Myeloma: 2016 Year in Review and Outlook for 2017

The treatment options for myeloma continued to evolve in 2016 with new agents, immune based therapies and repurposing of existing approved agents. High-dose therapy and autologous stem cell transplantation remain the backbone of upfront treatment in myeloma.

We are talking to Dr. Ravi Vij, about the evolution of myeloma treatments in the past year and what we can look forward to in the new year.

Full Transcript:

Priya Menon – Good evening and welcome to CureTalks. This is Priya Menon from India on CureTalks' 118th episode. CureTalks is a social initiative with a mission to heal the world through information, discussion, and sharing of knowledge. We organize online talks by inviting guests from around the world to discuss a wide range of health and wellness issues. Our diverse group of panelists come from all walks of life. They are doctors, nutritionists, professors, researchers, patients, parents, caregivers, and health professionals; and today on CureTalks, we are discussing multiple myeloma.

I would like to begin by wishing everyone a very happy 2017. Our myeloma series on CureTalks is one of the most popular. I would like to extend my thanks to the myeloma panelists and world-renowned myeloma specialists who have so very generously chosen to spend their time on CureTalks, educating people on latest multiple myeloma research and treatments; and it is quite an exciting time for myeloma research with the four new drugs being approved recently and a lineup of new drugs, treatment options, and combinations a patient can choose from for this year. We are talking to Dr. Ravi Vij, Professor of Medicine, Washington University School of Medicine, about the evolution of myeloma treatments in the past year and what we can look forward to in this new year. My co-host for the day is myeloma survivor and editor of myelomasurvival.com, Gary Petersen. Joining Gary on the panel is myeloma survivor and advocates, Jack Aiello and Yelak Biru. Welcome to CureTalks, everyone. Like always, we will be discussing questions sent in by our listeners. If you want to ask a question, please press 1 on your keypads and we can bring you on air. You can also email the question to priya@trialx.com or post the question on CureTalks' website. With that, I will hand over to Gary to take the discussion forward. Gary, over to you.

Gary Petersen – Thank you very much, Priya. We certainly do appreciate the opportunity that you bring to us to review what we are doing in the area of multiple myeloma for all of us and I happen to be very, very pleased. Often times people ask me, what is a myeloma specialist? You know, there is really no degree for a

myeloma specialist, but as I was looking at Dr. Ravi Vij's background, I come to understand that if I just read it, people can really understand that Ravi Vij, Dr. Ravi Vij is, in fact, one of those unique people who are so skilled with this disease that they are myeloma specialists.

Gary Petersen – Dr. Ravi Vij is Associate Professor of Medicine at the Washington University School of Medicine in Bone Marrow Transplant Section. He received his medical degree in India and did followup training and residency at Rush-Presbyterian-St. Luke's Medical Center in Chicago and Fellowships in Oncology Bone Marrow Transplantation with Stem Cell Biology at Washington University. He is a member of ASCO, ASH, The St. Louis' Society of Clinical Oncology, and The American Society…., Association for the Advancement of Science. He serves on numerous national committees, including the Myeloma Transplant, leukemia, committees of the alliance for clinical trials in oncology, and the steering committee of the MMRC. His honors include Multiple Myeloma Research Foundation Innovator award in 2013 and the MMRC Center of Excellence award. He is an author of over a 100 peer review publications as well as a book called Contemporary Management of Multiple Myeloma and has provided several chapters and books as well. He served as a reviewer for several journals, including Blood, The Journal of Clinical Oncology, Bone Marrow Transplantation, Experimental Hematology, and Haematologica. His primary academic interests include treatment of myeloma, stem cell transplantation for hematological malignancies. He leads many clinical trials and has established a large myeloma tissue bank at Washington University with strong institutional focus on studying the genomics of this disease, which are really critical to understanding what causes myeloma and how to cure myeloma. So, as you can see, this is Ravi Vij…, Dr. Ravi Vij embodies the myeloma specialist. So, thank you, doctor, for being with us today.

Dr. Ravi Vij – Thank you for that kind introduction.

Gary Petersen – From ASH and ASCO, Dr. Vij, it looks as though 2016 was another huge year for the advancement of multiple myeloma treatment. Can you provide a summary of the evolution of myeloma treatment in the last year?

