Myeloma Control vs. Cure with Dr. Vincent Rajkumar

Listen to one of the most brilliant myeloma specialists in the United States Dr. Vincent Rajkumar talk about Control versus Cure for Myeloma. Two different treatment philosophies – cure or control is an ongoing debate in patient care. How long can we survive on a control approach? How soon will cure become a reality? Tune in and hear all about if from the expert.

Full Transcript:

Priya : Hello everyone and welcome to the Cure Panel Talk Show on myeloma. I am Priya Menon, Scientific Media Editor at CureTalk, Cure Panel, joining you from India and I welcome all of you this evening to a discussion on multiple myeloma. This is Cure Panel's 45th episode and we have a very eminent and world-renowned expert with us today, but before I go on into the details of today's show, I would like to inform everyone who is listening that on 7th of March at 6 p.m. Eastern time, we have our next myeloma panel with Matt Goldman and we will be discussing Fundraising for Myeloma. The monthly panel in March is scheduled for 28th and our expert on the show is Dr. Robert Orlowski.

In January, we talked to Anne Quinn Young of MMRF in our panel discussion where Anne explained to us the new initiative MMRF has undertaken to aid and help myeloma research; and today, it's my pleasure and honor to welcome Dr. S. Vincent Rajkumar of Mayo Clinic to the Cure Panel Talk Show. Dr. Rajkumar, it's great to have you here with us.

Dr. Rajkumar : Thank you very much. I really appreciate it.

Priya : We have a very informed and experienced panel of patient experts supporting Dr. Rajkumar on the panel today – myeloma advocates and survivors, Pat Killingsworth, Cynthia Chmielewski, Lizzy Smith, Nick Van Dyk. My co-host for today's show is Editor of myelomasurvival.com and myeloma survivor, Gary Petersen. Welcome to the show, everyone! Today, we are discussing the much debated topic of myeloma cure versus control. Cure and control are two different treatment philosophies, but the debate is of extreme importance in patient care. While long-term survival is considered to be equivalent to a cure by many physicians, the "cure" word is being used more often by the myeloma fraternity. How long can we survive on a control approach? How soon will cure become a reality? These are some of the questions that we are discussing with Dr. Rajkumar today. I will now hand over to Gary who will introduce us to our experts and begin with the discussion. Gary, you are on air!

Gary : Priya, thank you so much for your very nice introduction and before we go on to the formal discussion, I would like to sincerely thank Dr. Rajkumar for all his efforts to give myeloma patients more life and for his work…..

Dr. Rajkumar : Thank you so much, Gary.

Gary : You have been remarkable and it's obvious to everybody on the panel. If you look at all of our blog posts, we hold you in the highest of regard and we really appreciate the fact that you have worked on low-dose dex and shown that it is equal to or better than high-dose dexamethasone. You don't know it, but you probably saved one heck of a lot of marriages (laughter) and prevented some roid rage; and finally, I would like to also thank you for using your middle name instead of your first name. (Laughter) I guess I might have a little trouble with, I think it's Sunda-ra-rajan. Is that close or?

(Laughter)

Dr. Rajkumar : Not even close (laughter).

Gary : Not even close, I am sorry. Okay. Enough for the humor. Dr. Rajkumar is an eminent professor of medicine at the Mayo Clinic in Rochester, Minnesota, and is a key member of what I consider definitely a myeloma dream team, they put together some of the best folks in the world in the Mayo system and that includes doctors, Rajkumar, Kyle, Lacy, Kumar, Chanan-Kahn, Roy, Fonseca, Stewart, and Reeder – I mean just a group of remarkable people. He is engaged in clinical, epidemiological, and laboratory research in myeloma and related disorders. He serves as the principal investigator of several clinical trials for the treatment of myeloma, but most of all it is his remarkable work that he has accomplished in a leadership role throughout the world for multiple myeloma. In my opinion, he is one of the most renowned myeloma specialists in the world. He is also active in ASH and ASCO and is the Chair of the myeloma committee of the Eastern Cooperative Oncology Group. Quite a mouthful but I had to cut it short because there is so much more that you have accomplished as well. Thank you for coming, Dr. Rajkumar.

Dr. Rajkumar: Well… Thanks, Gary! That was an unbelievable introduction. I don't know whether I deserve all of that, but I really appreciate it and you know what we are doing is basically, this is what gives me joy. It's not like I am suffering when I do this.

Gary : And we certainly are very appreciative of that, that you are so committed and so, so skilled in what you do. Now, cure versus control almost sounds like a bad, like Olly versus Frazier. Could you explain what is your definition of cure and what your definition of control is and if a difference in philosophy exists and why it exists?

Dr. Rajkumar : Well, thank you very much for having me and this, I think, is a very important topic to discuss. It's also quite complicated because it's not that easy to get the full perspective out even to, you know, physician colleagues and I wrote an article in 2008 in the Mayo Clinic proceedings mainly based on a patient whom I saw. I had a patient who came to me and this patient had already been to one center in which he had been advised, and this was like a physician, advised to just watch and wait and then had gone to another center where they had said that he needed multidrug induction, tandem transplantation, and maintenance and a confused physician-patient comes to see me, to say like, you know, this is like the absolute two extremes that somebody could offer a patient. Now, what do I do and you can see the dilemma that happens when, you know, a person in the medical field can get confused with just remarkably divergent opinions, what people who are not in the medical field who are suddenly diagnosed with myeloma can face if they get such, you know, such divergent opinions and it got me thinking that, you know, part of the problem in the myeloma field related to, it's not whether a patient should be treated with a curative approach or a controlled approach, that's not the philosophical difference. The philosophical difference is whether at this point a particular physician feels myeloma is curable or not and if a physician feels that myeloma is curable, then they try in their best of intentions to try and use the best available active treatment early in the disease course, as aggressively as possible, seeking a complete response, whereas if a physician feels that myeloma is still like chronic lymphocytic leukemia or indolent non-Hodgkin's lymphoma, a generally incurable neoplasm, then such a physician would hesitate to put patients through intense therapy because it will affect quality of life and they would like to do it more as slow-and-steady-wins-the-race approach. And, why would anyone choose control if you can actually cure a disease?

