Welcome and Introductions

Blake A. Morrison, PharmD

[Slide 1] Greetings everyone, and thank you so much for joining us. [Slide 2] My name is Blake Morrison, and I'm the Vice President of Medical and Scientific Affairs at the Multiple Myeloma Research Foundation. From this point forward, we'll just say easily the MMRF. I'm so pleased to welcome you to this telephone and Web education program that's intended for patients and caregivers but will also benefit healthcare providers on the line as well.

The American Society of Hematology or ASH (American Society of Hematology) Annual Meeting concluded just over a month ago, and we are so thrilled to bring you highlights from this meeting hot off the convention floor. It's certainly no easy thing to try to distill a lot of the excitement down to a few key points, but our faculty today, I believe, will be up for the challenge.

I'd like to thank Amgen, Inc., Genentech, and Takeda Oncology for funding this important program and for their continued appreciation for the need of this kind of information for patients, particularly coming out of critical meetings like ASH.

The MMRF was founded in 1998, and we are the number one private funder of myeloma research worldwide. Our focus has always been on accelerating new treatments to extend and improve the lives of patients and ultimately find a cure. Through the work of our affiliate organization, the Multiple Myeloma Research Consortium or MMRC, we've opened over 50 trials involving 25 different therapeutic agents.

We are pleased to share with you that we now have over 1,000 patients that are participating in our CoMMpass (Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile) study. We have launched two online gateways, one for researchers and one for patients. The MMRF researcher gateway allows researchers to analyze clinical and genomic data coming from our genomics initiative and from our CoMMpass study. The MMRF community gateway allows patients to find other patients just like them who have had similar experiences with the disease and also to find information and clinical trials specific to their type myeloma.

We also provide a number of educational programs to the entire community, both healthcare providers and patients and caregivers live, online, and in print. You can always visit our website at (www.themmrf.org) to find the latest information on myeloma and its treatments, including updates coming out of these meetings, as well as information on upcoming education programs.

[Slide 3] This year has been an exciting year for treatment options for multiple myeloma. This past November alone there were three FDA (Food and Drug Administration) approvals with daratumumab, also known as Darzalex™; ixazomib, also known as Ninlaro®, and elotuzumab, also known as Empliciti™. These three are in addition to the approval of panobinostat, also known as Farydak®, in February of 2015. Our presenters will share the latest on the newly approved treatments coming out of the ASH congress.

[Slide 4] Our presenters today are Dr. David Avigan from Beth Israel Deaconess Medical Center in Boston, Massachusetts, and Dr. Sagar Lonial from the Winship Cancer Institute of Emory University.
Hospital in Atlanta, Georgia. They will provide an overview of the ASH data related to the treatment of newly diagnosed myeloma all the way through to transplant, maintenance therapy, and relapsed and refractory myeloma. They will also provide an update on data surrounding the treatment of high-risk smoldering myeloma, which is a rapidly evolving field.

After the presentations, we will open the program up for questions from both telephone and Web participants. We really encourage everyone on the line to complete that evaluation after the program because it helps us plan for future programs, not only teleconferences, but others as well.

[Slide 5] Now, it is my pleasure to introduce Dr. Sagar Lonial. Dr. Lonial, please take it away.

**Smoldering Multiple Myeloma**

*Sagar Lonial, MD*

Thanks, Blake, and I appreciate everybody taking time out of their winter afternoon to be here to hear what I think was really just some amazing stuff that was presented in the context of multiple myeloma at the meeting. It really has been a tremendous year. There really aren't adjectives to be able to describe how big a year it's been for patients with multiple myeloma. And I think starting out a little bit of the discussion with smoldering myeloma is a good place to at least begin.

[Slide 6] So I think as we start, there were a couple of things that have happened in the last couple of years that have changed the way we define smoldering myeloma from symptomatic myeloma. And the first is that historically we thought about CRAB (calcium, renal insufficiency, anemia, and bone disease) criteria, meaning the presence or absence of hypercalcemia, a high-blood calcium; kidney problems; anemia; or bone disease as being the real definitions of the difference between symptomatic and smoldering myeloma.

But what the International Myeloma Working Group (IMWG) did in the last year was refine that definition a little bit more and include three additional sets of patients. And the first are patients who have greater than 60% plasma cells in their bone marrow, the second is patients who have a free light chain ratio greater than 100, and the third is somebody who by PET (positron emission tomography) scan or by MRI (magnetic resonance imaging) has greater than one focal lesion by bone, by those imaging tests. And if you've got any of those three, you no longer have to wait for CRAB criteria. You now are, by definition, symptomatic myeloma.

Now there are additional criteria that are being evaluated to differentiate smoldering patients from MGUS patients or patients with monoclonal gammopathy of unknown significance. That's certainly a work in progress; and there are, in fact, ways to risk-stratify the chance of progressing from smoldering to symptomatic myeloma using very simple tests like the magnitude or size of the M protein (monoclonal immunoglobulin), the free light chain ratio, and whether or not a patient has greater than 10% plasma cells. And using those three very simple criteria, one can come up with a low risk, intermediate risk, or high risk of progressing to symptomatic myeloma within a short, intermediate, or long-term period of time.
So, I think these are all things that are on the horizon, and I think it is the unique changes in the definition and the constantly evolving criteria for patients with smoldering versus symptomatic myeloma that really makes sense for patients to go to a myeloma center and get seen by somebody who sees this, perhaps participated in the guidelines, as you make decisions about what to do and how to be observed in patients who have smoldering myeloma.

It is important to realize that despite all of these changes in evolution, the most recent definition for what to do with a patient who truly has smoldering myeloma is either participate in a clinical trial or be observed. There are not subsets, as of this point in 2016, who have smoldering myeloma that we recommend treatment in the absence of a clinical trial.

