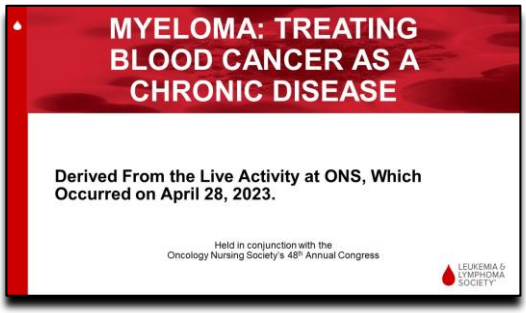


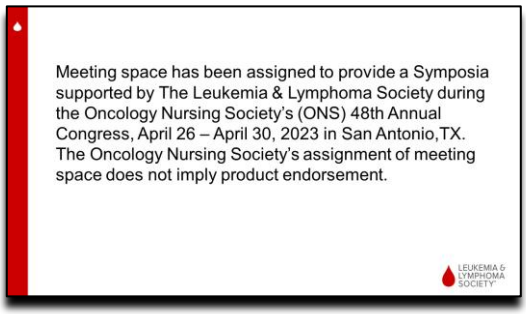
Slide 1: Myeloma: Treating Blood Cancer As A Chronic Disease

Lauren Berger, MPH: Hello everyone. Good afternoon.

Slide 2: Welcome and Introductions

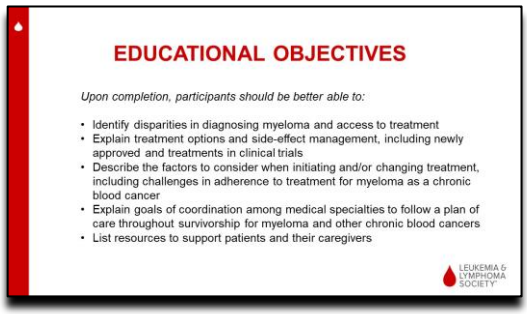
I'm Lauren Berger from The Leukemia & Lymphoma Society. And on behalf of The Leukemia & Lymphoma Society, we are so pleased that all of you are here today. Obviously, the group that's gathered here is interested in the topic, interested in sharing together and discussing with each other, and we're really, really pleased that you have decided to come here. Also, we hope this provides a really important and valuable learning opportunity as well as some fun.

We will provide an overview of FDA-approved treatments and others being studied in clinical trials, including oral therapy, systemic therapy, transplant, CAR T-cell therapy, and bispecific antibodies. The focus will be on the nurse's role in administering treatment, side effect management, educating and supporting patients, the role of the interdisciplinary team, and assessing resources for survivorship support. Disparities in diagnosing and treating Black Americans, low income and other underserved populations, as well as issues that impede patients' access to treatment will also be discussed.



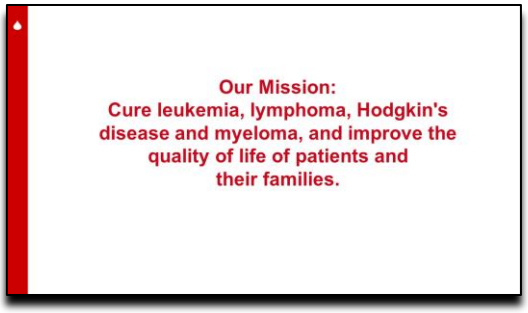
Slide 3: ONS Disclaimer

Meeting space has been assigned to The Leukemia & Lymphoma Society to provide this symposia.



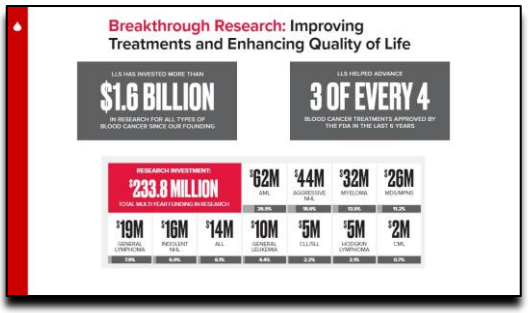
Slide 4: Educational Objectives

The educational objectives are listed on this slide.



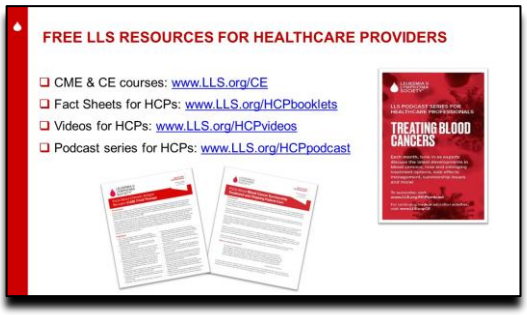
Slide 5: Our Mission

The mission of The Leukemia & Lymphoma Society is to cure leukemia, lymphoma, Hodgkin's disease, and myeloma and improve the quality of life of patients and their families.



Slide 6: Breakthrough Research

I'd like to tell you a little bit more about the impact that LLS has had for patients. Over the past 70+ years, LLS has invested more than $1.6 billion in cutting edge research, funding nearly all of today's most promising advances, including immunotherapy, genomics, and personalized medicine. LLS supports the full spectrum of research from basic, laboratory-based research to large scale clinical trials. This research has had great impact on getting and moving therapies to patients.



Slide 7: Free LLS Resources for Healthcare Providers

I am now pleased to share free resources from The Leukemia & Lymphoma Society for both you and your patients. For you, The Leukemia & Lymphoma Society offers free CE and CME online courses as well as a podcast channel for you where you can listen to health care professionals discuss treatment, side effect management, and strategies to support your patients. New and interesting topics are listed every few weeks, and we continue to record and add new ones.

To access these, as well as our videos and fact sheets for HCPs on a variety of topics, please visit LLS.org/CE.

Slide 8: Free LLS Resources for Patients

Leukemia & Lymphoma Society Information Specialists are highly trained oncology nurses and social workers who provide accurate, up-to-date disease, treatment, and support information, including financial. Your patients can contact them directly, or you can complete a referral form. Information Specialists can also help you access and order multiple copies of free booklets for your patients. Our Clinical Trial Support Center Nurse Navigators are registered nurses and nurse practitioners with expertise in blood cancers. They work one on one with patients via telephone to provide user friendly information. They help them find appropriate clinical trials and personally assist them throughout the entire clinical trial process. They also provide information to the patients to bring back to you their health care provider. And you as nurses can also contact these specialists. This is a unique service from The Leukemia & Lymphoma Society.

We also encourage you to refer your patients for free one-on-one nutrition consultation with one of our registered dietitians. Consultations are available by phone for patients with all different types of cancer, not just blood cancers, as well as all ages. And they're available in languages, all different languages using our interpretation service.

For information or to refer or connect a patient with an Information Specialist, a Clinical Trial Nurse Navigator, or a registered dietitian, please use the URLs listed here on the slide. I hope you will consider all of these specialists as an extension of your health care team.

Slide 9: Free LLS Resource for Patients and Caregivers

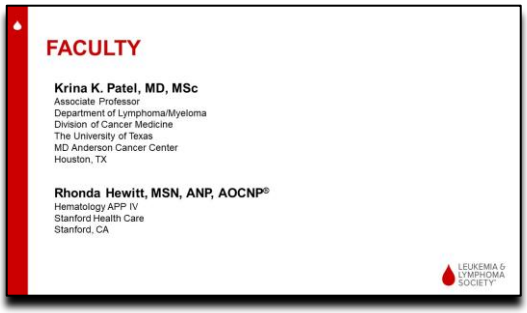
LLS also offers blood cancer disease-specific information and support resources to both patients and caregivers, including telephone and web education programs, videos, podcasts, and booklets. You may know about LLS's financial assistance program, and I encourage you to stay on top of what funds are available by going to our website.

Slide 10: Free LLS Resources for Your Patients

Booklets. As many of you have come to our exhibit and you've seen many of our booklets perhaps in your clinic, the booklets are available in English and Spanish; and through our targeted and culturally appropriate programs and services, LLS is committed to addressing the needs of underserved communities impacted by a blood cancer and those facing systemic and structural barriers to optimal care.

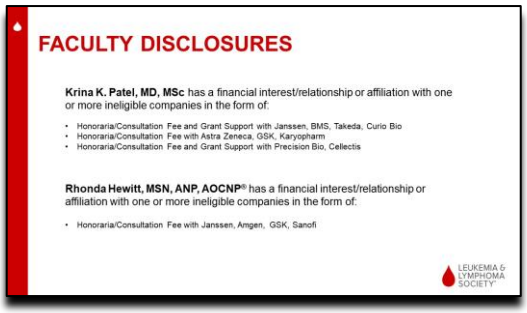
One of those initiatives is Myeloma Link, a national outreach program that raises awareness of the higher incidence of myeloma in the Black community. Visit LLS.org/myelomalink. This is a national outreach program.

And here are examples of some of the booklets that I just mentioned. Once again, they're available at no charge to give to your patients or for yourselves. If you have any questions on any of the resources, please contact an Information Specialist. And we know that you are key to patient treatment, support, and helping with survivorship challenges for myeloma, which is a chronic blood cancer, as well as for all other types of cancer. And we at The Leukemia & Lymphoma Society are here to support you and your patients, so please reach out to us.



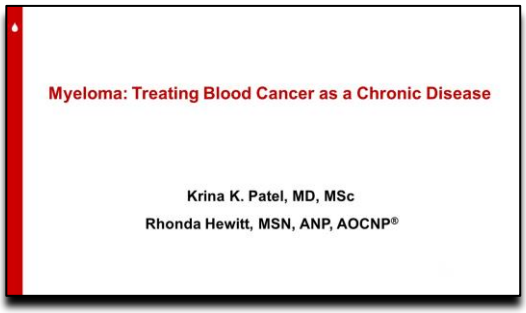
Slide 11: Faculty

Okay, I am now honored to introduce our faculty. Dr. Krina Patel is an Associate Professor in the Department of Medicine at MD Anderson in Houston, Texas. Ms. Rhonda Hewitt is a Hematology Advanced Practice Provider at Stanford Health Care in Stanford, California.



Slide 12: Faculty Disclosures

Their faculty disclosures are listed here. Dr. Patel and Ms. Hewitt, thank you so much for volunteering your time and expertise with us. I know that you are looking forward to sharing information, a patient case, and discussion; and it is now my pleasure to turn the program over to you.

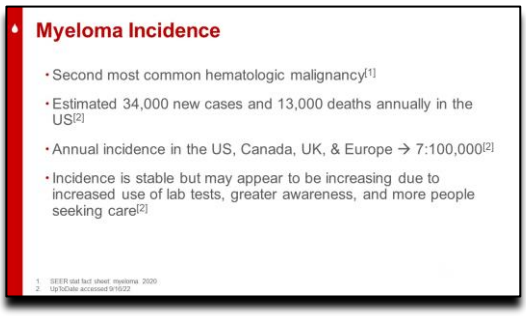


Slide 13: Myeloma: Treating Blood Cancer as a Chronic Disease

Dr. Patel: Well, thank you so much for having us, and I think the next hour, hour and 15 minutes, we will go through our slides and a case and, hopefully, this is going to be like Myeloma 101.

I was telling Rhonda last night, you know, whenever we have, like fellows or nursing students, PharmD students coming through my clinic. I always say if you can do myeloma, if you can diagnose myeloma or you can do all the response from myeloma, it's one of the most difficult ones. I still have to look it up sometimes. If you can do that, you can do anything. So, hopefully, we'll be able to help with that today.

Ms. Hewitt: Yeah, I totally agree with what Krina says that I think myeloma is probably the most complicated, hem malignancy that we deal with; and so today we're going to spend a little bit of time before we get into talking about the therapies and stuff, talking about the pathophysiology of the disease. And hopefully with that base, that knowledgebase, it will help you to understand the disease a little bit more and really to understand the things that your patient's at risk for before we move into talking a little bit more about the therapies and the nursing management for some of those things.



Slide 14: Myeloma Incidence

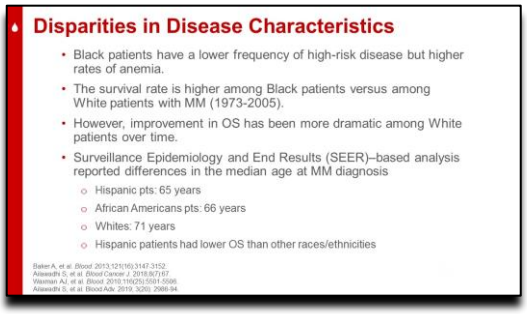
So myeloma, as you may know, is the second most common hem malignancy. Lymphoma trumps it, but it's the, second most common liquid tumor that we deal with, which about 34,000 patients being diagnosed each year in the US. The annual incidence is about 7 per 100,000 people. And the incidence of myeloma seems like it's, it seems like a disease that's more common now, that we see more commonly; but the incidence hasn't really changed. It's really that there's an increase in awareness; and people are getting tested earlier and more people are seeking care for their disease.

Part of that is because historically we treated myeloma with chemotherapy, and with a disease that has a median age of, onset of 70 like myeloma, chemotherapy doesn't work well or isn't an option for some of our elderly myeloma patients. And we'll talk a little bit more as we get in why chemotherapy may not actually work well in the disease process itself as well.

Slide 15: Age, Sex, & Ethnic Distribution

So, as I said, median age at diagnosis, 69 or 70. Most people, it's more common in men than in women, just like all hem malignancies. It's also more common in the Black population than Whites and even less common in the Asian population.

The five-year survival rate from 2012 to 2018 is documented at 57.9. I hope that our five-year survival rate that we see in clinical practice is actually better than that because we've learned a lot in myeloma therapy over the last decade or two decades as to the importance of combination therapy, the importance of using novel agents as opposed to chemotherapy agents. And, so I think, our supportive care is also better. So hopefully when the next survival rate gets published, it will be higher than this. It is a disease that's very sensitive to therapy, but it's also a disease that we currently say we do not have a cure for. I'm sure everybody in the room has a patient who has had myeloma for 26 years or 27 years, but they have a little bit of myeloma still. So we don't use the word cure for myeloma, but many of us think that we may be close to seeing and to being able to use that word at some point in time.