Dr. Ravi Vij – Yeah. I think that is certainly, you know, understatement. It seems that we had a banner year in 2015 with the approval of four new drugs and maybe, you know, we were in for a period of, you know, lying low in new therapeutic developments in myeloma, but, no, 2016 proved that the field is showing tremendous advances. I think that certainly the gamut of advances has been right from findings in genomics to further confirmation and of minimal residual disease as an endpoint in myeloma to trials both with stem cell transplantation which I think continues to form the backbone of therapy and incorporation of new treatments into the transplant paradigm, including the use of Kyprolis-based induction regimen and then towards the end of the year, at the American Society of Hematology meeting, we saw new drugs and new targets as well. I think that we have seen some data emerge even in 2015 on the utility of checkpoint inhibitors and I think we saw more data on pembrolizumab. We also saw a new target BCMA emerge in 2015, and 2016 had many more trials reported with CAR-T cells targeting BCMA and also an antibody drug conjugate. So, I think BCMA is probably going to be a target that will lead to new therapeutic advances in the years to come. We also saw data emerge on venetoclax which is a drug that is on the market for chronic lymphocytic leukemia, but it appears that it may turn out to be a drug that…, especially for certain subsets of patients with myeloma, has very robust activity. Selenexor, another drug that has been reported on earlier but saw a large body of data presented at the American Society of Hematology meeting, looks like another drug that could be, you know, one day commercially available for multiple myeloma and we saw certain other intriguing, you know, presentations during the year and publications and manuscripts. So that, I think, is a broad overview of the field but certainly would be, you know, willing to go into depth and detail on what interests the audience.

Gary Petersen – Okay. Also, what do you see as the significant developments for treatment this year, in 2017, building on what we've seen in 2016?

Dr. Ravi Vij – I think we are going to see more trials in a read out with the agents that I have discussed. We'll see more transplant studies, possibly the European ones mainly, reported. I think that there will be,

you know, more data on these agents, that I just went over, emerge. I don't think that there will be any major change in the paradigm of treatment. It is still going to be, I think, for those who are transplant eligible that transplant either at time of initial diagnosis or at time of post progression would remain the treatment of choice. The use of induction regimen continues to evolve. Velcade, Revlimid, and dexamethasone for transplant-eligible patients is, I think, the most accepted de facto standard of care, if there is one, but intriguing data has emerged with the use of Kyprolis-based three-drug regimens like Kyprolis-Rev-dex. So, I think that there is increasing use of the Kyprolis-based three-drug regimens which may continue to in 2017 be the focus of more attention. We may, in the induction regimen, see certain trials read out. Elotuzumab with Revlimid and dexamethasone is approved for use in relapsed refractory disease, and data on frontline use of the regimen is awaited. Maybe 2017 will be the year, I think, it is data that has, you know, continued to be followed by the Data and Safety Monitoring Board and depending on when the events that are pre-defined occur, we may see data. So, I think that in the future, probably not in 2017, we will also see possibly data on ixazomib and Revlimid with dexamethasone in frontline treatment and following that further down the road, daratumumab-based three-drug regimens.

Dr. Ravi Vij – I think that with the advent of monoclonal antibodies, people are now starting to study four-drug regimens which are based on proteasome inhibitor, immunomodulatory drug, steroid, and monoclonal antibody. So, I think that we may see some data emerge in 2017 on these four-drug regimens. I don't think it will become close to any standard of care, but tolerability and efficacy data may start to emerge. Post transplant, I think that once again maintenance therapy with Revlimid will remain the standard of care, but there are a number of trials looking at either ixazomib or monoclonal antibodies in combination with Revlimid that we may see some pilot data emerge. Once again, they will not become any standard of care in 2017 but will be important to see how the data looks like at first glance and I am sure there will be unpredictable, you know findings emerge from genomics. It is an area of active research, and one can never predict what this field will come up with and I think that people will now, I think, start breaking up myeloma into smaller buckets and perhaps start to evolve paradigms of treatment for certain chromosomal or cytogenetic risk groups. There will also be molecularly targeted treatment based on mutation analysis that trials these umbrella trials and basket trials are new trial designs that have started to emerge in other cancers and I think in myeloma we will start seeing these emerge where basket trials are based on certain mutations that you give patients uniform treatment irrespective of their cancer diagnosis, whether they are lung cancer, colon cancer, or myeloma, for that matter if they have a mutation, they are all enrolled in a single trial. Such trials have already started and I think will continue to evolve, but then there are these umbrella trials which are slightly different than the basket trials where you restrict yourself to one disease, so in this case it would be myeloma, but you break the disease up based on their genetic profile and tailor individual treatments to certain genetic subsets.

