The New Optimism of Combination Therapies in Multiple Myeloma Treatment.

Clinical trials of new combination therapies are showing promising results and can be a game changer in myeloma treatment – Combining standard drugs with monoclonal antibodies, t-cell therapies with stem cell transplants, myeloma vaccine combinations and more. We are talking to Dr. Saad Usmani on the most relevant combination therapies and new myeloma treatments in the works patients should keep track of.

Full Transcript:

Priya Menon – Good evening and welcome to CureTalks. I am Priya Menon, Scientific Media Editor of CureTalks, joining you from India; and this is CureTalks' 103rd episode. Today, we are talking about multiple myeloma. Before we begin with today's talk details, I would like to take a few minutes to mention about the new study CureTalks is involved with. The study called America Walks is the first mobile app study on walking. The study is sponsored by our sister concern, Trialx.com, and is led by Dr. Chintan Patel. The purpose of the study is to determine your walking pattern and how much you are actually walking. You can also compare your walking habit with that of your friends and peers in your state as well as in your country. To participate in the study, all you need to do is download the app on your iPhone or your android phone. The details are available at trialx.com/americawalksstudy. So, let's get America walking.

Priya Menon – Coming to today's talk, my co-host is myeloma survivor and editor of myelomasurvival.com, Gary Petersen; and supporting Gary on the panel is our myeloma panel of Jack Aiello and Cynthia Chmielewski. Welcome to CureTalks. Clinical trials of new combination therapies are showing promising results and can be game changers in myeloma treatment combining standard drugs with monoclonal antibodies, myeloma vaccine combinations, T cell therapy with stem cell transplant, and more. The myeloma panel is talking to Dr. Saad Usmani on the most relevant combination therapies and new myeloma treatments in the pipeline patients should keep track of. Dr. Usmani is director of plasma cell disorder program and clinical research in hematologic malignancies at the Levine Cancer Institute. Welcome to CureTalks, doctor.

Priya Menon – Before I hand over to Gary to introduce Dr. Usmani and begin with the discussion, I would like to remind our audience that we will be addressing questions sent in by listeners towards the end of the discussion. If you have a question for Dr. Usmani, you may press 1 on your keypads and let us know or you can mail your question to me, priya@trialx.com, or post it on our CureTalks website. With that, its over to Gary. Gary, you are on air.

Gary Petersen – Well, thank you so much. I appreciate all that you do, Priya, and…, and the fact that you are probably up late, late, late or early, early, early, I can't remember. What is it?

Priya Menon – Yeah, its… (Laughter) Its early, its like around 2:30 a.m. here.

Gary Petersen – Yeah, we really do appreciate that. Yeah, you have given up your sleep for all of us here in the United States and…, and much later than that for the folks in Europe, but thank you so much for all that you do for us and…, and we will be thinking about you this weekend as we celebrate Pat Killingsworth, our dear friend and associate, who will be sorely missed this weekend as we have his myeloma survival school, but obviously its a sad, sad day for us, but its great that we have Dr. Saad Usmani here today; and Dr. Saad Usmani is the clinical associate professor of medicine at UNC-Chapel Hill School of Medicine. He is also the director of the plasma cell disorder program at, I think its Levine Cancer Institute, director of clinical research in hematological malignancies at the Levine Cancer Institute, Carolinas Healthcare System. So, Dr. Usmani received his medical education at Lahore, Pakistan; and I am not sure that's the same as Dr. Asher Chanan-Khan, who is here in Jacksonville, completed residency in internal medicine at Sinai-Grace Hospital/Wayne

State University in Detroit, Michigan; fellowship in hematology and oncology at the University of Connecticut Health Center in Farmington, Connecticut.

Gary Petersen – Dr. Usmani is a member of the International Myeloma Working Group, the Southwest Oncology Group Myeloma Community, the American Society of Hematology, the American Society of Clinical Oncology, and the American Society of Bone Marrow Transplantation. He also serves on the ASCO, American Society of Clinical Oncology Scientific Committee on lymphoma and plasma cell disorders, the ASH committee on plasma cell neoplasia, and NCI Myeloma Steering Committee. Dr. Usmani is on the educational review board of numerous medical journals, has authored, co-authored more than 70 peer review research manuscripts and 90 abstracts at national and international meetings. He has also served as the major PI and co-PI for over 35 clinical trials (phase I-III), a specialist in hematology/medical oncology, bone marrow transplantation. Dr. Usmani's clinical and translational research has focused on high-risk multiple myeloma and for all of us who have multiple myeloma, we recognize that if we can solve the key to high-risk multiple myeloma, we will, in fact, have solved the key to all myeloma. So, Dr. Usmani, thank you so much for all that you do for us and…, and not only that, all…, all of that which I just talked about, I understand that…, that you are…, you are, in fact, torn between doing this and everything I just said and…., and being a world class cricket player. Is that correct?

Dr. Saad Z. Usmani – (Laughter) Thank you so much for…, for the introduction, Gary, and you are right, you know, it was…, it was a tough decision, but I was young and…, and my father just like any…, any Pakistani or…, or Desi parent, as Priya and I would call it, you know, he…, he showed me the way. He told me the way.

