Myeloma Treatment Without Transplant

Treating myeloma without transplants, Dr. Berenson advocates 'Least is Best' treatment philosophy and in conversation with the Cure Panelists, Dr. Berenson explains his treatment approach.

Full Transcript:

Priya : Hello, everyone! A very good evening and welcome to the Myeloma Cure Panel. I am Priya Menon, Scientific Media Editor of Cure Talk. On behalf of the Cure Talk team of me, Sharib Khan, and Chintan Patel, I welcome all of you this evening for a discussion on multiple myeloma. We will be moderating the call and bringing people live on the show. This is Cure Talk's fourth myeloma Cure Panel and the Cure Panel Talk Show is doing very well with over 11,000 replays of this broadcast. The Cure Panel Talk Show was launched In August as a series of monthly teleconference calls where we brought together disease experts, patients, bloggers, activists, and family members for a discussion on latest cases. Cure Talk will continue to conduct Myeloma Cure Panels every month and we encourage myeloma advocates, patients, and bloggers to co-host the show with us. For more details of our forthcoming Cure Panel discussion, please visit Cure Talk website, trialx.com/curetalk. Our next panel discussion has been scheduled for January 2013.

Today on the Cure Panel, we have eminent myeloma expert, Dr. James R. Berenson from the Institute for Myeloma & Bone Cancer Research, IMBCR. On the panel, we have noted myeloma author and activist, Pat Killingsworth; myeloma survivor and advocate, Jack Aiello; myeloma blogger and patient, Matt Goldman. A big welcome to our expert, Dr. Berenson, and the panelists to the Cure Panel Talk Show. Today's show is co-hosted by Gary Petersen, editor of myelomasurvival.com. Gary is a six-year survivor of multiple myeloma and works with myeloma specialists to provide life expectancy and survival statistics through his site. Gary, I welcome you to the Cure Panel Talk Show. We have over 50 people…We have over 50 people dialed into our show and I extend my hearty welcome to everyone who is listening to the panel discussion. Before I hand over to Gary, I would like to briefly go through some important rules which would make your Cure Panel experience smooth. If you are listening in to the panel through your phone as well as the computer, please mute or stop the online broadcast for better audio quality. All panelists are requested to stay within the time limits allotted. Callers will be invited to ask questions at the end of the discussion. They can let us know by pressing 1 on their keypad and we will bring them online live. Gary would now introduce us to the topic of discussion and the expert. Gary, its all yours.

Gary Petersen : Yes. Thank you very much, Priya. First and foremost, I want to acknowledge all of the patients, myeloma patients, and caregivers that have chosen to participate on this panel discussion. The panel members, Pat, Jack, myself, and Matt, all believe that being your own best advocate and obtaining as much knowledge about multiple myeloma and treatment options is really critical to improve survival. So, all of the panelists, Jack, myself, Pat, and Matt, have one thing in common and that is we all have been treated by some of the very best multiple myeloma specialists and believe this is one of the few reasons for our successes as well and now I have the privilege to introduce the featured panel member who is one of the world's most renowned multiple myeloma specialist. He is a thought leader and is at one end of what I call the treatment continuum. This treatment continuum goes from the least treatment is best to the most treatment is cure philosophy. I believe that those people at the extreme of this continuum are some of the major change agents and thought leaders that add the most to improving survival rates and life expectancy. Dr. Berenson is at the least is best end of this continuum and is also the President and CEO of his own practice in West Hollywood, California, doctor to the stars I would guess; medical scientific record for the Institute For Myeloma And Bone Cancer Research; Chief Executive Officer of Oncotherapeutics. He is also a member of the National Institute Of Health. He is a member of the scientific boards of the Multiple Myeloma Research Foundation and International Myeloma Foundation and he serves on both the foundation and the scientific boards of the leukemia, lymphoma, and myeloma societies. For the sake of time, I will just say that

his education and training are nothing less than stellar. Dr. Berenson's five-year survival rate is the best yet recorded on the website, www.myelomasurvival.com and his patient's are 5.7 times more likely to survive under his care than at the average cancer facility. Doctor, I want to take this opportunity to thank you for your support and encouragement for my work and I would like for now to turn it over to you so that you can outline your non-transplant program and treatment protocol. Dr. Berenson!

Dr. Berenson : Thank you, Gary. Good afternoon or evening, depends on where you are at. Umm… As Gary says I have been really focused on myeloma for many years. I will tell you that I stumbled into that about 30 years ago when my wife was pregnant with her about-to-be 27-year-old developed hand problems. At that time, my cousin was a very prominent orthopedic surgeon in Los Angeles and was taking care of her and I was at the time at Caltech sequencing antibodies in the genes that lead to the making of an antibody and so it became obvious to me when my cousin grabbed his kid in the swimming pool and had fractured ribs, diagnosed with myeloma and he was such a great doctor that I should work on myeloma, so I have been doing that since the mid 80s and I must tell you things have really changed. At that time, his survival was just 25 months. We had no options, not even transplant, which was just beginning to be thought about and he was rapidly gone from us unfortunately.