**Upfront Therapy**

*Sagar Lonial, MD*

[Slide 7] So let's move on now and talk a little bit about newly diagnosed myeloma patients, and there were a number of trials that were presented in the context of newly diagnosed myeloma patients. [Slide 8] Probably one of the most important trials that was presented at ASH this year was what's called the [SWOG (Southwest Oncology Group)] S0777 clinical trial. And this was important for a number of reasons.

And just to give you some background, there has been a large debate in the myeloma community about whether two drugs are sufficient to treat a patient with newly diagnosed myeloma or whether three drugs represent the standard. And there is certainly institutional bias on answers to that question. I can tell you at my center we have always recommended three, at least for the last six to eight years. I suspect that David Avigan, on the call as well, probably is a three-drug institution as well. But this was certainly an area that didn't have a huge amount of data to really support three versus two, other than retrospective studies.

And so the SWOG study designed a trial looking at RVd (lenalidomide-bortezomib-dexamethasone) versus Rd. And, remember, Rd, or lenalidomide and dexamethasone, was a standard regimen, particularly suited perhaps for older patients whereas RVd is a standard proteasome inhibitor (PI) and IMiD (immunomodulatory drug) combination. And the real goal of this trial was to understand whether three really made a difference over two in terms of progression-free survival and overall survival. And just to put these two endpoints in perspective, progression-free survival means how long a patient stayed in remission that first time, so after receiving the initial therapy. Overall survival just means how long the average patient survived in this trial.

[Slide 9] And as you can see from the current slide, there's a big difference not only in progression-free survival, almost a year benefit for the triple over the double, but there's a big difference in overall survival as well as a difference in overall response rate. And that means that more patients responded and, in fact, more patients achieved a deeper response. So, given these findings, I think it's really very exciting to identify that now RVd has become a national standard, based on this large, randomized, Phase III trial that showed not only longer duration of remission but actually significantly improved overall survival.
And it's good that this won for a couple of reasons. The first is there is another trial that was presented at the meeting from the French (Intergroupe Francophone du Myélome) group where they looked at every patient receiving RVd as their induction therapy and then a randomization to either early versus late transplant. And what we learned from that is that RVd, followed by a transplant, actually gives us one of the longest durations of first remission we've ever seen in a large, randomized, Phase III trial with pretty impressive overall survival as well.

So, I think this idea of a triplet being standard therapy has really come to us from the SWOG S0777 trial; and, again, in my view, I think that RVd now represents the standard induction therapy for most patients in the context of newly diagnosed myeloma.

_Sagar Lonial, MD_

So, let's move on now to the addition of new drugs to the RVd backbone. And several years ago Jonathan Kaufman, MD from our center presented data on RVd plus vorinostat. And you may recall vorinostat is an HDAC inhibitor or histone deacetylase inhibitor that did not get approved for treatment of patients with myeloma because there was a pretty significant toxicity profile associated with vorinostat. And when we combined vorinostat with RVd, we could only use half the dose that one would normally use; and we did see a pretty significant improvement in depth and overall response rate.

[Slide 10] So Jatin Shah from MD Anderson Cancer Center actually did a trial combining panobinostat, a newer version of an HDAC inhibitor that has a different safety profile than vorinostat did and combined again a lower dose of panobinostat, 10 milligrams, with full doses of RVd. Again, I'm trying to build on the three-drug backbone over time.

And what I think he showed quite nicely in his trial is that the depth of response was better for the four-drug regimen over the three-drug regimen, and that certainly was a very encouraging endpoint for that. It needs a larger study and longer follow-up to really understand whether the addition of panobinostat is a significant improvement, in addition to RVd, versus RVd as it stands alone at this time point.

[Slide 11] But I think as you can see on the next slide, that while certainly we now have Phase III data supporting three drugs over two, many of us are beginning to ask questions of four drugs versus three. And whereas the last trial added in this new class of drugs, an HDAC inhibitor to RVd, the next trial from the UK actually took a carfilzomib combination with lenalidomide, with dexamethasone, and added in cyclophosphamide. And this is actually an interesting and important trial because we know when bortezomib or Velcade® was combined with lenalidomide and dexamethasone and cyclophosphamide, the results did not look any better than when you just gave RVd alone.

And this, again, was a trial from the UK where they compared people getting just carfilzomib, lenalidomide, and dex or KRd versus patients getting KCRd, the addition of cyclophosphamide to the IMiD and the proteasome inhibitor combination. And at least from the initial review of the data, it did appear that patients who received the four-drug combination that included carfilzomib, had a much better depth of response than we saw with patients who only got three drugs.
Now we need additional follow-up, we need additional data to really understand the adverse event profile for this. At least the early review of the data suggests that the toxicity of the four-drug combination was not appreciably different from the toxicity of the three-drug combination. But, again, it's very early days; and I think we do need additional follow-up to really fully understand that.

What I would say is that many of us are now interested in a four-drug combination that makes that fourth drug an antibody. And you're going to hear more about the monoclonal antibodies from Dr. Avigan later on in this call, but I will tell you that I think the true four-drug combination is going to be an RVd or a KRd-type backbone in combination with either daratumumab or elotuzumab, and you'll hear more about both of those as we go forward later in the talk.

[Slide 12] Now what I've talked about is predominantly the management of younger, fit patients. There is some data that was presented on older transplant ineligible patients as well; and I think it's important to realize that the goals of therapy for those older, frailer patients may be the same, but the way you get there may be slightly different. And so optimizing treatments to get them a little bit more tolerable is an important endpoint when we're talking about management of transplant ineligible frail patients. And I would put a caveat out there to say that age, at least in the US, is not a discriminator of whether or not a patient is eligible for a transplant—at least not at our center, and I suspect Dr. Avigan will say the same. It's actually frailty that's probably the more important discriminator of whether a patient is eligible for a transplant. So age, in and of itself, is no longer a valid way to make that definition.

