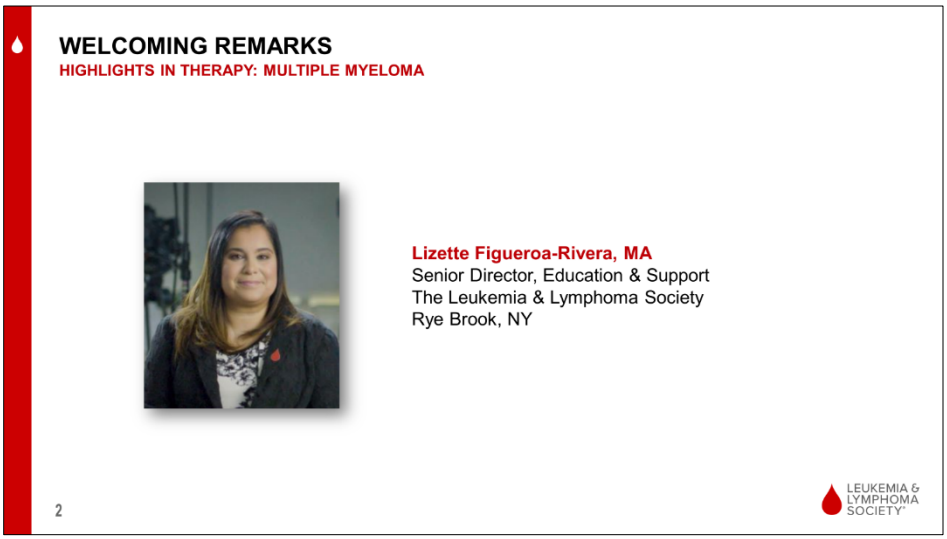
WELCOME AND INTRODUCTION



Lizette Figueroa-Rivera, MA
Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Andrew J. Cowan for volunteering his time and expertise with us today.

Before we begin, Izak, a myeloma patient, will share some welcoming remarks.

Izak, Myeloma Patient
Hi, my name is Izak, and let me begin by stating emphatically that I have been very “lucky in my unluckiness” ever since I was diagnosed over 12 years ago with high-risk multiple myeloma (MM). I'm so grateful for all of the amazing scientific advancements in this field, including the three new FDA (U.S. Food & Drug Administration)-approved bispecific drugs and the futuristic CAR (chimeric antigen receptor) T-cell (thymus lymphocytes) transplants. [I am grateful] for the health insurance I have to cover my treatments, [for the] exceptional healthcare and support I've received, and let me not forget to mention the LLS with its online group chats, informative webinars, and copay assistance.

I've learned to take one day at a time, do what is in front of me today, and remember that people are not statistics. We are all unique individuals.

In spite of my high-risk diagnosis, I was fortunate to get seven years of stringent complete remission after a stem cell transplant 12 years ago and other treatments following my relapses and remissions. I'm currently regaining my full strength and immunity defenses after successful CAR T-cell transplant – truly miraculous.

Like most of you, I was understandably scared, confused, and overwhelmed when I was first diagnosed. Ninety percent of my bone marrow was malignant, and I had debilitating back pains. Today, I look toward a promising and hopeful future. The philosophy I embraced at the time, and still try to maintain on a day-to-day basis, is to partake in and embrace anything and everything I can to improve my status. Integrative oncology that includes acupuncture, Qigong, exercise when I can, mindful meditation, therapy, and the all-important support groups, nutrition, and to educate myself as much as possible, and with all this to maintain perspective and a positive attitude. For me, it gives me a sense of some control over my life and well-being – an appreciation of everything around me daily.

Although I cannot prove scientifically that this has affected my treatment and outcome, I can say that it has altered my consciousness about my disease and quality of life overall rather than feeling victimized and asking, “Why is this happening to me?” It has empowered me. I feel like I have some control, and I can do whatever I can to improve the quality of my life in spite of my myeloma.

I'm happy to see that some of you embrace this too as you are here today to learn what we can from this LLS webinar. So welcome, and I leave you with one more bit of advice: My doctor told me he wanted me to walk ten miles every day. A week went by, and I called him and said, "Doc, I'm 70 miles from my house. What do I do now?"

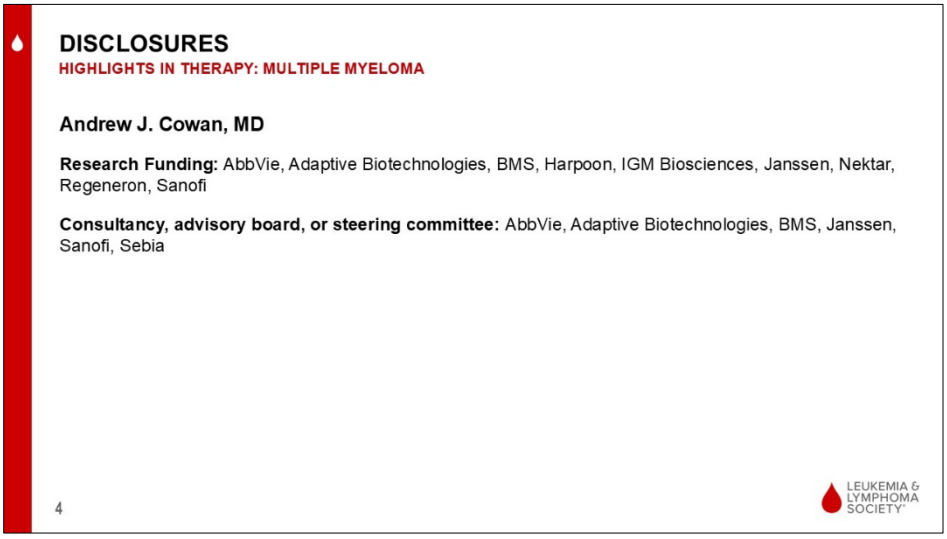
Lizette Figueroa-Rivera, MA
Well thank you, Izak, for not just sharing your story but continuing to bring us humor and hope through your many years of treatment. And I know that you are an active participant in our Myeloma Online Chat, and you may join him on Mondays on our chats. You may visit LLS.org/Chat for more information. Now, let us be there for you during this time, and please continue to let us know what you need.

We would also like to acknowledge and thank Genentech, Inc. and Biogen and Johnson & Johnson for their support of today's program.

PRESENTATION

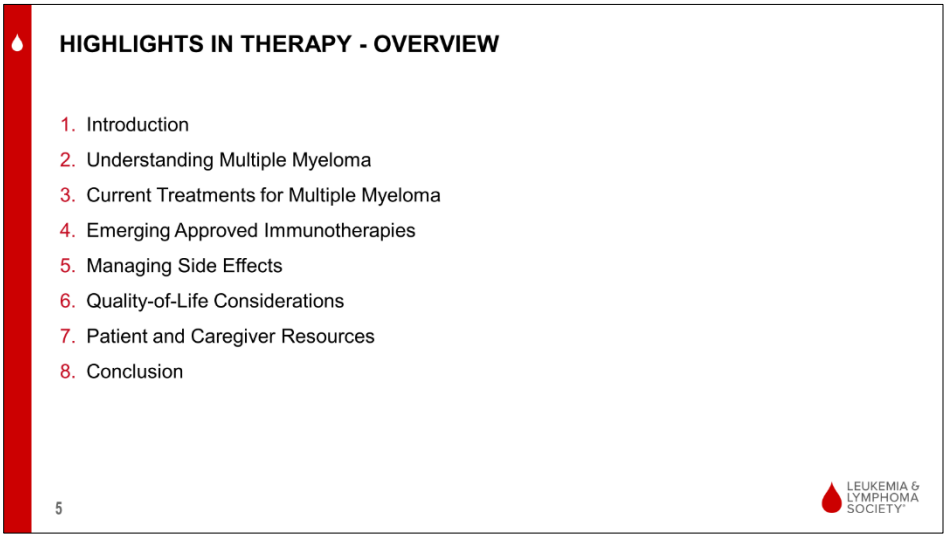
Lizette Figueroa-Rivera, MA
I am now pleased to introduce Dr. Cowan, an Associate Professor for the Division of Hematology and Oncology at the University of Washington, as well as an Associate Professor for the Clinical Research Division at the Fred Hutchinson Cancer Center and a Clinical Director of the Hematologic Malignancies/Hematology, Myeloma Program at UW Medicine in Seattle, Washington.

Dr. Cowan, I am now privileged to turn the program over to you.



Andrew J. Cowan, MD
Thank you so much for the very nice introduction, and I want to extend a hearty thanks to LLS for inviting me to talk today. It really is such an honor to talk to all of you folks here.

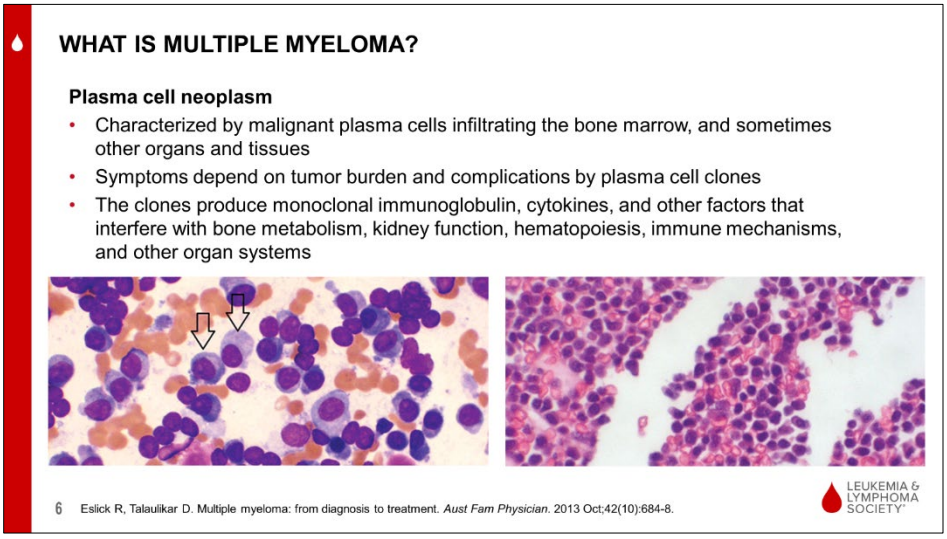
Shown here you can see my disclosures.



So today, this is going to be kind of a crash/bang tour of myeloma. While we're not going to go in-depth on any one topic, I hope we are able to cover many of the most important topics that come up either for someone who has a new diagnosis of multiple myeloma or someone who's been living with the disease and fighting it for many years.

You can see here some of the topics we're going to cover: talking a little bit about basics about the disease, current treatments for multiple myeloma, some emerging immune therapies (which were only possible, might I add, because of patient participation in clinical trials), managing side effects, quality-of-life considerations, and then we'll wrap it up with some patient and caregiver resources from LLS.

Apologies also. I am getting over a cold, so please forgive any throat clearing or nose blowing. I'm pretty sure I can make it through the whole talk though.



TRANSCRIPT

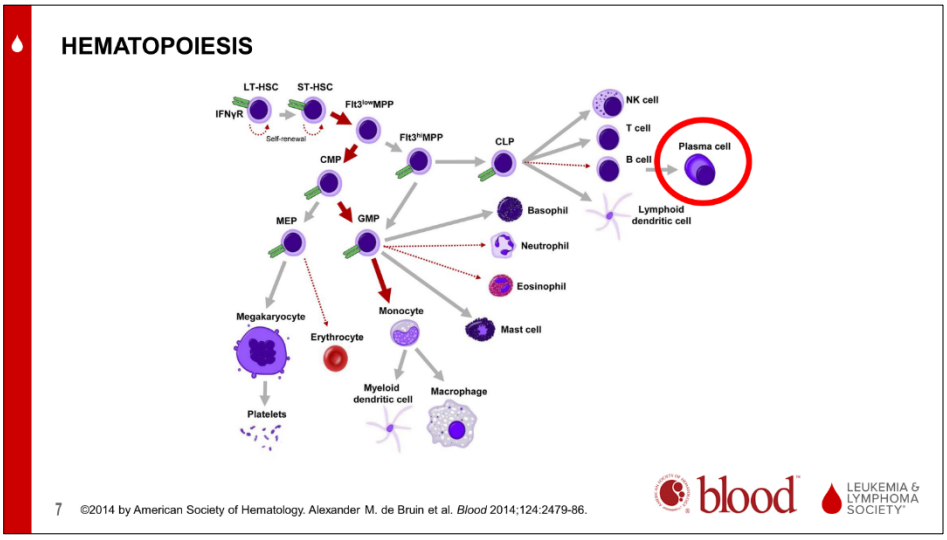
What is multiple myeloma? Multiple myeloma is – part of what drew me to this many years ago – a unique blood cancer, unique in how it manifests. It's very different from other solid tumors and other cancers that we're familiar with like colorectal or breast cancer.

The cell that multiple myeloma comes from is a plasma cell. Plasma cells are a very important component of our immune system. They're responsible for producing these proteins called antibodies that help your body fight off infection by binding to bacteria, viruses, and helping your body basically get rid of it [i.e., the infection]. Just like many cancers, we find that multiple myeloma still has some of the features that make it like a plasma cell; and one of them, as we'll talk about in a little bit, is the production of antibodies. That is really one of the major ways that we follow and track the disease is by the M spike (monoclonal immunoglobulins). That is a protein that's basically an antibody that's been produced by the plasma cell.

Basically what happens with this disease [is that] we get malignant plasma cells infiltrating the bone marrow. Occasionally, it can spread outside of the bone marrow into other organs and tissues. Symptoms really depend on tumor burden and complications by plasma cell clones, and what a clone is, is basically a genetically identical cell. And that's one of the hallmarks of cancer.

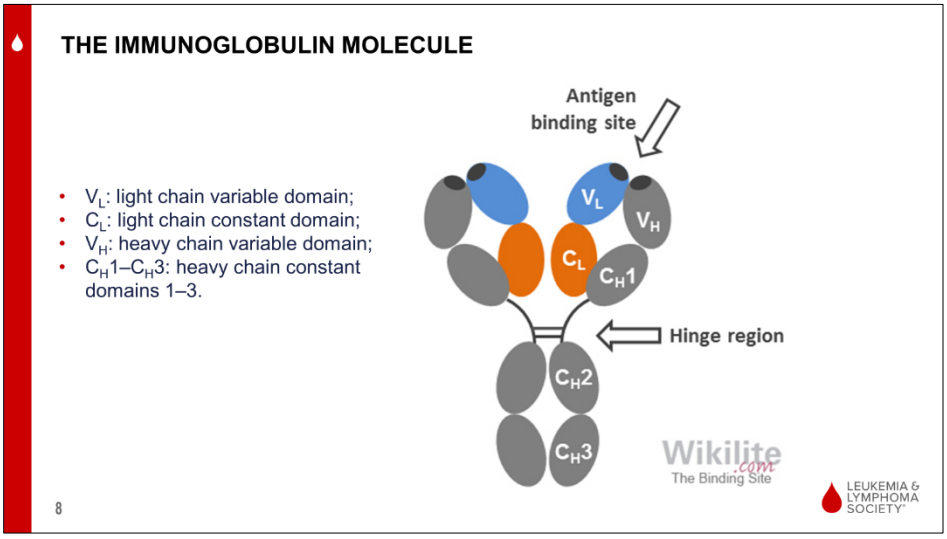
And so we have all these genetically identical cells. Sometimes we have subclones that emerge from the original clone. They produce these antibodies (we call them monoclonal immunoglobulins or M spikes), cytokines (which are inflammatory proteins), and other factors that interfere with bones and result in myeloma bone disease, which can cause fractures, kidney function from elevated free light chains, sometimes impaired hematopoiesis (which is production of red blood cells, white blood cells, and platelets), other immune mechanisms and other systems.

As shown here, you can see on the bottom, this is what a slide of a myeloma biopsy looks like; and those large kind of fried egg cells, that's the myeloma cell. And so that's a plasma cell. When we see too many of them, that's the hallmark of what a biopsy would look like when someone has this disease.



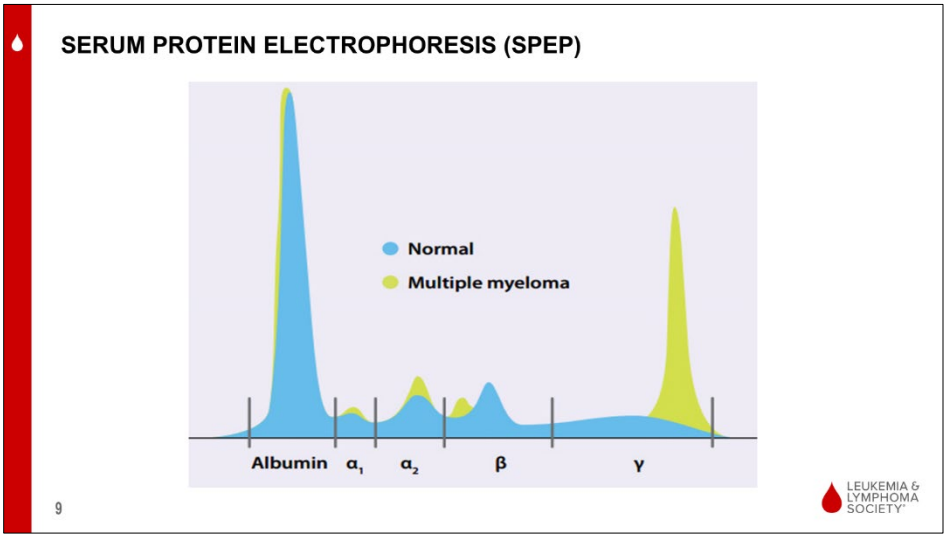
TRANSCRIPT

I mentioned hematopoiesis a little bit earlier, and I think this slide nicely shows where the plasma cell fits in in the scheme of hematopoiesis. What is hematopoiesis? Hematopoiesis is the production of platelets, red blood cells, white blood cells in the immune system from stem cells. And anyone who's had a stem cell transplant knows that stem cells can remake the entire immune system, and so that's shown here. We start out with stem cells up in the top-left corner that turn into other cells that produce things like platelets, macrophages, other parts of our immune system, and then produce T cells and B cells (bursa-derived lymphocyte); B cells which eventually mature into plasma cells. That's where plasma cells come from. They come from B cells. And so it's sort of considered a B-cell malignancy like lymphoma and chronic lymphocytic leukemia, but it's a very different type.



I mentioned the immunoglobulin, and this is really important. Anyone who has multiple myeloma, and anyone who is helping to take care of someone who has multiple myeloma, it's really important to sort of understand what this means. An immunoglobulin, again, is also sort of synonymous with an antibody. Antibodies are these proteins. They look like this under a microscope, and they bind to proteins on the surface of virus and bacteria and help your body get rid of it.

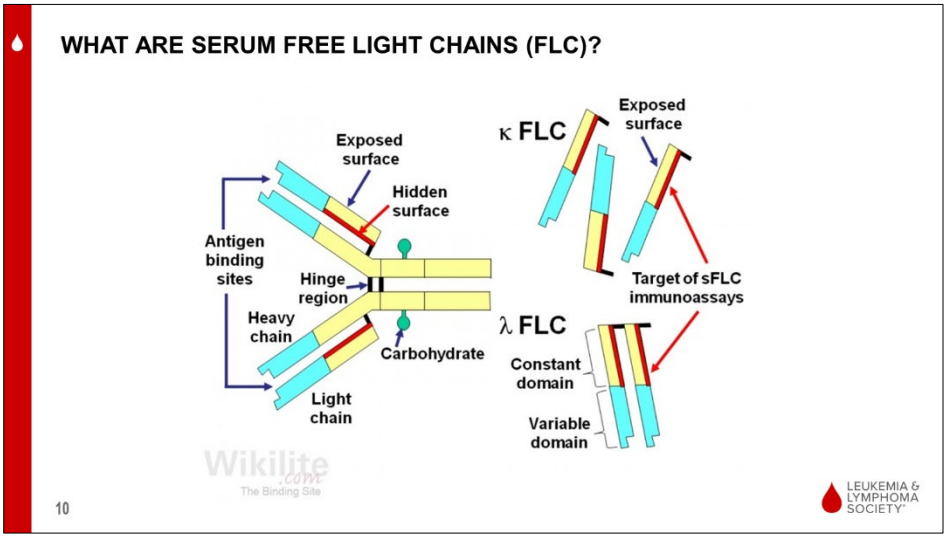
And so every antibody has an antigen-binding site, shown here in the upper right and a hinge region. Antibodies are made of a light chain and a heavy chain region.