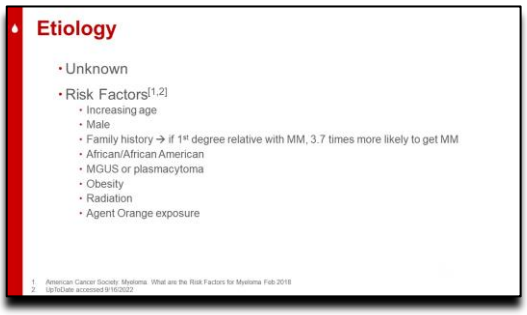
Slide 16: Disparities in Disease Characteristics

And then, Krina, did you want to talk a little bit about why we see this more commonly in the Black population?

Dr. Patel: I think this is a really important topic; and, you know, myeloma, any patient today that has myeloma, one in five are Black. So 20% of our patients are actually Black. And the risk of disease, right, so when we talk about patients who are 26 years out, those are patients that usually have low-risk disease, which we'll get into in a little bit versus high-risk disease. Those are our patients that act a little bit more like our acute leukemia patients that we're just constantly treating them with different therapies in a short amount of time.

And what's interesting is that our Black patients actually don't have a lot of high-risk disease. They have a lower incidence of high-risk disease. However, the survival rate, because of that, is higher among Black patients than amongst White patients, up until 2005. However, the improvement in overall survival in the last two decades, we haven't seen that in our Black patients as we have in our White patients. So there's definitely a disparity of access, which is one of the problems, but it's much more complicated than that. And I think this is something that all different groups of, you know, pharmaceutical companies, physicians, nurses, and institutions are really working to figure out what this is. Sometimes it's socioeconomic status. Sometimes it's not. So we're kind of piecing all these little things together to say how do we get all our patients the appropriate therapy?

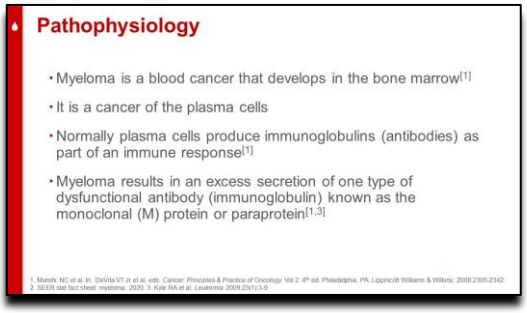
And, again, you know, when we talk about the average age being 70, well that's for White patients. For our Hispanic patients, it's actually the youngest. So the average age is 65. And if you look at, for African American Black patients, it's 66. So even when you're diagnosing, sometimes patients are going to their PCP and someone might say, "Well, your kidney function's probably off because of your hypertension or something else because you don't really fit the age for myeloma." And then they go years without being diagnosed. And by the time they're diagnosed, they're in end-stage renal disease, right. So we have to improve from the very beginning, and I think some of this data will hopefully help upstream as well.



Slide 17: Etiology

Ms. Hewitt: Great. So when we talk about what causes myeloma, the reality is we don't actually know the etiology. That's unknown. We do know that there are certain risk factors. We've just talked about this as a disease that's more common in the Black population, so being Black is a risk factor. Being male is a risk factor. Increasing age is a risk factor.

It's not a genetic disease, but if you have a first degree relative that has myeloma, you're 3.7 times more likely to get myeloma. And then if we could take every single myeloma patient and go back in time, the natural trajectory of this disease is all of those patients started with monoclonal gammopathy of unknown or uncertain significance. And MGUS can actually develop, as many of you know, into several different problems. But one of the problems, if we follow along myeloma, it, MGUS patients can develop myeloma. There's about a 1% incidence per year that those people will develop myeloma. And then some other things like obesity, radiation, and agent orange exposure of also being associated with the development of myeloma.



Slide 18: Pathophysiology

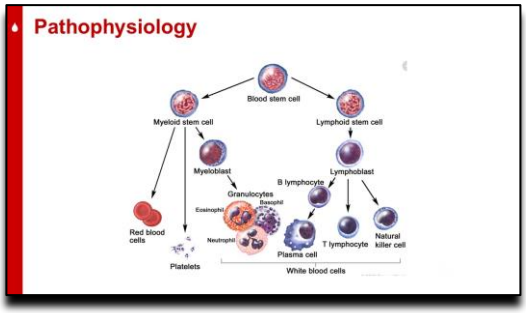
So when we think about cancer, you think about, okay, what is the cell that's being, involved; and what is that cell's normal function in the body? And in the case of myeloma, the cell that's involved is the plasma cell.

The plasma cell is a very important cell in our bodies because it really plays a huge role in immune function. It produces our body's immunoglobulins, also known as our antibodies. And, you know, if you have a patient who has a malignancy of their cells, of their plasma cells, so their cell that's supposed to be producing their body's antibodies, that patient is going to be at really high risk for infections.

And, in fact, infection remains the leading cause of death in our myeloma patients. So really important as a nurse, when you're working with these people, if you have, you know, sometimes elderly patients when they have infections, they don't have the classic signs like in, high fever or something. They may just present with fatigue, lethargy, and, in fact, they might have a pneumonia or something. So when you're seeing those patients, and something doesn't quite feel right with them, something's going on, you want to do a little bit of investigation and bring that to the attention of the rest of the team too.

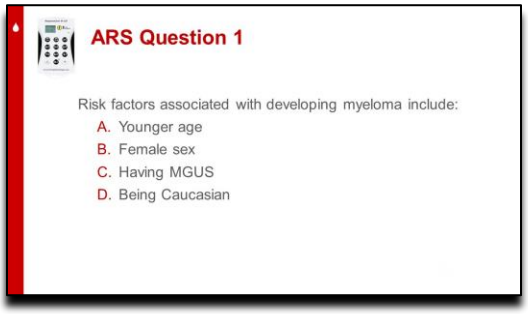
So with a malignancy of the plasma cell, in the case of myeloma, what happens is you get this overproduction of a dysfunctional immunoglobulin or antibody. And, in fact, not only do you get that overproduction of that immunoglobulin that's involved, but you get a corresponding decrease or immune paralysis of the other immunoglobulins.

So, if you remember, there's five main types of immunoglobulin – IgM, A, D, G, and E. IgG is the most common type involved in myeloma, so your patient might have a really high dysfunctional IgG production, and their other immunoglobulins are messed up as well. So it really messes up immune function.



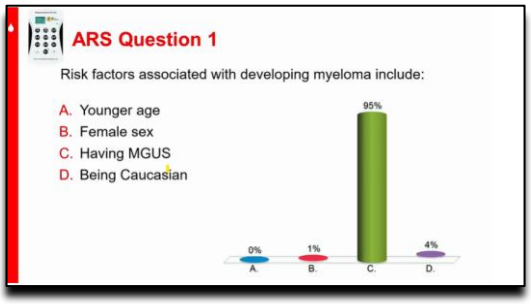
Slide 19: Pathophysiology

So this shows a couple of things. So at the bottom there, you see the plasma cell; and I wanted to point out, so that's the cell that's involved in myeloma. And there's a couple of things that I wanted to point out. Because that cell, you can see that everything starts with the stem cell. The other cells above it are going through division, and if you think about what I said about myeloma not being a disease that often responds well to chemotherapy, chemotherapy works on cells that are going through cell division. Myeloma is a disease of what we call a terminal cell. The plasma cell is not going to divide, and that's one of the reasons that myeloma patients don't respond well to chemotherapy, and it's why most of the therapy that you see these days is novel or targeted therapy.



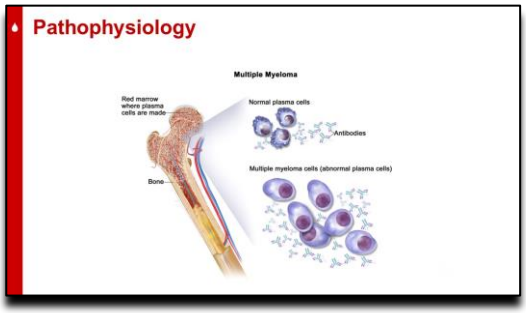
Slide 20: ARS Question 1

Dr. Patel: All right, so our first ARS question. Risk factors associated with developing myeloma include: A) Younger age, B) Female sex, C) Having MGUS, or D) Being Caucasian? It's one right answer.



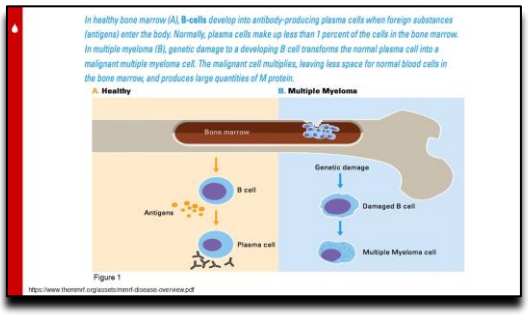
Slide 21: ARS Responses

Right, C, having MGUS. There you go. Perfect. Everybody with myeloma had MGUS at some point, so great job.



Slide 22: Pathophysiology

Ms. Hewitt: Okay, so disease, it's a hem malignancy. Those cells are being produced in the bone marrow. You see at the top normal plasma cell production, antibody production, and at the bottom myeloma cell production.

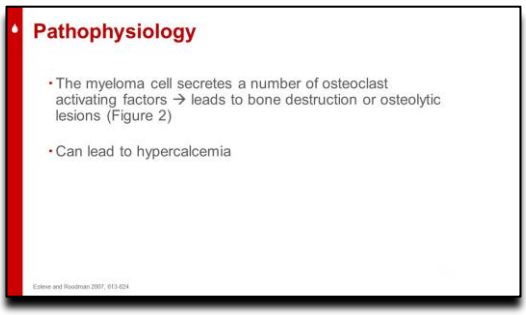


Slide 23: [Image]

So what happens when you have a bone marrow process, a bone marrow malignancy going on and you have an overproduction is that those plasma cells that are being produced in the bone marrow, in a normal situation, we have about 1% of plasma cells that are in the marrow so that if we're exposed to something foreign and our body needs to activate those cells and create antibodies, those cells get called into play.

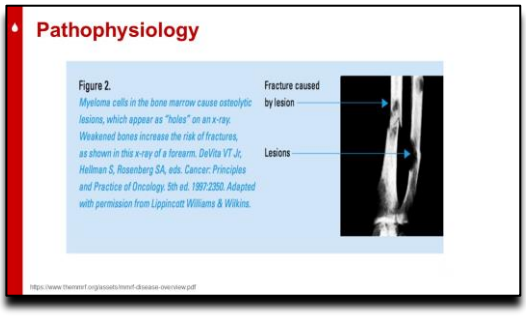
In the case of myeloma, you have, your patient has too many plasma cells being produced; and really you get this crowding out. It's a lot more complicated than that, but we talk about this crowding out. So too many plasma cells being in the marrow. So that takes up space where normal hematopoiesis is. So your patient can develop things like anemia, thrombocytopenia, neutropenia because there are too many plasma cells in the bone marrow.

And this also leads into, you know, this picture here. It looks like those plasma cells are chewing through the bone. That's not exactly what happens.



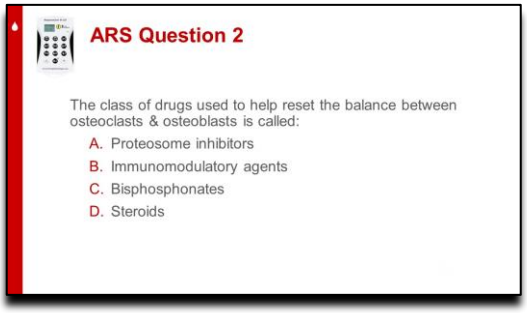
Slide 24: Pathophysiology

The plasma cells actually secrete a number of things that are called osteoclast-activating factors, and remember our bones stay strong because they're constantly being remodeled. They're being broken down and rebuilt by osteoclasts and osteoblasts. In the case of a patient who has myeloma, their osteoclasts, the cells that break down bone, they're being told to work faster. So those cells are working faster, and the osteoblasts cannot keep up. So your patient is actually at risk for holes, literally developing osteolytic lesions which are holes in their bones. And if you think of what are bones primarily made of, they're made of calcium, right? So that is why your patient is at risk for hypercalcemia, because they have this process going on. The myeloma cell is telling those bones to break down.



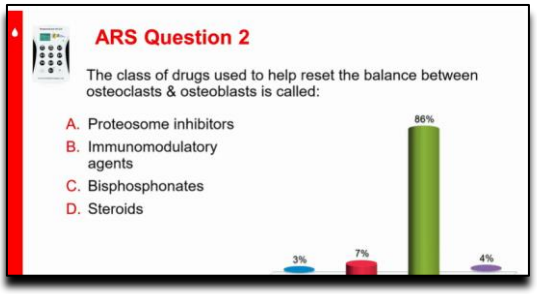
Slide 25: Pathophysiology

And you can imagine if your patient has a hole in their bone, if you take a blood pressure, if they have a hole in their femur, they step off a curb, those patients are at risk for pathologic fractures. So we used to see more frequently myeloma patients would lose height over time. We now give supportive care to reset this balance between osteoclasts and osteoblasts.



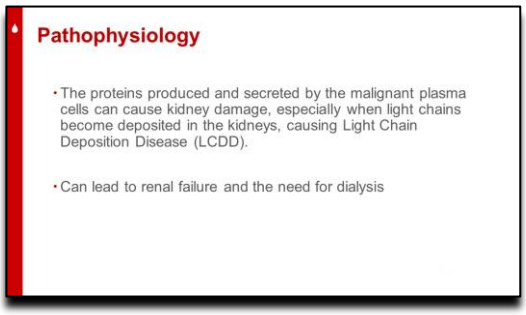
Slide 26: ARS Question 2

So what is the class of drugs that we use to reset the balance between the osteoclasts and osteoblasts? Is that proteasome inhibitors, immunomodulatory agents, bisphosphonates, or steroids?



Slide 27: ARS Response

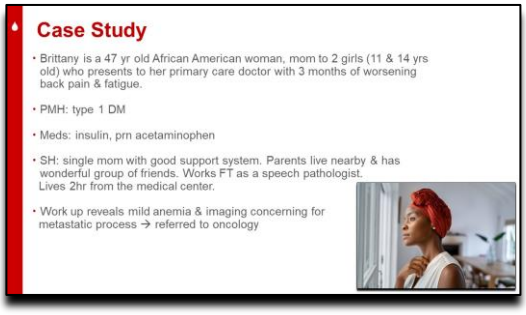
Excellent. We also, there is also something that you, many of you may use called denosumab that can be used instead of bisphosphonates; but bisphosphonates are one of the classes of drugs that we use for bone health.