The problem with myeloma is it's very difficult for us to know even in 2014 is it a curable disease or not. It's one thing to say whether we have cured some patients. Of course, we have, and we have cured patients even in the melphalan-prednisone era, but in order to call a disease as curable, we have traditionally used a different metric. One of the metrics we have used is looking at the survival curves and trying to see if there is a plateau or a steady decline with time. Diseases like Hodgkin's disease, large cell lymphoma show a clear plateau, which means that there will be a certain number of patients who die in the first year or two, but those who achieve a complete response by year two or so will then be cured and the disease almost never comes back. And, I have always used that metric and I have also used the metric of if I can see a young patient in the eye and say "I can cure you," can I say that or not and I cannot say that still with a straight face in myeloma. We are operationally curing very elderly patients because you can prolong overall survival by 10

years, then, of course, some patients will die of other diseases, you know, heart and lungs problems, before the myeloma comes back, but a young patient who is diagnosed brand new with myeloma still has a very low probability that they will be actually cured and see a full-fledged 40-year survival and that's my metric. So, having said that, I think we should try in our research, and this is what I wrote in 2008 as well, that we should try to do clinical trials that try to get a cure and use the best available tools that we have early in the disease course in order to do that as well as do trials that try to control the disease because at this point we are not certain which approach will actually work out and so I do encourage clinical trials trying to cure the disease at the same time in parallel doing trials that prolong overall survival without necessarily curing it. And, there are success stories in both philosophies. CML is a good example.

Now, if you ask are we curing patients now? You said some physicians think that 15% to 40% of myeloma patients are being cured, do I think that that's happening? It's very hard to say. You will have to look at what the data is right now. The first thing to recognize is if you just look at clinical trials and try to get your numbers, then you will be mistaken because half of the patients diagnosed with myeloma are not considered eligible for trials because they have other co-morbidities or poor performance status and are systematically excluded from trials. So, the results that you see in publications are biased because they include only patients who are fit enough to enroll in clinical trials. #2: Many of the best results are in patients who have been transplanted and that's only 50% of all myeloma patients can be considered eligible, so you are seeing a select number in the results of trials. Even in this select number if you look carefully at the results, a different picture emerges. For example, if you look at the CALGB trial which looked at maintenance with lenalidomide, that's the modern trial. It used modern induction, transplantation, maintenance with lenalidomide. With that strategy, only a third of the patients were in complete response and there is no evidence that there is a plateau in the survival curve. Patients continue to relapse with time, so it's not that we have cured patients in that trial. The best example of possible cure in myeloma in terms of trials is from the Arkansas Total Therapy trials. If you look at the most recent Total Therapy trial that's been published, the Total Therapy 3, about half of the patients in the Total Therapy 3 trial, a 150 of the 300 patients, achieved a complete response and stayed in complete response for five years straight and one could say, well, are we curing half of the patients who participated in the Total Therapy 3 trials. Probably not, because if you look at Total Therapy 2 that happened a few years prior to that, at 10 years this number still keeps dropping. It is not like it stays fixed as it would in a curable disease such as Hodgkin's disease. So, this is where we are right now. I want to make it very clear that I do encourage clinical trials and pursue clinical trials for both cure as well as control. My philosophy is that if a patient is not participating in a clinical trial, I am hesitant to recommend a curative approach for low-risk, standard-risk patients because such an approach is not only unproven but can also cause harm.

Gary : I see. So, you are not sure that, you know, because we have gotten, at least I have heard in the past that, you know, Arkansas says 40% of their patients are probably cured and a number of other doctors have said something like 10% to 15%, which include Dr. Hari, Dr. Berenson, Dr. Vij, and a number of others who thought they were effectively cured, if you use that term.

Dr. Rajkumar : Yes, I think you can say operationally cured 15% to 20% of patients or 15% to 30% of patients, but still I would say that we have to be very careful in whether this is, like I said, it's one thing to say we are curing some patients, it's another thing to say we have a curable disease because the philosophy changes immediately. Acute leukemia is a curable disease and we throw the full kitchen sink because we have to cure it. Same thing with diffuse large B cell lymphoma or Hodgkin's disease. We think we may be curing, but do we have proof that we are curing? The only study with a plateau is the Arkansas study and in as all trials where they have done allogeneic transplantation. In the Arkansas study, we just need more long-term follow up because at this point it looks like Total Therapy 3 is showing a plateau with almost 40% of people alive and disease-free at five years and whether that will hold out to 10 years, whether those patients are actually cured or not, only time will tell.

Gary : I don't know if you have it or not, but I know that you do review your survival statistics. Do you have your own internal statistics that show a plateau?

Dr. Rajkumar : No. In fact… No. You would be hard pressed to find any survival curve that matches the Arkansas survival curve that was in their most recent paper on leukemia in 2013. Not a single study comes to mind where there is a 50% complete response rate that is sustained for five years straight. So, they have the best data. Whether it's due to selection or whether it's due to the intensity of therapy, we don't know, but it must be kept in mind, Dr. Barlogie is not doing these treatments outside of trial. These are clinical trials. He is getting informed consent from the patient that the treatment may or may not actually prolong life had they done a different sequence.

Gary : Out of curiosity, are the limitations too that are involved in those trials on Total Therapy 3 the same as other trials or pretty closely the same and as biased as far as the population?

Dr. Rajkumar : Yes, because in order to go through Total Therapy 3, a patient has to be fit enough to just basically live in Arkansas for a while and endure two back-to-back transplants, which occur after a seven-drug induction.

Gary : Okay. Yeah. You mentioned that once before when we had a conversation, it was a long time ago and I was just going on myelomasurvival.com, and the one thing that hit me at that time was when you said – Yeah, well, you can look at one of the trials, but you got to know that all those people aren't that sick or something similar to that, which kind of floored me. I didn't know exactly how to respond.