Gary Petersen – (Laugher) Told you the way! Well, we are so thankful that he showed you the way because we certainly appreciate all that you have done and continue to do in…, in myeloma…, in myeloma research and myeloma…, myeloma care as well. So, Dr. Usmani, we have been blessed by an outpouring of new drugs this year. Its amazing how many new drugs have come just in the myeloma space where 1% disease and…, and for me, that's amazing that people like yourself would even operate in that…, in that area because, you know, there's so many other opportunities out there, but it happens to be one of the most difficult and most promising and…, and…, and I think for most people just a challenge and thank you for being there, but…, but what are the drugs and what are those drugs and the combination of those drugs would you see has the most promise for the future?

Dr. Saad Z. Usmani – Gary, this is truly an exciting time to be a myeloma researcher. Despite our challenges of still understanding and grasping the disease biology, we have been, you know, very successful and…, and fortunate in many ways to… to have the ability to investigate, you know, several different mechanisms of actions or drug classes in myeloma today; and I think with these new drug approvals, I think we are still scratching the surface. Even though we have, you know, nine drugs that have been approved in myeloma and four last year, we have to appreciate that, you know, even though these are newer drugs, for the longest time, you know almost a decade, all we had in terms of novel therapies was a class of drug called IMiD or immunomodulatory drugs and proteasome inhibitors. So, what…, what's the most exciting thing in the past two or three years as a myeloma researcher and…, and early drug development clinical trialist is that we have new drug classes like HDAC inhibitors and then monoclonal antibodies that are targeting specific surface markers and pathways that are being developed. So, all of those things are…, are very exciting. You know, the…, the senior myeloma researchers from the 80s, 90s, and even early 2000s, you know, their challenge was ,trying to move away from conventional chemotherapies which cause a lot of side effects and.., and…, and truly move more towards selective therapeutic targets and trying to improve the side effect profile of.., of these drugs. So, I think we have been very fortunate that we are in an era where we have a lot of these therapies in development; and I would be happy to elaborate on them based on, you know, what you would like to ask me.

Gary Petersen – Well, you know, I guess, what are the…, what are the…, you know, there are so many or there are four new drugs that came up, panobinostat, daratumumab, Ninlaro, what…, you know, what are the combinations of those drugs that you see that have the most promise for the future?

Dr. Saad Z. Usmani – Okay. I think panabinostat when it was approved by the FDA, it was approved based on its combination with a proteasome inhibitor, bortezomib, and it…, even though it had demonstrated overall survival benefit, we were concerned about the side effect or safety profile where we saw lot of GI side effects and…, and increased neuro…, neurotoxicity effects with that combination, but the bottom line with that combination specifically was that that platform worked for patients. Combining a proteasome inhibitor and IMiD had been for the longest time our…, our mainstay for treatment, but now we had a new platform, which is PI combining with a new class of drugs called HDAC inhibitors. So, you know, in reality, panobinostat will probably partner better with safer or…, or better tolerated proteasome inhibitors. I see for panobinostat the combination with Kyprolis or carfilzomib will likely be better tolerated and that's probably where we'll find this, you know, this drug being partnered with.

Dr. Saad Z. Usmani – Ninlaro or ixazomib is the first order proteasome inhibitor that has been approved for patients beyond one sideline of treatment in combination with lenalidomide and dexamethasone and that provides a very good all-oral option for patients where you want to combine an IMiD with a proteasome inhibitor as the line of treatment. The elotuzumab which is an antibody targeting a surface marker called SLAMF7 which is the, you know, highly expressed by the plasma cells. That also got FDA approved in a very similar line of treatment, so… , so patients who…, who had one prior line of treatment up to three prior lines of treatment. The exciting thing about that combination is…, is that elotuzumab, even though its an antibody and it needs to be infused, it does not have a lot of side effects and in patients who are responding, we are seeing sustained responses in a very unique mechanism. So…, so the patient's own immune system is being utilized to suppress the myeloma cells and control the disease and…, and that's…, that's quite exciting.

Dr. Saad Z. Usmani – The fourth drug, I believe, daratumumab is probably the most exciting monoclonal antibody right now by virtue of its single agent activity in patients who have more advanced myeloma, who have had at least three prior lines of treatment or they have become double refractory, which is, you know, refractory to lenalidomide as well as to bortezomib, which again have been our mainstay for, you know, myeloma therapy for over a decade. The…, the challenges with daratumumab are the longer infusion times, especially during the first cycle of treatment, and…, and infusion-related reactions which may happen in about half of the patients, but mostly those infusion-related reactions are mild and…, and easily managed by treatments that…, that we would give for allergic reactions to other monoclonal antibodies that we have utilized for diseases like lymphoma. You know, daratumumab is the first monoclonal antibody that actually has single agent activity in fairly advanced relapsed refractory patients. It had a response rate of roughly 31% in a combined analysis on 148 patients.

Dr. Saad Z. Usmani – The data was presented at ASH, which would mean that, you know, one in three, roughly one in three patients receiving the therapy will have benefit and…, and the exciting thing about that was, you know, you have now a monoclonal antibody that has activity on its own. You have a mechanism of action that has activity on its own. You can combine it with a proteasome inhibitor on its own as well as with an IMiD, so we are moving away from just an IMiD combination with the proteasome inhibitor. We now have these different drug classes; and we can combine these drug classes together and…, and, you know, the patients will continue to benefit from these combinations. So, you know, the…, the overall message that I would like to give, you know, we have all these drugs that are being FDA approved, but the way that we are thinking about these drugs is how do we combine specific drugs in a drug class with another drug in…, in the next drug class and…, and which patients do we choose to go for…, for certain combinations. That is something that we as…, as myeloma researchers have to work on over the next five years.