We care about antibodies because when there are too many of them that are produced by a clonal plasma cell, we see an M spike, and so this is a test that we get to look for an M spike. Your doctor will commonly be ordering this if it's applicable to you to track your myeloma. The test is called the serum protein electrophoresis or SPEP, and it's usually paired with immunofixation.

SPEP tells us how much abnormal protein there is in a blood, in your serum. Basically [for] this test we take a sample of your serum, [and] we put it on a laboratory test called the gel electrophoresis. This separates out proteins by size and charge, and normally we should see this blue pattern here where there's a large spike of albumin. Albumin is a very common protein in our blood. It helps maintain, keep the blood, keep water and fluid inside the blood vessels. But we also see fairly low levels of alpha 1 (α_1), alpha 2 (α_2), beta (β), and gamma (γ); and these are where we see these other antibodies.

When we see a spike in the gamma region, that's the M spike; and that's something we see in anyone who has a plasma cell disorder, whether it's smoldering multiple myeloma, whether it's MGUS (monoclonal gammopathy of undetermined significance), or whether it's multiple myeloma. So, that's a hallmark feature; and most patients, probably 90% of patients are going to have a detectable M spike by SPEP.

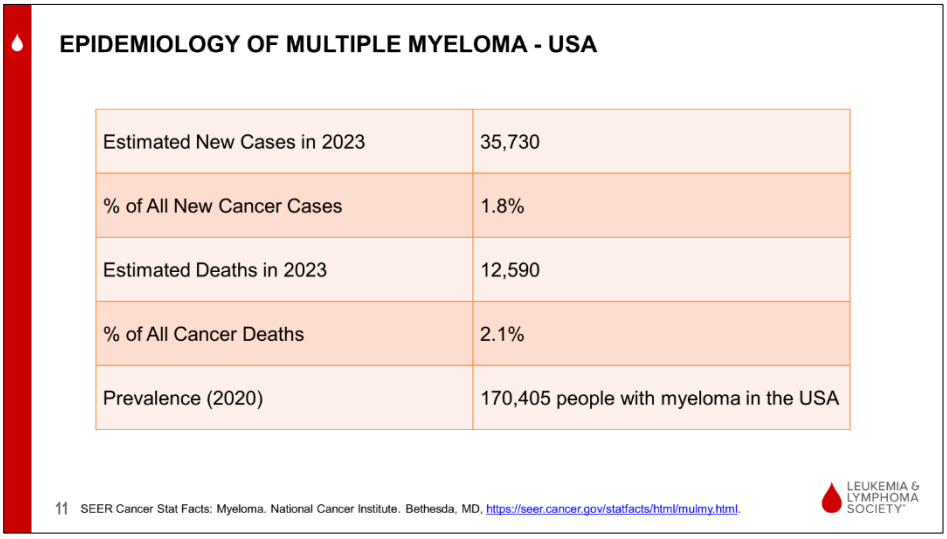


Serum free light chain, that's another test we commonly get to evaluate multiple myeloma. Serum free light chains are part of that antibody molecule. They are part of the antigen-binding site. They're actually manufactured separately inside the plasma cell and then put together to create the antibody molecule.

Serum free light chains are important for several reasons. One, for some patients, they're going to be the primary way that we track the disease. And there's this test called the serum free light chain test that your doctor is probably ordering or should be ordering every month. And what that will tell us is [whether] there an elevation in kappa (κ) or lambda (λ); and every patient is either going to be an elevated kappa or an elevated lambda.

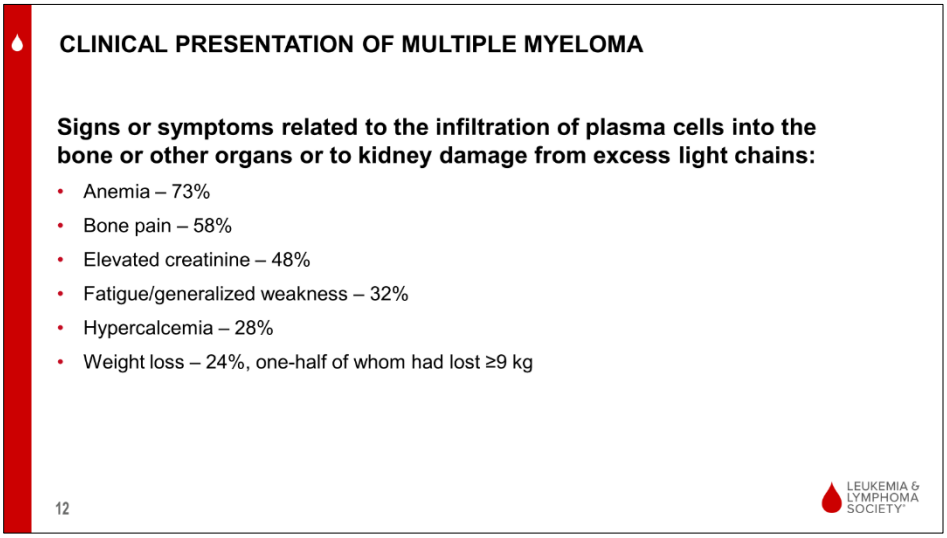
Same goes with the antibodies. There are five types of antibodies that people can have: IgG (Immunoglobulin G) and IgA (Immunoglobulin A) are the most common, IgM (Immunoglobulin M) and IgD (Immunoglobulin D) are slightly less common, and IgE (Immunoglobulin E) is very rare if ever reported. So, most folks are going to be IgG or IgA, and it's uncommon for that to change, although there are reports of that happening. For the most part, whatever your type was, it's going to be the same throughout your entire disease course.

So, serum free light chains are important, not only because they can track the disease, but also if serum free light chains are really elevated, that's what leads to kidney failure. And so when they're above 80 milligrams per deciliter or 800 milligrams per liter, some labs use, there is a much higher risk of developing renal failure. We know that this myeloma kidney disease comes from these free light chains.



How common is multiple myeloma? Well, multiple myeloma is not the most common disease. It's, I think, the second-most common blood cancer. It's 1.8% of all cancer cases in the United States. There were an estimated 35,000+ cases in 2023, and comprises 2.1% of all cancer deaths. What I think the real important point here is the prevalence. So, there are two things we look at with epidemiology. One is the incidence, and that's the estimated new cases in 2023. That's the raw incidence. We get an incidence rate by dividing that for the population. And so for multiple myeloma, it's about 7 per 100,000 people in the United States.

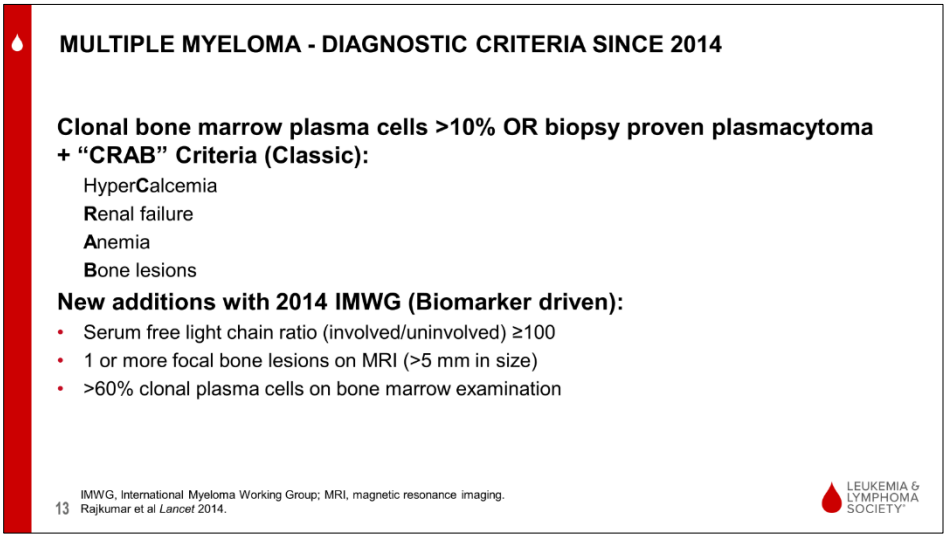
The highest incidence is in Australia where I think it's slightly higher than that, and we see much lower incidences in other parts of the world. We don't fully understand why the incidence rate varies between countries, but we know it's around 7 for 100,000 in the United States. But, interestingly, we see 170,405 people alive with myeloma in the United States today. What does that tell you? It tells you that people are living much longer with the disease. If the incidence and the prevalence rate were about the same, we know that most people don't survive very long, but that's not the case as you can see clearly here where the prevalence is probably 5-fold higher than the incidence. So that, I think, is a really nice way to show how much we've seen advances in the diagnosis and treatment of this disease.



How does multiple myeloma present? This is a super common question, and I think the challenge of multiple myeloma is that the symptoms of the disease are often just common symptoms in general. If you go to a primary care doctor, one of the most common things they see is bone pain or back pain; and back pain is a common presenting complaint of multiple myeloma. Fatigue, fatigue is another super common complaint in primary care; and so it's because the symptoms sort of overlap with common reasons that people see the doctor, unfortunately, a lot of times it can take a while to get a diagnosis.

Sometimes people might get labs checked, and they might have an elevated total protein. That's a way that sometimes folks have found out that they have myeloma because that total protein is elevated because of the M spike. Anemia that's unexplained is another reason that people get diagnosed. Elevated creatine or kidney dysfunction from the free light chains, the myeloma cast nephropathy, hypercalcemia, and weight loss. But the most common is anemia.

Most people with multiple myeloma didn't know that they had something like MGUS or smoldering, which we know most of the time predisposes people to getting this disease. And so, unfortunately, it does sometimes take a while; but I think it just highlights that we need to improve awareness of the disease amongst primary care practitioners and to have a low threshold to order an SPEP, which, frankly, is a very cheap test compared to a lot of tests that we order and gives a very easy way to start thinking about the disease.

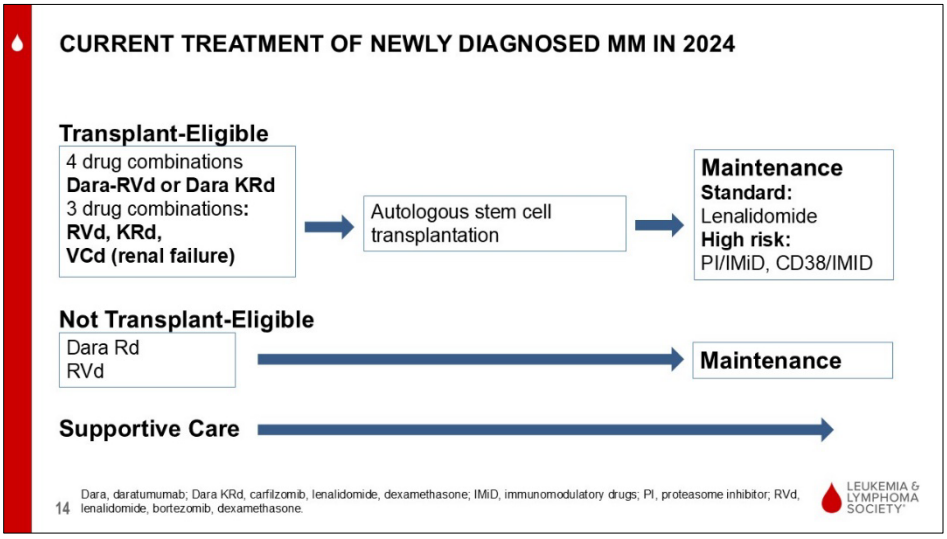


What is the diagnosis? How do we make a diagnosis of multiple myeloma? For 10 years now, it's hard to believe it's been 10 years since the most recent diagnostic criteria came out. These have been the diagnostic criteria. So, basically, someone has to have a bone marrow biopsy that shows greater than 10% plasma cells or a biopsy-proven plasmacytoma plus the CRAB (hypercalcemia, renal failure, anemia, and bone disease) criteria; and the CRAB criteria is a mnemonic. It's a mnemonic that doctors use to help remember the symptoms. And that includes hypercalcemia, which is the C, elevated calcium. Renal failure is the R, and that's kidney failure. Anemia and myeloma bone disease, which are the bone lesions which are usually, when we look at an x-ray, there are osteolytic bone lesions which are basically punched out holes in bones.

There are some new additions with 2014, not necessarily new anymore because it is a decade old, but the most new, I suppose, and that is the inclusion of the serum free light chain ratio of involved/uninvolved greater than 100; more than one focal bone lesion on MRI (magnetic resonance imaging); and greater than 60% clonal cells, plasma cells on a bone marrow examination.

Increasingly sometimes we have folks who are diagnosed with multiple myeloma based on these biomarker-driven criteria where they don't have any symptoms. And so it can be kind of a disconnect between being told by your doctor, "Hey, you have a bad cancer." But, "Hey doc, I feel fine." And it's worth knowing why we include these. It's because these were previously patients who would have been considered to have smoldering MM, meaning asymptomatic myeloma. We don't always treat that, but these patients who had these features had a very high risk of developing active myeloma within the next year.

And so because of that, we opted to basically include them as a part of having myeloma to try to make sure we're getting patients treated before they get hypercalcemia, renal failure, anemia, bone lesions with the idea that why wait. If we know patients have a biologically high risk of developing the disease, we should try to treat before onset of symptoms. And so that's sort of the philosophy that led to inclusion of these in the diagnostic criteria.



So, let's shift gears a little bit and talk about treatment. I'll discuss the data that support some of these sorts of recommendations; but in general, this is how I think about treatment of newly diagnosed multiple myeloma in 2024. For folks who are transplant-eligible for an autologous stem cell transplant (patient's own stem cells for transplant), we typically would recommend starting with a four-drug combination, most commonly daratumumab (Darzalex®), lenalidomide (Revlimid®), bortezomib (Velcade®), and dexamethasone (Decadron®) or Dara-RVd. Dara-KRd (daratumumab, carfilzomib [Kyprolis®], lenalidomide, and dexamethasone), which substitutes the bortezomib for carfilzomib could be considered in some patients, especially if someone has neuropathy and we want to avoid making that worse with bortezomib; but it's not clear that one is better than another necessarily

Three-drug combinations might be okay, but I think for the most part anyone who is transplant-eligible, Dara-RVd should be considered and offered based on some of the studies I'm about to show you. Stem cell transplant is the next box here, and stem cell transplant is still something that we very much think is part of the treatment of newly diagnosed multiple myeloma. The key part of the transplant is not actually the transplant itself but rather it's the administration of high-dose chemotherapy, a drug called melphalan to further improve the depth of response in people who have gotten upfront treatment with Dara-RVd.

Transplant is something you want to have a pretty in-depth conversation about with your doctor and with the transplant team to understand risks and benefits and really to help you make an informed decision because the decision to pursue transplant is one that you should make with your doctor. You should not feel forced to get a transplant. But we still think transplant is a very important part of treatment with, as I'll show, based on the results of a large study that was done.

For maintenance, maintenance just refers to a lower dose of the drug that we were getting when we started, but the goal is to try to keep the disease at bay. Numerous studies have shown that maintenance is beneficial at improving survival, and so I recommend maintenance to everybody after a stem cell transplant.

We didn't really talk about this because there's just so much to cover, but one of the things we commonly look at with multiple myeloma, which is alluded to here in the slide, is whether you're standard or high risk. Just so you know, the high-risk markers are things like deletion 17p (loss of all or part of the p arm of chromosome 17), and the translocation between chromosomes 4 and 14 and translocation 14;16. Those are the three that are most commonly accepted. There are others like a 1q amplification (gain of chromosome 1q), translocation 14;16. And just note that those are commonly considered high-risk features.

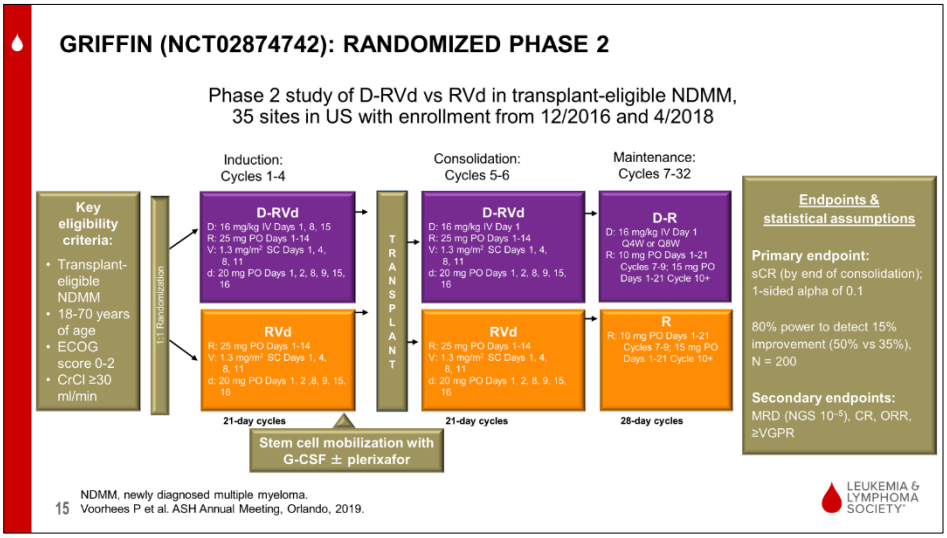
There are other features of the disease that can be considered high risk, like having an anaplastic morphology or having a plasma cell leukemia. Anyone who kind of falls into those would be considered high risk. For patients who are high risk, we commonly would recommend two drugs for maintenance, usually a proteasome inhibitor, that's what PI is, and that includes drugs like bortezomib and carfilzomib or CD38 (cluster of differentiation 38) plus an IMiD (immunomodulatory drug). Standard risk, we typically would consider lenalidomide, although with PERSEUS (multicenter, randomized, phase 3 study), I think using daratumumab and lenalidomide is very reasonable; and we'll cover that data in a second.

For folks who are not transplant-eligible, we typically would start with daratumumab-lenalidomide and dexamethasone or the RVd regimen, which is lenalidomide and bortezomib and dexamethasone followed by maintenance. And then supportive care is really important, and we'll talk about that a little bit later. Supportive care starts at the time of diagnosis and continues throughout. What is supportive care? Supportive care is paying attention to all the other things besides treatment, and so that includes aspects such as preventing infections. We know that myeloma treatment causes an increased risk of infections, particularly shingles and so often almost always anyone getting a CD38 antibody or a proteasome inhibitor should get an antiviral for prevention of shingles.

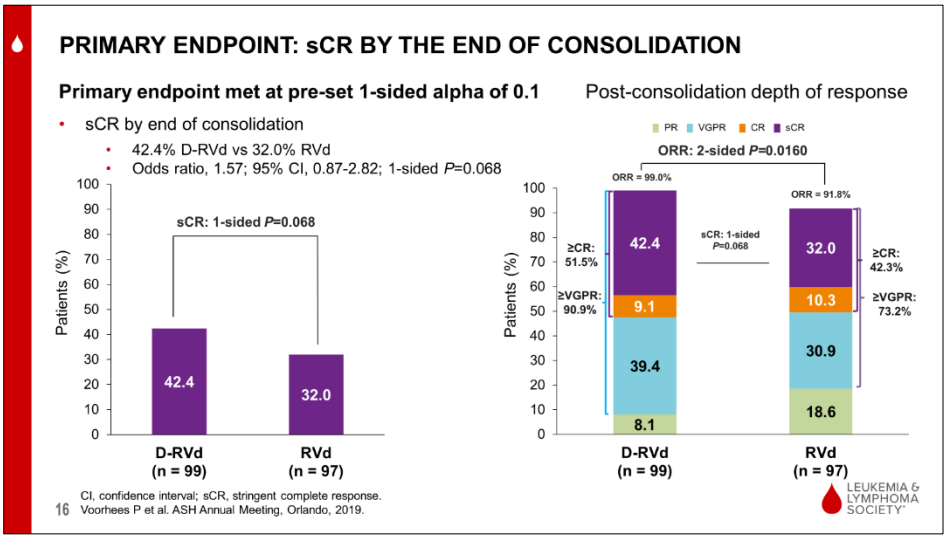
Bone health, paying attention to bone health. We know that drugs such as bisphosphonates (i.e., risedronate [Actonel®], alendronate [Fosamax®], ibandronate [Boniva®], zoledronic acid [Reclast®], and pamidronate [Aredia®]), and denosumab (Prolia®) can reduce the risk of myeloma-related bone fractures or bone events. And so this should be something you discuss with your doctor.

