sure that we are spending money in a worthwhile direction.

Gary Petersen : – Well, thank you so much, doctor. One of the things I see is like, most drug companies have to get a return on their investments and, of course, they have to please their shareholders, me being one of them. So, generally, a drug has to have a huge payback to obtain funding and I believe most funding comes from large drug companies. Does this Myeloma Crowd Initiative, Research Initiative, hold prominence for older drugs, non-drugs, and those with a poor financial payback which may be the cure to make it to clinical trial?

Dr. Noopur Raje : – Oh, absolutely! I think you have hit the nail on the head here and, you know, part of the reason to do this, Gary, is, you know, I don't think anybody is in this for what are the returns here, what are the profits, what is the business plan. That's not what we are talking about here. I think what this is going to allow us to do is good science, which is bedded science by the research community, by expertise in the field, and by patients as well and really the end of the day is, you know, whether we use it to develop older drugs or whether we use it to understand or do science in a more, you know, in a better fashion because, you know, funding is a problem right now and certainly big pharma can fund their big clinical trials, but they don't necessarily fund the right science to back those clinical trials. The other thing is there may be a lot of stuff we might want to do which is very scientifically driven but not necessarily in the best interest of a pharmaceutical company for example, and that's the kind of research which I think will happen through this kind of an initiative, which is the Myeloma Crowd Research Initiative, I think. So, you know, I am honestly looking forward to how this all pans out. I do hope we are able to fund and do really, you know, ground breaking and kind of transformative research, so to speak, which can really impact patient care in the next couple years or so.

Gary Petersen : – Yeah. That's my hope as well. So, you… You…, you have helped me confirm that in my own mind. Pat, did you want to have somebody else ask a couple questions and certainly I have got more, you know.

Pat Killingsworth : Sure. Sure. Let's… Let's hear from…, let's hear from Jenny.

Jennifer Ahlstrom : – Oh, hi, everyone!

Pat Killingsworth : – Hi, Jenny!

Gary Petersen : – Hi, Jenny!

Jennifer Ahlstrom : – Hi! My question for you is more of precision meeting. So, in the last few weeks, the White House held a very large precision medicine and announced a meeting and announced the large initiative that they wanted to fund precision medicine and I know based on research that you have done,

some people may…, may or may not know what that is, but I guess you can explain that and I know you have been working on, like, targeting BRAF and things like that… As we look for… So, I guess, first my question is what's the relevance of that to you and your research and in the world of myeloma and then the second question would be to relate it back to what we selected as for this Myeloma Crowd Research Initiative, when we asked you and the other doctors that are involved, what's the most critical thing to go after, most of you just emphatically said go after high-risk myeloma and when I first started doing the interview, similar to this Cure Panel interview, about a year and a half ago, I would ask people about the testing for these high-risk features or specific genetic features like BRAF and NRAS and KRAS and people said, well, you can test for them, but really it's not going to make a difference in your treatment and based on what you are doing, based on what other people are doing and now we are seeing proposals come in, specifically for high-risk features, it's really important for patients to know what type of myeloma they have. Is it not?

Dr. Noopur Raje : – No… Absolutely! I think it's critically important for people to know. It's critically important for us to look because unless we look and see what those genetic mutations are, we are not going to know that they even exist and then we are not able to get to the next level of whether or not we should be targeting this. So, as of right now, I am going to tackle your questions two fold, Jenny. Your first question was on precision medicine, I think. You know, we in the myeloma world are a little bit behind the rest of solid tumor oncology in terms of precision medicine and the reason for that is very simple. It's simple because it's not that we don't understand the genetics of myelomas much. It's because myeloma tends to be a very genetically complex disease. It's not as if it has a single genetic mutation which is driving myeloma. We have now done whole genome sequencing on multiple myeloma patients and, you know, we found lots of different genetic abnormalities and there's not one single driver mutation which is dictating what happens to myeloma and just a, you know, simple example for folks to understand would be, you know, when you have CML for example, that is chronic myelogenous leukemia, you have the BCR-ABL kinase gene which is affected. You have that impacted and once you target that, you are going to see long-term survival. Well, that's not true in myeloma. What we have seen in myeloma is, you know, the incidence of some of these targetable mutations is quite low. So, we, at least at our institution, will do bone marrows even at the time when the disease comes back and I think that's critically important to do that bone marrow and, you know, there are a lot of kind of molecular testing platforms now available to do those on these marrows and these are platforms which will allow you to test for genetic mutations. We at Matt General use what we refer to as the SNaPshot analysis, you know, throughout the rest of the country there's the foundation medicine platform available as well. There are other platforms which are being developed like, I know at the Dana-Farber they are developing the OncoPanel. So, you know, as long as it's done, as long as we can figure out what that signature of your myeloma is at that time, it's really useful.

