Welcome and Introductions

Joan Levy, PhD

[Slide 1] Thank you so much. Hello everyone and thank you so much for joining us. **[Slide 2]** This is Joan Levy, and I am the Vice President of Research for the Multiple Myeloma Research Foundation (MMRF). I am 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.

First, I'd like to thank Amgen and Takeda Oncology for funding this important program and for their continued appreciation for the need for this kind of information to be disseminated to patients and their caregivers.

The MMRF was founded in 1998 by Kathy Giusti, 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 with our affiliate organization, the Multiple Myeloma Research Consortium or MMRC, we've opened over 60 trials involving more than 30 different agents.

We are pleased to share with you that we now have finished enrollment in our landmark study CoMMpass℠ (Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile), that is comprehensive, clinical, and molecular analysis of a thousand newly diagnosed patients from the time of diagnosis over an eight-year course of their disease. 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 the CoMMpass study and other genomic initiatives. The MMRF Community Gateway allows patients to find other patients who have similar disease types and experiences and also to find information about clinical trials specific to their type of 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 educational programs.

[Slide 3] This is an extremely exciting and encouraging time for treatment options for myeloma patients. In 2015 alone, there were four FDA approvals involving new drugs for the treatment of patients with relapsed and refractory disease. They include panobinostat or Farydak®; daratumumab, also referred to as Darzalex® ixazomib, known as Ninlaro®; and elotuzumab, called Empliciti™. Three of these drugs, Darzalex, Ninlaro, and Empliciti were all granted approval by the FDA within a two-week time frame at the very end of last year—truly record-breaking in oncology.

As you will hear from our speakers, Farydak is from a novel class of drugs called histone deacetylase inhibitors or HDACs. Ninlaro represents a proteasome inhibitor that is given orally, and both Darzalex and Empliciti represent two different types of antibody therapies.

[Slide 4] Our presenters today are Dr. Craig Cole from the University of Michigan in Ann Arbor, Michigan, and Dr. Amrita Krishnan from the City of Hope in Duarte, California. Dr. Cole will provide an overview on the latest proteasome inhibitors and HDAC inhibitors, and Dr. Krishnan will provide an overview of latest antibody therapies and immunomodulatory drugs.

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 other formats as well.

It's now my pleasure to introduce Dr. Craig Cole, and he will provide an overview of proteasome and HDAC inhibitors. Dr. Cole.

Myeloma Overview

Craig E. Cole, MD

[Slide 5] Thanks, Joan, and I'd like to thank everyone for dialing in and listening in today; and it really is an incredibly exciting time in multiple myeloma research as so many breakthroughs have happened. I'd also like to thank the Multiple Myeloma Research Foundation for having this meeting to help educate and empower patients.

[Slide 6] This is a graph or a representation of the multiple myeloma disease course. On the one axis is time and how long patients have the disease, and then that is, on the other axis is disease burden or how many plasma cells are what the M protein is. And usually, in fact, we know that all myeloma patients start out in an asymptomatic or monoclonal gammopathy of uncertain significant state; and at some point, their disease will change into active myeloma where they'll have one of the CRAB or calcium, renal insufficiency, anemia, and bone disease criteria for active myeloma.

They then receive their first therapy and then go into a plateau, and then at some point their disease will come back, and they'll have their first relapse; and then a salvage therapy is given. And that's when the disease becomes relapsed myeloma. After potentially a number of different relapses that occur over time, eventually the disease will get to the point of being difficult to respond and then become relapsed/refractory.

One caveat that I would make of this slide is that this slide is a bit older, and I would say that these days we're able to achieve in that first plateau, remission phase, we're actually able to achieve deeper remissions than what that line would represent. And because of all the new therapies that we

have, patients are actually able to have a number of different relapses because we have so many new medications to treat relapsed myeloma.

[Slide 7] And this slide does have some of the definitions, and sometimes it's confusing about what's relapsed and what's refractory myeloma. Relapsed myeloma is when the disease returns after an initial therapy. After that initial plateau, the monoclonal protein goes up or there's new calcium or bone disease. And since there's no cure for myeloma, it is likely that patients will have a relapse at some point. And at the time of relapse, a second therapy or third therapy is given; and then they achieve another response.

Refractory myeloma is when the disease doesn't respond to therapy after usually a long period of time of having myeloma or only respond very briefly. And this rarely occurs when patients are initially diagnosed and usually after they've had myeloma for years.

Proteasome Inhibitors

Craig E. Cole, MD

[Slide 8] So, now I'll talk about the class drug known as proteasome inhibitors, and I like to describe proteasome inhibitors as the plasma cells are protein factories. They produce that protein that's detected in the blood, a lot of the monoclonal protein. They're also very dependent of the bone marrow microenvironment, so they need a lot of protein glue to glue themselves to the bone marrow.