Not only that, immunomodulatory drugs such as lenalidomide and pomalidomide (Pomalyst®) and others have a risk of causing blood clots; and so we commonly recommend drugs to prevent those, such as aspirin or maybe a direct oral anticoagulant, for example, like Eliquis® (apixaban).

Finally, there are the quality-of-life aspects; and many of these drugs can cause neuropathy – bortezomib being the most common one. We'll talk about that later. But also managing side effects like fatigue, gastrointestinal side effects, risk of falls, and loss of strength; and we'll talk about that a little bit later. But supportive care is super important. And if we don't manage supportive care correctly, we don't get as much benefit from these treatments. These treatments are amazing. They've prolonged people's lives, but we have to pay attention to quality of life and making sure that the rest of a patient's health is supported throughout getting myeloma therapy.



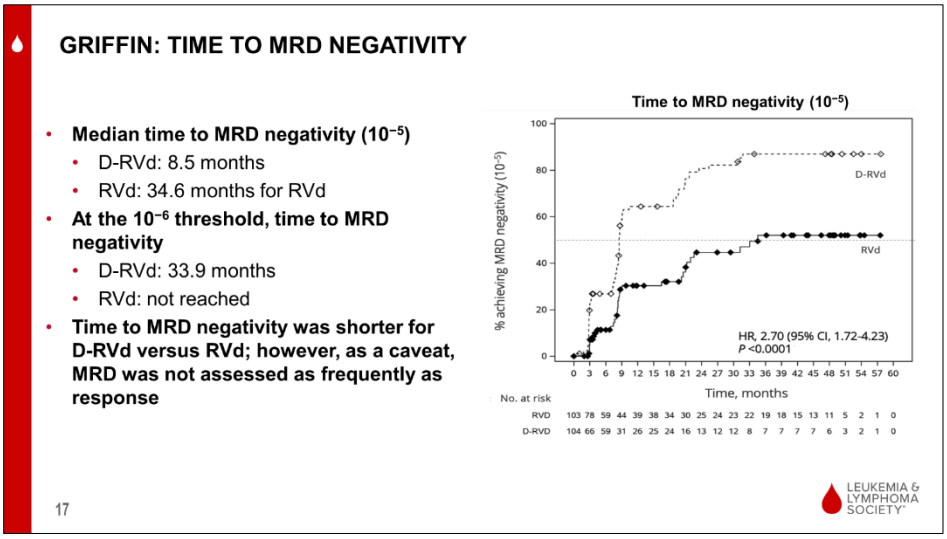
Let's dive into a little bit of the data. I'm going to present a couple of studies here that support the use of daratumumab and RVd, just so everyone can understand why this is a new standard of care. The first study that showed this was beneficial was the GRIFFIN study, which was a randomized phase 2 study comparing the RVd regimen to Dara-RVd with transplant and maintenance.



This study showed an improvement in rates of stringent complete response. What does that mean? It means there's no evidence of myeloma in the bone marrow, in the urine, in the blood, either by SPEP or free light chain. So, basically, as close as we can get to what the solid tumor doctors sometimes like to say NED, no evidence of disease.

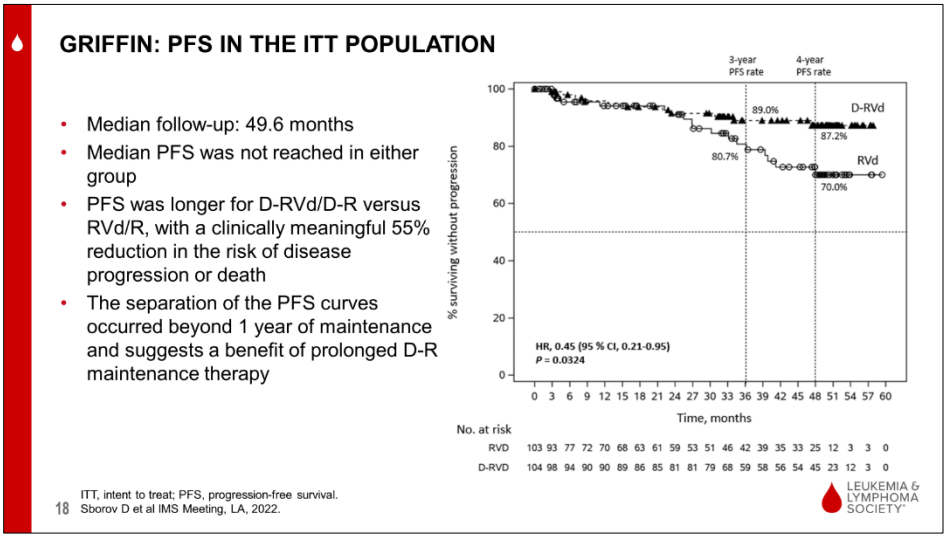
And so this met its endpoint. There was a higher rate of stringent CRs (complete responses) in patients who received Dara-RVd with transplant and maintenance compared to RVd, 42% versus 32%, and also, a higher response rate in general. Ninety-nine percent of patients had any response, meaning reduction in the monoclonal protein or free light chains compared to only 91% of patients who got RVd. So, I think that's a pretty dramatic improvement, especially if you consider the 9% of

patients or so who don't respond to RVd; we know that those patients don't do quite as well. So, we're really moving the needle quite a bit with Dara-RVd.



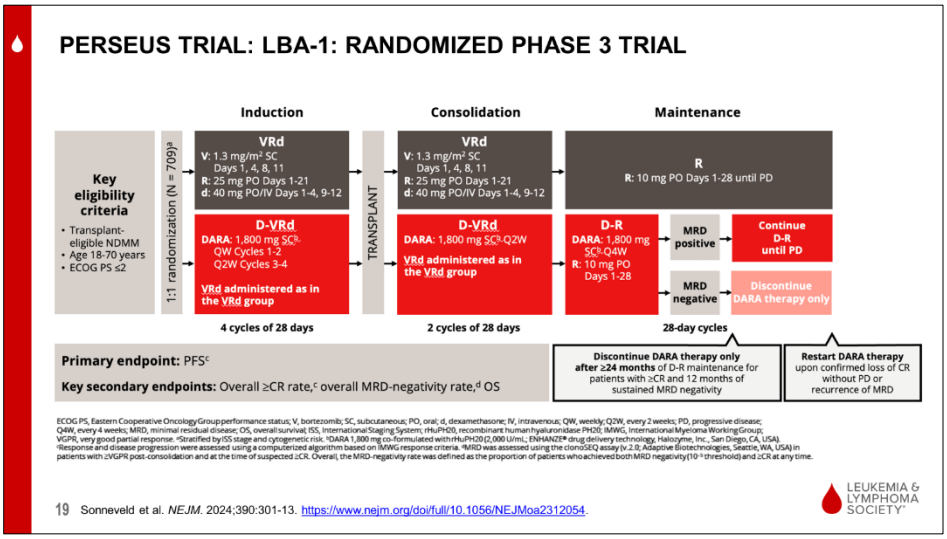
We also saw with GRIFFIN that the time to minimal residual disease (MRD) negativity was improved. So, you're asking yourself, “What is MRD?” For some of you who may not have heard this term before – a lot of you probably have – MRD is referring to tests that can detect disease at a much lower threshold than conventional tests. The most common test is the clonoSEQ® test; this is a DNA-based test that detects myeloma in the bone marrow, and basically this can detect disease that we can't see with standard tests, like flow cytometry of the bone marrow.

And so what we've seen with studies is that if you can get to a state where there's absence of MRD by this next-generation test, this next-generation sequencing, we know in general that patients tend to have longer remissions. They stay in remission longer, and we know that that always typically equates to having better survival. So, MRD is increasingly becoming something that we are paying attention to, and this study showed that patients achieved MRD negativity much quicker with Dara-RVd compared to RVd. And more patients achieved MRD negativity, as you can see here on this graph, which shows the percentage of patients achieving MRD negativity with either RVd or Dara-RVd.



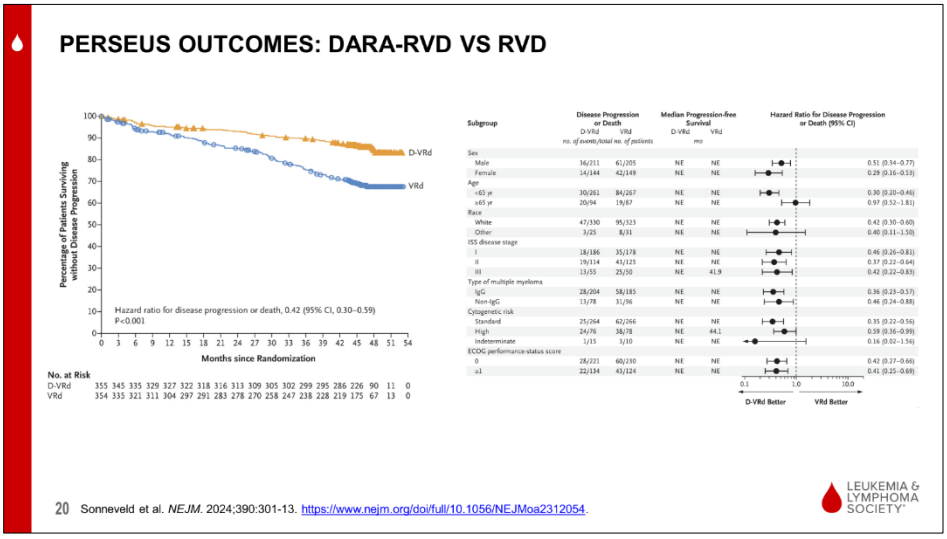
So, the other thing that oncologists typically look at with a treatment is a measurement called progression-free survival or PFS. So, what is that? PFS is a measurement where an event happens if someone either passes away or the disease progresses. And so it's a rough way to look at how long is this treatment keeping people in remission? So, when we see improved PFS, what that means is, in general, people are living longer without the disease coming back, which we think is really important with myeloma because of how bad some of these disease complications can be.

In GRIFFIN, it took a few years; but we saw an improved PFS after three years and four years in patients who received Dara-RVd compared to RVd. So, great we have this smaller phase 2 study.



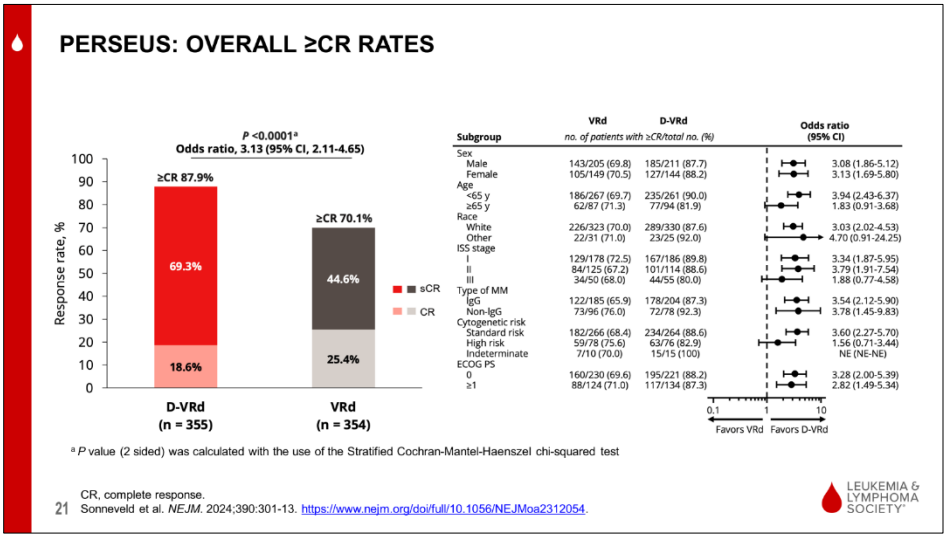
Next, there's the PERSEUS study, which some of you might have heard of; this was a larger study. It was done globally, so they had sites in Europe, in Australia, and Asia. This study was a very similar design to [the] GRIFFIN [trial], except they had a lot more patients; and it was a global study. Patients received either RVd or Dara-RVd. They had to be transplant-eligible, 18 to 70 years [of age], and have good performance status. Everyone either went Dara-RVd or RVd followed by transplant,

followed by consolidation, and then followed by maintenance with either lenalidomide or daratumumab and lenalidomide. One difference between [the] PERSEUS and GRIFFIN [trials] is that [the] PERSEUS [trial] allowed folks who achieved MRD negativity to stop daratumumab after 12 months of sustained MRD negativity, and so that's a little bit different.

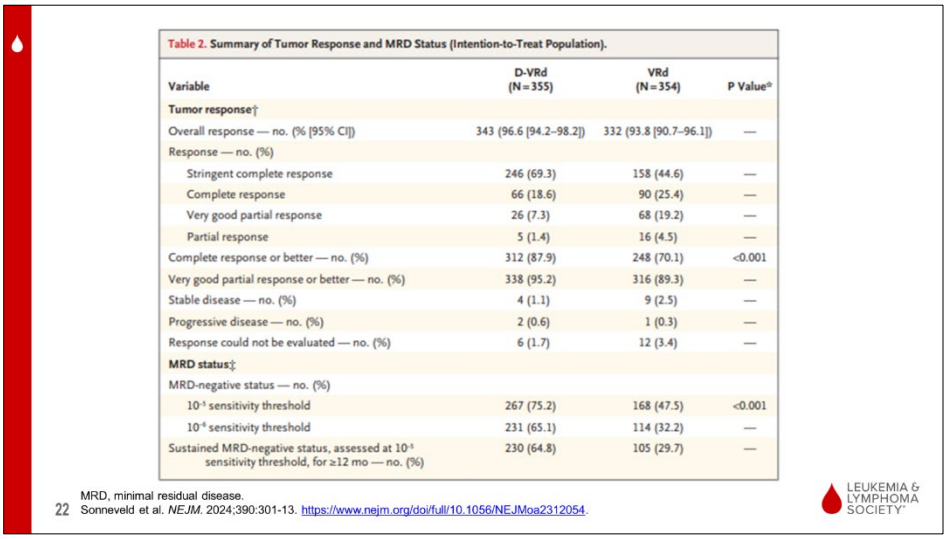


The outcomes are shown here, and again these are one of these, we call these Kaplan-Meier curves that I've shown you so far that show PFS. The yellow on the top is the Dara-RVd arm. The blue on the bottom is the RVd arm. And I think it's pretty clear that the folks who received Dara-RVd fared much better. There was a dramatic improvement in PFS that was statistically significant, and this was seen across almost all subgroups.

I think what's really striking here is if you follow folks out 48 months, which is this tick just two to the left of the graph, we're seeing almost 90% of patients still without progression at four years, which is pretty remarkable; and you compare that to RVd, which is only 70% or so. So, this is, I think, really dramatic and confirms really what we saw with [the] GRIFFIN [trial], and we see it across all subgroups, even in the high-risk subgroup.

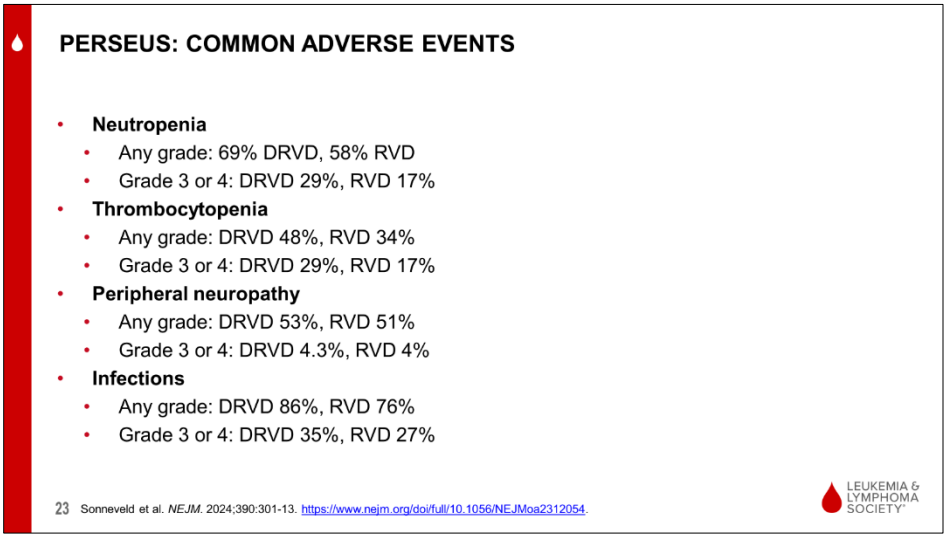


Similarly, responses are better in patients who received Dara-RVd, which should be no surprise based on the GRIFFIN study; and we see here 87% of patients had a CR, a complete response or better, compared to 70% of patients who received RVd who had a CR – again, seen across most of the subgroups.



And this, again, shows these responses and also shows the rates of MRD negativity. And note at the bottom here, I hope you can all read this, I would argue, the very high rates of MRD negativity among the patients who received Dara-RVd 65% versus 32%, with 65% of patients achieving sustained MRD negativity for more than 12 months compared to 30% of patients who received RVd. So, I think these data are so clear that this is a vastly superior therapy.

So, you're asking yourself, “Well gosh, Dr. Cowan is saying that this is better; but what about the side effects? We're adding another drug. Does this make my quality of life worse?”



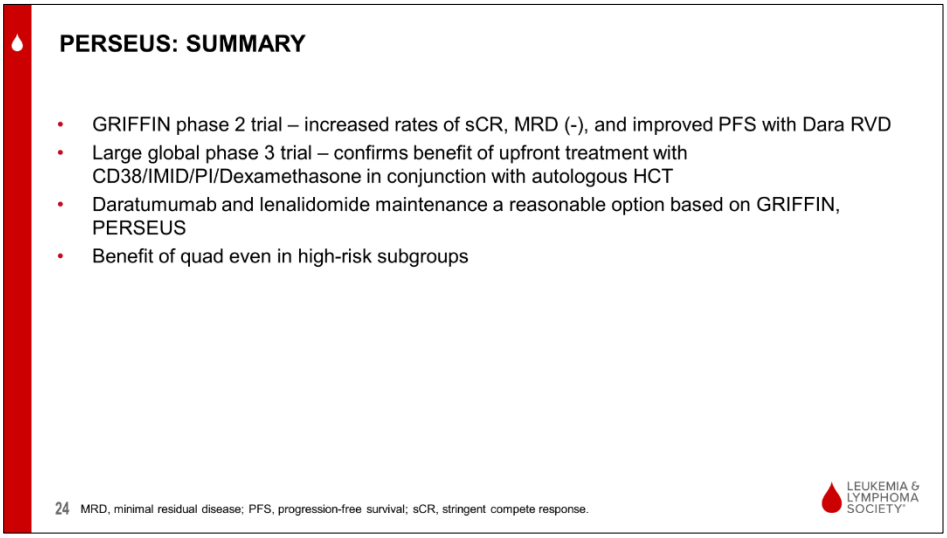
Well, I think that's a very fair question anytime we're adding therapies. What is this doing to my quality of life?

So, pulling from PERSEUS [trial], what are the common adverse events? Neutropenia is; I just pulled these out of things that I thought were important. There's, obviously, a lot of side effects that you could read through with your doctor; and you should. But neutropenia was slightly more common with Dara-RVd seen in 70% versus 58%, with grade 3 or 4 neutropenia seen in 29% versus 70%.

