The Art and Science of Relapsed/Refractory Multiple Myeloma: A Practical Guide to Complex Therapeutic Choices

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Dr. Hari: Good evening, and welcome to this CME Symposium on *The Art and Science of Relapsed/Refractory Multiple Myeloma: A Practical Guide to Complex Therapeutic Choices*. I am Parameswaran Hari from the Medical College of Wisconsin. I am a last minute replacement for Dr. Shaji Kumar who couldn't be here, and since Milwaukee is only an hour and half away, I drove over replacing him, adequately I hope. I'm joined by my illustrious colleague, Dr. Saad Usmani from the Levine Cancer Institute in Charlotte, North Carolina. We hope we'll have a robust discussion. We have scheduled this event as two talks. The first part will be led by me and then we'll have a short question and answer session, and Saad is going to close out and discuss the cases that we have upfront. Now we go to my portion of this symposium which is *The Current State of Care in Relapsed/Refractory Multiple Myeloma* and the management of early relapse and the choices of agents. This is my disclosure slide.

Looking at the myeloma treatment paradigm, which is extremely familiar to all of you here, we start off with diagnosis and risk stratification. For most patients the disease burden is probably the highest at initial diagnosis. If you follow these patients over time very carefully, you will never really allow the patients to have the same disease burden as at diagnosis when you are following them over time. However, that does not mean that the disease does not become more aggressive; it does become more aggressive with each subsequent relapse. So, induction followed by continuous therapy is one option for nontransplant-eligible patients; and for transplant-eligible patients it's induction, consolidation, and maintenance. This consolidation step typically involves autologous stem cell transplant, in some cases autologous stem cell transplant followed by some consolidative treatment where you give very similar treatment to induction. For example, VRd consolidation where you get a triplet consolidation followed by len maintenance. That would be the standard approach. Patients then relapsed with increasing biochemical markers and sometimes clinical relapse. We'll go to the types of relapse as we further proceed.

Relapsed myeloma is really the problem with myeloma. It is nowadays almost inevitable as patients presenting initially will get into remission. Our response rates for initial triplet induction with better and better agents are approaching the 90% to 100% range, albeit induction followed by transplant, getting people into the first remission is not really that much of a problem anymore. However, relapse is almost inevitable and that is the biggest challenge in facing myeloma right now. If you look at patients who are diagnosed between 2001 and 2005 versus those diagnosed the next five-year period, you can see that the length of remission for the first remission has gotten better, and the improvement and the number of patients living with myeloma is about 50% at six years for these patients who are diagnosed

approximately 10 years ago. Most of us now believe that if you drew the same curve for patients who are getting diagnosed right now, we are approaching 8 to 10 years with the better agents.

The problem with relapse is that relapse correlates with development of resistance. We saw that, the patient that we just presented, the 67-year-old lady with translocation (11;14) myeloma, acquired a 17p deletion at relapse, so really that is a problem. You get more resistant disease at relapse and it becomes more and more resistant as time goes on. This is very elegantly shown in this slide where the first line of therapy, you receive an overall response rate of almost 60%, the second line gives you 45%, the third line gives you 30%, 15% and it keeps on going down. Basically, you get remissions that are shorter and response rates that are lower with each regimen. As you can see, the longest remission is with the first-line therapy, whereas the sixth-line therapy it is measured in a few months. Again, this is the number of single nucleotide variants per patient, which is a measure of clonal heterogeneity, as you can see that untreated and treated patients, as with further treatment, the heterogeneity of the myeloma and the aggressiveness get worse.

Here is the other elegant slide which many of you may have seen already. This is the same patient followed over time. As you can see, this is the clonal heterogeneity in this patient. Each clone is shown by a different color. This is a single patient, multiple bone marrow biopsies at multiple times of relapse, and each clone is tracked by the color. As you can see, this orange or reddish orange color is the major clone at diagnosis when it's 72%, but at that same time you can see there are three other clones within this patient's marrow. First remission, the same clone comes back when the patient relapses, 64%, but you can see that there is the grey clone which is now growing. Here was 11%, 31% is represented by that grey clone. The next time that the patient relapses, a completely different clone, the blue which was only 10% over here, even lower here, now that is the major clone. Subsequent relapse, it's the grey clone. Here was orange, here was blue, here was grey, and finally the patient is at the stage of secondary plasma cell leukemia which is uniformly fatal with the current technologies. It is a completely different clone evolved out of one of these previous clones that's over here, 96%. It's nothing similar to what the patient had before.

This basically tells us that some of our therapies actually select for clones that are more aggressive. Every time the patient relapses, the patient relapses with a slightly different clone or a recurrence of a pre-existing clone, but the heterogeneity within that changes. We call it clonal tides which means, like the tide coming in from the sea, a tide of single clone comes in, receives something else so the same one comes back. Many people believe that if a person relapses the first time, a third of a time it is the same one that was initially present, a third of the time it's a linearly evolved one from the previous one, and another third of the time it is something that was subclonal at initial diagnosis that now comes back since you have removed the dominant clone. This again is the biology of relapse and this is what makes relapse so difficult to treat.

How does that translate clinically? That translates in a couple of different ways. One, if it's the same clone that comes back and if it's sensitive, you could actually use the previous treatment and you could maybe save another drug for a later time which then brings us to the question of sequencing. When a person has myeloma and they have relapsed, you've already committed that this person is now going to relapse several more times during their lifetime and you will have to treat them each time. It is very

difficult for a person who has relapsed once to now think about a long-term remission without relapse, although if you look at everybody who had an auto transplant and maintenance, something like 15% to 20% of patients are out 10-15 years in their first remission. Those patients are going to do extremely well, but the vast majority of patients have been to relapse and the first relapse is just a harbinger for subsequent relapses. To rationally choose combinations, we have emerging data on what to do when we have high-risk disease, what to do when we have specific mutations such as translocation (11;14). Adapting treatment to individual patients and individual relapses means we need to understand the disease heterogeneity even better and that, again, like the patient that we just saw in the initial presentation, important to do a bone marrow biopsy because if you didn't do a bone marrow biopsy at relapse you wouldn't actually have known that the patient now has a 17p deletion, you would just assume that the patient is an (11;14) patient.

