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WELCOME AND INTRODUCTION

TRANSCRIPT

Operator

Greetings, and welcome to the *Living With Myeloma: Managing Side Effects and Quality of Life* telephone and Web education program.

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

[Slide 1 – Welcome and Introductions] Lizette Figueroa-Rivera, MA

Thank you and hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Sagar Lonial for sharing his time and expertise with us today. We have over 800 people participating in today's program from across the United States and several countries around the world, including Brazil, Canada, Greece and Nigeria.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Senior Vice President of Research, Dr. Rick Winneker, who will share a few words. Rick, please go ahead.

Dr. Rick Winneker

Thank you, Lizette. I'd like to add my welcome to the patients, caregivers and healthcare professionals attending the program today. The Leukemia & Lymphoma Society (LLS) exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years, LLS has helped pioneer innovations such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. I'm very pleased that today you'll be hearing about some of those current and emerging treatments for patients with myeloma.

To date, we have invested over one billion dollars 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 program demonstrates, we are the leading source of free blood cancer information, education and support, and we touch the lives of patients and their communities through our 58 chapters across the United States and Canada. LLS also acts as the voice for all blood cancer patients. We advocate for patients, survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

We are very fortunate to have as our presenter today Dr. Sagar Lonial, one of the nation's leading experts in 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 information on myeloma. Thank you all, and now I'll turn the program back to Lizette.

Lizette Figueroa-Rivera, MA

Thank you, Rick. We would like to acknowledge and thank Bristol-Myers Squibb, Celgene Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, and Takeda Oncology for support of this program. If you have not already accessed the slides, you can view or print them from our website at www.LLS.org/programs. Following the presentation, we will take questions from the audience.



[Slide 2 – Sagar Lonial, MD, FACP] Lizette Figueroa-Rivera, MA

I am now pleased to introduce Dr. Sagar Lonial, Professor and Executive Vice Chair for the Department of Hematology and Medical Oncology and Chief Medical Officer at Winship Cancer Institute at Emory University School of Medicine in Atlanta, Georgia.

On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Lonial, I am now privileged to turn the program over to you.

PRESENTATION

Sagar Lonial, MD, FACP

Thank you very much, and I really appreciate the opportunity to be here and to present some material and information on myeloma for a couple of reasons. One, The Leukemia & Lymphoma Society really does an amazing job at trying to support many different aspects of patient care and research. As a former recipient of a Leukemia & Lymphoma Society Translational Research award, I can tell you the funding is really critically important for our ability to bring new treatments and new concepts into care. So, I'm really honored to be here and speak on their behalf.

What I'd like to do in the next few minutes is give you a little bit of a primer on what is going on in myeloma therapy, what are some changes that are occurring in terms of basic definitions that I think are really important for caregivers and patients to understand and then try and give you an insight into some of the future developments in terms of treatment options, and then leave it open after that to talk a little bit about questions and answers.

[Slide 3 – Disclosures]

Before we get too far, these are my disclosures. I do some work with a number of different companies, all of whom are trying to make new drugs and new therapies available to patients down the road.

[Slide 4 – Multiple Myeloma (MM)]

So, let's start off with, again, a level-setting concept here, and that is just to talk a little bit about some of the basics of myeloma therapy and myeloma in general. As you can see, in 2010 there were basically 20,000 new estimated cases of myeloma in the United States. It's estimated that in 2014 that number is somewhere around 24,000. It may not necessarily be that there's an epidemic of myeloma going on but more likely the fact that as patients are aging, we're starting to see things that occur more frequently when patients age. As you can see, the median age of diagnosis for myeloma is about 70 years now. But what we're also starting to identify is younger patients who have precursor conditions such as MGUS (monoclonal gammopathy of undetermined significance) or smoldering myeloma, and we're going to begin to touch on that a little bit in the course of the next few minutes as well. But, as you can see, because we're doing more frequent testing, patients are going to the doctors more often; we're starting to pick up things a little bit earlier in routine bloodwork that we weren't picking up about ten or 15 years ago.

Now, the median survival data that I'm showing you is actually very old data. This is data from the early 2000s where the median survival with conventional therapy was three years and the median survival for patients who had high-dose therapy and autologous transplant was thought to be four to five years. I can tell you at least from retrospective analyses done at our own institution, for standardrisk myeloma patients, we expect the median survival to be in excess of ten years, with a median expected survival for almost all patients of somewhere between five and seven years, and most of them leaning towards the seven- to ten-year range. So, the treatments that we've got access to now that we didn't have five or six years ago have really been critical in our ability to change what I call the natural history of myeloma.

Finally, if you start to look at population incidence, it is slightly more frequent in men than in women. That's about 60/40, so not a big difference there. But what we do notice that is really intriguing is a higher incidence among African Americans, and that doesn't just apply to myeloma in general. That actually applies to the precursor conditions of MGUS or smoldering myeloma as well, which tend to occur much more frequently in African Americas; the average age of presentation for an African American with myeloma is, on average, ten years younger than a non-African American. So, there may be some biologic reasons why that occurs in terms of genetics, and we're privileged to be part of a multicenter trial that's being done across the country where, actually, patients from Georgia contributed the largest fraction of material. We're actually going to sequence the DNA of African American patients with myeloma to try and better understand why that risk seems to be higher.

Finally, I'm going to show you some data towards the end that speaks to what I would call long-term control and maybe even cure in a fraction of patients with multiple myeloma, which is a word we've hesitated to use in the past but I think is a word that we should begin to use more frequently. We just need to work on increasing the fraction of patients who achieve that long-term disease control or cure.

[Slide 5 – Multiple Myeloma - Description]

So, let's go over some basics about myeloma. Some of you may be caregivers or family members that have not accompanied your loved ones to the office and so may not have had the opportunity to hear the description of myeloma from a physician.

Multiple myeloma is basically what we call a plasma cell dyscrasia. What that means is that plasma cells are cells that live in the bone marrow, and the job of plasma cells is to make antibody. So, when myeloma cells become malignant or cancerous, they still make antibody, and that's an important hallmark of how we approach treatment for patients with multiple myeloma. So, while targeting cancer and cancer genes is certainly important, targeting normal plasma cell biology is also important, and we'll talk about that as we go further through the discussion.

Now, as those myeloma cells grow in the bone marrow, they start to crowd out normal bone marrow, and that can cause complications such as anemia. The secreted antibody can clog up the kidneys, and that can cause kidney failure. As myeloma cells grow, they start to recruit in cells called osteoclasts. The job of an osteoclast is to chew holes in bone, and so it's not uncommon to see patients present with bone pain because of those holes in the bones, fractures because of weakness in the bones, hypercalcemia because the calcium is pulled out of the bones and into the blood, or



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osteoporosis or osteopenia. Certainly, in patients you may see osteoporosis out of proportion to what you'd expect for their age or ethnic background. So, again, there are a number of clinical scenarios that can present simply because of accumulation and overgrowth in the number of plasma cells within the bone marrow.

[Slide 6 – Myeloma Cells]

Now, I always think it's important as we battle—and I always describe part of what we do when we treat myeloma as a battle—is to visualize the enemy. So, what you see in front of you right now are malignant plasma cells. Now, these are not normal plasma cells; they are cancerous plasma cells or myeloma cells. The way you can get a clue with that is on the right side of the picture you can see a cell with two nuclei, and that is not normal. That should not be there. What you see is that bluish cytoplasm, the area outside the nucleus, and then that white area that's right next to the nucleus. That white area is where all the antibody is being produced, and that's really important to keep in mind because, while myeloma cells are cancerous, they still maintain important parts of their day job, and their day job is to make antibodies.

Unfortunately, that antibody doesn't really protect you against infections, which is what most antibodies will do. It just is produced in excess and hangs out in the blood and gives us a marker by which we can assess disease activity. Is the marker high? Is the marker low? In order to be called complete remission, that antibody production by that clone has to be effectively eliminated, and that's one of the ways that we measure response over time.

[Slide 7 – Hematopoiesis]

So, where does the plasma cell or the myeloma cell fit in the grand scheme of things? Well, if you look at what I call the family tree of blood, at the very top you can see the "Holy Grail" of transplant and of biology in general—that stem cell all the way up at the very top. That stem cell at the very top gives rise to all the cells within our blood and our bone marrow. If you pay attention there at the bottom, you'll see a box that just came up on the plasma cell.

