Multiple Myeloma and the Immune System
November 12, 2015

Speaker: Rafael Fonseca, MD

Slide 1. Welcome & Introductions

OPERATOR:
Greetings, and welcome to Multiple Myeloma and the Immune System telephone and web education program.

It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you, Ms. Rivera, you may begin.

LIZETTE FIGUEROA-RIVERA:
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), I would like to welcome all of you.

Special thanks to Dr. Rafael Fonseca for sharing his time and expertise with us today.

Before we begin, I’d like to introduce The Leukemia & Lymphoma Society’s Vice President of Patient Access and Outcomes, Elisa Weiss, who will share a few words. Dr. Weiss, please go ahead.

ELISA WEISS:
Thank you, Lizette. I’d like to add my welcome to the patients, caregivers, and healthcare professionals attending the program today from around the world.

The Leukemia & Lymphoma Society exist to find cures and ensure access to treatment for blood cancer patients.

For more than 60 years, LLS has helped to pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and the quality of life for many blood cancer patients.

To date, we have invested over $1 billion in research to advance therapies and save lives.

Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this myeloma program demonstrates, we are the leading source of free blood cancer information, education, and support. We touch patients in their communities through our 61 chapters across the United States and Canada. And through our very knowledgeable Information Specialists, who make up the LLS Information Resource Center. These Information Specialists answer phone and email requests from all over the country.

LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate cancer treatment and ensuring they have access to quality, affordable care.

We are very fortunate to have as our presenter today Dr. Rafael Fonseca, one of the nation’s leading experts in multiple myeloma. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I’d like to thank him for providing us today with important, up-to-date information on multiple myeloma.

Thank you all. And now I’ll turn the program back to Lizette.
LIZETTE FIGUEROA-RIVERA:
Thank you, Dr. Weiss. And we’d like to acknowledge and thank Bristol-Myers Squibb, Celgene, and Novartis Oncology for support of this program.

Slide 2. Multiple Myeloma and the Immune System

LIZETTE FIGUEROA-RIVERA:
I am now pleased to introduce Dr. Rafael Fonseca, Getz Family Professor of Cancer and Chair of the Department of Medicine at the Mayo Clinic in Scottsdale, Arizona. Dr. Fonseca is also Associate Director of the Center for Individualized Medicine at the Mayo Clinic.

Dr. Fonseca, I’m privileged to turn the program over to you.

Slide 3. Disclosure

DR. RAFAEL FONSECA:
Thank you very much and welcome, everyone. I will be talking over the next hour or so about myeloma. And we decided to put a special emphasis on the immune system, both because of the relationship that myeloma holds to immune cells and our immune system, but perhaps more importantly because of what we’re learning about immunity, and then how we’re going to be able to use a whole new set of tools that belong in immunotherapy for the treatment of the disease.

And again, you’ve heard about the support we have from various companies who have made this program possible, with whom I’ve worked over the past several years.

Slide 4. Multiple Myeloma

Now for multiple myeloma, it’s a relatively common hem-disorder. It’s really only second to non-Hodgkin’s lymphoma. And in the United States alone the last few years show that there’s 24,000 new cases that will be diagnosed. And one interesting feature is that when you look at myeloma, alongside with prostate cancer, this is one of the cancers that has the greatest difference in incidence between African-Americans and Caucasians, and it’s twice as common in African-Americans.

People have done studies looking at blood samples from a blood bank in Ghana, where we actually know now as well that the prevalence of the pre-malignant condition—and we’ll talk a little bit more about this later, the MGUS (monoclonal gammopathy of undetermined significance) —is also twice as common there than it would be in Caucasians. And part of this is believed to have some genetic component and perhaps one of the key drivers, although this hasn’t been completely elucidated, is the ability to mount immune responses with different intensity. And again this is something that we continue to investigate, and others as well, too, to see if we could understand the reason for the differences better.

Slide 5. Plasma cells and Immunity

Now I know we have a lot of people, and some of you may have more expertise in understanding some of the immune system, but just so that we talk about the general background, as you know inside our bones, in the space we call the bone marrow, is where we contain the majority of cells that circulate in our blood and that includes, of course, the usual, the red cells, the platelets, but also includes the white cells. And it is within this population that we call the white blood cell or the white blood cell count, that we have the majority of cells that are associated with immunity.
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Dr. Rafael Fonseca:
Now if we just talk about the white cells, we still are talking about a very broad group of cells, and it turns out that myeloma is a cancer transformation of one of those subtypes of cells, the so-called plasma cells.

I show those cells on the right side of your screen. The plasma cells belong to the subclass of white cells that we call the B cells. And they really are the most mature form of B cells. These are cells that were primed all through their development to produce these proteins that we call antibodies. And you see a set of plasma cells there, pushing out antibodies into the blood stream. The cartoon tries to show that those antibodies, what you see, like little Ys there, sort of bind to something that is not part of our body, a pathogen, that is a virus or a bacteria. And then the rest of our system actually recognizes that and goes and attacks that. So these are really ways—a very smart way, very elegant way—in which our body can tag elements that are not part of our body, that indicate the rest of our immune system to go after and attack them and get rid of them.

And normally this is a very, very well coordinated process. Every now and then when a mistake occurs in the process, most often because of a small change in the genetic content of those cells, this leads to the expansion of those cells, the uncontrolled growth of the cells, and that’s what gives rise to myeloma and related conditions.

