High Risk Myeloma Treatment Options

Myeloma is classified as high-risk based on presence of cytogenetic abnormalities and poor treatment outcomes. Despite many new drugs and drug combinations being approved, long term benefits for high risk multiple myeloma patients is less clear. We continue our discussion on high risk myeloma with Dr. Robert Orlowski and talk about the treatment options that are available for a high risk patient.

Full Transcript:

Priya Menon – Good evening and welcome to CureTalks. This is Priya Menon joining you from India on CureTalks' 120th episode. Today, we are discussing high-risk myeloma treatment options. My co-host for the talk is myeloma advocate and editor of myelomasurvival.com, Gary Petersen. Joining Gary is myeloma advocate, Cynthia Chmielewski and Yelak Biru. Before we begin with today's topic discussion, would like to remind our myeloma community that its been a year since we had to say goodbye to our beloved friend and myeloma panelist, Pat Killingsworth. Like every year, its that time of the year for Pat's Myeloma Survival School; and this year in Pat's memory, the event is from March 3rd to March 5th. Its an incredible way to learn tips for living with myeloma and the latest in research in a friendly beach setting. You can still sign up for the program by going to myelomacrowd.org.

Priya Menon – Coming back to today's discussion, myeloma is classified as high risk based on presence of cytogenetic abnormalities and poor treatment outcomes. Despite many new drugs and drug combinations being approved, long-term benefits for high-risk multiple myeloma patients is less clear. We discussed post transplant outcomes for high-risk myeloma patients with Dr. Parameswaran Hari recently. We'll continue our discussion on high-risk myeloma with Dr. Robert Orlowski on treatment options that are available for a high-risk group. Before I hand over to Gary to begin with the discussion, would like to inform our listeners that we will be addressing questions sent in towards the end of the discussion. If you have a question for our panel, please press 1 on your keypads and let us know and we can bring you on air to ask your question or you can just email them to priya@trialx.com or post it on the CureTalks' website. With that, I hand over to Gary to introduce our expert and begin with the discussion. Gary, you are on air.

Gary Petersen – Yes. Thank you so much, Priya. We appreciate you providing this big platform for us to find out more about multiple myeloma and specifically high-risk multiple myeloma, which is so very important. Now, Dr. Robert Z. Orlowski is the Chairman and Interim Director of Myeloma and Professor of Medicine in the Departments of Lymphoma/Myeloma and Professor, Experimental Therapeutics Division of the Cancer Medicine, at The University of Texas M.D. Anderson Cancer Center in Houston, Texas. Many people believe that center has to be one of the best, not the best, in the world. He is board-certified in internal medicine and medical oncology. Dr. Orlowski earned his doctoral degree in molecular biophysics and biochemistry from Yale University and his medical degree from Yale University School of Medicine. He completed his internship residency in Internal Medicine at Barnes Hospital at Washington University in St. Louis School of Medicine. Dr. Orlowski has published numerous book chapters, articles, and abstracts on cancer therapy, with a focus on molecular pathogenesis of oncologic disease processes and the mechanics of action of chemotherapeutics. His clinical research efforts focus on translation of promising laboratory-based findings into novel clinical trials for patients with hematological malignancy. He has published and is a reviewer for several journals including Blood, Cancer Research, Journal of Clinical Oncology, New England Journal of Medicine. He has received several awards including Leukemia and Lymphoma Society Scholar in Clinical Research and the Jefferson Scholarship Academic Medicine. So, you can see, he is well versed and in my opinion one of the premiere myeloma specialists in the world and also someone who is at the tip of the spear when it comes to myeloma research and now looking at the very important high-risk multiple myeloma. So, welcome aboard, doctor.

Dr. Robert Z. Orlowski – Well, thank you very much for that great introduction and thanks to both Priya and Gary for hosting this show and talking about high-risk disease and, Priya, if you are in India, hopefully we'll be able to see you next week because many of you may know that the International Myeloma Workshop which happens every two years is happening next week in New Delhi.

Gary Petersen – Very good. Well, Dr. Orlowski, maybe to start this off, if you can tell us what is high-risk multiple myeloma and why should people with myeloma be concerned about testing for risk?

Dr. Robert Z. Orlowski – Yes. Thanks. That's a really great question. We know now from the work of many great researchers in the field that myeloma is not the same disease in each patient, and those of you who are part of support groups or have friends with myeloma probably already know this because everybody's journey through this disease is a little bit different. When we look at the genes that are changed in each individual's myeloma cells, we can find that there are certain subtypes and of course, the genes are different because if they were not, the cell would be a normal cell, which would be called a plasma cell. So, based on which genes are abnormal, we know that some patients with these groups will do average; some will do better than average in terms of, for example, the chance of achieving a complete remission for the duration of that remission; and others will have, unfortunately, what we call, high-risk disease and these are people with abnormalities just in their myeloma cells that typically will predict for a lesser response duration to therapy and what happens is that in the high-risk setting, you have people whose durability of remission is much shorter and they tend to need a second therapy much sooner. If you do what's called FISH analysis and "FISH" the term stands for fluorescence in situ hybridization. This is a kind of test which is most commonly done on bone marrow, fresh bone marrow cells.