The general principles of treating relapse is that duration of initial response is a very good indicator of disease biology. We have actually done studies of patients who relapsed after an auto transplant. Generally, if you relapsed within two years, and in some cases 18 months, depending on where you drew the line, after an auto transplant your prognosis is extremely bad irrespective of whatever your original cytogenetics was. Duration of initial response is a dynamic marker of prognosis that we don't actually have when you first see the patient. At that time you are basing your prognosis on the staging system beta2 microglobulin, LDH, circulating plasma cells, FISH studies, and in some cases gene expression profiling if you do that; whereas a patient with none of these bad markers, if they relapsed within a year after an auto transplant and on maintenance, you now have an even worse prognostic marker that was not available at that time so that patient now needs to look at very aggressive treatment. That patient is so different from somebody who, for example, had a (4;14) deletion, was on induction transplant and maintenance and then they relapsed five years. They had a marker that was a higher risk marker, but their first remission lasted four or five years. It's very important to understand the duration of initial response as a dynamic marker for prognosis.

The second general principle is that in every study that we have looked at, a triplet always trumps a doublet. We don’t have data that a quadruplet trumps a triplet but we have a lot of data, as you will see, that a triplet is always preferred over a doublet, and one of the agents in that triplet needs to be something that you know is likely to work from a class or from an agent that you would think that patient is not refractory to. You have the luxury of that only in the first relapse or the second relapse. Once relapses accumulate, you probably have to go back to agents that you may not know or not 100% sure they would be nonrefractory to. Obviously, consider performance status, age, comorbidities, etc., and take into account the previous toxicities such as neuropathy. You wouldn’t go back to a neuropathy inducing drug, for example.

The final principle that often we see patients are reluctant to, and in some cases we are reluctant to, is that you have to treat to a maximum response and then at least leave them on one drug. Maintenance is even more important when you treat relapse perhaps than when you treat initial disease. In both settings, maintenance is proven, but treating to a maximum response and taking off that treatment which was what I was started on as a fellow in the late 90s which is treat to a plateau and stop. That is really not the paradigm now. We have to leave them on an agent until the next relapse and so they would be refractory with that agent at the time of relapse but you keep that out. Many a time it means

convincing the patient because patients generally don't want to be on treatment when they're feeling good and when they see the numbers are down.
Some of the other factors in selecting relapse therapy are in this slide. Obviously, there are some very obvious ones like age, performance status, renal insufficiency, poor marrow reserve, neuropathy, comorbidities, etc., which are patient factors. I'd just like to focus on a couple of things. With the rapidity of relapse, in the middle column there, disease, where a rapid relapse where your M-spike or free light chains are doubling in three or four months which indicates relapse that needs to be treated. There are patients who have very slow indolent relapses where the M-spike is hardly progressing, but it has reappeared and it's there and the patient — in that case you would do an adequate imaging, you would watch them very closely. There are patients that you could wait and not do anything about, but those patients are a tiny minority. Patients with extramedullary relapses where they have lymph nodes or organ based relapses are a major challenge and they need aggressive treatment. Plasma cell leukemia where if it is a first presentation of plasma cell leukemia at relapse we call it a secondary plasma cell leukemia. That is, again, a highly aggressive disease with very poor survival despite all our efforts. So, the rapidity of relapse and the clinical nature of the relapse is another important factor to consider. Obviously, treatment factors such as route of administration, we have agents now that are IV, subcutaneous, and oral; risk of toxicity; chest thrombosis; myelosuppression, and neuropathy. We have left the risk of second primary malignancies over there, but once the patient has relapsed I actually don't even talk about second primary malignancies because that's an issue for the person who had a long first remission. Once the patient has relapsed it's almost certain that myeloma is going to be the cause of death for those patients.

Overall, it's important to have a strategic approach which obviously needs to be evidenced based and rational whenever possible. Again, as you get further and further out with more relapses, it becomes less and less evidence based, and it needs to be personalized for the patients. We are not yet at the point where we are thinking about early relapse versus late relapse, first relapse versus third relapse, etc., but that's the way the FDA approves drugs these days and that's the way the studies have been done, but we may get to a point where we use genomic medicine, not precision medicine, to define the relapse and kind of predict what drugs the patient is likely to respond to. That is happening — that will be coming but not quite there yet.

One of the important questions that people always raise when I talk to people who were referred to me is, "Can I use a previous regimen again as salvage?" That again, we go back to the depth of response to the original regimen, toxicity from that original regimen, and how successful was it in prolonging a long remission. If a patient, for example, was — even now, we have patients who we treated a while ago who got, say, a triplet induction and auto transplant and no maintenance because the data for maintenance came in the late 2000s. There were patients who are seven or eight years out who never received any maintenance and they are now — or they had maintenance for one or two years and they have been off maintenance for a long time, the question is, “Can they go back to RVD which was their original regimen?” Absolutely fine because you would expect such a patient with a long remission and a long disease-free interval to be responsive to RVD and you would expect them to be responsive to all three drugs in that setting. The duration of what is a good duration of response, most people would argue that about 18 to 24 months is considered a really good duration of response, but again it is important that patient should not be refractory to these drugs or relatively resistant to these drugs.

These are some of the options in first relapse. Obviously in the U.S. the use of thalidomide is very limited. We have three proteasome inhibitors bortezomib, carfilzomib, and ixazomib all of which are FDA approved for first relapse or early relapses; pomalidomide is not in this category here because it's not yet in that indication so far. Traditional chemotherapy, cyclophosphamide and anthracyclines are still there; and monoclonal antibodies daratumumab in combinations and elotuzumab in combinations are both approved for early relapses.

Let's now look at the studies that inform us and let us choose the drugs. Again, going back to our initial treatment paradigm, patients are going to come to us these days through one of these pathways — triplet induction transplant maintenance and then relapse; transplant non-eligible patients who got triplet induction and stayed on at least one of these drugs, either VRD followed by R maintenance or VCD (which is Cytoxan which is also known as CyBorD, Cytoxan, bortezomib and dexamethasone) and stayed on bortezomib maintenance and then they relapsed; and RD patients who are even more transplant ineligible, I guess, and stayed on a doublet, but these days most of us actually use some form of triplet. Even in the patients who would have gotten RD in the olden days, we would use RVD light with the lower regimen of bortezomib because that is clearly a better regimen in the VRD versus RD study that was already published. In any case, we would have patients in this sort of a setting. Most of them would have been on lenalidomide maintenance or bortezomib maintenance, and some of them would have come without any maintenance. Obviously, you would choose based on what they had initially and whether they had a transplant or not.