And all of you who are familiar with the disease will immediately recognize that it’s because of the protein production that we can use that as a marker to gauge the disease response to treatment, to make diagnosis, and so forth.

Slide 6. Antibodies
If I took a very powerful microscope and expanded it greatly, one of those little Ys, one of those antibodies, it would look something like this. And what you would see is that it’s a molecule that’s formed by four components. There’s two of what we call the heavy chains, those are shown in blue there. The part that is light blue, that’s the part that becomes very specific and binds to those viruses and bacteria. And the darker blue is what prompts the immune system to go after whatever is bound there. So we have two of those usually.

And then we have two of what we call the light chains. Those are shown in the red and pink colors. For reference, the blue chains can be of any one of five types. But most commonly they’re either the alpha, gamma, or mu, which would make this protein be an IgA, an IgG, or an IgM. And that’s why when we talk about immunoglobulins, we are characterizing the type of heavy chain.

Now they circulate for the most part, bound like this foursome. And then you have two of the light chains, and again you know that these are kappa or lambda.

Each one of those cells that commits to form part of our immune responses has to choose one heavy chain and one light chain, and for the rest of their lives they will only produce that. So for instance, plasma cell that is responding to a specific bacteria will produce an IgA lambda and that will stay like that forever.

So when one of the cells becomes abnormal and starts growing excessively, then it will produce the very high concentrations in the patient’s blood of the IgA and the lambda, and that’s why we will use that for monitoring. And we’ll talk a little bit more about the specifics on that later.
Slide 7. Importance of progression events

**DR. RAFAEL FONSECA:**

When we talk about myeloma and related conditions, we have to make a very important distinction between those patients who have the early stages or the benign stages of the disease, and those patients where treatment is really indicated.

As a community we’ve come together with this acronym of CRAB, which denotes the four key areas that we have to be looking after when we try to decide if a person needs treatment.

Now I always say, as a pneumonic, that CRABs have dangerous parts. That is the claws and they’d have not-as-dangerous parts, which would be the legs. Now in my mind the not-as-dangerous parts are those that relate to a low red cell count, and that’s the A for anemia, or the elevated calcium. Because while those two can be problematic, we can usually treat them with our medical interventions and they usually are reversible, so they tend not to be long-lasting.

Now the claws of the crab are what I show in the bottom part of this slide. R is for renal and that is the problems associated with kidney disease, and we’ll talk a little bit more about this. And B is for bone. And while we have things that can help fix that and sometimes can reverse some of the problems that occur there, some of the more serious complications can be very long-lasting. And they will have, of course, significant implications for quality of life of a person.

Now one of the key things we have to do is we have to be able to distinguish which patients are at risk for the R, for the renal problems, and that picture shows a lady who’s sitting, associated with a hemodialysis machine, which in this case replaces the kidney function and, unfortunately, can sometimes be a life-long necessity for the person.

Slide 8. Renal Metabolism of FLCs

I showed you before the immunoglobulins, that Y, and I told you that we have two of those light chains. Well, it turns out that those light chains are small enough, and as you know they’re smaller than the heavy chains, but they can actually filter down into our urine, and that’s what I pretend to show with this particular cartoon. This is a medical cartoon that shows you what a microscopic kidney structure looks like. These are little filters. You see the blood vessels on the top left, and from there water comes through and other salts come through, and that comes down and then goes through this tubule system and ultimately collects as urine.

But if you do have a lot of these free light chains, they can end up plugging the kidney structures. There’s a little box in the center of this slide that says cast injury. And what it means is that in patients with myeloma, who have a very high concentration of these light chains, that may plug the kidneys, for the lack of a better word. And that’s one of the markers that we use now to try to determine who may be at risk for renal problems. And then again some of those basic principles of understanding immunity and the types of the protein that we have, will allow us to determine who’s at greater risk, who may need additional interventions, and who we need to monitor more closely.
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Slide 9. Bone Lytic Lesions

DR. RAFAEL FONSECA:
The other part I mention is bone lesions. And this is a slide that shows on the right side, for instance, the skull of a person who has myeloma. And you see those darker areas, those darker circles, which are characteristic of the lesions that are induced by multiple myeloma.

Now those lesions in the skull tend to, of course, be concerning and as we discuss with these patients, this is potentially problematic. But actually they tend not to be of any serious consequence. So we know they’re there, we use them to make the diagnosis. It is those lesions that are associated with either the long bones, those bones that are going to be weight-bearing, or the destruction of the vertebral bodies in the spine, that will create greater problems for the individual.

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Slide 10. Sensitivity of methods for detection of FLCs

Now one thing I would urge you all to do, if you’re not doing this, is that as you talk to your doctors, one of the key tests to be done is this free light chain. And that’s shown here by this three letters, FLC. That’s for free light chain. It is very important that it contains that word free because that’s a very specific assay that is known for its detection.

What I show you here is how sensitive it is compared to all the other tests that we have normally for monitoring myeloma. All the ones in red are blood tests. The one in yellow is the urine test, the urine collection. And the one in blue is the serum free light chain. And it is important, of course, because of the problems I previously alluded to, with regards to the kidneys. But also because this is a test that allows us to go way down in measuring the concentration of these proteins.