[Slide 13] Now what about looking at all oral approaches for the management of patients who are transplant-ineligible or frail? And there are a couple of trials that were looked at using the newly approved oral proteasome inhibitor ixazomib, also known as Ninlaro in combination with other agents in the context of myeloma.

[Slide 14] And there was one trial that looked at ixazomib, the oral proteasome inhibitor, in combination with cyclophosphamide and dexamethasone. And the ICD regimen looked at two different doses of cyclophosphamide, either 300 or 400 milligrams was the dose that was delivered. And what appeared to be the case was that the 300 and 400 were somewhat similar in terms of overall response rate. The 300 was tolerated probably a little bit better than one would expect, mostly because you got a little bit less of the chemotherapy there. And, again, the overall response rate for both arms was over 80%.

And this is really coming on the heels of data that has been published now using ixazomib in combination with Revlimid® (lenalidomide) or what I call the RId regimen to get rid of myeloma. RId (lenalidomide-ixazomib-dexamethasone), which also showed very good tolerability and was a completely oral regimen for the management of patients with myeloma, whether or not they were considered transplant eligible or ineligible.

[Slide 15] Now the next trial that was presented is using the newer proteasome inhibitor, carfilzomib or Kyprolis™, in combination with melphalan and prednisone. And melphalan and prednisone is not typically a regimen that any of us in the US use anymore, so I don't know that there's a lot to directly draw out from this specific trial, except to know that there have now been multiple trials in both older and younger patients that have used carfilzomib as a proteasome inhibitor for the management of patients with newly diagnosed myeloma.
And what we learned from this trial was that there was a pretty significant combination effect and that the observed maximum tolerated dose of carfilzomib was 70 milligrams per meter squared. You could go pretty high in terms of the overall response rate for carfilzomib in combination with melphalan and prednisone. And that at the right dose and schedule, this did appear to be a well-tolerated and safe regimen for newly diagnosed myeloma patients.

[Slide 16] Now to sort of wrap up some of the data in the context of newly diagnosed myeloma, I want to show you data on the RVD Lite regimen. And this is a way to take that best regimen that we know of, a regimen that we think is most active and now has Phase III data supporting its use in patients across the board, and try and modify the dosing schedule a little bit to make it more tolerable for older, frailer patients. And this is data presented from the group out of MGH (Massachusetts General Hospital) that looked at modifying the dose of lenalidomide to 15 milligrams given on a standard 1 through 21-day cycle. Bortezomib was given again, you can see, in combination with either full-dose dex or modified-dose dexamethasone on either a weekly or a twice weekly schedule, depending upon the setup here. And, again, as you can see, there was not only a pretty significant overall response rate, 90%, but this is a way to potentially modify the use of RVD to make it eligible for even more patients that we've seen before. And there are certainly ways to talk about how to do this in the context of many of the other proteasome inhibitors, both carfilzomib and ixazomib in combination with lenalidomide. And I do believe that in 2016 now, the IMiD PI combination, you can choose your IMiD, you can choose your PI is the best regimen for newly diagnosed myeloma patients across the board, whether they are older or they are younger.

**Relapsed/Refractory Disease**

*Sagar Lonial, MD*

[Slide 17] So to keep things moving forward, I think what I'm going to do is just a couple more slides, and then I'll turn it over to Dr. Avigan. [Slide 18] In the context of relapsed and refractory myeloma, again, we talked earlier about Ninlaro or ixazomib as a potential salvage therapy. And as Blake alluded to earlier, we were very excited when ixazomib was approved by the FDA in November of last year. And, actually, I think a patient at our center was one of the first patients to get it after commercial approval. We were very excited about that as well.

[Slide 19] And the trial that got us, the ability to use ixazomib in patients with myeloma, was a randomized Phase III trial that compared patients who received either ixazomib with lenalidomide and dex, the IRd regimen, or just lenalidomide and dexamethasone. And there were over 720 patients that were randomized between these.

And what we saw at the data presented most recently by Dr. Moreau at ASH was that the duration of remission was significantly higher for the ixazomib combination, 20 months versus 14 months; the complete remission rate was almost double; the VGPR (very good partial response) rate was higher as well; and the overall response rate was higher; the time to response was faster; and the duration of response was also much faster for patients who received the three-drug combination versus patients who received the two-drug combination. And this is really clinically very important because, again, this allowed us to get access to ixazomib. Ixazomib is oral, and that gives us a pretty significant foothold in terms of all oral regimens going forward with a very different safety profile. The
incidence of neuropathy with ixazomib is much lower than we see with bortezomib, again, giving us new treatment options for patients that are more convenient overall.

[Slide 20] There were additional trials presented at ASH, looking at ixazomib in combination with other drugs. One looked at it in combination with pomalidomide and dexamethasone. Again, in a relapsed/refractory patient setting, you can see in a small number of patients a very high overall response rate, suggesting this combination is, in fact, quite active. [Slide 21] And there are other ixazomib trials being looked at in relapsed and refractory disease, looking at either weekly or twice-weekly dosing. And what I can tell you is that the advantage of the oral agent is that weekly dosing is almost the same efficacy as the twice weekly with a much lower side effect profile. So, I think this is the way that most of us are probably using it as we go forward.

[Slide 22] Now just to round out my section of what I'm going to talk about, there are other oral agents that are in development; and these include another oral proteasome inhibitor called oprozomib. There is selinexor or KPT-330, which is a brand new class of drugs called the SINE (selective inhibitor of nuclear export) agents or expo1 inhibitors. There are anti-PD-1 antibodies that you're going to hear a little bit about from Dr. Avigan. There is ibrutinib, which is a bruton tyrosine kinase inhibitor. There's also isatuximab, which is an anti-CD38 monoclonal antibody and then filanesib, which is a KSP (kinesin spindle protein) inhibitor that we've talked about in the past as well.