There are a couple of subgroups that are considered high risk. One is called deletion 17p, and that is a group where there is a piece of the short arm of chromosome 17 which is missing. According to the International Myeloma Working Group, if you have a translocation between chromosomes 4 and 14, meaning that there is material from one chromosome that has moved over to the other, that's considered high risk and then there are other translocations including between 14 and 16 and between chromosomes 14 and 20 and some people also consider that there is an area on the long arm of chromosome 1 called 1q21, which is amplified, meaning that rather than removing copies, you actually have increased numbers of copies of the genes in that area and these are some of the high-risk groups and its important for patients to know if they have standard risk or if they have high risk because there is an increasing, I think, acceptance that high-risk patients need to be treated differently and also you really do want to know what your prognosis is. Now, fortunately, the high-risk group is probably about 20% or 25% of patients at diagnosis. So, the number of people that are high risk is small and the odds are with you that you are in the intermediate or standard risk group, but still 20% to 25% is quite a few patients and it is important to know that.

Gary Petersen – Okay. Well, thank you very much. One thing I had heard also is that risk…., high risk can also be like comorbidities such as kidney damage and that also with time after treatment it becomes your myeloma can, in fact, morph and it does morph into a high-risk classification as part of high risk I guess is that it returns very quickly after treatment. As a result, one would think that high risk is, therefore, very important for all of us who are not cured and have myeloma. What are your thoughts on that?

Dr. Robert Z. Orlowski – Let me address the second part of your question, which is whether high risk can develop later in the disease if you start off with "good risk" and I, of course, say quote unquote because there's nothing good about having myeloma. Many people will start out…, in fact, as I mentioned earlier, the majority will start out with what is called standard or good-risk myeloma, but there are times when patients will progress and they will progress to a high-risk form that can be either because the myeloma cells develop new mutations that weren't there before and its the same mutations that I mentioned earlier that can develop or in some cases what can happen is that the myeloma at the time of diagnosis is a mixture of different cells. Sometimes the high-risk clone is at a very low proportion at the beginning and can't even be detected, but then when you get chemotherapy, the chemotherapy tends to kill off the standard-risk myeloma types and over time you are in reaching for the higher risk subtype and so it may be rather than a new mutation, you are simply selecting out a small population that was present at the beginning that may be

couldn't even be detected.

The first part of your question was whether there are clinical aspects of high-risk disease and you mentioned in particular renal failure. Most patients, and this is probably 75% or 80% of patients, if they present with new renal failure which is due to the myeloma, 75% to 80% of them can have that renal failure either improved or completely reversed if chemotherapy is started in a timely manner. Usually, those are patients that have stage 3 disease based on the old international staging system, but because we now recognize that these molecular abnormalities are probably more important than the clinical stage in the revised staging system, just having a high beta-2 microglobulin, for example, which is one of the protein levels that is used for staging and it used to be that, let's say, if your beta-2 was 7, on the old international staging system, you would have been stage 3, which would have been the highest and your prognosis would not have been as good as stage 1 or 2, but in the revised system, what we now know is that just a high beta-2 microglobulin by itself without any high-risk molecular features only puts you into stage 2 and so that shows you that these molecular abnormalities are really more important, although of course, if you have other medical problems which may make it more difficult to get chemotherapy, that's never a good thing.

Gary Petersen – Thanks. Given that why high risk is so important and we know what it is based on your explanation, what do you feel are the best available treatments for each high-risk characteristic you currently have as a treatment in your armamentarium?

Dr. Robert Z. Orlowski – Also a great question. We don't yet know for sure whether there is a best type for each of the individual subcategories. For example, if you have a deletion 17p, should you get chemotherapy combination A or should you get chemotherapy combination B and should that be different than if you have a 4;14 translocation and many people are doing research to try to understand that better because I think what we need to do is basically have what I like to call designer drugs where a particular combination is used for a particular type of patient who has myeloma of, let's say, deletion 17p, but we are not there yet. What we do know is that of the drugs that we have proteasome inhibitors and these could be bortezomib or carfilzomib or ixazomib are very good in combination with other drugs for high-risk myeloma, so you should definitely get a proteasome inhibitor. We often will include an immunomodulatory drug like lenalidomide and also, of course, a corticosteroid. So, minimally I would say that if you have high-risk disease and you are relatively healthy, that kind of three-drug regimen would be the standard.