The two mainstays of therapy are still IMiDs and proteasome inhibitors. An IMiD-based regimen is of course a choice in a person who basically relapses while on bortezomib maintenance or who has no prior IMiD exposure so you expect that agent to be most effective in them, and intolerance or refractoriness to a proteasome inhibitor. Similarly, a PI-based regimen would be in patients who are sensitive to a PI such as prior bortezomib use with good response, len refractoriness, intolerance, or rapid relapse while on len maintenance, and preference for certain translocations. You know it's basically (4;14) and even patients with translocation such as (14;20) with a high light chain production phenotypically. Those are the patients you would expect to respond very well to a proteasome inhibitor-based regimen. These two agents, either PI or IMiD, form the basis of your triplet. You have to use a good PI if you are treating those kind of patients as a backbone and you would have used an IMiD as the main backbone if somebody, say, relapse is on bortezomib maintenance and has a rapid relapse. Obviously, clinical trials with novel agents is another option.

Let's look at the patients who are not refractory to bortezomib. These are the patients where you would base the regimen off of a backbone of a proteasome inhibitor. If you wanted to treat those patients with a doublet, the obvious choice would be to use the most powerful proteasome inhibitor that we have available which is carfilzomib. This is a second-generation proteasome inhibitor. It is given IV, and the dosing and the scheduling are especially key with this agent. For carfilzomib, there's a head-to-head trial of patients who were bortezomib exposed and a bunch of patients who were not exposed to either; but in this study, head-to-head comparison, carfilzomib versus bortezomib. This study shows a median progression free survival of 18.7 for Kd, carfilzomib-dex, versus nine months for bortezomib, so double the progression-free survival, and now we have overall survival data also favoring carfilzomib. This is clearly the most powerful agent that we have when a patient has been previously bortezomib exposed but expected to be bortezomib sensitive.

Another agent that is available based on studies is panobinostat which is — I think of it as an agent that can restore sensitivity to a bortezomib-type regimen. Here in this study, bortezomib-dex alone versus bortezomib-panobinostat and dex was compared and it gives you a PFS advantage of about three to four months. Unfortunately this agent is really not used that much in the U.S. these days because in a setting where bortezomib is not expected to do very well but you would still expect the patient to be PI sensitive, you have better agents to use. You have either carfilzomib-based combination or an ixazomib-based combination. You have either PIs to go to so the use of panobinostat is rather limited at this point and it adds a few months to the Vd regimen. Another choice is to go completely different and go with an antibody, daratumumab-bortezomib-dex or DVd was studied in the CASTOR study where daratumumab patients in this arm got dara-Velcade-dexamethasone or dara bortezomib-dexamethasone, and on the control group got bortezomib dexamethasone for nine months. You can see the dara arm continued, the dara arm data on maintenance. The overall response rates, VGPR rates, and CR rates were all better for daratumumab, and the median progression-free survival was 7.2 months for the bortezomib-dex, very similar to the previous studies we had -- nine months, eight months, seven months; whereas it was not reached for dara group. Again, this is another agent that could be combined with bortezomib in patients who you would expect bortezomib to work.

Elotuzumab-bortezomib-dex is another combination. Again, as you can see, this is not an FDA-approved combination. The approved combination is for elotuzumab, lenalidomide, and dexamethasone. This improves the median PFS from about 7 months to 9.7 months. Going back all the way, you have Kd which improves it from 9 months to 18 months, PVd which goes from 8 to 12, here 7 months to not reached, and here from about 7 months to 9.7 months. Those data are summarized in this slide, and you have access to those slides.

Now let's look at patients who are expected to be IMiD sensitive. This is a second group of patient. Again, as I said, the logic is to pick the backbone first and then build around it. These are patients where you would expect the IMiD to be the main drug that you are using and then build around it. These are patients for whom — again, the ASPIRE study is the only study that at this point in time that we have overall survival benefit for in a triplet involving an IMiD. We have carfilzomib-rev-dex versus rev-dex, so it's a double versus triplet study. We have an overall progression-free survival advantage of 27 months versus 17 months a 10-month advantage for the KRd group over Rd. Now we have overall survival data for the study as well.

This is an IRd versus Rd study. Ixazomib is another second-generation proteasome inhibitor and it's orally bioavailable, it's given once weekly. This is again an attractive regimen for a patient who chooses an all-oral regimen. Here again, we have a progression-free survival advantage of 15 months versus 21 months for the triplet versus doublet. Here again, you're building around an IMiD based backbone and we have, “I” is the proteasome inhibitor ixazomib. Elotuzumab-Rd, here is the approved indication for elotuzumab. This is an agent without single-agent activity in myeloma. It acts on a receptor on the surface of plasma cells as well as NK cells known as the SLAMF7 receptor. We actually don’t know the exact mechanism of action; it may be direct action on the plasma cells, it could be optimization of the plasma cells for macrophages and other NK cells and other immune cells, but it is an immune active agent. One of the advantages of this regimen is that a portion of patients, almost 25%, continue on very

long remissions on elotuzumab. Very similar to what you would expect with an immune active agent, but at the outset it's very difficult to predict who is going to be in that 25%. Unless you use it, you wouldn't pick up the 25% of people who are out there in a long remission out for years. Here again, you can see that the PFS advantage was from about 15 months versus 20 months for the median, if you just look at the median.

Of course then, we have the antibody daratumumab. Here is dara-Rd versus Rd. Here again, the progression-free survival data is what we have right now but I fully expect this to also show overall survival difference going further forward. You can see that the 12-month progression-free survival was 83% versus 60% for DRd versus Rd. The message is clear, a triplet seems to be better. You can combine in the triplet formulation a proteasome inhibitor, either ixazomib or carfilzomib, or an antibody such as elotuzumab or daratumumab. These are the combinations and the PFS differences are over here so I'm not going to go over this, it's in the slide set that you already have.

This is a summary of what we just discussed. You would first think about what you're going to use as your backbone depending on prior exposure and your expectation of which agent is going to be more sensitive, IMiD or PI, and then build around it. Also, slow biochemical relapses where the relapse is very slow and you think you can recapture the response without using an agent that is single-agent active. You would choose something with just elotuzumab where you are not really using up a myeloma active regimen but you might capture at least 25% of patients who are going to be out for years still on rev with elotuzumab and they would still be sensitive or expected to be sensitive to proteasome inhibitors, daratumumab, and all the other agents that we are going to discover.