Slide 28: Pathophysiology

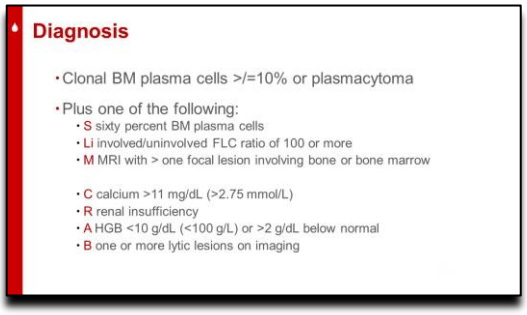
So that myeloma, let's go back to that myeloma cell and what it's doing. So it's producing all of this dysfunctional immunoglobulin or antibody. That immunoglobulin is actually a protein, right? And the production of that protein can cause a lot of problems in the body. One of the things that happens is that patients can get the light chain deposition within the kidney. The kidney is really just a filter. It's there to filter things out. And if you think about any filter or even your bathtub drain, for those of you who have long hair, when you get things that are clogging up that drain, it doesn't work very well. So deposition of protein within the kidney can lead to renal failure and also the need for dialysis.

And really 20 to 40% of patients present needing dialysis at diagnosis, and time is of an essence there. The sooner we treat those myeloma patients, the more likely we're going to be able to reverse that myeloma kidney damage.



Slide 29: Case Study Slide

So let's introduce our patient here. So Brittany is a 47-year-old Black woman. She's mother to two girls who are 11 and 14 years of age. She presents to her primary care doctor with three months of worsening back pain and fatigue. Her past medical history is significant for Type 1 diabetes. She's on insulin and PRN acetaminophen. She's a single mom with a good support system. Her parents live nearby. She has a wonderful group of friends. She works full time as a speech pathologist, and she lives two hours from the medical center. Her workup reveals mild anemia, and her imaging is concerning for metastatic process, excuse me. And so she's referred to oncology.

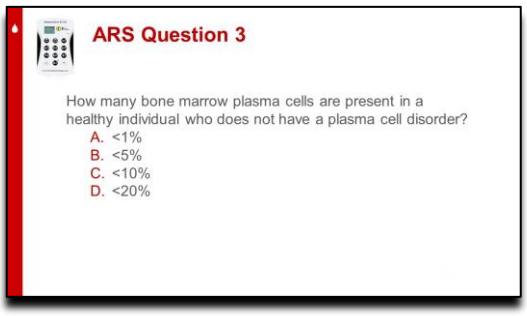


Slide 30: Diagnosis

In order to earn a diagnosis of myeloma, these are the criteria that have to be made. So you have to have a clonal bone marrow plasma cell population of at least 10% or a plasmacytoma. A plasmacytoma is literally just a soft tissue collection of myeloma cells, so a myeloma tumor if you will. So you need 10% plasma cells or a plasmacytoma plus one of the following. And I'm going to start with the second part, the CRAB criteria, because the CRAB criteria are historically what we called the myeloma-defining events. And what those criteria are, are really evidence of end-organ dysfunction. So hypercalcemia, renal insufficiency, anemia, and bone disease. That means that your patient's myeloma is already causing destruction or end-organ dysfunction.

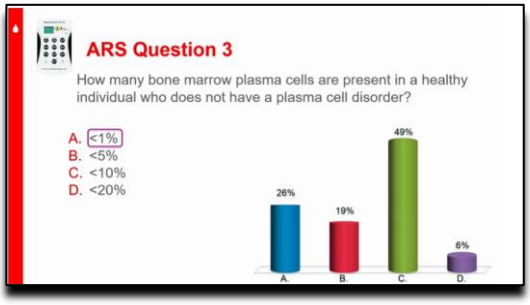
And we used to historically wait until patients had evidence of end-organ dysfunction before we treated our patients with myeloma, but we now know that there's a subgroup of patients that we can pull out early and not only will they do better from an overall survival, but they'll do better from a progression-free survival as well. And when we talk about progression in myeloma, what we're talking about is all of these things. We're talking about, you know, needing to go on dialysis, getting a pathologic fracture, things that really compromise somebody's quality of life.

So if we can pull these people out early, so if somebody has 60% plasma cells in their bone marrow, but they don't yet have a bone lesion, we know they have enough disease that we need to treat them early. If if we take their light chains, so an antibody is made of a heavy chain, those immunoglobulins and then the light chains, the kappa and the lambda. One of the light chains is involved, is always involved in myeloma, and you take the involved over the uninvolved. If that ratio is greater than 100, that patient needs therapy for myeloma. And if we use a more sensitive way to look at the bones than x-rays, so MRI, PET/CT, PET/MRI, if we use one of those tests, if a patient has more than one lesion on their scan, they need myeloma therapy.



Slide 31: ARS Question 3

So how many bone marrow plasma cells should a healthy individual have: less than 1%, less than 5%, less than 10%, or less than 20%?

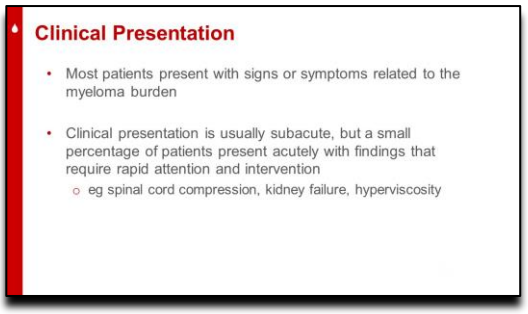


Slide 32: ARS Response

Ah, we got you there. So you need 10% or more to be diagnosed with myeloma, but in a normal situation, we only have 1%, less than 1% of plasma cells in our marrow. Those cells are waiting if we get exposed to something foreign that they're going to activate and produce the antibodies that we need to deal with that exposure.

Dr. Patel: I'm just going to add one qualifying factor to that is clonal plasma cells too.

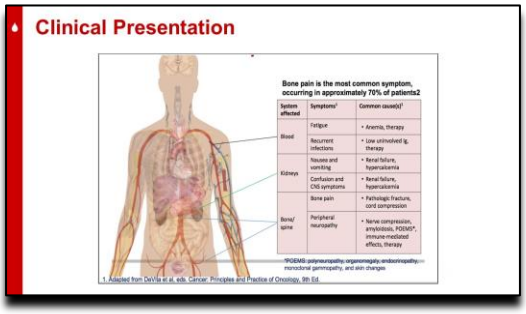
So when we talk about MGUS, someone can have, you know, 2% or even less than 1%. But if they're clonal, meaning they're all kappa or all lambda, that's when we know that someone has MGUS or smoldering if it's a little bit right at 10% versus normally we should have polyclonal so that they're making all different kinds of antibodies for us. So the genetic piece will make a difference too.



Slide 33: Clinical Presentation

Ms. Hewitt: Absolutely. So how do people present? The most common way that people present with myeloma is that they have signs that the disease is causing, that the tumor burden is causing a problem. So often the presentation is subacute, meaning that, you know, maybe somebody presents with infection. By far the most common presenting symptom is bone pain. Up to 70% of your patients will present with bone pain.

But, and some people can present with acute renal failure, cord compression, hyperviscosity. But most of the time, like Krina was alluding to, you know, when you have those younger people, it's kind of these vague complaints that they present with like maybe they have some back pain. Maybe they've had frequent infections or they're fatigued or something like that, something that, you know, unless you're thinking, oh, this could be myeloma in this patient population, they may not actually get the appropriate workup.

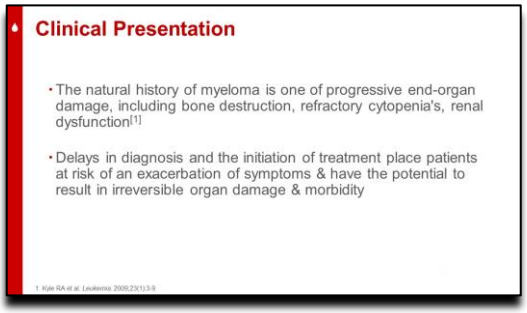


Slide 34: Clinical Presentation [Image]

So, if we think about where is this protein causing a problem, we can think about the symptoms that people, that your patients may have. So if we think about the blood, those bone marrows, or those plasma cells can be taking over the bone marrow space. Patients can have anemia, which gives them fatigue. There, they get 100% get infections. Right, their immunoglobulins don't work well, and they can also have neutropenia as well.

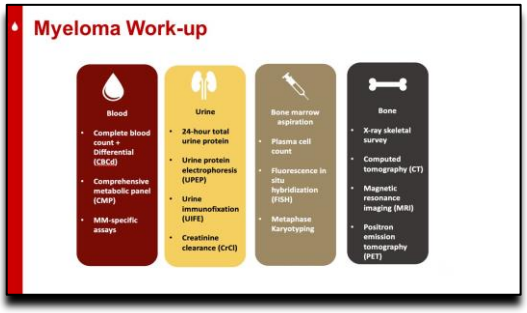
The kidneys are not happy when the light chains are deposited within the kidney itself, and that can lead to renal failure, that process where their bones are being chewed up. The calcium goes into the blood. The way that it gets out is through the kidneys, so hypercalcemia can cause moans, groans, bones, and stones. So altered mental status, nausea, vomiting, kidney failure, those types of things with hypercalcemia.

And then if you have cord compression, your patient can have issues, obviously, with spinal cord compression. And then interestingly, we blame our therapies for causing peripheral neuropathy, but the disease itself can actually cause peripheral neuropathy as well. And so that can be related to the disease or it can be related to the therapy that patients get, are getting.



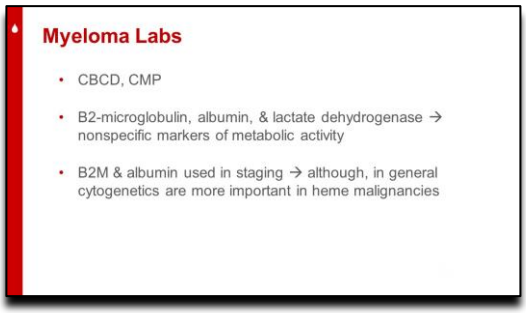
Slide 35: Clinical Presentation

So the natural history of this disease is one of progressive end-organ damage, including the bone destruction, refractory cytopenias, and renal dysfunction. And really the delays in diagnosis and in initiating therapy really put patients at high risk for exacerbation of symptoms and potential irreversible organ damage and really morbidity too.



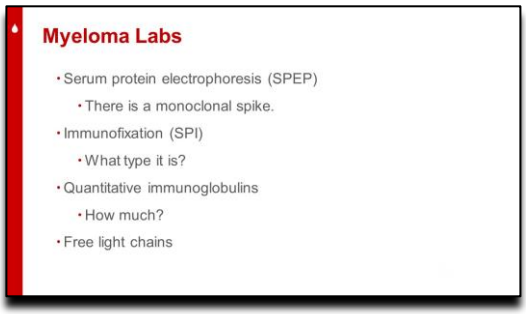
Slide 36: Myeloma Work-up

So when we talk about myeloma workup, we have to look at where in the body is this protein causing problems. So we look at the blood and the urine where the protein is being spilled. We look at the bone marrow aspirate in biopsy, and we look at the bones themselves.



Slide 37: Myeloma Labs

In the blood, we're looking, we look at the CMP and the CBC, and so we want to know does the patient have anemia? We want to know what the renal function is, those types of things. Myeloma-specific labs we'll talk about a little bit later. The beta-2-microglobulin, albumin, and lactate LDH, those are nonspecific markers of metabolic activity. When they're high, that usually is not a good thing. Well, actually, when albumin's high, that is a good thing. It usually gets lower as, the longer somebody's sick.

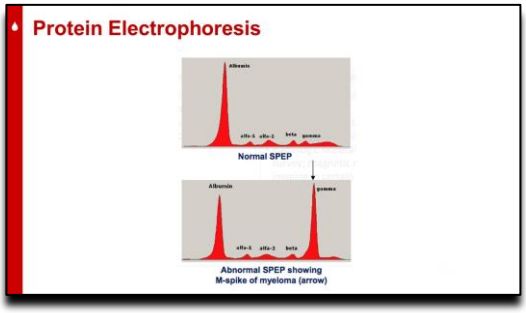


Slide 38: Myeloma Labs

But in general, cytogenetics in most hem malignancies will be more important; and we'll talk about that a little bit later.

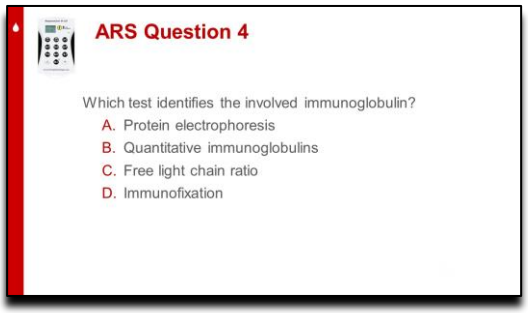
So myeloma-specific labs, we look at a few things. So your serum protein electrophoresis, that will tell you that your patient has a monoclonal protein spike. It doesn't tell you how much it is, and it doesn't tell you what kind it is. In order to know what kind it is, you do immunofixation. And then quantitative immunoglobulins will tell you how much, how much protein is there.

And then we also use this free light chain ratio. It used to be when I started working in myeloma that we didn't have the free light chain ratio, and so we only looked at the immunoglobulins which are really not as sensitive. And so we used to say that 80% of people are what we called nonsecretors. But today with the use of the free light chain ratio, less than 1% of people we can't find their protein, either in their blood or their urine. So, using the free light chain ratio has really helped the way that we treat our myeloma patients.



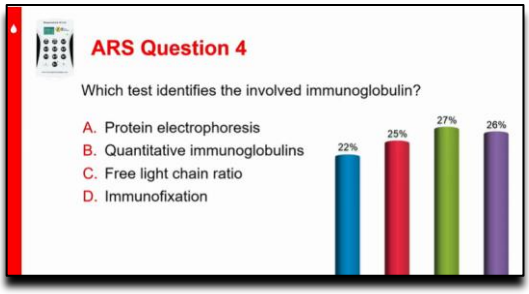
Slide 39: Protein Electrophoresis

So the top graph shows you, this is when you do a protein electrophoresis. This can be done in the blood or the urine. The top graph shows you what we should all have in a normal situation. We have an albumin spike and then a bunch of little bumps. If someone has a monoclonal protein spike, so you're going to, like you see in myeloma, you will see one extra spike. People call this the M protein because it looks like an M. It looked, it can be called a myeloma protein. It's your M spike, right? If that bottom graph had three or four spikes on it, that would not be myeloma because myeloma is a monoclonal protein spike. And if that patient had three or four spikes, we'd probably be sending them to nephrology because it's probably a kidney problem.