Now, fortunately, during the last decade has brought us a plethora of new drugs and more importantly new combinations that we learned how to use these drugs to very much advance the treatment of myeloma not only in terms of longevity and how long people live, but importantly their quality of life and in the 90s there really were few options. So, at that time, we were doing chemotherapy and we thought more was better, i.e., transplanting patients with heavy doses of chemo, but being married to an actress, one of her producers and directors is actually on our board at the institute. He used to say to my wife when she was on stage, its not about more, its about being more specific and the last 12 years have brought us drugs that are an attempt to be more specific, I can't say we have got to the final road here in terms of being specific like we are with CML, but we are certainly getting there. So, drugs like first, thalidomide followed by the cortisone inhibitor, bortezomib, and then the newer analog Revlimid. Now we have carfilzomib just approved. We are about to see pomalidomide and the beauty of these new drugs is their ability to make other drugs work better and what we have learned from our work in the laboratory is that you can give smaller doses of these drugs together and if one causes say a nerve problem and the other a bone marrow problem, if you give them in smaller doses together, you will have less side effects and hopefully that's what we are seeing better results and I like to say that its not about the cancer or the myeloma. Its not even about the patient, start taking care of the whole person and that was taught to me by my mentor, who had lymphoma develop in the mid 80s and 30 years later, he is cured and living a completely normal life and he being an oncologist had learned it the old-fashioned western way that has since then learned to really think about the whole body, the whole person, not just about that bone marrow cancer in the case of myeloma.

Now, work at the clinic is a result of a lot of effort we make in our non-profit Institute For Myeloma & Bone Cancer Research, where we do pre-clinical work to advance the cure of myeloma patients. We try to develop new drugs, trying to figure out how to use drugs already approved more effectively and more safely, both in the test tube and in animal models in which the patients, myeloma including several today, are grown up in mice and then drugs are tested to hopefully lead to new therapies and we have used these then to move into clinical trials which are completed with our own patients and the outpatients throughout the country as part of our clinical research organization, Oncotherapeutics and then those trials hopefully lead to the widespread use of effective treatments or proven-out clinical trials and I saw examples of all that this morning in the 25 or 30 myeloma patients we saw who were both on and off trials and some of them even screening for new trials of new drugs that are yet to be approved.

So, I would tell you its a very exciting time in myeloma and I would tell you that my approach to the disease is that its now thankfully a marathon. My assistant is going off to Hawaii to do medicine for cancer research just tomorrow. He is a marathon runner and I like to say its better for him to run 10-minute miles and run all 26 rather than to run 5-minute miles and drop out of mile 5 and I think a lot of my colleagues do it that way. I certainly believe that ultimately the goal is to eliminate the disease completely, but I think one has to be careful about throwing the baby out with the bath water and I believe that we can develop targeted therapy

that only will touch the cancer and leave the rest of the patient alone, but I would tell you we are still not there in 2012. So, at this point I do not believe that more is better. I believe we have to be smarter and be more specific with how we approach this disease and I also believe that we not only need to treat the myeloma, but we need to take care of the rest of the patient, so as many of you know, I have been a strong advocate for maintaining bone health, for maintaining the patient's nervous system, reducing the risk of neuropathy that is numbness and tingling with sometimes pain in the extremities and also really important and what's becoming a big part of myeloma patient's lives these days is to maintain your mental health, that is, your outlook and also your functionality and to make sure that all of that is very best. We are actually doing trials to attempt to make that better for myeloma patients. We are doing national trials right now looking at that and I think… I think I can stop there and let you guys shoot some questions from the panelists and then from the callers.

Gary Petersen : Okay. Well, thank you very much for this little background. My first question will be from the time, you know, for a long time, you had not favored transplant and the less is best or quality of life part of the treatment continue. For a long time, it had appeared that the thinking was trending toward this philosophy; however, recently I see momentum moving toward more is best or the aggressive approach. As it is now, your program has shown outstanding results with your five-year survival being the best reported. What is your treatment philosophy now as far as, you know, a protocol… in a typical low-risk patient?

Dr. Berenson : Well, I think that again. Yeah. I mean.. I give… I think we have to think about this disease in its long term and I think unfortunately a lot of what's published is short-term results which is much to the advantage of drug companies, much to the advantage of academic institutions, but not necessarily to the advantage of you guys, the patients. So, quick responses look very good in papers, but what I like to see is my friend, Jeffrey, at the top of Mount Kilimanjaro with the sign "thank you for getting me up here," while he is on a clinical trial or my good friend and identical twin like me, Maureen, who is on the Great Wall of China. I think that the key here is to let people live their lives and if you will, I think its also in many patient's best advantage to watch and sit on the sideline while we try to figure it out and although you see data suggesting that the deeper the response, the longer the remission, I certainly am not a firm believer in that philosophy. I do believe if you pummel patients with many drugs and they don't have robust responses, their likelihood of doing well is not very good. That does not necessarily mean by starting slowly, patient may at the end of the day have a much happier and longer life for a myeloma patient.

Gary Petersen : Okay, Jack, would you like to follow up with your question?

Jack Aiello : Sure. I am Jack Aiello. I am a 17-year survivor and appreciate being able to talk with you again, Dr. Berenson. We have met a couple times, once being interviewed by Andrew Schorr and up here in San Jose you have made presentations. My question… My first question to you is still in the area of transplants most patients consider it still one treatment option. You can find different studies. Last year in blood the Spanish group reported that the relapse rate is very low for patients who have had a transplant and have been in remission for greater than 11 years possibly signifying a cure for patients.

Dr. Berenson : Well, I would also tell you I have many patients on the initial Velcade and my own Velcade trials that have never had a transplant and are in complete remission and they are likely to do well and possibly be cured as well. So, I am not sure what all that means. I would certainly argue if you… I would certainly argue if you don't have any disease. You are probably going to do better if you haven't had any measurable disease for 20 years than those patients who pop up with disease in a year or two. That seems obvious.