Now, looking at patients who are totally open where they are not refractory to either lenalidomide or bortezomib. These patients are in a good place because they have both IMiD and PI sensitivity to literally every available agent. In these agents, these are the patients for whom you could consider RVd. We actually don’t have an RVd versus Rd or RVd versus Vd study in relapse. We don’t have any such studies, and they won't be done but it would be a very reasonable choice to use because you would have a lot of other agents in your back pocket if you just recapture the great response with RVd. You could actually, in some of these patients, I have patients who were transplanted, say, in 2006 or 2007 who didn’t get maintenance and now, seven or eight years later they are relapsing. You could literally do the same thing all over again RVD induction for four cycles, do another auto transplant, put them on maintenance now. You would expect them to have a very long remission again, and by the time they relapse again we would have a whole different era of myeloma with other agents too. For these patients, again, VCd is another choice with Cytoxan, bortezomib and dexamethasone.

Now, going back to the opposite end of the scenario where the patient is clearly refractory to both lenalidomide and bortezomib. You're thinking about, at this point, single-agent activity of daratumumab. Daratumumab is an antibody with considerable single-agent activity. Overall response rate in multiple relapsed patients was 31% and you can see even some people getting to stringent CR, CRs and VGPR, so about 13% in those kind of responses. It's clearly a drug with excellent single-agent activity although I don’t recommend anybody getting treatment with a single agent at this point, except if you had a novel immunotherapy or a clinical trial for that matter. Here is the change of drug class. The bottom line is that when a person is refractory to both bortezomib and/or proteasome inhibitor and IMiD, you would

have to change the drug class. The regimen will have to be built in that point around the monoclonal antibody such as daratumumab.

One other point important to mention, we talked quite a bit about carfilzomib and ixazomib and other proteasome inhibitor such as second-generation proteasome inhibitors. These are data that were recently presented at the ASCO meeting. As you all know, one of the problems that patients have when we use carfilzomib is the schedule. The approved schedule that was initially approved was two back-to-back days each week for three weeks in a row. That is six clinic visits for a patient to receive an IV drug in three weeks, so that's quite tedious and a lot of patients have to travel a lot, patients don't want to sit in the IV and get it, they prefer — but it is a very powerful agent and the optimal dose range is quite wide. You can actually have patients responding in 20 mg/m^2 all the way up to 56 or 70 mg/m^2 per week. The A.R.R.O.W. study was presented at ASCO and compared two different dosing schedules, once-weekly at 70 mg/m^2 or twice-weekly at 27 mg/m^2. The first week, both sets got 20 mg/m^2, so essentially start out with 20 for one week and then go to 70 mg/m^2 weekly or 27 mg/m^2 twice weekly on back-to-back days. Overall response rates were superior for the once-weekly regimen at 70. From 41% to 63% and the VGPR rates or deep responses were also significantly better for patients who received the once-weekly regimen. Now we have an agent that now then becomes once a week in use. Another regimen that is especially useful in patients who have multiple relapse and they are lenalidomide refractory but expected to be proteasome sensitive would be KPd — carfilzomib, pomalidomide, and dexamethasone. This was the original study in multiply relapsed patients presented by Dr. Shah. This was relapsed/refractory patients and showed a median PFS of seven months.

This is another pomalidomide combination with daratumumab, pomalidomide, and dexamethasone. This is also an approved regimen by the FDA. As you can see here, in a 75-patient study, 71% overall response rates with 43% VGPR or better, so pomalidomide is an excellent drug to combine with daratumumab. Here is again the indication to use this would be both of these regimens, KPd or DPd, would be the patients that we see now who are on lenalidomide maintenance or you go up on the lenalidomide dose and you still have rapidly progressing relapse. You need an agent that is effective and expected to work. You would choose either carfilzomib or daratumumab and combine it with pomalidomide because you can capture lenalidomide resistance with this combination.

Finally, talking about salvage auto transplants. Many of our patients, approximately a third of the patients with myeloma undergoing autologous transplant as the course of their first treatment, almost all transplant centers collect enough for more than one transplant and almost all of these patients have cells in storage which are usually available even 15 years down the line. Those cells would still be good in most places. One of the options that is very, very seldom thought of but highly effective, especially for a patient who has had at least a two- to three-year remission from their first auto transplant, is a salvage high dose treatment. Many of these patients don't make their way back to the transplant center because of a couple of misconceptions. One of them is that they think it's not approved by insurance. It's actually approved by insurance. Medicare in the past had a rule that they would only do it once in a patient's lifetime but that rule is hardly ever applied these days and many patients in Medicare have received transplants twice.

These are data for patients who received — this is a study from the UK. Patients who had relapsed myeloma were randomized to chemotherapy versus a salvage high-dose treatment with autologous transplant. This is the progression-free survival curve and this is the overall survival curve. As you can see, the study showed a positive overall survival benefit for patients who could undergo a salvage high-dose treatment. The questions are, should you send them back to the transplanter? Question is will the patient want it? If the patient tolerated their first auto transplant well they are likely to say, "I can do it again." Did they have at least 18 months of progression-free survival free benefit? I would say 18 months is where you draw the line. If they didn't have 18 months you probably shouldn't do it but if they had three years or more you should almost certainly think about is as one of the big options, somewhere between 18 and two years is the sweet spot where you would definitely think about doing it, and patients who did not get maintenance in their first transplant but still did very well, it would be almost be a loss if they didn't get a second transplant and maintenance because maintenance has clearly transformed the outcomes for patients who undergo a transplant.

There are so many chemotherapy drugs. This is more relevant for patients who have multiply relapsed disease where we are running out of the novel agents such as anthracycline, cisplatin, etoposide, BCNU. These are agents that many myeloma experts still use and regimens such as Vd PACE or Kd PACE which are especially applicable in the setting of multiple relapses, plasma cell leukemia-type relapse, CNS disease, etc. Then there are a lot of emerging options that are in clinical trials. We heard at ASCO about the bortezomib-pom-dex or VPd data. There is daratumumab and carfilzomib combination. Isatuximab is another monoclonal antibody which is CD38 directed. For patients who are refractory to both IMiDs and PIs, we have dara-pom-dex, dara-carfilzomib-dex and dara with checkpoint inhibitors which is again in early phase trials in myeloma. The only problem with using that is unless it's done in a trial, you will be opening yourself up to a lot of litigation possibly because it is FDA black box warning.