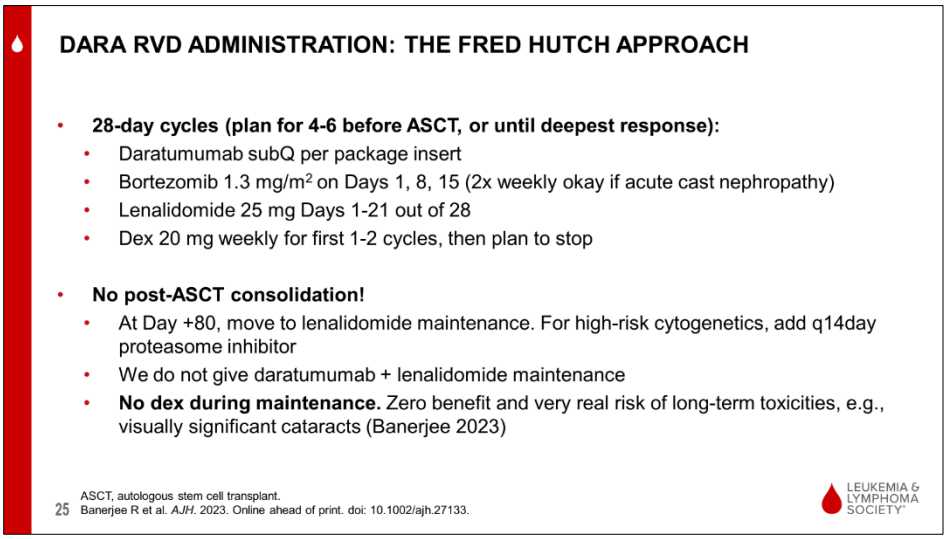
So, you're asking yourself what do these ratings mean. Grade 3 or 4 just refers to how low the neutrophils went, and neutrophils are these fighter white blood cells that your doctor should be checking when you're getting treatment. If they're super low, it predisposes you to specific infections, particularly bacterial infections. We get worried when neutrophils are low, and we often will give growth factors or give antibiotics so that people do not get these bad infections.

Thrombocytopenia or low platelets also really common, more common with Dara-RVd. Peripheral neuropathy, fortunately, was similar between the two groups. So, daratumumab should not worsen neuropathy, and that's what we would have expected based on the side effects of this drug. Fifty percent of patients had any grade neuropathy. Fortunately, very few patients had grade 3 or 4 neuropathy, which would be neuropathy that impacts quality of life or ability to do ADLs (activities of daily living).

Infections were also more common with Dara-RVd, which is not surprising because daratumumab is a monoclonal antibody that suppresses the immune system. So, it's not surprising to see this. I think it highlights the importance of being vigilant about infections when we're treating people with this regimen.



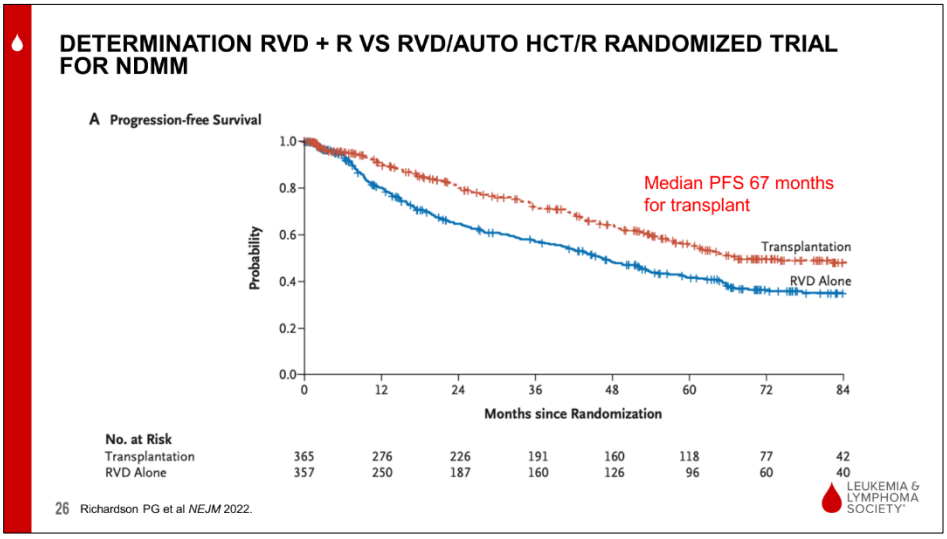
So, to summarize, we now have seen two trials that have shown a benefit for daratumumab and RVd. I think this confirms that this should really be a standard of care for anyone with newly diagnosed multiple myeloma who is transplant-eligible. There are other studies, of course, that have shown benefits of a quad regimen, but I think these are sort of the most clinically applicable trials in the United States, and that's why I chose to highlight them. The other point I would make is that I think daratumumab and lenalidomide maintenance is a reasonable option based on [the] PERSEUS [trial], although there is still some debate about this in the field.



How do we give this at Fred Hutch (Fred Hutchinson Cancer Center)? And this is just an example. I think what I wanted to highlight here is that often in these studies, bortezomib is given twice a week. We feel pretty strongly that weekly bortezomib should be preferred. There is less risk of neuropathy. It's more convenient. Patients aren't spending as much time coming in to get infusions, so hopefully most of you all, if you've gotten this or are getting this, are getting this weekly. If you're getting it twice a week, I think probably try to talk to your doctor and see if they're willing to change. We don't think that this impacts how well the treatment works. We try to make sure that we use dex

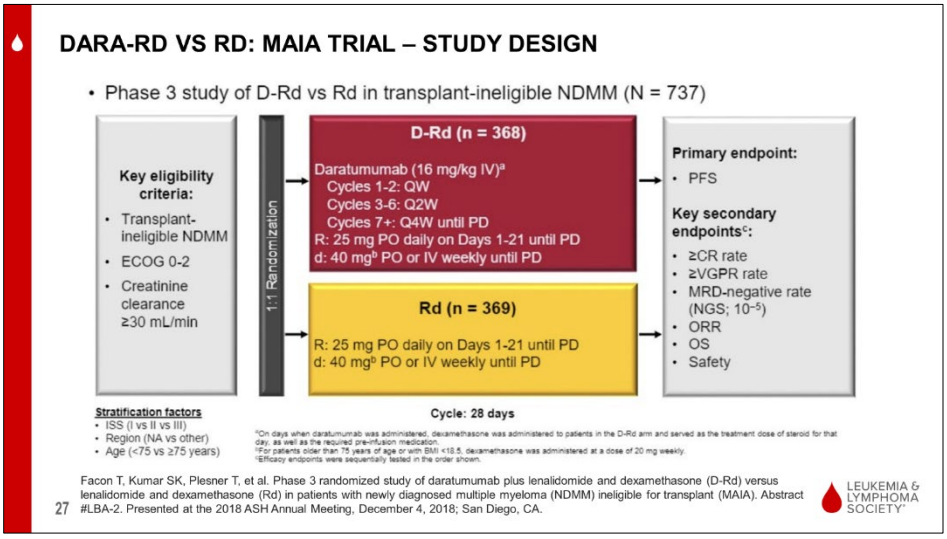
(dexamethasone) appropriately, but we also stop it if people are having side effects, and so we commonly would deescalate dex in our practice.

So, after transplant, we generally don't give consolidation. For a long time, we were giving just lenalidomide maintenance, but I think it's very reasonable to give daratumumab and lenalidomide maintenance; and really nobody should be getting dex during maintenance. So, please, try to get off the dex during maintenance if you're not already because that can really lead to a ton of consequences like worsening diabetic glycemic control, proximal muscle weakness, and visually significant cataracts.

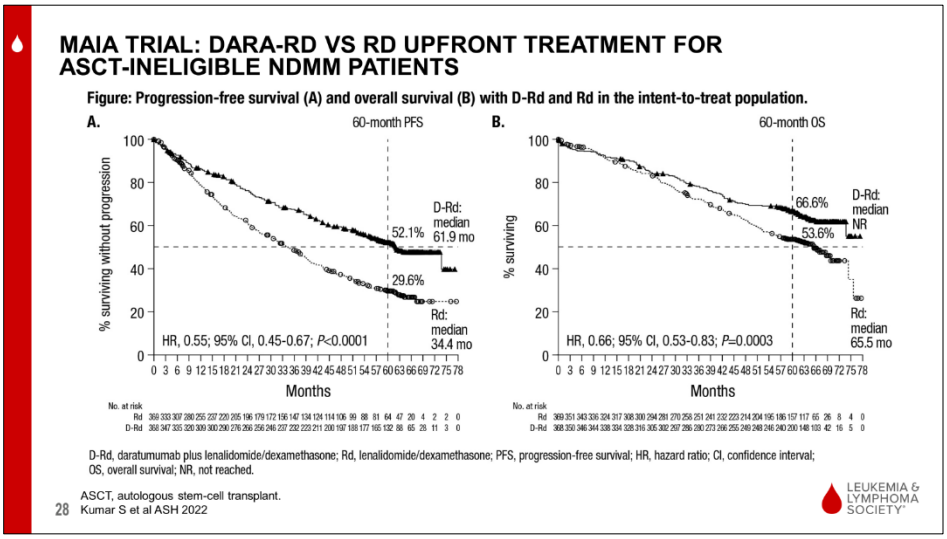


What about transplant? So I've been talking a lot about transplant; and, I think the data are still really clear that transplant improves progression-free survival for newly diagnosed myeloma. The most recent study we have that demonstrates this is the study called the DETERMINATION (phase 3) study, which compared RVd, transplant, and lenalidomide maintenance to RVd and lenalidomide maintenance and has showed an improvement in progression-free survival with transplantation by about 19 months.

You can see these curves here. The red curve is the transplant curve. The RVd curve is blue. We assume that this benefit would be seen with Dara-RVd as well, although that study is probably not ever going to be done. I think this RVd data is good enough to say that transplant still plays an important role and should be considered in anyone who is transplant-eligible.



What about folks who decide not to undergo transplant? I have to admit this data are a little bit subject to change. Some of you might have heard that the study called the IMROZ (a randomized, multicenter, open label phase 3 clinical trial), which is a study of quad therapy for folks who are not transplant-eligible, there was a press release recently that that was a positive result. We don't yet have a paper or presentation, but I think, pending those results, some of this could change. But as of today, the MAIA trial (a prespecified interim analysis of a phase 3 clinical trial) and the SWOG S077 trial (a randomized, open-label, phase 3 clinical trial), the most informative for folks who are transplant-eligible, the MAIA study compared daratumumab-lenalidomide-dexamethasone (Dara-Rd) to lenalidomide-dexamethasone in transplant-ineligible multiple myeloma.



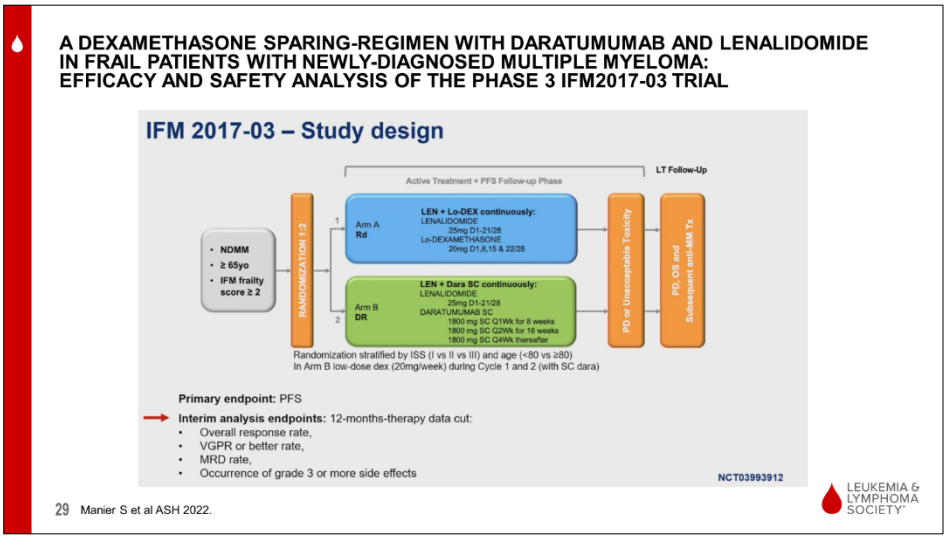
I think these results are pretty amazing. They did a long-term follow-up of the data here and showed that the 60-month progression-free-survival rate was 52%.

So, that means if you follow folks out 5 years, half will have relapsed and half will have not. So, that's actually not too dissimilar from [the] DETERMINATION [trial using] RVd transplant maintenance

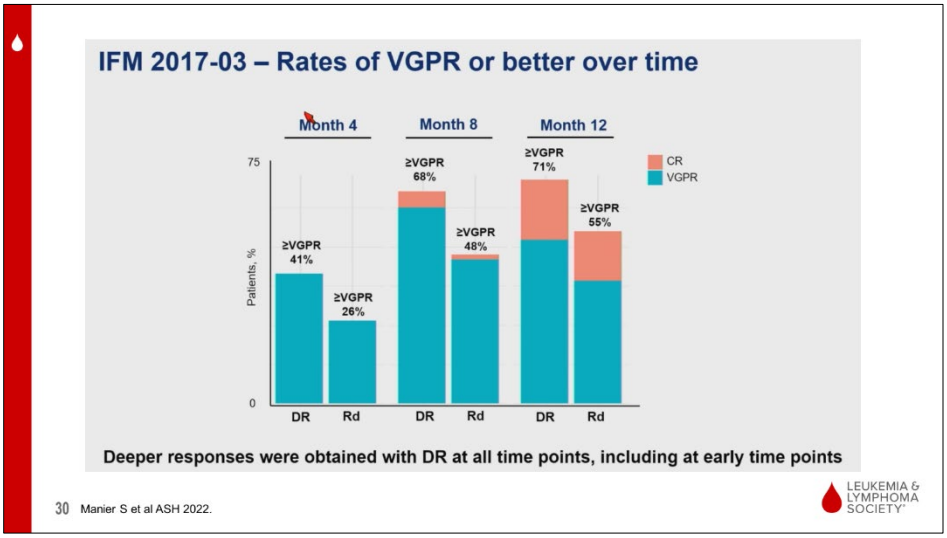
which showed a medium PFS of 67 months. So, that's pretty remarkable; and this is a population of patients much older, much more frail, who achieved really excellent outcomes just with daratumumab-lenalidomide and dexamethasone.

The other regimen that you can consider would be RVd. I personally feel like the MAIA data are more practical in sort of more older, frail populations because there's no risk of neuropathy with daratumumab. And so I think that's really impactful to have this really great regimen that does not cause neuropathy available to us. I think we do have to be mindful of infections for sure, but these are really powerful data. The RVd regimen is very reasonable too though. We don't know for sure which one is better, but I think RVd is reasonable. We want to make sure we don't continue people on bortezomib forever though because of the neuropathy risk.

And one situation we might consider RVd over Dara-Rd would be someone with high-risk chromosomal features where often we really still think it's important to include a proteasome inhibitor; and so that might be one situation that might lead your doctor to recommend RVd over Dara-Rd.

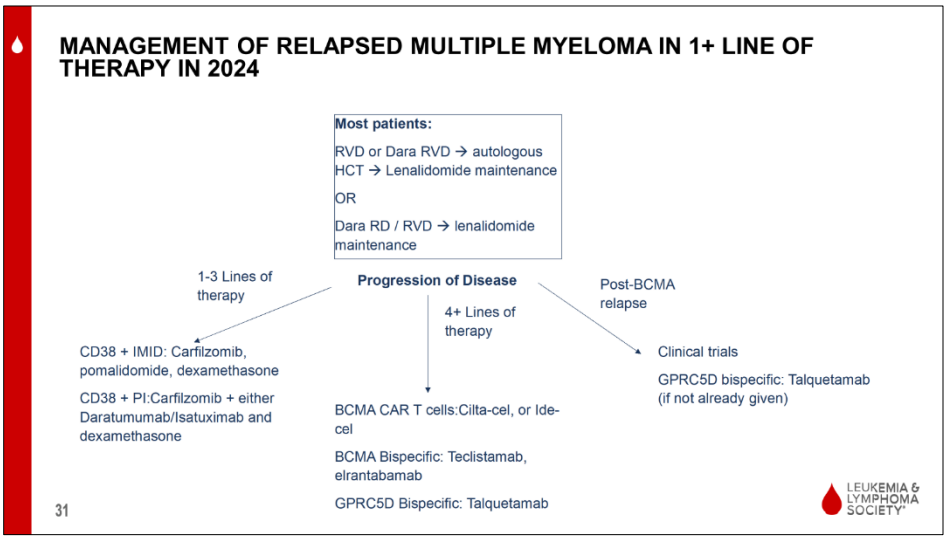


What about reducing steroids, and this is also really important in sort of the more frail population. There was actually a study in France that looked at trying to minimize or lessen the use of steroids for newly diagnosed multiple myeloma; and this is actually a study that was done, it was basically a dex[amethasone]-free regimen with daratumumab and lenalidomide compared to lenalidomide plus low-dose dex[amethasone].



And they show pretty interesting results. At month 12, the folks who received daratumumab, lenalidomide, and no dex[amethasone] had a VGPR (very good partial response) or better rate of 71%, which is pretty impactful compared to the patients who received len (lenalidomide) plus low-dose dex[amethasone] with only a VGPR better rate of 55%.

So, I think these data support that it is okay to titrate down dexamethasone, especially if it's causing side effects, especially if it's making it difficult to sleep, especially if it's causing glycemic control issues. These are all very valid reasons to try to lessen the dex[amethasone] exposure after you've been on it for a while. I'm not talking right at the start. I'm talking you've been on this treatment for a while. It's okay to reduce the dex or even stop it.



So, shifting gears a little bit, let's talk a little bit about relapsed multiple myeloma. Relapsed multiple myeloma, unfortunately even with all these treatments that I've just outlined that are so effective, so good at getting people to remission, we know that the disease comes back. And this can take months. It can take years, hopefully years for most people getting modern therapy.

But this is kind of an outline of how I think of what to do when people relapse. So, for people who've had, when I talk about a line of therapy, by the way, you'll see that here, that just means a treatment, so a cocktail of drugs. So, whether that's Dara-RVd and transplant, that would be one line of therapy. Carfilzomib-pomalidomide and dexamethasone, that would be considered a line of therapy. So any cocktail where you're changing it up to try to treat the disease coming back, that would be a line of therapy. This comes up with CAR T because right now CAR T can't be given and bispecifics can't be given unless people have had four lines of therapy, which is what's on label and hopefully that will change soon with the FDA reviewing data from CARTITUDE-4 trial (a global, phase 3, randomized, controlled trial), and [the] KarMMa-3 trial (a phase 3, randomized study), which we'll talk about in a little bit.

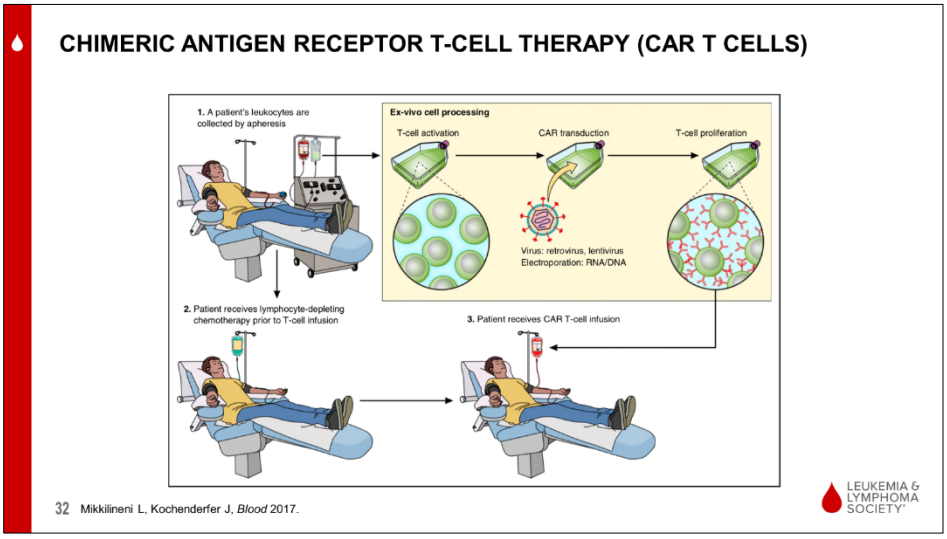
Amazingly, for folks who have one to three prior lines of therapy, we would typically consider a CD38 monoclonal antibody with either pomalidomide or carfilzomib. Both would be very reasonable. There are a couple studies, [the] CANDOR [trial] (a phase 3, randomized, open-label trial) and [the] IKEMA [trial] (a prospective, randomized, open-label, active-controlled, phase 3 study), which looked at isatuximab (Sarclisa®) which is a CD38 antibody with carfilzomib, or daratumumab with carfilzomib. Both are very effective combinations in that sort of one to three prior lines of therapy.