So, the plasma cell is the end of the line for B cells. For those of you who are astute biologists or physicians, B cells are what give rise to the most common of childhood cancers called ALL, acute lymphoblastic leukemia. B cells also give rise to many of the lymphomas. But at the end of a B cell, you see the plasma cell, all the way down there at the bottom. Again, the job of that plasma cell is to make antibodies and protect you from infections over the course of time.

[Slide 8 – The Immunoglobulin Molecule]

So, when I see patients, oftentimes they will ask me, "What is my isotype? What is my heavy chain? What is my light chain?" So, I thought it would be useful to give you a little bit of information on what people are referring to when they talk about the heavy chain and the light chain. This is a pretty complicated slide or figure, but what I want you to focus on is really just two sections. Every immunoglobulin (Ig) molecule is made up of one heavy chain, and that's the big Y that starts all the way at the top and works its way all the way down to the bottom. Basically, it's four different sections with a hinge in the middle. That's the heavy chain that goes on both sides.



Every antibody and almost all myeloma patients will have a heavy chain that's either IgG or IgA. In less common cases, it can be IgD and very, very rare cases it can be IgM or IgE. Those are the heavy chains that most patients, when they ask what's their heavy chain, it's one of those five choices. By far, the most common is IgG. The second most common is IgA.

Then, you'll see on the sides something referred to as the light chain, and the light chain is much smaller. It's only two segments there, and it's on both sides. So the heavy chain is in the middle, and it's basically a Y. Then the two light chains, basically, fit in on either side of the top part of the Y. The reason that's important is light chains, while there's one heavy chain for every antibody, there are two light chains. The two light chains are the same. It's either a kappa or a lambda. You only have two choices for light chains: kappa or lambda.

So, when you want to know more about what your antibody is that's being produced by the myeloma cells, the question you need to ask is, "Do I have an IgG or an IgA? Do I have a kappa or a lambda?" Then, your doctor or your team will tell you more specifically what you have, and that's important because when you follow things like the serum protein electrophoresis (SPEP), they're going to tell you we see the IgG kappa paraprotein, and it is X grams. Or, if you look at the free light chain assay, which many of you are starting to use more frequently now—we use it on every patient that we see at our center—they'll tell you the kappa light chain for you is elevated or depressed or the lambda light chain is elevated or depressed, and that gives me information about disease activity.

So, the immunoglobulin molecule is made up of one heavy chain and two light chains. Light chains are either kappa or lambda, and heavy chains, most commonly, are IgG but can be IgA or even a couple of other important scenarios as well.

[Slide 9 – M Protein Analysis]

So, the phrase or the word that you all hear quite often is what's the SPEP? What's the M spike (monoclonal immunoglobulin)? What's the M protein (monoclonal immunoglobulin protein)? What's the paraprotein? Where does that come from? Well, that comes from a technician in the laboratory that basically takes out the serum from your blood and runs it on a gel. When they run the serum on the gel, what you see on the top is typically what a normal serum protein electrophoresis looks like, and you see all of those different peaks, including albumin, alpha-1, alpha-2, beta, and gamma. The gamma is where most M proteins live. As you can see, in a normal serum protein electrophoresis you get a very broad gamma peak because you have lots of different kinds of antibodies being produced, whereas in myeloma, on the bottom, you lose that broad peak in the gamma region and you get what's called the M spike. That's where it comes from. It's the monoclonal protein spike within the gamma region, and you lose many of those broad, protective immunoglobulins over time.

So, when you hear us referring to some of these—the lingo around how we assess myeloma—this is where it actually comes from. This is what it actually looks like in reality.

[Slide 10 – Criteria for Diagnosis of Myeloma]

So, I've given you a little bit of background on the disease and a little bit in terms of what to expect. How do we start to put patients into different categories of plasma cell disorders? There are three basic categories of plasma cell disorders, and we're going to start from the least worrisome on the left



to the more worrisome on the right. The least worrisome is a category called MGUS (monoclonal gammopathy of unknown significance), where patients have a smaller M spike and fewer than 10% plasma cells in the bone marrow. More importantly, they have no signs or symptoms of organ damage.

The organ damage piece is really important because there are many patients who can have MGUS or smoldering myeloma, and it can stay smoldering or MGUS for a long, long period of time. I'm going to show you some data on that in the next slide. But, more importantly, those patients are not treated. Patients with MGUS and smoldering, outside of clinical trials, are not offered treatment because the natural history may be that many of them never develop signs or symptoms of myeloma.

Now, if you look to the right side, there's a third category, and that's called active, or what we call symptomatic, multiple myeloma. In this category you usually have more than 10% plasma cells, but you don't have to. You usually have an M spike that can be small or it can be large. But, more importantly, you've got signs or symptoms of end organ damage, and that end organ damage is manifested by anemia, bone lesions. Remember, I mentioned earlier that there are holes in the bone that form because the plasma cells recruit in osteoclasts or high calcium or patients who develop abnormal kidney function. That is the way we have discriminated patients who we observe with MGUS or smoldering from patients who have active or symptomatic myeloma. So, this is an important set of information as you try to understand what category you fit in at any given time point.

[Slide 11 – Smoldering Multiple Myeloma (SMM)]

Now, if you start to look at smoldering myeloma and MGUS in general, what you can see in the MGUS curve on the bottom is that roughly 1% of patients will convert from MGUS to myeloma per year-1% per year. So, if you have MGUS for ten years, only 10% will convert. On the other hand, smoldering is 10% per year, so it's a much higher number-ten times higher. At five years, 50% of patients with smoldering will have converted to myeloma. But interesting enough, if you can get beyond five years, the risk of conversion drops much lower. So, what I often tell patients with smoldering myeloma is, "The longer you stay smoldering, the more likely you are to stay smoldering." While that seems inherently obvious, it is, in fact, true because the rate of conversion drops after five years. It doesn't mean patients don't convert. It just means the risk of conversion goes from 10% per year to only 2% per year, and it starts to look a lot more like MGUS.

That's, actually, I think, really important because we are not offering treatment to most of these patients. So, if you can tell a patient with MGUS or smoldering after five years your risk of progression is much lower, that can be a really important piece of information to provide to a patient and their family to give them some comfort in terms of what's going on now.

Now, what we've also learned is that not all patients with smoldering are the same; in fact, we've spent a lot of time as a myeloma community trying to tease out different kinds of smoldering to figure out who's going to convert to myeloma sooner versus later.

[Slide 12 – Free Light Is Useful for Risk Assessment in SMM]

So, if you look at this figure right here, this is using just the free light chain assay that I mentioned earlier as a way to discriminate high-risk smoldering from low-risk smoldering. If you have an

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abnormal free light chain ratio, that puts you on the top curve; if you have a closer to normal free light chain ratio, that puts you on the bottom curve. In fact, when you start to put all of this together into a scoring system, you can see that patients can be broken down into three groups: high risk, which is up here on the left with the highest risk of progression; intermediate, which is here in the middle with an intermediate risk of progression; and then low-risk smoldering over here, which has a very, very low risk of progression at ten years. Only half the patients will have converted at ten years.

This is important because the two groups on the left, the high-risk and the intermediate-risk in the middle, we're starting to enroll in clinical trials to ask questions about whether they should be treated earlier rather than waiting. But I want to highlight very clearly the standard of care for these patients remains observation.

[Slide 13 – Updated IMWG Criteria for Diagnosis of Multiple Myeloma]

So, how do we use all that information? Well, here comes some new stuff. I told you before that if you don't have CRAB criteria (a high calcium, kidney problems, anemia, or bone disease), you don't fit into the category of symptomatic myeloma or multiple myeloma. That just changed. As of a few months ago, the International Myeloma Working Group (IMWG) redefined what it takes to be myeloma, and they did so because we had some new tools.

The first thing that's been added is if your bone marrow has more than 60% plasma cells, you now count as myeloma. The reason is that if you have more than 60% plasma cells in the bone marrow, your risk of converting to myeloma within two years is over 90%. If the risk is that high, why wait? Why wait for something bad to happen when you know that nine out of ten patients are going to convert within two years, and you may be able to prevent some bad things from happening.