Jack Aiello : Yeah, my question was going to be because of studies like yours as well, how does the patient decide whether or not being considered for transplant?

Dr. Berenson : Well, I would say my philosophy is based on being an MD, do no harm, so I would rather not put a patient at risk. I do believe that there are small proportion, like the 5% the number I would guess, who benefit from transplant and do have long-term remission, but there's probably at least that similar percentage who again on Velcade or Revlimid-based therapy do the same thing. The problem in 2012, we can tell you that 10% or 15% of myeloma patients who have evil disease including the last patient I saw in clinic today, but we can't tell you there is any therapy that's going to prevent them from having a lousy course with myeloma and probably dying within a couple of years.

Gary Petersen : Thank you.

Jack Aiello : Is it a high-risk patient then?

Dr. Berenson : Yeah.

Jack Aiello : Understood.

Dr. Berenson : Now, the high-risk patient now fortunately, that has shrunk considering with the Mayo Clinic considers high risk. I certainly don't and certainly the recent data suggests that many of the things they call high risk, they are no longer high risk. Missing chromosome 13, 14, 16, 4-14, all of these aren't necessarily high risk anymore.

Gary Petersen : Is that satisfactory, Jack?

Jack Aiello : Yep. Thank you.

Gary Petersen : Okay. Pat!

Pat Killingsworth : Good evening, Doctor! Hopefully, Jack and I will see you at ASH next week. Are you going to be in Atlanta?

Dr. Berenson : And I will be presenting a lot of good stuff, yeah.

Pat Killingsworth : Great! I have the shortest question of the bunch, although its interesting. I just got an email from a British patient who was asking about salvage maintenance therapy isn't even approved in England and she was hoping for some possibly good news, like definitely on the way, but my question was just about salvage therapy, RVD or VRD is becoming the pretty much standard care or Revlimid then for maintenance and all other things. What do you find works best for patients who are no longer responding to Velcade and Revlimid?

Dr. Berenson : Well, I mean I think its a very difficult one to answer without having a specific patient in front of me because it depends on whether the patient has seen Revlimid and filled it and not tolerated and has seen it in multiple combinations and the same for Velcade and its really a tough question to answer. I would tell you that we are using a lot of Kyprolis or carfilzomib right now. We are just presenting data in a few days

on the ability to overcome resistance to Velcade by simply substituting out Velcade with carfilzomib regardless of whether that patient has been on steroids with Velcade; alkylating agents like Cytoxan, melphalan, or bendamustine with Velcade; anthracyclines like Doxil with Velcade; thalidomide or Revlimid with Velcade. If you fail, then you just simply take out the V and put in the C or the K, Kyprolis. You have a very high likelihood of responding which is somewhat shocking given the fact these drugs are both proteasome inhibitors, but I would tell you we certainly had the basis for that insight from laboratory work we have done with another proteasome inhibitor called delanzomib and it published on, which is much more similar actually to Velcade than is carfilzomib to Velcade and we could use that drug in Velcade-resistant animals and get beautiful responses. So, I think that this really greatly increases the possible choices for myeloma patients, meaning every single place you have used Velcade and failed, you can now use Kyprolis or carfilzomib. So, there is really no one way to answer that question. I very much believe in being specific not only in terms of targeted therapy to myeloma but dealing with each patient's issues individually, so we don't assembly line anything in our clinic. We certainly conduct trials that are well designed and carried out, but in patients who are not on trials there's no way that I can tell you there is one way to do this.

Pat Killingsworth : Are you finding substituting the K for the V, the numbers I saw had like a 23% response rate or something… are actually better than that?

Dr. Berenson : Yeah, the problem with that study and I certainly will know all this literature is that that study which led to FDA approval involved 266 patients who had been exposed to Velcade and had then at some point shown progressive disease and then had received carfilzomib as a single agent with a response rate if you count partial responses of 23, if you count minimal, meaning 25 to 49 as well. You could put that up in the high 30s. You have to remember, however, that that 23% response rate is as a single agent A and is among patients who may have gotten RVD or DVD or CyBorD, so they didn't necessarily just fail single-agent Velcade. So, they set the bar pretty high. What I am telling you if you take a combination treated patient with Velcade and you simply pull out the V and put on K, you have a very high likelihood of having a sustained response. This is in a clinical trial that we will be presenting in a few days at the ASH.

Pat Killingsworth : Oh, that's great and hopefully the same thing can happen if you substitute the P for the V and patients really have some options. Give me the pomalidomide for the Revlimid.

Dr. Berenson : Right. That's exactly what we are trying not to…and we are doing, we are presenting data on that with Doxil and dex, but we hope to spread the love and do the same type of design that we have done with the K for the V, with the P for the R, if you will.

Gary Petersen : Thank you. The listeners know what the K means and the P, so…

Dr. Berenson : Yeah, the P is pomalidomide which is basically the drug that will be FDA approved certainly at the latest early next year and its a combination, especially taking the structure of thalidomide with Rev and putting it into this palm and we are seeing very robust responses in these early… Its only data, but I think its pretty promising.

Gary Petersen : Sounds great. Is that good enough, Pat?

Pat Killingsworth : Perfect. Thank you, Doctor.

Gary Petersen : Okay. Now, the next person who is going to ask you a question you know very well, Doctor, and that's Matt Goldman and he has to be one of your patients. Matt, you are ready?

Matt Goldman : I sure am. Thanks, Gary. Hi, Doctor!

Dr. Berenson : Hey, hi!