So, plasma cells are protein factories, both producing protein and gluing themselves to the bone marrow. And with all that protein production by plasma cells, they produce a lot of waste. The proteasomes are actually little trash compactors or little toilets, I would say, inside the plasma cells that get rid of all the excess waste. What proteasome inhibitors are things that stop up the myeloma cell toilet so that the cells then back up their toxins and actually destroy the myeloma cell. So, it's very specific for myeloma cells, and we have a number of different proteasome inhibitors, or toilet stoppers I like to say, to destroy the plasma cells.

[Slide 9] Velcade® (bortezomib) was the first one. It was initially given IV, and then given under the skin and has been the now, one of the mainstay drugs to treat multiple myeloma, both relapsed and newly diagnosed. And it's a reversible proteasome inhibitor, so it's like putting a paper towel in the toilet. It'll back it up for a little while, and then it will go through.

Kyprolis® (carfilzomib) is actually like putting cement in the toilet. So, it's an irreversible proteasome inhibitor that was approved for relapsed myeloma and also in combination with Revlimid® (lenalidomide) and dexamethasone. That's an IV infusion that's usually given twice weekly for three weeks, and that's one of our newer drugs.

And just recently approved is Ninlaro, the oral version of Velcade. It's a reversible proteasome inhibitor that's a pill that you take once a week and you usually combine it with Revlimid and dexamethasone.

On the horizon are two other proteasome inhibitors. One is marizomib, which is a complete proteasome inhibitor. It's like putting a grenade inside the toilet. It will blow it away, and it's given as an IV infusion. It has some side effects that need to be worked out, and it's currently in clinical trials. And oprozomib is an oral version of carfilzomib that's also in clinical trials. One inconvenience that has been with carfilzomib is that it's been twice weekly.

[Slide 10] There was a study called the CHAMPION (weekly carfilzomib in combination with dexamethasone for progressive multiple myeloma) study, which actually looked at giving carfilzomib just once weekly. And it has a promising response rate of 77% in patients that were refractory to Velcade or bortezomib, and it's given just once weekly and was able to delay the time for relapse up to 14.3 months. And thank goodness it has a very tolerable safety profile. There were no excessive toxicities seen in giving it just once a week; and, most importantly, it was effective. And so now what will need to be done is a Phase III study comparing to make sure that the once weekly is as good as a twice weekly in a Phase III trial.

[Slide 11] ENDEAVOR has been a fantastic trial for us to really understand the workings of carfilzomib. And it was a study using carfilzomib given twice weekly for three weeks, as compared to bortezomib, the older reversible proteasome inhibitor. And what that study found was the time of response or the time it took for a patient to relapse after therapy was better with carfilzomib than with Velcade and especially with the carfilzomib lasting up to 22 months as compared to 10 months with bortezomib. And especially when patients have had prior lines of therapy, again, the carfilzomib, the irreversible proteasome inhibitor had excellent response rates and a longer time to relapse with more lines of therapy.

It also gave us an idea of some of the side effects, and one side effect that we saw with carfilzomib is that it can cause high blood pressure. It can cause higher blood pressures during the infusion. And so now we know that it's critical and important to follow up with your primary care doctor to make sure your blood pressure is controlled before you're receiving carfilzomib.

[Slide 12] And then ixazomib came out; and, again, a very exciting oral version. We have been tied to the clinic with the other proteasome inhibitors, and with ixazomib we now have an oral proteasome inhibitor. And there was a dose comparison study that was done looking at 4 milligrams versus 5.5 milligrams, and I think one important point is to see that these patients had not received a proteasome inhibitor but had an excellent response rate for the 5.5 milligrams at 51% as opposed to 31%, and, again, a very well-tolerated drug, even at the higher dosing. **[Slide 13]** And, of course, we now are frequently using three drugs to treat myeloma and to use the new ixazomib as a third drug with lenalidomide and dexamethasone was explored in a Phase III trial where patients either received ixazomib-lenalidomide and dex or they received just lenalidomide or Revlimid and dexamethasone alone.

These patients had prior lines of therapy, and three drugs with ixazomib was better than two drugs with a better overall response rate of 78% for the triplet, including the ixazomib. And the duration of response was fantastic at 20 months for the triplet combination and the progression-free survival or the time it took to relapse 20 months, excellent as compared to the doublet therapy from dexamethasone. And it was well-tolerated and we do use, and that's the combination that was approved by the FDA.