Gary Petersen – The checkpoint inhibitors, that's another class of drugs, which is kind of amazing to me is that we have daratumumab which is a monoclonal antibody, which is a brand new class of drugs where we have the IMiDs and the proteasome inhibitors, then we have daratumumab which is another class of drugs and as checkpoint inhibitors is another class of drugs as well. So, what…, what, you know, what kind of things can you say about that new class which is the…, the checkpoint inhibitors which seems to be a very exciting thing for many myeloma researchers?

Dr. Saad Z. Usmani – For sure, I think the checkpoint inhibitors have really changed the landscape of

oncology in general. The early data and excitement started from solid oncology research, specifically in metastatic melanoma and metastatic renal cell carcinoma when drugs like ipilimumab and nivolumab were being evaluated, but now we have drugs like pembrolizumab which have shown, you know, very unique and significant activity in…, in solids. The reason why I say unique, essentially you are…, you are trying to wake up the immune system which had become tolerant to these cancer cells and enabled the immune system to…, to make clonal T cells to go after cancer cells, which is…, which is very unique; and in…, in a normal person, in a younger person when…, when these…, when our body cells are dividing and making mistakes in division, one of the functions of the immune system is to take out the abnormal cells and that's…, that's one of the functions of…, of the immune system, but over…, over time as we age and our immune system becomes less competent, the immune system can become tolerant to these cancer cells and then eventually these cancer cells can start evading the immune system and what…, what these checkpoint inhibitors are doing is waking the immune system up and activating it to…, to try to counter the…, counter the cancer cells.

Dr. Saad Z. Usmani – So, this mechanism of action in general across the board for cancer is…, is very exciting; and we have several clinical trials where we are now evaluating monoclonal antibodies that are targeting the checkpoint inhibitor in a checkpoint pathway and combining them with proteasome inhibitors as well as IMiDs. You know, its…, its very likely that we will be combining some of the monoclonal antibodies that have single-agent activity with…, with each other, so its very likely that…, that we…, we may have an anti-CD-38 monoclonal antibody being combined with a checkpoint inhibitor in early phase clinical trials. We have been talking…, you know, several myeloma researchers have been talking to different companies to…, to come up with a clinical trial, you know, with that concept in mind and you can imagine, you know, having the advantage with monoclonal antibodies is the…, the safety profile being very favorable. If we can potentially come up with a two-monoclonal antibody combination, that may benefit our patients from the time of diagnosis onwards and it can keep the disease under check, you know, potentially for a long time. So, there is a lot of excitement there.

Gary Petersen – Well, thank you, doctor. Of these new combinations in drugs, do you see any of which are effective used…, used on patients with high-risk multiple myeloma and I know that, you know, that's one of the things that you are very much involved in is the high-risk multiple myeloma and that's kind of the area where we as cancer patients understand that ultimately we all end up at is, no matter how we start, we end up high risk and…, and if we don't solve high risk, then ultimately, you know, we pay the price. So, do you see anything there?

Dr. Saad Z. Usmani – For sure, the way…, the way that I would explain this is as follows: We have in the past developed myeloma therapies in a normal plasma cell biology way. So, when the proteasome inhibitors were developed, we understood that the proteasome is very important for the plasma cells, a normal plasma cell, and if you shut the proteasome factory down, then you can kill a normal plasma cell. So, we…, we took that concept and applied it to malignant plasma cells when we developed the proteasome inhibitor. Then, as we started to become more savvy, we started to think of specific pathway-driven therapy. So, if you recall, there were FGFR3 inhibitors being evaluated in clinical trials for myeloma. There are AKT inhibitors being evaluated for clinical trials in myeloma and what…, what that…, that approach is trying to do is go after the biology of the malignant plasma cells so that the second category of…, of the way that we are approaching, treating, you know, developing treatments for myeloma, check out the pathways that are active in specific patients and try to develop a…, a drug that can target that specific pathway in a malignant plasma cell.

Dr. Saad Z. Usmani – The unique thing about the monoclonal antibodies, however, is the monoclonal antibodies generally don't care what's going on inside the myeloma cell. They are going to go after what's on the myeloma cell surface. So, if the cell has CD38 overexpression, the myeloma…, the monoclonal antibody is going to tack that plasma cell and…, and try to take it out through three or four different mechanisms. So, the reason why…, why I am bringing that up is, there is a lot of excitement about the activity of monoclonal antibody in high-risk patients. The reason why high-risk myeloma becomes high risk is because of the genomic chaos that's going on inside the myeloma cell; and if we are developing strategies that do not care what's happening inside the myeloma cell but are going to be engaging the bone marrow micro environment and the immune system to go after the myeloma cell regardless of whatever pathways

are activity inside that cell, then that's a very different way of looking at treating a particular disease.

Dr. Saad Z. Usmani – So, I…, I truly believe that…, that with some of these monoclonal antibodies that are in clinical development that we will have good meaningful activity in high-risk disease. We will…, we are hoping to partner some of these monoclonal antibodies with available platform drugs for high-risk myeloma patients. The SWOG 12-11 trial was the first, you know, NCI-mandated SWOG cooperative group run clinical trial that combined elotuzumab for high-risk patients with RVD. That particular trial is now opening two new arms, hopefully later this summer, where one of the arms will be KRd and the other will be KRd daratumumab and…, and what we are hoping to see is, you know, meaningful, long-lasting responses and…, and survival outcomes for high-risk patients, again with…, with the caveat that, you know, with daratumumab we have already seen patients who have fairly advanced disease with deletion 17p who've been through every known available FDA-approved option and patients…, some of these patients are doing extremely well for extended periods of time with single-agent monoclonal antibody.