Dr. Rajkumar : Yeah. Well, systematically, you know, we just tried to do a trial which included patients with performance status 3 and 4 who are typically excluded from all the trials and, you know, we actually weren't able to get that trial approved, so these patients about half of the myeloma patients are not even going to be able to participate in trials. And that's why if you see, in fact, Dr. Neil Love was asking me a question a couple of days ago – Why is it that when I ask you academic physicians that you say that you have a, you know, five-year survival rate of 80% and then when I go into the community they are saying that their five-year survival rate is 30% and are they doing something wrong and the answer is no. They are seeing a different patient population.

Gary : Hmm…. Interesting! Well, what we'll do at this point, Doctor, is we'll both go on to…, unless you had a few other things you wanted to comment on, we will go on to the questions from the panel. Is that alright with you?

Dr. Rajkumar : Yeah. Absolutely!

Gary : Okay. Fantastic! My first. And actually what we are going to do is we are going to one question per member and then open it up for questions from the listeners because unfortunately what happens is we all get so excited about asking our own questions that we don't leave enough time for the folks who are listening in, so we are trying another approach to maybe get some more time for them.

But, my first question has to do with MRD and it's the first round and so then we will go to listener questions and then hopefully have time for another round, but the MRD or minimal residual disease and also the Black Swan Program has taken center stage with the International Myeloma Foundation; however, after, when I went to, I get some of my treatment at Mayo, Jacksonville, if they did discuss, they said no, so is Mayo doing this test in other locations, the minimal residual disease test, and are any Mayo locations, you know. What is your position with regard to this Black Swan initiative and the use of minimal residual disease as a means to achieve cure?

Dr. Rajkumar : I am very heavily involved in the Black Swan Program. I was one of the original people who was involved in setting up this initiative along with Dr. Durie, Dr. San-Miguel, and Dr. Landgren and this initiative, the first goal of this is to develop a standardized method for defining what is MRD0, that means minimal residual disease zero. In other words, no evidence of clonal plasma cells, no evidence of myeloma cells after the treatment is done. And like I told you, in clinical trials we want to pursue cure and we are designing trials to do that, but in order to do that you need to have a metric that everybody can agree on and

use to say, yes, we have now achieved a zero disease state and so we needed to develop the tool for that first. And that program is going according to plan and will be, it's being developed by the Spanish investigators, Bruno Paiva, Alberto Orfao, and it will be a computerized method that once it's up and running, any institution would be able to do it on the standard flow cytometer, so that we can talk to each other, that when we say somebody the MRD is zero it means the same anywhere it is tested.

The test also is very, very sensitive. It just goes down into like, you know, a lot more than what other tests can do at this point to detect residual cells and we hope that if you can achieve and sustain minimal residual disease that that would be the path to cure and then there will be trials done, trying to go along that path and then use this tool at each year to see if we are achieving our stated goal. Mayo is very much involved and we are also going to send our folks to Salamanca. Next month there is a meeting where there is going to be hands-on training for various centers to do this test, to learn how to do it and then everybody comes back and validates it for a few months before it goes live. There are several other flow cytometry tools and molecular tools that people have developed, but we think that this is probably the most practical one and something that everybody can agree on and also will be standard across, you know, various labs and various countries.

Gary : Oh, thank you for that explanation. It sounds very exciting, at least from a patient perspective, you know, that the whole field of medicine for myeloma is going in that direction.

Dr. Rajkumar : Right.

Gary : What I would like to do now is go on from here with the other questions from the panel and I will start off with Pat Killingsworth. Pat, you online?

Pat : Hi Gary! Hello Doctor!

Dr. Rajkumar : Hi Pat! How are you?

Pat : I am good and as a former Mayo Clinic alumnus, I am pleased to get a chance to speak with you. Dr. Dispenciary? was my doctor for a while and Dr. Gilman was back before he became sick was my doctor when I was diagnosed in 2007. Shall we switch gears and talk about the other possible curative option which would be allo transplants. I have been following that adding Velcade and/or Cytoxan at times during the process that doctors are able to get a good control of graft vs host, and the procedure is becoming safer. I wasn't going to plan to put mine off, before years, when I was first diagnosed back before I was into do that I think, but now I am looking at this – I have two friends, they are tough guys, long-live survivors, but they both recently did an allo as salvage therapy, and it worked for both of them. They are between a year and a half and two years out and they were given, you know, the three month affairs an order speech before the procedure itself. I know it's rough but, you know, I guess it's the easy alternative if you have got the stomach for it, so I guess I have got two questions. The first is, how do you or how does Mayo look at using the allo transplants in myeloma patients in general and then what about the salvage therapy option?

Dr. Rajkumar : First of all, I really admire you. I have read many of your posts on Myeloma Beacon and just like Gary, you both are doing just absolutely fabulous work for the community of myeloma patients and your question is also like extremely pertinent and very much in line with the previous topic that we had of cure versus control and actually the great example to you, to illustrate, you know, the dilemma that we face. For years, we have known that the only, no, I wouldn't say only at this point, but one of the really sure ways of curing myeloma might be an allogeneic transplant because it has worked in other diseases like CML and AML and it produces cures and there have been plateaus in the survival of myeloma trials which have used allogeneic transplantation. The main problem had been that the mortality risk was so high that if… Imagine you are a young person and you are faced with the dilemma of, you have a 50% chance of dying within the next few months and then if you make it, you have like a 20% chance of living for 20 years or longer. That's the dilemma that no mother would want to face or no wife would want to face, you know, let alone the patient and so the question is, you know, how could we possibly offer this option. In CML, it was done because it

was a 50-50 chance. In myeloma, the long-term cure rate was probably not that high. It was there, but it was more like 20% or so and the mortality rate was still as high or more than CML. So, we never used it. We had trials that were stopped because the first two-month mortality rate was 40% or something. Later on, people started realizing maybe we can do a mini allo and then, you know, everything will be good. We'll have low mortality rate, 10% mortality rate, but maybe we'll have the same level of cures. But that didn't pan out, I mean, particularly the big US trial showed no benefit at all with a mini allo transplant compared to just the auto transplants and then you have all the graft vs host disease and everything and now on the other hand, we have come almost full circle.