Dr. Ravi Vij – I think that at a broader level this may have started happening with venetoclax. I think that the data that emerged with venetoclax at the end of the year showing that patients who had translocation 11;14, especially if they had overexpression of this protein called pCL2 had very impressive responsive rates; and even if patients had progressed on prior treatment with, like Velcade, you could actually salvage patients by just adding venetoclax. So, I think that those kind of things will continue to emerge and its somewhat, as I said, unpredictable what the next finding will be, but we hope that this will continue to evolve. All the stories that we started in 2016 will continue in 2017, including checkpoint inhibitor trials; and other immunotherapy approaches, I think CAR-T cells are certainly becoming a very active area of research, and 2017 I am sure will see more trials with CAR-T cells being reported. This is a very novel and powerful technology, albeit with potential for serious side effects as well, so needs to be still vetted and done in the context of closely designed clinical trials, but I am sure that with time one will get over some of the initial hurdles in this technology.

Gary Petersen – Good! Well, thank you so much, doctor. One other question and then I will turn it over to the panel, is I just noticed that Dr. Rajkumar and Dr. Durie and the whole panel at ASH had come up with treatment guidelines and I also noticed that you and Dr. Kumar along with Dr. Noopur Raje had worked together to provide a similar template for India, kind of paying it backwards if you want to call it that, but coming up with a template, is treatment philosophy becoming more congruent?

Dr. Ravi Vij – I think that again there are certain broad themes that certainly are emerging. I think that there is no complete consensus on how to treat myeloma that fits each individual. Such a cookbook approach is probably not even warranted. I think that we are actually in one way headed into personalized treatment, which actually suggests that trying to develop a congruent approach may not be the right thing to do and I think in some ways that is also supported by the science in this area that myeloma is not one disease, that at the genetic level there are different kinds of multiple myeloma which behave somewhat differently in clinical practice and trying to develop a strategy to treat everybody in one way is probably not the right way to proceed, but I think certain general things about the disease are, you know, emerging in that people are feeling that continuous therapy is probably better than the previously accepted approach of treat to best response, stop, and restart treatment. I think that more and more… There are still some who are not entirely convinced, but more and more people do feel that giving treatment, though maybe at less intensity after initial period of aggressive, you know, delivery is probably best for most patients. There may be some patients where getting them into a deep remission and stopping may be the way to go, but that subset has yet to be, you know, defined. It may in the future be able to be better defined if some patients could just stop treatment and resume at time of progression.

Dr. Ravi Vij – I think that giving patients better three-drug combinations and perhaps in the future four-drug combinations to increase depth of response, which in the future may actually incorporate, even on a routine clinical basis, assessment of minimal residual disease testing would be, you know, something that I think most top leaders would think is the way the field is headed. The minimal residual disease can quantify with current technologies, one cell in a million are cancerous in myeloma and that level of resolution and depth of response is something we've only recently started, you know, looking for mainly in the context of clinical trials and it has been validated that if you go that deep, you will have usually better outcomes both in terms of keeping the disease in remission for longer and improving longevity and I think that more and more trials are going to be, you know, looking at how they perform with that new benchmark in mind, the depth of response with MRD analysis will be what lot of people will be talking about as the ideal goal to achieve. So, I think that those kind of things, certainly people are, you know, developing some congruence of, but is there one treatment that fits everybody, is there a gold standard of treatment. I don't think so. I think that there are still many options both in frontline treatment and for relapsed refractory disease that can be tailored to an individual's unique situation.

Gary Petersen – Thank you so much, doctor. Jack, you online?

Jack Aiello – Yep. I am online and I really appreciate the comments you have already made, Dr. Vij, and I also had one favor to ask of you. Dr. Goldstein was my doctor at Stanford for about 10 years and I know he is one of your colleagues there now in St. Luke's and, I'd appreciate it if you could say hi for me.

Dr. Ravi Vij – I definitely will. I didn't know that.

Jack Aiello – Thank you! So, at ASH, one of the late breaking abstracts was Dr. Stadtmauer's report on the StaMINA trial, which showed that there was no efficacy difference when comparing a transplant to a transplant plus consolidation to a tandem transplant where all of these would be followed by maintenance and again, there was no difference whether you were looking at standard or high-risk patients in terms of efficacy and I wondered what your thoughts and responses and wondered if you could comment on that finding.