Slide 40: - ARS Question 4

So which test identifies the involved immunoglobulin: the protein electrophoresis, quantitative immunoglobulins, free light chain ratio, or immunofixation?

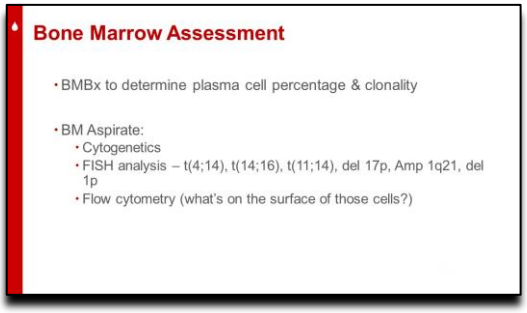


Slide 41: ARS Response

Dr. Patel: Oh, all right, well maybe I can take a crack at this. So, all right, well let's see who got it right. So we're asking which one identifies. So we're asking what tells us what protein it is. So the answer would be D, immunofixation. Good job.

And just to go back to that question, what I can tell you is, so the SPEP gives it, gives you a protein amount; and it tells you, hey, there's something that's monoclonal. The IgGs tell you how much IgG there is. It also kind of correlates with the SPEP and the amount of protein. But the IFE is what's going to tell you that this is IgG kappa or IgA lambda. Right, so that's the one that identifies the actual protein. If you put the kappa and the immunoglobulins and everything together, you can guess what it's going to be. But, you know, there are a few patients because all I do is myeloma. So I have a few patients that might have two or three SPEPs, and they could actually make little different ones. And so really the IFE is what tells me what's monoclonal or not.

Ms. Hewitt: Yeah, and it is a bit of a trick question because at my institution, and maybe at some of your institutions, I can no longer order a separate protein electrophoresis and immunofixation. The test is actually linked together, so, but somebody got it.



Slide 42: Bone Marrow Assessment

Okay, so when we look at the bone marrow, we want to know how many plasma cells are there and also the clonality, right? If it's not a clonal protein, then it's probably not myeloma. And really what we're looking in the aspirate is we're looking at cytogenetics, the FISH test for high-risk cytogenetics and FISH findings, and we're looking at flow cytometry. Flow cytometry is really when we put things through and we look at what's on the cell surface of that cell.

When patients come, both of us work at big academic centers. And when patients come to us, we often repeat the bone marrow biopsy and aspirate at my institution. And that is often because these tests are not done or maybe they weren't the best quality. I don't know if you have the same thing at your institution.

Dr. Patel: Yeah, you know, I try not to repeat things for my patients, unlike leukemia where they need this. We have those proteins to follow, right, so the less I have to do for my patients the better, that they don't have to go through another biopsy, but this is so important, again, for risk and to know exactly how I need to treat that patient in the future and how I need to follow them.

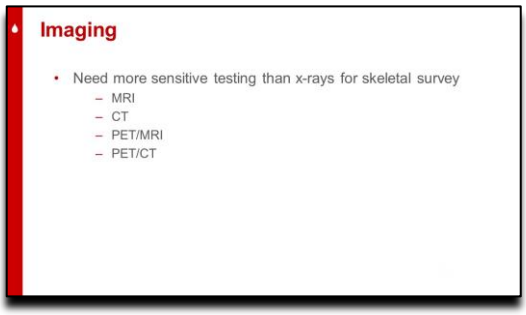
So, you know, as we see these proteins that we talked about, light chains will go up and down with infections. They'll go up and down with stress, dehydration, so you can't always follow those. And for my patients who are high risk, I want to know early so that if I see that trending up, I'm going to act on it much more quickly than someone who is standard risk where I know it's probably not related to the disease. Right, multiple myeloma, as we'll say again and again, is different for different patients and its different diseases.

And so the way you do the bone marrow is also important, so not just looking for these. Those FISH studies, the 4;14, 14;16, and 17p and now 1q are all high-risk features that tell me I need to watch these patients much more closely, even when I'm done with transplant or other therapies that we'll talk about. And then 11;14 is so important because we finally have a drug, and I'll talk a little bit more about that later, venetoclax, for patients who have that. And about 20% of patients have that, so we're going to try to make these things druggable in the future to know who should get what, we're not completely there yet, but that's why it's important.

But besides just testing for it, the quality of the test. So if someone doesn't have at least 10% myeloma cells from my pathologist, they can't do these tests. They can't run it. The quality control goes down, and so you really have to take that first pull or the second. You know, if you're going to do a second pull, you have to take more cells to make sure they have enough plasma cells to even run the test. And so that's what I'm reading on those path reports. How many cells do they have? And if they say it's negative, but they only had 3% cells, that goes out the window for me, right, so I have to repeat it.

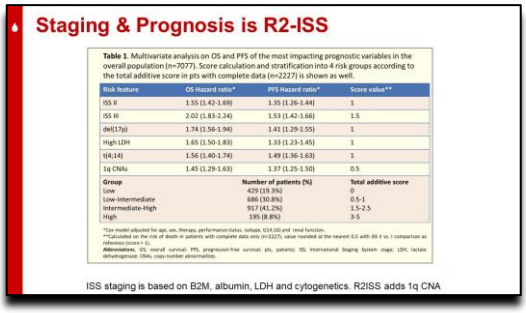
Ms. Hewitt: Yeah. And I think that's really important, especially as we start to use tests like MRD and stuff in myeloma because as someone who does the bone marrow biopsies and stuff, when you're sending something like for clonoSEQ ID, that is usually sent in a tube that has heparin in it. So when we pull, we usually pull EDTA tubes first. So if you have a patient who's doing an ID test, for example, you want a really high number of tumor cells, so you want to pull your MRD ID first before you pull your aspirate.

So often it means that that patient who's coming in gets two, what we call first pulls or first sticks. So they have to get two bone marrow aspirates on the same day. But it's, like Krina said, it's so important; and it's important in how we treat our patients, and it's also important in how we follow the disease.



Slide 43: Imaging

So, and then I think this is the last one for kind of like when we're working people up. We really need to be looking at tests that are more sensitive than x-rays. Historically, we use skeletal surveys for our myeloma patients; but these days we're using MRIs, CT, PET/MRI, PET/CT. And we've always known that those tests are at least 20 times more effective. We just didn't know, or more sensitive. We just didn't know what to do with that data. But now utilizing that SLiM CRAB, if patients have more than one lesion on a more sensitive way of looking at their bones, that is a patient population that we want to pull out early and treat early.



Slide 44: Staging & Prognosis is R2-ISS

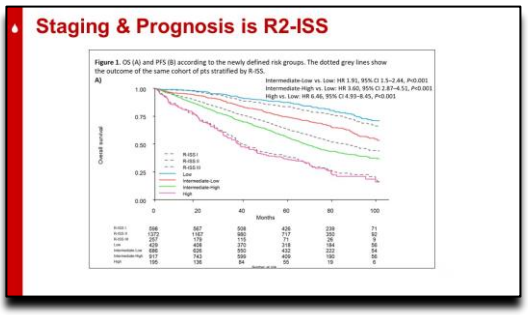
Dr. Patel: Yes, okay. So, in terms of staging, I kind of talked about my high-risk patients. I stage every patient that comes to me. You know, they want to ask what stage am I? Am I metastatic? And I have to say, well, this is not a solid tumor. This is a blood tumor, so it's different. We don't think about metastatic Stage IV or not.

But in myeloma we have this ISS staging, so the history is we had the Durie-Salmon staging that actually dealt more with how much bone disease you had and how much myeloma was causing clinical problems. And that was before my time. And then when I came in as a fellowship, it was the RISS. And the ISS staging basically looks at the labs we were talking about. The beta-2 microglobulin, the albumin, sort of these surrogate markers that kind of tell us if the myeloma's bad or not.

And then more recently, this is the most updated is the R2-ISS, and I'm not going to go through all those hazard ratios. But really what it tells us is that if you have Stage III disease or actually high risk versus, so it went from three stages to four. Low, low-intermediate, intermediate-high, and high. And it's just telling us more and more which of our patients really are going to do well with the therapies we have already versus which of the patients are probably not going to do as well.

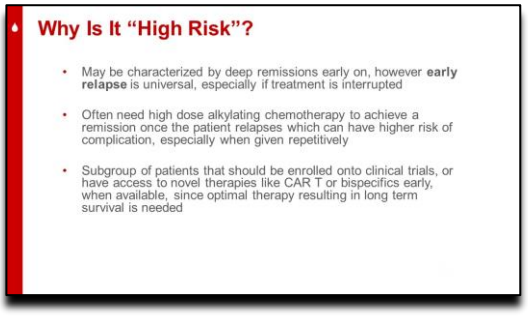
We don't have an algorithm to treat myeloma, and you'll see that as we talk about induction treatment versus relapsed-refractory, but my patients that have higher-risk disease, again, their disease comes back sooner, even on treatment. So I'm going to be more aggressive with those patients versus my patients who have standard-risk disease and are doing well. I have the option of taking therapy off slowly to help their quality of life.

And that's where this helps us. And again, the LDH was added recently. The 1q for this specific, that's another genetic abnormality we see on FISH that was also added to say patients are high risk now. So this just got changed probably six months ago.



Slide 45: Staging & Prognosis is R2-ISS

Perfect, and again, this is more curves showing that the patients in blue are the low risk, that had the least likelihood of probably going to respond to all of our therapies; and they're probably going to do well for, you know, initially induction. The ones who do well for five, six, seven years and then relapse versus the pink line at the bottom are my ultra-high-risk or high-risk patients that even two years after transplant I'm starting new treatments.



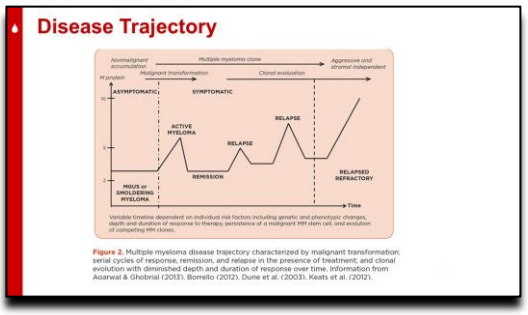
Slide 46: Why Is It "High Risk"?

And so why is it high risk? Again, characterized, so patients can trick you. They'll come in, and I give them treatments, and they go into these amazing responses. They go into what we call a complete response. I can't find any abnormal proteins in their blood or urine, and they can go into that even in the first two, three cycles. But what happens is they relapse early, and so we know that the myeloma cells, they sort of disappear to the level we can't see them; but then they come right back as soon as you take that pressure off.

And often I tell all my patients about stem cell transplant if they're eligible, but these are my patients I really push to go through transplant to really give them that longest time before next therapy. And sometimes, unfortunately, when they're relapsing early, these are my patients I ended up putting in the hospital for second-, third-line of therapy for DCEP or hyper-CVAD or things that we kind of use for leukemia patients.

Now, I'll say the story's sort of changing now that we have CAR Ts and bispecifics and that's evolving, so we have a lot of hope. But again, as of right now, these are my patients I'm trying to get through to get to those lines of therapy that are novel.

And again, that's the biggest thing. CAR T and bispecifics, a lot of our early trials that I'll talk about later were my high-risk patients because I really wanted them to get the novel therapies. We know that in myeloma, if patients with high-risk disease are going to do well with a therapy, our standard-risk patients actually do better. So when we talk about potentially curing our myeloma patients, it's first going to be our standard-risk patients, so we want to get these therapies to them as well. But in clinic, it's what does my patient right here need the most? And again, it's an evolving story. Lots of hope, but those are my patients I'm watching very, very closely.



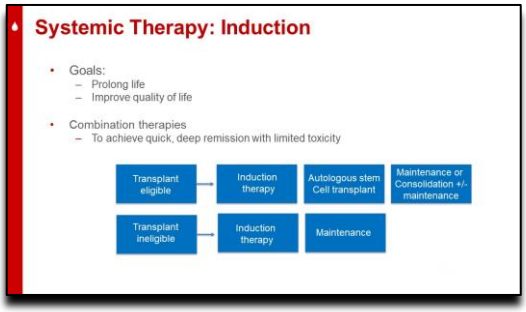
Slide 47: Disease Trajectory

Ms. Hewitt: So this is, any myeloma talk that you go to, you will probably see this. So this is the natural trajectory of the disease. As I said, people start with MGUS. Then they develop smoldering myeloma. And during that time, they're usually asymptomatic. We usually meet people when they have disease symptoms, symptoms of disease burden.

So this graph, or this picture is meant to show you, so people have active disease. We expect myeloma patients respond to

therapy. The best time to treat any cancer is usually the first time you treat it, right? So you usually get the most tumor kill with your first line of therapy, and that translates in myeloma to the longest remission, usually.

As our therapies get better, we may be starting to turn some of that around, but patients will eventually relapse; and when they relapse and we treat them again, they usually go into a remission again that's shorter. It's not as deep, not as much myeloma kill. And eventually the disease becomes relapsed and refractory, and that's what we're trying to ward off, right?



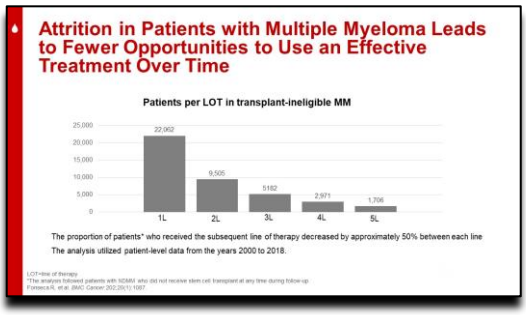
Slide 48: Systemic Therapy: Induction

So what are our goals of therapy? Our goals are to prolong patient's life. Our goals are really to find a cure, but right now our goals are to prolong our patient's life and to improve their quality of life.