[Slide 23] And there were many trials presented on all of these agents, actually; but for the sake of time, I think I'll turn it over to Dr. Avigan to really talk more about the role of immune paresis and immune-based therapies in myeloma.

David E. Avigan, MD

Thanks, very much, Sagar. I really share your enthusiasm about a lot of the exciting work that was really showcased at ASH and I think gives us a real sense of optimism and hope for the future about really a wonderful sort of horizon of new therapies that are going to be available to our patients.

You've been hearing about some of the exciting work that's been going on with targeted novel therapies, and I want to spend a little time talking about some of the immune-based therapies that have been looked at, which I think is a really exciting area of cancer therapeutics that has really gained a lot of attention in the past few years.

There's been a really growing appreciation about how the immune system is very important in the development and some of the complications of myeloma. It plays a big role in how the disease progresses, and a lot of our therapeutic sort of trials now are trying to target different parts of the immune system, to either build it up as a force against the cancer cells themselves or to repair some of the damage that the cancer seems to do.

[Slide 24] So, in this first slide, I just list some of the abnormalities that we see in the immune system in patients with myeloma. We know that their antibody levels are low, and that leaves people vulnerable to certain types of infection; and we often see increased sinusitis or upper respiratory infections. And this may also play a role with the disease itself.
We know that myeloma cells actually hide from the immune system in all kinds of elaborate ways. They present themselves in a way that the immune system sees them as normal cells and not as foreign cells, and that actually turns off responses. They live in a complicated microenvironment in the bone marrow that actually has cells like myeloid suppressor cells or regulatory T-cells that actively suppress immune responses and prevent the immune system from activating against the disease.

And as you were hearing, there’s a particular pathway called the PD-1/PD-L1 pathway, which seems to be critical in inducing tolerance against the disease so that the immune system does not act against it. And that's become a big focus of therapy right now.

And the end result of this is some of the main pillars of the immune system, the T-cells and NK cells, for example, become much less effective. So, that's really our goal as we think about the different types of therapies to see how we can heal those different areas, repair them, and create an effective immune response. And I think one of the real appeals and promise of immune therapy has to do with the fact that the response can be broad and can target a variety of different types of myeloma cells. And, importantly, the immune system is built to create memory. So once you create a response, there is the possibility of an ongoing surveillance, the same way we’re protected after a vaccine, for instance, for measles for life against attack from that pathogen. We would hope that we could create long-term protective effect against the disease.

So here you see listed some of the sort of main areas that are a focus of therapy that were talked about at ASH. We're going to go through them one at a time. Firstly are the antibodies which are, again, biologic molecules that bind to tumor cells and actually kill them directly in that binding or act as markers to the immune system to come kill as a secondary effect. There is the targeting of some of these suppressive pathways, and we're going to talk about PD-1 blockade as a way of reversing the tolerance that tumor cells create so that they are then recognized and killed.

CAR T-cells are a very exciting area where people have essentially engineered T-cells out of the body to become activated and to bind to the cancer cells using an antibody tail, and there was an exciting study presented at ASH.

And then, finally, cancer vaccines, a subject near and dear to my heart, have been used to try and teach the immune system to see cancer cells and specifically myeloma as foreign and to go after them. We’re going to be talking about one example of that.

So to start with the antibody work, I'm going to start with talking about an antibody called elotuzumab, which is an antibody that targets a protein called SLAMF7 or CS1, which is present on myeloma cells, and this was recently approved to be used in combination with lenalidomide in patients who had one to three prior therapies. And this is based on a very exciting paper that Dr. Lonial was actually the first author on, in which it was shown that when you add elotuzumab to Revlimid and Decadron (dexamethasone), that that combination is significantly more powerful than the Revlimid or lenalidomide and Decadron alone. And this is really a very exciting observation because as a drug by itself, elotuzumab did not have a lot of activity; but when used in combination, it seemed to make a very big impact. And that had to do with the fact that it by its nature binds to both the myeloma cells and certain immune-activating cells such as natural killer cells, activating the cells to kill and seek out the myeloma.
And so there was a study that was presented which was essentially a follow-up on the ELOQUENT-2 (Phase III, randomized, open label trial of lenalidomide/dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma) study, which is that study I mentioned, that showed the efficacy and was responsible for the approval of this drug in combination with lenalidomide and Decadron. And they wanted to basically see what was the long-term follow-up in terms of how patients were doing down the road in the three-year follow-up period. And what was seen is that this effect seemed to have a sustained benefit to patients. There was ongoing 30% reduction in the risk of disease progression or death in the patients who received the elotuzumab in combination with lenalidomide and Dex versus those who just got len-dex (lenalidomide-dexamethasone) alone. [Slide 28] And on this slide you can see it graphically presented that this effect at one year and at two years was sustained, and this is very important because as was mentioned earlier, we sometimes know that combining drugs together can lead to better short-term effects and better responses. But if that doesn't mean anything for the long term, then the sort of significance of that is not as clear. But here you see that this initial improvement in response seems to have a durable and ongoing effect that is seen.

And there was another study that looked at the combination of elotuzumab and bortezomib and, once again, seemed to show advantage in using the combination of all three versus just the bortezomib and Decadron alone.

[Slide 29] Now the next drug that we're going to talk about is daratumumab. This is another antibody that has recently been approved, a very exciting drug that binds to CD38, which is a marker seen on all plasma cells, both the malignant and nonmalignant cells. And this is approved for patients who've had at least three prior lines of therapy and who've been refractory to a proteasome inhibitor and an immunomodulatory drug. So, again, patients who've had some frontline therapy with lenalidomide and bortezomib, for example.