One of the things we are doing through SWOG, which used to be called the Southwest Oncology Group, now its just called SWOG, which is one of the cooperative groups involved in the National Clinical Trial Network. We finished a study where we compared VRd, which of course is bortezomib, len, and dex to VRd with elotuzumab, which is one of the monoclonal antibodies and we hope that the combination with elo will be better, but so far we don't have yet sufficiently mature data to be knowing that for sure, but the next study which is going to open probably in either March or April will be again two arms, one arm will be carfilzomib with lenalidomide and dex and the other arm will be same three drugs but with the addition of daratumumab which is a different monoclonal antibody. Many of you have probably heard about that and the hope is that these antibodies will work whether you have standard risk or high-risk disease because all they really care about is whether the protein to which they attach on the myeloma cell is expressed or not and so far it seems that that's not influenced by whether you have standard risk or high-risk disease. So, that right now is the best three-drug combo of proteasome inhibitor, an IMiD, and a steroid, but do look for trials that maybe are able to add an antibody and other immunotherapies we think will be exciting as well including CAR-T cells as well as what are called BiTE which stands for bispecific T-cell engagers and I think those will be exciting to look at in trials.

Gary Petersen – Good. And… My next question is, looking into the future and knowing that you are part of the High-Risk Myeloma Moon Shot at M.D. Anderson and also have been on the scientific board of the Myeloma Crowd Research Initiative, that…, what are…, what do you see are the future myeloma treatments that may finally get us to cure?

Dr. Robert Z. Orlowski – Oh, I appreciate your mentioning the Moon Shot, which is an M.D. Anderson

Initiative that was started before the Moon Shots that were announced by Vice-President Biden and President Obama, at the time. One of the areas we focused on is high-risk myeloma because of the recognition that there is an added need for improvement and there are a couple of trials that we are doing there. 1) For people who already have high-risk myeloma, what we are doing is adding on top of stem cell transplant, a combination of natural killer cells. So, these are cells that are isolated actually from cord blood. They are expanded in the laboratory and they are then infused into patients after they get the high-dose melphalan during the transplant and the thought is that these cells have anti-myeloma activity and hopefully they will result in a further reduction in the amount of myeloma and its still early. So, we don't know for sure, but the data so far looks very promising because we have looked at in particular what's called MRD or minimal residual disease and that's been done through a number of tests, but the most common one is looking at the bone marrow with a technique called flow cytometry or flow immunophenotyping and that's a fancy way of basically saying that you are fingerprinting every cell that you get in that bone marrow aspirate to see if its a normal white blood cell, a normal plasma cell, or an abnormal myeloma plasma cell and what we found is that patients who get these NK cells have a much higher rate of MRD negativity and most studies that have been published so far show that if you have MRD negativity, you have a longer time in remission, a longer time before progression, and a better overall survival than if you are MRD positive, so that gives us a lot of confidence that we should continue to follow that approach.

The Crowd-Funding Initiative, and Jenny Ahlstrom has been the champion of that, has raised private donations for research into high-risk myeloma and they funded two projects, one of which is in Germany, looking at different CAR-T cells or chimeric antigen receptor T cells and we hope to be able to get those into the clinic pretty soon and the second is a project that's actually being done in the US at Johns Hopkins where a different cell type, not NK cells but cells from the bone marrow of the patient are harvested. They are expanded in the laboratory and then they are re-infused again with the thought that they will add to the immune benefit against myeloma. That's work being done by Ivan Borrello and so far has been very positive as well. So, essentially, I think my message to people is, stem cell transplant is still very often considered an important thing in myeloma. If you have so-called good risk or standard-risk myeloma, you can get a standard stem cell transplant and that's kind of like having vanilla, but if you have high-risk disease, you don't want just vanilla ice cream, you want vanilla with sprinkles on top and what I mean by that is you want something in addition to the high-dose melphalan and I think either these NK cells or the lymphocytes at Hopkins or other approaches really should be looked at because you want to try to achieve as low a level of disease as possible, especially in high-risk patients.

Gary Petersen – So, it sounds like immunotherapy is the future of high-risk disease.

Dr. Robert Z. Orlowski – I definitely think its one of the future positives in the field. Many of us are working also on, as I mentioned earlier, designer drugs which we hope will be active against, let's say, one drug for deletion 17p and one drug for 4;14 and one drug for amplification 1q21 because when there are different genes that are abnormal, the biology of that myeloma should be a little bit different than someone with a different subtype and we should be able to learn enough about the biology that we figure out what the best target is. We are not there yet, but I think we are getting close and as just one example, I have talked a couple of times about the 1q21 amplification. One of the genes in that region is called MCL1. This is a gene which helps myeloma cells to survive against chemotherapy and there are now coming trials with inhibitors of that particular protein and the exciting thing there is that although these probably should be active against all myeloma types, it should be especially good against the 1q21 subtype. So, we are getting to the point where we have got these designer drugs I have mentioned.

Gary Petersen – That sounds like a lot of exciting things are happening in myeloma. So, we really do appreciate your leadership position in those efforts. Cindy, are you online?

Cynthia Chmielewski – I am. Can you hear me?

Gary Petersen – All right. You want to ask your questions?