And how we do that is with combination therapies. We know that combination therapy really helps us to achieve a quick, deep remission. And when we add drugs, we are usually not adding a lot of toxicity. There's multiple clinical trials that show that three drugs are way better than two in myeloma, and that should be the standard of care. And really in many academic centers for drugs, it's becoming the standard of care; and I think that that will become the standard of care, you know, more broadly, pretty quickly.

So the first thing we do with myeloma patients, as Krina said, is we figure out are they transplant eligible or transplant ineligible? For a transplant-eligible patient, what their therapy looks like is we want to get them in a deep remission and then take them to autologous transplant and then give them maintenance or consolidation therapy, plus or minus maintenance therapy. People stay on therapy for most therapies anyway. We tell them they're going to be staying on therapy for the rest of their life, and that's really an important time when nurses come in to help the patient to realize that this is a chronic blood condition. They're going to be sitting in your waiting room, and your patients, if you work in a practice where there's solid tumor patients as well or even if it's just all liquid tumors, there's going to be other patients that have a disease, they come, they get their therapy for a set time, and then they go on with the rest of their life. And that's not going to be your myeloma patient.

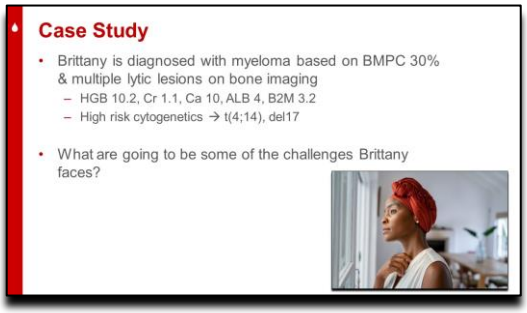
Your myeloma patient will be a patient for the rest of their life. And that's a hard thing to come to terms with, and it's really something that, you know, you as nurses will be the people that are the face that they see the most often, and you'll spend a lot of time talking with patients about that. Whether your patient's transplant eligible or transplant ineligible, because ineligible patients, you give them induction therapy and then they stay on maintenance therapy for the rest of their life or till unacceptable toxicity or disease progression when we switch them to something else.



Slide 49: Attrition in Patients with Multiple Myeloma Leads to Fewer Opportunities to Use an Effective Treatment Over Time

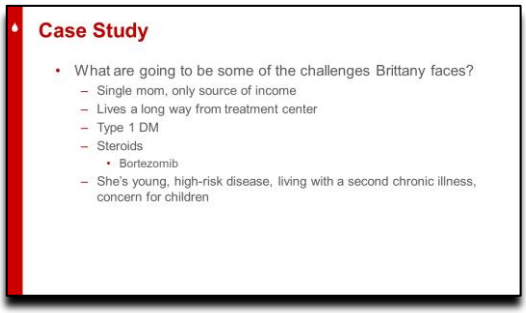
Part of the reason we want to use our good therapies and our combination therapies early in myeloma is there's a huge attrition rate when you go from first-line therapy to second-line therapy, third line; and some of this is because, you know, we work in oncology in a very unique area of medicine, right? People come to us and they're sick, and what do we do before we make them better, we make them sicker. So many of our patients, you know, they look great. And it's like, "Oh, I have this 76-year-old myeloma patient, looks really great. I'm going to treat them," and then we treat them and we're like, "Eh, they don't look so great anymore."

So many patients will opt not to go onto second-line therapy. Maybe they will actually die of an infectious complication or maybe, I've had many patients, and I'm guessing you have too, who were elderly and they get diagnosed with myeloma; and they're like, "You know, I actually lived a really good life. I'm 83 years of age. I don't want to do any therapy." But those patients do a line of therapy because their family is not reaokaydy for them to not do a line of therapy. So some people have decided from the get-go they're only going to do one line. But the bottom line is we should use our best lines of therapy early because that wards off all that end-organ dysfunction, gives us the best tumor kill, best disease control for patients.



Slide 50: Case Study

Dr. Patel: So coming back to our case, so Brittany is diagnosed with myeloma based on her bone marrow plasma cells are 30% and her bones show multiple lytic lesions. So her pains were from the bone lesions. Her hemoglobin's 10.2, creatinine 1.1, calcium normal at 10, albumin's 4, beta-2-microglobulin 3.2. She does have some high-risk cytogenetics. She actually has two. Translocation 4;14 and deletion 17p. So again, outside of the R2-ISS, when I see this, I call this ultra-high-risk. These are our patients that really we want to do everything we can from the beginning and then just keep going. So we had heard about all her other diabetes and everything else, so what are going to be some of the challenges that you foresee that a patient like Brittany would face going through their treatment?



Slide 51: Case Study

Ms. Hewitt: Yeah, absolutely. So she's a single mom, remember, so she's got the only source of income. She lives a long way, two hours. I mean that's a long way for most people to travel for therapy, so two hours from the infusion center. She also has Type 1 diabetes already, and what do most myeloma therapies include in their steroids, yes. So she has Type 1 diabetes, so steroids are going to be a problem. And then what's the number one side effect of bortezomib?

Ms. Hewitt: Peripheral neuropathy. What other disease that she has can cause peripheral-? So, she's at high risk for peripheral neuropathy, uncontrolled diabetes. She's also very young, and she has high-risk

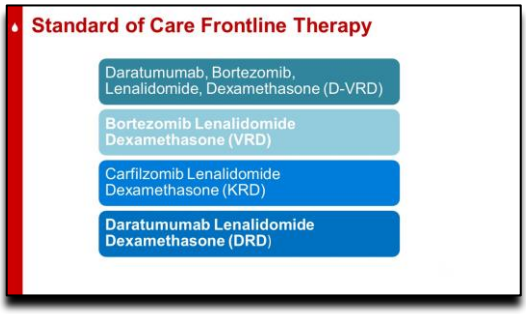
disease, so, and now she's living with a second chronic illness. And being 47 and having a diagnosis like that, she's, her kids, right, remember, like first-degree relative with myeloma. Her kids are 3.7 times more likely to develop myeloma as well. So she has concern for her kids, not only because she's a single mom, but…

Slide 52: Considerations for Myeloma Therapy

So when we think about myeloma therapy, we've talked about some of these things. We, our deepest remissions are usually with the first line of therapy. So, when we get more tumor kill, that translates into a longer remission. Many patients don't go on to the next line of therapy, so we want to use good therapies early.

We also have to look at like how frail is this patient because the chronologic age or like the number for some patients, it doesn't matter so much. We have to look at the frailty, and if somebody is frail, we might start them with a doublet. And then when we get better disease control and they perk up a little bit, we can add a third agent in there.

If somebody relapses, we want to look at what classes of drugs did they receive and let's give them different drug classes. We also want to, maybe for functional status and age, consider dose modification. And for patients who are transplant eligible, avoid those myelotoxic agents; and really this is key. Like the stem cells should be harvested in your first remission before your patient develops more mutations within that cell.



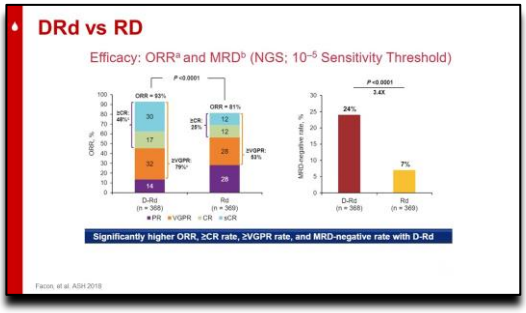
Slide 53: Standard of Care Frontline Therapy

So looking at standard frontline therapy, I think the most commonly used regimen in the US is the second one, bortezomib, lenalidomide, and dexamethasone. But more and more we're seeing the addition of daratumumab to give a very deep remission to those patients. And if you have a high-risk patient, you might see swapping out the bortezomib for carfilzomib. And then in your transplant-ineligible patients, probably in the last like maybe year and a half or so, daratumumab, lenalidomide, and dexamethasone was approved for transplant-ineligible patients as frontline therapy.

Slide 54: NCCN Guidelines for Newly Diagnosed Myeloma Therapy

Dr. Patel: Yes, again, when my students or trainees are coming in, you know, they look at the NCCN guidelines; and they say, "How do you choose from all these different options?" So we just talked about the four most common that we use, but because patients are different and they have different comorbidities or social issues that they can't come in and maybe I need to do an all oral therapy because that's all they're going to be able to get, you know, that all plays a role. And so initially, I joke with them and I say, "Take an arrow and just throw it and see what it lands on." But in reality, we actually like this. We like the fact that we have all these options because we can personalize

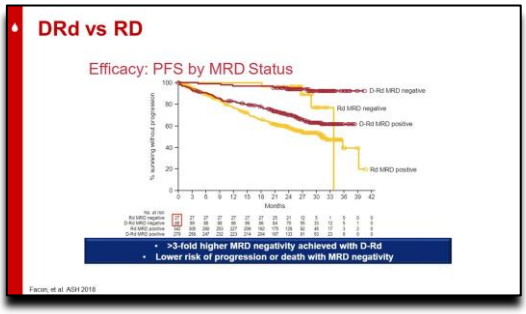
treatment because, again, myeloma's different. Multiple myeloma really is multiple, and so it helps us really say, what is the patient's goals and what are our goals, and how can we meet that together?



Slide 55: DRd vs RD

Ms. Hewitt: So this is a good example that three drugs are better than two drugs. So I think this one is from the MAIA clinical trial which looked at patients who were transplant ineligible; and this data's actually really interesting or really exciting I would say because these patients who basically started behind the starting line because these patients were not eligible to go to autologous transplant, either they had too many comorbidities, they were too old, whatever the reason was. But when we follow these patients and we follow their progression-free survival and their overall survival, were actually out at 60 months, so 5 years. Those timepoints haven't been met in the clinical trial, so those are rates of survival, progression-free survival, overall survival that we used to quote for patients who were transplant eligible. So it's really amazing to see this in a patient population who's starting behind the starting line.
The reason that you see that is adding that third drug gives you deeper remissions. More patients become MRD-negative or have like, you know, a greater than 90% reduction in your tumor. So better tumor kill without adding a lot of extra toxicity.

Dr. Patel: One thing I was going to add is lenalidomide here is at the lower dose, so 15. So again, these are frail patients that, you know, potentially; and this was an international study, so in Europe over 65, they don't usually take anyone to transplant. That's not in the US, but again because it's an international study, again, that lower dose of len, the lower dose of dex, 20 milligrams in patients that are above 75, that helps the toxicity piece and why patients can actually continue then versus when try to do high doses of everything we get that attrition because of toxicity. So, yeah, multiple reasons why I think this actually won out.

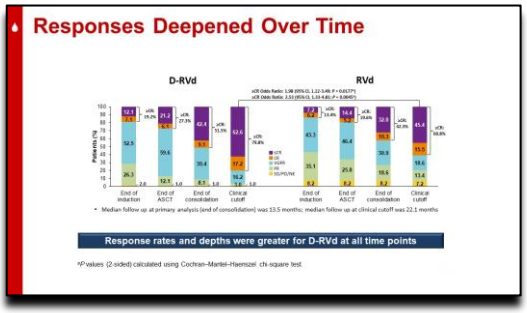


Slide 56: DRd vs RD

Ms. Hewitt: Yeah, and then this actually points at a couple of things. So more and more we're seeing the use of MRD negativity, and you know, we see this across many diseases. But if somebody becomes MRD-negative, they usually do better. Did you want to make another comment on this?

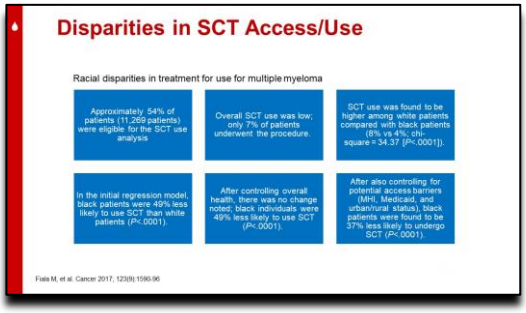
Dr. Patel: Yeah, no, I agree. The triplet, even when you're MRD-negative in the DRD, which is that red line at the top versus the RD, the patients who are MRD-negative, so they still both got to that MRD-negative, but the people that got the third drug actually stayed in remission longer because MRD is a great prognostic tool for us, but it's one timepoint.
So the question is are these going to get resistant faster and come up versus the patients who are getting that third drug? It's going to keep it down longer. Right, so again, even when you get to MRD-negative, having been on the triplet, you still get an advantage.

Ms. Hewitt: Absolutely.



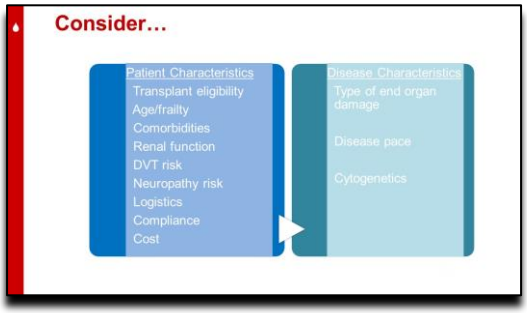
Slide 57: Responses Deepened Over Time

Ms. Hewitt: And then, continuous therapy too. So continuing therapy, we see that the myeloma burden continues to go down, and we used to give people treatment holidays all the time. And maybe we can do that with some of the CAR Ts, but in our other therapies, continuous therapy continues to give myeloma kill.



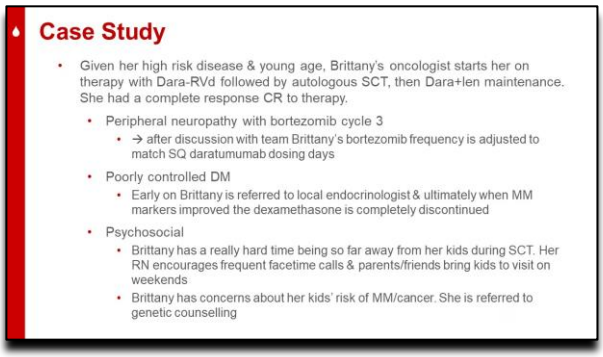
Slide 58: Disparities in SCT Access/Use

Dr. Patel: Perfect, so yes. Coming back to, you know, again, disparities. We talked a little bit about our Black patients can actually do just as well or better if they actually get access to our treatments. And this was one really good paper that was one of the original papers in 2017, so there's a lot more now; but looking at just SEER data type stuff where how many patients are actually getting to transplant? We don't know exactly the reasons why they don't or do, but 54% of patients out of 11,000 were eligible for transplant in this review, but the use is only 7% of patients. So not all those patients are transplant ineligible, right? And they found that during transplant was used higher among White patients compared with Black patients, 8% versus 4%. So it's low across the board, but even lower for our Black patients. And Black patients were 49% less likely to use transplant than White patients, and then after controlling for, you know, you might think, "Oh, it's comorbidities or other things." But after controlling for overall health, there's still no change noted. So even patients who are, you know, same comorbidities, same level of health that were probably eligible, just didn't get to the transplant. And same thing with access barrier. So looking at patients who had Medicare versus urban or rural status, still, there's a little change but still 37% less likely to still get to that transplant.