Other drugs that you can get in this space would be selinexor (Xpovio®)-bortezomib and dexamethasone. Selinexor is a selective inhibitor of nuclear export. Elotuzumab (Empliciti®), pomalidomide, and dexamethasone, these are all just options that you could consider and talk over with your doctor.

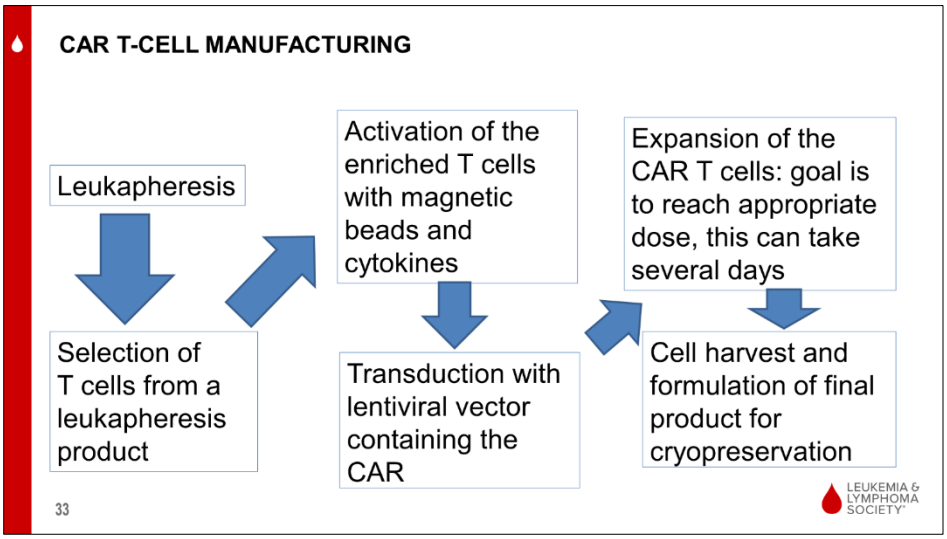
But ideally at this point, I should have mentioned this earlier, it's a good idea to see someone who focuses in myeloma. Even when you get diagnosed. Even with your community doctor. See them once just so they know who you are, just so that you kind of get plugged into the system, and it can be really helpful just as you go on through having myeloma, which is like a chronic condition. Making sure you check in when you need a new treatment. Is this really still the state of the art? Am I eligible for a clinical trial?

And I think one important point that should be in all of these one to three prior, any of these kind of categories, consider a clinical trial. Clinical trials are so vital to advancing our knowledge and to getting drugs approved that I think it's really important to consider them. I mean this could be a whole talk in and of itself on why to consider clinical trials. But one important one is that none of these drugs we would have unless folks had participated in clinical trials. So, they're always optional, but just remember why they're important. Always ask your doctor, when you're needing a new line of treatment, “Am I eligible for a study? Can I see a myeloma specialist to get a second opinion?” And the answer to both should always be “yes,” but ultimately you get to choose. You and your physician get to choose how you want to treat.

For folks who've had progressive disease with more than four lines of therapy, that's where we start thinking right now about BCMA (B-cell maturation antigen) CAR T cells, BCMA bispecifics, or GPRC5D (G protein–coupled receptor, class C, group 5, member D) bispecifics. And then for post-BCMA relapse, really the only drug that kind of comes to mind immediately would be talquetamab (Talvey®), which is a recently approved GPRC5D bispecific antibody, or clinical trials, which seems obvious.



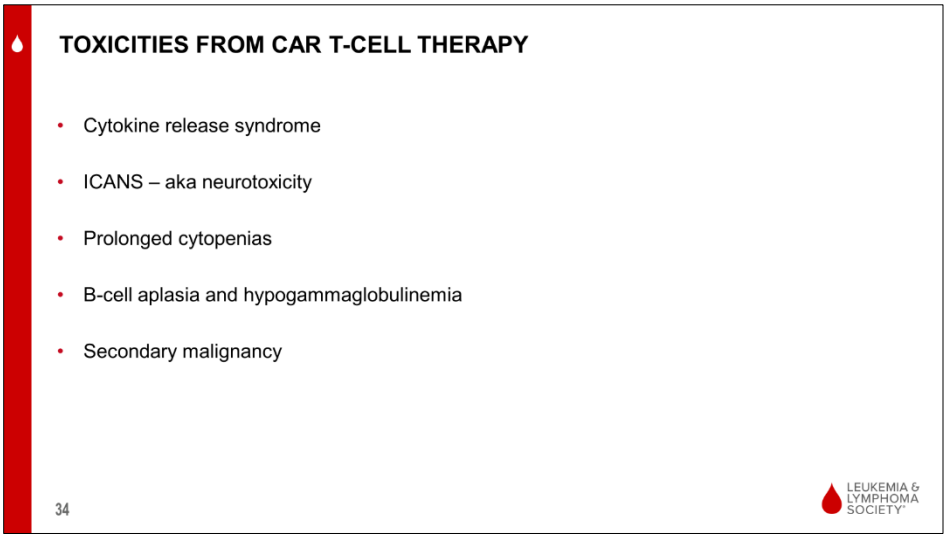
Let's talk a little bit about CAR T-cell therapy, since that, I think, is of high interest at this point, especially in the one to four prior lines of therapy with the FDA reviewing some data from these studies. CAR T-cell therapy is an immune-based therapy, and it really marries kind of advances in genetic engineering, understanding the immunology, [and] understanding disease biology. It's kind of an amazing therapy. Basically, what we do is we take your T cells out of your body, we use a virus to genetically modify the T cells so that they now can target the cancer, and then we give them back to patients; and that process is shown here.



CAR T cells have to be manufactured, which is part of why there's been some resource limitations with respect to how many patients can get it. There are other reasons for that too, but one of them is just this manufacturing, which has been scaled up; but it's still a bit of a challenge.

So, when we manufacture CAR T cells, we start with leukapheresis. We select the T cells, and then we activate them and transduce them with this virus. And then we expand them and harvest and

formulate the final product. That's the process of how we create CAR T cells. And this can take several weeks, depending on the exact product and the specifications.



What are some general toxicities from CAR T-cell therapy? These are listed here. Cytokine release syndrome is one. This is that syndrome that is characterized by fever, low blood pressure, sometimes low oxygen, and this is pretty common in patients in getting CAR T or, I should also mention, these are toxicities that can also be seen with bispecifics, so there's some overlap here.

Immune effector cells, neurologic syndrome, or neurotoxicity sometimes overlaps as cytokine release syndrome, sometimes not, typically can present with patients ([for example], can present with sort of handwriting abnormalities or confusion or lethargy). Another thing that can happen after CAR T-cell therapy are these prolonged low blood counts. We call this ICAHT (immune effector cell-associated hematotoxicty) or prolonged cytopenias. B-cell aplasia or hypogammaglobulinemia basically refers to reduced production of antibodies, and this can lead to an increased risk of infection. Sometimes doctors will give a product called IVIG (intravenous immunoglobulin) to help deal with this.

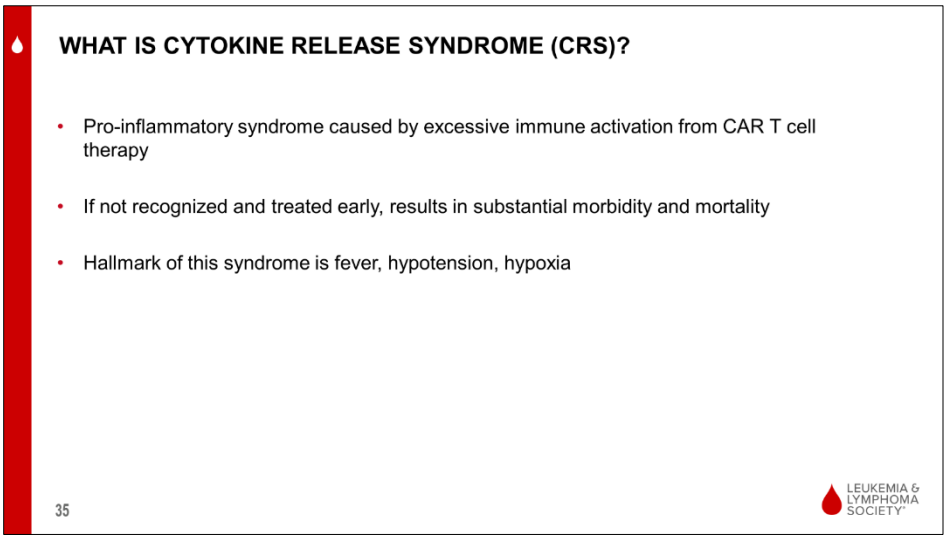
And then secondary cancers. And this is a hot point, after many of you have probably seen press releases from the FDA that they were concerned about this. Basically it's this idea that when we're doing any kind of genetic engineering, and this is borne out not only by CAR T cells but by other studies that have looked at genetic manipulation, there's a theoretical risk that we could, perhaps, turn on some gene that could turn a cell cancerous.

Now to date, we've treated many patients with CAR T cells who have lymphoma and now many patients with myeloma, and there have been some potential cases that could qualify as secondary cancers caused by this mechanism. Frankly, this is something we've always counseled patients could be a risk, or at least I have, and it's something that – And the fact that we've found it means we're looking for it, and that gives me confidence in the systems that we have that we're able to detect rare events and get on top of them.

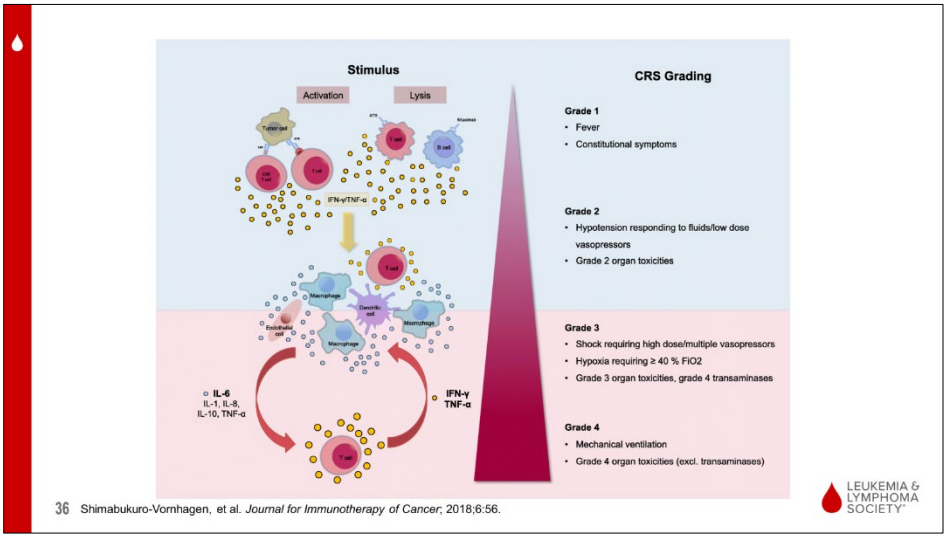
And so I think this risk is not only theoretical, it may be real. If it is real, I think that it seems clear to me also that the benefit of the treatment in terms of treating the myeloma probably far outweighs the

risks of these. It's something you definitely want to talk to your doctor about. I think you want to get all the information about it. But it's clear that, and this happens with other treatments, [with] stem cell transplant there's a risk of secondary cancers. But we know that patients do better long term with transplant despite these risks, and the same goes with lenalidomide, which has a risk of causing secondary cancers but has also been shown to improve survival.

So, we have to remember what is the thing we know we have to deal with, and that's myeloma. And then there's always this uncertainty, there's uncertain things like toxicities and secondary cancers fall into that. And so I think you have to keep that perspective of the known thing that we're dealing with and how to best treat that and that the benefits of that outweigh these risks. But it's important for you to be informed about this; and I think, ultimately, it's only a decision that you can make in conjunction with your doctor.



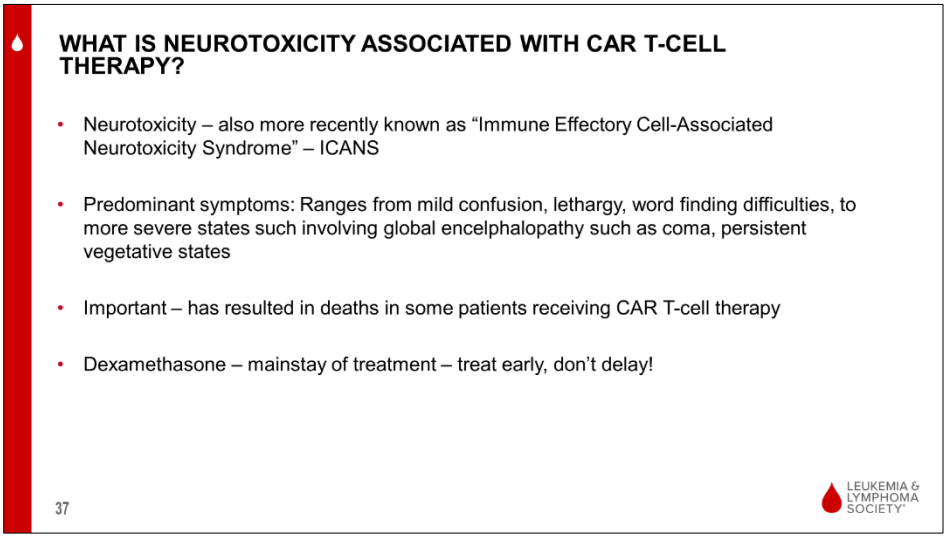
So, we talked a little bit about this, and basically cytokine release syndrome (CRS) is a proinflammatory syndrome caused by excessive immune activation; and the hallmark is fever, hypertension, hypoxia.



This kind of shows how this happens. Basically you can think of CRS kind of – Let's say, for example, what do T cells normally do? When you get an infection, they recognize that there's a virus, and they produce these proteins called cytokines. The cytokines cause your immune system to say, "Hey, let's wake up. We've got an invader here. Let's go into attack mode."

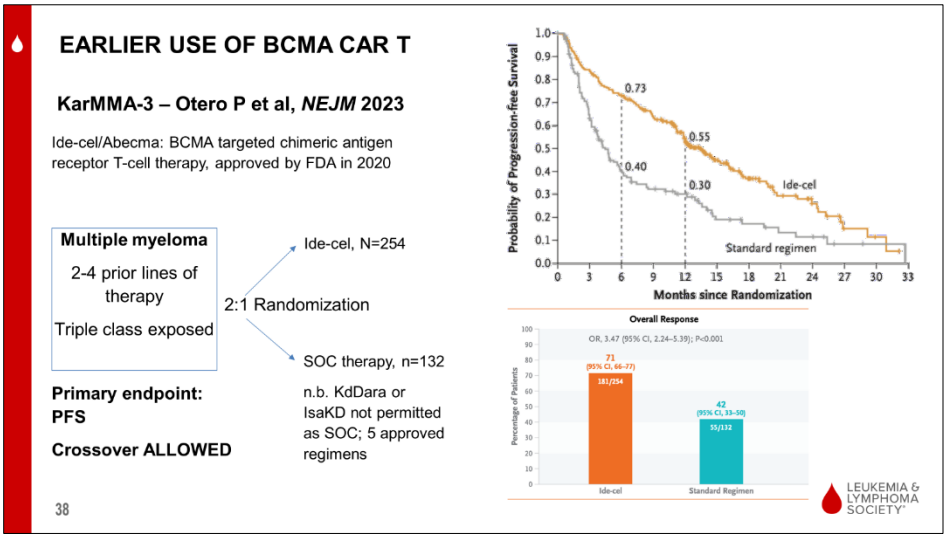
And so, largely, why do you feel sick when you get influenza? It's not totally because of this, but a lot of it is because of what happens to the immune system. The activation immune system causes things like fever, can sometimes cause low blood pressure, can sometimes make your blood pressure drop.

And so that's basically what's happening here with CAR T cells. We take our T cells which normally are supposed to be out there fighting infections, and we're now telling them to target cancer cells. And that results in a syndrome very similar to what you might get say with a viral infection. Down here you see more severe CRS. That's less common, but it can happen; and it's always important to review these risks with your doctor when you're thinking about getting CAR T cells and what the risks of these treatment-related side effects are and how they could affect things like having a bad outcome. Fortunately, it is rare, but they can happen.



The neurotoxicity, which is now known at ICANS (immune effector cell-associated neurotoxicity syndrome), can happen with or without CRS. It ranges from sort of mild confusion or lethargy to more severe states like global encephalopathy. Frankly, the latter is quite rare. Important to know this has resulted in deaths with some patients receiving CAR T-cell therapy. With early treatment and with early recognition, that has become less common; but it's still something to be aware of and something for caregivers to be aware of too because it can be really scary when you see your loved one very confused or lethargic, and it's important to know that this risk is there.

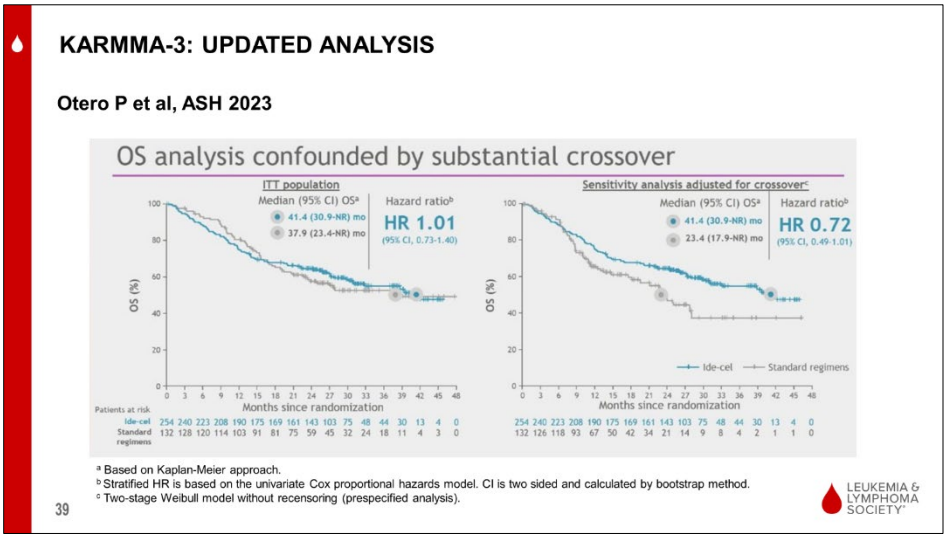
And we treat this with dexamethasone. I should mention also that we treat cytokine release syndrome, the one we talked about earlier, with tocilizumab (Actemra®), which is an IL-6 (interleukin-6) antibody. That's a cytokine and dexamethasone.