Gary Petersen – Well, you know, one of the things that I have noticed, at least in my local IMF support group, is that like you mentioned 17p, it seems like Ninlaro was one drug that seemed to be very effective against, you know, that particular chromosomal abnormality and if you had, you know, given the fact that 17p, the average life expectancy for high-risk patients is about two years, has consistently been that, here like three or four years on just Ninlaro and then recently when on another clinical trial which was I think ABT-199 and…, and her myeloma is undetectable. So, that…, that I thought was amazing.

Dr. Saad Z. Usmani – Yeah. So, ABT-199 is…, is another exciting, you know, class of drugs. Its Bcl-2 inhibitor and, you know, with…, with terms, you know, coming back to, you know, I'll try to come to Ninlaro first and, you know, that…, that is a phenomenal response and the way that most myeloma experts think of Ninlaro is an oral proteasome inhibitor, first in its class, but…, but has in terms of efficacy, it may not be able to overcome the high-risk features of p53 deletion or translocation 4;14 on its own. It can certainly improve the outcome, but it cannot overcome the poor prognostic, you know, features that are conferred by translocation 4-14. We feel that in terms of its activity, its very similar to bortezomib because it again belongs to the same class, is structurally very similar, and…, and we do not see it as being more efficacious than bortezomib. So, in terms of activity, its going to be, you know, what we feel is about the same.

[00:29:23] Dr. Saad Z. Usmani – If we had done a clinical trial looking at RVd versus Rd, I think RVd would have fared, you know, comparatively, you know, would have been comparable to IRd in the eventual outcome analysis, but having an oral regimen with better side effect profile to bortezomib is…, is what is, you know, the better measure of…, of ixazomib's advantage. You know, it is an oral agent. It causes less neuropathy than bortezomib. We have known that bortezomib can help or proteasome inhibitor-IMiD combination can help improve the outcomes in some TP53 or p53 deleted patients as well as translocation 4;14 patients, but we also know that.., that, yes, there is some benefit, but the poor prognostic implications aren't overcome. So, we still need to do a better job in finding better answers and combinations for high-risk disease. These anecdotal experiences tell you about how heterogeneous the disease is. There are patients who have p53 disease, who can actually do extremely well. The percentage of those patients is very low, but there are patients who can have extended survivals with even the standard available therapy.

Gary Petersen – Well, thank you, doctor. I…, I just think its amazing how many and what a team exists in the myeloma space and I…, I mean, the doctors, the researchers, the IMF, the MMRF, and the myeloma advocates, you know, and…, and how you guys have done such a great job in…., in…, in coming up with one-third of all cancer drugs for a 1% disease. Its crazy! You know, its…, its…, to me its a myeloma miracle and…, and I thank you and…, and all the people who…, who contribute to that. We have nine major drugs prior to this year for multiple myeloma and now we have four more. Basic math, you know, tells me there are 511 possible combinations with nine drugs and an astounding 8,191 possible combinations with 13 drugs. (Laughter) How does…, how does any specialist navigate this kind of complexity?

Dr. Saad Z. Usmani – The way that I would, you know, I would reiterate some of the messages that I tried to give early, the way that we are thinking of these drugs is by drug class. So, you know, within the IMiDs we

have thalidomide which we don't, which is FDA approved, but, you know, has…, doesn't have as much use here in the United States any more than it does in Europe. Then, we have lenalidomide and pomalidomide, each with its own utility in a certain…, you know, line or setting in myeloma. Then, we have the proteasome inhibitors – bortezomib, carfilzomib, and ixazomib. The HDAC inhibitors, we have one drug class. With an anti-CD38, its daratumumab right now, but _____ which is a Sanofi drug, its not far behind. With anti-SLAMF7 antibody, we have elotuzumab.

Dr. Saad Z. Usmani – The way that…, that we are thinking of combining these drugs again is, you know, for the upfront patients we still think of patients in a transplant eligible or ineligible way. So, we are trying to combine the best therapies to eradicate the disease as much as possible in…, in all patient groups, but to get to that point, we still have to combine these therapies in a disease…, in a…, in a meaningful way. We cannot do this in a…, in an Arkansas total therapy way where we are throwing all these drugs. So, we have to be a little thoughtful; and as we think about disease, we also have to think about cost. So, the way that we are approaching treatments, you know, we already have this platform of proteasome inhibitors and IMiDs that we have been using along with steroid. We have to think of partnering the best agent that will give us the best response for…, for this class of, you know, for different classes of drugs. For transplant-eligible patients, we are thinking of combining monoclonal antibodies with the three-drug combination like RVd or carfilzomib or KRd. For transplant-ineligible upfront patients, bortezomib or lenalidomide are being combined with monoclonal antibodies in the upfront setting. The idea is to improve the depth of response and survival outcomes.

Dr. Saad Z. Usmani – When patients are relapsing, one of the things that…, that we are looking at is prior treatments received, what kind of responses patients had to those treatments, what kind of side effects they had to those treatments, and what are the disease features that relapse. Whether its a biochemical relapse or a clinical relapse and…, and, you know, its not a simple decision or at least it…, it is a very personalized decision that has to be made for each patient. One key element that we are starting to grasp now in a better way is that, you know, we have been approaching myeloma treatment in a one-size-fit-all way for a long time, but myeloma is biologically a very heterogeneous disease. Its very likely that, you know, the 25,000 odd patients that are diagnosed with myeloma every year, they belong to 10 different categories biologically and its very likely that each of those biologic categories are going to respond to different drugs in different ways. We have to tease that out so that we can make the best decisions for our patients. So, you know, you've rightly said, I mean how does any myeloma specialist navigate this complexity. We are still trying to figure that out. Its not an easy answer.