[Slide 14] Of course, we couldn't stand still for just using the Revlimid, and so there was a triple combination explored using pomalidomide, the latest version of Revlimid. And in that study, again, in patients who had received multiple lines of therapy, an excellent response rate of 62% in patients that had received multiple prior therapies.

[Slide 15] Bortezomib has also been explored, the sort of grenade of the proteasome inhibitors in heavily pretreated patients. And, again, in these heavily pretreated patients, the newest proteasome inhibitor had partial responses of 64% and partial responses of up to 79% in patients that had prior treatment with carfilzomib and other proteasome inhibitors. **[Slide 16]** So, the horizon looks very promising for the class of drug with both marizomib and oprozomib, which is the oral version of carfilzomib when combined with pomalidomide. Again, excellent responses in the way of 86% and the duration of response lasting up to 287 days, and, again, the combination was well-tolerated.

HDAC Inhibitors

Craig E. Cole, MD

[Slide 17] And so I'll move onto a second class of drugs that I'll be talking about, which is the histone deacetylase inhibitors or the HDAC inhibitors. And this is a very interesting class of drugs using a very interesting biology. So, there are 11 different types of histone deacetylases and histone deacetylase inhibitors. There are some that are very specific for myeloma, and there are general histone deacetylases. And their basic premise is that cancer cells require access to the DNA, and DNA is stored on histone. So, when it's time, for a cancer cell to produce a protein, they'll unravel the DNA off the histone. So, of course, histone deacetylase inhibitors keep the DNA stuck on the histones so the cancer cells can't use them to produce protein. The interesting thing is, is that histone deacetylases have that purpose, but they have a number of other biologic properties inside the plasma cell that we can utilize.

[Slide 18] Farydak is a pan-histone deacetylase inhibitor, so it operates on several different mechanisms of the histone deacetylase, not only unwrapping DNA, but other cellular methods that are inhibited in the plasma cell. And it was approved in combination with bortezomib last year.

Ricolinostat is a very interesting drug in that some research was done finding that the histone deacetylase of the 11 different types of histone deacetylase, number six appears to be a very excellent and promising target specifically for myeloma. So, this is a more specific drug, selective just for the HDAC6, which we think is more important than myeloma. That's currently in clinical trials, and

ACY-241 is another histone deacetylase inhibitor just for number 6 which we think is, again, the most important one in multiple myeloma.

[Slide 19] Panobinostat, which covers a lot of the histone deacetylases, is not as specific as the other two but has been undergoing a number of clinical trials in combination, given that it is fairly well-tolerated and is able to be combined with other medications; and you can see that there a number of different combinations that the drug is being used with.

[Slide 20] Ricolinostat, the histone 6 deacetylase inhibitor is probably, in the initial trials that we did with ricolinostat, is very well-tolerated. It's a liquid that is purple or grape flavored and has fewer side effects and, again, has a very good response rate. So, pomalidomide-bortezomib and lenalidomide going from a response rate of 29% up to 55% in combination. These drugs don't work as well as single agents but work very well in combination.

[Slide 21] And, finally, the ACY-241, again, a specific myeloma, HDAC6 inhibitor, combined with triplet therapies, is also under investigation in a very exciting new avenue of treatment.

And so that ends my part of the presentation on the histone deacetylase inhibitors and the proteasome inhibitors.

Joan Levy, PhD

So, thank you so much, Dr. Cole. Before we move on, I would also like to articulate a few takeaways from Dr. Cole's talk.

First of all, proteasome inhibitors really remain a critical treatment component for newly diagnosed and relapsed myeloma. This class of myeloma therapy is really becoming a standard of care in all phases of the disease. In addition, new generation proteasome inhibitors are available and in clinical trials, which are designed to increase effectiveness, decrease side effects, and improve the method of delivery such as the oral proteasome inhibitors.

And, finally, the histone deacetylase inhibitors that Dr. Cole just spoke about, the HDACs, have become a new and exciting class of drugs in myeloma therapies. We are just seeing the genesis of the application of these agents, which will also help in the fight towards more effective therapies for multiple myeloma.

At this point, it's my pleasure to introduce Dr. Amrita Krishnan, and she will provide an overview of antibody therapies and immunomodulatory drugs. Welcome, Dr. Krishnan.

Antibody Therapies

Amrita Krishnan, MD, FACP

[Slide 22] Thank you very much, Joan; and, again, to reiterate what Craig said, and thank you to you and the MMRF for the invitation to speak, I also wanted to say thank you. I know some of my patients are listening, and I appreciate that you listen to me in clinic all the time, but you're on your other free time of voluntarily listening to me as well. So, I will hopefully, cover some of the things that are relevant to what you tuned in for.