Cynthia Chmielewski – Sure. Thanks, Dr. Orlowski, for being on today's call and I want to go back to something that we were talking about last time I talked to you, which was probably almost over a year ago and it was like maybe a designer type drug idea for the deletion of 17p and there was something that you were calling survivin protein that might have been aimed at patients that had 17p deletion. Can you give us an update on that research, if anything came out of that?

Dr. Robert Z. Orlowski – You have a very good memory, Cindy. So, thanks for asking that question. That's part of a project which is still ongoing in our laboratory group to try to figure out what are the soft spots, if you will, of deletion 17p myeloma so that we can then attack them and survivin was one of the targets that we had picked up on the initial screen. When we repeated the screening though, it fell out and it turned out that at least according to laboratory data, perhaps it wasn't such a good target after all and in part because of those data we did not wind up pursuing it in clinical trials because if we can't convince ourselves that its a good target in the laboratory, we shouldn't be asking patients to go on a trial of a drug in the clinic. We are, as I mentioned, still working on that project and we actually have some more data about other targets now that we have validated and we hope to be able to have something in the clinic for deletion 17p soon, but we are not quite there yet.

Cynthia Chmielewski – Okay. Great! I am glad to hear that. When we don't see things working in the clinic, we drop that and move on. So, its sometimes nice to hear that too and I am saying not everything is successful. Next question was, what do you see as the role of an allogeneic transplant in an otherwise healthy young patient that has high-risk multiple myeloma?

Dr. Robert Z. Orlowski – Well, certainly patients that are young and have a matched donor, an allo transplant is a consideration. We actually had this debate interestingly on Thursday. We have a patient conference every Thursday where we review all of the new patients that have come into the institution with myeloma and we make sure that we are doing the best thing for them and this is a collaborative conference which involves the transplant doctors and the radiology doctors and radiation doctors and this question of allogeneic transplant for high-risk disease did come up. Its certainly something that can be looked at. My personal view based on the data is that we don't have firm evidence that an allo transplant is of benefit either in standard risk or in high-risk myeloma and so this really should only be done in the context of clinical trials. I personally, and this was my argument on Thursday, I personally have never seen a patient cured of myeloma with an allo transplant. That doesn't mean that we shouldn't be looking at new ways to make it work better, but my preference for a newly diagnosed patient who is young with high-risk disease would be to give them the best chemotherapy combination that we have, probably for a young patient, think about following that with an autologous transplant and then if they get to MRD negativity, as I mentioned earlier, to follow the transplant with a very aggressive maintenance therapy and one example of that is we do have a study here at M.D. Anderson of maintenance with lenalidomide and elotuzumab and the reason for that is that when elotuzumab was studied in the relapsed setting, even patients with deletion 17p had fairly good outcomes with that combination and so we've now moved it earlier for post transplant maintenance. The main issue with the allogeneic transplant is that even at very experienced centers, the mortality is 15% to 20% and that happens within 100 days. So, that's a lot of patients to lose for something that we are not sure is curative and that's why I am a little hesitant to recommend it routinely.

Cynthia Chmielewski – Okay. When you are talking about an aggressive therapy after a stem cell transplant consolidation, was there any time you consider a second transplant in the high-risk population tandem transplant?

Dr. Robert Z. Orlowski – Great question! There are some data that suggest the possibility that a tandem transplant may be a little bit better than a single transplant for high-risk disease, but other data don't show that. So, frankly, we don't really know for sure and I think what's important, as I mentioned earlier, is this MRD negativity. The less myeloma you have in particular for high-risk disease, also for standard risk but particularly for high risk, the less myeloma you have, the better. My feeling is that if you are MRD negative or very close to it after the first transplant with high-risk disease, that probably a second one may not be that beneficial and you should go right to the aggressive maintenance. Now, if the first transplant gives you a nice

reduction in the amount of myeloma but you are still not in complete remission or not close to MRD negativity, then I think a second transplant could certainly be considered.

Cynthia Chmielewski – Okay. Great! Another question, I know there's a lot more emphasis on genetic testing these days, I know some of the projects like the MMRF are doing a lot of next generation sequencing. With all this genetic testing that's going on, have any new targets been found?

Dr. Robert Z. Orlowski – Well, there seems to be a certain panel of genes, if you will, that represent the majority of the mutations that are present in newly diagnosed myeloma patients. Some of those are already able to be targeted. For example, there are mutations in genes that are called NRAS, KRAS, and BRAF and there are drugs that are used in solid tumor patients which can help in that mutation and they are being studied in myeloma. There's already evidence that they may be of benefit. There are still though many mutations that are seen in myeloma patients that are newly diagnosed which we don't yet have particular drugs for and as the myeloma relapses and becomes refractory, the number of mutations starts to go up and then the problem is there can be so many mutations that we don't know which ones are important and which ones we should target versus which ones we should leave alone because one of the hallmarks, one of the characteristics of high-risk myeloma, is what's called genomic instability, that means that when the myeloma cells divide and they make copies of the chromosomes or the instruction manual, they make many more mistakes than normal cells and any mistake is essentially a mutation, but not every mutation is important than helping the myeloma cell to survive and you only want to target the mutations that are important to the myeloma cell and the problem is, there can be so many of them that we are not sure which ones are important. So, there is still a lot of work to be done.