Dr. Noopur Raje : – We have actually gone ahead and, as you pointed out, done a trial which is very different from how you think about trials for multiple myeloma. Specifically, you know, most of the trials that you hear about, think about, are for either newly diagnosed or relapsed refractory myelomas and it's all multiple myeloma patients. What we are now doing and what I have been fortunate to be a part of is what's called a basket trial. Now, this basket trial included all kinds of tumor types and the only unifying piece here was the BRAF mutation. Now, based on our whole genome sequencing studies, we know that in myeloma the incidence of BRAF mutation is about 4% to 6%. So, if you test a 100 people, you are going to find 4 or 6 out of those 100 who are going to have this mutation. Now, if you have that mutation, there almost always tends to be a driver mutation and we then can use a single agent like vemurafenib which is a BRAF inhibitor, which in the myeloma world is not, you know, most of our folks who have myeloma have not heard of what vemurafenib is, but I have certainly had patients who have been treated with vemurafenib and as a single agent have had nice responses and we are going forward doing a larger study. We have looked at other mutations, Jenny, and those include things like KRAS and NRAS mutation and these KRAS and NRAS mutations have, you know, they are present in a higher proportion of patients, seen in about 20% of people and we hope to have targets going forward and those clinical trials are just in the stages of being developed as we speak, where we would like to use drugs like MEK inhibitors, which is what these KRAS, NRAS mutations kind of signal through. So, I think our understanding of the genetic platform or the genetic mutations in myeloma is going to be critically important. Having said that, I do want everybody

to remember is once you have the BRAF mutation does not mean that the BRAF inhibitor is the answer to all of this because myeloma unfortunately is really smart and it tends to keep outsmarting us. So, your BRAF inhibitor is able to control your myeloma for a little while and then as is typical of most myelomas, the disease comes back again with a different clone which takes on significance. So, I think testing all of these at different stages of when the disease comes back is incredibly important and going forward, the way science is moving, our hope is that we will…, understanding first these mutations is going to be relevant and then finding the right target for this mutation is going to also be critically important and that's how, you know, we at the NCI, which is the National Cancer Institute's Steering Committee are trying to create platforms where we can then treat patients based on just genetic abnormalities. So, that's where we are with kind of precision medicine. We are still where in, I would say, not infancy stages, but I am happy to say at least that we are moving forward in the right direction and over the next few years we will learn more and be able to do more.

Dr. Noopur Raje : – As far as high risk is concerned, you know, the definition of high risk changes. Now when we think about conventional definition of high risks, when you talk about BRAF and some of these other mutations, they don't necessarily categorize into high risk. When we are thinking about high risk, we are thinking about the true, true conventional, you know, FISH parameters where we are looking at deletion 17 for example, the (14;16) translocation for example. Those are kind of considered the high-risk features because as of right now, although these patients do way better than they did several years back when we didn't have all of the treatments we have today, they are not doing as well as, you know, we would like myeloma patients to survive for years and years and years and that's not necessarily happening in this subset of patients and that's why when you asked us the question is, where is the unmet need, you know, we go round and I go round the country, the world, talking about how great things are with myeloma and how much we have learned and how much better we are getting, but there is a subset of myeloma patients who don't do well and I think it's really critical that we identify what that subset of patients is and how can we use treatment strategies to kind of overcome those high-risk features. So, that's kind of slightly different from precision medicine and that's where we really need to focus our attention. It's a much smaller group of patients and that's why when you look at clinical trials, Jenny, you are not going to find people just focusing on high-risk population because they are very hard to accrue to. There's about 20% or 30% of people and, you know, it's hard to get everybody on to that one trial, but I think that's where again working collaboratively, working together, educating patients, educating the clinicians who take care of these patients, if there are options for these folks and kind of studying them in a consorted fashion is going to allow us to make some progress going forward.

Jennifer Ahlstrom : – Thank you so much for answering as always. It's a great way to answer those questions.

Pat Killingsworth : Thanks, Jenny. I… You know, Priya, I would like to… Are there any listeners that would like to ask a question?

Priya Menon : – We have quite a few listeners, Pat. If you really have a question for our panel, you can please press 1 on your keypad and we can bring you on air to ask your question live or if you want to send it…. Yes, we have… Yeah. We have a caller on line, Pat.