Dr. Ravi Vij – Well, it certainly came as a little bit of a disappointment that we haven't been able to move the needle any further than to what we have already demonstrated that transplant followed by Revlimid is the treatment of choice. We had hoped that in situation of a period of more aggressive treatment before going on maintenance post transplant or doing two transplants may actually be the thing that will be next advanced for transplant-eligible patients at least based on this trial that did not come to fruition, but I think that there are couple things that we need to be aware. One is that the European did another trial, the European Myeloma Network, and they asked similar questions, both in terms of the value of consolidation and the value of tandem transplantation and reached somewhat contrary conclusions. It remains to be dissected out why two

different results were achieved. They were certainly different populations, different kinds of drugs that were delivered, but the Europeans found that consolidation did improve outcomes and tandem transplant did improve outcomes as well and the other thing also is that the myeloma trials often are unable to show differences in early followup, but sometimes you see with longer-term followup that the analysis changed. So, I think that one will still need to follow these patients a little longer to be sure that the conclusions hold up with time.

Jack Aiello – I remember one of the doctors at that meeting asking about the length of induction also compared with the European trials and maybe the greater number of cycles inductions was used in STAMINA compared with Europe resulted in less difference between the three options.

Dr. Ravi Vij – Yeah, I think that there are postulates as to why the contrary results. There were different drugs that were used, the duration of treatment was different, though I think it is difficult to compare across trials, but all I can say is that the paradigm of consolidation and tandem transplant will probably continue to be explored in future trials. I think especially consolidation is an area of active research. Tandem transplantation is something that we've been studying now for more than a decade and a half and have kind of had, you know, somewhat contrary results from studies, but consolidation is a relatively new area of research.

Jack Aiello – My next question, you have mentioned minimal residual disease several times. So, my next question is when do you think MRD testing will be available to all myeloma patients who are in a complete response, essentially as common as the question and SPEP or free light chain test?

Dr. Ravi Vij – Yeah, I think we are slowly headed there now. One of the things is that the MRD analysis is done by two different technologies. One is called flow cytometry and one is called next generation sequencing. Now, the flow cytometry assay is non-proprietary, can be done in different institutions, but the problem there is it is a test that lacks standardization and you could get different results from different institutions. Also, its ability to detect minimal residual disease is a little less than what the next generation sequencing assay does. So, I think that the field is moving towards perhaps coalescing around next generation sequencing as it has to try to make commercially viable option. Now, the issue therein is that the test is proprietary to one, you know, provider adaptive which was formerly Sequenta is the company that does the test and the company at the moment, you know, seeking to get the data to file to get the test approved by the approving authorities. It is not yet a test that is Medicare approved, nor is it FDA approved. They are trying to get those designations and only then will it be covered by insurance. So, if a test is not covered by insurance, its difficult to adopt it as a clinical standard. So, we hope that within the next year or so that hurdle will be crossed and once that hurdle is crossed, I think you will start seeing it being utilized commercially much more. Still I think we will have to spend a few more years on even after commercialization of the assay is what to do with the results of the test.

Dr. Ravi Vij – We do know, as I said, that when you are MRD negative compared to when you are MRD positive, you are likely to have better long-term outcomes, so that's prognostic, but really the value of a test is even further enhanced if you can utilize that information to tailor your treatment and in that regard, people are wanting to, you know, study this test to try to inform treatment decision and two things that have been put out there as possible utilities for the test yet to be verified and studied are, 1) for those who have had MRD negativity, can we after a period of time stop the maintenance standard? As I alluded to a few minutes ago, maintenance or continuous therapy is thought at the moment at least for patients with myeloma the way to go, but it is an option that is fraught with side effects. It is also an option that is expensive. So, if we can call out a subset based on MRD analysis that if you are MRD negative for, say, 1 or 2 years and you can stop treatment, can some of those patients have very good long-term outcomes without any treatment. That is one potential thing that needs study. The other thing is that for those who are not MRD negative, should we either change treatment or intensify treatment to get them to that level of response to improve their outcomes. That too is unknown at this time, but with time we will, I am sure, gather data and then these tests will have practical utility.