Matt Goldman : I want to go in a different direction with my question. I am sort of keen…

Dr. Berenson : Speaking of, by the way, let me interrupt that for one second. Speaking of individualized treatment, Matt has gotten the treatment, I can guarantee you, nobody in the world has gotten before him, but him, which was remarkably effective. Right, Matt?

Matt Goldman : Its… Yeah, exactly and just to let everyone know I was diagnosed maybe 18 months ago. I have been seeing Dr. Berenson for 16 months and he had me on the maintenance program for the last four months and that seems to be pretty successful. My question, Doctor, I am sort of curious about your clinical research or if there is other research about maybe some of the causes of myeloma, environmental factors, exposures to toxic…

Dr. Berenson : Yeah. Well, clearly there are environmental factors. There is data now suggesting that we have known for some time that farm working is a risk factor and now we know pesticide exposure. We did a study in the 90s. Unfortunately, we didn't publish it, just presented at the ASH meeting, in women with myeloma and found silicone gel breast implants and I probably saw of five those patients today, including the last patient I saw in clinic. That certainly has not been a published study and needs to be done. We also found computer use and I have a myriad of aerospace workers with myeloma, but those studies have not been completed to confirm with. I know it to be true and then we have flight attendant as a risk factor in women. A family history of lupus or rheumatoid arthritis and certainly family history of MGUS, myeloma, macroglobulinemia, or amyloid – these are all known risk factors, but I do think there are environmental factors that come into play here. The other scary thought is I have several husbands and wives with myeloma and that makes you think possibly of an infectious thing or possibly environmental within the house, we don't really know for sure.

Matt Goldman : Uhhmm… And… So, part two of that is, is that do you spend a lot of time on it or is that work happening simultaneously?

Dr. Berenson : Well, I tell you, having published hundreds of articles, the hardest study I ever tried to do was and now we completed was this epidemiology study in women, so these are extremely difficult studies to complete. I think they are very important to complete, but they are difficult.

Matt Goldman : Okay. Thanks.

Gary Petersen : Okay. Its back to me. My next question really has to do with the data that you have presented on survival and if I look at it correctly, it looks like some 10 years ago before novel agents, you have shown that you have a 16-year observed survival that's nearly 40%. Now, here…

Dr. Berenson : The problem… The problem with that analysis is its limited by, as you know, the time of followup, so if you have only one patient at 16 years and that's the only time point, it becomes a little bit over interpreting the data, just say that that's your average survival. You have to be very careful. What we are doing now and you will like hearing, is in the other room couple of people are updating their survival data in our clinic, which we now have around for about nine years, so we have a lot more followup on it. I think its going to be actually astounding what the data is going to show. I think its going to be well upwards of 10 years, but I don't want to tell you for sure until we get the final data done. I would also chime in, however, I think there is a lot of data out there that can be quite misleading for larger institutions in which the data that is published is on patients they don't really take care of and they don't necessarily follow very closely. That means Joe who comes in once a year and flies from say Detroit over to the Mayo Clinic, they don't really follow him or treat him in between and they don't necessarily know what happened to him and he may have passed away. So, he is a tick mark on the chart that really is not representative of what really happened to the patient and they also are not really taking care of him. So, I want to be able to take credit for the patients I am actually taking care of.

Gary Petersen : Okay. Did I misinterpret it then? It looked like that graph showed 100 patients and I assume that was 100 patients starting 16 years ago…

Dr. Berenson : No. No. No. It could be 100 patients that started 16 years ago but doesn't mean that are being in followup. Its, you know, 16 years.

Gary Petersen : Okay. But then, does that mean 40 people are alive at the end of 16 years. Or, did I misinterpret that?

Dr. Berenson : I think… I think that's probably not accurate. I think what you are looking at is what's called the Kaplan-Meier plot, which is an estimated survival plot. Its not a real curve and that's how all survival curves are published by the way in oncology, but you need to know whether the median followup was one month, one year, or 10 years. That has very different meaning. Now that we have had our own clinic for about nine years, I can with much more assurance tell you about long-term survival data than I could have even three or four years ago when we published the last set.

Gary Petersen : Thank you. Jack, your next question.

Jack Aiello : Doctor, could you describe your bisphosphonate protocol? For example, does every myeloma patient get Aredia, Zometa, maybe denosumab or only patients with bone stiffness or must have left the treatment. Do you agree with the UK results showing Zometa showing overall survival benefit? Do you prefer Aredia versus Zometa, things like that?

Dr. Berenson : Yeah, sure. So, first of all, let's start with the D, which means do not use denosumab. So, Dmab or Xgeva should not be used in myeloma. The company says we don't have data, we do. Its such bad data. So, in the 190 patients which was admittedly a subset of a larger trial, the 95 or so that got Zometa had a survival advantage over the Dmab. Now is that because Xgeva does something awful to myeloma patients. Is it because they just happen to have a bad group in there, there we are going to do poorly regardless or most intriguing could it be because Zometa improves survival because of the anti-myeloma effect, which we have not only demonstrated in the lab, but I have patients including one of our board members, who has actually raised the most money for the institute coincidentally, came to me in '99 for a transplant through the Dean of Medicine at UCLA and I said no, you are going on Zometa. It hadn't been approved at that time and coincidentally it is going off patent in about 90 days and so he went on that drug and went into remission with no steroids, no chemo, no nothing, for about eight years. So, certainly, there are patients that will respond to Zometa but not that common if they do have. So, the group went through a large trial, a thousand patients essentially got chemo with clodronate which is like baby aspirin, a very weak bisphosphonate, and then the other thousand got Zometa which is like morphine if you will in terms of storing and they not only have less bone events, less fractures, and less requirement for radiation or surgery to bone, but most importantly, they actually live longer.