More and more people are doing this. This is still something of a revolution. But again I would urge you to discuss this with your doctors because this could become a very important marker under certain circumstances.

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Slide 11. Progression of the Disease

Now again, going back to how we classify myeloma, in this particular slide in the center, I show on color pink what we call active myeloma or just simply multiple myeloma. On the left side you see the two preceding stages, MGUS or monoclonal gammopathy, then the so-called smoldering multiple myeloma.

These are two conditions that I wanted to mention during the conference today because in general patients are asymptomatic and should have no consequence. There is perhaps a suggestion that some of the patients with more advanced smoldering may have potentially some affliction of the immune system, but for all practical purposes, someone who has MGUS or smoldering, and after you have a detailed discussion with a physician, should really try to carry on as much as possible a normal lifestyle. And there should be no limitations.

I have occasionally seen patients who have been told, for instance, to restrict their travel or not engage in certain activities, and I would say that in 2015 someone who has smoldering can really carry on with activities as anyone else would.
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Slide 12. Importance of progression events

DR. RAFAEL FONSECA:
I previously showed you the CRAB. And in years gone by, about five years ago, it was almost a badge of honor for myeloma doctors to say we don’t want to treat too early because we don’t want to intervene before we really have to. But then that is, of course, something that is helpful because a lot of patients can be spared treatment for a while, but of course the question was asked, are there some patients where one should consider treatment before we get those claws of the crab to create damage.

So an international group got together, and this was published just recently by Dr. Vincent Rajkumar and was published in the journal *Lancet Oncology*, where they looked for other markers that may tell you that progression to the aggressive version of the disease may be closer. And they came together, arbitrarily, they said let’s see if we can find some markers that would tell us about a risk of progression of 80% within the next two years.

Slide 13. Importance of progression events

And after some work they were able to come with these three recommendations. This is important to note. The first one was what medically we call extreme plasmacytosis. And that means that if you do a bone marrow, there’s a very high proportion of this abnormal plasma cells, usually we talk about 60% or greater. I previously mentioned also the light chain. If the light chain numbers are very, very high, such that the ratio of the abnormal versus normal is over 100, then one could also consider treatment at that point. Or if a person has an MRI done—and that is not to say that everyone should have one at the early stages—but if you have an MRI done and there’s more than one focal lesion, this would make the medical team worry and think about the possibility of progression in the near future. So those are things that need to be considered.

Slide 14. Prevalence of MGUS

These disorders of the immune system, and myeloma is obviously a cancer version of the plasma cells, actually tend to be quite common. And the classic studies have been done by Dr. Robert Kyle. He has looked at large populations of patients and has shown that if you look at patients, for instance, who are age 50 or greater, up to 3% of them will have the protein abnormality. And one goes over the age of 85. So up to 7.5% of patients have that. So this is a pretty high number.

And this is important because just the protein presence alone is not an indication that the person has cancer or that the person requires treatment. And perhaps one of the most important consults we do is that we actually have to make that distinction of who has the early stages and who has more advanced stage where treatment is actually indicated.

Slide 15. General Principles

For those of you in the audience, just medically speaking, I showed you that heavy chains can be one of three types predominantly. When we talk about myeloma and a person who has an abnormal protein, it’s usually of IgA or IgG. If a person has IgM, and that’s why I put that in my first line, the IgM usually talks about a different set of disorders. There are some rare exception to this, but someone who has an IgM monoclonal protein will not progress to multiple myeloma. It’s more associated with a sister disease that we call Waldenstrom’s (Waldenstrom macroglobulinemia).
DR. RAFAEL FONSECA:
And it’s very clear that patients who have low levels of this protein, such as a serum concentration of the M spike or the M protein of less than 1.5, a normal free light chain or the IgG type, they will have a risk of progression of less than 5% over 20 years. So if you have those three criteria, the risk of progression to myeloma is actually quite low. And below I put some of the signs that we would normally educate physicians and residents about things to look out for.

Slide 16. Smoldering Myeloma
Between this MGUS and multiple myeloma, again, we have this smoldering myeloma. And smoldering indicates by its name that one is at greater risk for this being active. So much so that if a person gets a bone marrow biopsy and they have greater than 10% plasma cells in their bone marrow, we would call them a smoldering, and the implications are quite important. If a person is diagnosed with MGUS, and this is shown in this graph here, about 1% per year of them will have to go on to the active phase of the disease, to myeloma. So what we call the risk of progression is 1% per year. So at five years, what you see on the X axis there, you see at five years, we say 4%, at 10 years 10%, at 15 years 16% and so forth. So it’s a pretty fixed risk of progression, which is rather small.

In contrast, and you see that on the top curve, the one that is shown there with smoldering multiple myeloma, for the first five years after a person’s diagnosis, the patient has the risk of progression of about 10% per year. Meaning that at the end of five years a person with smoldering has a risk of up to 50% of progression, and then that over time tends to even out and then looks more like the actual risk of progression of MGUS.

Now the only way we can make the distinction between the two situations is by doing the test, that is the bone marrow aspirate biopsy. Fortunately it’s something that does not need to be repeated often, but if one is interested in clarifying further whether someone has smoldering or MGUS, a bone marrow test must be done.