I should add, just to build on what Craig had mentioned in regard to the oral proteasome inhibitors, we just completed a trial that was through the MMRF using that combination of the ixazomib-pomalidomide-dexamethasone. So, we hope to present that data at the upcoming American Society of Clinical Oncology meeting also; and it was a really tremendous effort that couldn't have been done without the MMRF and the institutions that participated.

[Slide 23] So, let me move on now to antibodies. So, as Joan mentioned, we were tremendously lucky to have two antibodies approved last year specifically for myeloma. Now you can see on that list there's four antibodies listed, and so just because something's not approved yet for myeloma doesn't mean that we are not basically borrowing it and already moving ahead to study it. And with that I mean the pembrolizumab.

So, the ones that were approved for myeloma, literally within the span of two weeks of each other, were daratumumab and elotuzumab; and we'll go into a little bit more details about them and their targets. The one that's not yet approved, but certainly is under great study, is isatuximab, which, as you can see, is the same target as the daratumumab.

[Slide 24] So, we'll start with daratumumab. So, we have obviously in the myeloma world been looking for an antibody for many, many years; and why is that? Well, one, obviously, targeted therapy means that you can hopefully spare a lot of other side effects because you really are only, hopefully, targeting the malignant cell. The other part of it is if you're targeting just a specific cell, hopefully you also are more efficacious, so you can do a better job at really killing that cell.

So, daratumumab targets CD38. Now the issue with CD38 though is it is a fairly widely expressed antigen, meaning something that certainly is on the myeloma cell at quite high amounts; but it is also on our other hematopoietic or other blood cells. And as you'll see, when you look at some of the, the side effects are things to be aware of daratumumab. That's one of the reasons, meaning in regard to the blood group typing issue with daratumumab because CD38 is also expressed on red blood cells.

[Slide 25] Now daratumumab, as you can see, that current approval for patients who had very advanced disease, the patients who were refractory to both a proteasome inhibitor and IMiD, or patients who had a minimum of three lines of prior therapy.

Now the approval was accelerated approval based on two different trials, and we've participated in one of those studies, the SIRIUS study, and I can tell you our study coordinators have never seen anything like it. When we opened the trial, we filled it within two weeks. And that just tells you how excited we were as well as other patients were about this drug. And you can see here that with relatively short follow-up, we saw a tremendous response rate or about a third of the patients responding. And, again, just to put that into the context that these were patients who had very advanced disease. Many of them were refractory to the approved agents that we had in regards to the proteasome inhibitors and the immunomodulatory drugs. The other thing we were gratified about, if you can see here, that overall survival of 19.9 months.

The next curve, and our understanding of antibodies, really, is sort of evolving. So, certainly, and so we're constantly looking at the data as we collect more and more data to figure out how do we best use them and what are the signals we're seeing?

[Slide 26] So, one of the things was clearly we saw, in people responding, we saw very long responses, which was very gratifying. But what we also saw is even in patients who had less than those partial responses, that you could also see a long tail on this curve. So it suggests that even getting stable disease with an antibody could be a good thing, and people could have a long period of stable disease.

[Slide 27] Now, naturally, as you've seen from Craig's talk, we always take one agent; but it's sort of like cooking. We're not happy with that just by itself, and we always create a new recipe. And so it certainly made sense that it didn't take that antibody and see what are the best things to combine it with.

And pomalidomide, that Craig had mentioned earlier, was a natural choice; in part because what pomalidomide can do is it increases the CD38 expression on myeloma cells. As we talked about too, the nice things with antibodies, some of the toxicities are not the same; and so you can also combine them without getting sort of additive toxicity.

So, in this trial, we combined daratumumab with pomalidomide and Decadron® (dexamethasone); and you can see a response rate of 71%. And I think even more interesting to those of us was that in those patients who had double refractory, so were refractory to a prior bortezomib or carfilzomib or lenalidomide, 67% of them responded. And the side effects were well-tolerated. So, the next step is really going to be trying to prove that even more in what we call a Phase III trial, which would be the combination of three drugs versus two drugs.

[Slide 28] Now, also, basically right after the approval of daratumumab came elotuzumab's approval. Elotuzumab targets something slightly different, so it targets something called SLAMF7 or signaling

lymphocyte activating molecule, which is on the surface of myeloma cells but also, importantly in this case, on the surface of NK cells. And why is that important? Because we think that the elotuzumab, in contrast to daratumumab, really needs another agent to help optimize its activity. So, as you can see here, it was approved in combination with lenalidomide for a somewhat less advanced population, patients who had had one to three prior regimens. And part of the reason you had to give the lenalidomide is to further augment this NK cell activity to lead to the optimal killing of myeloma cells.