Now, you could argue they live longer because they have less bone problems and so therefore they weren't all, you know, lodged up but not able to get out, so if you have less mobile, you tend to not live as long, but that was analysed and it was not because of that. It was actually probably because of the anti-tumor effect, which we certainly know occurs in the laboratory. Now, I certainly do not use anything but Zometa. Even I did all my original work on Aredia, but I did put Zometa in the first place in 1995 in the world, but I think the drug is more potent and I don't believe for a minute that there is any real data that says it leads to more ONJ and I would tell you the first six patients I saw in clinic today, every one of them had ONJ. They are all doing just fine. So, just because you have a small area of exposed bone doesn't mean your life is going to fall apart if this is managed correctly.

Jack Aiello : So, do you keep patients on Zometa forever or…

Dr. Berenson : [00:31:36] Yeah. I like to quote the first marketing director at Novartis, Karen Kaminski. When I asked her about that back 12 to 13 years ago how long she would keep them on, she said, Jim, just remember Zometa is better for ever and she did have a Bostonian accent (laughter) and so I don't stop and I don't even stop to get ONJ. The only thing that makes me stop is if they get a fracture in the femur that's atypical, which you can see with these drugs occasionally or if the ONJ gets really severe, which is rare, or if

the patient has protein in the urine or a lot of it which can happen long term, not really reported, or their kidney goes haywire, which is pretty about rare.

Jack Aiello : And you keep monitoring monthly?

Dr. Berenson : Yeah. I don't think there is any data that says giving it every three months like Mayo and the guidelines from ASCO, there is no data that says that does anything. So, I hate people making guidelines without any data. Now I certainly admit to your studies, but we completed in the 90s with both drugs, that is Aredia and Zometa were only two-year studies and that's because myeloma patients back then lived two years, but that doesn't necessarily mean that okay, let's just quit giving it because we don't have data beyond that. We certainly don't have a lot of data on maintenance with these drugs beyond the original treatment in myeloma and yet we keep them going, whether its Velcade, whether its Revlimid.

Jack Aiello : Thank you very much.

Gary Petersen : Pat, do you have another question or should we go on to Matt?

Pat Killingsworth : No, I am good. I would like to hear what some of the callers have to say.

Gary Petersen : Okay. Matt, your next question.

Matt Goldmann : Yeah and this is really a followup to what you were just talking about, Doctor. In terms of sort of preventative actions you can take to keep your bones in good shape, how do you deal with some of that with folks such as me who have more serious kidney problems?

Dr. Berenson : Yeah, its problematic as Matt says if you have severe kidney problems and you are not on dialysis. We don't want you to go there. We don't want to give you drugs like bisphosphonates, Aredia, or Zometa as they could damage the kidneys overtime and then you are on dialysis. Now if you are already on dialysis and you have been on it permanently, you could use these drugs, but in patients like Matt who have kind of somewhat compromised kidney function, we are going to stay away from those drugs and of course, people will say, well, maybe we should be giving those folks the Xgeva or Dmab from Amgen, I say absolutely not. We don't know whether that is actually hindering survival at this point, so really the only thing you can do is make sure your vitamin D levels are okay and take enough, which is 1 g of elemental calcium a day to keep your bones healthy but last but not least exercise. Weight bearing exercise keeps your bones healthy. So, in terms of drug therapy, there really isn't anything beyond vitamin D and calcium that we know, is any good for myeloma patients with compromised kidney function that are on dialysis.

Matt Goldmann : Okay. Thanks.

Gary Petersen : Okay. Back to me. Doctor, the 15% of high-risk patients that you talked about before, I think you already answered this, so…, but in your answer you said that you really don't have anything that can help them at this point.

Dr. Berenson : You see…I am not going to say you… I am not going to say you we that we don't try. I can certainly tell you should do, but I can't tell you with assurance that we have any magic bullets for that poor prognosis group.

Gary Petersen : Like K, T, D, which you know, is not something that might… the carfilzomib, pomalidomide, dex, you know, that big gun might have some impact or is there just nothing at this point that anybody can….?

Dr. Berenson : There is nothing that, I mean, can assure the patient they are going to do well. We just don't have good guns for that right now. I mean I would probably throw more than less, but I can't tell you that's the right thing to do, but I will, you know, its just kind of philosophy without any, you know, real data.

Gary Petersen : Okay. Jack, your last question?

Jack Aiello : One last question. For the standard risk patient, do you have a typical first treatment like everyone would typically get Revlimid-dex or Revlimid-Velcade-dex and then I got wondering how carfilzomib and pomalidomide when they are approved for newly diagnosed patients how might that change that?

Dr. Berenson : Well, I think that pomalidomide is certainly not the drug that Celgene is pushing to move to a front line setting. I do think its a player. I think one has to be careful interpreting data similar to what I was mentioning with Kyprolis 23% and believe its a very poorly active drug and in this case, pomalidomide 9% and Revlimid failures because my view is what the drug does as a single agent is its ability to make other things look better. These are like supportive casts that ensemble if you will, they make better music together. That's what they really do. So, its going to be really complicated now with the addition of carfilzomib in late July and pomalidomide probably in the next two to three months.

Jack Aiello : So, today is there a standard first line treatment you give?