[Slide 30] And the exciting sort of finding with this drug is that just even by itself, it shows significant activity against even relapsed and refractory disease. So here you see a study that was presented at ASH by Dr. Usmani where they combined the experience of two studies, the GEN501 and SIRIUS trials, that looked again at single-agent daratumumab given in patients with relapsed/refractory disease at these standard doses, 16 mg/kg; and we're talking about nearly 150 patients. And what was seen in the summary data was that patients were able to stay on study for a significant period of time. The overall response rate, again, to a single drug here was 30% in this group of patients; and the survival was nearly 20 months. And so this sort of showed a very important proof of principle that just even as a single agent in refractory disease, there were significant responses, some of which were quite durable. And if you look at the next slide, you'll see that those patients who were responders, some of them seemed to have ongoing disease control, even for the long term.

[Slide 31] There were several studies looking at the combination of daratumumab and other agents that Dr. Lonial actually referred to earlier, including one looking at the combination with lenalidomide and Decadron and one looking at the combination of pomalidomide and Decadron. And, not surprisingly, these had very high response rates when used in combination and even significant CR rates in patients who still had relatively relapsed and refractory disease.
Now the next category of agent that I wanted to talk about is the PD-1 antibody. So as I mentioned, PD-1 is a very important pathway. It is a marker on T-cells that when it binds to its ligand called PD-L1 on the myeloma cells, it causes those T-cells to shut down and not become activated. So it's a way that the myeloma cells, essentially, hide from the immune system.

This has been shown to be a very important pathway in cancer in general, and there have been some really astounding results in patients with solid tumors who were treated with these types of antibodies or patients, for instance, with melanoma, a skin cancer, lung cancer or kidney cancer. There was a subset of those patients who seemed to go into long-term durable response with exposure to this antibody merely through activating the immune system.

So, there's now been an effort to try and look at how this works in myeloma, and there's been a thought that this is probably going to work best when used in combination. And so here you see a trial where the pembrolizumab, which is a PD-1 antibody that was used in combination here with lenalidomide, and what they saw was that in this particular trial, 34 patients were treated; and they reported on the first 17 that they had response data on. It looked like 13 of these 17 risk patients were showing response. Even a fair number of these patients were refractory beforehand to lenalidomide, so the addition of this immune-activating agent seems to have a real effect on efficacy, although we have to see what the long-term effects will be.

And in the second trial where this PD-1 antibody was looked at in conjunction now with pomalidomide and Decadron, again, a large number of patients. You see 75% were refractory to both, the proteasome inhibitors and IMiDs. And you see, again, a nice response rate that showed that there's real activity in combining these agents together; and now we're waiting to see the longer term effects.

I wanted to mention about the CAR T-cells or what we call chimeric antigen receptor T-cells. This is a really exciting area of investigation where people are taking T-cells which are normally the killers of the immune system, but as mentioned in cancer and specifically in myeloma, they're often shut down and blocked from working.

So here what people did is they take them out of the body and engineer them so they both become activated in a chronic way and recognize certain specific markers on tumor. This has been developed by several leading investigators around the country, including the University of Pennsylvania, at the NCI, and at Memorial and other places. And what was found is that when this strategy was used in acute leukemia, even patients with relatively refractory disease were induced into complete remissions in a majority of the situations; so that was very exciting and people wanted to say, well, how about myeloma? Can we target myeloma cells as well?

Now the first study that was published from the University of Pennsylvania involved targeting CD19, which is not normally an antigen we think of in myeloma. It's on the B-cells that lead into myeloma. But they thought that maybe it would have an effect by hitting those earlier cells that might affect myeloma as well. And they did have, in an early report that was published in The New England Journal, some effect, at least in a subset of patients where it looked like the disease was shrinking, even in relatively advanced disease when they were exposed to these T-cells.
Now at ASH, there was an exciting trial that was presented from a group at the NCI and MD Anderson Cancer Center where they looked at a target called BCMA (B-cell mutation antigen), which is a marker that is on mature myeloma cells, and they saw that when you infused T-cells that were engineered to recognize this that you get responses. And they looked at this in different dose levels; and when they went to the highest dose level, they saw two patients who appeared to have a very dramatic response with complete clearance of the bone marrow findings of plasma cells.

Now, it's important to say that this was associated with some toxicity because when the immune system gets activated, it can cause symptoms, and they were able to navigate that by giving certain medications to deal with those side effects.

Maintenance

David E. Avigan, MD

Now I wanted to sort of end the talk, talking a little bit about maintenance and vaccine therapy. Now we know, as was said earlier, that we have great strategies with triplet and quadruplet therapy to get people into good responses, that autologous transplant can often consolidate those responses, and so patients have high rates of achieving complete remission. We know that if you, at that point, just watch folks, that most patients will have their disease come back over the next few years. There's been a lot of interest in using that time period when the disease is at a very low point to use lower dose treatments to try and prevent recurrence or delay it. And this has been looked at in a couple different ways, one with several studies involving lenalidomide where low-dose lenalidomide was associated with an almost doubling of the period of remission. There have been some, I would say, controversy about whether that actually leads to long-term improvement in survival or just the improvement in the time of remission; and studies have said different things. But people have been very interested in incorporating these kind of strategies, not just with the IMiDs but also now looking at the new oral proteasome inhibitors and other approaches to try and, essentially, maintain responses after transplant.

Now we've been very interested in using vaccines for this purpose. The idea of a vaccine is that we are introducing the cancer, the myeloma cells to the immune system in a way that those cells all of a sudden look foreign and so that the body is able to make an immune reaction. And what we would hope after transplant, that immune reaction could be used to target residual disease. And what you see here is the vaccine design that we have in the upper left corner where we take patient-derived myeloma cells and we create a hybridoma or a fusion cell with these immune-educating cells known as dendritic cells. And that combined cell is able to drive very dramatic immune responses, and we completed a trial where we looked at this in patients who underwent standard transplant and then went through a series of vaccines. And the punchline was that we, in that period of time after transplant, were able to nearly double the number of patients who were in complete remission when they received this vaccine.