Pat Killingsworth : This might be a record, Priya, be halfway through the show and be taking…, taking calls.

Priya Menon : – Person calling in from…(503) 727-5303, you are on air. Please ask your question.

Caller : – Yes, doctor. Thank you very much for your presentation. Over the last week, there was some information release regarding a head-to-head battle between high-dose Kyprolis versus Velcade, but it tended to… I think it had to do with relapsed only and as you can read on the Myeloma Beacon, it seems like there were some issues with respect to the trial arguably for example, whether patients have been previously treated with Velcade or Kyprolis in the past and whether they had an effect on the ultimate efficacy of the test. Question for you, do you see this affecting front line treatment for those of us that just

started CyBorD for example, we are obviously focused on Kyprolis versus Velcade.

Dr. Noopur Raje : – Sure. So, you know, obviously the ENDEAVOR study, which is what you are referring to, was a very positive study suggesting nearly doubling of the progression-free survival in the Kyprolis arm compared to bortezomib. You are absolutely right about pointing out that these were patients who had had prior proteasome inhibitor therapy. I don't think we have the details of the trial just as yet, but I think the important message here is, you know, and so a lot of the patients who went on to that study, for example, had previously received bortezomib and therefore, you know, the data for the bortezomib arm is going to be a little bit weaker for sure. I think end of the day whether you use bortezomib or carfilzomib, these are both good drugs. I think one or the other should certainly be a part of whatever treatment you are getting for your myeloma. As far as a head-to-head comparison, the upfront study, we are doing a study and that combination is carfilzomib-lenalidomide-dexamethasone versus bortezomib-lenalidomide-dexamethasone and that combination is being studied in ECOG trial. It's accruing as we speak. Now, whether or not that trial is going to allow us to see the differences between these two is not clear. The way to think about this though quite simplistically is, you know, you want to put a couple of drugs together. In your case, they are treating you with bortezomib and Cytoxan and that's perfectly reasonable and end of the day you have to make sure that you get into the best possible response that you can and that's going to dictate what happens going forward. So, all of these drugs are good, new drugs and which combination to use over the other is, you know, that's something we are going to learn along the way. I think over your lifetime, you are pretty much going to see each one of these drugs, whether you see them all upfront or you see them later on in the course of your disease is, you know, depends on where you get treated and so on and so forth. So, I don't think that's going to make a huge difference to be honest.

Caller : – Thank you.

Priya Menon : – Umm… I think, Pat, you can continue with the discussion.

Pat Killingsworth : They are excited to be… They are escorting a group down to your studio there in India, I guess, I don't know who had there.

Dr. Noopur Raje : – Pat, that's the Matts General and an ambulance coming into our emergency room at Matts General, which is….every 10 minutes, yeah.

Pat Killingsworth : So, I…, I was… I was kidding before that that this might be a record to have…, have…, have someone, a caller gets to ask a question halfway through because our panelists tend to like to talk as you have noticed. We don't just ask questions. We take about 5 minutes before we finally get them out. Jenny, you are pretty good at that, though. You…, you didn't…, you didn't do that so much, but, yeah, I think, you know, this is the type of thing where again to have you come down to Florida which…. and by the way, for the record, Dr. Raje is not taking advantage of this unfortunately. She is flying down and flying back in the same day, can you believe that? So, I…, I… She must love that, that Boston weather, right?

Dr. Noopur Raje : – I know. Right?

Pat Killingsworth : It takes the time to do that, that you would be exhausted. You are going to need Sunday to recover probably, but hopefully you can walk on the beach a little…, a little bit and…and stick your toes in the water.

Dr. Noopur Raje : There you go… I am looking forward to it. I…, I think it's going to be fun, exciting, and, you know, it's…, it's good to get your perspective on whatever all of us are doing and, you know, working on this collectively really makes a big difference. So, absolutely, I am…, I am looking forward to it. It will be fun, Pat.

Pat Killingsworth : Awesome and…, and we are… We are going to have some downtime, but Dr. Raje is going to be featured in a…, in a Q&A with patients, I mean, basically that's…, that's what we are going to do.

We are going to do this type of thing and Dr. Raje will be there and if you have got some questions, you can…, you can ask them up close and personal. So, Gary, you had a few more questions or I am sorry, Priya, were there any other callers that wanted to ask?