[Slide 29] So, the approval was based on a Phase III trial. So, patients were compared to what was felt to be a standard treatment of lenalidomide and Decadron, two drugs, versus the three drugs – the elotuzumab-lenalidomide-Decadron. **[Slide 30]** And you can see that patients who had the three drugs had a marked improvement in the progression-free survival, 19 months versus 14.9 months or a 30% reduction in their risk of disease progression.

Immunomodulatory Drugs

Amrita Krishnan, MD, FACP

[Slide 31] Now as I mentioned, there are other drugs out there not yet approved for myeloma but certainly approved in the setting of melanoma which also has made tremendous strides and non-small cell lung cancer. And just too kind of put this in context, really this is sort of that whole field now of immuno-oncology. So, we're recognizing more and more that it's not just targeting a cancer cell that's important, but it's also augmenting the immune system that can help fight cancer.

[Slide 32] So, in this case, this cartoon just shows you that cancer cells are very smart. They know how to hide. So, part of the way they hide is by inhibiting their attacker, so those immune cells, through this interaction of PD-L1, which is expressed on the myeloma cell, and PD-1, which is on the immune cells or the T-cells that are coming to attack the tumors. So, if the tumor can inhibit this, it basically stops the T-cells from working as well.

Now on the other hand, if we can interrupt this pathway and it allows, it sort of frees up the T-cells to then attack the tumor, and so that's sort of this concept behind these PD-1, PD-L1 inhibitors. And, as I said, they've been improved already in other diseases and they've shown great activity, and we've now looked at them in myeloma – some small studies that have shown very promising results.

[Slide 33] So, the first one was combining the pembrolizumab with lenalidomide. Again, so here again, constantly you're hearing lenalidomide-pomalidomide as the combination drug, really in part because of the effects of stimulating the immune system. And you can see a response rate of 76%.

But I think even more interesting was that you could use it in patients who haven't become refractory to lenalidomide and then when you added this pembrolizumab, or I guess I should say, the patients who had been previously lenalidomide-refractory could still have the potential for responding to that combination. And the responses seem to be fairly durable, and safety was also very favorable.

[Slide 34] And here's that other drug again, so pomalidomide, similarly, this is patients who probably had a little bit more treatment and the same kind of story. So, response rate very good, 60%. And the so-called double-refractory patients also had over 50% of them responding and with manageable side effects. So, this is, I think, something you're going to see more and more in the future; but to say that too, that's not the only checkpoint inhibitor. So, the PD-1, PD-L1 antibodies kind of fall in the category of checkpoint inhibitors; and the MMRF is also running several studies using the PD-L1 inhibitor atezolizumab – I think one of the hardest things is pronouncing them – in various settings, and the transplant setting as well as in the relapsed disease setting. So, we are going to be excited. We are awaiting more results from those studies as well.

[Slide 35] As I mentioned, there are other antibodies out there. The SAR antibody has also shown extremely promising results in patients who have advanced refractory disease. The trial is going to open combining this now with pomalidomide. Similarly, the CD138 antibodies have also shown promise. These generally have been done in conjunction with either lenalidomide or pomalidomide and then the CD40 antibody. So, antibodies are definitely here to stay, and we're going to see more and more of them, in fact.

[Slide 36] So, I spent a lot of time talking about pomalidomide and lenalidomide, and just to kind of refresh your memory, I think many of you probably are well aware of those drugs as they have been a mainstay, a backbone of our treatment, starting with the thalidomide, moving on to lenalidomide, which is probably stronger and somewhat more favorable in terms of side effects. And then more recently the pomalidomide.

[Slide 37] Now, as I mentioned earlier, I think what's so wonderful about those drugs is really that they are affecting the immune system; and that's why it allows us to use them in combination with all those other drugs – the antibodies, as well as the proteasome inhibitors. So, we really consider them the sort of backbone of treatment, as well as they also directly can affect the myeloma cells.

[Slide 38] So, you've heard about how we use them as a backbone, and then you've also seen now, we then take them and add them onto all these new drugs that are out there, so ixazomib, panobinostat, and the various antibodies.

[Slide 39] Obviously, this is not the end of the story for myeloma at all. It continues to get even broader and broader, as you see here a list of just all the other new classes of drugs that are under study that we look forward to, sort of, in the future. So, for example selinexor, it's a nuclear plasma protein inhibitor. Again, antibodies different target, this concept of targeted or personalized therapy, sequencing patients' myeloma, and targeting specific mutations. So, a drug approved in other diseases now also showing activity in myeloma. You probably heard a lot about ibrutinib lately because it just got a new indication in CLL. But we have multiple studies also looking at it in myeloma, both by itself as well as in combination again with those IMiDs. So, pomalidomide, we just opened a trial with pomalidomide and ibrutinib. And then other various classes of drugs.