Gary Petersen – Well, thank you, doctor, and…, and…, and…, and I often say, you know, to people who write to me on, you know, my…, my blog, myelomasurvival.com, that you need a doctor who is right in the mix of it to even attempt to navigate through such a minefield of possibilities and, you know, that I think that it was Dr. Colombo who said that if…, if your doctor doesn't see hundreds of patients with multiple myeloma that…, that they really aren't in a position to treat the disease because its that complex.

Dr. Saad Z. Usmani – I agree with Antonio's comments there. The challenge in the United States is not every region has a myeloma-specific program, you know. Eventually I think we will get there, but for…, for patients who are listening to this show and, you know, who…, who are being treated by a local oncologist and…, and you are not close to a myeloma center, its totally okay to continue your care with your current doctor if you…, you are comfortable but do seek out an opinion from a myeloma expert who lives close to you and have them as a backup to…, to look over things. This is something that…, that I keep on stressing. You are absolutely right. I mean the way that the field is changing, you have to have a myeloma expert in your back pocket who can help guide things, especially with subsequent lines of treatment.

Gary Petersen – Okay. Well, thank you, and that's kind of been my message over time is that there is a skill set that you obtain after you have been treating hundreds, maybe thousands of myeloma patients that nobody else can duplicate if they only see one or two. Jack Aiello, are you there?

Jack Aiello – I am, Gary. How are you?

Gary Petersen – Okay. Jack, I am so sorry to hear about your…, your father. That is so, so sad, I…, I can't even imagine, you know. I just thank you so much for…, for coming and contributing today. I know that you…, you must be in a…, having a very, very sad time. So, thank you, Jack.

Jack Aiello – Well, I am always appreciative of getting to talk to Dr. Usmani and I hope you are doing well, doctor.

Dr. Saad Z. Usmani – Hi.

Jack Aiello – I want to follow up on one of the questions in comment that was made about Ninlaro, which is also called ixazomib for the listeners out there and its the newly approved oral proteasome inhibitor unlike its cousins that are infused, the carfilzomib or the Velcade; and I am wondering, doctor, if you are having patients with the use of Ninlaro off label such as in induction treatment, first line treatment, or more likely even in maintenance where it becomes a much more convenient oral therapy versus the other two that I mentioned and as the maintenance, are you prescribing it to be used alone or with Revlimid or dexamethasone or both? Can you talk about that?

Dr. Saad Z. Usmani – Sure, Jack. You know, we have… What I can tell you is 2016 has been a challenging year for many patients from insurance perspective. I have had a lot of challenges trying to get… So, that…, that was my…, my first inclination now. You know, patients who are receiving bortezomib as, you know, as the single-agent maintenance because they have, you know, specific disease features or…, or convenience because they didn't want to be on an oral agent everyday. You know, when we try to get ixazomib, we are…, we are getting push back from the insurance companies. They would…, they would only approve it if its utilized with lenalidomide and for patients with one prior line of treatment. I have been able to get away with two patients, but for most of my patients I have had refusal and I have been unable to get this for the upfront setting at all. You know, I think it…, it would be a really cool idea, especially for transplant ineligible patients who may have high-risk disease, in…, in whom we are considering a proteasome inhibitor-IMiD induction to have that oral option, but we are getting…, I am…, I am personally getting a lot of push back from insurance companies despite the fact that we tried.

Jack Aiello – So, at this point, if I wanted Ninlaro on maintenance, I might be advised to see whatever clinical trial might exist for that. Correct?

Dr. Saad Z. Usmani – That is correct.

Jack Aiello – And same question along the lines of daratumumab, do you think there is going to be benefit in using daratumumab, Darzalex also called, in induction therapy and in what combination and with dara, when you are using it, how are you finding patients managing the long infusion times or dealing with side effects? So, kind of a two-part question.

Dr. Saad Z. Usmani – So…, so daratumumab is being evaluated in upfront clinical trials in the first relapse as well as the upfront setting. In the upfront setting, there are two large randomized phase III trials that have fully accrued. Well, one has fully accrued and the other is…, is…, is going to fully accrued in another four or five months. In the upfront setting, there is a trial that is comparing the combination of daratumumab with Rd or len/dex and…, and comparing that with len/dex on its own and this trial is for transplant ineligible folks. A very similar designed trial is…, you know, was…, was conducted or is being conducted in the first relapse setting and that trial had finished accrual about a year and a half ago. Its… Similarly, daratumumab, bortezomib/dex versus bortezomib/dex large phase III is being run in transplant ineligible, newly diagnosed folks as well as first relapsed patients.

Dr. Saad Z. Usmani – In fact, you may have heard about the press release today that the combination of the…, the trial in the first relapsed setting combining daratumumab with bortezomib and dexamethasone, you know, came…, came back with a positive result at the first interim analysis and these data will be presented at…, at the ASCO meeting in June 2016, which is very exciting, which means that, you know, the three-drug

combination for our first line setting patients was able to give a positive result very, very early. So, it was, you know, the difference was…, was so stark that they don't need a second interim analysis. So, its really exciting. The company is very mum about the results and…, and, you know, we are probably going to hear about this at ASCO in a couple of months.