The same is for point number two, which is a serum free light chain ratio of greater than 100. Ninety percent of patients with that at presentation will have progressed to myeloma, and what we think we're doing is actually saving patients from developing kidney failure by not waiting for them to have a problem but intervening early to try and prevent a problem.

The third category down here at the bottom of that far right box is greater than one MRI (magnetic resonance imaging) focal lesion. Historically, we have used X-rays to try and identify bone disease, but we know that by the time an X-ray is abnormal, 70% of the bone has been damaged or lost. An MRI or a CT (computed tomography) scan can pick that up much sooner. So, if we see bone disease by MRIs, which can be more sensitive than CTs in some situations, that now has bought the patient a diagnosis of symptomatic myeloma, and we don't watch that patient any longer.

So, these are the three changes to the CRAB criteria. Outside of that, patients continue to fit into their categories of either smoldering or MGUS as we go forward over time. I think these are important things to think about as we define what it means to have multiple myeloma.

So, let me start off with some of the good news as we start to talk a little bit about therapy because what I want to do is touch on some general principles of initial therapy and then talk on some general principles of how to manage or talk about relapsed myeloma, and then get to questions that I know many of you all are posting on the Web over the next few minutes.



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[Slide 14 – Improving Survival in MM] Sagar Lonial, MD, FACP

So, what you see here is survival data by decades, and I think this is really important data. This was generated by Dr. Shaji Kumar and his colleagues at the Mayo Clinic because what they showed was that up until about the year 2000, nothing that we did improved the survival of patients with myeloma as a large group. This is looking at a population of patients, not just individual young patients or old patients or patients that had a transplant. It's looking at everybody. As you can see, since 2000, we have begun to have pretty significant improvements in overall survival, such that the most recent five years, from 2005 to 2010, gives us some of the best survival that we've ever seen. This is what I refer to when I say, "We're changing the natural history of multiple myeloma."

The natural history is that red curve down at the bottom, 1960 to 1965. That's when you basically have no drugs or you have largely ineffective drugs. What you see is that the median survival for all patients on average is about two to two-and-a-half years.

What we have now, through the advent of more aggressive therapy, through the use of high-dose therapy and autologous stem cell transplantation, as well as proteasome inhibitors, IMiDs (immunomodulatory drugs), and new classes of drugs that are coming, we've been able to change the natural history. That's a really exciting thing. Very few cancers can show you a curve like this and say that they've actually changed the natural history of the disease as a consequence of active research and investigation.

[Slide 15 – Goals of Induction Therapy]

So, a patient is diagnosed with multiple myeloma, and they need to start on therapy. How do I or many of my colleagues think about the goals of that initial induction treatment? Well, in my mind, there are a couple of important goals. You want to achieve a maximal response. You want to get as good a response as you can. You want it to occur quickly. You want this to occur in a way that actually improves how functional the patient can be, and you want it to have minimal effects on quality of life and not limit stem cell mobilization.

Those are really the keys across the board. The only difference between a really old or frail patient who's not eligible for a transplant and the general concepts that I mentioned here for a younger patient really have to refer to the impact on stem cell mobilization, because if you're over the age of say 75 or 78, the likelihood of moving forward with a transplant is going to be lower. Notice I didn't say zero; it may be lower. So, you don't have to worry so much about stem cell reserve or stem cell mobilization. Whereas if you are younger than age 75 and in reasonable shape, many of us would consider that patient suitable for transplant.

This is a really important difference in the way we approach patients in the United States versus how they're approached in Europe. In Europe, if you're over 65, transplant is taken off the table. It is not an option. We know that high-dose therapy in transplant continues to improve overall survival (OS) for patients, so being able to offer it to the greatest number of patients is really important as we think about outcomes down the road.

[Slide 16 – Benefit Associated With CR] Sagar Lonial, MD, FACP

So, we want to achieve a major response. What about looking at: Why do we want to achieve a major response? What's the advantage of that? Well, as you can see, in terms of progression-free survival (that's the PFS at the top) or overall survival (that's the OS that you see down at the bottom curves), patients who achieve major responses—CR (complete response), VGPR (very good partial response), sCR (stringent complete response)—stay in remission longer and live longer; that's part of the justification for why we want to achieve a major response with our initial induction therapy.

Now, an important area where there can be some confusion is: If you don't achieve a CR with your initial induction therapy, should you switch to something else? In general, the answer has become no, you shouldn't. You should pick the regimen that has the highest chance of achieving a complete remission. But if you don't get there, then your goal is still to try and collect stem cells and get that patient to a transplant because we know that transplant can have a major impact on survival. You don't necessarily have to change treatments until you get a complete remission.

Now, this is somewhat of a controversial area, but there has been data presented very recently by the Center for International Blood and Marrow Transplant Research, or the CIBMTR, that shows that switching treatments doesn't necessarily improve outcomes for patients if they don't achieve a complete response or a very good partial response following their first induction therapy. Generally, at our center and many others, we don't recommend making a switch. We recommend continuing on the current therapy. But, again, the goal is to pick a regimen that gives you the highest chance of achieving a major response.

[Slide 17 – 3 Drugs Are Better Than 2]

Now, one of the ways that you do that is by combining drugs. This is, again, another area of some controversy. In many of the oncology circles, the concept is that you use one drug or you use two drugs, and you just keep cycling through them one at a time, not really taking into account the potential benefit that may be gained when you put drugs together. I'm going to tell you one of the things I didn't have in my disclosures early on is that I like combinations. I think combinations are much more effective. I think they're much more active. I do believe that you have to be cautious of combinations when you're worried about side-effect management.

But we didn't cure Hodgkin's disease and non-Hodgkin's lymphoma (certain types) and testicular cancer by giving drugs by themselves. We cured those diseases by combining drugs together, by trying to hit the cancer from many different sides in many different ways at any given time. Because of that, I believe that combinations really represent our best chance at trying to eradicate myeloma and either induce long-term disease control or cure.

So, in order to do that, you have to put drugs together that work together really well. As you can see from this graph, three drugs are better than two in terms of overall response rate and in terms of how many patients achieve what we call a VGPR or better. So combinations, whether they are proteasome inhibitors with Cytoxan[®] (cyclophosphamide) or proteasome inhibitors with an IMiD, represent to me the most potent combination that we can have for newly diagnosed myeloma patients. Hopefully, in the near future, we will have antibodies available, and there will be a way to not





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only go from two to three drugs but to go from three to four drugs as part of our initial treatment for newly diagnosed myeloma.

[Slide 18 – Factors That Influence Improved Outcomes]

So, how do we get those better outcomes as I showed you earlier? Well, there are a number of things that we've done. One, better induction, more effective induction therapy. In the olden days when transplant was first demonstrated to be a benefit, the benefit was because about 25 to 30% of patients achieved a complete response after the transplant compared to much lower in patients who didn't achieve the transplant. We're now achieving 30 to 35% CRs, or complete remissions, just with induction therapy alone; that number jumps to 65 to 70% when you include a transplant on top of it. So, better induction and better drugs are clearly important parts of this discussion.

We're also using things like longer duration of maintenance therapy, longer duration of therapy and, again, more patients are getting access to high-dose therapy and autologous transplantation, particularly in the United States where age is not used as an independent factor for whether or not a patient can have a transplant.

[Slide 19 – Transplant in Era of Novel Agents: Survival Benefit Continues]

Now, as we really talk about the role of induction therapy and the importance of transplant in the management of patients with newly diagnosed myeloma, it is important not to lose sight of some of the important gains we've achieved through the use of high-dose therapy and transplant. I didn't show you papers from the *New England Journal of Medicine* published in the 1990s that talked about the benefit of transplant. This was a paper in the *New England Journal of Medicine* last year where patients received lenalidomide and dexamethasone as their initial treatment and then were randomized to either transplant, the high-dose melphalan arm or low-dose melphalan in combination with lenalidomide—the gray bar. What I think you can see pretty clearly here is that patients who had the transplant stayed in remission longer, almost double as long as patients who didn't have it; in fact, they lived longer compared to patients who did not have the transplant.