Dr. Usmani: Alright, so I'm going to cover the second half of this session. What do we do for patients beyond that first relapse and managing heavily pretreated patients? We've already reached on the speaker disclosure slide early on, but I put this on here before I move on.

What are the current options for patients who are in their second or beyond prior lines of treatment? We encourage these patients to participate in clinical trials at most academic centers, but then if patients are having a rapid relapse we would be using conventional chemotherapy for situations where patients have either bulky extramedullary disease or rapid relapse with high disease burden and renal failure or presence of secondary plasma cell leukemia, but we are using that as a bridge. We want to cytoreduce the patients quickly and then bring them to this middle column right here where we will be using either an IMiD- or PI-based regimen. Some of these Hari has already discussed in previous slides so I'm only going to be sharing them on this slide and the next slide just to put things in context. We are either utilizing a carfilzomib-based triplet where we would partner it up with an IMiD, cyclophosphamide, or sometimes panobinostat. There is a phase two data where carfilzomib appears to be a better proteasome inhibitor partnered with panobinostat. Most of us are utilizing panobinostat in this setting and with quite a dose reduction because of its GI toxicity and fatigue. Then we've got pomalidomide in partnership with, again, a proteasome inhibitor, cyclophosphamide, and clarithromycin. There is a regimen called ClaPD that was developed by Dr. Niesvizky at Cornell which appears to recapture response in some patients. It's a much cheaper option for some indolent kind of relapses in that setting. Usually translocation (4;14) patients benefit preferentially from proteasome

inhibitor regimens. When we have a 4;14 patient, we are trying to pick a PI ahead of others. When patients get to a double- or a triple-refractory state, autologous stem cell transplant is only a short-term fix. We would use this in someone whose blood counts, platelet counts are really low. We still have their stem cells left over. We might cytoreduce them, give them the stem cells so that their blood counts can come up and they may qualify for clinical trials. One of the issues in relapsed/refractory patients is having a beaten up marrow with platelet counts in the 20,000 and 30,000. Patients may be feeling fine but they can't get through the clinical trial because the clinical trial requires at least 50,000 platelet count if the marrow is more than 50% involved. If it's less than 50% involved, they require 75,000 or more platelet count. For those kind of issues, we would use an auto but generally not something that we recommend. Allogenic stem cell transplant only in the clinical trial setting for a young high-risk patient would we choose that option. We have daratumumab in combination with pomalidomide and dexamethasone that we utilize quite a bit for second and beyond relapses in clinical practice. In several groups, there was a phase 1 and 2 trial out of the original umbrella study that we did with daratumumab that Ajai Chari had presented maybe a year, a year and a half ago, it got published in *Blood* I think late last year, but several groups have published their own experience in advanced refractory patient populations. Even in patients who haven't had previous data or previous pom, you can still get a third of the patients to respond to a dara-pom-dex based regimen.

When we talk about the possible approaches that Hari discussed, there are patients who are going to be on all these different regimens in their first relapses. This slide is already there in your packet, but potential options for patients who are relapsing off of this first-line regimen, triplet regimens, are listed here. You are either basing them off of data or KPd. EPd is starting to emerge as a regimen in that setting. These are based on new data that were just presented at the EHA meeting in mid-June of 2018, but we are expecting that we might get regulatory approval for this combination. Again, to answer your question where elo will find its life kind of builds on that.

So what is next, though? We have improved the overall survival of myeloma in the last 15 years from two to three years to 10 years at the median and we had one agent when I started my training and now we have 10 but we are still seeing these patients who are becoming refractory after three or four lines of treatment. We are to talk about some of the agents that you will find in the clinic fairly soon. The first one is selinexor. Selinexor is an exportin 1 inhibitor. Exportin 1 is a protein, it's a nuclear exporter protein that is present on the nuclear membrane and it helps export out majority of tumor suppressor proteins as well as the glucocorticoid receptor. What selinexor does is block the nuclear exporter. It is enriching p53, the tumor suppressor genes, as well as the GC receptor within the nucleus, first making the cells susceptible to cell death. It's a first-in-class exportin 1 inhibitor and there are others that are in preclinical and early development.

The first data were presented at ASH in 2016 by Dan Vogl from UPenn showing that in pento-refractory, previous highly refractory patient populations of five median prior lines of treatment including patients who were daratumumab refractory, the overall response rate with this drug was about 21%. No matter which way you cut the pie in terms of the number of doses that patients got, PI refractory status, IMiD refractory status, all refractory status, it appeared to be working in all groups. One of the critiques in terms of side effects has been if this was not a cancer drug, it would be a great weight loss drug because patients have a lot of GI side effects and appetite issues. It appears that selinexor when given with dexamethasone — again, we talked about dexamethasone. The tolerability of selinexor is better when

taken with steroids, and interestingly with proteasome inhibitors as well. Selinexor will likely get a nod perhaps later this year or early next year for quad-refractory myeloma patients, but it will likely find its partnership with proteasome inhibitors in combination studies.

Then you all had this question given to you in the pre-assessment about venetoclax and which chromosome abnormality it may actually be more active in, specifically in myeloma. Venetoclax is already approved for CLL. It is a BCL-2 inhibitor which is a pro-apoptotic protein and venetoclax binds to it promoting cancer cell death. Again, it appears to have more activity in translocation (11;14) cells where there is a correlation with high ratio of BCL-2 to MCL-1 and BCL-2 to BCL2L1.

Shaji had presented this abstract, it's actually published now, showing the single-agent activity of venetoclax being 21% in a group of 66 patients, but looking at translocation (11;14) patients specifically, an overall response rate of 40% was seen, including 4% stringent CR rates. Again, this is a median of six prior lines of treatment, fairly heavily pretreated patient population where you were seeing this kind of activity. Venetoclax/dexamethasone, and venetoclax/dexamethasone/proteasome inhibitor-based combination clinical trials is making its way through the regulatory pathway towards approval for myeloma patients, all patients, and for translocation (11;14) specifically, so there are enrichment trial designs as well general trial designs moving forward with venetoclax.