Jennifer Ahlstrom : – And… And I have a… I have a question, Pat, if you don't mind.. I didn't want to take up too much time, but, Dr. Raje, you have done work on HDAC inhibitors also and we have seen so many new announcements in the last two weeks. It's really stunning, all the FDA approvals. So, with panobinostat being approved and several of the others now coming like, you know, coming into for newly diagnosed patients, how do you as a patient…, or how do you recommend that your patient choose between combinations, let's say, you know, a panobinostat combination versus using a monoclonal antibody type of combination if somebody is in the relapsed refractory environment? The benefits, I guess, of so many new announcements is that you have more…, more tools in your arsenal, but at the same time it's a little more confusing for patients.

Dr. Noopur Raje : – Absolutely. So, really it also depends on what the relapse was, how the relapse was, and what you have in terms of a trial. Drugs like panobinostat that you just heard last week, Jenny, has gotten the FDA approval based on the PANORAMA data, PANORAMA-1 and 2, which I think is really exciting for myeloma. This is a new class of drugs, which has been approved and I have done a lot of work not with pano but with a newer version and that's called ricolinostat and we are still early in development of ricolinostat. The difference, though, is, you know, what PANo is morphed by the name as you can tell, PANo is more of a PAN HDAC inhibitor, so certainly works, certainly has high response rate, certainly improves progression-free survival, but with it being more of a PAN HDAC inhibitor, it tends to be a little more toxic as well. So, although it is approved, I think it's going to be used with some caution, with a lot of monitoring, and people need to be able to tolerate it. So, a lot of what we end up speaking for patients depends on, you know, existing comorbidies, what they can and cannot tolerate and then ultimately dose adjusting so that you are able to tolerate these drugs and do as well as you can. So, PANo is great. We aren't specifically working on this more selective HDAC6 inhibitor and what we have seen, you know, we have phase I and II studies which are ongoing as we speak and we have been able to keep people on these drugs for a long time and in general, these have been fairly well tolerated. Obviously, we will have to wait and see in phase III trials whether or not we can reproduce the…, or whether or not they will pan out in terms of efficacy. We are certainly excited. I think it's the first time that we are seeing a class of drugs which as a single agent does not have a lot of activity but again based on science, we decided to combine it with either an IMiD or a proteasome inhibitor and the data there looks really quite promising. So, that's a good thing As far as monoclonal antibodies, you know, we are very excited about monoclonal antibodies and it's not so much, you know, I know everybody worries about have I picked the right treatment or not. Ultimately, none of these monoclonal antibodies are as of yet approved. So, if there is a clinical trial which is right for you at your site, take advantage of that clinical trial. The way we see some of these drugs is, you know, they are not targeting certain genetic abnormalities, so we hope that these are risk agnostic treatments and even in high-risk disease will actually play out by targeting whatever protein that they are supposed to target.

Dr. Noopur Raje : – In general, monoclonal antibodies are quite well tolerated and we have, you know, there's excitement around three of them right now. You have elotuzumab, which you will hear the data on in late May, early June, at the ASCO meeting. Then, you have a couple of…, you have daratumumab, which has been, you know, the data on daratumumab looks amazing and very exciting and then you also have the Sanofi SAR compound, which is very close at heels. It is the same target which daratumumab targets, which is CD38. So, all of these, I think, hold a lot of promise and in the course of your disease, if you can have access to these drugs, it would be fantastic to have access to them. So, you know, work with your clinicians, work with your healthcare team at your institution and see what's available and ultimately again depending on where you are, the eligibility of those trials, you will be exposed to them and again like I was saying to the earlier speaker, whether you pick bortezomib or carfilzomib, it doesn't matter as much as of right now. You know, end of the day, you are going to have exposure to all of these and it is incumbent upon us as the research and academic community to try and get these approved as quickly as possible so that you have the choices available to you and you can actually pick and choose. We are in a happy…, happy place, Jenny. You know, it can be a tough position to be in, but I would rather be picking and choosing drugs

as opposed to saying, I have 1, 2, and 3 and that's about it. So, you know, having the luxury of choices and options as we…, as the disease keeps coming back is always a good thing. How it plays into the continuum of treatment is something which was going to evolve over time. I don't think we know whether treating upfront is the best thing, treating at relapse. End of the day, my sense is that we are always going to be using a cocktail of drugs and antibodies. It's going to be very similar to how we treated HIV in the old days and, you know, myeloma has certainly become a chronic disease in the majority of patients, not all patients, which is why we want to focus on high-risk disease, but in the majority of patients the chronic has to become even more chronic and even more chronic is, I think, the first step to curing the disease. So, I do think that all of these options we are going to hopefully get there and how we sequence them is going to be something we have to learn over the next 5, 6, 7 years going forward.