Slide 17. Multiple Myeloma Treatment Lines
I’m going to show you a few slides regarding treatment. And I want to highlight some of the things we’re doing for treatment. And these are sort of the usual phases of treatment induction, which is shown there in the orange box on the left. It’s of course the first treatment the person gets, just to get things under control and clean out the bone marrow. The consolidation phase, usually we do stem cell transplant. I will not say a lot about it, but suffice it to say that in 2015, the community thinks that the majority of patients should be treated with stem cell transplant. At an upcoming meeting, many of you know the American Society of Hematology (ASH) meeting, which is happening just in three weeks, a very important large study will be presented, where stem cell transplant is being compared with the novel agents alone, that is without stem cell transplant, and it still appears to show superiority. So for the majority of patients we do consider stem cell transplant an important aspect of treatment. And then maintenance strategies. And if the disease were to come back, of course, strategies for rescue.

Slide 18. mSMART SCT Eligible
Now we at the Mayo Clinic have elected to come together as a group and provide some treatment recommendations. So I won’t walk you through all of this, but I just wanted to highlight a couple of things.
DR. RAFAEL FONSECA:
This mSMART has been published and it’s available on the web. It’s mSMART.org. It represents our consensus approach for treatment recommendations for myeloma patients. And this is constantly being updated. And again we won’t go through all the details, I’m just going to highlight that at the very first level what you see there with the blue boxes, we look at what we call risks, so we try to make classifications according to the risk of the disease. And then subsequent to that we make specific recommendations for treatment. And again this is research that’s available to you. It’s meant to provide guidance to healthcare professionals regarding what are some of the treatment options. And of course this has to be always tailored to individual aspects of the patients and sometimes other health issues that may dictate to go one way or another. But again mSMART.org.

Slide 19. Long Term Outcomes after SCT in MM
Before I go into some of the novel treatments, I’m going to start by showing you some data regarding the outcomes with stem cell transplant. And of course this is always a big proposition, it’s a scary proposition. So when I meet with patients and we get the question, what do I want to achieve with the stem cell transplant, I frequently will cite the study from Dr. Martinez from Spain. It was published in 2011. And they looked at very long term outcomes of myeloma patients who underwent stem cell transplant.

Now what they did is they broke down the patients into those that attained what’s called a complete response, those that had a response but not quite complete, meaning they still had some detectable protein, and then those patients that really didn’t respond to the treatment itself, the transplant treatment.

Slide 20. CR vs nCR/VGPR/PR vs less
And these are the results. The blue curve shows those patients that attained a complete response, the red curve those patients that have a response but not quite complete, and again the tan colored line shows patients who had either stable disease or who progressed.

Now if you see the X axis here, this is a follow-up of 20 years in the bottom, on the left side you have what we call progression-free survival. What that means is that every time a patient requires a next line of treatment, a new treatment, the curve will drop down a little bit. And if you follow the blue curve, you will see that it flattens out some time around 10 to 15 years. So what that means is that even with 20 years of follow-up, about a third of the patients having achieved a complete response will not require any further treatment. In this particular study a third of the patients were here in this blue curve, so a third of a third means that about 10% of patients would need transplant as the last treatment for their disease.

For the patients who are in the other two curves, the red or the tan, that is a group of patients that, of course, at some point required a different type of treatment or additional treatment. But what this study shows us, as you see again on the left side, is that there are some patients for which transplant can be a definitive treatment.

Now with some of the more modern approaches we think we can put a larger proportion of patients into the blue curve, and if these principles hold true, then hopefully a growing number of patients will be controlled very long term from their disease.
Slide 21. Dexamethasone

**DR. RAFAEL FONSECA:**

Now just to humor you a little bit, and since we were just passing through Halloween, I'm going to say that this is dexamethasone. Dexamethasone is truly a hard part to deal with when it comes down to myeloma therapeutics and that’s why I put that little devil there. Dexamethasone is a steroid. As all of you know, this is something that we use frequently in combination with some of the other drugs. The reality is that dexamethasone augments the response of many of the treatments we have, so it does work well. People often ask what does dexamethasone do, isn’t this like a steroid like prednisone? Yes, it is prednisone. It turns out that immune cells and plasma cells and B cells and all the cells in our body, when they’re exposed to steroids, they have this internal program that signals for them to go on and die. And that’s why we give dexamethasone in combination with our regimens. Now we’re fully cognizant that this is one of the hardest parts of treatment. The sweetest person can get a little bit edgy and sometimes family members don’t like us when we do this. This derails the sleep pattern and has so many other consequences, so just know that there’s a lot of people interested in finding alternatives to this, perhaps modulation of the doses, and the proper management of dexamethasone is one of the key aspects of proper management of multiple myeloma.

Slide 22. IMIDs

We have another group of drugs, and I’m sure many of you are familiar with them, that are called IMIDs. The IMIDs are old derivatives of thalidomide. Thalidomide is shown there on the left. You see the molecule. And then we have the second generation, which is lenalidomide, and the third generation, which is pomalidomide on the far right. As you can see, the molecules are actually quite similar. Thalidomide on the bottom part has that—for those of you who are chemistry aficionados—you see has that oxygen, the hydroxy group. Then lenalidomide has the NH2, the amino group. And pomalidomide combines them both, the NH and the oxy group.