What we've learned in the last year and a half is that BCMA, B-cell maturation antigen, is a very attractive target for myeloma therapy, whether it is antibody drug conjugates such as the 916 compound by GSK or CAR T-cells that I'm going to be talking about. There are a lot of different strategies being developed that are targeting this BCMA which is broadly expressed on malignant plasma cells. The 916 compound is a humanized IgG1 anti-BCMA antibody which has MMAF as the warhead of its antibody drug conjugate. It works through the usual antibody dependent cellular cytotoxicity, but also works through antibody drug conjugate, so warhead delivery to the cancer cell. It also leads to immunogenic cell death as well BCMA receptor signaling inhibition. With several different mechanisms, we were actually very pleasantly surprised with this data than when it was presented at ASH in 2016 because that year the focus was on BCMA CAR Ts. CAR T was the focus that year and we had a lot of CD19 CAR T data being presented and the first BCMA CAR T data being presented by UPenn. Interestingly, Adam Cohen was also presenting this abstract. This abstract actually got more excitement within the myeloma community because of these data. Even though there were just nine patients presented overall in the initial paper, patients who had optimal dosing, 3.4 mg/kg or above, and these are heavily pretreated, all were dara refractory patients, and you're seeing six out of nine patients having a partial response or better with this strategy. Now, this group has expanded. We are going to be seeing data at ASH, the BCMA antibody drug conjugate program. There are phase 3 trials being planned with this compound and it's going to be making its way into the clinic in the next two to three years. One interesting approach was how do we overcome proteasome inhibition resistance in myeloma? There are several clinical trials that are trying to look at overcoming immunomodulatory drug resistance as well as proteasome inhibitor resistance. This was actually presented by Peter Vorhees. It was an early phase 1 clinical trial with an AKT inhibitor, afuresertib, in combination with bortezomib. It showed pretty decent overall response rate in bortezomib refractory patient population, but for some reason we haven’t heard a lot of data with this compound. This was a Novartis compound. It was being developed alongside panobinostat and it has taken a backseat. I would be really interested seeing where it goes, if we can resurrect this kind of an approach.

Another compound that we heard about two years ago, and we haven't seen it go anywhere again because of excitement of immunotherapies and monoclonal antibodies, is selective HDAC6 inhibitor ACY-241. This was a small phase 1a/b study that was done on 40 patients in combination with pomalidomide and dexamethasone. This patient population had a median of three prior lines of treatment and included 22 patients who were all len and PI refractory, showing an overall response rate of about 50% which was very, very interesting. You would expect the response in a PI/IMiD refractory patient population receiving pomalidomide and dexamethasone of somewhere around 25% to 30%. This combination was certainly doing something above and beyond what we would expect from pomalidomide and dexamethasone; but again, it has kind of died down in the noise of a lot of the immunotherapies, especially the excitement around CAR Ts across the spectrum of hematologic malignancies.

Chimeric antigen T-cell receptor approach which was honed by Carl June at UPenn is now transcending into all different hematologic malignancies looking at many different targets. This is a basic structure of what a chimeric antigen receptor looks like. It has an ectodomain which is the antigen recognition portion of the CAR, there is a transmembrane domain where it crosses the lipid bilayer of the T-cell, and then there is a co-stimulatory or stimulation endodomain where those T-cells are kind of revved up as they are given back to the patients. The first data that were presented were very interesting. This is a patient who had eight prior lines of treatment, was refractory to everything that is known in terms of conventional chemotherapy as well as novel agents. After a single administration of BCMA directed CAR T this patient went into a very good partial response and remained in that very good partial response for beyond a year. That was the UPenn data.

The BCMA CAR-T construct and program that is farthest ahead in development is the Bluebird CAR T program that is now owned and being developed by Celgene. The bb2121 phase 1 dose escalation and dose expansion cohorts were presented by Noopur Raje at ASCO just a couple of months ago. She reported on the patients who had response data that was evaluable. Patients who went on to consent and collect cells, all of them had successful manufacturing of their products. The overall response rate was 94% for the evaluable patients, including 56% of the patients having a CR or better. MRD negativity — 10 patients were evaluable and it was MRD negative in nine out of 10 of those evaluable patients. Five patients had ongoing response beyond the one-year mark, demonstrated in this particular slide. We also had the LCAR-B38M CAR T-cell data that was presented. These data are from the Chinese Nanjing BCMA CAR T which is a different construct. This particular CAR T construct targets two different epitopes of BCMA, so the cell dose being given to patients is much lower than the bb2121 and that's why we are not seeing as many side effects like cytokine release syndrome and urotoxicity with this construct. This is right behind development through the Celgene Bluebird CAR T product because Nanjing was barred by Janssen late last year and they took over the development program. You'll be hearing more and more data about these two particular constructs.

CAR Ts are not without toxicity. There are a lot of if's and but's around them. Patients get cytokine release syndrome and can get very sick, it's like getting a sceptic shock very rapidly and the patients have to be managed in the MICU setting. Generally we are giving them — they are usually on vasopressors and they are getting tocilizumab. We try to hold back on dexamethasone as much as we can but if they start also developing neurotoxicity then we pull out the steroids as well. The steroids

obviously will not be very kind to the CAR Ts that we've administered to patients. You're also worried about off-target toxicities. Insertional oncogenesis remains a hypothetical concern although we haven't seen any cases being reported of it.

Then we have several monoclonal antibody based therapeutic strategies. The most common ones are antibody dependent cellular cytotoxicity, complement-dependent cytotoxicity, and direct apoptosis due to antibody engaging the cell surface. I've talked about the antibody drug conjugates where a toxic payload is delivered to the cell in addition to these different mechanisms. Besides BCMA, Seattle Genetics is also running an early phase clinical trial looking at CD48A. We won't have any data to share at ASH this year but data is coming from that phase 1 and will likely be presented next year.

Another very exciting class of drugs, and I say exciting with a lot of fervor here because this could be the poor man's CAR T. Bispecific monoclonal antibodies bring together this — again, they have CD3 attached to one head of the monoclonal antibody and a tumor-specific antigen recognition portion on the second arm of the antibody. It's kind of bringing together the T-cell with the cancer cell and letting the magic happen. There are several targets that are being looked at with bispecific monoclonal antibodies. This slide actually shows you what the antibody does more elegantly. You have the human CD3 monoclonal antibody portion and you have the tumor associated antigen monoclonal antibody portion attached to the antibody. You are activating the T-cells and bringing them together to the cancer cells, and that's how tumor lysis takes place. The side effects with bispecific monoclonal antibodies are very similar to what you would see with CAR T-cells. You see the cytokine release syndrome, neurotoxicity and other side effects. This is not a new technology. Bispecific monoclonal antibodies came into clinical trials back in the 90s but were pulled off from early phase clinical trials because of cytokine release syndrome and neurotoxicity concerns. The first success story was blinatumomab when it got approved for relapsed ALL and it's in clinical use now, but there are a lot of second-, third- and fourth-generation bispecific monoclonal antibody platforms that are being evaluated in clinical trials.