So, the argument that many are making now—that transplant has had its day and it's now no longer needed because we have so many good new drugs—is an interesting question. It's a question that we're asking in clinical trials, but it's not a question that has an answer right now because, as you can see, even with the use of new drugs, transplant does continue to improve progression-free survival, how long patients stay in remission, and overall survival. I think that's something we cannot forget. Overall survival is an important benchmark, especially among newly diagnosed patients where oftentimes it's hard to show an improvement in overall survival because patients are living so much longer. Despite that, you can see a big difference in overall survival favoring the group that had a transplant.

Now, one interesting caveat to this trial is that if you look at the complete remission rate between the old trials that showed the benefit of transplant, patients who had a transplant had a much higher CR rate than patients who didn't have a transplant. So, we thought that the main benefit of transplant was achieving a complete remission, but if you look at Dr. Palumbo's trial here, the incidence of achieving a complete remission was the same in the high-dose group versus the group that did not receive high-dose therapy in transplant.



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The black and the gray curves had identical complete remission rates. So, that makes you wonder: What was it that the transplant did that really made a difference if CR wasn't really the answer?

[Slide 20 – Getting to MRD: New Definitions for CR]

The answer really comes in this cartoon that some of you who've heard me give a talk before may have seen used before, and that is the iceberg idea—that just because the patient is in a complete response, or a CR, doesn't mean that all of their myeloma is gone. In fact, we know that's not the case because patients will relapse even after having achieved a complete response.

The difference between the transplant and the nontransplant curve on the slide that I showed you before was that more patients in the transplant curve achieved a molecular or flow CR compared to those who did not have the transplant. We know that achieving a molecular or a flow CR is able to induce more durable, long-lasting remissions and, in many cases, has been associated with improved survival.

So, the goal of the transplant is not just to get you to a complete remission. In fact, many patients of mine have asked me: "I'm in a complete remission. Why do I want to do a transplant?" The answer is to get you lower on that iceberg, to get more patients into molecular or flow cytometric complete remission because that gets us one step closer to cure, and it also significantly reduces the amount of tumor burden that's left in the body over time. So, the benefit of transplant on top of novel drugs, new drug induction, is not just to achieve a complete remission, but it's really to try and drive disease burden down to lower and lower levels over time.

[Slide 21 – What Happens When the Best Are Combined?]

So, if you start to take some of these strategies and put them together, this is data published from the IFM (Intergroupe Francophone du Myélome) in a journal last year. These are patients that all got RVD (Revlimid[®] [lenalidomide]–Velcade[®] [bortezomib]–dexamethasone) induction; you can see it on the left. They all got a transplant, they all got RVD and a consolidation for two cycles, and then they all got lenalidomide maintenance.

If you look, this is actually progression-free survival—how long patients stayed in remission. If you look at that top curve, the blue curve, those were patients who were flow cytometric-negative; we call those patients MRD, or minimal residual disease, negative on the top curve. None of them have relapsed with a median follow-up of three-and-a-half years.

On the other hand, patients who were MRD-positive, the black line or the grayish line, many of those patients have, in fact, relapsed. If you look at the whole population in aggregate, you can see the yellow line in the middle suggests that somewhere in the middle is when you include the MRD-negative and the MRD-positive. But this really, to me, begins to justify the importance and power of achieving not just a conventional complete remission but actually getting patients to MRD negativity because it can translate into really long durable remissions and my guess is, ultimately, increase the cure fraction of patients across the board.



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[Slide 22 – Current Considerations for Initial Treatment of MM] Sagar Lonial, MD, FACP

So, what is my summary of how to approach treatment options for patients with newly diagnosed multiple myeloma? Well, again, I feel pretty strongly that three-drug induction followed by an autologous transplant is an important standard part of treatment for a newly diagnosed transplant-eligible patient. I think all patients should be offered maintenance therapy after transplant. I don't think the maintenance should be the same for every patient.

At our center, depending upon what the genetics and the risks were at diagnosis, we tailor the maintenance therapy based on that, and I know a number of different sites are beginning to do this as well. I showed you data on MRD, or minimal residual disease testing, and it is an important research tool to help us identify which patients are achieving MRD negativity and what treatments can help us get there. But at this time in 2015, I don't think we can make treatment decisions based on MRD status yet because there are a number of variables there that we have not really explored or evaluated in the context of large clinical trials where patients are getting uniform, aggressive and modern therapy. So, I won't tell you to despair if you're MRD-positive or to be ecstatic if you're MRD-negative yet, but I think we're going to understand what to do with that information in the very near future.

[Slide 23 – Recommendations for Salvage Therapy in Multiple Myeloma]

So, unfortunately, despite our best efforts, for many patients who receive the best of induction and the best cytotherapy and transplant and the best maintenance, relapse continues to be an important issue that we have to deal with over the course of time. As you can see here, these are the NCCN (National Comprehensive Cancer Network) Guidelines; that's the national group that gets together once a year and tries to pick what they call "recommended or preferred regimens" for patients with relapsed myeloma. This is the NCCN as of March 2014. My guess is that the 2015 version will probably change a little bit and represent the addition of new drugs that we're going to talk about in the next few minutes.

But as you can see, Category 1 means there is the highest level of evidence from randomized phase III trials. Category 2 represents that there is small phase II data, suggesting these are active or phase III data is on the way. Then, other regimens that are NCCN [category] 62a as well are listed there on the lower left.

[Slide 24 – Questions in the Relapsed Setting]

So, what are the academic or important questions that are being asked in the myeloma community in the relapsed disease setting? I'm telling you these because, as you start to see studies that are going to come out at ASCO (American Society of Clinical Oncology) this year and at ASH (American Society of Hematology) in 2015 in December, I want you to think a little bit about if any of the studies that I'm hearing about are addressing some of these important questions.

The first is, is three drugs better than two among patients in early relapse? You heard me say that I think three drugs are clearly better than two for newly diagnosed myeloma patients. But for a patient who's got first-relapse disease, are three drugs better than two? We don't know the answer to that, and I think we're getting some information. The ASPIRE (Carfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide and Dexamethasone for the Treatment of Patients with

Relapsed Multiple Myeloma) trial that was presented at ASH this year suggested that three drugs improved progression-free survival, and there are hints that it may improve overall survival as well. But those are really important questions.

For patients who are in late relapse, meaning second, third, or fourth relapse, tolerating three drugs may be very difficult for those patients. So, is two more than enough for those patients? I think that's an important question because, as you start getting into later and later relapse, quality-of-life questions become much more important because patients are a lot more beat up from their initial therapy. So, thinking about two drugs rather than three in that situation may be an important concept or consideration.

[Slide 25 – Selecting Salvage Therapy: General Principles]

Finally, how do we choose among salvage treatments in early relapse? How do you choose whether you're going to use a proteasome inhibitor-based approach like what was done in ASPIRE or an IMiD-based approach like what was done in the ELOQUENT (phase III, randomized, open-label trial of lenalidomide/dexamethasone with or without elotuzumab in subjects with previously untreated multiple myeloma) trial, which has not been reported on yet, but really uses lenalidomide and dexamethasone as part of the backbone and adds a monoclonal antibody to it as part of salvage therapy. So, these are questions that we don't have the answers to right now, but these are important questions, I think, in the myeloma community as of 2015.

Here's some general concepts or principles that I use; in fact, this is from a talk I gave a few years ago at the ASH meeting when I gave the educational session on myeloma about an algorithm that I think about when I try and decide if or what I'm going to use in the relapsed setting. Again, you have to think about what patients have had before. What were their side effects when they had the treatment before? What is the biology of their current relapse? Is it an aggressive, rapidly progressing relapse, or is it a slow, indolent relapse which most myeloma patients have early on? How do you apply drugs like bortezomib, carfilzomib, pomalidomide, lenalidomide, and what we hope will be emerging agents, such as elotuzumab, ixazomib, daratumumab and the recently approved agent panobinostat? How to do all this, how to put them all together and make a decision for an individual patient represents a challenge. There's no simple, easy algorithm by which to do that. If I gave it away, nobody would have to come see me.