Dr. Saad Z. Usmani – So, for…, for the transplant ineligible folks, dara is moving forward as part of, you know, as an independent mechanism of action that can be partnered with proteasome inhibitors. For the transplant eligible folks, its being combined with a three-drug combination. I can share, you know, some of my anecdotal experience with this combination in earlier lines of treatment. The depth of response is fairly robust and as we know that the deeper the response, the better the progression free and survival outcomes, you know, with therapies and myeloma. One of the major challenges with daratumumab has been the infusion time, especially the first infusion, you know, my site has been involved with dara development for over three years. So, you know, we…, we are…, we know that we need…, if…, if patients are coming in for daratumumab, its better to start the day early for their first dose. So, generally, patients are coming in between 8 and 9 a.m. and getting started on therapy so that they can finish on time within six or seven hours if they don't have a reaction, but if they do have a reaction, you know, it can make for longer days up to 8-1/2 to 9 hours and…, and there have been some instances that other investigators have reported that because they started late, they had to admit patients to finish the infusion. The way that the company is trying to mitigate that is by developing a subcutaneous infusion of daratumumab and that phase I is…, is accruing actively and I have several patients on that…, that study. The infusion time is about 30 minutes and its given subcu.

Dr. Saad Z. Usmani – The other thing that the company is…, is developing is a more concentrated formulation of daratumumab so that the infusion can be given much quicker. The side effects that we are generally facing are…, are low-grade side effects. So, patients presenting, you know, at when they are one hour into their infusion, they are developing some…, some itching, scratchy throat, runny nose, and giving Benadryl and…, and a small dose of steroids can, you know, mitigate the side effects. For the patients who develop grade 3 reactions where they are developing some shortness of breath or muscle spasms, you know, breathing treatments and high doses of…, of steroids or antihistamines may have to be given, but once that reaction is…, is over and the patients are re-challenged with daratumumab, we don't see the side effect or the infusion reaction coming back. We think the reaction happens because the daratumumab, you know, CD38 is expressed on many different cell sizes, including the respiratory epithelium. So, you know, there may be, you know, an inflammatory reaction in the respiratory epithelium the first time the patients are getting in and that's why we get those side effects.

Jack Aiello – Are the infusion times being decreased at all in subsequent infusions?

Dr. Saad Z. Usmani – Yes. So, from the second infusion onwards, the infusion time can be reduced to between three to four hours.

Jack Aiello – Thanks so much. Its always a pleasure talking with you.

Dr. Saad Z. Usmani – Thank you, Jack.

Gary Petersen – Yeah, thanks, Jack. Cindy, are you online?

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

Gary Petersen – Okay, Cindy! Your questions?

Cynthia Chmielewski – Okay. The first question I have, doc, is kind of a followup to what you were talking with Gary about, the importance of seeing a myeloma specialist and also the disparity is that, you know, there are some areas of the country where its not really easy to get to that myeloma specialist. Its not like where I was in the northeast. As the idea of telemedicine for myeloma specialist hasn't been

discussed, having virtual consultations like through Skype once your lab results or blood results are sent to a specialist. What do you think about something like that?

Dr. Saad Z. Usmani – I think that is an awesome idea and…, and it would be, you know, a great idea to develop regional myeloma team or boards like that. You know, we…, we are developing a mechanism here in the Carolinas of…, of making that available, you know, that mechanism available. It hasn't been rolled out yet, but the idea is, you know, you have a monthly teleconference where the community doctors can discuss their challenging or difficult cases with the myeloma experts at my program and, you know, I think we need to have more engagements like this with the outside communities which are, you know, three or four hours away from…, from the nearest myeloma center. I think that that's…, that's a fantastic idea, Cindy.

Cynthia Chmielewski – Great! I would like to be able to use some of this technology that we have to service the areas of the country that, you know, are kind of underserved. My other question is, I saw something about a new formulation of melphalan has been recently approved. Can you talk a little bit about what that means and how…, how is it different from the melphalan that we all received during our stem cell transplant?

Dr. Saad Z. Usmani – Sure. So, you know, the…, the way that melphalan has been formulated previously, you know, was, you know, for the longest time, I am…, I am trying to recall the name of the new formulation, but nevertheless, you know, the new formulation is a Captisol-enabled melphalan.

Jack Aiello – Evomela.

Dr. Saad Z. Usmani – There you go. Thank you. Evomela. So, Evomela is Captisol-enabled. Captisol is the same chemical compound that is utilized to stabilize carfilzomib, for example, and…, and the advantage of…, of using Captisol is to stabilize melphalan and…, so that it doesn't degrade and its PK or…, or pharmacokinetics and pharmacodynamics are…, are more…, more stable. So, the stability of the…, of the compound is…, is extremely important. The other concern that we have had with the older formulation of…, of melphalan, you know, is the potential for, you know, erratic toxicities, not simply the GI toxicities, but, you know, the concern about cardiovascular side effects or toxicity. So, you know, having this Captisol-enabled melphalan helps mitigate some of those concerns. I think Dr. Hari out of Medical College of Wisconsin was the myeloma investigator who evaluated the…, this…, this new formulation for patients in, you know, who are getting their stem cell transplant in the upfront setting as well as in the relapsed setting and…, and found it to be as efficacious as standard melphalan with some benefits from the side effect intolerability perspective as well. So, you know, it…, it…, it doesn't…, its not a major scientific advance but certainly makes, you know, the melphalan delivery a little more stable.

Cynthia Chmielewski – Okay. That sounds good. We talked a lot about….