Slide 59: Consider

So again, considering in terms of induction therapy, just kind of summarizing, you know, what Rhonda said, but there's patient characteristics and then there's disease characteristics. And so again, you know, frailty is a big thing. Comorbidity, renal function, I can't harp enough, dose-reducing len for renal function patients. And as their renal function improves, then increasing it because that toxicity piece is so big. DVT risk, this is big for our myeloma patients; and so really making sure that they're on the appropriate anticoagulation. There's different ways you can do it, so we talk about the art of medicine all the time, that maybe different centers do it a little bit differently. But again, just knowing what your patient's risk is and being able to treat accordingly.



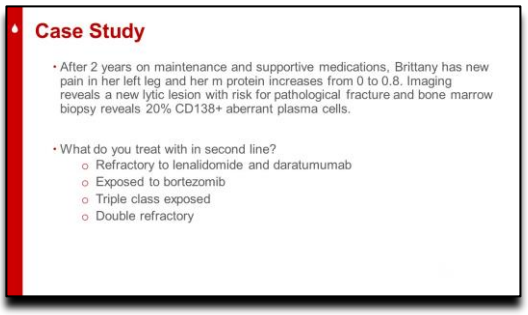
Slide 60: Case Study

Ms. Hewitt: So back to Brittany. So given her high-risk disease and young age, Brittany's oncologist started her on therapy with dara-rev-dex, followed by autologous stem cell transplant, and then dara-rev maintenance. She had a complete response to therapy.

She did have some complications. So not surprisingly, she had peripheral neuropathy with her bortezomib after cycle 3. And with discussion of her team, the frequency was actually adjusted to match her sub-Q daratumumab. And that's something that you probably often see. We will either decrease the frequency that we give the bortezomib, or we will, and/or decrease the dose of bortezomib that we give patients; but we'll try to keep them on therapy, provided we're not increasing the neuropathy. Her diabetes was poorly controlled, and this is one of the areas where we tend to bring in other health care providers. So in the case of Brittany, she was referred to a local endocrinologist who ultimately, as her diabetes markers came down, we actually were able to take her off of the dexamethasone, which is great.

But we, you know, we manage blood cancer. I don't really want to be managing somebody's diabetes. I'm not the best person to do it. I don't want to be managing somebody's like cardiac dysfunction, so we really do involve other teams in myeloma care, and we utilize our diabetes nurse educator a lot too.

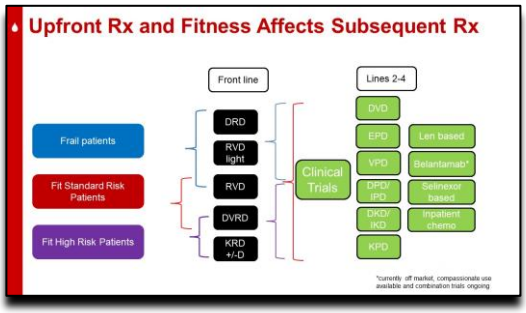
In the case of Brittany, you know, she had preexisting diabetes, so she was, before myeloma, she was well-controlled. But she, and then the other issue that she really had was psychosocial. So she was two hours from home; and this was actually during COVID. She had a hard time being away from her kids during that time, and she had had a primary nurse, and her primary nurse was really good with suggesting Facetime calls with her kids when she was able, when they were able to visit, the parents and friends brought the kids to visit on the weekend. And Brittany, as we talked about earlier, had concerns about her kids because of their risk of developing myeloma, so she was referred to genetic counseling.



Slide 61: Case Study

So after two years on therapy and supportive medication, she has new pain in her left leg; and her M protein increases from 0 to 0.8. Imaging showed a new lesion, lytic lesion with risk of pathologic fracture and bone marrow biopsy showed that she had 20% CD138+ aberrant plasma cells.

So when you're looking at second-line therapy, Krina, in this patient population – she's refractory to both lenalidomide-daratumumab, exposed to bortezomib, triple-class exposed, double refractory – what are some of the things that you're thinking of?

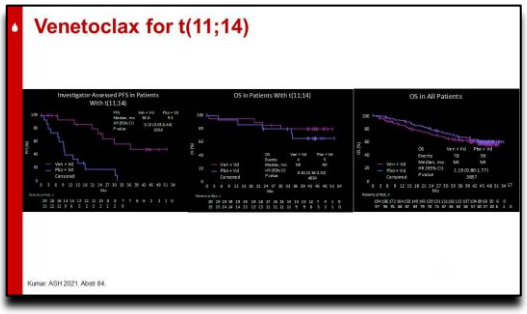


Slide 62: Upfront Rx and Fitness Affects Subsequent Rx

Dr. Patel: Yeah, here's my brain on a slide. So I made this for a conference a year ago, and it really, it took like an hour to really make sure what do I do in clinic? And this is not the same for every myeloma physician. And you'll see, you know, I really do characterize again, just like we did at induction, I'm categorizing my patients. Are they frail? Are they fit standard risk or are they fit high risk?

I also look at my frail patients and look if they're high risk or a standard risk, but sometimes with their frailty, I might not be able to be more aggressive anyway, right? So that's why I only have one category. But it depends on what they got frontline. So if I had a patient who was frail and got DRD, well all those other options in the next line, of course, clinical trials for us. You know, we do a lot of clinical trials, and we want to do better than what we have and maybe we can finally cure our patients because of the clinical trials we're doing. But it depends on what they had before.

So, if they were exposed to certain drugs, I could use them again. So I have some patients, even though we tell all our patients they need to be on therapy forever, I do have some patients who are on maintenance for four or five years; and they're still doing great. And they're having some side effects like diarrhea or chronic other issues, I might stop them because they're standard risk and they've done well for so long. We still follow them very closely. But if they've been off of those drugs, I can kind of use them again potentially. I'll use them with different combinations. As we said, we want to confuse that myeloma because these plasma cells, they were meant to live forever. And, this is why we can't cure it. So I trick it by changing, let's say if I, you know, had just done DRD, that maybe I'll go to a bortezomib-based regimen for my frail patients as long as they don't have horrible neuropathy. So bortezomib-pomalidomide-dexamethasone versus any of my high-risk patients where at the bottom in the purple I'm doing the quadruplet initially or KRD +/- there initially. Then I'm really trying to get them into a clinical trial like a CAR T or a bispecific in that early line versus sort of at the lower. You know, I'm doing more carfilzomib-based if they didn't get carfilzomib, or I'm doing dara-based if they didn't get dara. And really it's what combination can that patient tolerate and what risk is there disease? I need to give them the most aggressive therapy.



Slide 63 Venetoclax for t(11;14)

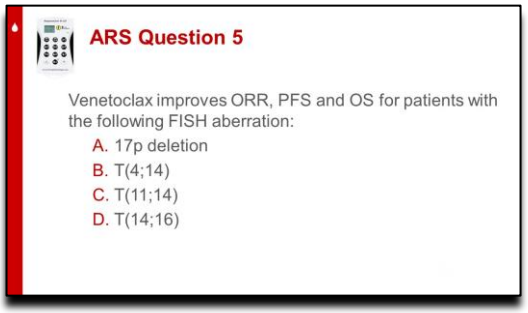
All right, and then this is, again, coming back to that 11;14 for myeloma, so this study, I think it was the BELLINI study, basically originally venetoclax was tried because it worked so well on leukemia and even lymphoma. We tried it on all our myeloma patients. And unfortunately, the original study, we actually had more deaths in the patients who got venetoclax versus placebo with bortezomib.

So this study was going into just the patients who had 11;14 because when people have 11;14, they have something called BCL-2 high, so they're making this extra BCL-2, and venetoclax actually kills that pathway. So when we figured that out, we said, "Of course, duh, we should only be treating patients that actually have that pathway activated." Right, that makes sense.

So, when you look at that, those patients, you see this huge difference in the patients who got venetoclax in the brighter purple versus the darker purple was placebo. When you see a difference that big in

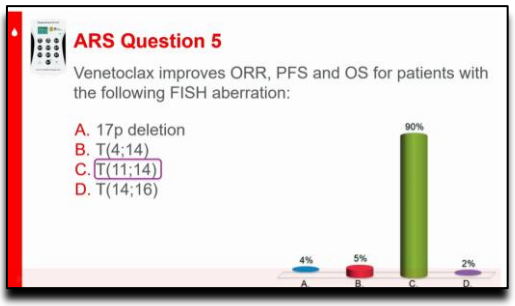
progression-free survival, that tells us that we're keeping that myeloma really well-controlled for the, you know, the patients who have 11;14.

And over time, we actually saw a survival benefit, which is really hard to see in these trials because our patients live for so long when they get other therapies. But to actually see a survival benefit for the patients who had 11;14 with venetoclax, you know, that's sort of why we're pushing so much. And even though it's not approved for myeloma, because it's approved for leukemia and lymphoma, we can use it off label in that sense. We are able to order it, so this is where I tell all patients with 11;14 to at least talk to a myeloma specialist at some point so they can help figure out when to give this until it's officially approved.



Slide 64: ARS Question 5

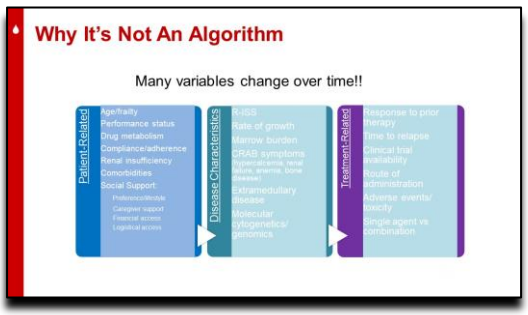
Ms. Hewitt: Venetoclax improves the overall response rate, progression-free survival and overall survival for patients with the following FISH aberration: 17p deletion, translocation 4;14, translocation 11;14, translocation 14;16?



Slide 65: ARS Response

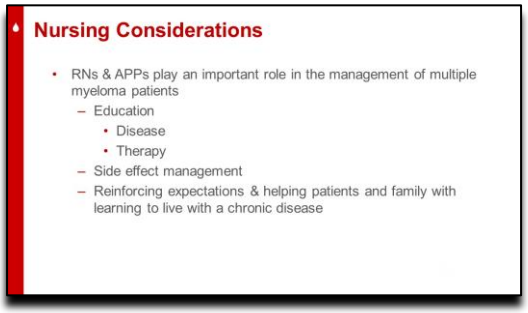
Dr. Patel: Yeah, good job because there's lots of 14

Ms. Hewitt: Yeah, great job.



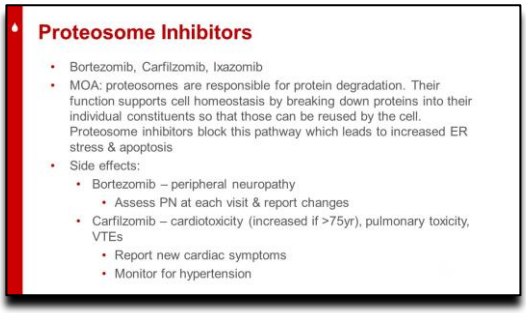
Slide 66 Why It's Not an Algorithm

Dr. Patel: Okay, so again, I'm not going to go into this, but again, it's not an algorithm; and it's patient-related disease characteristics and treatment-related, especially in the relapsed-refractory patients. And that changes with each one.



Slide 67 Nursing Considerations

Ms. Hewitt: Okay, so let's talk a little bit about nursing considerations. As I said, nurses, APPs, we play a really important role in the management of these myeloma patients. Education, both in disease, education, and therapy, side effect management, and reinforcing expectations, helping patients and family learning to live with a chronic illness.

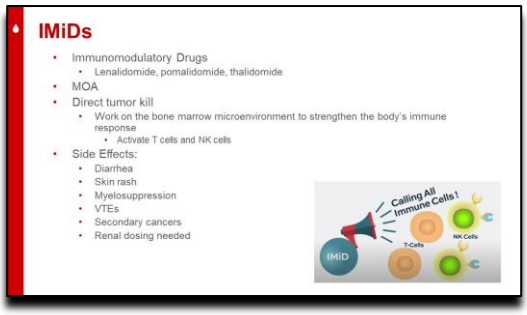


Slide 68: Proteosome Inhibitors

We're going to talk next about a few classes of drugs. So the proteasome inhibitors, these are bortezomib, carfilzomib, ixazomib. These drugs, the way that they work, so myeloma cells have a lot of proteasomes, basically; and proteasomes are responsible for breaking down proteins. They're responsible for protein degradation, and they help when you have a lot of proteasomes. It keeps the cell happy because proteins that have been used don't accumulate. The cell stays nice and clean.

How proteasome inhibitors work is they break or they block that mechanism, and so used proteins accumulate in the cell, and that leads to cell death, cell stress, and apoptosis. We have to watch for side effects for these, so bortezomib we talked about peripheral neuropathy for these; and peripheral neuropathy in your myeloma patient should be assessed and documented at each visit because all of us, even those of us who don't have myeloma, we're really bad historians. If you ask them how has this changed over time, carfilzomib we worry about cardiac toxicity. We especially worry about that in patients who are over 75 years of age. We also worry about pulmonary toxicity, and we worry about blood clots as well, especially at the higher doses.

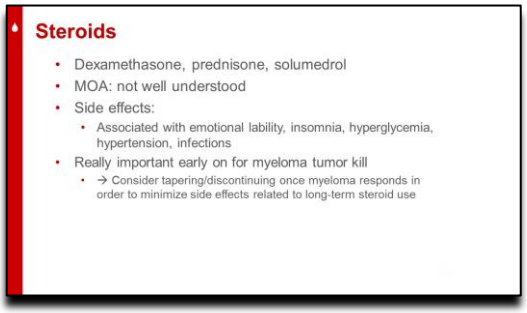
So we want to report any new cardiac symptoms. We also want to monitor for hypertension in this patient population because that can develop from the carfilzomib; and if a patient has hypertension, they are at higher risk for having a cardiac complication.