Cynthia Chmielewski – Okay. Makes sense and finally, any new updates on extramedullary disease?

Dr. Robert Z. Orlowski – Yeah, good question also. So, extramedullary disease for those of you who may not know, that is myeloma that is outside of the bone marrow and usually it can be in sort of a ball of cells and unfortunately these things can show up just about anywhere, and patients who have extramedullary disease are often felt to be at higher risk because the myeloma cells now are no longer dependent on the bone marrow cells for survival. They can exit the bone marrow through the blood and they can attach in other areas. Right now, there are no specific drugs or therapies that are approved for extramedullary disease and in general, the recommendation is again, just as is the case for high-risk disease, to be fairly aggressive with that. Sometimes if you have only one place involved with this mass of myeloma cells, radiation can be quite effective, but still I think the standard of care is to do combination therapy, think about proteasome inhibitors and immunomodulatory drugs, and also think about antibodies and also some evidence suggests that deacetylase inhibitors like panobinostat may be good drugs, but those are really definitely situations where if you haven't seen a myeloma specialist, if you have extramedullary disease, if you have high-risk disease, you really should get to a major center of myeloma expertise, even if its only to get an opinion for therapy that you can take back to your local hematology/oncology doctor because the local doctors don't really have as much experience with high-risk disease as people at the major centers do.

Cynthia Chmielewski – Okay. Thank you so much. Gary, you can go on.

Gary Petersen – Thank you very much, Cindy. Yelak…

Yelak Biru – Yes, Sir.

Gary Petersen – Your questions please?

Yelak Biru – Thank you! First, I want to thank Priya for also introducing Pat's Myeloma Beach Educational event that's happening in early March because I really believe without the bread crumbs left by those that traveled this path before us and those of us living today would not be benefiting from the rapid advancements in the treatment of multiple myeloma that we have seen over the last several years and that you, Dr. Orlowski, discussed today and, Dr. Orlowski, nice to meet you over the phone and thanks for joining

us today. I know you have a busy clinic schedule. You have a busy travel schedule and research schedule, but I can't tell you I will not see ice cream in the same light again going forward, the way you described it earlier. Can you explain what FISH testing and gene expression profiling are and how you see myeloma testing, its manifestation, and eventual treatment evolving from one to the other over the next several years? Should we as patients now be asking our doctors to get GEP?

Dr. Robert Z. Orlowski – Well, I do hope you can still enjoy some ice cream. Maybe it won't be vanilla, but maybe it will be chocolate. In terms of the FISH and the gene expression profiling, right now the FISH should be routinely available everywhere and gene expression profiling also should be routinely available. It used to be done by one company and that test has now been transitioning over to Quest and they are validating the assay, so there may be a couple weeks or a month or two during which the testing won't be available because they are making sure that they can do it correctly, but after that it really should be. My feeling is that as of right now patients should probably be getting both and these are covered by most insurance plans, including Medicare for those of you that are worried and sometimes you can get complementary information and what I mean by that is some patients will have high risk by both tests, by the FISH and by the GEP, but sometimes you can have, for example, deletion 17p on FISH, but when you do the GEP, the patient can actually have low-risk disease and although we don't know for sure there are some data that suggest if you are deletion 17p by FISH but low risk by GEP, you may actually have low-risk disease. So, they sometimes don't agree and sometimes that can give you additional information.

I think moving forward into the future, you also asked what will we be doing at that point and I do think that moving into the future we will be probably doing more of what's called next Generation sequencing and the reason is that the FISH test only looks at a certain number of abnormalities and it looks for large changes, whereas if you have, for example, just one small mutation, it may not be picked up by the FISH, but it will be picked up by next generation sequencing and so, for example, that can be the difference, if you will. I hope this doesn't sour you on flying, but, you know, if you are flying at 30,000 feet in an airplane and you are looking down on the ground, you can't see a single person and that's kind of what a small mutation looks like. The FISH is what happens when you are travelling at 30,000 feet. You can't see a small mutation, but with the next generation sequencing, you can. So, I think ultimately we will be doing that, but we are not quite there yet. Many places, though, do offer it and I would say if you have it available, definitely get it done because again, for example, I mentioned the RAS mutations or the RAF mutations. There are some drugs that are now aailable that may be helpful for those particular subtypes.

Yelak Biru – So, is it true that based upon what you just said, next generation sequencing can potentially be used for both classifying you as low, medium, high risk as well as assessing your response to treatment?

Dr. Robert Z. Orlowski – Well, it can be helpful in assessing risk because, for example, if you find a mutation in the p53 gene which is in the 17p region, that may indicate that you have high-risk disease even if you don't have deletion of 17p by FISH. Right now, we are not yet at the point where we can use the results of the sequencing to predict what treatment would be best for that individual, but I do think we are moving in that direction. So, I think that that's going to be important in the future.