So, let me stop there and turn it back over to Joan.

Joan Levy, PhD

Thank you so much, Dr. Krishnan. Before we go on, I would like to reinforce a few points that were mentioned in her presentation. First of all, we are developing agents, including antibodies that will activate different parts of our immune system to recognize myeloma tumor cells and destroy them. In addition, antibodies will most likely have to be used in combination approaches, as Dr. Krishnan mentioned and, therefore, in concert with other drugs.

For example, seven sites in the MMRC are involved in the company-sponsored Genentech-Roche trial of testing their PD-L1 inhibitor, atezolizumab that Dr. Krishnan referred to, in combination with Rev-dex in early relapse patients. And what's very exciting is that Genentech-Roche just announced the other day a new collaboration with Janssen to add additional arms to this same study to test this immune checkpoint inhibitor of PD-L1 in combination with daratumumab, therefore demonstrating support for additional novel immune combination strategies. And, thirdly, antibodies are in one sense risk-agnostic. They may be very helpful in combating high-risk disease.

So, with that, we can move on to the question and answer session. And for everyone on the line, if you have not caught all of the complicated drug names, please visit our website for more information. As a reminder, an archive of this program with the transcripts and slides will be posted on our website in a few weeks.

Question & Answer

Joan Levy, PhD

[Slide 40] It is now time for the question-answer session. I would like to remind all of you that we have hundreds of people on the phone and on the Web. For everyone to benefit, please keep your questions general in nature, and our experts will provide an answer general in nature.

Joan Levy, PhD

So now we're going to take our first question from the Web audience; and, actually, Drs. Cole and Krishnan, both of you can answer this question, which is do you envision that these newly approved drugs can be used early on in the disease since they've been approved in relapsed/refractory? Dr. Cole, would you like to go first?

Craig E. Cole, MD

Oh, sure. No, these drugs are actually currently being used in clinical trials in the upfront setting; and there was a recent trial that was through the Multiple Myeloma Research Consortium of elotuzumab combined with the antibody that Amrita had talked about, combined with Revlimid-Velcade-

dexamethasone. And the trial, just like a lot of the other antibody trials accrued very quickly; and we're very, very excited about finishing that trial. So it is the new drugs are already being used in the upfront setting. Ixazomib has also been used in clinical trial for newly diagnosed patients combined with Revlimid and dexamethasone. And there are very exciting trials, including using the daratumumab antibody for smoldering myeloma, the precursor or the earliest version of multiple myeloma.

Joan Levy, PhD

Dr. Krishnan?

Amrita Krishnan, MD, FACP

I mean I think Craig covered it pretty extensively. I don't have anything really more to add, just to say that there's also multiple huge European trials going on right now with daratumumab so using it in combination with chemo for newly diagnosed patients, then transplant, then using it after the transplant; and there's also trials in the United States just opened using it for patients in combination with Revlimid and dex for newly diagnosed patients.

Joan Levy, PhD

And to follow that, what about use of these drugs as maintenance therapy after stem cell transplants?

Amrita Krishnan, MD, FACP

I could probably say certainly that the European trial is doing exactly that. So, I mean I think you're very prescient, Joan, in terms of where the field's moving so that trial, daratumumab before the transplant, the daratumumab after it in one arm of the trial. So, again, trying to prove that clearly is it going to be a benefit?

Ixazomib we also have under study, and that's a trial running through the MMRC where patients after they're transplanted are getting quote/unquote "sort of intensive consolidation," so a little bit stronger chemo with ixazomib-lenalidomide-dex and then are assigned to either ixazomib or lenalidomide as maintenance. So, absolutely, and I think, and certainly ixazomib is a very attractive drug for considering maintenance with since it's oral. So, I think we're going to see more and more studies with it.

Joan Levy, PhD

Great.

Craig E. Cole, MD

And for the similar disease, for non-Hodgkin's lymphoma, for that disease they had an antibody that they have been using for lymphoma for almost a decade called Rituxan® (rituximab); and they've been using Rituxan for maintenance therapy for lymphoma. And so, hopefully, we will be able to explore to see if some of these new antibodies could be used as maintenance therapy for multiple myeloma in the future.

Joan Levy, PhD

So, another question from the Web is, and we alluded to that in actually my summary on antibodies, but how effective are some of these newer treatments in treating high-risk disease, such as patients with 17p deletions or other types of abnormalities that are considered to be higher risk? Dr. Krishnan?