People have found that the high mortality that we had with myeloablative transplants were from, you know, inadequate prophylaxis, inadequate donor selection, inadequate prophylaxis for cytomegalovirus, the CMV infection, and you know all other prophylactic and supportive care measures that we have and nowadays people believe that the mortality rate for a full allo, even a myeloablative allo, is not any more than maybe a non-myeloablative or a mini allo. And so, there is a resurgence of interest. And then, there are some studies like the ones from Sweden which suggest a benefit with allo transplant and so we are going back to that. Mayo's position is we are back doing allo transplants. We had never stopped it completely, but I myself have recommended allo transplants to many young people who have failed others as a salvage modality and starting to consider it for high-risk patients in the first relapse setting. I believe it is one of the ways to cure multiple myeloma. It still has so many side effects that we don't want to do it for all patients upfront but for selected patients with a good match who are willing to tolerate and accept a high treatment-related mortality in exchange for the probability of long-term survival, it's a great treatment option. I would not count, I would not rule it out and we certainly do it at Mayo and many other centers.

Pat : Are you starting to play with the Velcade, using the Velcade during conditioning consolidation?

Dr. Rajkumar : We have not done that, but I have heard about those studies. People are doing it both in auto and allo. We have not done that. Our approach, the main thing that we have changed recently and I think it has to be patient by patient. Remember, the one, the most recent patient that I did was somebody who was less than 50 years of age and we just went ahead with a full myeloablative transplant and that there will be like total body radiation and everything and so the exact conditioning used is still case by case, but it looks like from talking to people, including Dr. Gerald and others, that even the BMT CTN is coming around to maybe we should re-explore a full allo and not count it out as we did a few years ago.

Pat : Thank you, Doctor.

Gary : Thank you very much. We have a relatively new member to our panel, Lizzy Smith, and Lizzy has just put together a website called Myeloma Crowd and it just kicked off just a while ago with Jennifer Ahlstrom and Lizzy that's going on right now. Lizzy, are you there?

Lizzy : I am here. Can you hear me?

Gary : Yes, I can. Welcome to the panel.

Lizzy : Thank you. Thank you for your time today, Doctor, and for taking our questions and I will give a little plug out. Our site is www.myelomacrowd.org and one of the things that the site is attempting to do is encourage more patients to consider participating in the clinical trial and on that thought, I was wondering if there were any current medical trials that you found most, I don't know if exciting is the right word, but potentially moving towards a cure or just some new great treatment?

Dr. Rajkumar : Well, there are a couple of trials that are being planned, both for high-risk smoldering multiple myeloma. They are in the planning stages. One by Dr. Kumar for the US and by Dr. San-Miguel for Spain, but they are probably at least a year away . Those two trials are designed specifically to see if we can cure myeloma and they are working on the hypothesis that one of the reasons we have not been able to cure the disease is because we treat patients after the bone disease has happened and after kidney failure has

happened because after all myeloma is defined as myeloma only when the CRAB features occur and that would be analogous to treating breast cancer only after it's metastasized to bones and so the idea is maybe we should be treating patients, before these things happen at the high-risk smoldering stage when the cells are still susceptible to treatment, and then in those patients used all of the available approaches, including, you know, the best drugs, transplant, maintenance, and so on. So, those trials are being planned. It's a big ship in the paradigm, you know, of myeloma treatment and I really want to see these trials become a reality.

In terms of the ones that are, important ones that are available right now that I would like accrual to, we don't know what the best front line regimen is for multiple myeloma and there is a trial by ECOG which is carfilzomib-Revlimid-Dex versus Velcade-Revlimid-Dex and that trial also asks a maintenance question whether maintenance should be given for two years or indefinitely. That's open, available across the country. For high-risk patients, SWOG has a trial of Velcade-Revlimid-dex, VRD versus VRD plus elotuzumab. Millennium has a trial for elderly patients of a completely oral regimen 9708 len/dex versus len/dex, and these are the newly diagnosed ones and then there are many other trials going on with several interesting drugs for the relapse refractory setting.

Lizzy : Okay. I have a followup on the maintenance indefinitely.

Gary : Lizzy, we have one question a piece.

Lizzy : Okay. I'll wait.

Gary: Okay. All right. Next round.

Thank you.

Gary : Okay. All right. We will go to Cynthia's question now. Cynthia, you are online?

Cynthia : I am here. Thanks. Thanks, Doctor. How are you doing? And I am sorry. I missed the beginning of the talk, I was coming home, something driving across the city and it was crazy trying to get out the city, so if I ask a question you already covered, I apologize ahead of time. Talking about the cure versus control, do you believe that everyone could be cured of myeloma at some time or do you think some people will always have some of that mild residual disease in their blood and if you think so, I mean there is always a group of people that will always have some MRD in their blood, how do you know how long to continue treatment through maintenance? Do you continue it for two years if there is a stable disease or do you continue to treat it indefinitely until they relapse. What are your thoughts?

Dr. Rajkumar : Well, great to meet you again! I mean, we just participated in that tweet chat.

Cynthia : Yeah.

Dr. Rajkumar : It's always great to interact with you and it's a hard question because, you know, we are and I think you asked me this earlier as well. We need to cure myeloma. We do not need to cure MGUS. Okay? The monoclonal protein is not the enemy. Three to four percent of the general population has a monoclonal protein and 90% of them will never get multiple myeloma and the protein is there and no one knows about it and it's just there. Trying to eradicate it actually will cause more harm because these are, I mean you are trying to kill the immune system and that's been around for, you know, through evolution. It's meant to stay and it's very hard to kill benign cells because they are almost like your nomal body, you know normal cells. The problem in myeloma is that unlike other cancers we are not able to look at these cells and say which one is an MGUS cell and which one is a normal cell and which one is a myeloma cell. It turns out the MGUS cell and the myeloma cell both make the protein.

Yeah, yeah.