My colleague, Dr. Hari, had mentioned the precision medicine kind of approaches. There are several different clinical trials that are looking at gene mutation specific agents in myeloma and they are listed here. The interesting thing is all we need to know about the gene mutations in myeloma, we already have discovered them in the last five years. Myeloma is not a one head disease and most of the gene mutations happen late in the game. The most common gene mutations are at a level of between 8% to 10%. The NRAS, KRAS, BRAF pathway is probably the most common one, then you've got FGFR3 mutations which are, again, roughly 7% to 9% but then the rest of the mutations are in the 2% to 4% ballpark. Majority of myeloma patients, more than half of the patients, don’t have any gene mutations, so when we start talking about developing a strategy where we can utilize this kind of precision medicine approaches in myeloma, it's not treatment with single agents; it is treatment with a backbone regimen based on the mutation that patients may have and then applying an inhibitor that will target that specific pathway.

This is a master protocol that we have been trying to — this is just the original skeleton from the Multiple Myeloma Research Consortium that I'm a part of in developing a master protocol where we will be able to take our high-risk early relapsers, give them the standard of care backbone, and that backbone will be the same, then based on their actual mutational status, we'll add specific drugs. This is

still in the works. It takes a lot of effort getting seven different drug companies excited about participating in something like this, but the idea would be if we see a signal, we are going to then expand that particular arm and add more patients.

Now I'm going to get into a more interactive discussion about some of the cases. A 67-year-old woman presented with mild normocytic anemia and renal insufficiency. She was diagnosed with revised ISS stage II IgG kappa myeloma, had a translocation (11;14) at diagnosis. She had RVd for induction for four cycles, got to a VGPR, had a stem cell transplant, went into a CR, then was on maintenance for three years with good tolerance. She is still on len maintenance and now her M-spike is going up, her hemoglobin is starting to decline a little bit. She still is fairly active, asymptomatic. You restage her; her bone marrow is now showing 30% plasma cells and the FISH has translocation (11;14), and she has now also picked up deletion 17p. How would you describe the treatment options for this patient? What questions to ask? What treatment options should I consider? Can I use a lenalidomide-containing regimen for this patient? What lab values and tests need to be done to track response or monitor for side effects? Is there a clinical trial that may be suitable for the patient? These are some of the questions that you're thinking about as you're thinking of picking a regimen.

Without further ado I'm going to just jump over to what happened to this patient. The salvage induction options in someone who is becoming len refractory, so daratumumab, bortezomib, dexamethasone. The patient got bortezomib for four cycles three and a half years ago. She is bortezomib exposed but she got a pretty decent bang for her buck. Dara-vel-dex would be a reasonable option. Carfilzomib-dex, if you were to pick a doublet, would be a reasonable option. Hari had shared with you the Kd versus bortezomib-dex clinical trial as a particular example. In this patient— by the way this is a real patient, second autologous stem cell transplant would be a reasonable option as well. This is what happened to my patient. She got dara-Vd for six cycles, she went into a VGPR, she got an autologous stem cell transplant, and then she was placed on bortezomib maintenance q.2 week. That was a little over two years ago. She's doing fine now.

I have a second case here, 64-year-old man who presented again with anemia and persistent back pain and was worked-up, found to have revised ISS I IgG kappa myeloma. He had deletion 13 on the FISH panel. So, deletion 13 is considered standard risk in the year 2018. Patients get RVd for induction for six cycles. He got six cycles because we were chasing response. He only got to about 70% reduction in his M-spike so he had a PR. Then he gets a stem cell transplant and achieves very good partial response. Then he gets len maintenance for a year. Good tolerance, but then he achieves stringent CR at his one-year anniversary and decides to come off of lenalidomide maintenance at that time. Now he's been off of treatment of len maintenance for over two years and his M-spike is coming back. His M-spike came back about two months ago. He is coming back to see you and the M-spike that was just traced two months ago was at 1.1 g/dL. He is still asymptomatic but he wants to be treated now for his disease because the pace of which it is rising, and I agree. We did the restaging and he had 50% kappa restricted plasma cells. His cytogenetics and FISH are still normal. Skeletal survey is actually showing new lytic lesions compared to the survey he had six months ago. Again, going back to this question, what treatment options do I have? Are there any clinical trials? What additional testing do I need to do? Can I use len-containing regimen or the same regimen again in this patient?

As I discussed options with the patient and I talked about RVd retreatment, I offered him dara-len-dex at that time because of — my concern was no M-spike two months ago to 1.1. My concern was the disease was, even though he was asymptomatic, half of his marrow was myeloma and things are going rapidly. I did not entertain elo-len-dex. Carfilzomib or a proteasome inhibitor. K (carfilzomib) I wanted to reserve for later so I did not pick that as the top option. Would a second autologous stem cell transplant be something to consider in this patient who's almost five years out from the first auto? That would be the other consideration. I ended up giving the patient RVd for six cycles and guess what? The patient got to a PR and then a VGPR after Mel auto and then went on len maintenance. A little over a year into len maintenance now and doing fine. The reason why the patient came off of len was he traveled a lot, he got to a stringent CR and did not want to put himself at risk for thrombosis because of all the air travel that he did.

The third case is that of a 78-year-old woman, revised ISS II kappa light chain myeloma. She had a pretty rough initial course, acute renal insufficiency at presentation requiring hospitalization and that's how the diagnostic workup was done. The serum kappa light chain level was pretty high with a ratio of 275. The patient got started on Rd as induction. She did get post dose of dex while she was in the hospital. She did get a dose of cyclophosphamide to control her disease. She transitioned to the outpatient setting, wanted to be on an all-oral regimen, was still an ECOG of two and a half to three at best, but she got to a PR as best response and then was on dose-reduced len at 5mg. Now she is 18 months into treatment and the M-spike is rising on len maintenance. Same questions, older transplant ineligible patient, fail patient, got a doublet, still an ECOG of two at best. What would you do? Would you think about this patient in the len refractory setting? You have a lot of options, so what would be some of the options?

Alright, so options Vd, CyBorD, dara-Vd, Kd. I did not put IRD because she is len refractory. Again, those patients were excluded but in her case I did utilize ixazomib. We did give her a dose attenuated Vd for four cycles just once a week. She got to VGPR and then we were able to get ixazomib for her which she was taking every two weeks and she's doing fine.