Dr. Berenson : No. Well, I give most patients Velcade, Doxil, and dex. I don't use RVD. I also use a fair bit of alkylator, usually oral Cytoxan or melphalan with Velcade in those patients that hate steroids. Both of those we published. I don't like giving the doses in the CyBorD. I don't think you need that much. The same with the Doxil, we give low dose on Velcade days with much better tolerability and excellent activity. So, I think, yeah, you need to play with those schedule. What happens with drug companies, you get an FDA approval and they put their feet up on the table and go to sleep for 13 years and somebody else will count the cash, but fortunately some of the newer companies, I have been impressed with Onyx that makes Kyprolis or carfilzomib, but they are really exploring dosing schedules, from what's been done previously or more probably to the point not been done by Millennium with their proteasome inhibitor Velcade or bortezomib in the development of that drug.

Jack Aiello : Are you having any trouble getting the Doxil or is that readily available?

Jack Aiello : No, that… That problem is over. I mean, we never really had a problem because you could get it anyway. By the way, you could get it from Sun Pharma's like the Doxil, we really haven't had a problem.

Jack Aiello : Good. Thank you.

Gary Petersen : Matt, you have one last question?

Matt Goldmann : I am actually good. I think maybe some of the callers might have some questions…

Gary Petersen : Okay, all my questions have been covered. All right. So, with the callers. Priya, could you start bringing people online?

Priya : Thank you, Gary. That was a wonderful discussion. Dr. Berenson, I have a question for you. When do you absolutely recommend transplant, if you ever do?

Dr. Berenson : I don't ever recommend transplant.

Priya : Can you share with us what you are going to present at the ASH this year?

Dr. Berenson : Sure. We will be presenting data on a new marker for myeloma that's a solubilized receptor we recently published on called B cell maturation antigen, which I think will allow us to more accurately follow myeloma patients. Its pretty cool. Its a receptor on the plasma cell, the malignant cell, and it seems to be elevated to myeloma and be able to follow like the M protein and even in patients with non-secretory myeloma. We will also be presenting preclinical data on a number of new drugs in development, including Gilead's Pr3 kinase inhibitor in combination with chemo, bortezomib, dexamethasone. We will also be

presenting some new data related to antigenesis and also be presenting a number of clinical studies related to pomalidomide as well as carfilzomib.

Priya : Thank you, Doctor. Thank you. We will move on to the questions from the callers now. Callers, if you have a question, you now press 1. We will bring you live online. (Pause) Eliot, you may now ask your question. (Pause) Eliot, you are there? (Pause) Hello! (Pause) We will move on to the next question. (Pause) Gregory, you may now ask your question.

Caller 2 : Okay, thanks. I was wondering what Dr. Berenson thinks about a clinical trial involving elotuzumab and Revlimid and dexamethasone as a treatment plan for a patient who is in the standard risk category stage I.

Dr. Berenson : As first treatment for the myeloma?

Caller 2 : Yes.

Dr. Berenson : Yeah. Well, I certainly will be careful. I mean, I think if you look at the trial with better eye that was published, you will notice that the vast majority of people who were in that trial had never seen Revlimid, so in the single-arm Revlimid plus elotuzumab and dex, I believe about 80% of those patients have never seen Rev. So, you don't know if those responses are simply Rev and dex and that was in a relapse setting and I can tell you my experience with histone deacetylase inhibitors taught me that less is more. I went to one of the companies and they told me how great their drug was with Velcade and dex and I said, well, that's because those patients had never seen Velcade and dex and then we did the proper study of Velcade and dex with no.., sorry, Velcade alone with this drug and Velcade failures and we got no activity.

Caller 2 : Okay. So, just to summarize that, are you saying that the data from Dr. Moreau, I think he practices in France, he presented at ASH, that what appeared to be his high expectation from elotuzumab are not necessarily accurate?

Dr. Berenson : Well, you know you have to do the real trial. Its a randomized trial, I mean the same dance was told to us about the HDAC inhibitors and that seems to be a pile of side effects and not much there other than toxicity. I could have told them that from my own experience in the lab, but in the clinic it just didn't pan out. So, you know, I mean we will see what happens, but there may be something there, but remember as a single agent this drug doesn't do anything, elotuzumab.

Caller 2 : Sure. It seems to be a drug that enhances or allows the Revlimid to conduct, to do their work.

Dr. Berenson : Well…targeted that, theoretically that's true. We will see if that's true. I mean its nice laboratory work, but we will see.

Caller 2 : Okay. Should I… umm…. ask a followup question later, if I may, or ask it now?

Gary Petersen : Ask it now.

Caller 2 : Great! Thank you and I appreciate everyone's participation in this and Dr. Berenson's, the opportunity to ask him questions. Dr. Berenson, you had mentioned a protocol for a general standard of care that involved Velcade, I believe the second drug was Doxil and then dexamethasone.

Dr. Berenson : Right.

Caller 2 : Umm… I am not familiar with Doxil. Umm… Could you…

Dr. Berenson : Doxil is a drug the Mayo Clinic doesn't mention and so therefore a lot of people never get it with myeloma. By the way, that's also true. Thalidomide which is a disservice and its a very active drug and

we certainly have seen that in the lab and clinically. So, we have done several studies, both with Celgene as well as with the group over at Millennium with Doxil and Velcade, Doxil and Rev, and its a really active drug and its a chemotherapeutic agent. We give it differently than its been FDA approved to give, so we give low metronomic doses on Velcade. Its been really well tolerated with a very high response rate. We have also used it with Kyprolis or carfilzomib including several patients in clinic today with excellent results. Then, we do DCD in some folks who felt DVD if you ask, those who have failed Doxil, Velcade, dex and we have also used Doxil, carfilzomib, dex.