So, when we treat patients, some people get a complete response in the sense that the monoclonal protein goes away because we manage to kill everything or we think we killed everything. In some people, the protein is still there and it may mean that they have some myeloma left and some MGUS left and in some patients the protein is there, but what is residual is actually not from the myeloma, it's from the benign clone, from the MGUS and there's no way of telling one apart. So, if you look at all the trials, you have a choice you can make. I mean the best complete response rates are in the Total Therapy trials and even they don't get a CR in 40% of patients. What do you tell those 40% of patients? That they have failed and they are not going to do well? No. Because actually some of them will do just as well and may even live longer than the patients who got a complete response.

In fact, in Dr. Barlogie's trials, the people who got the fastest complete response often did not, it did not sustain for very long. The Spanish group may be on to something here. They seem to be able to discriminate using their flow assay. Whether residual cells that are left behind after treatment represent the myeloma clone or just the precursor MGUS clone and if they are able to do that successfully, then our goal becomes easy. We don't need to kill all plasma cells. We just need to kill the myeloma cells and then it will give us a tool and the MRD tool that they are developing all ties into that. They also found in a study recently published in a journal called Leukemia that about 8% of myeloma patients have what they called an MGUS-like profile, that means their cells look more similar to MGUS even though they had lytic lesions and these patients actually lived much better than all the other myeloma patients even though their protein didn't go away. They had a 10-year survival of 60% or more. So, these caveats are there and a lot depends on how we are defining complete response, which I think is quite primitive and that's probably part of the problem. We need to define it as eradication of myeloma cells, not eradication of the monoclonal protein.

Cynthia : Okay. Now that you explained it, I am much thorough on this. Thanks so much.

Dr. Rajkumar : Thank you.

Gary : Thank you, Cynthia. And what we would like to do now, Nick Van Dyke is going to be a little late and so we will bring him on in the second round of questions, but what we would like to do now is to give our audience a chance to ask some questions with you, Doctor, and what we would like is for those who are on the phone, if you just hit the 1 on your keypad, that will put you in the queue and then Priya will bring you online live, so if you do that we really appreciate it, you know. Do come online, we prefer you ask the question as opposed to us asking it for you. It's just, you know, it's just what we would like to see. Priya! Would you bring somebody online?

Priya : Thank you. Yeah. Thank you, Gary. There is a person calling in from (303) 693-6866. You are on air. Please ask your question.

Caller : Hi Doctor! Very good, informative, you know, stuff that you just said, but my question is like if somebody is treated, like diagnosed with myeloma at an early stage, what kind of a recommendation would you give for treatment, like aggressive or, you know, not that aggressive to begin with?

Dr. Rajkumar : When you say early stage, are you meaning smoldering multiple myeloma or myeloma but it's just…?

Caller : Myeloma but it's just like if somebody just slided into myeloma according to the oncologist.

Dr. Rajkumar : Right. So, I will just briefly give you, you know, how I approach a newly diagnosed multiple myeloma patient because that would generally cover your question. When I see a newly diagnosed myeloma patient, the first thing I want to know is to make sure it is indeed multiple myeloma and not something else. That's because the monoclonal protein, as I mentioned, is present in a lot of people and they don't have multiple myeloma and one can get anemia and kidney disease due to all kinds of other reasons beside myeloma and we need to make sure that what we are dealing with is indeed multiple myeloma and not something else. I usually tell people that that is the most critical decision and the exact regimen I use,

whether it's len/dex or VRD is not going to affect survival as much as making the correct call on the diagnosis.

Right.

Once you make that call, then the next step that I do is to try and figure out if the patient is transplant eligible or not, mainly because if the patient is transplant eligible we should collect stem cells three or four months down the road before giving too much treatment. Otherwise, it will be difficult to collect stem cells and it takes a while to arrange for the collection. It takes a while to get the insurance approval and the correct institution that will collect the stem cells. So, we want to make that clear and done first and so I try and find out if the patient is transplant eligible or not using, you know, various parameters including age and performance status and other co-morbidities that they might have and then the actual treatment itself, I mean in 2014, particularly given the most recent ASH results has made it a little bit easier. Most of us do not like to use melphalan frontline and we have two ways of going about it. In the US, some physicians just simply use a regimen called VRD for all patients and then after four months collect stem cells. On the other hand, at Mayo we use more of a risk-adapted approach, mainly because VRD is more toxic and it is much more expensive. It is possibly not a major concern if patients have insurance in the US, but in other countries people have to sell their house to buy VRD and I really don't have any proof that that actually will make them live longer. If I did, then I would tell them to do that, but we don't. We don't even have a single phase III trial with that regimen. So, in the absence of that, we recommend for most patients either just len/dex or CyBorD which is Velcade-Cytoxan-dex, both those regimens are reasonably, they are very active. They are just as good as VRD in some comparative studies that we have done and at the same time half as expensive.

Uh.. hmm….

And the duration of therapy will depend on, you know, whether we do a transplant or not and so on.

Caller : Well, is that more effective to get like the tandem, the double transplant than versus the single or it just depends on each individual?

Dr. Rajkumar: As far as whether to do one transplant or two, in an eligible patient we always consider one transplant. In young people, we collect enough for two and then at Mayo we do one first and one later on if at all we need it. But, we rarely do tandem.

Yes.

Except for Arkansas, I don't think anybody does a routine tandem transplant, maybe a few centers here and there, but most people do one now, one later or just one. There are studies that were done using tandem transplants comparing two versus one. Only one or two of them showed a survival benefit and even those studies, the survival benefit was restricted to a small subset of patients. And, so, we don't generally do two transplants back to back as a routine thing.

Caller : Ahh…. Okay. Thank you so much. That was very helpful.

Gary : Priya, next caller.

Priya : Yeah. The next caller on line, person calling in from 817741. You are on air. Please ask your question.

Caller : Yes. Thank you, Dr. Rajkumar, for all your information and help and thanks to the panel. Umm… Is there any indication that elotuzumab with dex and Revlimid for induction and then a stem cell transplant, that combination, that's it by the way an autologous transplant – Any indication that six months after that or eight months down the road the patient would have blood counts pretty much across the board from platelets to other components, although the neutrophils have risen to about 1600?