Jack Aiello – Thanks for a very clear answer. My last question kind of follows what Gary asked about what will happen in 2017 and beyond? I think I heard you say that in 2017 you wouldn't expect treatments to result in standard of care approval. So, is that along the same lines of in 2017, you wouldn't expect the FDA to either approve new treatments or new treatment indications like they did recently when they approved daratumumab, for example, to be given, it would be the Vel-dex or Revlimid-dex in 2017?

Dr. Ravi Vij – So, I would say that the chances of new treatment per se being approved are a little low. These candidates that are up for, you know, I think the next group of drugs that would go before the FDA for approval are mentioned broadly as checkpoint inhibitors, mainly pembrolizumab, venetoclax, and Selenexor. I think that these drugs have launched, you know, large phase 3 studies that will probably take little longer than 2017 to read out. Now, there are obviously other methods to get drugs approved called accelerated approval and there are moves to try to get Selenexor and perhaps even venetoclax accelerated approval for a subset, but that is something that may or may not be (a) acceptable to the FDA as a strategy and (b) it will probably again not, you know, happen in 2017 and then I think that as far as the ability to get new indications for existing drugs, I alluded to the fact that, you know, the one trial that we have been waiting for a long time to read out, which may read out in 2017, is the frontline treatment trial of elotuzumab, Revlimid, dexamethasone versus Revlimid-dexamethasone. If that trial reads out, it may still be either towards the end of the year or early 2018 before the FDA approval comes because even if after a trial reads out, you got to get all the data together for an FDA submission and it takes several months even after the submission for the FDA to give its verdict.

Jack Aiello – And you said that was the elotuzumab, not the daratumumab trial. Right?

Dr. Ravi Vij – Correct. The daratumumab trial is going to be, I think, at least another couple of years away, maybe if they have remarkable results and you see, as you saw with their relapsed refractory trials and interim analysis, very promising results, then it may happen sooner, but I think that probably not in 2017.

Jack Aiello – Thanks very much, Dr. Vij. I will turn it back over to Gary.

Gary Petersen – Yeah. Thank you, Jack. Yelak, you online?

Yelak Biru – I am. Thank you, Gary.

Gary Petersen – Good.

Yelak Biru – Thanks, Dr. Vij, for making time to answer some of our questions. When you were discussing the emerging consensus around continuous therapy may be better than treat the best response and stop and then start again, can you comment how that approach translates to high-risk smoldering multiple myeloma patients? Is the consensus there now, you should treat high-risk smoldering myeloma patients early and forever then?

Dr. Ravi Vij – Yeah. So, the thing is that obviously we have had trials in the past for high-risk smoldering myeloma. The trial that caused most excitement a few years ago was one that was done by the Spanish group for high-risk smoldering myeloma that showed actually that Revlimid and dexamethasone possibly improved longevity for patients with smoldering myeloma. Now, that trial's findings have not been accepted at least on this side of the Atlantic by most folks and there is confirmatory trial ongoing to see if we can replicate that data. The criticism of the Spanish data is that it used non-standard methods to define high-risk disease and there were different criteria on defining progression in the two arms of the study. Now, the issue also is that since that time a lot of the high-risk smoldering that we defined have moved into the bucket of multiple myeloma already and based on their redefinition, that group of smoldering myeloma at least, you know. would warrant institution of treatment as myeloma. So, we are having to re-define what risk-smoldering myeloma is as the definitions changed, you know, about a little over a year ago now and so, with that, I think we are only now starting trials for high risk afresh with a new definition in place which will take a while to read out. All clinical trials right now, if you read a textbook or take an exam as an oncologist, the

right answer is for smoldering myeloma, there is no standard of care and observation alone is the recommended treatment, but it is, I think, a very ripe area for investigation to see if we can change the national history of the disease by intervening early and in that regard, a lot of different approaches are being tried.

Dr. Ravi Vij – Monoclonal antibodies, both elotuzumab and daratumamab, are being looked at and some people are actually taking an even more aggressive approach to smoldering myeloma, which I think is appropriate in the context of a clinical trial but can't obviously be, you know, endorsed outside of a trial where they are actually talking about giving them very aggressive induction, four-drug induction, than actually doing a transplant for smoldering myeloma, which again, their rationale is, if you really want that, if you want to go after a disease when its absolutely at its beginning stages, do it aggressively like a sledge hammer-like approach and maybe you can cure some patients. So, again, I think those trials are starting. So, it will be a few years, I think, before any change in the standard of care recommendations to high-risk smoldering myeloma is made.