Yelak Biru – So, my next question was going to be around, can you explain the concept of clonal evolution and why and how one progresses from low-risk myeloma to high-risk myeloma, but I think your answer to Gary may have covered that. So, I am going to change my question a little bit and ask you, should you treat with your best options early and aggressively and potentially kill your low-risk myeloma and potentially leave you with high-risk myeloma as you explained or should you save your bullets in your revolver which today are cyanides for use later on?

Dr. Robert Z. Orlowski – Well, you have described a discussion and debate that we've had in the myeloma field for decades and we don't yet have a firm answer and different people may have different answers, but my answer is you are best off giving your best and most aggressive therapy upfront and trying to get to as low a disease state as possible and I'll give you a couple of reasons for why I make that answer. First of all, every time the myeloma relapses, it becomes less sensitive to therapy even with drugs that it may not have

been exposed to before. So, it is good, of course, to save some things for later, but if you use a drug later, its not going to work as well compared to if you use the drug earlier. So, that's reason #1. Reason #2 touches a little bit on your question that you passed on, which was the clonal evolution. Clonal evolution occurs because when we treat with chemotherapy, some of the cells just by blind luck for them and bad luck for the patient may be resistant and most of them are sensitive. So, when you treat with chemotherapy, the sensitive ones die and the resistant ones may be left over and sometimes clonal evolution occurs because new mutations develop. We talked about that these cancer cells make many mistakes when they divide and make copies of their chromosomes. If you hit the myeloma with the best regimen upfront and you suppress it down as low as possible, the chances of new mutations occurring decline because, for example, if you have, let's make it easier, if you have a million myeloma cells in your bone marrow and they are dividing, they are more likely to make a mistake and make new mutations than if you have a thousand myeloma cells that are in the bone marrow and dividing. So, the lower you drive it down, the less the chance of clonal evolution occurring.

Yelak Biru – That's reasonable. So, we have heard myeloma is not one disease and I think you mentioned that at the beginning of the call as well. I have also heard other researchers compared to where other blood cancers are, basic myeloma biology research is several years, if not a decade behind. So, I am going to ask you a hypothetic question. If today's show was going to go in a time capsule and be opened by a resourceful young scientist down the line, what advice would you give them around basic myeloma, where they should focus their research in order to look for myeloma understanding forward and in order to potentially cure all myeloma or at least subtype of myeloma definitively?

Dr. Robert Z. Orlowski – Well, first of all, its, of course, not easy to compare different fields, but one of the things that is different about myeloma, let's say, for example, we compare it to chronic myeloid leukemia or CML. That's a disease where 95% of patients have one abnormality in the chromosome in the leukemia cells that causes that disease. Myeloma, we don't have 95% of patients with one abnormality. We have 10, 15, 20 different subtypes and that makes it more complicated because again each of those subtypes behaves a little bit differently. So, that's one thing to say. A second thing is, we've really been, I think, going gangbusters in terms of research because in 2015 there were five new drugs or new drug combinations approved. In 2016, there were three new drugs or combinations approved and there's lots of other exciting things that are coming and I think one could argue that myeloma research in terms of drug development has certainly been making huge strides and patient survival has not just doubled but probably tripled over the past 10 to 15 years. So, in some ways, I think its fair to say that we've been doing really well on the research front, but I do think in terms of areas that need more attention, and there are some, we still don't understand as much as we should about the impact of myeloma on the patient's immune system and how we can reverse that. We know that myeloma suppresses the immune system in the patient, but we are not sure yet how to change that, turn the tables on the myeloma and activate the patient's immune system.

Dr. Robert Z. Orlowski – So, I think that's an important area for research, and the second area would be to develop biomarkers and a biomarker is essentially some kind of test. For example, it could be Next Generation sequencing, which allows us to determine what is the best therapy for an individual patient and that's also an area that I think is very promising because one of the frustrating things with myeloma for patients and physicians and families is that we kind of have a certain playbook that we follow, but even though many patients will respond, some will not, and if we could predict that ahead of time and switch to something which would be predicted to be better, that would be ideal for the patient because they would get what would be their best therapy sooner. They wouldn't be exposed to chemotherapy unnecessarily that doesn't have a good chance of working and yet as expensive and have lots of side effects and from a societal perspective, we would also save money. So, those are some of the areas where I think research really can make a big difference and I actually think that we are going to be at the point with everything that we are doing now, within the next five to 10 years that we will be curing a large proportion of patients, not just putting them into remission but actually curing them. Now, that's not everybody, but I think it will be a large proportion.

Yelak Biru – I think our challenge as patients is to attempt to be alive when you guys are there in 5 to 10 years. Gary, that's all the questions I have.

Gary Petersen – Okay. Well, thank you, Yelak. Appreciate it. Now, Jack Aiello is on a plane right now, but he left a couple questions, which he would like me to ask. First one is, I know high-risk factors for smoldering multiple myeloma are different from high-risk multiple myeloma, which examines chromosome mutations; however, are these mutations also important for smoldering multiple myeloma patients?