Gary Petersen – One other thing on that same line is, I understand that because its re-formulated, this melphalan, that you can get higher doses and as a result, you know, these higher doses will allow you to have a better outcome. Is that…

Dr. Saad Z. Usmani – Yes. So, you know, with the old formulation, you know, the degradation…, melphalan degrades fairly quickly once its mixed in the bag. With the Captisol-enabled melphalan, you know, the degradation issue, just like you said, you know, will be…, will be overcome.

Cynthia Chmielewski – So, that…, so that the melphalan will be available in your body for longer period of time. Is that what that means?

Dr. Saad Z. Usmani – No. That…, that means that the dose that you calculated to give to your patient is the dose that will be delivered.

Cynthia Chmielewski – Okay. That's what degradation is. Okay. That sounds fair.

Dr. Saad Z. Usmani – So…, so, you know, the…, the chemotherapy is in the bag and its…, its breaking down even before the patient gets the dose.

Cynthia Chmielewski – Oh, I did not realize that. Okay. So, the way that its encapsulated, whatever that word is, it makes…, it won't break down as fast, so when it gets delivered to your body, its the dose that the doctor intended you to get.

Gary Petersen – It…, it kills your immune system better.

Dr. Saad Z. Usmani – And it can be…, so it can be…, technically it can be given over a longer infusion and…, and you can, you know, infuse it slower than…, than you would the regular propylene glycol-containing melphalan.

Cynthia Chmielewski – Okay. I think I got it. I have to read little bit more, but I think I got it. The other questions that I had, you may have some new listeners here on the phone tonight and we have been talking a lot about the high-risk myeloma. Can you just give us a brief understanding of what is high-risk multiple myeloma about? What percentage of people who are diagnosed with myeloma have these high-risk features and what do you think are the most exciting clinical trials for this group of people?

Dr. Saad Z. Usmani – All right. That is a very loaded question and you have asked… You know, I will try to answer it efficiently.

Cynthia Chmielewski – Okay. I am sorry.

Dr. Saad Z. Usmani – No, no, not a problem. So, in a very simplistic way, you know, high-risk myeloma is any myeloma that will result in a patient passing away within two years of diagnosis. Now, that…, that is a very simplistic way of…, of…, of putting this, but I do want to highlight that, you know, within high-risk myeloma, there are features that are patient specific and then there are features which are disease specific, that…, that can, you know, cause you to have high-risk disease. You know, you can have even easy-to-treat disease, but if you are not getting the right treatments because you have other comorbidities that will prevent you from getting treatment, you know, that myeloma may be high risk for…, for that particular patient despite the fact that they don't have, you know, nasty chromosome features or, you know, poor risk by gene expression profiling, but high-risk myeloma by disease biology is a very…, very broad group.

Dr. Saad Z. Usmani – There are many different ways in which we identify high risk. There are certain clinical features. There are patients who present with circulating myeloma cells in their blood stream, which we call plasma cell leukemia. We know that that kind of myeloma tends to be very aggressive. Then, there are patients who have extramedullary disease, which means myeloma outside of the bone marrow. So, patients presenting with myeloma collections in the liver or skin, even in the CNS or brain, those patients tend to not do well with standard treatments and have a high risk of relapse. Then, there are features on FISH testing which is a special test done on the bone marrow aspirate sample where we are looking for specific chromosome abnormalities. The translocations of chromosomes such as chromosome translocation 14;16 or 14;20 are considered high risk. Translocation 4-14 is considered intermediate to high risk. There are certain abnormalities on FISH like deletion of 17p which is considered high risk. So, these…, these FISH abnormalities, what they really mean is in the patients, chances of disease relapsing after frontine therapy is high because the myeloma cells tend to be a little more aggressive and perhaps more resilient to the available treatments.

Dr. Saad Z. Usmani – There are other second generation tests like gene expression profiling which can identify patients at high risk of relapse within their first two years of diagnosis. All in all, about 20% or 2 out of 10 myeloma patients will have high-risk disease and it will be, you know, one of these features that will be able to identify high-risk disease. It is a very heterogeneous population of patients and…, and which, you know, again, I…, I said this earlier on the show, that myeloma is not one disease, its many different diseases. So…, so the high-risk definition or…, or the high-risk category also includes these different…, different features.

Does that answer your questions, Cindy?

Cindy Chmielewski – It does. Thank you so much. I…, I think people have a better understanding of that. My other questions, I am just going to save for some other time because I see the listeners have some questions and we are starting to…, well, we are out time and I just don't want to take too much of your time up. So, thank you so much.

Dr. Saad Z. Usmani – You're welcome.

Gary Petersen – Dr. Usmani, do you have a few more minutes to take our listener calls?

Dr. Saad Z. Usmani – Yes, Sir.

Gary Petersen – Okay, fantastic! Thank you so much. Priya, could you…

Priya Menon – Thank you, Gary.

Gary Petersen – …bring on some of the callers?

Priya Menon – That was a wonderful discussion. Yes. We have a caller. Person calling in using **********, please ask your question.

Caller 1 – Good afternoon, Dr. Usmani. This is Dana Holmes. How are you today?

Dr. Saad Z. Usmani – Hey, Dana. How are you?