Yelak Biru – Okay. Thank you for that. I know you have given a full show on this topic, but can you talk about groundbreaking work your university, Washington University, is doing around nanotechnologies? What is nanotechnology? What is potential implication for the treatment of myeloma?

Dr. Ravi Vij – Sure. So, nanotechnology is disease diagnostic, you know. It is a technology that can help any kind of cancer. We certainly have got Center for Multiple Myeloma nanotechnology established with NIH funds about a year and a half ago and are trying to use the technology to further the approach of both diagnostics and treatment for multiple myeloma. So, nanotechnology is the use of very small molecules that literally you can fit, you know, hundreds of them on to the thickness of a human hair literally and to use these compounds to deliver drugs in a targeted manner to give drugs to improve their effectiveness to side effect profile and using this technology to better image multiple myeloma, developing technologies better than PET scans for multiple myeloma. Those are the approaches that we are exploring in multiple myeloma with nanotechnology, but as I said, nanotechnology has applications not only in other cancer, it has applications in other areas of not only medicine but engineering and so its a very broad field, more to do with material science and biochemistry and bioengineering and we are collaborating with these people who are far removed from the day-to-day treatment of cancer to use their expertise to improve outcomes of patients with multiple myeloma. So, this is something…., but also intriguingly, you should know that the benefits of nanotechnology have in some ways already been demonstrated in myeloma. Not too many people realize that Doxil which is a drug that's the FDA approved for myeloma few years ago is a nanotechnology, you know, product. It encapsulates adriamycin in these liposomes which are nanoparticles to guide better delivery of these. So, that was the first generation compound. Now, we have much better ways to encapsulate and deliver drugs…, better drugs for delivery. So, we are hoping that this will further improve one-day outcomes of treatment of patients with myeloma.

Yelak Biru – Perfect! Thank you for that. So, my last question is around drugs and drug courses. Last year, if you remember, you along with Dr. Vincent Rajkumar were the myeloma experts advising ICER in the St. Louis area last year. I was there also representing patients and last year the SWOG 777 study was published and three-drug combinations are becoming standard of care and you also earlier mentioned we may be over time transitioning to four-drug combos, not necessarily as a standard yet. Can you discuss what, if anything, can be done to increase access to myeloma treatments cost effectively because most of these novel therapies are costing a lot of money and not everybody has access to that. So, what is your vision, if you would…, how we may be able to make drugs available and accessible by a bigger patient population?

Dr. Ravi Vij – Yeah and this is obviously an area that I am not absolute expert on, value-based payments and, you know, drug cost economics. My role at ICER was as a disease data expert to advise a panel of people who were having, you know, some expertise in this area to try to guide their decision making by telling them about how we treat myeloma. I, do you know, was not a voting member of this panel but was essentially telling the panel what the paradigm of treatment for myeloma is. Now, as far as the approach to

improving access to drugs goes, I think that partly it is tied into the paradigm of value-based care and drug access is something that has multiple dimensions. Access may also mean access to physicians that can appropriately direct treatment, but I don't think that was the intent of your question. I think you are hinting more at the cost-to-benefit paradigm. Is that what your question is more clear towards?

Yelak Biru – Yeah. I was expecting… Yeah.

Dr. Ravi Vij – Correct. Yeah. So, the thing is, as you know, there are several now more efforts to try to see how we can define value in oncology. ICER certainly is one organization that is trying to do it with an approach of quality, you know, QALY, quality-adjusted life year approach, which to a lot of people is not acceptable. It is an approach that the Europeans have, you know, followed for a while, but culturally and, I think, socially in the United States has been very difficult to sell, but…, and whether it is the right approach is also very questionable and I think that I am not an expert on QALI and can't say how those calculations hold up, but the good thing is that there are other organizations like ASCO, American Society of Clinical Oncology, which has its own value framework that was, you know, put out there last year, which seems to have a totally different approach to determining the value of drugs and they base it based on the kind of trials, phase 1, phase 2, whether there are quality of life improvements for patient in these trials and a number of other factors. I think that approach has the endorsement of the society to which most oncologists belong.