And while they’re structurally very similar, they’re quite different when it comes down to side effects and potency. In the United States we don’t use thalidomide that much more, unless under special circumstances, and primarily because patients who get thalidomide on the long term will develop sensory neuropathy. So they will have the neuropathy primarily with a numbness and feeling abnormalities. That is uncommon, I would say rare, almost non-reported both with lenalidomide and pomalidomide. And they also have higher potency, so that for instance, patients who have been treated with lenalidomide and can do well, even if they progress sometimes, they will respond to pomalidomide.

Slide 23. Journal of Clinical Oncology Original Report

Now speaking of this last drug, this is a graph from the paper published by one of my colleagues, Dr. Lacy, who’s at Mayo Clinic in Rochester. What you see there in blue is actually the reduction in the concentration of the protein. And it’s in order from those that respond the least to the ones that respond the best, to the far right. And on the Y axis here where it says change from baseline, you can see 100%. And there are some patients that will have a complete response to pomalidomide, and I’m showing this to highlight some of the possibilities that we have with these new medications.
Slide 24. Pomalidomide in MM

DR. RAFAEL FONSECA:
This is a patient of mine. What you see there is the PET scan. If you're not familiar with them, you'll see this is obviously a full body image. We see the brain takes quite a bit of that glucose that we use in the PET scan. You can sort of see out the shapes there for the liver and the heart. And you see those big dark spots in the center, which are the kidneys. Of course they concentrate the tracer that people get in PET scans, that's then subsequently concentrates in the bladder. But what you see some time around where you could imagine the groins of this patient are, you see all those black spots, it's kind of like a smattering of black spots, those are all lymph nodes. And these were lymph nodes in a patient who had received already five or six lines of treatment. We treated this patient with pomalidomide and that gave us another year of disease control. So that's just to highlight some of the effects that we can get with some of these new medications.

Slide 25. IMIDs and Vaccinations
Since we're talking about the immune system, one of the things that is actually quite interesting is that the IMIDs, and again this whole group of drugs, has an interesting effect that they can augment the immune response, and I'll walk you through this slide. My colleague Dr. Borrello, who's at Johns Hopkins, asked the question, okay, if we give vaccinations to myeloma patients, what happens if they're getting the lenalidomide, the Revlimid®? So on the left side, what says cohort A, are patients who were vaccinated before they were on treatment. And cohort B is patients who were vaccinated while on treatment with lenalidomide. And what you can see in those two graphs, which is particularly notable on the right side, is that the higher those bars go, the better the response of the vaccine. And he was able to show actually that vaccination provided better responses when the patients were on treatment. So this is something we're hoping to use as we learn more about the immune system and ways to go about the treatment of myeloma.

Slide 26. Mechanisms of Action: Proteasomal Inhibition
The other group of drugs that is very important for the treatment of the disease, and are part of the backbone for this, are what we call proteasome inhibitors. In this slide what you see there, what's called is a substrate, which is about right there in the center of the slide, is just something that exemplifies a protein and proteins are inside the cells. And then when the cells don't need proteins any more, they send to the garbage disposal, which you see there in orange with all those purple and tan circles. And the myeloma cells produce so many proteins that if you disrupt this it's like just blocking one of the main thoroughfares in a large city. Creates chaos and the cells die.

Slide 27. Proteasome Inhibitors
We have a number of proteasome inhibitors that are used in the clinic, so we use bortezomib—the Velcade®. Carfilzomib as well, too, is available commercially. And there's a number of other proteasome inhibitors that are in development, such as the ones shown there. There are some clinical trials that will be presented soon that will highlight the importance of the oral medications for this.
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**Slide 28. Bortezomib and Carfilzomib**

**DR. RAFAEL FONSECA:**
Now the FDA has approved these drugs for use. I won’t go into too much of the details. But I’ll just say that both of them are part of our armamentarium, both for the treatment up front and also as a rescue strategy.

**Slide 29. APEX Clinical Trial**
The main study that led to the approval of this drug was called the APEX trial and this is again something that shows in the blue curve, it’s similar to what I showed you before, this need for next treatment was actually pushed out in patients who had the treatment with the bortezomib, with the proteasome inhibitors.

**Slide 30. Transplant Outcomes**
Also if we use them up front, you’ll see there now shown in orange, the proportion of patients that actually would fall into that blue curve from the Spanish studies, which really show that we can put a larger number of patients into this complete response category. And again our hope is that this will translate into very long-term benefits for patients and outcomes.

**Slide 31. Single-Agent Carfilzomib: Heavily Pretreated Patient Population**

**Slide 32. Single-Agent Carfilzomib: Response Rates**
Carfilzomib is the other one we use and I’m just going to show you very quickly here that it has significant activity in patients who have been treated before. And it turns out it’s really one of the most powerful proteasome inhibitors we have. This remains an intravenous medication, it’s something that we’re using mostly in the setting of clinical trials as front-line therapy for the disease, but is also backbone now for the treatment of disease that has come back.

**Slide 33. Proteasome Inhibitors – Zoster**
Since we’re talking about the immune system, I just want to tell you one of the very important aspects is that patients who are being treated with either carfilzomib or the bortezomib, the two injections for proteasome inhibitors, the Velcade® or the Kyprolis®, they need to be put on prophylaxis with an anti-virus medication. This is the acyclovir. Acyclovir greatly prevents herpes zoster, the shingles. In the absence of this, about one in six patients will develop shingles. So we really want to make sure we stress that patients who are put on this drug should be taking their acyclovir, unless your doctor tells you there’s another reason why you’re not receiving that medication.