Jennifer Ahlstrom : – Well, I so appreciate having the options. I think it's really been miraculous what's been happening in myeloma and what it tells me is that I am going to get my very best care as a patient. I need to be going to a myeloma specialist who has access for these clinical trials, that knows in detail what's happening in the world of myeloma. So, to me, it's just an extra push that says, I need to be seeing a specialist.

Pat Killingsworth : Wow! You and…, you and Gary sure agree on that, Jenny, and of course…, of course, I do too. It's… Yeah. It's too much for a medical oncologist to, you know, they are not going to have enough patients to…, to justify the amount of work it takes to understand all of these different therapies and which patients which therapy might work best. So, you are absolutely… I think you are absolutely right. Gary, quickly, do you have another question and then, then, we got…, we need to…get into that shameless promotion of the event part.

Gary Petersen : – Sure… I am looking forward to your shameless promotions, by the by.

Pat Killingsworth : Were you looking forward to the event, you have just got to take the ferry across a river and bam (!) you are here.

Gary Petersen : – That's… That's the plan. So, Dr. Raje, we have some remarkable progress in low-risk disease and…, but success in high-risk myeloma, as you had noted, has escaped all the smartest minds in the world and as I understand, in most myeloma it will morph into the high-risk presentation. Yet, most clinical trials do not focus on high-risk disease. I think you mentioned before that you thought that that was a key and I think you are absolutely right. I think that if you find the cure for high-risk myeloma, you find the cure for all myeloma. Why… Why is there such a void there in…, in clinical trials and what are your thoughts about how we might be able to overcome this?

Dr. Noopur Raje : – Sure. That's a tough question to answer, Gary. I don't think necessarily that there is a void. I think the issue is how we design trials. So, what we typically will do is design a trial for all myeloma because, you know, just focusing on high risk, you don't want to forget about the patients who are going to do any well anyways because, remember, the 80% of patients, if you really give them whatever a high-risk patient is going to get, you know, that's like you said, Gary, is probably you are going to cure those patients. The other thing to remember is risk is an evolving definition. You know, in the old days, we called having deletion 13 a poor prognostic factor. We don't refer to that as a poor prognostic factor anymore. We still call deletion 17 a relatively poor prognostic factor, but we don't know what happens in the context of using, say, elotuzumab or in the context of using daratumumab. Our hope is that if we subject patients to treatment such as this in our clinical trials and are able to demonstrate an efficacy in people who we today define as high risk doing better than not getting the drug, that would allow us to then focus and hone in on this specific trial. We are actually beginning to do this already, Gary, so that there is a push to work collaboratively all academic institutions and part of the issue is numbers for high-risk disease. Right? If you just focus on high risk, you don't have as many patients and myeloma is not a common disease as you all know. You know, on an average you have 25,000 patients who are diagnosed in this country with the disease and then if you narrow it down to the 10% who have high-risk disease, at the outset you are narrowing it down to, you know, very few patients and not all patients are candidates for clinical trials. So, those kinds of limitations do

exist for all of us. Having said that, in the relapse refractory setting, we as consortiums, we as groups, come together and work on clinical trials where we put patients on these trials collaboratively and try and learn from them.

Dr. Noopur Raje : – So, there is an ECOG initiative looking at high-risk disease and, you know, the one thing to remember is we…, which is again a good thing by the way, we keep redefining risk and why do you redefine risk? You redefine risk because what was bad risk yesterday is no longer bad risk today. So, that's also an evolution and that's something which all of us need to embrace, need to understand, and that's why, you know, we need to morph our clinical trials depending on how we are defining risk. So, I think end of the day, it's important that we treat people uniformly, that means use one kind of a protocol, seek them, and then see what the impact of that treatment on standard risk, high risk, low risk and then identify by doing so are you still able to identify high-risk population or the treatment cocktail that you have has been able to overcome those high-risk features. So, those kind of studies are already happening, but again if we can focus on genetically agnostic kind of treatment strategies, I think in the long run is going to be a better feature. Going forward, you know, we have talked about different themes here. We have talked about doing more precision medicine and then talking about more kind of global risk agnostic medications and end of the day, I think the platform for trying to really control this disease for a very long time is going to be a combination of all of these, the combinations of what we already have with some of the newer drugs like the HDACs with the monoclonal antibodies and I do want to include cellular therapies in this, you know, we are making advances with cellular therapies. We started off the radio conversation talking about oncolytic therapy, but there is something else which we haven't talked about and that's CAR-T cells, which are T cells which are engineered to try and attack your myeloma. So, that would also be an approach which is going to be irrespective of what your genetic risk is and to use modalities such as this in kind of, you know, either sequentially, in continuum or collectively together, is ultimately going to get up to a point where hopefully we will not have low risk, high risk, moderate risk, but all myeloma will be kind of, you know, very treatable with a very, very long-term outcome.