Dr. Ravi Vij – Then, there is the NCCN approach, which is the National Cancer Network and that is an approach based on what we call evidence block. They give different weightage to five different parameters but leave it to the voting members or the panel in that disease state who with their best acumen ascribe values to each of those, you know, treatments and they upfront admit that these physicians are probably not qualified to make these determinations but feel that by pooling a diverse group of 20 to 25 specialists that they will at least be able to put out there something which is halfway coherent. So, that is another approach. There is the approach that is being led by Memorial Sloan-Kettering which is called Abacus which is a different approach to defining value, which one of these is the right approach or whether an amalgamation of these is best remains to be determined, but as regards how to bring down drug costs, again I am not a policy expert, but I think most of use have read the debates that rage in our daily newspapers about ways to bring down drug costs including allowing the importation of drugs, allowing Medicare to negotiate drug prices to perhaps, you know, what the industry favors, which is perhaps ascribing different prices to the same drug dependent on the disease for which it is being treated. So, they want to explore models where if a drug gives one year improvement in survival in one disease, it is for that disease actually got a different price than a disease b where its benefit is more modest, or to have approaches that are being explored again in some parts of Europe where you actually are given the drug for a certain number of cycles free of cost and then if it works, then you pay the full tab; if it doesn't work, you don't get the drug anymore and you don't pay for it.

Dr. Ravi Vij – So, there are all these different approaches that the various stakeholders wish to, you know, pursue and I think that one of the simplistic things that I said at the panel was that perhaps nobody doubts that drug companies do have to, you know, recover their developments costs. These are very expensive drugs to develop. For every drug that comes to market, probably 10 fail. So, we do recognize that the industry does a yeoman's job in bringing these drugs to market. These are very high-risk gamble, but perhaps with time as people outside the United States become a little more affluent, we could spread the charges, you know. I made a very simplistic statement that if you want to recover 3,000 dollars, you could sell it to three people for a thousand dollars or you could sell it to 30 people for 100 dollars and still recover the 3,000 dollars you want. Granted that there are regulatory hurdles in these other parts of the world, they are becoming more affluent. Its not as easy to just go and say, you know, we will just start selling more drugs in more parts of the world, but I think that it is something that you need to at least think about.

Yelak Biru – Thank you for that great overview. Gary, I am done.

Gary Petersen – Yes. Thank you very much, Yelak. What I would like to do now is open it up to the callers. Priya, do I have any callers online? If not, there is a couple of questions, one of which the doctor has already

talked about.

Priya Menon – Yes. Thank you, Gary. I think we have a couple of questions that have been sent in by our listeners. Dr. Vij, the first one is, it seems as though there are so many drugs to treat myeloma now. I am really confused. I have stage III disease and I am 65. Is there a best initial treatment?

Dr. Ravi Vij – Again, as I sort of alluded to in my initial comments, there is no one best initial treatment. I think that you do have to tailor treatment based on an individual and this depends on not only the age and the stage but also on other factors like what we call the performance status of the patient, what the vital organ functions of a given patient are, to some extent what their chromosomal feature of the disease is. So, I think that for those that are otherwise healthy, most people feel that a three-drug combination of bortezomib with lenalidomide and dexamethasone or VRd as we call it, is as close to a standard as people would be willing to accept, but then people want to improve upon that and are exploring even outsider trials, drug regimens like Kyprolis with Revlimid and dexamethasone, which at least in the United States, in most areas is a covered benefit through insurance because it is what we call Compendium listed by the NCCN at a level of evidence that Medicare has already pre-approved for coverage.

Priya Menon – Thank you, doctor. The next question is about venetoclax and Selenexor. I think I heard you mention one of these right at the beginning. The listener writes in saying venetoclax and Selenexor are two new names that I am hearing in the myeloma circuit. Can you talk a bit about these new drugs?