So, I think practically speaking, how we do this is often individualized. There are not clear biomarkers to tell us this patient has this problem; give them drug X, whereas the other patient has that problem, give them drug Y. There's a lot more room for judgment and treatment approaches.

[Slide 26 – Drugs in Relapse]

So, what are some of the drugs that we have in relapsed myeloma? Well, I'm going to give you a couple of important categories on some of those drugs, and then I'm not going to go into all the specifics individually to show you data. I'm going to show you a couple exciting and important drugs I think that are coming down the pike.



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First, in terms of proteasome inhibitors, bortezomib was the first, carfilzomib was second, and MLN9708 or ixazomib is not far away. Finally, oprozomib is an oral version of carfilzomib that is being tested in a number of clinical trials and formulations as well.

In terms of the IMiD category, we have lenalidomide and pomalidomide. Those are both approved and out there, and we're going to talk about ways to make len (lenalidomide) and pom (pomalidomide) better in the context of immune-based therapies.

We have histone deacetylase (HDAC) inhibitors. The most recently approved is panobinostat, and we have ACY, and that should be 1215, not 2115. This is a newer, what is reported to be a kinder, gentler HDAC inhibitor with much less GI (gastrointestinal) toxicity and is being tested in very early clinical trials at this time point.

In terms of antibodies, there are a number of antibodies that are in development. Elotuzumab and daratumumab are probably the furthest along in terms of clinical development, but there are two other CD38 monoclonal antibodies as well. There are also antibodies targeting NK cells. There are antibodies targeting CD56, lots of different potential proteins that are in development as well.

Finally, the other category, which means they don't fit into one of those big backbone concepts, are things like kinesin spindle protein inhibitors, such as ARRY-520; cyclin-dependent kinase inhibitors such as dinaciclib and the KPT compound, which is a brand new category that's being tested, the nuclear export transport inhibitors, or selinexor is the other name for KPT. That one is being tested in a large, phase II trial right now as well. So, there are a number of different categories to be excited about because each of these is going to help improve how we treat patients and will give physicians and patients more tools as we begin to think about how to treat relapse and relapsed/refractory multiple myeloma.

[Slide 27 – Tao of Myeloma Therapy: Mutations Are Not Everything]

Now, I want to just take one moment before we go too far and give you what I think really differentiates multiple myeloma from pretty much every other cancer in the book. That is that while, as I mentioned earlier on, myeloma cells retain their day job, and their job is to make antibodies. So, while mutations and understanding the importance of sequencing is very important in cancer in general, and may help us in the management and treatment of patients with myeloma, sequencing would not have given us the two most active drugs we have in myeloma, and that is proteasome inhibitors and IMiDs, because there are no mutations in those genes that cause cancer cells to be sensitive to those drugs. The reason myeloma cells are sensitive is because they are plasma cells; that's basic plasma cell biology, not what I call cancer biology. So, if we're going to ultimately cure patients of myeloma, we can't just focus on mutations and say this mutation means we use this drug, this mutation means we use another drug. We have to think about normal biology as well and partnering some of those mutation-driven drugs like they use in lung cancer with plasma cell drugs like proteasome inhibitors and IMiDs and monoclonal antibodies.

It's going to be what my colleague, Larry Boise, calls marrying the yin and yang of myeloma—the normal biology to the cancer biology—that's ultimately going to lead us to eliminating myeloma and, ultimately, we hope, curing the disease over time.

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[Slide 28 – Targets for Monoclonal Antibodies] Sagar Lonial, MD, FACP

So, I'm going to end with just a really exciting area, which I think is the monoclonal antibodies, and the reason I think it's so exciting is—and I'm going to see if anybody gets this joke—and that's the idea that a cancer that makes too much antibody doesn't have an antibody to treat it. I call that oncologic irony. It's not that we haven't had targets. We've had multiple antibody targets. You can see on the slide multiple targets that are potentially useful for the treatment of patients with myeloma. But until recently, none of them have really worked. It wasn't until very recently that we started to develop and identify how to make antibodies more effective in myeloma.

[Slide 29 – Daratumumab Response]

The first and most active single agent that we have in an antibody is daratumumab. Daratumumab is an antibody that targets CD38, and this is present on almost every myeloma cell. As you can see here, patients had responses in a phase I clinical trial, so very, very exciting data because, obviously, daratumumab has really helped fight the battle in patients with relapsed and refractory myeloma. We've got many, many patients at our center treated with daratumumab alone or in combination, and it clearly is a very active treatment option for patients over time.

[Slide 30 – Elotuzumab Background]

But as you start to think about making antibodies better, what we learned from elotuzumab is the idea that elotuzumab is also present on all plasma cells, on all myeloma cells. While elotuzumab alone may not do a lot, combining elotuzumab with a drug that activates immune function actually makes it quite effective. This is data from a mouse model where that was, in fact, the case. But as you know, mice don't get myeloma unless we give it to them. So, the only model that really matters is the human model, and this is what happens in humans who get elotuzumab in combination with lenalidomide and dexamethasone.

[Slide 31 – Progression-Free Survival (PFS) From the Phase II Cohort]

What you see is a progression-free survival or duration of maintenance of almost three years in the red category there—the patients who got 10 milligrams per kilogram of elotuzumab. This concept of combining a monoclonal with an IMiD drug that activates immune function, activates NK cell number and function, is really, really important. As you'll see not just with elotuzumab, but with daratumumab and other CD38 monoclonals, this synergy is really, really very powerful. The power of this synergy is not manifested just in response rate. The power is manifested in how long that remission can last and what may actually end up being, we hope, a plateau on some of those curves, suggesting that you may be able to induce very, very long-term remissions among certain subsets of patients.

So, the antibodies and the immune therapy pieces are very, very exciting because we've not had any in myeloma that have been effective. Hopefully, very soon we will.

[Slide 32 – Safety Summary: IMiDs in 2014]

So, I'm going to end with a couple of questions or a couple of slides on safety summary and sideeffect management. These are the big issues that we think about with the IMiD category of drugs.

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[Slide 33 – Managing Myelosuppression With IMiDs] Sagar Lonial, MD, FACP

I think it's important to realize that, with both lenalidomide and pomalidomide, myelosuppression or suppression of the white blood cells and the platelets is probably the biggest issue, and so there may be times where treatment is interrupted, where the dose is reduced, or where the use of G-CSF (granulocyte colony-stimulating factor) or Neupogen[®] (filgrastim) is added to try and increase the white blood cell count over time. These are standard things that your physician may do as they see you on drugs like lenalidomide or pomalidomide over time.

[Slide 34 – Thrombosis in Myeloma: Risk Factors and Prevention]

The other big issue with the IMiD class of drugs is thrombosis, or DVT (deep vein thrombosis), or pulmonary embolism. Dr. Antonio Palumbo published a paper from the Myeloma Working Group a long time ago that showed very nicely that, for patients who only had one risk factor, the use of aspirin was likely safe as a prophylaxis measure for patients who were getting an IMiD, and that represents probably almost three-quarters or 80% of patients with multiple myeloma, whereas patients who have more than two risk factors probably need more than just an aspirin for prophylaxis. Those patients likely need low-molecular-weight heparin (LMWH) or maybe even full-dose warfarin.

[Slide 35 – Thrombosis in Myeloma: Risk Factors and Prevention (Cont'd)]

Many of the new oral anticoagulants (or the NOACs) had been substituted for warfarin because it's a lot easier to do. In an off-label situation, we often do that as well. But just remember the FDA (Food and Drug Administration) has not yet said that you can safely replace warfarin with NOACs in this situation. Many of us do it in clinical practice, but you are a little bit off the reservation—not in a bad way, just not necessarily following FDA guidance in that situation.

[Slide 36 – Other Important Safety/Adjunctive Issues]

Again, what are some other important issues that I think patients should take away? That is bone protective therapy. Bisphosphonates are recommended for almost all patients with myeloma, regardless of whether or not they have bone lesions by X-rays. The duration and the frequency is subject to some level of discussion amongst different myeloma physicians, but I think clearly the use of bisphosphonates is really very important.