This has led to an exciting national effort that the CTN (Clinical Trials Network) is leading. This is a cooperative group from the NIH (National Institutes of Health) in which patients will be treated in centers around the country and will be randomized to receive either standard maintenance with lenalidomide or the vaccine plus lenalidomide to see whether the vaccine has an effect in
improving remission rates and prolonging survival. [Slide 40] And we did include, I presented at ASH, an example where we combined vaccine with a PD-1 antibody to look at two approaches to amplifying the immune response and were able to see that many of our patients were able to generate very strong immune responses by being exposed to the combination of vaccine and PD-1 blockade.

**Minimal Residual Disease**

*David E. Avigan, MD*

[Slide 41] And the last topic is to just mention some of the exciting work that's going on with minimal residual disease detection. [Slide 42] As we've talked about in this entire presentation, our novel therapies are getting us into a much better position where we can not just reduce the disease burden but really what we hope is move towards eliminating it. And in order to know how we're doing in that department, well we need to have more sensitive ways of detecting disease. In the old days where we didn't really see much in the way of complete responses, there was no need for this. But now that we have these more effective strategies, there's been a lot of interest in trying to develop ways to assess for minimal residual disease; and this can be done either through a technique called flow cytometry where we use careful protein detection on the surface of cells to look for very small numbers of cells, even 1 in 10,000 or 100,000 or special gene-type sequencing which allows us to even look for 1 in a million abnormal cells. And the idea is that we can use these strategies as a way of trying to see where are we with this treatment, have we gotten into a real full response, and might this then be a way to make decisions about what other treatments are needed?

And so with that, let me end my piece, and then I think we're going to move towards the question-and-answer period.

*Blake A. Morrison, PharmD*

Thank you both, Dr. Lonial and Dr. Avigan, for very comprehensive and informative sessions; and really in summary I'd just like to say that the last couple of years, and especially in 2015, we've seen really, really impressive and important advances in the therapeutic approaches and the drugs available for treating multiple myeloma.

But with that said, there's even more exciting times potentially ahead; and so the work that you and other researchers will be doing to optimize the way we use our existing drugs and introduce new therapies, new mechanisms of action and also biologic therapies in the future will be very, very exciting and important work that will be coming forward. So thank you both.
Question-and-Answer Session

Blake A. Morrison, PharmD

[Slide 43] So we're now going to switch and go to our question-and-answer session. For everyone on the line, if you've not caught all the complicated drug names, please visit our website for more information. As a reminder, an archive of this program with the transcript and slides will be posted to our website in a few weeks.

Blake A. Morrison, PharmD

Okay, we will take our first questions from the Web audience. We have a number of interesting ones that have come in from many folks in the audience, so let me start; and I will direct the question to both presenters, and you guys can negotiate who wants to take the answer.

First and foremost, was there any research presented that indicates that treatment is better than closely monitoring smoldering myeloma with a high-risk of progression? So, Dr. Lonial, maybe you want to take that since you gave the session on smoldering.

Sagar Lonial, MD

Yes, thanks, Blake. So I think that there was one trial from the Spanish group that showed a difference in treating patients with what they called high-risk smoldering myeloma versus observation. The problem with that study is that it, first of all, was a very small study; and so one or two patients one way or the other could have affected the outcome. Not a really large study that I think we're used to seeing. And the second is that many of those patients, I think, in the US would have had slightly different imaging done; and my suspicion is the rapidity with which some of those patients progressed almost fits more with a symptomatic myeloma phenotype as opposed to a smoldering phenotype. And so I think if you take that study out, there are no other trials that say that early therapy impacts outcomes as compared to continued observation.

I think we're trying to do many studies to try and identify what might be good treatment options, and these include things as simple as single-agent Revlimid, which I run through the ECOG (Eastern Cooperative Oncology Group) network. There are trials looking at daratumumab as a single agent. David is leading trials looking at a vaccine in the context of smoldering myeloma, and in Spain they're actually treating them as if they have myeloma with four cycles of carfilzomib-len-dex followed by stem cell collection and a transplant and maintenance therapy. So I think you can go from low intense to high intense, but so far none of them have demonstrated that early therapy is better than observation.

Blake A. Morrison, PharmD

Very good. Thank you, Dr. Lonial. Next question is about some monoclonal antibodies. So it was mentioned on the talks that the antibody drugs are available today for the relapsed/refractory setting, but there is work going on to bring those forward into the newly diagnosed settings. Perhaps one of the two of you can comment about the trials that have begun using the antibody options in the frontline therapy.
David E. Avigan, MD

Okay. Well I think that there's; again, as was mentioned, the initial work that was done was in the setting of relapsed/refractory disease and looking both at single agent and now combination therapy. I think based on the data that was presented, showing that triplet therapy really makes an important difference, not just in terms of short-term response but long-term outcome, there's been some effort now to incorporate these drugs in frontline treatments; and there are active studies in both of the antibodies that we talked about, elotuzumab and using as well daratumumab as part of combination therapy with some of upfront triplets. So that work is ongoing right now.

Blake A. Morrison, PharmD

So an interesting question about the approval of Ninlaro. So the question is how does the new oral version of Velcade, just approved by the FDA, compare in side effects with the injection version? And, in particular, the focus is around the incidence of neuropathy.