Dr. Ravi Vij – Yes. So, venetoclax, as I said, is a drug that is approved for treatment of leukemia called chronic lymphocytic leukemia, wherein it has shown very remarkable activity. People have explored venetoclax as a single agent in multiple myeloma. For all commerce, it had a relatively modest benefit, but for those 20% of myeloma patients that have the translocation 11;14 on chromosomal analysis, it showed that 40% of these patients responded to this drug and then when combined with Velcade, the responses were even in patients who had prior progression on Velcade, even more robust. So, that is why I said this may be the first drug that in the future we may see approval for a certain subset of myeloma. Most drugs in myeloma or all drugs in myeloma right now are approved for all patients with myeloma. In the future, this drug may get based on how it is developed, a more narrow indication though the trial currently being done does hope to get a broad approval because even in the non 11;14 translocation, it has activity, maybe not as good as the 11;14 translocation group and then as regards Selenexor goes, once again it is a drug that has single-agent activity. About 20% of patients who had failed all available treatments that the FDA has approved responded. When combined with, again, Velcade and when combined with carfilzomib, it showed that about two-thirds of patients that had progressed on those drugs, Velcade or carfilzomib, responded when Selenexor was combined with the drug, suggesting that it re-sensitizes the cancer cells to these drugs in some way. The drug is something that again is being looked at as a single agent for accelerated approval as I mentioned. They are enrolling a hundred more patients with what we call penta-refractory disease, that is patients who are refractory to the five drugs, carfilzomib, Velcade, pomalidomide, lenalidomide, and daratumumab and if the FDA buys that, you know, we may see the drug come to market sooner than waiting for a full phase III large study to read out. The drug, however, does have some side effects in terms of gastrointestinal intolerance with nausea, diarrhea, weight loss being issues for some patients. So, it is something that one needs to be aware of.

Priya Menon – Thank you, Dr. Vij. Gary, I think you have a couple of questions more. Maybe we can just ask them and then.

Gary Petersen – Sure. If monoclonal antibodies were the big story for 2016, it seems like new targeted therapies and immunotherapies took center stage this year and what are the significant findings in this area of research?

Dr. Ravi Vij – I think that the two things that probably we've mentioned in this area to emphasize is, one is CAR-T cells which are very, you know, much in the news in a number of diseases where genetically modified immune cells are introduced that are sort of targeted to the tumor of interest and with this, as I said, BCMA is

the target that most of these trials have utilized with very impressive responses even in patients that had progressed on eight or nine different kinds of treatment, but as I alluded to, there are some patients with this treatment that get seriously ill, end up in the ICU with infection-like problems and some unfortunately have serious issues with confusion, delirium, and a few cases where this has unfortunately led to, you know, adverse outcomes with patients succumbing to the side effects, but as I also alluded to, I think that these are things that we will, with time, be able to get over and so CAR-T cells are one area.

Dr. Ravi Vij – I think that the checkpoint inhibitors which is another group of drugs that we have seen reported in our daily newspapers on the front pages as being miracle drugs for a variety of diseases, right from lung cancer to, you know, to kidney cancer to melanoma, are showing that when combined with either Revlimid or pomalidomide have very robust activity. So, those two are the immunotherapy modalities that are the farthest advanced, but immunotherapy is a very, very broad area of research and there are a number of other approaches, including vaccine therapies, what we call engineered antibodies where you just don't use the antibody like you do daratumumab or elotuzumab, but you actually change the structure of the antibody to make it more effective, giving rise to these other technologies called BiTEs or Dots and then antibody drug conjugates where the antibody is linked to a chemotherapy molecule to target it to the myeloma cell. Those are all areas that I think we will see result in the next year or two, start to look very encouraging.

Gary Petersen – Are you aware, well, do you know about MILs… Dr. Borello…

Dr. Ravi Vij – Yeah. Sure. So, MILs is one of those other areas of immunology that is showing the marrow-infiltrating lymphocytes that Dr. Borello from John Hopkins has published in Science Translational Medicine a few months ago, was very impressive. There are other…, you know… There is another company called Adaptimmune which has a very slight variation on the MILs which is directed at this antigen called NY-ESO 1. So, all these are things that at least in initial single-center studies have looked promising. We need to see how their potential holds up with more broad applicability when studied in other centers as well.

Gary Petersen – Okay. Well, I think all the other questions that I had, we've pretty much covered. So, doctor, thank you so much for your time. I know you are pressed to go to another call in just a few minutes. So, I think I'll turn it over to Priya to close.

Dr. Ravi Vij – Thank you very much and thank you for your invitation.

Priya Menon – Thank you, Gary. Thank you so much, Dr. Vij. I think lot of interesting myeloma information and quite a lot to look forward to in this year. So, thank you very much. Thank you, Gary, Jack, and Yelak. The talk will be put up on CureTalks' blog site for playback along with its transcript. Please visit curetalks.com for details on our upcoming talks. We are also very excited to announce that we now have a CureTalks channel on Roku TV. So, if you miss this talk you can always catch it on CureTalks Roku TV. Thank you! Have a great evening.

Dr. Ravi Vij – Thank you!

Gary Petersen – Thank you.