Dr. Rajkumar: I don't know that that would be a result of the elotuzumab particularly. Are you on any maintenance after the transplant?

Caller : No, because the platelets are less than 50. They were around the 41 level the last time, a high of about 42, but as soon as they got close to 50, my local myeloma specialist said that I could go on Revlimid, say, for maintenance, low level, I don't know, I guess we start around 10 mg or so and see how that goes.

Dr. Rajkumar : Yeah. So, first of all about the drug, elotuzumab is not approved for myeloma therapy yet. It is in clinical trials and it has shown a lot of promise in combination with Revlimid and dexamethasone in the phase II setting. Therefore, there are two phase III trials, one is called ELOQUENT-1 and the other one is ELOQUENT-2. One is in newly diagnosed patients and one is in relapsed patients. Both these trials are looking at Revlimid-dex versus Revlimid-dex plus elotuzumab. We will need the results of those trials to see if the drug works and if it does, you know, whether it meets the threshold for FDA approval. So, that's, those are the stages left. Right now, it looks very promising. Even though it doesn't have single-agent activity, it seems to have a lot of synergy with Revlimid and dexamethasone. Now, there's no reason to believe that that drug is causing the low platelet count or the low hemoglobin. I think that's probably something to do with engraftment and hopefully with time it will recover. Sometimes, people have used, you know, if they have some stem cells extra that they have re-infusion of some extra stem cells to get their counts back up. Revlimid can cause prolonged neutropenia, but then in your situation it's the platelets and the hemoglobin, so I think it's probably something to do with engraftment kinetics.

Caller : I see. Also, low while blood cells, somewhere around 2.3.

Okay.

But, thank you very much. I appreciate your comments and all your help.

Thank you.

Gary : Thank you. Priya, one more question and we will go back to the panel.

Priya: Uh, yes, Gary. There is a person calling in, I think, from Skype or a caller card. You are on air. Please ask your question. (Pause) Yeah. Okay. If you are calling in using Skype or a caller card, you are on air. Please ask your question. (Pause) If you are using Skype, yes, many callers are using Skype actually, Gary. If you are using Skype or caller card, your number does not appear on the dashboard here. Can you please… You are on air. Please ask your question. (Pause) I think, Gary, we can proceed with the panel questions.

Gary : Panel questions. Okay. I'll do that.

Yes.

Gary : Doctor, I think that you almost answered my next question and actually it was and I made a statement which doesn't necessarily coincide with what you mentioned, which is that RVD is now the standard care by many institutions and here is data out from my depth study shows that the addition of Daratumumab in vitro has a 50% myeloma killing potential over just RVD and I was wondering if you know anything about plans for trials and the use of that in a clinical trial and whether that's a breakthrough combination.

Dr. Rajkumar : Daratumumab is an antibody that is directed against the CD38 antigen which is present on plasma cells. There is one other antibody that also looks at, targets the same CD38. Both of these have shown single-agent activity, which is not very common. I mean, we try hundreds of myeloma drugs and very few give a real partial response as a single agent without, you know, dex or Velcade added. So, this is very promising. I think daratumumab is a very promising new drug. There are definitely trials planned in combination with both Bortezomib as well as Revlimid as far as I know; however, I don't have any results of clinical trials and so I don't know exactly how they will pan out.

It ‘s certainly encouraging that this drug has been given a fast track status by the FDA, which means that it will be reviewed quicker and hopefully, I think, I don’t know, I am not ready to anything about the company, so what I am thinking is just speculation. Hopefully, they will be able to get the drug approved on a phase II trial like carfilzomib and pomalidomide were approved, which means that the drug works in relapse refractory disease as a single agent even in patients who have failed Velcade and Revlimid together. But, there will be more data. I am sure that there will be trials done with Velcade, with Revlimid, and all these possible combinations. It’s one of the few drugs that I am very optimistic will stand a chance and get approved.

Gary : Good. Thank you very much. Pat, do you have another question?

Pat : Sure thing. Sure thing. Doctor, at what point will Mayo and other institutions outside of Arkansas start making a Total Therapy-type treatment regimen available as an option to patients because even if the curve doesn’t totally plateau out, you must admit it it was pretty impressive or do you think that’s just because a healthier patient population is involved?

Dr. Rajkumar : Yeah, I know. This is a great question, Pat, and a couple of things that I want to mention. At ASH a couple of years ago when I was giving a talk, I was talking about Alessandro Liberati who was a physician in the Italian cancer research community who died of myeloma and just prior to his death, he was very much involved in evidence-based medicine and all that, but prior to his death he wrote a letter to the Editor to the Lancet, in which he mourned the fact that the type of trials we are doing in multiple myeloma that he searched and found in the literature were all like minor trials, like you know VRD versus CRD or VRD versus RD in incremental benefit. None of the trials he could find actually tested philosophies of big concepts and then, you know, he wrote that letter and then a week later he passed away of multiple myeloma and that’s really the main problem we have. I have been in this field for a long time. I have been a student of evidence-based medicine.

I know the pitfalls that we have gone through with so many different cancers. History is full of examples where physicians think they know what’s best and actually are later on shown to be wrong by a randomized trial. There has been no randomized trial comparing a Total Therapy-type approach versus just saying okay, you take len/dex and when that stops working, we will give, you know, we will do len/dex and a transplant and then we will just watch you and then when it comes back we will give you a little bit of len/dex and little bit of bortezomib and so on as needed and try to see which approach will give a longer life and there’s been no trial like that. We just have guess work and the pros and cons are quite striking because on the one hand let’s say if I get multiple myeloma today and I go to Arkansas, my life is no longer what I know of. I mean, it will be a life dedicated to multiple myeloma from that point onwards. On the other hand, if I choose, if I say well, I don’t know that that will actually make me live longer, so let me just do, you know, slow and steady, then I could probably continue to live, I mean I might be practicing and doing myeloma work and research for the next 10 years and still be the same-looking person, with, you know, the same face and everything. So, that’s the dilemma.