Sagar Lonial, MD

So, I think that's a great question, and I can tell you one of the first patients we treated on the Phase I trial of ixazomib was a patient who had grade 3 peripheral neuropathy from Velcade and had to come off, and it was pretty significant. But over the course of the next two or three months, that neuropathy went down to grade 1. She was pretty much back to her normal functional status, but her myeloma started growing back. And so we put her on ixazomib at that time point when it was in early Phase I clinical trial, and she responded and stayed on therapy for over five years. So I think the side effect profile of ixazomib is actually quite different from Velcade in the sense that the neuropathy incidence is much, much lower even than what you'd see with subcutaneous Velcade. And the only thing that is somewhat unique to ixazomib is skin rash, which tended to occur at higher doses and perhaps a little bit more nausea. But, again, most of this is managed and rarely is an issue in terms of long-term ability to deliver the drug.

Blake A. Morrison, PharmD

Excellent, thanks for the clarification on that. Staying on the Ninlaro scene here, another question comes up, which I think is very important for clinical implications, is ixazomib effective in patients refractory to either Velcade or Kyprolis?

Sagar Lonial, MD

So certainly the late study that I presented by Dr. Moreau, comparing ixazomib-len-dex versus len-dex did not enroll patients that were resistant to either of those two drugs. The early trials looking in the Phase I setting were very, very small numbers of patients; and so I think it's hard to really interpret that. My personal sense is that I don't think that they can necessarily, overcome resistance to bortezomib or to carfilzomib, unless the reason a patient came off was because of intolerance. But I don't think we have enough data to really say that with confidence.
I'm going to direct this question to Dr. Avigan. Interesting one and I think it's on the top of many of our minds. The question is if antibodies target different things, why not combine antibodies in one treatment? You've talked about that.

Yes, that's a very good question; and I think we're all aware that one of the major sort of mechanisms by which cancer becomes resistant is this idea that the cells either modify themselves or that they're, within a tumor, there are different types of cells. So when you just target one thing, it allows cells that don't have that target on them to kind of grow back and cause a recurrence or resistance to the therapy. And so clearly one of the concerns with antibody treatment is that if you have a protein target, that's not the life blood of the tumor, and then you can just essentially develop variants that are negative. And so you might think then if you use a couple antibodies that are targeting things at the same time, that that might be helpful.

One of the things one has to always think about when combining treatments is the idea that the toxicities can also combine with each other. One of the things that we worry about with antibody treatment is infusional reactions where patients can develop side effects. Usually, often with the first or second time that they're getting the drug where they can get fever or chills or even an effect on blood pressure.

So I think one of the potential concerns about multiple antibodies at the same time might be that that could get exacerbated. But I actually think that the idea is, in general, a good one. We know in diseases where we have a longer experience, let's say like in lymphoma, we're using a drug called Rituxan® (rituximab), which is very good at binding a particular antibody-targeted lymphoma, that over time you do get the emergence of lymphoma cells that no longer express that target. So it would be an interesting way to go after it by hitting several antibody targets at the same time.

The only other thing to think about is that one of the reasons why antibodies, in and of themselves, sometimes may not be perfect is that they have to penetrate into the tumor itself, into areas that antibodies may have trouble getting to. And then that way using several at the same time wouldn't get around that problem, but I think it's an interesting thing to think about and to potentially study.

Okay, thank you. One more question and maybe both of you guys want to take a stab at this one. Patients with high-risk features continue to be the most challenging in terms of clinicians treating them. And so the asker is asking about presentations made at ASH regarding treatment of high-risk multiple myeloma at diagnosis or high risk at relapse and if there was any new data presented at ASH that brings some new found hope to this unique patient population.

It's a great question; and it's clearly one of the most fundamental unmet needs in the field right now. We've gotten certainly much better at identifying what are the factors that would let us know who's at...
higher risk at the beginning, and some of that has to be certain sort of genetic changes of the cells that patients at higher risk often have or show us. And we know that standard chemotherapy and transplant often are not terribly effective.

There was data initially that some of the biologic agents, such as bortezomib and some of the second-line agents such as Kyprolis may mitigate some of that. In other words, they may work well, even in patients that we thought were traditionally more in the high-risk setting. And there was some data looking at that at ASH, kind of combination therapies with some of those agents showing better outcomes or less difference than we were accustomed to seeing with more standard treatments.

But I think it remains an unsolved question. I know one of the areas of interest is donor transplantation, which is an area that we know can be extremely effective but also quite toxic, and there’s been a lot of questions about how to use or not use that therapy in patients. There will be some work looking at donor transplantation up front in the patients that were a particular high-risk phenotype that the CTN is going to be looking at, I know. So, that's one area that people are exploring.

*Blake A. Morrison, PharmD*

Dr. Lonial, do you have anything to add?

*Sagar Lonial, MD*

Yes, I think the other thing is to really better use the drugs that we have currently; and I think the three drugs versus two is an important step forward because we know that if you hit a high-risk patient with just one drug, the likelihood of rapidly developing drug resistance is pretty high. And so combination therapy up front, combination therapy in the maintenance and consolidation Phase, our group has published data looking at RVD as maintenance therapy for patients with high-risk disease showing pretty impressive overall survival and duration of remission compared to historical data for patients say with 17p deletion, one of the really high-risk subsets of patients.

I think the other area that certainly is encouraging for patients and for us who treat patients is that the antibodies in the immune-based approaches that are much less toxic than allogeneic or donor transplantation may offer some benefit here as well. In the elotuzumab data that we presented at ASCO (American Society of Clinical Oncology) and then was updated at this meeting, we did show that the addition of elotuzumab appeared to improve outcomes for patients with 17p and 4;14 translocation compared to Revlimid and dexamethasone alone, at least not just in terms of response, but in terms of how long patients stayed in remission.

And I think on the other side of the antibody story, we know, at least somewhat anecdotally, that the use of pomalidomide, which does have significant activity in 17p-deleted patients, in combination with daratumumab, also appears to be very, very effective as well for high-risk patients. So I think the new drugs we have will definitely give us hope in the ability to deliver therapy for a longer period of time, which I think is the key to remission in high-risk patients, and the incorporation of new drugs like antibodies, which I think will make a big difference as well.
Okay, thank you both. All right, we're going to switch over for the last few minutes and take questions from the telephone audience. So, Operator, do you want to take the first question?