Slide 69: IMiDs

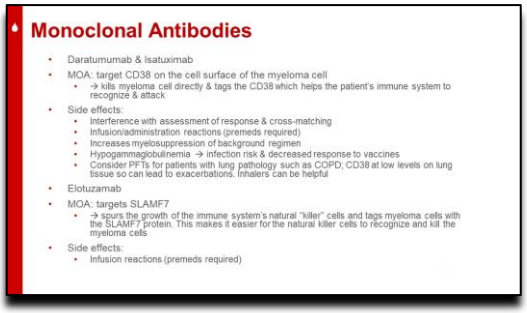
Your IMiDs or immunomodulatory agents are lenalidomide, pomalidomide, and thalidomide, which is not widely used in the US. How these drugs work is they cause direct tumor kill. So they work on the bone marrow microenvironment to really strengthen the body's immune function. That's why they're called IMiDs. They activate T-cells and NK-cells. They do have side effects, so diarrhea, skin rash. Interestingly, both of those side effects can happen anytime. So that patient that you mentioned who was on lenalidomide for four years, I've had people who have been on maintenance lenalidomide and suddenly out of the blue develop a skin rash or a diarrhea. And usually just holding until that toxicity resolves, you can usually rechallenge at the same dose or you may need to dose reduce.

Myelosuppression is common with IMiDs, and usually how we manage that is with dose reduction. Blood clots are also common with this, and so anybody who receives an IMiD is probably at least on low-dose aspirin. At my institution, we don't use full dose anticoagulation. Secondary cancers and, as Krina mentioned, renal dosing is really important in this patient population.



Slide 70: Steroids

Nobody knows how steroids work in myeloma. It's a big mystery, but they work well; and they're great upfront, but we should get people off of them because there's a lot of, once you have that myeloma under control, the toxicity associated with prolonged steroid use is worse than the benefit that you're getting.



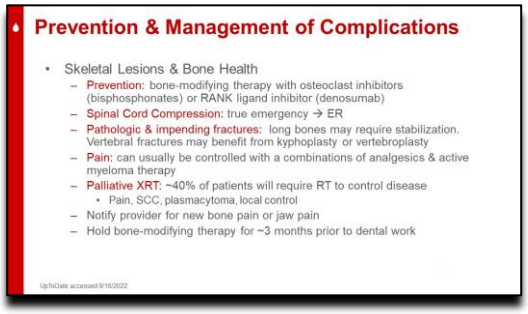
Slide 71: Monoclonal Antibodies

Your monoclonal antibodies, daratumumab and isatuximab both target CD38 on the cell surface of the myeloma cell. Monoclonal antibodies, what are you going to see? You're going to see some hypersensitivity, infusion reactions, or if you're giving daratumumab, which has the sub-Q injection, you can see some injection site irritation as well because that's got the tissue expander in it as well.

So these drugs, daratumumab and isatuximab are also what we call IgG-bound. And remember, IgG is your most common myeloma immunoglobulin that's involved. And so there can be interference with both response and cross-matching because CD38 lives on a cell surface of red blood cells as well.

Infusion administration reactions, myelosuppression, we tend to blame the background regimen. So, for example, if somebody's on dara-rev-dex, we blame the myelosuppression on the Revlimid usually. But when we give daratumumab to patients, especially if you're giving sub-Q daratumumab to a small person because it's a flat dose, you're, in effect, giving them more than you would- If you're giving 1,800 milligrams to a 50-kilo person and you're giving 1,800 milligrams to a 100-kilo patient, the person who's 50 kilos is getting twice as much drug per kilogram, right? So you get more myelosuppression in your smaller patients.

Because CD38 also lives on in some of the lung tissue, if you have a patient who has certain lung pathology such as COPD, you may consider PFTs or, before administering; and you certainly, in that patient population who gets bronchitis, asthma, you want to make sure that they have their inhalers at home and ready to go. Elotuzamab is another monoclonal antibody. It's target is different, SLAMF7. You can also see infusion-related reactions with this.

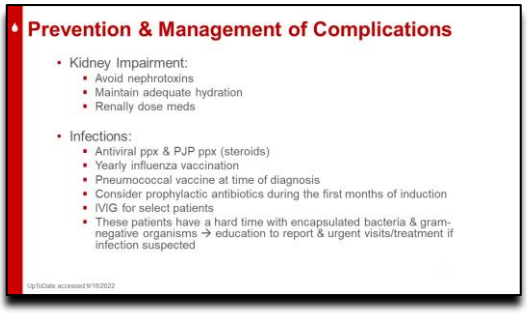


Slide 72: Prevention & Management of Complications

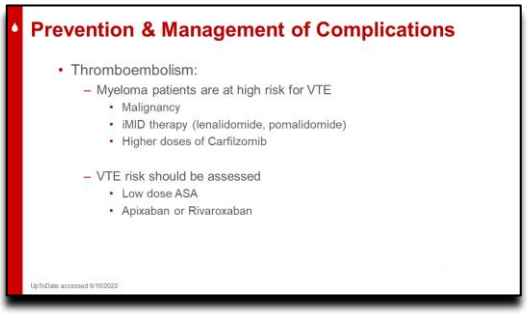
So prevention and management of complications, I mentioned that bone pain is the most common side effect seen with myeloma patients. So we want to prevent bone issues. So for bone heath, we use these bisphosphonates or RANK ligand inhibitor. The only one available is denosumab.

If you think somebody has a spinal cord compression, that is a true emergency. So back pain, new back pain in a myeloma patient needs to be evaluated. That patient needs an MRI.

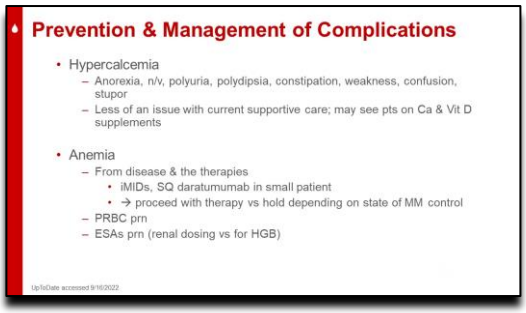
Pathologic and impending fractures are really important that those patients get imaging and that their limb or whatever is stabilized. Pain management is a big issue with myeloma patients, so we use combinations of anesthesias, and we also use palliative radiation for these patients.
So, and you probably know with, about risk of osteonecrosis with the jaw with the bisphosphonate therapy.



Slide 73: Prevention & Management of Complications
Kidney impairment is a big thing. We want to avoid nephrotoxins, renally dose our meds, infections, remember number one cause of death in myeloma patients. So antiviral prophylaxis is really important in myeloma therapy. PJP prophylaxis, keeping immunizations up to date. Maybe giving these patients, if they're getting frequent infections, giving them IVIg support.

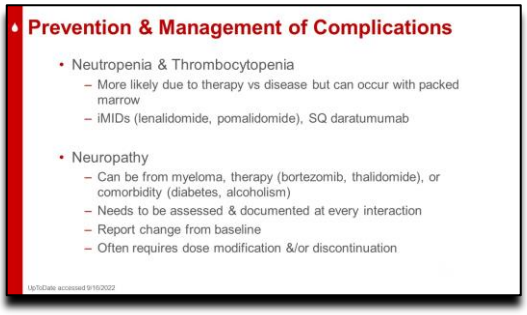


Slide 74: Prevention & Management of Complications
Blood clots, we talked about that. With IMiD therapy and carfilzomib, we consider low dose aspirin, plus or minus anticoagulation.



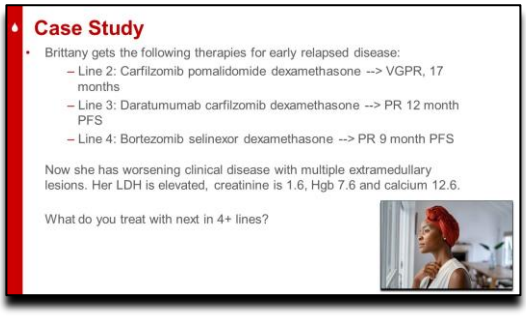
Slide 75: Prevention & Management of Complications
Hypercalcemia is really a problem that we see more at diagnosis than we see when people are on therapy now, and unless they have a florid relapse and that's because you're giving those agents for bone health. And those agents, bisphosphonates and denosumab are, they actually will drive the calcium low. And many of your myeloma patients actually will need calcium supplementation and vitamin D supplementation.

Anemia can be from the disease and from the therapy, and that's really important when you have somebody who comes in and you're trying to decide like, you know, should we give therapy to this patient? If that patient has myeloma with a packed marrow of 80% plasma cells in the marrow, the only way you're going to improve those cytopenias is by treating the myeloma. And so you may see that we're saying, "It's okay. Go ahead and treat this patient, but, you know, we'll give them a transfusion as well." But on the flip side, if you have somebody who's myeloma is under control and suddenly they come in and they're neutropenic or anemic, we might say, "Oh, we need to hold therapy because maybe they have a viral illness that dropped things or something else is going on."



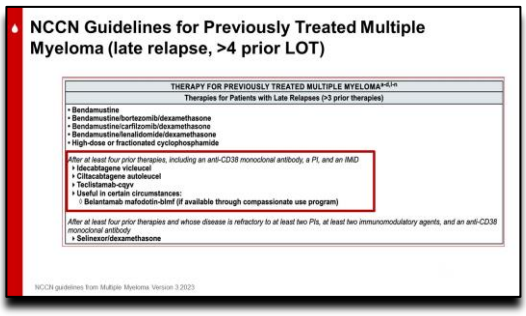
Slide 76: Prevention & Management of Complications

And I mentioned that with neutropenia, thrombocytopenia there. Neuropathy I mentioned can be from the disease or from the therapy, so you want to be monitoring for that.



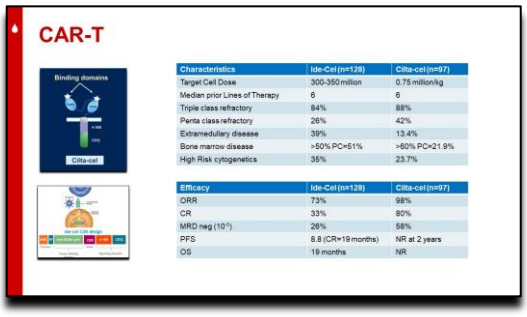
Slide 77: Case Study

When we go back to Brittany, so she gets the following therapies for early relapse. In line 2 she gets carfilzomib-pomalidomide—dexamethasone, gets a VGPR. Then she gets daratumumab-carfilzomib-dex PR. And Velcade-selinexor-dexamethasone, another PR. And she has worsening clinical disease with extra, multiple extramedullary lesions. Her LDH is up, her creatinine's up. She's anemic, and her calcium is 12.6. So what are you thinking of after these patients have had four lines of therapy?



Slide 78: NCCN Guidelines for Previously Treated Multiple Myeloma (late relapse, >4 prior LOT)

Dr. Patel: Yeah, so I wishing that we had a clinical trial to get her onto a CAR T or a bispecific earlier because, again, as you see as these patients keep going, they get less and less time; and their disease becomes much more aggressive. And again, high risk in a shorter amount of time. So now at least she's fourth line where I could try to get her some of these other therapies. So, we have CAR Ts, we have idecabtagene, ciltacabtagene. We have our newest bispecific that got approved, teclistamab. And then as of right now, belantamab you can only get through compassionate use. We were using it for our frail patients who really couldn't go through CAR T or bispecific, so I think eventually it'll come back. But right now, it's off because of the Phase III. It didn't beat pom-dex, so again, hopefully in the near future we'll see it come back for our patient who can't get some of these other novel therapies.

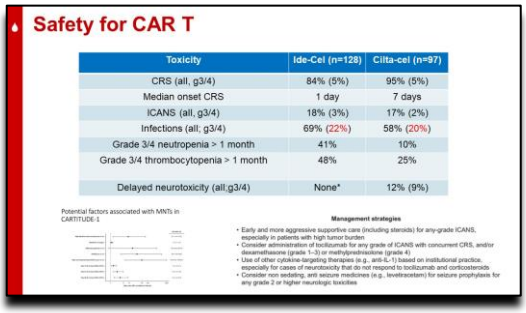


Slide 79: CAR-T

I'm not going to belabor all of this because I want to make sure we have time to get to the last ARS questions, but this is my favorite topic of all time. CAR T-cell therapy and myeloma. That's my COI. And again, there's two CAR Ts that have been approved for myeloma, cilta-cel and ide-cel. You know, again, target dosing is different. The actual CAR Ts themselves are different, so the expansion once the patients get it is different; and I'm happy to answer questions outside of here, and I've done lots of different videos that people can refer to on how these work. But really, the response rates, 73% for ide-cell, 98 for cilta-cell. These were patients that had six lines of therapy already on trial. Brittany has had four lines, right? So these are patients that have

everything. To get that kind of response rate, I mean we've never seen anything like that, even in early induction treatments. We don't necessarily see it that high, right, so again, just phenomenal responses and depth of response.

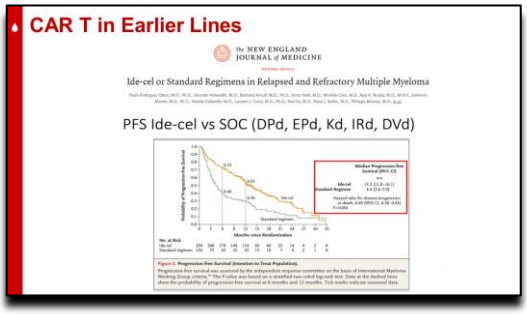
So patients who are getting CR, 33% for ide-cel, 80% for cilta-cel. These were different patient populations, but still to have, you know, that level of deep response.



Slide 80: Safety for CAR T

And the biggest thing, again, you know, we talk about cytokine release syndrome and we talk about neurotoxicity, not just ICANS where patients can have, we ask them these questions, you know, to make sure that their cognition and their writing is okay.