Next is hydration. I tell people to minimally drink two to three liters of fluids per day, and that's at a minimum. If they're doing strenuous work outside or it's the middle of the summer, increase the amount that you're drinking in any given day. Again, when it comes to GI and nutritional status, a well-balanced diet is probably sufficient. There is almost no data at all saying that avoiding sugar does anything other than make you miserable. I'm not saying that you should have an all-sugar diet, but I think you want to just make sure that you have a well-balanced diet that includes all of the major food groups and, again, let's you have a good quality of life over time.

[Slide 37 – Discussion: Speaking With the Patient About Adverse Events]

Again, talk about these issues—antibiotic prophylaxis...thromboprophylaxis. Your myeloma team should be well-versed at trying to help you work your way through much of this. We have many people on our team that help our patients deal with many of these issues and other issues that arise over the course of time as well, and this allows you to be an informed patient but still contribute to your care over time as well.



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[Slide 38 – PETHEMA Cure With Old Drugs: What About All the Clones?] Sagar Lonial, MD, FACP

What I want to leave you with as I wrap up is the idea that the first statement in many papers that I read about myeloma starts off saying, "Multiple myeloma is an incurable, plasma cell disorder," and then they go on and say whatever they're going to say. I don't like that statement because, as you can see in this analysis from Spain published in 2011, with data of over 15 to 20 years' follow-up for some of those patients, there are clearly subsets of patients who have what I would call a functional cure. Our goal in 2015, 15 years after this data, is to try and increase the fraction of patients who are on that blue curve, meaning ongoing, overall survival, and ongoing complete remission, or at least increase the number on the red curve, which is the number of patients in VGPR or better, because that's ultimately a mark of when we have succeeded at our goal to eradicate and control myeloma in the long term.

[Slide 39 – Conclusions]

So, in conclusion, the definitions of who has myeloma versus who has smoldering or MGUS are in evolution. I think you'll see more changes to that definition in the next few months. Aggressive therapy continues to require three-drug induction, consolidation and a transplant as well as maintenance therapy. Options in relapse are continuing to increase and right now are really based on how patients are doing and what they've seen, not just based on a biomarker that says, "You're Patient X, and you should receive drug X or you're Patient Y, and you should receive drug Y." We aren't quite there yet, but the good news is that with more choices, we're going to have to get there because we can't just pick as we like any longer in the future.

Finally, immune therapy, which is every patient's favorite approach to treating cancer, is on the way in myeloma with what we hope will be one, if not two, monoclonal antibodies approved in the next year. If that happens, then I think it's a totally different ballgame because monoclonals are going to do to myeloma what rituximab did to lymphoma. With that, I think I can stop and take questions.

[Slide 40 – Patients and Families]

QUESTION-AND-ANSWER SESSION

[Slide 41 – Question-&-Answer Session] Lizette Figueroa-Rivera, MA

Thank you so much, Dr. Lonial, for your very clear and informative presentation. It is now time for the question-and-answer portion of our program.

We'll take the first question from our Web audience. Doctor, Joanna asks if cord blood transplants are an option for myeloma patients.

Sagar Lonial, MD, FACP

That's a great question. Cord blood represents another form of an allogeneic transplant. The data on allogeneic transplants right now is in evolution. I don't think it's something that can be routinely recommended for most patients because the risk, the morbidity and the mortality associated with that process remains quite high, as does the relapse rate. So, yes, cord blood can be used. I think there was a paper from the Japanese very recently showing that you could do a cord blood transplant in



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patients with myeloma. I don't know that the outcomes of those transplants were very good, but certainly from a technically feasible aspect, it is certainly technically feasible.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and we'll take the next question from the telephone audience please.

Operator

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

Patricia, calling from New York

"Yes, my question is in the treatment of relapse and the combination of drugs, is dex (dexamethasone) always necessary? I seem to have had a bad reaction to it and have been taken off and just wanted to know the possibility of the treatment being good without it, if it's good, or whatever your opinion is on this particular subject."

Sagar Lonial, MD, FACP

The question about the utility of dexamethasone is one that I'm always asked by patients because nobody likes taking dex, and yet, as physicians, we always seem to use lots and lots of dex. So, let me try and go on both sides of the discussion here.

First, the advantage of dexamethasone is that it kills myeloma. Dexamethasone is very potent and very effective at killing myeloma cells. In addition to that, dexamethasone seems to make drugs like lenalidomide and pomalidomide and thalidomide even better—you more than double the response rate when you add dexamethasone in with those two drugs.

Now, given all the downside to dexamethasone, the question remains: Does it just stay at the same normal dose forever? The answer is no. Most patients can't tolerate real doses of dex for more than four, five, sometimes six months at a time. So, the tapering and dose reduction of the dex is really critical to being able to maintain quality of life, maintain bone health, and not live with many of the terrible side effects of dexamethasone over a really long period of time.

I've got a number of patients that do have issues with the use of dexamethasone, and in those patients I may either really reduce the dose or switch to prednisone. Prednisone, while it is also a steroid, it's much less potent than dexamethasone, so you may have a little bit more room to titrate the dose, to find a dose that's safe. Or, in patients who simply cannot take any corticosteroids at all, whether it's dexamethasone or prednisone, you can get away without it, but you are potentially throwing out something that may be able to offer some benefit at least in the short term.

Lizette Figueroa-Rivera, MA

Thank you. Doctor, we'll take the next question from the Web audience. Donna asks about controlling side effects, specifically peripheral neuropathy pain.

Yes, so the best way to try and control or minimize peripheral neuropathy is to never get it. While that may sound easy on the surface, I think what it really requires is a lot of patient education on the "these are the things to expect with peripheral neuropathy" before you get it. It requires a lot of work with the infusion center staff and the nursing staff as well because they will often be there for many of the doses of Velcade before the physician is there. So, what we've done at our center is actually partnered with our nurses in the infusion center so that they have questions that they ask during each dose of Velcade to find out whether or not we should give the dose of Velcade. That has helped us to reduce the incidence of severe peripheral neuropathy at our center overall.

Now, once patients develop neuropathy, the keys are good pain control. One of the first things I often do is increase the amount of narcotics because of all the medicines we use to try and treat and control neuropathy, the most effective across the board is the use of narcotic analgesics. The patients feel better when they're on long-acting narcotics like MS Contin[®] or OxyContin[®], and it makes the amount of pain burden that they feel with neuropathy much, much better. There can be topical things that can be used. There can be additional drugs that are used, for instance, in diabetic neuropathy that can be effective as well. All of those are worth trying, but to me the single most important thing to do is to try and prevent it, anticipate it or use the long-acting narcotics to try and minimize its impact on activities of daily living.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from the telephone audience, please.

Operator

Our next question comes from Ira, calling from Nebraska. Please state your question.

Ira, calling from Nebraska

"Yes, I was wondering, I had been on lenalidomide for three-and-a-half years, and then I started resisting it and they tried the Pomalyst[®], and I started resisting it. Now they want to try the new Kyprolis[®], with the new IMiDs, and I was just wondering if it's too late for me to get a stem cell transplant because my stem cells might be rejecting it now?"

Sagar Lonial, MD, FACP

So, typically we know that transplant can be most effective earlier in the disease course. Later in the disease course, it may not be as effective. It doesn't mean it can't offer benefit. But the question is: Did you have stem cells collected early on or not?

Ira, calling from Nebraska

"No, I did not."

Sagar Lonial, MD, FACP

If you didn't, it's going to be harder to collect them now. The longer you're on lenalidomide, the more difficult it becomes to collect stem cells. We don't know about pomalidomide, but I suspect it's going to be similar. I think it would be worth trying to see whether you're able to mobilize stem cells, but typically after six months of lenalidomide, it does become a little bit more difficult. You were on for eight years, so-



Ira, calling from Nebraska

"No, I was on three-and-a-half years."

Sagar Lonial, MD, FACP

Three-and-a-half years. So, the fact that you're further away from those treatments now may have allowed the bone marrow a chance to recover from that, and so it might be certainly possible now to mobilize stem cells. But it's probably going to be tougher than usual.

Ira from Nebraska

"Okay, thank you very much."

Lizette Figueroa-Rivera, MA

Thank you, Ira, for your question. The next question comes from our Web audience. Margie asks, "What monitoring schedule do you recommend for someone posttransplant with no detectable disease? Any standard labs or bone marrow biopsies?"