I mean nobody has compared dramatically different approaches to know whether one approach actually makes you live longer or not and therefore when you see results you are not sure whether it’s because of patient selection or whether it’s a true difference. I do hear your point though that, you know, even if we didn’t believe that data, we should at least offer clinical trials which are available to patients who are interested in a curative approach and I think that’s probably the step that the trial that, say, Shaji Kumar is designing is going to take. We are going to do Arkansas-type therapy on smoldering patients and that, you know, makes Bob Kyle jump up and down his seat. That’s how radical it is for us.

Pat : Well, that’s one of the best explanations I ever heard and after reading the retrospective study done on Mayo Clinic patients showing that low-risk patients going through an incremental approach or, you know, younger low risk patients were living decades or that was a median that matches up quite nicely with some of the results from Arkansas, I believe, though I think it might be closer than an observer, outside observer might think.

Dr. Rajkumar : Yeah. And, you know, a lot is patient perspective and I want to, you know, again I go back to the ASH presentation. Right now, with myeloma the type of treatment a patient gets depends on which physician they see and it should be the other way round. I mean, we should really be looking at the patient and designing individualizing therapy, not just based on the tumor and the stage and the response to therapy and, you know, all those things, but the patient's wishes. Some patients, as far as I know, have a clear interest in cure and they are willing to take on extra risks, extra toxicity, and even try unproven things because they really don't care whether they live 10 years or five years, but they are only interested in will I live another 30 years and then there are some patients who are petrified of transplant and they would rather try and postpone it as much as possible and try oral therapy and live, you know, exactly the same way as everything is for as long as possible and then I will do all of that stuff later on and we have to get into the mindset of the patient and try and deliver what is in their best interest.

Thank you.

Gary : Very good. Doctor, do you have time for a couple more questions?

Dr. Rajkumar : Oh, yeah. Not doing anything much. (Laughter)

Gary : Oh, yeah. All right. Thank you so much. I appreciate it. I know you are very, very busy. Lizzy, your second question. Lizzy, you are online?

Priya: Lizzy, you are on air. Please ask your question.

Lizzy : Sorry about that. I had to unmute. Okay. So, I am intrigued about what you said about keeping the myeloma patients after they have a transplant on maintenance therapy for indefinitely. And that's kind of maybe, first I had heard of that, and I was wondering if you thought if that was going to be natural standard of care. You know, if there are positive benefits that will outweigh the negative benefits while staying on some of those medications for long periods of time?

Dr. Rajkumar : Yeah. Excellent question on maintenance and, you know, something that's evolving and so it's bound to change and probably my perspective is more conservative than most of my colleagues'. There have been two trials which looked at post transplant maintenance therapy and they gave conflicting results. One of them, the French trial has not shown a survival benefit, whereas the US trial did find a survival benefit, that is, if you took maintenance you live long and then both trials though had an extra risk of second cancers, a three-fold increase in the risk of second cancers like 2% and 1% in the people who didn't get it versus 7% to 8% in those who got the Revlimid maintenance, which then makes the whole thing a little bit more difficult to interpret because there are some risks and the survival benefit is plus/minus. And, so our group generally feels that we would use maintenance therapy in patients who really need it and even in the US trial, those are patients who fail to achieve a complete response after the transplant and the patients who are already in complete response or a very, very good partial response.

We would rather just give two months of consolidation like the French did and then watch. If we do decide to do maintenance, I personally feel that you should restrict it to two years or so because at that point is when the French trial really had an increase in the second cancers and I cannot be sure of the benefit beyond two years. The ECOG trial is looking at maintenance given for two years versus indefinite, trying to see which approach is better. In the non-transplant setting, you know, patients who don't have a transplant, the trial that was done in France and across the world presented by Dr. Facon at the last ASH meeting found that indefinite or Revlimid-dex given until progression was the way to go. It had the best survival and there was no increase in second cancers and that's because when you use len/dex alone in frontline therapy, there is no melphalan along with it and it does not seem to increase the risk of second cancers. On the other hand, in the transplant setting, you just gave high-dose melphalan and then you are exposing the patient to Revlimid on top of that and that may be the reason that there is an increased risk of second cancers.

Very good. Thank you.

Gary : Yeah. Cynthia! Cindy, your question and then that will be it and we will let the doctor get back to saving lives.

Cindy : That's a good idea. I guess I am thinking a little bit different. Now that myeloma is becoming more of a chronic condition for some patients and we are curing some, maybe we are close to curing some, is there any thought being given to like developing survivorship programs for these patients living longer and may be not in active treatment anymore and things that we should be doing as a survivor?

Dr. Rajkumar : Oh! Absolutely and I think both the IMF and the MMRF have several support groups and I am sure that institutions, many big institutions, also have programs, but it's so important. I have not seen a community of cancer patients as collectively organized as the myeloma community and it's really well organized. You also wouldn't find, by the way it's an aside, any other disease group where the physicians even with diverse philosophies are very, very close and friendly. I mean, I am on the call with Dr. Barlogie every week even though our philosophies are different and discussing his trials, what they are doing in Arkansas, so it's a very good group of people. If you think we are not doing anything correctly, please let me know. I am not sure exactly what you mean by more survivorship things, but whatever you think we should be doing that we are not doing, let me know.

Cindy : Oh! I am not thinking you are not doing anything. I am thinking just like do long-term things that myeloma patients should be looking for, like secondary cancers or things that maybe five or six years down that might be result of treatment that we had five years ago.

Dr. Rajkumar : Yeah. I think there are some things that I do want to point out. One is that people who have been on Revlimid for a long time should be really weary of diarrhea. That happens and it's really very disturbing and it's not easy to control. That happens in about 3% to 5% of patients who are on long-term Revlimid. Second cancers. That's not common, I mean it's increased but it's still only like 7% to 8% compared to what the baseline which is 2% to 3% at say, four years. So, but just be on the alert, particularly the type of second cancers seen which were like Hodgkin's disease and ALL, which we have not seen before. Anybody exposed to melphalan or to cyclophosphamide, longer term, as time goes on is at increased risk for myelodysplastic syndrome as well as acute myeloid leukemia and they are all small risks, but you want to be careful and somebody should watch out. Any time, some time, you are doing well myeloma wise but your blood counts are low, you have to bring it to the attention of the physician that I have had myeloma, it was 10 years ago and I had a transplant 10 years ago but, you know, if they had melphalan at that time, so you may want to check me for myelodysplastic syndrome or whether my bone marrow is working correctly. Neuropathy is another problem. I mean, many of the drugs we use cumulatively can cause neuropathy and is something to watch out for.