So, what are the data for CAR T-cell in multiple myeloma? So, there are two approved CAR T-cell products for multiple myeloma. There's Abecma® (idecabtagene vicleucel) and Carvykti® (ciltacabtagene autoleucel). Ide-cel or Abecma was the first one that was approved in 2020, based off

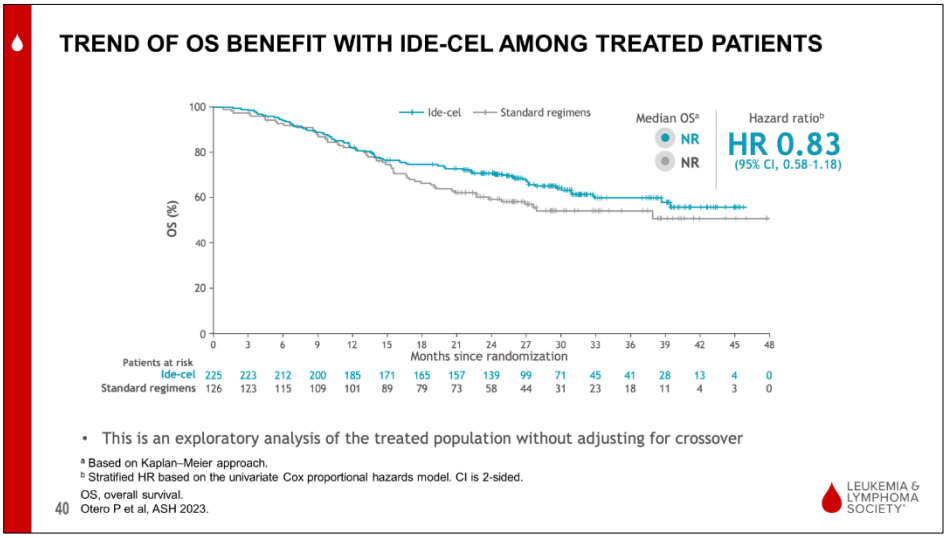
of the KarMMa-2 (a multicohort, phase 2, multicenter study) and KarMMa-1 (an open-label, single-arm, multicenter phase 2 study) studies; and so they studied this in patients with two to four lines of therapy who were triple-class exposed and looked at either ide-cel or standard of care therapy, and crossover was allowed.

The primary endpoint of the study was progression-free survival, and they indeed showed that this improved progression-free survival over standard regimens.

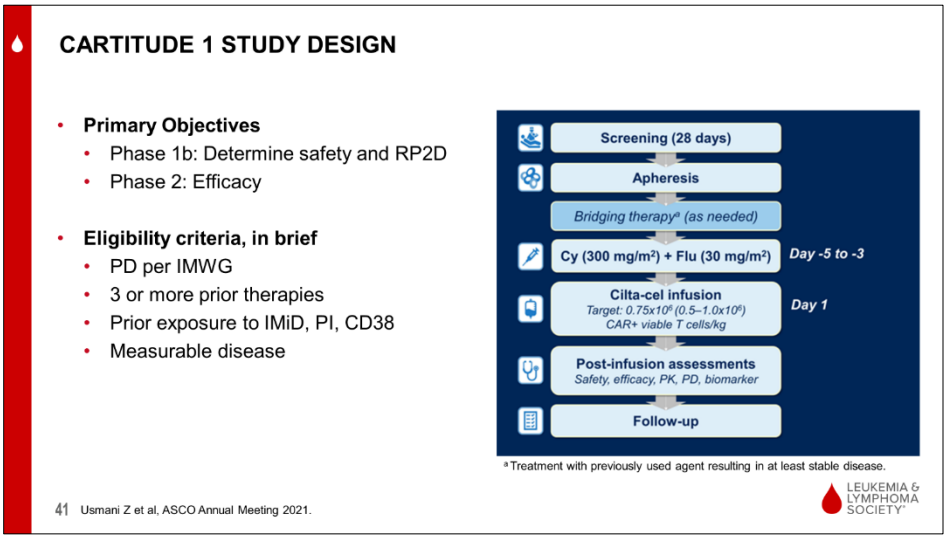


When they looked at overall survival, the two groups were actually quite similar, which initially was a little bit concerning until you remember that they allowed crossover. So, if patients were on [the] standard-of-care arm, they could get BCMA CAR T cells later. And so I think it's difficult, if you consider that most patients would probably get that, it's going to make survival analysis challenging.

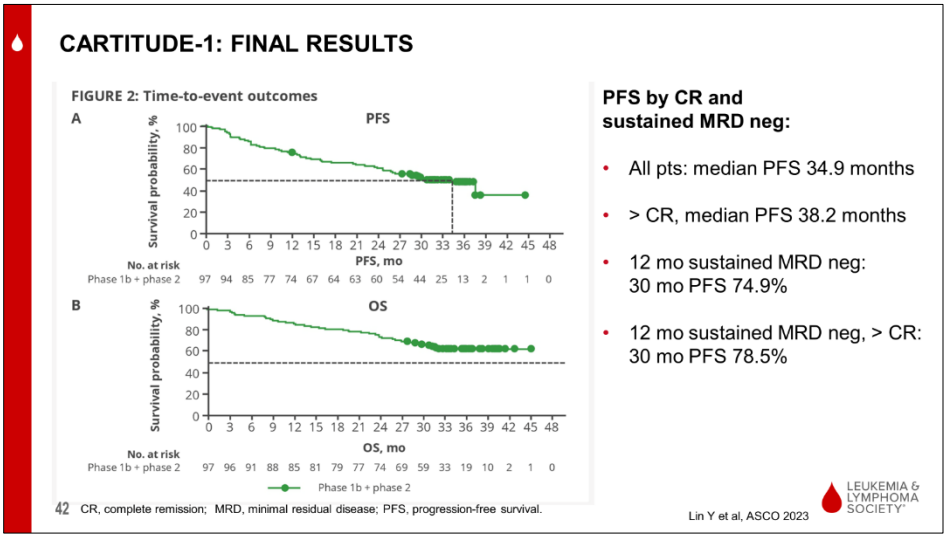
When they did a prespecified sensitivity analysis adjusted for crossover, they showed that there was a trend towards benefit of receipt of idecabtagene or Abecma and also a trend of OS (overall survival) benefit among treated patients.



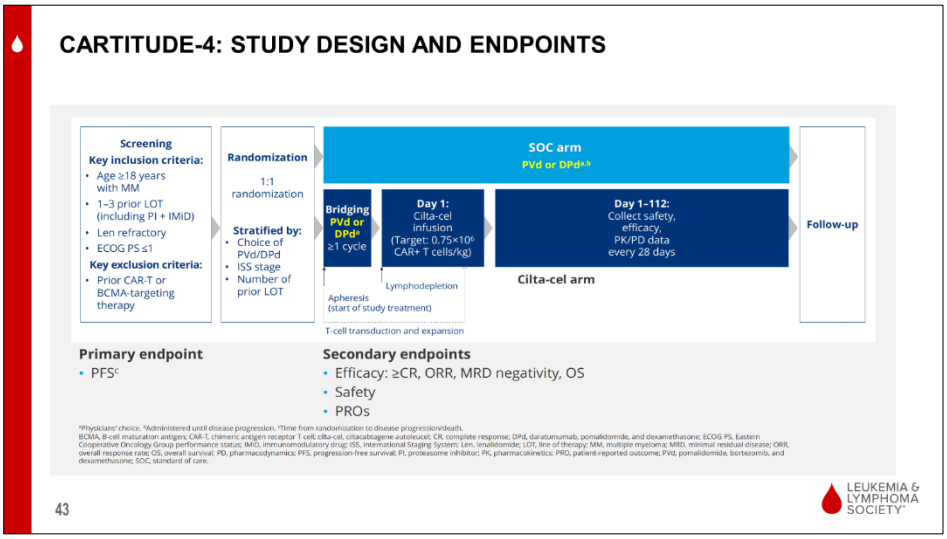
These were the data that were reviewed by the FDA, what we call the Oncologic Drugs Advisory Committee or ODAC which basically advises the FDA on what to do when there's a challenging decision about approving a drug. That happened a few weeks ago, and hopefully we'll hear about whether this new indication for Abecma gets approved very soon.



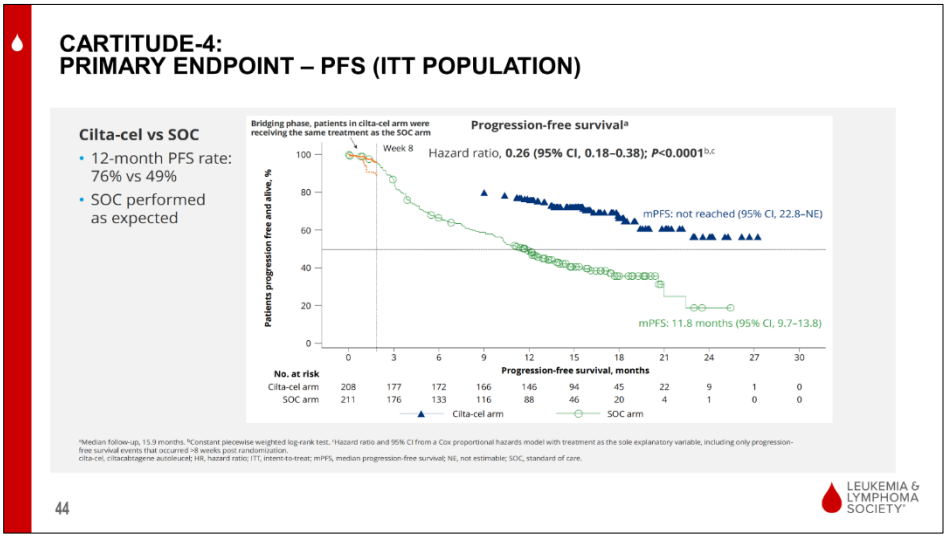
The other CAR T that's out there is Carvykti or ciltacabtagene autoleucel, and this is another BCMA-targeted CAR T. It was studied in the CARTITUDE-1 (a single-arm, open-label, multicenter, phase 1b/2 study) study whose design is shown here.



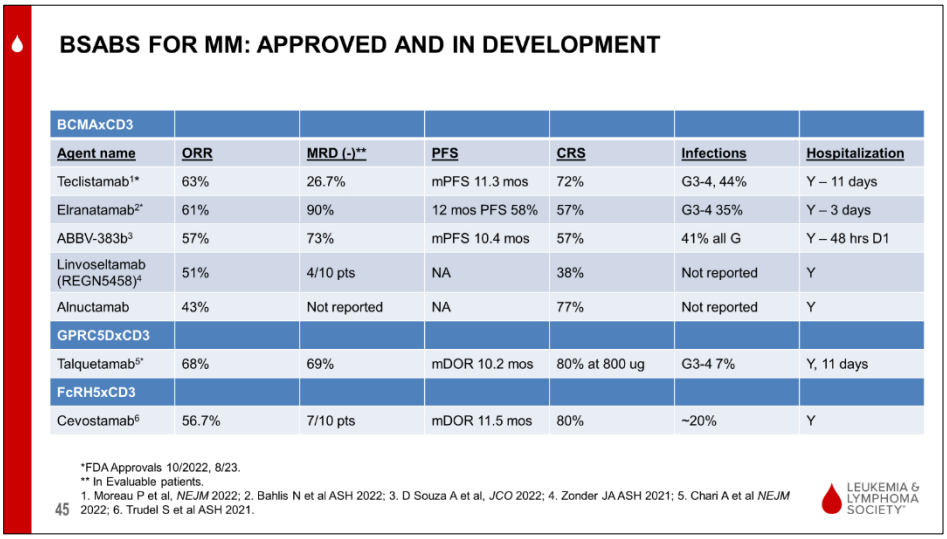
CARTITUDE-1 showed pretty impressive results, specifically with respect to PFS or rates of MRD negativity. And this is a group of patients who were very heavily pretreated. They'd had a lot of different therapies, and they had pretty remarkable, durable remissions with Carvykti with a medium PFS of almost 35 months and at 12 months sustained MRD negativity, at 30 months of 75% [PFS].



Carvykti was studied in [the] CARTITUDE-4 [trial], which is kind of a similar study design to [the] KarMMa-3 [trial], except for they allowed one to three prior lines of therapy and patients had to be len[alidomide]-refractory. So, it's a little bit earlier than KarMMa-3.



This study also showed, kind of in line with CARTITUDE-1, pretty dramatic improvement in PFS compared to standard-of-care regimens with a median progression-free survival that was not reached for Carvykti compared to a median PFS of 11.8 months. So, I am optimistic again that these data will lead to approval in these settings, but we'll see. I think we don't know yet.



BCMAxCD3						
Agent name	**ORR**	**MRD (-)****	**PFS**	**CRS**	**Infections**	**Hospitalization**
Teclistamab[1]*	63%	26.7%	mPFS 11.3 mos	72%	G3-4, 44%	Y – 11 days
Elranatamab[2]*	61%	90%	12 mos PFS 58%	57%	G3-4 35%	Y – 3 days
ABBV-383b[3]	57%	73%	mPFS 10.4 mos	57%	41% all G	Y – 48 hrs D1
Linvoseltamab (REGN5458)[4]	51%	4/10 pts	NA	38%	Not reported	Y
Alnuctamab	43%	Not reported	NA	77%	Not reported	Y
GPRC5DxCD3						
Talquetamab[5]*	68%	69%	mDOR 10.2 mos	80% at 800 ug	G3-4 7%	Y, 11 days
FcRH5xCD3						
Cevostamab[6]	56.7%	7/10 pts	mDOR 11.5 mos	80%	~20%	Y

*FDA Approvals 10/2022, 8/23.
** In Evaluable patients.
1. Moreau P et al, *NEJM* 2022; 2. Bahlis N et al ASH 2022; 3. D Souza A et al, *JCO* 2022; 4. Zonder JA ASH 2021; 5. Chari A et al *NEJM* 2022; 6. Trudel S et al ASH 2021.

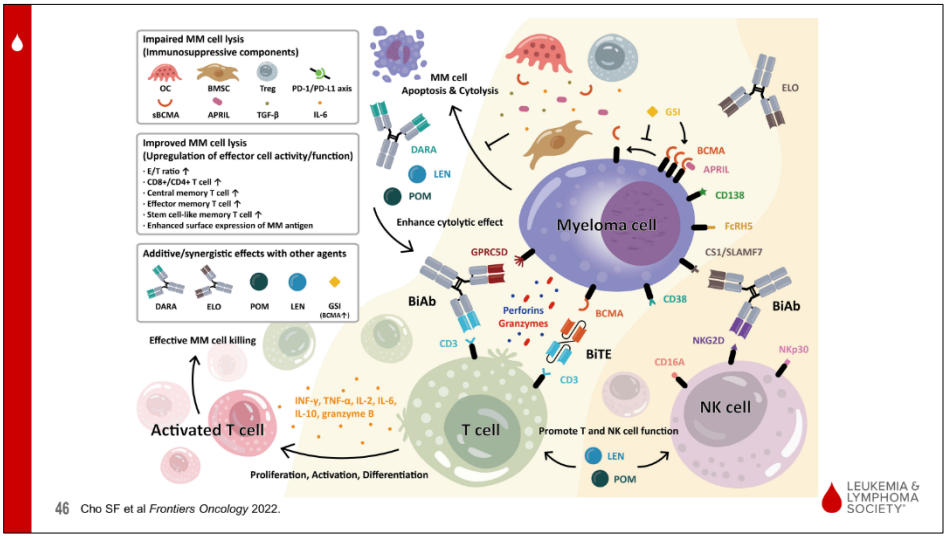
What about bispecific antibodies? So, bispecific antibodies are drugs that basically kind of, very similar to CAR T-cell therapy. We use the immune system to target the cancer, except for we have a protein that's been engineered to take the T-cells and bring them to the cancer cells.

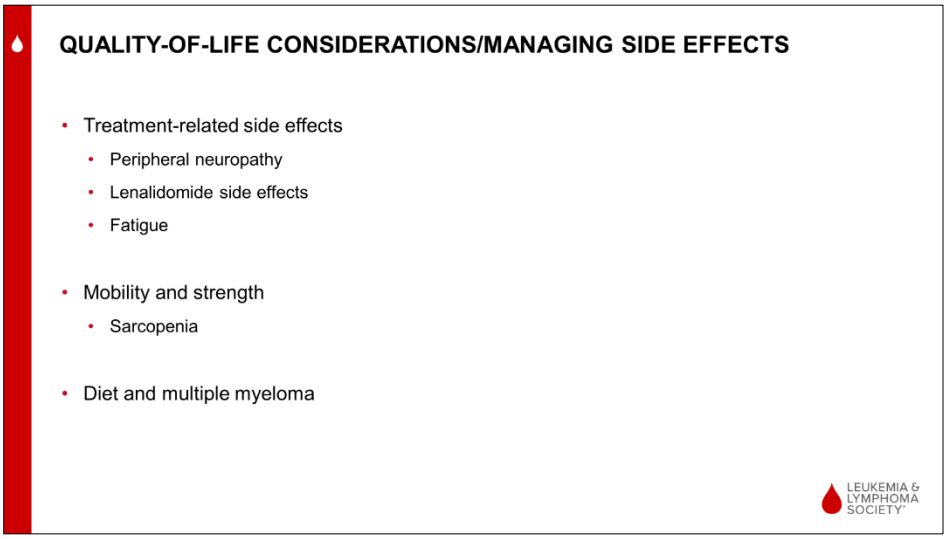
There are several bispecifics that are approved. The ones that are approved are teclistamab (Tecvayli), elranatamab (Elrexfio™), and talquetamab (Talvey®). There are others on this list here that are in development and may be approved in the coming years. So, it's nice to have lots of options kind of in the pipeline. These drugs compared to CAR T cell, maybe the response rates are not quite as high. But when people do respond, the responses tend to be quite durable or long lasting with teclistamab and elranatamab.

TRANSCRIPT

They also have risks of cytokine release syndrome just like CAR T, perhaps slightly higher risk of infections, severe infections compared to CAR T. And there is some hospitalization required for these drugs when they're given, which I think folks are looking at trying to get around by administering outpatient. But the studies were all done with hospitalization required.

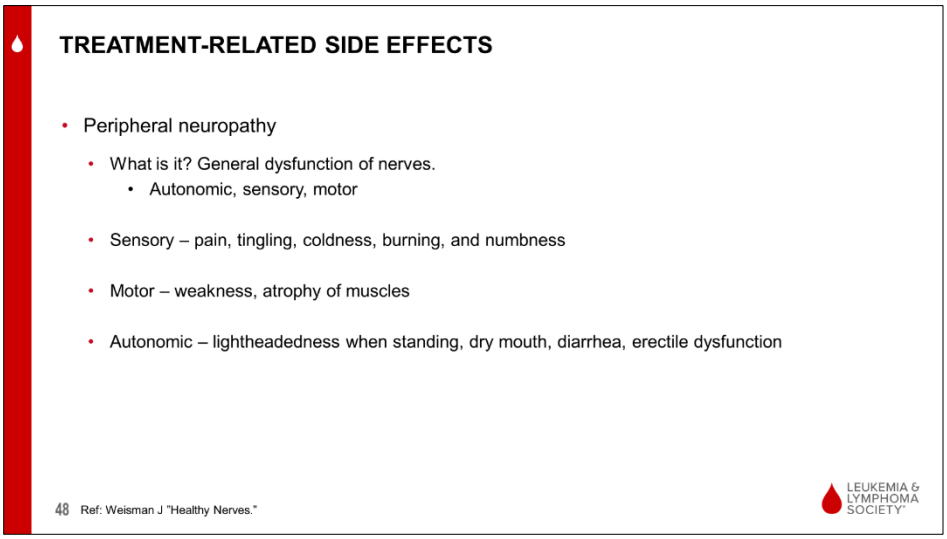
Talquetamab, in particular, has a particular set of side effects, including skin toxicity with rash and nail loss and also loss of taste that I think are a little bit of a challenge to manage at the moment. And so just really know that there are several of these drugs that are available, and there are others that are in the pipeline.