Sagar Lonial, MD, FACP

So, what we typically do is an annual bone marrow just to assess what the marrow burden looks like and to make sure that there are no other complications of treatment like myelodysplastic syndrome or things that are arising.

In terms of assessment of the M protein, if a patient is on maintenance therapy, we would assess the numbers every month. But I think assessing myeloma numbers, free light chain, urine, all those things probably every two to three months if a patient's not on maintenance, is probably reasonable in that situation.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from the phone audience please.

Operator

Our next question comes from Hilma, calling from Florida. Please state your question.

Hilma, calling from Florida

"Hi, I was on Pomalyst and dexamethasone. The oncologist took me off the dexamethasone, and then the levels started rising. As of tomorrow, I'm supposed to start the Kyprolis and Revlimid. Is there anything special to look for, or is it just maintenance, just checking like the regular medication?"

Sagar Lonial, MD, FACP

Yes, I think the use of carfilzomib and lenalidomide together, as was described in the ASPIRE trial, can be very active. But none of those patients had seen pomalidomide before. So, it's unusual to get pomalidomide before lenalidomide, so we don't know what the data for that combination will be in patients who, it sounds like you were resistant to, your myeloma was resistant to pomalidomide. So, I don't know how much benefit you're going to get with the addition of lenalidomide in that situation. Carfilzomib probably will have activity, but the addition of len I don't know.





Thank you for your question. The next question comes from our Web audience. Kathleen asks, "Can the genetics of your myeloma change through the years of treatments?"

Sagar Lonial, MD, FACP

That's a great question. There are some things that we think occur as what we call primary translocations, and that can be things like hyperdiploidy or 4;14 or 14;16 or 11;14 translocations. There are also things that are acquired over time, such as abnormalities in chromosome 1, development of 17p deletions and other proliferative kind of signatures that may start to occur over time. So, there are some that are there from the very beginning, and then there's a whole other list of ones that are acquired over time. The ones that are acquired over time typically tend to be bad because they represent ways that the myeloma cell has figured out how to get around what we normally try to do to control it. So, acquiring new genetic abnormalities typically does represent what we call clonal evolution.

Lizette Figueroa-Rivera, MA

Thank you for that explanation, doctor. The next question comes from our telephone audience please.

Operator

The next question comes from Bernard, calling from Iowa. Please state your question.

Bernard, calling from lowa

"Yes, I was diagnosed with multiple myeloma the first of December, 2011, and went on a government trial, Medicare-backed trial which included Velcade. I had to be taken off after the sixth treatment with Velcade because it completely dehydrated my system, and I was on a combination of lenalidomide and dexamethasone for about a year and a half. For the past year and a half, it was reduced from 10 milligrams of Revlimid to a 5-milligram level of Revlimid, and that's been holding everything within acceptable range over this period of a year and a half or better. I'm just wondering what your comments and information is on this continuance of Revlimid 5-milligram level."

Sagar Lonial, MD, FACP

Continuing it at 5 milligrams?

Bernard, calling from lowa

"Yes, and the continuation of the 5-milligram level of Revlimid."

Sagar Lonial, MD, FACP

Yes, I think while we start at 25 milligrams of lenalidomide as the starting dose, there are many people who are on either 10, 15 or 5 milligrams over time. So, whatever dose is tolerable and is associated with good disease control I think is a fine dose. I have many patients that are on 5 milligrams.

One of the side effects that has been identified recently with long-term lenalidomide use is what appears to be a chronic diarrhea-type situation. One of the things that we've identified through our work, as well as other work from the UK, has been the use of a cholesterol-lowering medicine called



Welchol[®]. Welchol is able to pretty significantly reduce, if not completely eliminate, the incidence of lenalidomide-associated chronic diarrhea. So, if patients who are on for more than a year have this as a problem, this is something you could ask your oncologist or your primary care physician to prescribe to try and better control that really important side effect.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and thank you, Bernard, for your question. The next question, doctor, is from Vita, and she's worried about getting secondary cancers since she takes Revlimid as maintenance, and she just wants to know what your thoughts are about the chances of getting secondary cancer on Revlimid maintenance.

Sagar Lonial, MD, FACP

Yes, this is something that's been looked at in a number of different studies. It's interesting, when I first started transplanting, doing autologous transplants in the early 2000s, one of the things that we told patients who were having an autologous transplant-this was before Revlimid-was that there was between a 5 and 10% risk of developing secondary myelodysplastic syndrome or leukemia after having had an autologous transplant. That was because we use so much chemotherapy before patients had the autologous transplant, drugs like Cytoxan and etoposide and other drugs like that, that we just don't use very much anymore, but that was between 5 and 10% risk of a secondary cancer.

With lenalidomide in the maintenance setting, that number is probably somewhere around 4 to 6%, so we're much lower than we were ten or 15 years ago, and in many ways it is associated with, again, alkylators. It's associated with low-dose melphalan as being the highest risk. High-dose melphalan is the second risk. So, to me it's about risk-benefit. If you look at the curves from a paper published by Dr. Antonio Palumbo a few years ago, the risk of dying of relapsed and refractory myeloma is much, much higher than the risk of developing a second cancer. So, while it does happen—and in those rare cases where it does happen, it's very challenging to treat and it's certainly unfortunate-a majority of patients don't spend their time dealing with secondary cancers. They spend their time dealing with relapsed myeloma. If lenalidomide can prevent that for a longer time, then in my mind the risk-benefit ratio favors it.

Lizette Figueroa-Rivera, MA

Thank you, doctor. We'll take the next question from the telephone audience please.

Operator

Our next question comes from Sharon, calling from Arizona. Please state your question.

Sharon, calling from Arizona

"Yes, I would like to know if one achieves complete remission, would you continue the maintenance drugs all the while you're in remission."



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So, the answer really gets back to that iceberg that I showed you before. The iceberg concept is that even when you're in complete remission, as we currently define it, there's still myeloma in the body. So, I would continue. Our goal is to get to lower and lower levels of remission, but as of now with the way we measure it, I would not stop just because the patient's in complete remission.

Lizette Figueroa-Rivera, MA

Thank you, doctor. Also, you mentioned Welchol for diarrhea: Could you please spell that for the audience that's on the phone?

Sagar Lonial, MD, FACP

Yes, it's Welchol (colesevelam hydrochloride).

Lizette Figueroa-Rivera, MA

Thank you, and we could also provide that information through our Information Resource Center. So, if patients after the call would like to call 1-800-955-4572 or even email us at infocenter@LLS.org, we can get that information to them.

Doctor, the next question comes from the Web audience. Joe asks if the interventions are different for nonsecretory myeloma.

Sagar Lonial, MD, FACP

Yes, nonsecretory myeloma is certainly much more challenging. What I do in that situation is just try to sort of be overaggressive in terms of my approach there because it's harder to follow those patients.

Now, using things like the free light chain assay and PET scans, you may get markers that you didn't get in historically nonsecretory myeloma patients, so you may have more information to go on than you think. But, in general, I tend to, what I guess you could term "overtreat" nonsecretory patients just so I can make sure that I'm not missing something and try and again get long-term disease control as best I can.

Lizette Figueroa-Rivera, MA

Thank you, doctor, and we'll take the next question from the telephone audience please.

Operator

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

Peter, calling from Michigan

"Hello, I've had two stem cell transplants, autologous ones, and the second one was very successful. But I do have recurrent disease as of about four months ago after a 32-month remission. However, I had a PET scan recently that showed, although I have about ten new lesions in my skull, that they have not progressed in size or number over the last three months, so my doctor had recommended no chemotherapy of any kind at this time. I have a nonsecretory condition. So, I'm wondering if you had any thoughts about following up. At this point, I'm going based on pain levels to determine if I have more testing."

that's certainly good.

Again, following somebody with nonsecretory is very tough because you don't have those markers that many of us use. To me, when to treat a patient whose myeloma has come back is dependent on a couple of factors. One is symptoms, and you just reported you're not having any symptoms. So,

The second is what's happening with the blood counts. In nonsecretory myeloma, blood counts often become an important surrogate for how active the myeloma is because, as the myeloma becomes much more active in the bone marrow, the hemoglobin, the platelets, the white count can all begin to drop because the myeloma is being crowded out as I mentioned earlier.