**Slide 34. ASPIRE Study Design**
I’m just going to show you briefly that as we have found that these drugs work well alone, they also work great in combination. This is one study that my colleague Keith Stewart presented, which is called the ASPIRE study. This looks at the combination of three drugs, in this case carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone for patients who were previously treated. And now that you’re familiar with the curves you’ll see once more that the yellow curve is being pushed out further.
Slide 35. Primary Endpoint: Progression-Free Survival

DR. RAFAEL FONSECA:
In this case I'm just going to draw your attention to the actual number. What they say median progression-free survival, so that means what's the median time until which the patients needed the next treatment. It doesn't mean that every patient is going to have this time. It just means that if you take 100 patients, about half of them will, you know, about right in the middle, will have the need for additional treatment at this time. And with the three drugs, that was in the axis of two years, whereas with the two drugs was 17 months. So one step further in progress towards controlling the disease.

Slide 36. Secondary Endpoints: Response
I'm just going to say that when you look at this three drug combination, and now on the left side you see what we call complete response or better, you see that yellow bar that shows that up to one-third of patients will respond quite nicely to this medication.

Slide 37. Adverse Events (AEs), Treatment Discontinuations, and Deaths
And in general this was very well tolerated. This is just a table that shows what proportion of patients had to discontinue treatment and where it says discontinuation due to AE, that means that patients had to stop treatment because something was happening with the drug that was being too toxic. And in this case it's 15.3 versus 17%, meaning even with three drugs a similar proportion of patients ended up discontinuing their medication. So it was well tolerated.

Slide 38. Other AEs of Interest
And I won't get into the details of some of the toxicity that we're trying to understand better, but certainly peripheral neuropathy, which is the second line, was no different between the two treatment arms.

Slide 39. KRD
Now people are asking this question. I'm just going too briefly show that the same type of can be used both in the front-line setting as well as in the setting of a second- and third-line treatment. This is one of several studies where Dr. Jakubowial shows that a high proportion of patients, and depending where you do the cutoff, actually have very deep responses.

Slide 40. Abstract 538 and Abstract 3220
Those are best shown here by the graph on the right. If you see what's there in orange, again, those are the patients that have the complete response, that in the Spanish study would have fallen into that blue curve, and with this combination, even before the patients would have a transplant, about two-thirds of them fall into this complete response category.

Slide 41. Response
And similarly we see that with other studies like this one from Dr. Mikhael, where he presented a combination of carfilzomib, cyclophosphamide, and dexamethasone as a highly active combination for the disease.
Multiple Myeloma and the Immune System
November 12, 2015

Speaker: Rafael Fonseca, MD

Slides 42–44. Treatment of SMM

DR. RAFAEL FONSECA:
Going back to transplant, I’m going back to smoldering and am going to mention briefly that people are asking the question, well, if you’re working to identify patients that can progress, can we do something about them. This is a very important study from the Spanish group again, Dr. Mateos. Where they asked the question can we treat early stage disease of smoldering myeloma. What they did is they selected patients who had very high-risk disease. They established some of the criteria, for instance, a very, very large number of cells in the bone marrow. And they were able to show that in fact early treatment was beneficial. And the curves there in different ways show that the time to next treatment and the survival numbers were quite favorable.

I will stress that in 2015 in our clinics we don’t recommend treatment for smoldering myeloma. But academically everyone is asking the question should there be some circumstances where we should consider this earlier on and you’ll see many more clinical trials coming out like that in the future.

Slide 45. Phase II trial for high-risk SMM
As an example of this, there are trials conducted by Dr. Landgren looking at again high-risk smoldering myeloma with the same three drug combination that I mentioned previously. And even though it has a low number of patients, you see that after eight cycles—and many of you are familiar with the term cycle, it’s usually about eight months—and again even with low numbers.

Slide 46. Response rates in relation to cycles of carfilzomib/revlimid/dex
One hundred percent of patients had achieved almost a complete response. So again this makes us all scratch our head and beg the question, should we be considering additional treatment earlier in the stages with the disease?

Slide 47. Daratumumab
To close, I’m going to show you just a few slides of some of the things that are going also with various immunotherapy approaches. There’s these antibodies that target one of the markers of myeloma cells. This marker is something we call CD38. What it is just a molecule that’s present in the surface of myeloma cells that can now be identified with an antibody that has been produced, so ironically a cell that produces antibodies, now we’re attacking it with an antibody, so the rest of the immune system actually fights it.

Slide 48. Targeting CD38 with Daratumumab
There’s a competing compound, something called isatuximab, which is another antibody that is being used for this purpose. You can think about these drugs pretty much like you would think about antisem. So this is something that’s infused into the vein. It’s a larger molecule, we have to watch out for reactions. But when we give it this has the ability to kill myeloma cells and this is just again one example. On the right side I show you what I previously called a cascade plot, so the further down the bar goes the better. And you see that patients who have extensive prior treatment still can have very significant responses to this agent.
Multiple Myeloma and the Immune System
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Speaker: Rafael Fonseca, MD

Slide 49. Dual mechanism of action by both directly activating NK Cells and through antibody-dependent cell-mediated cytotoxicity (ADCC)

DR. RAFAEL FONSECA:
There’s another molecule that’s called elotuzumab. This is an antibody that targets both myeloma cells and another part of our immune system, something that’s called NK cells. Those NK cells are a little bit more specific and they’re sort of professional killers. They find cells that shouldn’t be in our body and goes and kills them. And this elotuzumab drug, it turns out, it doesn’t work on its own, so even if I had it commercially available and I prescribed it for a patient, they wouldn’t be able to respond.