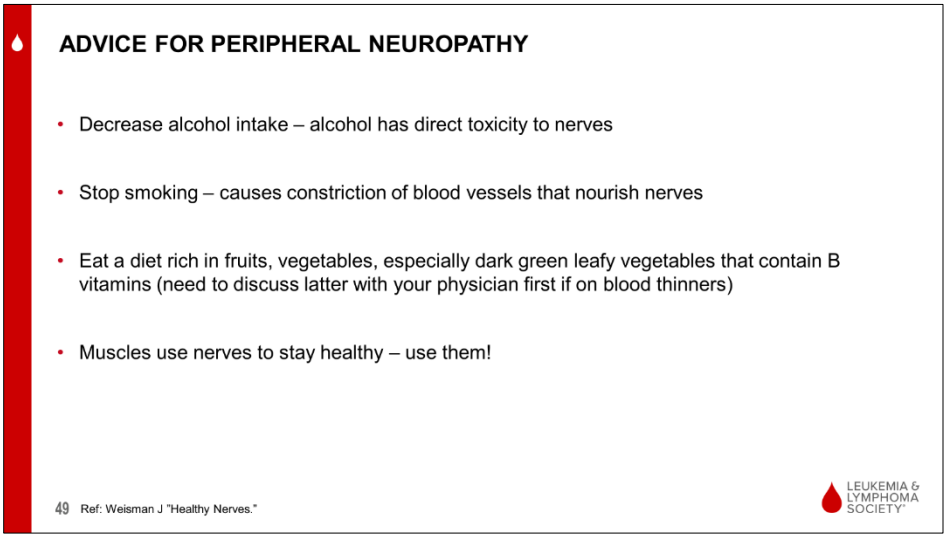
So, let's kind of switch gears a little bit in the interest of time and just talk a little bit about quality-of-life considerations and managing side effects. So, treatment-related side effects are a common conversation that I have with folks when talking about myeloma treatment. And the ones that come up most commonly are peripheral neuropathy, lenalidomide side effects, and fatigue. Mobility and strength is another one that comes up a lot. "Doctor, I want to go downhill skiing. Can I do that? I

want to go back to the gym and lift weights. Can I do that safely?" And so this addresses this issue of loss of muscle strength. The medical term for that is sarcopenia. And then finally a little bit about diet and myeloma.



So, what is peripheral neuropathy? Peripheral neuropathy just refers to a general dysfunction of nerves. There are three components of our nervous system: there's autonomic, there's sensory, and there's motor; and it can affect any of those. So, if you have a sensory neuropathy, people can have pain. They can have tingling, coldness, burning, and numbness. Motor neuropathy can result in weakness and atrophy of muscles. Autonomic neuropathy can result in lightheadedness when standing up, dry mouth, diarrhea, or erectile dysfunction. So, obviously, even mild neuropathy can really impact somebody's quality of life.

Now, you saw early I reported on rates of grade 3 or 4 neuropathy with some of these regimens, and they're only like 3 [percent] to 4%. But really any – I want to make it clear that any neuropathy can be really, really – I mean, I'm preaching to the choir here, any neuropathy can be really a bad outcome.

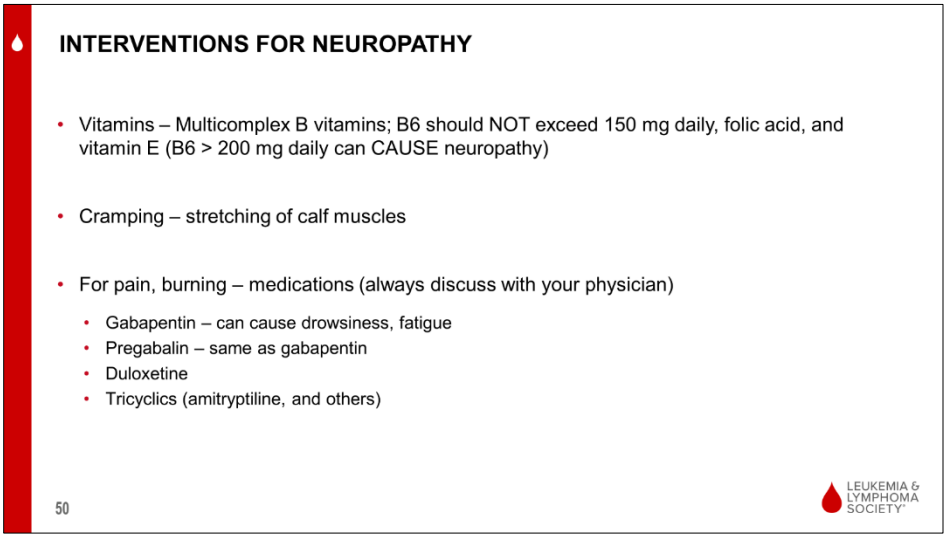


So, what is some general advice for neuropathy? These are just some tips I've given to folks, and this comes originally from a great piece of advice [and] some documents I received from Janice Wiesman who was an amyloid specialist at BU (Boston University) [who] unfortunately passed away a few years ago. But she had this whole document on healthy nerves; and so that's where I'm getting some of this from.

Decrease alcohol intake. Alcohol is direct toxicity to nerves. So, if you are drinking more than a few drinks per night, consider cutting down or consider cutting out entirely. Stop smoking. If you are a smoker, there are numerous reasons to quit. But if you're a smoker and have neuropathy, there's an added reason because smoking causes constriction of blood vessels that nourish your nerves.

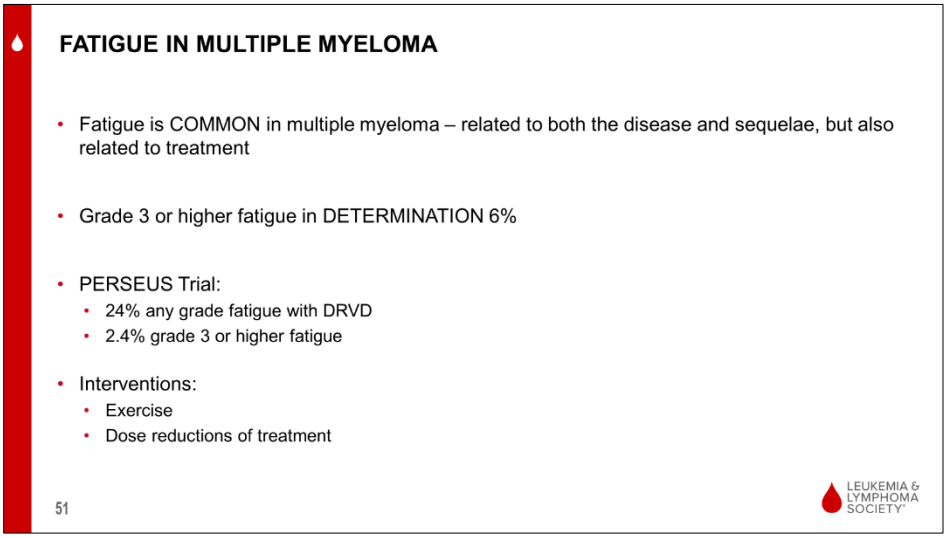
Eat a diet rich in fruits and vegetables, especially dark green leavy vegetables that contain B vitamins, and we'll come back to this later when we talk about diet. Make sure to discuss first with your physician if you're on any kind of blood thinner like warfarin (Coumadin®) because that can interfere with that.

And then really very simply, muscles use nerves to stay healthy, so use your muscles. Stay active. I like to tell people that walking is one of the most underrated activities; and I heard the comment at the beginning about how the patients' physician recommended walking ten miles a day. I typically start with lower goals. Maybe 30 minutes a day of walking. It doesn't have to be fast. You want to talk with your doctor first about this and make sure there's no safety considerations like risk of falls. But doing some walking is really beneficial. Not only are you getting outside, you're getting sunlight, but you're also using your muscles; and you're putting weight on your bones, and all that helps keep you strong. So, walk every day. I mean that's, that's really a very simple thing that you can do.



Are there interventions for neuropathy? Yes. So, there's this vitamin regimen that was originally sort of, I think, popularized by Dana-Farber [Cancer Institute] where folks take multicomplex B vitamins; and I think that's reasonable. The only caveat I would have to that is to say try to be really careful with B6 (pyridoxine). Don't take more than 150 milligrams of B6 per day because that actually can cause neuropathy if you take too much B6. So really be careful with the B6, especially if you're taking one that's got multiple in it. Try to look at the label and say, "Hey, how much B6 is in this." And if it's more than what I listed here, I'd probably avoid it.

Cramping, stretching of calf muscles can help. For pain and burning, there are some medications. Always discuss these with your physicians, of course. Gabapentin (Neurontin®) can cause some drowsiness and fatigue. It can be really helpful though for some folks with neuropathy. Pregabalin or Lyrica® has similar side effects to gabapentin. Duloxetine (Cymbalta®) is another one that you could consider, and then tricyclic antidepressants have also been used.

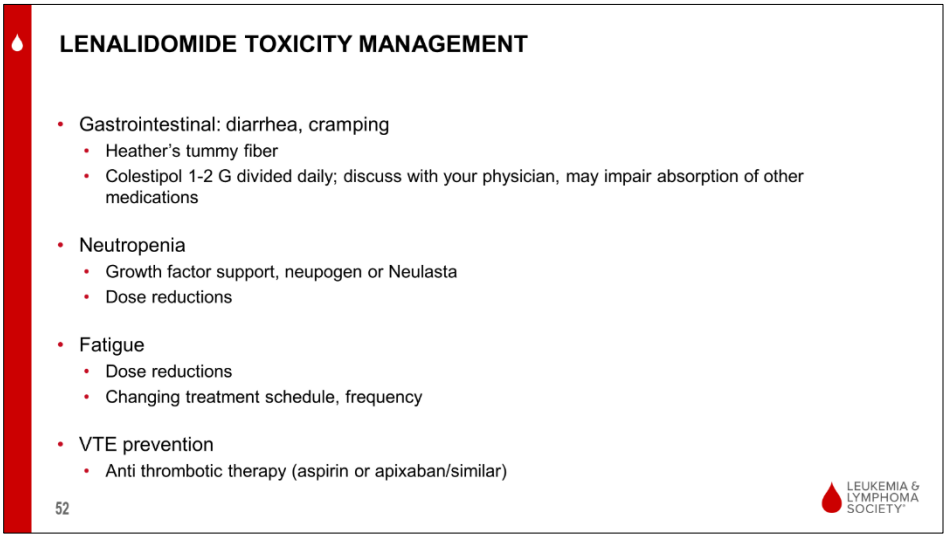


What about fatigue in multiple myeloma? Fatigue is super common in multiple myeloma. It's one of the most common things I talk about with people to sort of, not only just fatigue, but also kind of brain fog; and a lot of times this is related to treatment. Sometimes it could be from the disease. Sometimes it could be from pain medications. Sometimes it could be from chronic pain. But it's all kind of intertwined with myeloma. So, it's hard to separate.

Looking at the studies, grade 3 or higher fatigue in DETERMINATION [trial], that was the transplant study, [was] 6%. So, that may not seem like a lot, but we're talking about fatigue that's so severe it's impairing people's ability to do activities of daily living. So that's pretty significant.

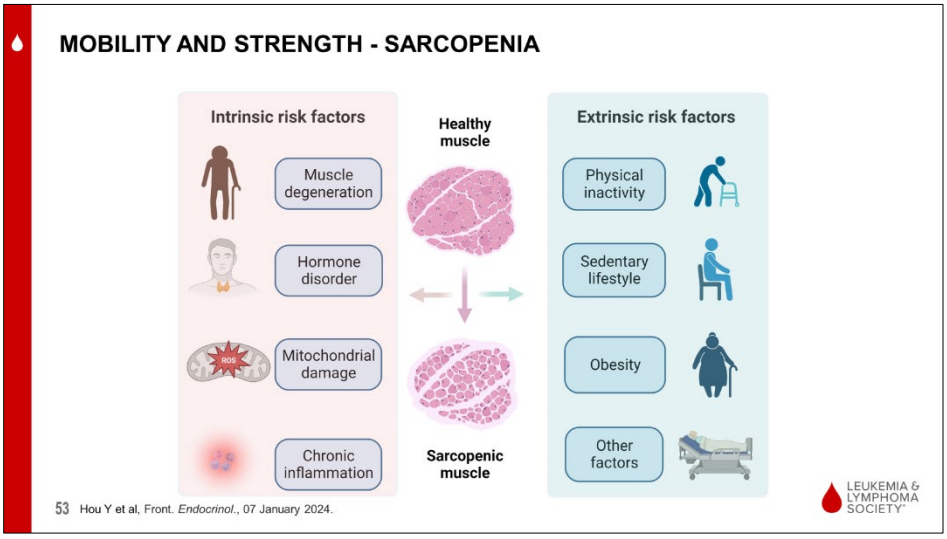
[In the] PERSEUS [trial], any grade fatigue [was] 24%. There is, unfortunately, no great intervention for fatigue. I typically think that exercise and walking is really important for trying to combat the fatigue. Dose reductions of treatment can also be helpful in some situations, but it doesn't always fix it.

So, bring up fatigue. Don't be shy. Don't feel like you have to suffer through fatigue just because you're getting cancer treatment. Talk about it. The goal should be to try to maintain some level of functioning despite being on cancer treatment for myeloma.

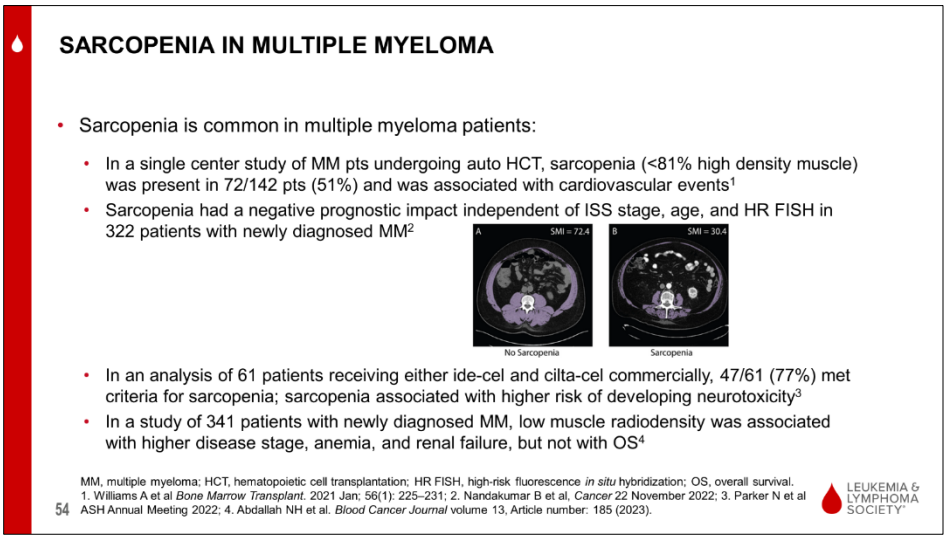


What about lenalidomide toxicity? This comes up a lot. So, the GI (gastrointestinal) side effects are really common with lenalidomide; and they include diarrhea, cramping, [and] sometimes constipation. For the diarrhea, anecdotally and I have no connection to this company, there's this product called Heather's tummy fiber that apparently our dietitians here at Fred Hutch think is helpful, so you could consider that. Colestipol (Colestid®) is a bile acid sequestrant. It can be really helpful for managing that diarrhea. Discuss it with your physician. It can impair absorption of other medications.

For the neutropenia where we have the low fighter white blood cells, often we use growth factor like G-CSF (granulocyte colony-stimulating factor) or Neupogen® (filgrastim) to manage that or dose reductions. For fatigue, dose reductions can be used. Also consider discussing with your doctor whether you could change the treatment schedule or the frequency. And then for blood clot prevention, consider everyone who's on lenalidomide or pomalidomide should be on antithrombotic therapy – aspirin, apixaban, or something similar.



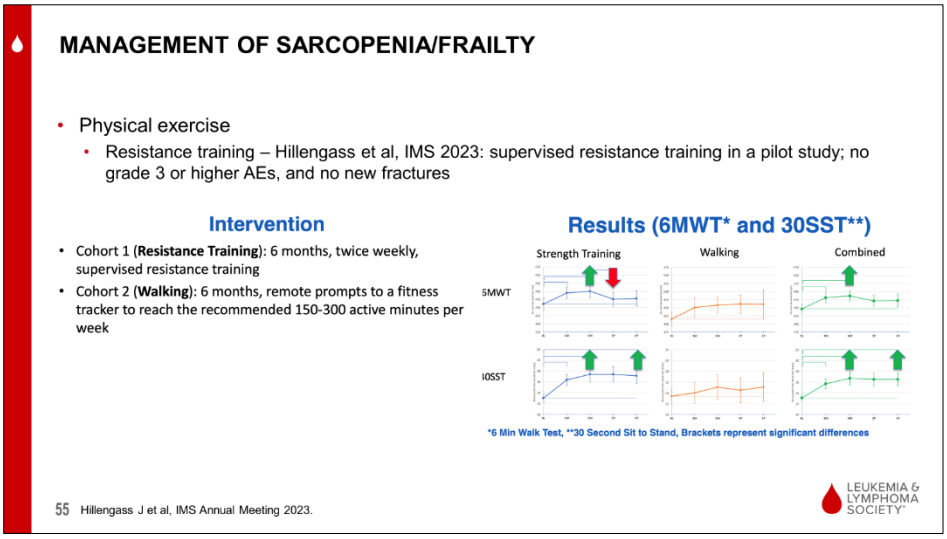
What about mobility and strength? So, we talked a little bit about this idea of sarcopenia. What is sarcopenia? Sarcopenia just refers to decreased muscle mass. There are lots of risk factors for this – I hope to explain to you why I think this is something we need to be looking at –but basically, chronic inflammation, mitochondrial damage, hormone disorders, muscle degeneration are intrinsic risk factors. Extrinsic risk factors include physical activity, sedentary lifestyle, obesity, and other factors. And so, unfortunately, with multiple myeloma, a lot of these factors may be present in folks who are getting treated; and this can lead to sarcopenia.



Indeed, we've seen in studies that this is pretty common. In a single-center study of patients who underwent transplant, sarcopenia was present in 50% of patients and was associated with cardiovascular events. In another study, sarcopenia had a negative prognostic impact, so it actually, it was associated with worse outcomes, independent of other known high-risk factors.

It's also been shown to be associated with risk of developing neurotoxicity in a study that was done in folks who were getting CAR T-cell therapy. In a study of 341 patients, low muscle radiodensity was

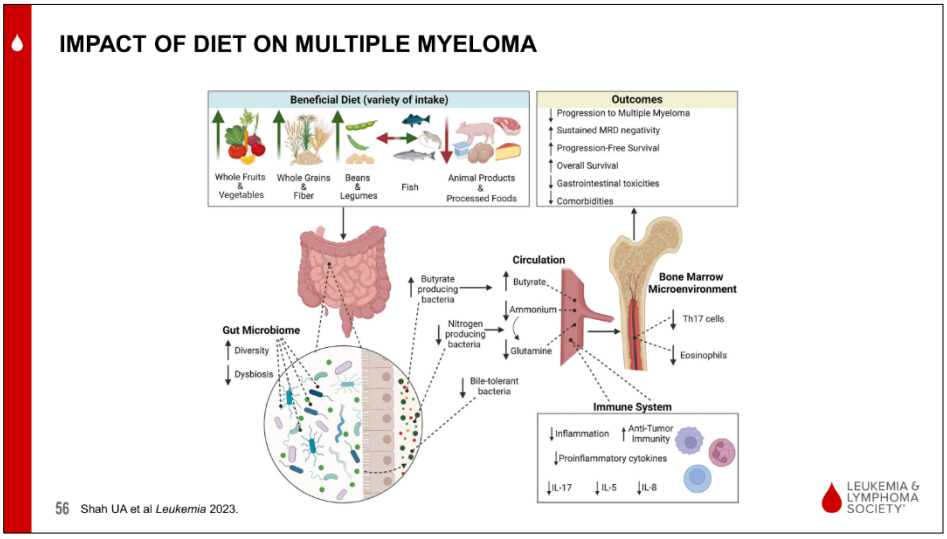
associated with higher disease stage. So, it's either something that goes along with some of these factors, or it's an independent risk factor.



So, we know that it's bad. What do we do about it? So, this comes up a lot. "Doctor, my prior doctor told me I couldn't do any exercise because I can break a bone." So this gets to a common concern with multiple myeloma, which is, we know that multiple myeloma patients are predisposed to having fractures. Is it safe to exercise? Is it safe to do resistance training?