Caller 2 : I see and how do you spell Doxil? Is it D-o-x-e-l?

Dr. Berenson : D-o-x-i-l. There's another product called Lipodox, L-i-p-o-d-o-x. So, some of the concern was that as a single agent the old version called the adriamycin didn't do much, but that doesn't necessarily mean anything to me in terms of its ability to work in this liposomal PEGylated formulation called Doxil, D-o-x-i-l, or especially when combined with other products.

Priya : Thank you, Gregory. Thank you. We have another question. The person with the number (954) 688-9090, please introduce yourself and ask your question.

Caller 3 : Sure. Thank you very much. My name is Kaul. My question is, Dr. Berenson, have you had any experience with curcumin as an adjunctive therapy?

Dr. Berenson

Dr. Berenson : Well, I have patients doing that. There was a recent published report suggesting it may have a hint of activity from an outside the US study, but it was a small study and really didn't have proven responses. My feeling is its a poor person's version of Velcade or carfilzomib and I don't know whether you can get enough of that and too much, but you know, its probably not doing a lot of harm.

Caller 3 : But, there is a new version that apparently is out recently which is the phytosome version where its been reacting with the… I forget what it is, but as a complex, it supposedly allows it to be much more available.

Dr. Berenson : There… Well, maybe, maybe, ley us see what happens with that.

Caller 3 : Okay, thanks.

Dr. Berenson : Priya, you have other questions?

Priya : Yeah. Yes, we have. The person with (858) 880-9528, please introduce yourself and ask your question.

Caller 4 : Hi! Quick question. You said that under no circumstances you recommend transplant. Can you elaborate as to why?

Dr. Berenson : Because my job is to keep my myeloma patients alive as long as possible with the best quality and I think transplant experience is bad and I also think that the transplanted patient compromises their ability to get future therapy based on the toxicity it does to your body. You know, you are told that you store away your stem cells and they remain unexposed to the chemo until they come back into your body, but your body is not a vacuum too. It has a lot of organs in it that get exposed to the chemo and that does toxicity and that is a problem, whether its long or more importantly the bone marrow. You need to stay in the game. If you can't stay in the game because we toxic out your body and that's not a very good thing to do.

Caller 4 : Appreciate it. Thanks.

Priya : Thanks. Well, number (716) 587-1012, please ask your question.

Caller 5 : Hello. Dr. Berenson. I have a quick question for you. What's your view about using either dexamethasone or prednisone as a maintenance therapy and one other question that I have is…I do have two questions. The other question that I have and I will just throw it out is do you believe that certain types of myeloma, for example, interstitial systemic myeloma, is the same as the typical myeloma or is it same as focal point myeloma? So, in other words, seems that I have a (audio not clear) and the question is would you use the same type of treatment for that as someone who has (audio not clear)?

Dr. Berenson : Well, I think… I think… I think… Yeah, I think you have a better prognosis in general, but you know, we don't know what works specifically for your brand. I certainly am a firm believer that if you have been on steroid-based therapy, you ought to remain on it. I am the one who ran the trial that showed that SWOG and we published 10 years ago to this year and we started it 20 years ago in which patients got chemotherapy that had dex in it called VAD and then either got prednisone or not and those who got prednisone as a maintenance lived longer. So, I keep people on steroids and I think its been a disservice that the Revlimid trial threw out steroids and kept Revlimid going on not only because of the marked difference in cause but also the survival advantage that had been shown. But, that's the way it goes, but if you have been on any steroid as part of you regimen, we keep you on them. We try to give the equivalent of what you have been on and the nature of treatment. That's usually the equivalent of 160 of dex a month. If you have been getting IV dex, we will continue it, usually every other week 40 mm, throw in Medrol. I think Medrol, M-e-d-r-o-l, is a much, much better tolerated steroid, that is the dexamethasone. I also think prednisone is not as well tolerated.

Caller 5 : So, in terms of like I am going, I am going on steroids?

Dr. Berenson : Yeah, I wouldn't start jumping and throwing it in. I wouldn't throw it in to someone who hasn't been on it and I think that's not a good thing to do.

Caller 5 : Oh, I have been on it, but you believe that there is a maintenance dose going forward. That makes sense.

Dr. Berenson : Yeah, I do. I think you should absolutely stay on, you should be on it. If you were on it as part of your regimen, I think you should. Now if you have been a year away from steroids, I wouldn't just start taking them, though.

Caller 5 : Okay. All right. Well, thank you very much.

Dr. Berenson : You are welcome.

Priya : There is a caller from number (915) 849-8655, you may please ask your question.

Caller 6 : Good evening, Dr. Berenson. I am a 37-year-old female and I was diagnosed with smoldering myeloma when I was 34 years of age and I don't fit the criteria as I have been told of active myeloma, but for the past three years I have severely been plagued with viral and bacterial infections on a frequent basis. So, is that typical of someone who has smoldering myeloma?

Dr. Berenson : Not really. It really isn't. I mean its interesting that we don't use a lot of intravenous gammaglobulin monthly and to treat myeloma, but when I have done it it does seem to reduce that incidence of infections, but its expensive and cumbersome to give it intravenously once a month. It would be something to consider if you get recurrent infections. The infections, by the way, are usually treatment-induced low

counts, but in your case we can't say that's the reason.