The third is the development of new bone lesions, because in nonsecretory myeloma, the blood counts in the bones are really all you have to go on as surrogates for disease activity. So, if I see that the bone lesions are starting to get more active, even though they may not be causing pain, that's probably going to prompt me to think very seriously about whether or not I'm going to treat because that's really one of the few markers that you have that anything is going on. While you may not be symptomatic now, I don't know how long you'll continue to remain without symptoms in the next few weeks or months.

Lizette Figueroa-Rivera, MA

Thank you, Peter, for your question. The next question comes from the Web audience. Doctor, Maria asks, "What kind of diet should one be on to keep up red blood cell counts, and how much calcium should a patient take?"

Sagar Lonial, MD, FACP

I think those are good questions. In terms of diet, as I mentioned earlier, a healthy, well-balanced diet is probably sufficient. If you want to take an over-the-counter vitamin, that would be fine. You don't have to pay lots of money for a really expensive vitamin. A regular generic vitamin is probably sufficient.

In terms of calcium, the general recommendation on calcium for osteoporosis prevention and things, calcium with vitamin D is probably reasonable. There's no reason to go to high-dose calcium, and so I think those are pretty standard recommendations.

Lizette Figueroa-Rivera, MA

Thank you, doctor. We'll take the next question from the telephone audience please.

Operator

Our next question comes from Phyllis, calling from Tennessee. Please state your question.

Phyllis, calling from Tennessee

"Yes, my question, Dr. Lonial, is I was on aspirin, and they took me off of aspirin for three weeks for surgery, which I never did get to have the surgery because I had passed out in a parking lot. Apparently, I had what you call thrombosis a while ago. I had three blood clots in the neck and one in the left leg, and one of the blood clots went to the superior vena cava, and that was 99% blockage. It was dissolved by rapid lysis technique by a vascular doctor, and the others were dissolved by





Phyllis, calling from Tennessee

heparin. I'm now going to be put back on the Pomalyst, which I was on, and I'm wondering if there was a side effect of the Pomalyst which caused this?"

Sagar Lonial, MD, FACP

So, we know that the IMiD class of drugs, like pomalidomide and lenalidomide, can raise the risk of thrombosis, and you were on a reasonable prophylaxis regimen before with aspirin. When you stop the aspirin, just because you've stopped the Pomalyst, doesn't mean that your risk goes away. This is a really important point that you've raised—that is, when people get catheters put in or when they go for surgical procedures and they're told to hold the aspirin, if you've been on an IMiD within the last 30 days, you can't just stop because the risk of thrombosis doesn't go away until at least four to six weeks after you stop the IMiD.

So, what we do in those situations is find out whether we really have to stop the aspirin because a lot of times to put a catheter in they don't have to stop the aspirin. Or, if you absolutely have to stop the aspirin because of a major surgery, then switching to an alternative anticoagulant like low-molecular-weight heparin or something along those lines is what we will often recommend in that situation. But we don't like to just stop the aspirin cold turkey because your risk of thrombosis doesn't go away, even when you stop lenalidomide or pomalidomide for a couple of days.

Lizette Figueroa-Rivera, MA

Thank you for that question. The next question comes from the Web audience. Joy asks about complementary and alternative treatments for side effects, specifically for neuropathy pain.

Sagar Lonial, MD, FACP

Yes, in principle, I don't have a strong feeling one way or another. I think if people are uncomfortable and in pain, we want to look for new and creative ways to try and make them more comfortable.

What I would say is that you want to understand how those can interact or interfere with the treatments that we're giving you, and I'll give you an example. There's published data suggesting that vitamin C supplements on the day of Velcade administration can interfere with Velcade's ability to kill myeloma. We have clues that green tea may do the same thing as well, and so these are fairly innocuous, commonly used agents that are not alternative or complementary in nature but interfere with the ability of us to give successful anti-myeloma therapy. If you don't know whether the drug or the concept or whatever they're going to give you interferes, then you're taking a risk that you may impact the activity of the drug or may impact the side effect profile of the drug that you're taking to try and control your cancer.

Sagar Lonial, MD, FACP

So, with most of it, there's no data. So, I don't feel strongly one way or the other. What I end up telling patients is just be aware that there may be an interaction, and it could impact your treatment.

Lizette Figueroa-Rivera, MA

Thank you, doctor. That's a very important point. We'll take the next question from our telephone audience please.

Operator

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Our next question comes from Jean, calling from North Carolina. Please state your question.

Jean, calling from North Carolina

"Yes, doctor. What are your thoughts on how kyphoplasty might help with back pain due to the compression fractures in your spine?"

Sagar Lonial, MD, FACP

Kyphoplasty is a really important part of how we try and treat patients who have chronic back pain associated with compression fractures. So, if done in skilled hands, you can have improvement in as fast as five minutes after the procedure. I think it's a really effective, really accurate, very safe way to do things, and it's a treatment that we certainly do recommend to many of our patients if they are suitable candidates for that procedure.

Lizette Figueroa-Rivera, MA

Thank you, Jean, for your question. Doctor, we have a question from Dinshaw, Leela, Diane_and Patty. They're all asking about the new treatment using measles to kill myeloma cells. They're asking if it's true and how the trials are going.

Sagar Lonial, MD, FACP

So, I think the concept and the science behind the data that we've seen is really very interesting. There were 27 or 28 patients treated in the trial, of which one may have had a brief response. So, I don't think it's time to run out and invest in measles stock right now, but I think the concept is certainly an important one; it's one worth keeping an eye on in terms of future potential developments to see whether this early laboratory-based concept can be broadened and generalized for more patients over time.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from the telephone audience please.

Operator

Our next question comes from Mary, calling from Florida. Please state your question.

Mary, calling from Florida

"Yes, my question is about dexamethasone again. You mentioned it with IMiDs, but how about with proteasome inhibitors?"

Sagar Lonial, MD, FACP

So, the concept of combining corticosteroids or dex with proteasome inhibitors is probably additive in the sense that whatever you were going to get with dex you'll get that with a combination with the proteasome inhibitor. But it's not synergistic with proteasome inhibitors in the same way that it is with the IMiDs.

Just to give you an example, much of the carfilzomib data that was published early on in the relapsed/refractory setting used either very little dex, only 4 milligrams per dose in the first cycle, and



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then no dex after that. So, the dependence of activity on corticosteroids is much lower with the proteasome inhibitors than it is with the IMiD class of drugs.

Lizette Figueroa-Rivera, MA

Thank you, and the next question comes from the Web. Doctor, Monica asks, "Can two or more antibodies that have different targets or functions be taken together to effect a better response?"

Sagar Lonial, MD, FACP

Great question. We've proposed just that trial. It's not started yet, and we don't know the answer. But thinking about combinations of immune-based approaches is certainly very exciting, and it is a concept that we hope will be tested very soon in the near future.

Lizette Figueroa-Rivera, MA

Great, thank you, and thank you all for your questions.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA

Please help me thank Dr. Lonial for volunteering his time with us today. We hope this information will assist you and your family in your next steps.

[Slide 42 – The Leukemia & Lymphoma Society Offers]

The Leukemia & Lymphoma Society offers online chats for patients and for young adults and caregivers. The chats are moderated by oncology social workers and provide forums for patients and caregivers to share experiences and support one another. For information on how to participate, please review the flyer in your packet or go to www.LLS.org/chat. If we were not able to get to your question today, please call The Leukemia & Lymphoma Society's Information Resource Center at 1-800-955-4572. Information Specialists are available to speak with you from 9 AM to 9 PM Eastern Time, or you can reach us by email at infocenter@LLS.org. We can provide information about treatment, including clinical trials, or answer other questions that you may have about support, including questions about financial assistance for treatment.

Again, thank you, Dr. Lonial, for sharing your knowledge with us today. It's refreshing to know that there are a lot of new advances with myeloma, and we're looking forward to all of the new clinical trials and the clinical trial results in the near future.

To all the patients, caregivers and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Goodbye, and we wish you well.