How do we improve factors beyond the first-line of therapy? Some of these things we've talked about already. When we start stratifying patients, our risk stratification system is a little flawed. The Durie-Salmon staging system told us about burden of disease. The ISS staging system told us about burden of disease, not a lot of information about biology of disease. You need to have both pieces of information to help make decisions for your patient. An anecdote that I share with my patients, you can have King Kong or the Green Giant. Similar in size but very different in nature; one will give you vegetables, the other will eat your head off. You can have a lot of myeloma that's easy to treat or a little bit of myeloma that's very difficult to treat based on disease biology. The ISS staging or even revised ISS doesn’t capture that as well. There are going to be better tools available in the future where we can prognosticate based on disease biology. It used to be fiction in the past but it's becoming reality with more and more gene mutational panels being available. Duration of initial response, primary refractoriness, acquisition of new abnormalities, all of those things are important. What is the patient's current performance status? They may have been either in poor performance status at the time of diagnosis which got better over time or vice versa. Presence of extramedullary disease and circulating plasma cells will dictate you picking out a more aggressive approach early on before you go to something different.

Disease heterogeneity is very important. Biochemical relapses do not always warrant start of treatment so the pace with which the disease is moving is going to be very important, especially for standard-risk disease. For high-risk disease, even if patients did not have high-risk disease, they could have acquired high-risk features rendering a very different kind of an approach for them. I almost never wait on a slow biochemical relapse in a high-risk patient because you know what's going to happen, you know what's coming next. Even in those patients, we act sooner than later. Presence of residual toxicity from previous therapies is important. Patient's performance status, we've talked about. Always remember to chat with patients about their own preference, their goals and their aspirations because they may have changed from the last time you talked to them.

When do we need to treat immediately? If it's a clinical relapse, patient has new symptoms, increasing size or newborn lesions, hypercalcemia, renal insufficiency, doubling of M-spike in two consecutive measurements, so a very rapid kind of rise, and even if it's a slow rise but the M-protein is getting over 10 g/dL, maybe it's time we should treat. I put that there as a joke but the bottom line being don't wait forever to treat. It's okay to watch patients but there has to be a certain threshold after which you have to treat. The other important thing I want to highlight with the next two or three slides and I'll get to them at one point as well is looking at risk stratification is important.

This is a slide taken from the ASPIRE trial looking at patients comparing standard- versus high-risk in terms of progression-free survival. If you look at the Rd group, for high-risk patients a median of 13.9 months versus 19.5 for the standard-risk patients, 29.6 months for standard-risk patients with KRd, but look at the addition of proteasome inhibitor in this setting. The PFS improved significantly compared to the doublet. It's not the same as standard risk but it's still much better than a doublet. Picking a triplet to get a better PFS and depth of response in high-risk patients is important. The other important lesson that this slide teaches us is that carfilzomib improves outcomes of high-risk patients in the early relapse setting but it does not overcome them. If this PFS was 29.6, I'd say hey it doesn't matter if it's a high-risk patient or not. When you add K, it works for both standard- and high-risk patients, and standard-risk patients actually do as well as high-risk patients, but that's not what's happening here.

Same is true for daratumumab. Addition of daratumumab gives a better depth of response for high-risk patients and better median progression-free survival for high-risk patients, but if you start looking at whether this PFS benefit is the same as standard-risk patients, it's not the same. The bottom line is if you're looking at just the high-risk category, Rd versus DRd, yes there is a significant improvement. Dara does improve outcomes of high-risk patients when it's added to Rd but it does not overcome the high risk conferred by those karyotypic abnormalities.

The only drug that we know of that works as well for deletion 17p patients as it does for standard-risk patients is pomalidomide, and that data we get in the relapsed/refractory setting because pomalidomide has not been studied in the frontline or even in the early first relapse setting, and these are the data. If you look at the median progression-free survival in the big study, pom low-dose, dex versus high-dose dex that led to the approval of pomalidomide and dexamethasone, deletion 17p patients actually did as well but perhaps maybe a little better than standard-risk patients in terms of median PFS.

What is the ideal duration of therapy? Currently the body of evidence is favoring treatment to relapse, progression, and/or intolerance. In clinical practice what we advocate is once patients have had a plateau of their response, the drug that's causing them the most grief can be discontinued but keep them on something. If it's a high-risk patient, I prefer dose attenuating the two active agents, generally discontinuing the dexamethasone altogether because it's a double-edge sword. Always take into account patients' preference, what they want to do. Logistics and healthcare cost are important. In Chicago we have a lot of good doctors in the area and easier access but if you go further out mid-west there are places where the closest oncology clinic, 2% oncology clinic, is 60 miles away, so some of those logistic considerations come into play as we pick therapies.

These are the two daratumumab phase 3 trials, the POLLUX trial that compared dara-len-dex to len-dex and CASTOR that compared dara-bortezomib-dex to bortezomib-dexamethasone. What you're seeing is MRD negativity rates in high-risk patients and standard-risk patients in both those studies. What you're seeing on the high-risk side is none of the patients how got a doublet got to MRD negativity. When you have a high-risk patient or a patient with high-risk features, you have to pick a triplet. What this slide is showing you, that addition of daratumumab increases the likelihood of even high-risk patients going into MRD negativity. I bet that if you did that study in the ASPIRE trial, if it was better designed with MRD analysis, you'd find similar kind of trends as well. Especially for high-risk patients, picking good three-drug regimens is very important.

In conclusion, therapeutic advances have really led to improvement of overall survival for myeloma but it's still a chronic disease. There is going to be relapses and remissions in patients and you need to develop a long-term strategy. There are a lot of other drugs that are coming down the pike which will make management of later lines of treatment more interesting. I think in the next two or three years we will have a much better sense of how we are going to navigate the pathways of myeloma patients in the standard-risk, intermediate-, and high-risk categories than we do now because we'll have all those options and we would be able to pick and choose and develop pathways like I showed a few slides in the first relapse and the second relapse setting. Risk stratification approach is going to be utilized more often. I showed you a drug class that works well for translocation (4;14), I talked about venetoclax for translocation (11;14) patients. For deletion 17p patients, pomalidomide is active and there are third- and fourth-generation CELMoDs coming down the line as well. There are other gene mutation, actually mutation specific drugs that are coming down the line as well. We are going to have a lot of these different options available and it will make a future talk for me very interesting.