Gary Petersen : – You have your own lab named after you. Congratulations on that!

Dr. Noopur Raje : – Oh, no, no, no! It's not named after me. It's my lab, that's all.

Gary Petersen : – Most people have to die to get something named after them and here you get your own lab. And as part of that, it works on the microenvironment of multiple myeloma and actually we haven't heard a bunch about that. We heard a little from Dr. Ghobrial Do you know how…, what does that hold for the…, hold… Does that hold prominence for myeloma treatment and maybe high-risk and low-risk disease?

Dr. Noopur Raje : – So, I do think it holds a lot of promise. You know, we focus…, so we do… In my lab, we do both looking at the microenvironment as well as the tumor cell and I do believe that the tumor cell is not, you know, all of these drugs which we have, drugs like the proteasome inhibitors, like the IMiD, play a very significant role in the microenvironment as well, Gary, and when I talk about the microenvironment it's everything which surrounds the myeloma cell and if you think about this conceptually, you know, sure you want to attack the myeloma cell, but you also want to take care of whatever is surrounding the myeloma cell, which is feeding the myeloma cell. So, a lot of the drugs that we have already talked about, which have been approved for myeloma, don't just work on myeloma. They do work on the microenvironment. For example, bortezomib actually has very profound bone effect as does Kyprolis or carfilzomib and the newer ones as well and going forward, you know, I think it's going to be a balance of seeing these bones or not just bone but everything targeted at the microenvironment. So, when we talk about cellular therapy, we are talking about the immune cells in the microenvironment. So, some of the monoclonal antibodies like the daratumumab and the elotuzumab how they work, sure they…, one mechanism is them killing the myeloma cell directly, but another mechanism of how they work is they interplay with the microenvironment and in this case, it's mainly the NK cells and the T cells. So, these are the ones which are then upregulated and these are the ones which then help fight your cancer. So, I do think all of these also play a role in the microenvironment. All treatment that we have for myeloma to date works on the tumor and the microenvironment. We, in my lab, had specifically, you know, my focus in the microenvironment, I have to

try and study the bone a little bit more because as you know, you know, bone disease is a huge problem in myeloma and we have made headway. There is still, you know, those clinical trials are very early right now, Gary. They are phase I trials. So, phase I trials are kind of, you know, still going through their dose escalation phases, but they are ongoing at least at not just my site but a couple of other sites as well and we just have to wait and see whether what we thought was going on in the lab really translates into what happens in people.

Dr. Noopur Raje : – I will tell you that early data we see in bones, so these are kind of bone-healing agents that we are working on and in the long term, you know, what I would foresee is most myeloma patients are treated with drugs like Zometa and pamidronate and the future was going to be, yes, you will have Zometa, pamidronate, and maybe denosumab one day, but in addition to those we'll also some of these bone anabolic agents like antibodies to activin A, which we are actively studying. We are trying to figure out whether DKK1 plays a significant role. So, these are all ongoing studies and until we are sure about which way to go forward with these, you know, that's part of the reason why you still haven't heard about them, but they are kind of not direct myeloma targets. They are trying to improve the surrounding microenvironment and ultimately in my mind, you know, if you really want to cure the disease, sure you have to target the tumor cells, but you really have to make the environment less friendly for myeloma cells to reside in and if you are able to do that, I think you are going to see long-term disease control and for those kinds of studies, we are going to have to wait years. We are not going to be able to know the data overnight, right? It's going to take a longer time for us to figure those out.

Gary Petersen : – Well, thank you so much, doctor, and, Pat, now let you get on to your…, your…, what did you call it?

Pat Killingsworth : Sure. Oh, shameless promotion.

Gary Petersen : – Shameless promotion! But, before that, I just got to say, it's just not Dr. Noopur Raje. I think from now on, she should be known as Super Duper Noopur.

Dr. Noopur Raje : – That's very sweet.

Pat Killingsworth : – Gary, stop trying to pick up our guest.

Pat Killingsworth : Doctor, that does make… That does make me think about that, is the… Should I drop the "e" or the "e" pronounced?

Dr. Noopur Raje : – Say it again, Pat.

Pat Killingsworth : – Is it… Is it Raj or Raje?

Dr. Noopur Raje : – It's Raje.