Caller 6 : Oh, I see. Low counts meaning, for example, a low white blood count…

Dr. Berenson : No, they are usually from a low white count.

Caller 6 : Well, mine is particularly very low. I am constantly neutropenic and also have leukopenia, but that's…

Dr. Berenson : Well, that's certainly the likely cause but that may be an indication to be treated.

Caller 6 : Oh, I see. Okay.

Dr. Berenson : I mean I have treated people just like you simply with steroids and its been able to do wonders to help them reduce the neutropenia and the infectious risk. Now, you would think that would be the opposite because relatively prednisone, Medrol, and drugs like that suppress your immune system, but in some cases will actually get the myeloma away and make room for some nice, healthy cells. Don't forget about steroids. They are cheap and they work to treat myeloma, but problem is a lot of people hate being on it because of all the damn side effects.

Caller 6 : Oh, I see. Very well. Okay. One last question again from me, Dr. Berenson. I am sorry (bad audio) myeloma who are immunocompromised with steroids. Is that correct?

Dr. Berenson : No. I mean its really… Talking about this specific case, a woman who basically has no reasons to treat her myeloma except for some recurrent infections and borderline neutropenia, I would be very slow to treat her. I wouldn't give her RVD or some huge amount of therapy. So, I would start slow with her, but I certainly, as I told you earlier, individualize the treatment, but most patients will have steroids in the group but not all. Look, you know, they hate steroids, they don't tolerate it, that sort of thing.

Caller 6 : Thanks. Dr. Berenson, we live in Texas, but if wanted care under you, I mean is that something that we would be able to coordinate being that we are still far away?

Dr. Berenson : Yeah, I do this all over the world. So, people come out and visit. Then, I try to coordinate their care locally and they can get their care locally, but we try to be the quarterback here and hopefully are more like Peyton Manning than the way Michael Dixon won. (Laughter).

Caller 6 : I see. Thank you. Nice analogy.

Priya : The caller with number (858) 273-5008, please ask your question.

Caller 7 : Yeah, Dr. Berenson. Talking about football, watching football, these players break an arm, they break a leg, they break a hand, then three weeks later they are back in the game. What are these people taking or what should we be taking other than Aredia or Zometa and what type of calcium works best for people?

Dr. Berenson : Well, I think the one important thing you have to remember is that calcium supplements are important and many doctors won't give it to you guys because they remember the old '80s before we had bisphosphonates that patients with myeloma in those days had no protection, so their calciums would go up. Well, in fact, bisphosphonates like Aredia and Zometa protect you from getting a high calcium, so you can be aggressive about getting a gram of elemental calcium daily. Okay? And then in addition, vitamin D, we all forget it, never gets measured, needs to be measured because most of you guys are low in vitamin D levels, so supplementing with vitamin D is a great thing. Also, avoiding falls and (bad audio) levels go up to be able to not have bad balance and fall down. All these are important beyond simply bisphosphonates. At this point, there has been an attempt to build bone because obviously as you know bisphosphonates prevent bone

loss. There has been an attempt to build bone with drugs like an antibody to DKK1 from Novartis and Actavis called Activin 1A. Its a receptor antagonist, but these really have not played out yet in the clinic in any sensitive way.

[00:57:30] Okay. Thank you.

Priya : We have a person calling through Skype, you may please ask your question now. (Pause) Yeah. There's someone who called in through Skype, we can't identify the number, you may please ask your question. (Pause) Hello! Yes. Please ask your question.

Caller 8 : Dr. Berenson, I wonder if you are involved in any clinical trials comparing transplant versus no transplant or if you are aware of any?

Dr. Berenson : There is one large trial being done with the Dana-Farber group and the French, which is RVD versus essentially RVD transplant. The problem is that the doses of RVD are so high that many patients aren't taking that. So, that's the problem. The other problem is that the outcomes for these trials, thanks to the survival today, will not be known until probably another 10 years. So, that's little bit problematic. So, I think its difficult. I would mention to you there is some data being done with MPR versus patients who had double transplant after having RD. So, RD and then randomized to MP with Rev versus two high dose melphalans from the Italians which has not shown a survival advantage yet, but I would also argue and you would too that MPR is pretty crummy therapy. It certainly was no better than MP.

Caller 8 : And those are the only trials that you are aware of? You are not engaging in any?

Dr. Berenson : No, I am not interested in answering that question right now. I think its, to me, not a relevant question because I hope over the next 10 years I could say to you we finally have real targeted therapy.

Priya : Thank you. I think we have listened to questions from the callers. Due to time constraint, we have to conclude the call. Dr. Berenson, it was a pleasure to have you on our Cure Panel. Thank you very much for taking time out and providing us with your valuable input. I thank our panelists, Pat, Jack, and Mattt, for their active participation. Cure Talk thanks all the listeners and participants. I hope that all of us have imbibed something relevant regarding myeloma treatment in this discussion. A big thank you to Gary. Gary, you have been wonderful and your support is something we bank on. Thank you. The broadcast of this… The recording of this broadcast will be available on Cure Talk from tomorrow. Thank you all for your support and we look forward to having all of you join us for the Cure Panel Talk Show in January 2013. Please visit trialx.com/curetalk where and the recorded telecast will be broadcast. Thank you so much. Thank you, all.

Gary Petersen : And thank you, Dr. Berenson. You did a wonderful job.

Dr. Berenson : Well, thank you all for having me. I always learn more from hearing from the patients than I do from hearing from other doctors and I think that was true today. I learned a lot. Thank you too.