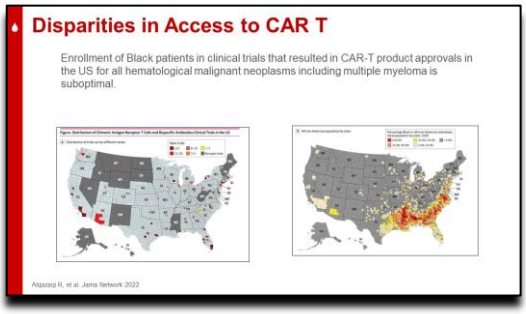
But really, neurotoxicity like peripheral neuropathies or all of a sudden they can get things like Guillain-Barré-type symptoms. That happens after the initial hospital, so we take care of the CRS and the ICANS usually in the hospital; but once they go out, it's the infections and the, some other, you know, peripheral neuropathies or other things that you guys have to look out for. And again, highlighted is infection.
So in CAR T, Grade 3/4 infections has been about 20%. In Grade 3/4, these patients are being hospitalized or needing IV antibiotics, and a lot of our patients have died on these trials from infections.



Slide 81: CAR T in Earlier Lines

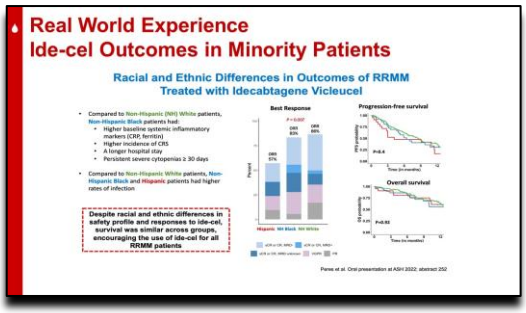
I'm going to come back to the infection piece in a second, but what's really awesome is that we have now one trial that's been and reported out in earlier lines of therapies, so this is ide-cel in earlier lines against standard of care options; and again, the PFS is 13.3 months versus 4.4.

You know, people look at that and say, "Wait, is that really a lot?" But these again were really our high-risk patients that we were trying to get to something novel. So for them, to be on a one-and-done therapy versus the other regimens that we usually have continuously to see that big difference at least tells us that, yes, this is better for this group of patients.



Slide 82: Disparities in Access to CAR T

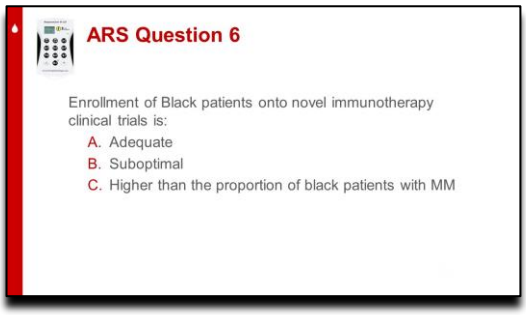
And, of course, there's other studies coming down the road; and we'll have the cilta-cel data at ASCO, so we can bring that up next year. And then coming back, you know, to access to CAR T, everything's been on clinical trial so far; and really where you look at where trials are done is not necessarily where our patients, our Black patients especially are. And so, you know, this is a callout to our pharma colleagues too, to have more trials in areas where there are a lot of our minority patients so they can actually get access to these therapies early, just like everybody else can.



Slide 83: Real World Experience Ide-cel Outcomes in Minority Patients

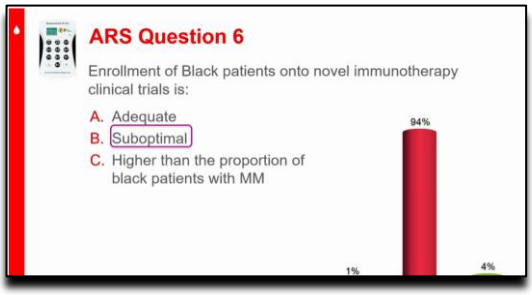
And again, looking at our minority outcomes for CAR T for patients who got standard of care as like real-world evidence, we have about 15 centers that are all looking at data together. We actually saw that, you know, non-Hispanic Black patients actually get a great response rate, 83%. Our non-Hispanic White was 86%. Our Hispanic patients was a little bit lower at 57%, still an amazing response compared to anything else we have. But we notice that these patients actually came into us when they had more extramedullary disease. Their disease was more aggressive, so now we're looking into are there biological differences? You know, what are the differences that can happen?

Same thing with toxicity. So not just efficacy, is toxicity different? So for our Black patients, we actually noticed that their baseline inflammatory markers were higher coming into like CRP things that we look for during CRS. At baseline, they already had high levels; and so it ended up that patients did fine, but they had a little bit more CRS, and they stayed in the hospital a little bit longer. So again, should we be getting these types of therapies early to those patients because then toxicity might be better?



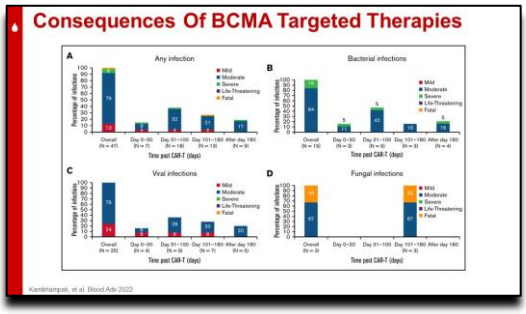
Slide 84: ARS Question 6

It's a lot to study, studies that were coming.
So Enrollment of Black patients onto novel immunotherapy clinical trials is: adequate, suboptimal, higher than the proportion of Black patients with myeloma? Hopefully I've made my point clear.



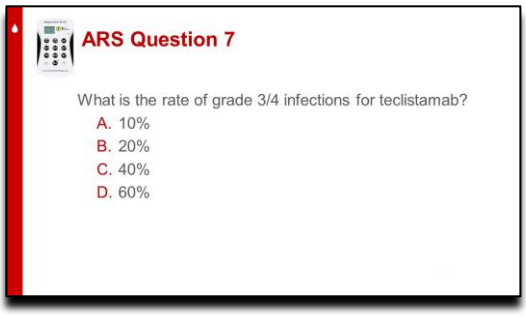
Slide 85: ARS Response

Fantastic, suboptimal. We need to do better, yes. And people are working on making it better.



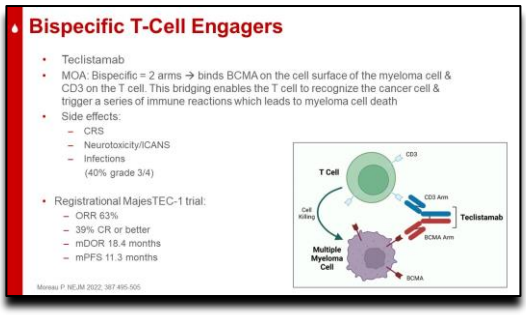
Slide 86: Consequences Of BCMA Targeted Therapies

And coming back, I won't belabor this too much; but this is post-CAR T looking at different kinds of infections. And again, you know, we see viral infections, so CMV, things that we weren't seeing before in myeloma patients. So someone has a prolonged pneumonia looking for those types of infections is really important. We don't see as much fungal infections, but again, it depends on where you are. So in Houston, we're humid, so we do check for fungal infections for some of our patients still.



Slide 87: ARS Question 7

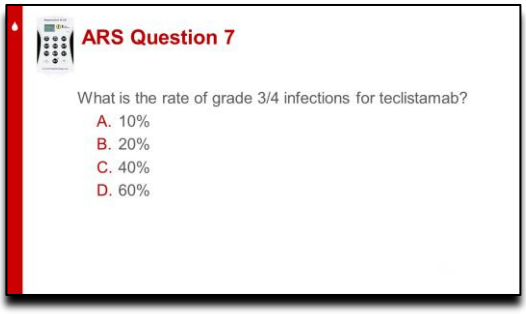
I'm going to give you the answer to this one. So teclistamab, amazing bispecific that we have for myeloma now.



Slide 88: Bispecific T-Cell Engagers

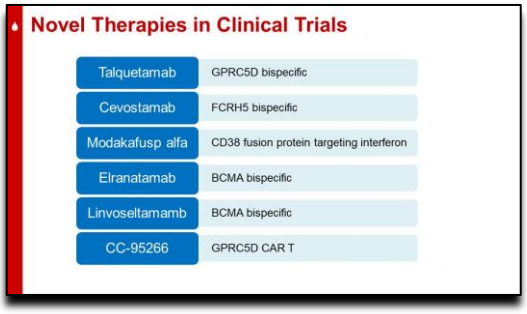
It's given once a week sub-Q, and it's supposed to be forever. So once you start, you keep going until you end up relapsing. So, difference between a bispecific T-cell engager and a CAR T, a one and done versus something that you can take off the shelf so patients who can't sit there and wait for cells to be made, because their myeloma is just taking off, we can actually do something off the shelf.

The response rate is 64%. Nothing's been ever done head to head. Still impressive but again a little bit lower than what we've seen in our trials for CAR T. But the median duration of response for those people who do respond, 18.4 months. So again, most of these patients would have been hospice. You know, survival is around 6 months, maybe a year, so still improving there. And the infection rates, the Grade 3/4, 40%. Again, you are constantly taking their T-cells out as you're using them to kill the myeloma. So now not only do you have hypogammaglobulinemia, not only do you get neutropenia, but now your T-cells don't work. So you're just taking everything out, so again, viral infections, fungal infections are the main thing.



Slide 89: ARS Question 7

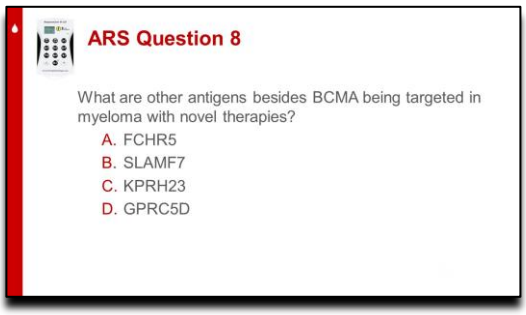
Okay, so the Grade 3/4 infections, 40%.



Slide 90: Novel Therapies in Clinical Trials

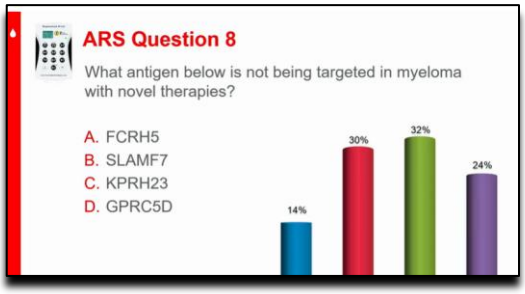
Okay, all right, and then again, novel therapies that are in clinical trials, the other big thing we found in myeloma is that not only do we have BCMA as a target, because it took us forever, lymphoma, leukemia at CD19. We tried CD19. It didn't work for the majority of patients. And so we found BCMA which was great, but now we're beating lymphoma and leukemia because we found more targets. So GPRC5D, FCRH5. We have SLAMF7 or CS1, and there's all these new therapies that are coming down the road, combinations. So again, when we talk about, we have the plateau envy because our patients aren't cured. We get these

great response rates, but people relapse. With these combinations, we're hoping we can finally kill those long-living plasma cells.



Slide 91: ARS Question 8

The last ARS question. I made one of them up. So what antigen below is not being targeted in myeloma with novel therapies?

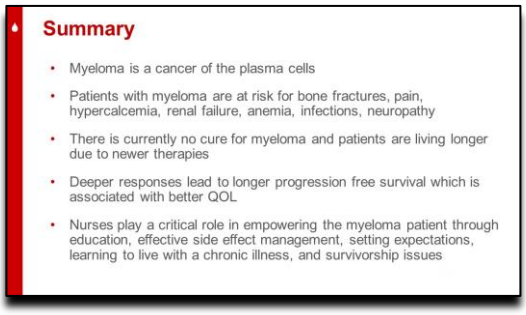


Slide 92: ARS Response

Yeah, I know, it was like alphabet soup, right? So C is our initials and the year 23. 32% of you figured it out, so good. Perfect.

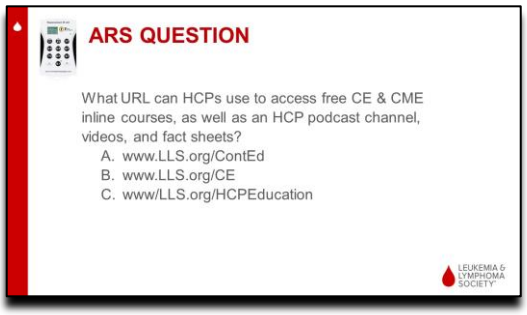
Slide 93: Patient & Family Resources

These are resources available. I think that at the beginning you had a list of some others, and we've included these ones.



Slide 94: Summary

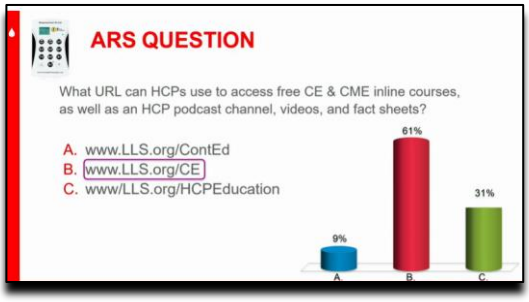
And this takes us to our last slide. So myeloma is cancer of the plasma cells. These patients are at risk for bone fractures, pain, hypercalcemia, renal failure, anemia, infections, and neuropathy. There's no cure for myeloma, but our patients are living longer and really you guys play a critical role in helping that patient along their myeloma journey with education, helping them to learn to live with a chronic illness and survivorship issues.



Slide 95: ARS Question

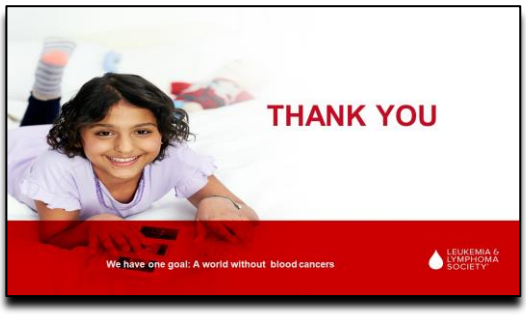
Ms. Berger: Okay, we'll take a few more seconds just to present one more question.

Okay, What URL can health care providers use to access free CE and CME online courses, as well as an HCP podcast channel for you and some videos and fact sheets? A, B, or C?



Slide 96: ARS Response

Okay, so the correct answer is B, and most of you got that.



Slide 97: Thank You

Special thanks to Dr. Patel and advanced practice provider Ms. Hewitt for sharing their time and expertise. And thank you to all of you. Have a great day.