Pat Killingsworth : – All right. I didn't… I didn't want to be mispronouncing your name. Umm… I just wanted to take a moment and if anybody is thinking about coming to the event, we still have about 18 spots. There's going to be… It's… It's 20 dollars to register and that includes four meals, believe it or not, dinner on Friday night, lunch on Saturday, dinner Saturday night, and brunch on Sunday and we are only charging that fee that's sort of a skin in the game type of thing so that, you know, people, you know, if you sign up for something and there's no…, there's no money involved, you are more likely to, if something comes up, not to come, but we are using that money to actually help people that don't…, can't really afford to come, help pay some of their gas money or…, or pay for a hotel room. So, we are… These registration fees are then…, a lot of that money is going to go back to some…, some patients and caregivers that otherwise couldn't afford to come. So, if you are listening and you have been thinking, oh, I would like to come, but it's just, you

know, you have got a hotel room and they are not inexpensive, you know, it's 100 dollars a night probably to stay here, you know, it's spring break and a touristy type of area or it's too far to go or whatever, we can actually… I just did a post about that less than a week ago. You could go on my blog and…, and look and get some details, but we just… The idea is to…, is to get the online myeloma community together face to face. So many of us… Sometimes I email with people practically everyday and I just thought it would be nice for us to get to know each other. I mean it is so inspiring. It is so energizing. Last year when, you know, we…, we probably stayed too late there around the Tiki Bar on the Waterfront in Tampa, but it was… I just didn't want to leave. It was so great talking with everybody, so I am looking forward to that and this year we have the added attraction or…, or onus or benefit of having Jenny run this walk on Saturday morning and I wanted to give Jenny a chance to talk about that a little bit, if you could, Jenny.

Jennifer Ahlstrom : Oh, sure. Well, we are looking forward to the walk and then we are helping put together the dinner as well and it's been so fun working with Pat and to do this together. So, I am so glad that we are joining forces to create an event that will be an annual event and something we can look forward to every year. As we know to back up Pat, if you don't mind, and just get a little bit of perspective about what the goal was to help fund research and that's part of the work of the run will be to do that. Our hypothesis starting out was that patients need to have a seat at the table to help find a cure. After interviewing so many doctors like Dr. Raje, they are working so hard, they are doing so many good things and they need help and support. The NIH has dropped funding and it used to be the…, I don't know how many, Dr. Raje would probably know more, but maybe 1 in 8 were funded, studies were funded, or proposals were funded and now it's more like 1 in 12 and they…, they need our help and if we need a cure, I had to ask myself do I want to wait for the standard process to be able to find a cure and the answer to myself was no, I don't want to wait. So, I want to get involved and do something. So, with that hypothesis, we decided to start the Myeloma Crowd Research Initiative where we bring together some of the top researchers in the world in myeloma and combine them with a team of patients who are highly active, very well-educated myeloma patient advocates and then we went through the process to choose a target with it, which is a high-risk target, which is what some of the doctors said was the most important target to go after. So, in…, in looking at this walk, it will be working to fund this research initiative. We have several things coming up and just to give you a little transparency about our process, we called for letters of intent during the month of February. Researchers around the world from many different countries submitted proposals and the doctors of Scientific Advisory Board is now reviewing those proposals and will narrow that number down to about 10 and then we will…, we will gather more information about those proposals and involve the patient community in helping to select that, including the Patient Advisory Board. So, it's the first time that really a patient group, very well-educated patient advocacy group, has come together with just an amazing research team to help select these proposals. So, that's kind of the background. Umm… The… The walk will help do that and as you think about myeloma, where a cure will come from, I kind of think, you know, what dollar will cure myeloma. It…, it could be that it's…, it's one dollar and when you think where…, where will that money come from? Myeloma is a small patient community. A lot of times you are not feeling that great and sometimes you don't feel like you can donate, but we will be presenting some things that the myeloma patient community can do and every time someone's diagnosed, I know this happened with me and I am sure it's happened with others on the call, is that when you get diagnosed with myeloma, you have this team that surrounds you, that says, "What can I do to help you?" and it's…, it's sort of challenging because sometimes you don't want to open it up completely and say, you know, come and clean my house or whatever, but we…, just to give you a little preview, we will be putting together activities that people can do on that team, donate, of course, but of course other things that they can do to help spread awareness and to help basically fan out so we have more support in the myeloma community to help find a cure. So, as part of the beach walk, the beach walk would be a really fun event and we will be having different stations along the beach walk where there are some preview things that you can do to help spread the news about myeloma awareness, especially with it being myeloma awareness month, and then the dinner is on Saturday night, will be something I don't think you want to miss. Dr. Raje will be speaking earlier, late afternoon, and then we will be going in for the dinner and we will have entertainment as well. So, I am really, really excited about it. It will be really fun event and something I don't think you want to miss.