Thanks, thanks.

Gary : Thank you so much, Doctor. Nick is online now. Do you have time for one more question?

Dr. Rajkumar : Yeah, sure. No problem.

Gary : Oh! Thank you so much. Yeah, Nick!

Nick : Thank you very much. I am not on mute, I hope. Can you hear me?

Yeah, I can.

Great! So, I apologize I joined late because I was at the doctors appointment. My questions on these panels are usually involved and broad. I apologize today since this involves a very specific, but it's something I think that you are very uniquely, maybe one of the only people who can even comment on this. I went through Total Therapy under Barlogie and like many other patients I experienced the oligoclonal bands in my blood during the recovery from transplant. Now, I was prepared for this and felt it was a good thing, so I was

untroubled. But four years later after I completed three years of VRD maintenance and a further year of Velcade, I then saw a monoclonal band, very faint one, under immunofixation. I saw the clean bone marrow, did not know what to make of it, and that itself was an unusual event and it was pretty jarring and the thing that kept me off the lid was a paper that, I believe, you and some of your colleagues published about the secondary MGUS that is being seen with some prevalence now. So, I am wondering what, you know, what was known in the community for some time about oligoclonal bands, why do you suppose it has taken longer to recognize this or hadn't even seen it, pardon me, and what, is it indicative of a different type of recovery or different response to different agents and lastly, if one had four years of clean blood and it then came back and resolved, is that a particularly unusual manifestation of this phenomenon?

Dr. Rajkumar : Yeah. Great question! First of all, the study that we did was actually one that looked at all of this more closely in a large number, but it had been reported before by others that monoclonal bands can be seen after a transplant and sometimes even after regular chemotherapy that are different than the myeloma band. So, what happens is like if you have say an IgG kappa multiple myeloma and then you go through a transplant and suddenly they are telling you have an IgA lambda monoclonal protein, that's when you say, well, that's second MGUS because it's not the type that caused the myeloma. It's a new protein. Of course, even that underestimates how often this occurs because if there was an IgG kappa itself that came up, we won't know it because, you know, it will all look the same. When we did the study, we found that about 25% of patients after a stem cell transplant will develop a new monoclonal protein that is different, either the kappa became lambda or the lambda became kappa, or IgG was different and became IgA. It represents a new clone. It's got nothing to do with the cells that caused the myeloma and that happens about 25% of the time, so not infrequently. It will not be picked up until somebody is actually checking the blood and again, you usually don't check the blood unless the monoclonal protein is negative and you are doing an immunofixation. So, it's only when you do the immunofixation you pick it up and what we find is that this kind of protein develops usually within 12 months. It lasts about six months and then it goes away.

The patients who had this kind of phenomenon lived twice as long as people who did not develop this and it gets you thinking, you know, what exactly is this telling us? I mean there is no great literature on this, but my simple explanation is that the development of a new clone and the ability to resolve it, it's like a very competent immune system that is left behind after the transplant and so that's why such patients are able to live longer because their immune system not only is healthy and reconstituted fully but is also able to abolish that clone and then make it go away with time. If the protein persists on the other hand, it actually does not have that same survival benefit. In your case, showing up four years after the transplant and then going away is quite unusual. I assume that when you said four years later it showed up, it was a different kappa, lambda, or an IgG, IgA isotype than the one that you had.

Nick : Yes. It was IgG, but they weren't able to determine. It was a very faint light chain, it didn't have a heavy chain, so I had IgG lambda, so it was within the same, you know, immunoglobulin but we don't know if it's the exact same clone.

Dr. Rajkumar : Yeah and I hope if it came and went, it's probably just the secondary MGUS and I hope it doesn't show up again.

Nick : Yeah. Thank you. It did come and went.

Priya : Doctor, we have a caregiver calling in from Ukraine. If you have any, maybe we can just take her call.

Dr. Rajkumar : Okay.

Priya: Person calling in from Ukraine, you are on air. Please ask your question. We have a couple of minutes.

Caller : Hello.

Yeah.

Priya : Yes. You are on air. Please ask your question.

Caller : I am sorry. I am calling outside from the US, from the Europe. My question is my father was diagnosed with multiple myeloma stage IIA on Durie/Salmon and my question is should he necessarily take chemotherapy. He has got radiation and he gets bisphosphonates. In our country, it's difficult to get treatment because government doesn't provide it for free and so is it necessary for him if he doesn't feel worse after the treatment to start chemotherapy.

Dr. Rajkumar : It's again, really sorry about your father. The problem is that it's very, very difficult to counsel unless I have a lot more information than what you have given. What I suggest, you have two options. First, if it is indeed multiple myeloma, yes, the radiation alone will not help. I mean there's got to be some systematic therapy, chemotherapy-type medicine that will need to be given. What I would suggest is my email is available online on my papers, just tell your doctor to email me and then we will discuss and decide what needs to be done.

Caller : Okay. Thank you very much. Thank you very much.

Priya : Well Dr. Rajkumar, thank you on behalf of everyone here. You have stayed more than an hour, I think, almost 15 minutes more. Thank you so very much. You have shared information which is very valuable. I have been receiving questions right through the show. My inbox is flooded with questions and hopefully you will get to spend some time. Gary, Pat, Cindy, Lizzy, and Nick, thank you so very much for your participation. And the audience, make sure that you mark your calendars. The next show is on 7th of March at 6 p.m. eastern time and we are discussing fundraising with Matt Goldman. And please visit curepanel.carefeed.net for details on our upcoming shows too. Thank you everyone.