So, I think it's great. One of the myeloma specialists over in Buffalo, New York, Dr. Hillengass, did a study of supervised resistance training in a pilot study. And so important that this was supervised, so if you hear this, it doesn't mean I can go to the gym and start doing the squat rack again or doing bench press. I think, if you want to do a resistance training program, talk to your doctor and try to find a way that you can get a supervised resistance training program.

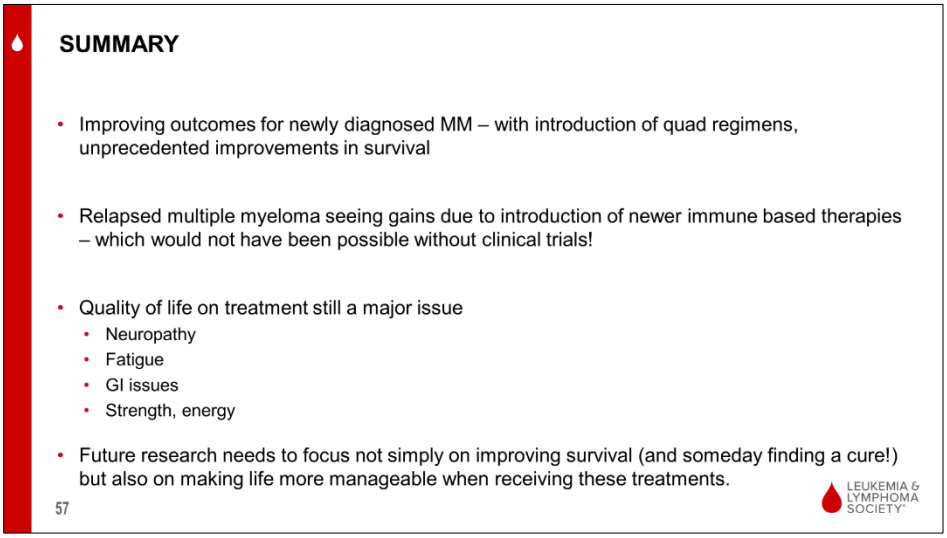
But what they showed in this resistance training program was an improvement in six-minute walk time and an improvement in strength training. So, this intervention seemed to be beneficial, this walking and resistance training cohort. And importantly, there were no grade 3 or higher adverse events and no fractures. So, I think this should be reassuring for those who have asked about this, that we can do this, it can be done safely, but it should be done in a supervised, monitored setting.



What about the impact of diet? And this comes up a lot. "Doctor, I have smoldering myeloma, or I have active myeloma, is there anything I should eat to help reduce my risk of progression or to treat the disease?" The long story short is, yes, your diet probably is beneficial. No, is it going to change the trajectory dramatically? It's unclear. More research needs to be done, but this is from a very nice review by Dr. Urvi Shah who's kind of a leading expert in the field of diet and myeloma.

This is a nice summary of some of the evidence to date which is all sort of epidemiologic. There is some more translational basic research on the gut microbiome or the bacteria that are part of our gut that have a close interplay with our immune system, but basically it kind of comes back to what I was talking about with neuropathy. This this would be advice I would give anyone. It's beneficial. You want to have a good diet, and that includes eating whole fruits and vegetables, whole grains and fiber, beans and legumes, avoiding processed foods, avoiding things like high fructose corn syrup – all that stuff that we know already is bad for our health.

There's an even added importance to try to have a good diet when you have multiple myeloma. You want to keep your body as strong as you can. Hopefully, we'll have more research in this area in the future, and I'm pleased to see that there's such an interest in this going ahead.



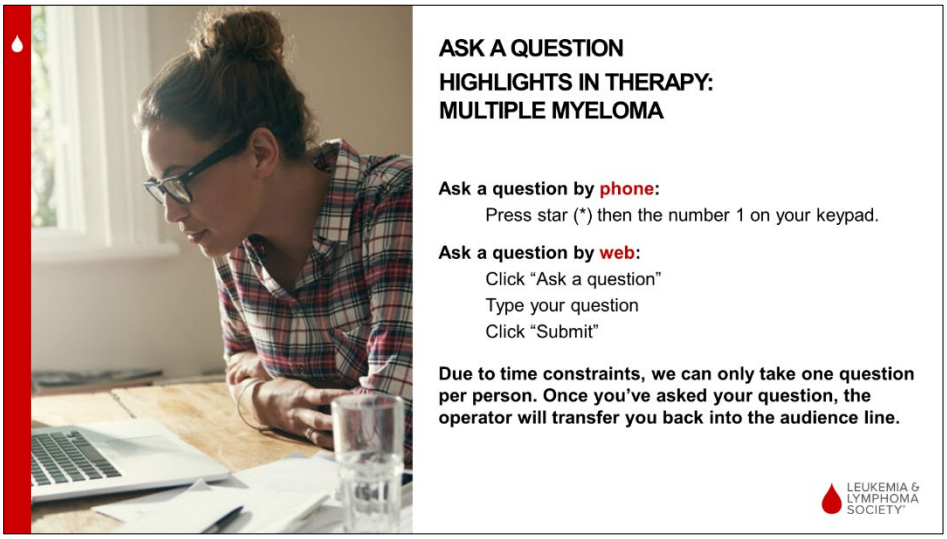
So, to summarize, we're seeing kind of unprecedented improvements in survival for folks with newly diagnosed multiple myeloma now with our quad regimens which are very effective. We're also seeing gains in relapsed multiple myeloma. Again, not to kind of harp on this again, but a lot of this is because of these clinical trials. Clinical trials are so vital to advancing the field. So, please think about trials when you're going through treatment. Talk to your doctor about them. They're always optional, but they're worth considering because sometimes you could get access to a treatment that you otherwise would not be able to access that's new and promising.

However, quality of life on treatment is still a major issue. Neuropathy, fatigue, GI issues, strength and energy are all aspects of life that I think we could do a better job of addressing. It's nice to see that we're starting to, and this is a major interest of mine as well.

And I think future research needs to focus not just on improving survival and finding a cure, but also on making life more manageable when getting these treatments, making it so that people can continue living a full life and not dealing with treatment side effects all the time.

So, with that, I will conclude; and I think we have a little bit of time for questions. Sorry for going over a little bit, but there was a lot to cover.

QUESTION-AND-ANSWER SESSION



Lizette Figueroa-Rivera, MA
Well, thank you so much, Dr. Cowan, for volunteering your time with us today to discuss multiple myeloma and the advances in treatment. As you mentioned, it is now time for our Question-and-Answer portion of our program. For everyone's benefit, please keep your questions general without many personal details so Dr. Cowan can provide answers that are general in nature.

Lizette Figueroa-Rivera, MA
Thank you. Doctor, our first question comes from Danielle. Danielle has smoldering multiple myeloma. She says, "I'm borderline on high risk. Anything I can do to slow the progression, and what increases risk? Anything to avoid?"

Andrew J. Cowan, MD
That's a great question. For smoldering multiple myeloma, really the only proven interventions to delay onset of multiple myeloma would be, there was a large study that compared lenalidomide to placebo. It was called the ECOG (Eastern Cooperative Oncology Group) study, and it showed that lenalidomide could reduce the risk of progression to myeloma. That's a therapeutic intervention. Obviously, lenalidomide as a ton of side effects; and so many people would, are not thrilled about that option.

There are trials out there. Many trials looking at early treatment of smoldering MM, so you may want to look at one of those. In terms of sort of lifestyle modifications, there's nothing proven, unfortunately.

I would say that, in general, my advice would be to try to maintain a healthy weight. Meaning, ideally, a BMI (body mass index) that's close to 25. Try to make sure that you're in good health in general, eating a healthy diet. Try to make sure other health problems like diabetes and such are controlled. I mean, I think you really want to optimize your health.

With smoldering MM, it's very variable in terms of how long it takes for someone to get myeloma. But you really want to make sure that your health is as good as possible if that did happen. I mean that's one way to think about it.

Could making those lifestyle modifications change the trajectory? I mean we don't have data that says it could, but we don't have data that says it couldn't. So, I think this is something where there's really no downside to changing your health. And so, I don't know if that's helpful or not; but getting a diagnosis like this is absolutely reason to try to optimize your health, for sure.

Lizette Figueroa-Rivera, MA
Thank you. And we'll take the next question from our telephone audience please.

Laura from Pennsylvania
I notice like I just took the Tecvayli, and that really didn't work for me. I had too many side effects; and then I did Talvey®, and that was back in November. And I had other complications and stuff. But I've done two stem cell transplants and CAR T, and I noticed, I go twice a week for platelets, and I noticed that after I did the CAR T is when, and platelets and hemoglobin was essentially why I'm going. And this has been over two years now that I've had the CAR T. I go twice a week for transfusions, and I notice that after CAR T. I'm 14+ years in, and you name it, I've probably been on it. So I just notice that I've just had so many transfusions, and I end up getting fungal pneumonia from a contaminated platelet transfusion.

Lizette Figueroa-Rivera, MA
So, doctor, what other treatments or how can she go about further treatments at this point?

Andrew J. Cowan, MD
Well, I mean I think it certainly sounds like, I just want to acknowledge it does sound like a challenging situation. Unfortunately, she's not alone. The issue of the low blood counts and the infections that she describes can definitely happen, especially when someone's had myeloma for that long and we start to see these cumulative side effects of treatment. Sometimes that can make it so that the folks are not eligible for clinical trials, which is what I would typically recommend.

I think, in general, kind of at that stage, we probably do want to look at trials. And so I would really, if she's not already, I would really talk with the doctor, see if she's eligible for any trials because I really think once we've kind of gone through all the BCMA, the GPRC5D drugs, that's really where we need more options right now. There are, of course, other things. If she hasn't had selinexor which could be a problem with the low platelets though. But, yes, that would be kind of my general advice.

Lizette Figueroa-Rivera, MA
Thank you, yes. And our next question, "What is the effect of immunotherapy on the kidneys and other organs?"

Andrew J. Cowan, MD
So, the effect of immune therapy on the kidneys and organs, well directly, there's not really an effect. Rarely people can have immune-related side effects that can affect the kidney, like inflammation of the kidney. We've seen that with some types of immune-based therapies that have been given to people with solid tumors.

So, theoretically it could be a risk with some of the bispecific antibodies. It's not super common. Most of the time, I mean the only real risk to the kidneys would be if someone had really bad cytokine

release syndrome, and that resulted in low blood pressure that affected the kidneys. But, fortunately, that's pretty rare. So, actually, we've given bispecific antibodies to folks who were on dialysis and have done so safely. I think it's not a common concern but definitely, there is certainly probably a theoretical risk, although in practice I haven't seen it be a problem usually.

Lizette Figueroa-Rivera, MA
Well, thank you. And our next question, "Is myeloma hereditary?"

Andrew J. Cowan, MD
That's a great question, Norma. For the most part, multiple myeloma is not hereditary. However, I think it's important whenever I see a patient with multiple myeloma I always ask like sort of a baseline family history – mom/dad, brothers/sisters, grandparents. You do find family cohorts or family trees where there is sort of a striking history of multiple myeloma or other plasma cell disorders. And I think in those cases that a referral to genetics is probably a good idea. At our clinic, we have a hematologic malignancies genetics program that sees these patients; and I think that's often the next step I would take.

It's clear that there are some families where there is a history of multiple myeloma. We're trying to understand these patients better, trying to understand what mutations might be driving this. We don't have anything quite yet like breast cancer, but we know that BRCA (BReast CAncer gene) 1 and 2 mutations confer a very high risk of developing breast and sometimes ovarian cancer. But a lot of research is being done in this regard. So, it's certainly worth investigating, worth asking about if there is a family history seeking a genetics referral.

Lizette Figueroa-Rivera, MA
Thank you. And we'll take the next question from our telephone audience, please.

Lawrence from Texas
Yes, I've been getting shots for the last two years. I was told I have smoldering myeloma. They told me after two years that the shots don't have the same effect, and they don't want me to take them anymore. And I also want to know what blood test did they figure my myeloma was smoldering versus another type of myeloma?

Andrew J. Cowan, MD
All right, well, without knowing what the shot is, it's a little bit hard to know how to answer the first part of the question, so I will skip that. But I can definitely answer the second question about smoldering versus myeloma. We didn't really talk about this, to be fair, but basically smoldering myeloma, you could almost think of as asymptomatic myeloma. So, there's more than 10% plasma cells in the bone marrow or the monoclonal protein is more than 3 grams per deciliter. But there's none of the CRAB criteria, there's none of the SLiM CRAB criteria, all those things we talked about earlier. And so there's no evidence that things are active. And so, in general, the practice has been for most patients with smoldering multiple myeloma to observe very closely because there is certainly a risk of developing myeloma.

The other thing that's worth mentioning is MGUS, which is present when the bone marrow plasma cells are less than 10% and M spike's less than three and, again, no evidence of myeloma by the CRAB criteria. And that's another condition we would generally just observe.

The field has sort of been investigating treatment of high-risk smoldering multiple myeloma in clinical trials, and so, I think those trials are worth looking at. But there's still quite a bit of debate as to whether high-risk smoldering or smoldering multiple myeloma should be treated. So, it's best to sort of get multiple opinions about it before making a decision.

Lizette Figueroa-Rivera, MA
Thank you. And our next question, "What makes people ineligible for transplant at this time?"

Andrew J. Cowan, MD
That's a great question. So transplant eligibility, what makes someone a good candidate for transplant? Well, like I mentioned earlier, at least at our center at Fred Hutch, patients need to have, we generally transplant few patients over the age of 75. And so while there is no upper age limit, I think the reality is as we get older and older, we get more and more health problems or inability to sort of, do all the things that are necessary to do a transplant. That's not to say that you couldn't get a transplant if you're 77 and you're a marathon runner and you're incredibly fit and you really want to do it. I think it's certainly worth exploring.

But the reality is there's very few folks out there like that. And so I think it just kind of reflects the population. But basically, what we're looking at is sort of ability to tolerate high-dose chemo (chemotherapy). And so this high-dose chemo is tough on your body, as anyone who's undergone a transplant knows. High-dose chemotherapy, the most common side effects would be nausea, diarrhea, fatigue, risk of infections. Many patients, at least at our center, end up getting admitted for one or more of these side effects.

And so, you've got to have some basic good level of health, of fitness. There's some conditions that might exclude someone from transplant, like having heart failure or being unable to sort of comply with the requirements of doing a transplant, coming into clinic every day, being within 30 minutes of the center, and having a caregiver.

And so it’s often is sort of a complicated discussion; and certainly, if someone has been told they're transplant ineligible, I'd probably want to meet with a transplant doctor, make sure that they agree, seek an opinion from a myeloma specialist because I think it can be sort of a complicated thing to determine.

Lizette Figueroa-Rivera, MA
Thank you. Our next question, "Can you have CAR T-cell therapy if you've had an allogeneic or autologous stem cell transplant?"

Andrew J. Cowan, MD
Yes, you can. We would probably wait a little bit after a stem cell transplant, and it would be uncommon to need to do a CAR T therapy so soon after transplant, but yes. Allogeneic transplants, which are not done as commonly for multiple myeloma anymore, but there are patients who had them

maybe 5, 10, 15 years ago who are now looking at things like CAR T therapy. And that is not an exclusion to getting a transplant.

You would definitely want to meet with an immunotherapy specialist to sort of go over the state of your – if you had an allotransplant, if you have chronic GVHD (graft-versus-host disease), other things that sort of might modify risks of side effects. But, in general, it's not an exclusion factor and neither is prior stem cell transplant. In fact, most patients who've had a CAR T have already had a stem cell transplant.

Lizette Figueroa-Rivera, MA
Thank you. And we'll take the next question from our telephone audience, please.

Rita from Rhode Island
I have been on lenalidomide for approximately 12 years. I'm in remission. Recently I've been getting pulled muscles, and they last approximately four to six weeks. I've had three of these muscles pulled within the past nine months. Is there any remedy for it? Do you think it is from the Revlimid® or any suggestions on what it could possibly be from?

Andrew J. Cowan, MD
That's a great question. I think what I'm more commonly used to, and sorry to hear about this. I know how tough those can be. But in general with lenalidomide or Revlimid®, muscle cramps are common. Getting pulled muscles, I haven't heard quite as much about.

It's certainly possible it could be related to lenalidomide. I mean I think one thing you could do; you could talk with your doctor about considering maybe a holiday from treatment and see if that helps with how severe these pulled muscles are or maybe reducing the dose. I mean, I think you probably want to at least explore whether there could be some relationship. There may not be. But probably want to make sure there isn't.

Lizette Figueroa-Rivera, MA
Thank you. And our next question is about something new for myeloma. "Is it possible to have liquid biopsies in regular blood without bone marrow biopsies by using mass spectrum for myeloma patients?"

Andrew J. Cowan, MD
That's a great question. So, the question is about the idea of like using blood tests to do an MRD test. At present, well, so the first part of the question, we don't really have a blood test that can sort of give us all the information a bone marrow can give us. What can a bone marrow give us? Bone marrow tells us not only, it helps us make a diagnosis of myeloma; but it also gives us the cytogenetic risk information that I kind of talked about a little bit earlier, the chromosomal changes. And those are important when we think about treatment and sort of risk, and so we don't really have a blood test that can give us all that.

Now that said, with respect to MRD, there are some blood tests that may come close to achieving the sensitivity that we get in the bone marrow with MRD testing. And that is still early, but I think there are some, there's a couple of assays out there that are intriguing and promising; and I certainly would

hope to see that type of technology advance because it would be wonderful if we're checking MRD if we had a blood test that could give us the same information as a bone marrow that could supplant the need to do all these bone marrow biopsies. So, I'm hopeful that some of these tests will sort of one day replace the need for a bone marrow. But I think at this point we don't quite have all the data yet.

Lizette Figueroa-Rivera, MA
Right, and it's exciting to see new advancements in the field. I am wanting to ask you what you're most excited about at this point with the progress through the years with myeloma research and myeloma treatment?

Andrew J. Cowan, MD
I'm really just so excited to see all these treatment options that have become available over the past five years. I mean, I distinctly remember a period of time before CAR T cells were approved when a patient wasn't eligible for a study for some reason; and patients, younger patients particularly with bad myeloma didn't survive. Now, just four years later, those patients are making it, and to me, that's really powerful.

I would love to be able to say that we're curing some patients. That would be amazing. But even just to say that, that there's hope. Even if something like, for example, like the Dara-RVd. If that doesn't work for some reason, we have this amazing therapy, CAR T-cell therapy or bispecific antibodies that can work, even when those treatments didn't.

Or even to say to a patient, you know, with [the] PERSEUS [trial] we're seeing at four years like such high percentage of patients still in remission, knowing that even when they relapse, there will be something like CAR T-cell therapy or another combination that we can give them that will keep them going. Or even when I see patients in my clinic that have been alive with myeloma for 15 or 20 years, I'm starting to think is there really an upper age limit, an upper time that I could say most of the time when you see a doctor today, they might say, "Well, you've got myeloma. [The] average survival is eight to ten years." I mean, but is there an upper limit to that? I would like to think there isn't, right? I mean that's really what we should be aiming for. So, there is a lot that I'm really excited about, and those examples I gave are kind of like, I think, emblematic of that.

Lizette Figueroa-Rivera, MA
Yes, we are very excited to hear about all of these advancements, and thank you so much, Dr. Cowan, for your continued dedication to patients and for being able to present this webcast for us today.

Andrew J. Cowan, MD
My pleasure.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA
Thank you. And for patients like Laura who called in, LLS can provide you with support and questions to follow up with your doctor on your next steps. And if we weren't able to get to your question today, please call The Leukemia & Lymphoma Society Information Specialists 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 out to us by emailing us at LLS.org/ContactUs.

Also, patients as well as caregivers can schedule a free personalized nutrition consultation with our dietitians at LLS.org/Consult.

LLS offers a variety of education and support services, including online chats like Izak mentioned, which are free live forums that are moderated by oncology social workers. We also offer free education videos and podcasts.

Please note that continuing education credit is not being offered for this program.

Again, thank you, Dr. Cowan for sharing your knowledge with us today, and we'd like to also acknowledge and thank Genentech Inc. and Biogen and Johnson & Johnson for their support of today's program.

To all of 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.