Dr. Robert Z. Orlowski – Yeah, great question, and actually Jack is a patient advocate within SWOG and I mentioned that because SWOG did a study looking at patients with MGUS and smoldering myeloma and whether gene expression profiling, in particular, can be of help in predicting risk and what we found is that just like GEP can be a predictor of high risk in newly diagnosed myeloma patients, the same is true in smoldering myeloma. If you have high-risk smoldering myeloma by gene expression profiling or if you have one of the high-risk FISH abnormalities, in general your risk of progressing to symptomatic myeloma is higher and it tends to occur sooner. Now, there are still patients, I actually saw a patient couple of weeks ago with a 4;14 translocation which theoretically should be high risk and yet this gentleman has been smoldering for over 10 years. So, clearly, even having a high-risk feature doesn't mean that you are 100% going to progress, but it does make it more likely.

Gary Petersen – Okay. Thank you. Also, he asks, I have heard that monoclonal antibodies like daratumumab responses are seemingly independent of high-risk factors. Is that true and if so, do these responses also translate into similar progression-free survival and overall survival, all counts?

Dr. Robert Z. Orlowski – Yeah, we did touch on that slightly, but I would love the chance to expand upon that further. Of course, the way antibodies work, at least most of the ones that we now have for myeloma, they attach to a protein on the surface of myeloma cells and they make them more visible to the patient's immune system so that it can go in there and attack. So far, the targets that the antibodies attach to seem to be expressed equally whether you have standard risk or high-risk myeloma. So, theoretically these should be very good drugs for high-risk disease. There are some data so far from clinical trials that suggest that that's true. The problem is that the followup on these studies is not as long as we would like for them to be. So, we can't be sure. I still have a concern because we talked earlier about the fact that high-risk myeloma, one of its characteristics is that they have many more mistakes that they make, these cells when they divide, more mutations develop and my concern is that because of these mutations, it will still be more likely that they develop a resistance mechanism than somebody who has standard risk myeloma, which tends to make fewer mistakes. So, I am still a little bit concerned that even the antibodies will not completely overcome high risk. I hope I am wrong, but we need a little bit more time to see.

Gary Petersen – Okay. Well, thank you. Priya, time for…

Priya Menon – Yes.

Gary Petersen – …our caller questions. Is anybody online or should I ask the questions that were sent in?

Priya Menon – Yeah, please do ask the questions that have been sent in. I think we have…

Gary Petersen – Okay.

Priya Menon – …just added couple more to the list, yeah.

Gary Petersen – Okay. All right. We have one caller who says my brother has just been diagnosed with multiple myeloma. He was being treated for a pulled muscle in his back for five months. When the treatment did not work and he was not getting better, they told him to come back in 30 days for an MRI. Within the 30 days, he lost all feeling in both legs and had to be wheeled in a wheelchair for an MRI. He was admitted in the hospital and he started steroid treatments, then radiation, now chemo. He has some feeling in his legs and can move his right leg. Left leg does not have as much movement or feeling. Will treatment help him walk? They are talking about sending him to a rehab after chemo. I was feeling very hopeful, but now I am not so much. I am worried they have told him he will not walk and he is not telling us. He is very depressed

and when we tell him he will beat this, he does not answer. What would the next treatment be? I know you are not privy to his records, but I assume it kind of has a course of treatment.

Dr. Robert Z. Orlowski – Well, of course, it sounds like a very challenging situation and I am sorry for your brother and your whole family. Often times, when people present with paralysis like this, its because of a plasmacytoma, which we mentioned earlier, that can be either just outside or even inside the spinal canal and it can compress the spinal cord which causes this paralysis. Occasionally what can happen is one of the vertebrae can fracture and a bone fragment can be pushed backward and put pressure on the cord causing paralysis. The good news is it sounds like he has had some recovery already and really what's important is that they do the steroids and the radiation and then follow that with chemotherapy because a lot of times people can recover completely to the point that they are able to walk, but it can take time. So, without seeing his MRI or other imaging of the spine, its tough to say for sure, but it is encouraging that he's had some improvement and I would try to be as supportive as possible because I think he still has a very good chance of hopefully recovering fully.

Gary Petersen – Would a second opinion be helpful, you think, in a case like this?

Dr. Robert Z. Orlowski – Well, its certainly worthwhile to have the treatment plan reviewed to make sure that, for example, the amount of radiation that is being given is appropriate, that the amount of steroid and that whatever next chemotherapy they are planning is appropriate. I would recommend that to any patient and family with a myeloma relative, a second opinion should be gotten. There actually was an abstract a couple of years ago at the American Society of Hematology, indicating that the average oncology practitioner sees between 1 and 2 new patients with myeloma each year and as you can imagine because every patient is different, that means they don't have as much experience as would be ideal and then towards the end of 2016 there was a paper published in the Journal of Clinical Oncology, which is one of the major cancer journals, which looked at outcomes for patients with myeloma depending on whether they were treated at a center that saw a lot, a little, or no patients with myeloma and the best outcomes, and these were survival outcomes, the best outcomes were in centers that saw lots of myeloma patients. So, experience does make a difference and also these centers that see lots of patients also tend to run clinical trials and clinical trials with new exciting drugs can be really important. So, hearkening back to the previous question about what could be done to improve outcomes and what you would want to put in a time capsule, the main things that patients can do is to try to ask about trials, if we could increase enrollment to trials, we would be able to really get to the point that we are curing people a lot more quickly.