Amrita Krishnan, MD, FACP

So, I think certainly that the daratumumab story, if you look at sort of the groups exactly with higher-risk disease, you can see that response rates are very similar. So, I think certainly they, to some degree, are able to overcome sort of the high-risk features. Obviously, the challenge is going to be, can those responses also last as long? And I think that that data's still probably a little too early. I mean I think that's probably kind of the data that we're going to be seeing emerging as we have longer and longer experience with those drugs. And I foresee that this year, in fact, we'll see that data at many of our meetings.

Ixazomib already in preliminary studies certainly has shown that it has, in those 17p deletion patients, also very good response rates. So, I think across classes, we can see that. And I think that what we're trying to learn, certainly with the checkpoint inhibitors, we don't know yet. But it certainly mechanistically would make sense if they really should even more so be responsive, regardless of the cytogenetic class of the patient.

Joan Levy, PhD

Right. Dr. Cole, would you like to add?

Craig E. Cole, MD

Yes, I think that's the real hope of, especially the antibody therapies, is that the constraint that we have had with classical chemotherapy in the prior treatments for myeloma is that some of the high-risk biologic features have to deal with the behavior of the plasma cells and their internal biology.

One unique thing about the antibodies is that the targets that the antibodies go after on the surface of the plasma cell are really independent of the internal mechanism. So, if you're a really mean plasma cell that's 17p deleted, you still have to have CD38 or CD138 on top of your plasma cell in order to be a plasma cell.

And so, I really do hope that as the data emerges that we'll see that antibodies are risk-agnostic. That it doesn't discriminate based on what the cytogenetics are, that it will hit the cells irrespective of the internal biology.

Joan Levy, PhD

That's great. Thank you so much. And one thing that we talked about is the use of some of these newer agents earlier in the disease. But what about the use of some of these agents in plasma cell leukemia or related conditions like AL (amyloid light-chain) amyloidosis? Are there ongoing trials to look at their effectiveness in these conditions?

Amrita Krishnan, MD, FACP

So, there is a trial looking at daratumumab in AL amyloidosis; and we certainly are very interested in using daratumumab in plasma cell leukemia and are hoping that we are going to be able to open a trial for that, given that that's an extremely high-risk condition. And certainly from the sort of scientific standpoint, it makes sense that daratumumab should work quite effectively there. Sort of similar, Craig had used the lymphoma analogy earlier. So, chronic lymphocytic leukemia is a condition where you have a lot of circulating lymphocytes and rituximab antibody was very effective at reducing that. So, plasma cell leukemia one would hope that the daratumumab could similarly have that degree of activity.

Joan Levy, PhD

Any comments, Dr. Cole, about the use of HDAC combos in other related disease types?

Craig E. Cole, MD

Yes, the HDAC inhibitors are, again, a sort of novel biologic entity in targeting for myeloma; and the good thing is that, in plasma cell dyscrasias. So, exploring the HDAC inhibitors in amyloidosis where the number of plasma cells is limited, but they're causing lots of tissue damage by producing the amyloid tissues, is going to be a really exciting area to explore for some of the more targeted HDAC inhibitors. And there are also antibodies being produced specifically for amyloidosis. One of the big problems with amyloid is that that protein gets stuck in the tissues, and it's difficult to get out and that there are antibodies being produced and exploring clinical trials just to try and remove those folded amyloid proteins out of the tissues, so people can heal.

Joan Levy, PhD

Great, I'm going to ask one more question from the Web; and then we'll switch it to telephone questions. So, and this is for Dr. Krishnan. I know your part mainly covered antibodies as well as immunomodulatory agents. There have been many questions, as you could imagine, on any thoughts on using engineered T-cells, CAR T (chimeric antigen receptor T-cell), BCMA (B-cell maturation antigen) constructs, or even engineered T-cell constructs with different entities. Can you just comment on that before we switch to the telephone questions?

Amrita Krishnan, MD, FACP

Sure, so you're right. You're absolutely right in regards to this concept of immuno-oncology, has just sort of blown wide open. So, CAR T-cells, I mean there are multiple different targets. Some of them certainly are the same targets that we see with these antibodies, and some of them are new targets. So, for example, you mentioned BCMA, which already has been used in the CAR T-cell construct. There are going to be some antibodies also in future trials against BCMA.

So, the great thing about the CAR T-cells is from preliminary data in small numbers of patients, clearly we've seen efficacy. But having said that the caveats are, obviously, number one, manufacturing of those T-cells is a very specialized procedure. So, it's not as widely applicable to patients as a commercially available antibody drug.

Second thing is, and certainly as we're learning more and more the side effects of CAR T-cells, so you don't get response without, unfortunately, side effects. So, that cytokine release syndrome, which can be a fairly fulminant syndrome where people can get high fevers, shortness of breath, and fluid in their lungs, and those kinds of things. It's manageable; but it clearly takes centers that are very experienced at managing those side effects. So, absolutely CAR T-cells are going to be a part of our armamentarium; but they're not going to be a sort of, I think, answer for everyone.