Pat Killingsworth : – It will be nice to get everybody together, won't it? It really will be and yeah, somebody

will be taking Dr. Raje back to the airport about the time we start dinner, I think.

Dr. Noopur Raje : – So, I'm going to miss dinner, Pat?

Pat Killingsworth : – You are going to miss…, we'll…, we'll…, we'll… You won't leave hungry, let's put it that away. We'll…, we'll get you something to eat.

Gary Petersen : – Maybe we can put a doggy bag together for her.

Dr. Noopur Raje : – There you go.

Jennifer Ahlstrom : – So, just to mention too, if…, if you can't attend Pat's myeloma beach party and you want to walk and help support research in myeloma, you can… We have an option where you can walk where you are. So, if you look at the Myeloma Crowd work site, on the upper right is a link to the beach party and one of the registration options are "just walk where you are." If you are going on a spring break and you want to get a shirt and we will send you a towel and you want to walk where you are and take photos of yourself, we will include them on the Myeloma Crowd website. So, there are lots of ways to support the event and the research initiative.

Pat Killingsworth : – So… I am blogging about that tomorrow too, Jenny. So… That was a great idea.

Gary Petersen : – And I think from our…, from the perspective of this group it's, you know, if you look at the UK, they have done an analysis and they find that only 3% of the entire population of the United Kingdom has ever heard of multiple myeloma and I doubt if we are much different than that. So, we've got a huge mountain to climb and it's these kinds of initiatives, I think, that can make the difference and we have… You know, and if you look at what we have done so far, it's that remarkable with what little they have got. We get half the funding of all other cancers, yet, you know, this group which includes Dr. Raje and all the people on this panel have come up with some great, great things. Just think if we gave them the resources that all other cancers get, just twice as much as we are getting right now, which is what other cancers get, what they could do. So, you know, I am just so excited about this possibility and just to get the word out, you know, people just don't understand. Even the LLS, the Leukemia & Lymphoma Society, doesn't even include us and we are bigger than…, than lymphoma, you know. We don't even get billing.

Dr. Noopur Raje : – I do get some funding.

Gary Petersen : – No, no. They are great.

Dr. Noopur Raje : – Yeah, not the billing. Right.

Gary Petersen : – They give the funding.

Pat Killingsworth : – Right, but they drop…, they drop you from the name.

Gary Petersen : – They don't even include us in their name. No wonder nobody has heard of us.

Pat Killingsworth : – You know, Gary, it's like a sports team. It's good to have a chip on your shoulder and a little bit of an inferiority complex. It keeps us all on our toes and working hard.

Gary Petersen : – That would… That would be me. That would be me.

Pat Killingsworth : – Priya, do we… Should we wrap it up? Do you have any more callers that have been…been waiting? We don't want to cut somebody off.

Priya Menon : – No callers, Pat, but I think we have actually exceeded our time and, Dr. Raje, thank you so

very much for being with us today and Jenny, Gary, and Pat, thanks a lot and the link for today's show we will be sharing with all our participants, which will be on Cure Talk's website by tomorrow and, Pat, I am wishing your…, your party the very best. Hope you guys have a great time. I will be waiting for pictures and, Jenny, I just really liked your "walk where you are" thing. It's very nice, it's very inclusive. I really appreciate that and we will be meeting again after Pat's party on March 26th with Dr. Bensinger where we will be talking about allo transplant. So, please visit curetalk.com for RSVP'ing for the event. Thank you, everyone. It was a great discussion.

Pat Killingsworth : – Priya! Priya, I should have… I should have mentioned…..that Cure Talk is sponsoring the beach walk and the beach party. So, thank you very much. Your organization is one of the sponsors and we really appreciate it.

Priya Menon : – That's a pleasure. Thank you, Pat. Thank you.

Dr. Noopur Raje : – Thank you. Thank you, Priya and Pat, Jenny, Gary. It was great being on…, on your talk show and I look forward to seeing you in Florida.

Pat Killingsworth : – Yeah, see you in a couple weeks.

Gary Petersen : Thank you, Super Duper Noopur.

Dr. Noopur Raje : – All righty. Bye.

Jennifer Ahlstrom : – All right. Thank you.

Gary Petersen : Bye, bye.