Slide 50. Elotuzumab Synergizes with Lenalidomide to Enhance Myeloma Cell Death
But if I go and I combine that with lenalidomide, again, and dexamethasone, it seems to trigger a very interesting cascade effect, where actually early studies showed some significant activity.

Slide 51. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma
And just very recently one of my colleagues, Dr. Lonial, presented this study where once more on one of those curves, he shows that the three compound was better than the two. And again the absolute number for those results continues to improve. So I think this is one step forward in treatment options for multiple myeloma.

Slide 52. Chimeric Antigen Receptor T Cells
Last but not least, I just want to show very quickly something you’re hearing about other diseases, something called the CAR-T cells. The CAR-T cells have been used extensively in other conditions, primarily leukemia. There is one patient that has been treated and was reported in this New England Journal paper just recently. This is a paper not without controversy. There’s some caveats and questions. But it just highlights the potential that we have now by priming and sort of training, if you may, immune cells to go after the myeloma cells and directly kill them. But again you’ll hear more about this. These are the so-called CAR-T cells, which are truly just designer cells to go and kill the cancer cells.

Slide 53. Follow-up from diagnosis
I started showing you many slides. I’m going to show you one last slide and this slide shows what has happened over the last several decades in the treatment of multiple myeloma. As you can see, the higher up the curves the better it is. In the years 2005 to 2010, we still see some progress as compared to 2000 to 2005. We don’t have the numbers here from 2010 to 2015, and of course in just a very short time we’ll be starting the curve for 2016. So while we fully recognize that we don’t have the final answers, we are hopeful that there will be continued progress and that we will have a brighter future for the treatment of the disease.

Slide 54. Teamwork
This is obviously efforts of many, many people at academic centers, supporting agencies, research institutes, and certainly a big part of the collaboration we have with the pharmaceutical companies and the biotech sector.
**Slide 55. Question-and-Answer Session**

**DR. RAFAEL FONSECA:**
And with this we can address some questions. I will thank you for your attention, and we'll pass on now to the question-and-answer session. Thank you very much.

**LIZETTE FIGUEROA-RIVERA:**
Thank you so much, Dr. Fonseca. It is time for the question-and-answer portion of our program.

We'll take the first question from our web audience. Doctor, Kathleen asks what can I do to support my immune system to better handle myeloma? I have been in full remission for four years and five months and work at staying in remission, and I know my immune system is critical to that, so any information on how to support it will be greatly valued, thank you.

**DR. RAFAEL FONSECA:**
Sure, thank you, that’s a very important – it’s a common question we get. When we talk about the immune system, we’re talking about a very, very complex thing. And I always warn patients, there’s nothing we can do that would be an intervention per se that would restore immunity. We want to prevent things that will damage your immunity, so for instance in a person who has received treatment, we would like to only use the treatment we need, we would like to not use as much of the steroids that we do. But there’s not per se an intervention from the medical side that we can do that will restore your immunity.

And I caution patients, sometimes people will say, well, there’s a supplement that quote-unquote boosts your immunity. That would be like taking a supplement that quote-unquote boosts your intelligence. We really are talking about similar complexity of things that you can’t really just do with a supplement or a pill. Of course, you can do things that are wellness, that will relieve the stress of your body. And we want people to have mindfulness, we would like people to engage obviously in a healthy diet, we want people to engage in some physical activity. And it doesn’t really have to be exercise, but just simply walk and things like that that could actually boost some of our natural body responses to boost that immunity. Those would be very, very important.

**LIZETTE FIGUEROA-RIVERA:**
Thank you, Doctor. And we’ll take the next question from the telephone audience, please.

**OPERATOR:**
Our first question comes from Elizabeth from Michigan. Please state your question.

**ELIZABETH:**
Hi. I’ve been on a low dose Revlimid® for two years, 5 milligrams, and dexamethasone 5 milligrams once a week. But I got excruciatingly bad cramps, and my doctor said she didn’t think it was from my Revlimid®, but I talked to the pharmacist and he said it was a very common side effect, so that was my call. I did go down to every other day with the Revlimid® for 21 days, and keep the dex every week. But I was wondering if you see that a lot.
DR. RAFAEL FONSECA:
You know, we do see that. I can tell you it is one of the medical mysteries to what causes cramps. If you go out and you read about cramps, people will tell you, well, you’re maybe low on potassium and magnesium. And certainly some of those things can cause cramps, but the vast majority of patients, 99%, don’t have any of those abnormalities.