Gary Petersen – Thank you very much. The next question is, why is plasma cell leukemia never mentioned when high-risk myeloma is discussed? As a member of the myeloma family, its prognosis is one of the poorest, yet no research is done on it and few clinical trials will ever even allow PCL patients to participate. What hope is there for PCL patients?

Dr. Robert Z. Orlowski – And for those of you that may not know what PCL is, PCL is essentially myeloma, but instead of the myeloma cells being just in the bone marrow, they also are circulating at a high level in the blood and this is a more aggressive form of myeloma. Fortunately, its rare and that's one of the reasons that you may not hear a lot about it because although there may be 32,000 to 33,000 new cases of myeloma diagnosed each year in the US, only 1% or 2% have plasma cell leukemia. So, even a large center like M.D. Anderson doesn't see them very often. You know, we'll see a few a month but not as often as would be ideal to do clinical trials. There are different types of PCL. There's what's called primary PCL which is if someone is newly diagnosed, then they have this leukemia and there's also what's called secondary PCL and that tends to be leukemia that develops many years into therapy. The leukemia that develops after many years of therapy tends to be very aggressive and difficult to treat, but sometimes patients with primary PCL or newly diagnosed plasma cell leukemia can actually have a good outcome with similar chemotherapy and stem cell transplant. So, PCL by itself is not a death sentence and can often be treated successfully.

Gary Petersen – Priya, if you could…, do you have a couple more questions?

Priya Menon – Yes, Gary. Thank you. Doctor, the next question is, I am a 10 years kappa light chain myeloma survivor, currently on daratumumab. After two infusions, I achieved CR. I have completed all weekly and biweekly infusions and now am on monthly maintenance cycle of dara infusions. My first question is, how did they establish maintenance cycle for dara? Why not every three weeks or every-two-month cycles? And second…, there's a second question, which is, what do you recommend when dara is no longer effective? Wait for few months or as you have suggested, switch between elotuzumab and daratumumab?

Dr. Robert Z. Orlowski – Well, let me tackle the second question first, what to do if the myeloma numbers start to go up and maybe it looks like daratumumab is not as active as it was. One of the things that many of us do is that we increase the frequency of the daratumumab from once monthly up to twice a month and we do find that many patients will have a good benefit from that. So, just progression doesn't mean you automatically have to switch away from the daratumumab. Switching to elotuzumab though could be an option or you may want to go to a proteasome inhibitor or a new drug. There actually are a number of studies looking specifically at patients progressing on dara and adding other immune therapies to try to stimulate the immune system to recapture the benefit. So, those are other options.

In terms of the first question, why not reduce the frequency of the daratumumab further; instead of once a month, why not give it once every three months. The half life of daratumumab is about two weeks. Half life is the time that it takes essentially for half of the drug to disappear from your body and the feeling is that five half lives is enough time for the drug to be completely gone and so if the half life is two weeks and we do five half lives, then if you don't get dara for 2-1/2 months, its completely gone from the body and then the concern is that the effect against the myeloma would be gone as well. So, that's one reason why probably doing it every three months would not be effective. Could you do it every two months? Maybe, but since it works so well according to the schedule that's been already tried, I am usually pretty hesitant to make any changes. The other thing to keep in mind is that there are some studies that are being done using subcutaneous daratumumab and the advantage of that is that it seems to have fewer reactions and it also can be given more quickly. So, that should improve convenience in the future, but I would stay on the once-a-month if that's where you are and by the way, congratulations for being a 10-year survivor and hopefully many more to come.

Priya Menon – Thank you, doctor. I think we have just exceeded the time. Thank you so very much for sharing such a lot of information with our audience and, Dr. Orlowski, we are very excited regarding the upcoming International Myeloma Workshop in Delhi. I think the entire myeloma doctor community is going to be here, and we are in touch with Dr. Malhotra and Dr. Kumar will be following the event. Hope to get some really good news out of the presentations and the research. So, we are looking so much forward to it. Gary, Cindy, and Yelak, thank you so very much for your participation and the great questions and Jack too, you are in plane right now, your questions were answered and we thank you for them. This talk will be made available on CureTalks' website for playback. We will also be loading in the transcript for the same. Please visit curetalks.com for details of our upcoming talks. Thank you, everyone. Have a great evening!

Gary Petersen – Thank you, doctor.

Dr. Robert Z. Orlowski – Right. Thank you.