Caller 1 – I am good. Thank you. You know, I just wanted to interject that I…, I as a smoldering multiple myeloma patient find that its a very important message to deliver to patients to seek counsel with a myeloma specialist and honestly not… If you have the precursor diseases, don't wait until you find yourself in the myeloma world. Try to get to a specialist before and develop that rapport in the relationship because I really, really do think that that's critical for a smoldering patient for lot of reasons, to get the right diagnosis, to get the right evaluation, and the proper monitoring during that smoldering times. So, I appreciate you encouraging patients to do that as well. I have a question for you about Darzalex. I created a Facebook group actually for Darzalex patients, not only anybody who is using it but anybody who is interested and we have had a lot of interesting discussions and conversations and information sharing. Its really been very, very helpful for patients and especially new ones that are heading into the infusions and, you know, some of these discussions are also uncovering that people are already getting it in…, in different…, under different situations that are probably off label at this point. So, its…, its…, its curious to me that…, to see that already happening and I realize that from a clinical standpoint people do need this drug, but I think from a data standpoint that you tend to lose some of the, you know, the data when this happens. So, this is a.., you know, the double-sided point and I wanted to find out from you your thoughts about using Darzalex after a stem cell transplant, like in a maintenance setting.

Dr. Saad Z. Usmani – I think that music in the background…

Gary Petersen – Sorry, that's my phone…

Dr. Saad Z. Usmani – (Laughter) That's not a problem, Gary. Yeah, I… I don't think that's a good idea personally, you know, the…, the…, especially in the absence of data, you know, I don't think that is a very good idea to utilize daratumumab in a maintenance setting and…, and its not that, you know, we…, we won't see any clinical activity, but its…, its again, you know, the principle that you need to have some data to support what you are doing and if you don't, yeah, don't go, you know, seeking therapies for patients in settings where it hasn't been really examined because you won't know how to gauge the outcome. So, the

maintenance setting in a post transplant situation, you know, I…, I am not so sure. I mean its a good question to ask in a clinical trial, but to do it off label, you know, it…, it is…, it is going to be physically difficult and…, and especially in the absence of data, perhaps not the right decision.

Caller 1 – Good. Good. I…, I am…, I am thankful that you mentioned that and clarified that because I think its an important message to send out to folks, but again, I don't know if it will do anything but just that its not that people are aware of that. I…, I have a member in my smoldering group who…, who transitioned to multiple myeloma and she had her stem cell transplant with Dr. Hari and, you know, he's developed a trial or someone did, whatever it is, but there is a trial that he is now introducing a checkpoint inhibitor after…

Dr. Saad Z. Usmani – Yes.

Caller 1 – …stem cell transplant. So, he's actually capturing that important data to be able to…, to share amongst the community, so that's…, that's really just so critical I think as a patient also to do it the right way. Dr. Usmani, what is your thought about…, about two weeks ago Janssen's announced that they are going to be combining daratumumab with a checkpoint inhibitor, something called and boy, is this a mouthful, atezolizumab. Its basically a checkpoint inhibitor. Its an anti-PD-1 and they are combining that in the study and its a phase I. What are your thoughts about combining a monoclonal antibody and a checkpoint inhibitor?

Dr. Saad Z. Usmani – I think that is…, you know, we've…, we've talked to Janssen and…, and several drug companies who have checkpoint inhibitors, you know, about that possibility and I am…, I am really excited about that clinical trial. I can also tell you that there are other clinical trials with…, with similar concepts that will be coming down the pike. So, this…, this is not the only checkpoint inhibitor plus anti-CD38 monoclonal antibody clinical trial that is going to be run. There are others coming down the road as well and the…, you know, the concept is…, is really exciting and I am looking forward to it.

Caller 1 – Do you…, do you see it moving into the smoldering patient population for clinical trials because that's honestly, that's like my dream cocktail at this point.

Dr. Saad Z. Usmani – That is quite possible, but, you know, it may not happen until either later this year or…, or early next year.

Caller 1 – I'll… I'll hold on to my smoldering shoe until then, Dr. Usmani, and…, and when you open that trial know that I will be at your doorstep. (Laughter) Well, then, thank you so very much for your time. You are always so receptive and its just so incredibly great for patients to be able to…, to communicate directly with myeloma specialists such as yourself and I appreciate what you do for the myeloma community.

Dr. Saad Z. Usmani – Thank you. You're welcome.

Priya Menon – Thank you, Dana. Dr. Usmani, we…, we are just like almost 10 minutes over time. I'll just ask you one more question which has been sent in by and we can wrap up. Question is, how is the scientific community tackling the increased adverse events therein which is a part and parcel of combination therapy?

Dr. Saad Z. Usmani – We're trying to develop therapies that…, that have less adverse events, that, you know. I have…, I have tried to highlight the advantage with monoclonal antibodies and their safety profile. The fact that, you know, ixazomib being an oral agent appears to have, you know, less neurologic side effects than bortezomib. So, it is an advance from a safety standpoint. You know, the…, the main idea is (a) develop therapies that have less of an adverse event burden, and…, and (b) identify those adverse events early so that you can dose reduce and mitigate the side effects. I think those are the two key elements that we have to work on.

Priya Menon – Thank you, doctor. Thank you, doctor, for extra time too. Again, this is amazing discussion, great learning, and great listening. Gary, Jack, and Cindy, as always, thank you for your support and today's

talk for listeners will be made available on CureTalk's website along with its transcript. You can visit curetalks.com for details of upcoming talks and thanks a lot. Have a good day.

Dr. Saad Z. Usmani – You are welcome.

Gary Petersen – Thank you. Thank you, doctor.

Dr. Saad Z. Usmani – Thank you, Priya, Gary, Cindy, and Jack.