But going back to your question, yes, some of the medications can cause cramps. We don’t really fully understand why. Sometimes we have to change doses. In the case of proteasome inhibitors, things like the bortezomib, we have to be careful because that sometimes indicates one of the components of peripheral neuropathy. I always tell me patients just make sure you stay well hydrated. Keep your legs warm at night. We see a lot of this with colder temperatures. Again, we don’t really understand why, but sometimes keeping the legs warm helps. There’s all sorts of folk tales about what may help with cramps. We don’t really have anything specific. And if they become problematic enough, we may have to change treatments. But usually it’s not a serious thing, it’s just a very bothersome thing.

LIZETTE FIGUEROA-RIVERA:
Thank you, Doctor. The next question comes from the web audience. Joyce asks about stem cell transplant and whether if the first transplant did not work, is it advisable to try a second time?

DR. RAFAEL FONSECA:
Well, it depend what that means, that it didn’t work. If a person has a stem cell transplant and shortly after the disease seems to be progressing, then our conclusion is that the transplant itself really doesn’t solve the problem of the myeloma for that person and we would tend not to do that again, at least not immediately. However, if a person had a transplant and three years later they had the disease come back, it would be one of the things that we would discuss as an option for re-treatment for the disease. So this is something that really it’s a highly individualized decision. If we had transplants obviously worked in a permanent way in everyone that would be great. But sometimes even just having the transplant add several years to our ability to control the disease, we would see that as something potentially good and, of course, the patient’s in the driver’s seat, but our counsel might be that the person could consider that again.

LIZETTE FIGUEROA-RIVERA:
Thank you. And we’ll take the next question from the telephone audience, please.

OPERATOR:
Our next question comes from Barney from Pennsylvania. Please state your question.

BARNEY:
Yes, sir, thank you very much for your very informative conference. My problem stems from bacterial meningitis. After my second time, my infectious disease doctor found an underlying condition. I don’t have the antibody that fights flus and colds. So they put me on immunoglobulin Gammagard®, and I found that that was – at the same time the underlying condition was multiple myeloma. And I found that the Gammagard® was made from human plasma cells. And my question is even though they’re clean and some doctors profess that they’re not really plasma cells that it’s made from, but my question is does the
BARNEY:
immunoglobulin have a balance to keep me – I’m nine years smoldering and I don’t take pills or anything.

DR. RAFAEL FONSECA:
That’s an excellent question. If someone has a low level immunoglobulin, you’re more prone for infection.
Now here’s what happens in myeloma. In our life as we go on, we get all these immunities, so every time you get an infection, you mount an immune response. So if you go down and look at the blood of a normal person, you would say, yeah, there’s a level of immunoglobulin, but as we break it down, it really is tens of thousands of different subtypes of immunoglobulin, each one of which will protect you against a different thing. In myeloma, the immunoglobulin is high, but that’s just because one of them is very, very high, but all of the others are in a very low level. So it seems ironic, but sometimes treatment with immunoglobulin will be indicated in someone who has recurrent infections.
Now the immunoglobulin usually will not protect from progression itself. We think that’s more of a—what we call sort of a bit of a more random process. But it certainly can protect you from recurrent infections. And I’m glad to hear, of course, the smoldering has been stable. Thank you.

LIZETTE FIGUEROA-RIVERA:
Thank you for the question. And the last question, Doctor, comes from the web audience. In myeloma, what alternative targets are there for T-cell immunotherapy, besides CD19? Are there any preliminary clinical results you can discuss with T-cell therapy, directed at alternative targets?

DR. RAFAEL FONSECA:
Well, thank you for the question. This is a very sophisticated question. My last slide, when I talked about the CAR-T cells, the cells were originally engineered to bind to this molecule that is called CD19, which is really not present, at least not in an abundant way, in myeloma cells. And I won’t get into all the technicalities of why there’s a controversy for this for that paper, but fortunately there’s many other molecules that are present in the myeloma surface, that can actually be used for that. So there’s some attempts at other molecules such as BCMA [B-cell maturation antigen], which is one of the other markers, but you can imagine there’s going to be more of this against CD38, CD138 and other markers that can be more specific. And people are getting really smart. Not only you can do that, but now we can also have switches that turn off some of the cells. So for some reason this sort of targeted cell, the very well trained killers, got out of hand. There’s also mechanisms to shut them down now.

LIZETTE FIGUEROA-RIVERA:
Thank you, Alma, for your question, which was our final question today.
Thank you so much, Dr. Fonseca, for your continued dedication to myeloma patients.
And for those of you who participated in today’s program, we hope the information presented today will assist you and your family in your next steps.
Slide 56. LLS Resources

LIZETTE FIGUEROA-RIVERA:
If you were not able to get your question answered today, please call The Leukemia & Lymphoma Society’s Information Specialists at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

The Leukemia & Lymphoma Society does have a Co-Pay Assistance Program for myeloma patients. To find out if you qualify, please call 877-557-2672, where a Co-Pay Specialist will assist you, or you may apply online at www.LLS.org/copay.

The Leukemia & Lymphoma Society’s Susan Lang Pay-it-Forward Patient Travel Assistance Program is now available to blood cancer patients with significant financial need who may qualify to receive financial assistance for approved expenses, which include ground transportation, air travel, and lodging-related expenses. To find out if you are eligible, you can call 844-565-2269 or visit www.LLS.org/patient-travel-assistance-program.

LIZETTE FIGUEROA-RIVERA:
Dr. Fonseca, thank you so much again for volunteering your time with us today.

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Goodbye and have a lovely day.

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