Joan Levy, PhD

Okay, great, thanks. So, now we'll take our first question from the telephone audience.

Operator

Thank you. Our first question comes from Gary calling from New York. Please state your question.

Gary from New York

Yes. My partner, Pamela, was on a trial of ACY-241 after having been on maintenance Revlimid for eight years; and after 1-1/2 cycles, it was working very well. However, it seemingly, suddenly affected

her short-term memory. She said she was in a fog during most of these cycle treatments anyway, but at one point it clearly affected her short-term memory and so far, and we're talking about three weeks ago, it doesn't seem to be improving. I just wondered whether there's any experience with such a reaction from your experience, Dr. Cole or Dr. Krishnan?

Craig E. Cole, MD

Yes, we did have some rare events of people having cognitive problems; and sometimes it was difficult. In the clinical trial we had with the ACY or the ricolinostat drug, it was combined with pomalidomide; and sometimes pomalidomide can cause the same sort of cognitive problems. And so we did see some of that on the clinical trial that we participated in.

One sort of thing about these novel drugs is that unlike chemotherapy, as in Cytoxan® (cyclophosphamide) and the older therapies that we use to treat all types of cancer that caused hair loss and nausea and vomiting, these new biologic agents behave differently in different people. And because they're biologic and people have different biologies, that they can have different side effects. And so we definitely have to keep a more open mind when we do clinical trials with these new drugs that people can have very different side effects. But, yes, we did see some of that in the trial.

Joan Levy, PhD

Okay, next question from the telephone audience.

Operator

Thank you, our next question comes from Karen, calling from Michigan. Please state your question.

Karen from Michigan

Yes, my question is for either Dr. Cole or Dr. Krishnan, and it has to do with the feeling about continuous maintenance therapy post-transplant with a complete remission. And I understand this has been discussed widely at the ASH (American Society of Hematology) conference. I was taken off maintenance therapy of Velcade because of the potential of side effects, and I'm quite concerned about being off any maintenance therapy.

Craig E. Cole, MD

I think that there's been studies that have looked at maintenance therapies, either lenalidomide or Velcade and depending on an individual's cytogenetic risk, that there are different levels of benefit. In general, there has been a tendency towards delayed time to relapse; and the question of do people

live longer on maintenance therapy isn't quite clear. And I think the longer that we study this, the better clarity we'll have.

The one trick about maintenance therapy is that if it's causing problems, if it's causing toxicity, because maintenance therapy is a long-term plan, that maintenance therapy is usually given for two years or even longer. You have to have a pretty comfortable seat on that long of a train ride, and so if it's causing toxicity and causing problems and probably not to feel well, sometimes the risks and benefits may not be worth suffering through a maintenance therapy. And especially with the field just under such incredible research that hopefully we'll have better drugs that emerge.

But if it's toxicities, and it's not a bad idea to hold tight. If it's fear of toxicities, then it would probably be worth another discussion with your doctor. And go blue, go Michigan.

Joan Levy, PhD

Okay, we have time for one last question from the telephone audience.

Operator

Thank you. Our next question comes from Sharon, calling from California. Please state your question. Okay, and your line is open.

Sharon from California

Well, the antibodies have been talked about quite exhaustively, and I don't want to dwell on them. I'm just someone that's taking only the antibodies and nothing in combination, and I haven't heard very much about just using them exclusively. So, if I'm saying something you've already said, you can disregard the question.

Joan Levy, PhD

Dr. Krishnan?

Amrita Krishnan, MD, FACP

So, I would say, certainly daratumumab, there is absolutely nothing wrong with using it by itself. And, in fact, that's what the original studies were using it as a single agent. So, if it's working then there's really not a need that you need to add something else with it.

Now elotuzumab, on the other hand, really doesn't have much response by itself; and so that one really has to have, in conjunction with lenalidomide to optimize its response.

Closing Remarks

Joan Levy, PhD

[Slide 41] Okay, thank you. So, 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 of the wonderful questions. But what we have done in the past is to get back to each of you who have submitted questions online with responses from some of our faculty and nurses that work with 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 or call 1-866-603-6628.

I want to especially thank our speakers, Drs. Cole and Krishnan, 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 that program evaluation form. We at the MMRF are so proud to work with so many centers worldwide to bring these new treatments forward to you today, to bring studies like the landmark CoMMpass study forward, and to make the gateways publically available. 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.

So, again, thank you so much to our faculty today and to all of you for joining us. 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 everyone.