Operator

Thank you. Our first phone question comes from Laurie, calling from California. Please state your question.

Laurie from California

As high-risk smoldering myeloma and given no clarity that early treatment is better than watchful waiting, I've been advised by one oncologist to treat now and one to not treat and to wait. What would be your specific criteria as the point at which to treat?

Sagar Lonial, MD

So, I'll start with this one, David. I think for me it's do you have any of the CRAB criteria or do you have any of the myeloma-defining events that I described, MRI with more than one bone lesion, free light chain ratio greater than 100, or a bone marrow with greater than 60% plasma cells. If you don't, then I would probably closely follow you and see what your M protein is doing. And if it's doubling every six to eight weeks, then sort of the writing is on the wall; and it's going to be sooner rather than later.

But many patients who have even a protein as high as 3 and 4 grams can sit at that level for a long, long period of time. And just the magnitude of the protein itself would not make me want to start on therapy sooner. I tend to want to watch people, unless they have one of those criteria.

David E. Avigan, MD

Yes, I would just echo that because I had this conversation in the clinic yesterday where we get an initial set of values at sort of the first point that we're meeting people; but the sort of rate of change is really almost far more important than the absolute number. And so if a patient looks like they are rapidly escalating and haven't quite crossed a threshold, we'll sometimes start therapy a bit early. If they have a higher number but the number is completely staying stable, we sit on them for as long as we can.

Blake A. Morrison, PharmD

Okay, next question.

Operator

Thank you. Our next question comes from Steven, calling from New York. Please state your question.
Steven from New York

Hi, this is Steven. I'm curious to the fact if there have been any trial programs with people in the MGUS stage, very early stage?

Blake A. Morrison, PharmD

So just have there been any therapeutic clinical trials looking at patients with MGUS, in treating MGUS, which is an interesting question.

David E. Avigan, MD

Yes, that's a great question. I mean I think there's been a lot of effort to try and understand the sort of biology of what causes a disease to go from this sort of premalignant state that is very common, and a lot of folks all over the country are in that situation, to those patients who go on to develop either smoldering or more active disease.

I'm not aware of therapeutic trials outstanding. There are efforts to look at what are the sort of genetic features of those situations and how they change and evolve, what's going on immunologically. But I think that because only about 20% of patients will go on to have an issue that I'm not aware of any therapeutic trials. So, Sagar, I don't know if there's…

Sagar Lonial, MD

Yes, I'm not, and I'm just thinking about it from a logistical perspective. If you have a disease where the risk of progression is 1% per year, but the adverse event rate is going to be higher than that, in many ways it's kind of hard to balance the risk and toxicity of therapy versus starting therapy initially. So I think, at least with what we know, it would be a little bit of a hard sell, I think, but certainly I'm not aware of any right now.

Blake A. Morrison, PharmD

Okay, thank you. Operator, next question please. We have just a couple of minutes.

Operator

Our next question comes from Pam, calling from Michigan. Please state your question.

Pam from Michigan

I'm wondering if you have any information on the toxicity or the side effects of the vaccines.

David E. Avigan, MD

So that's a great question. I think that to date, and each of the vaccines that are out there are different from each other, so I gave an example of the vaccine that we're using where we use the whole myeloma cell; and it's a personalized individualized vaccine. There are other approaches where people have used, for instance, parts of peptides or proteins that are common in myeloma cells or
there was an example where people used the measles virus as a way to try and stimulate the immune system to recognize the disease. So, I think each of those strategies are different from each other and may be associated with different side effects.

I would say generically vaccines to date have been associated with relatively modest side effects. We often see things like local inflammation at the site where the vaccine is given, muscle aches or sort of kind of flu-like symptoms you might see when you get a tetanus shot; and they tend to be transient.

I think there is always the possibility when you stimulate the immune system that you will target normal tissues and see something like what we call an autoimmune effect; and that can be anything from a rash, which may not be a big deal, to something that affects how well critical organs work.

We haven't seen a lot of that, but that may change as the vaccines, frankly, become more effective. With the CAR T-cells, there have been more significant side effects in patients who have developed a very profound immune response. And with the PD-1 antibodies, there have also been some examples of autoimmunity. And in the studies presented at ASH, there was some discussion of what thankfully were not common, but things such as inflammation of the lungs that can happen when you give a PD-1 antibody.

Closing Remarks

Blake A. Morrison, PharmD

[Slide 44] Thank you, Dr. Avigan. I want to thank everyone for participating in today's telephone and Web education program. I apologize that we weren't able to get to all the questions that were in the queue on the line, but what we have done, and what we will do again, we've done in the past, we'll do again, is reach back to each of you individuals who have submitted questions online with responses from some of our faculty as well as the nurses that work with us through our Patient Support Center. If you have additional questions and would like to speak to one of the nurses at our Patient Support Center, I encourage you to visit our website to speak to a nurse directly or call 1-866-603-6628, and you can ask your question there. But, again, if you submitted a question online, we'll make sure that we email a response back to you.

I want to thank our speakers, Dr. Avigan and Dr. Lonial, for their presentations. I also want to emphasize to everyone on the phone that we really do appreciate your feedback and comments and want to make sure that you do complete the program evaluation form that was in the confirmation email you received today.

We at the MMRF are so proud to work with so many centers worldwide to bring new treatments forward to you today, to bring studies like the CoMMpass study forward and make the gateways possible. To do all of this, we rely on the support of the entire myeloma community. If you are interested in supporting us, you can find out more information on our website [www.themmrf.org].

So, again, thank you so much to our faculty and to all of you in joining the call today. We all agree that being informed about your disease and treatment options is the best way to empower yourself and take control of your care. Have a wonderful day.