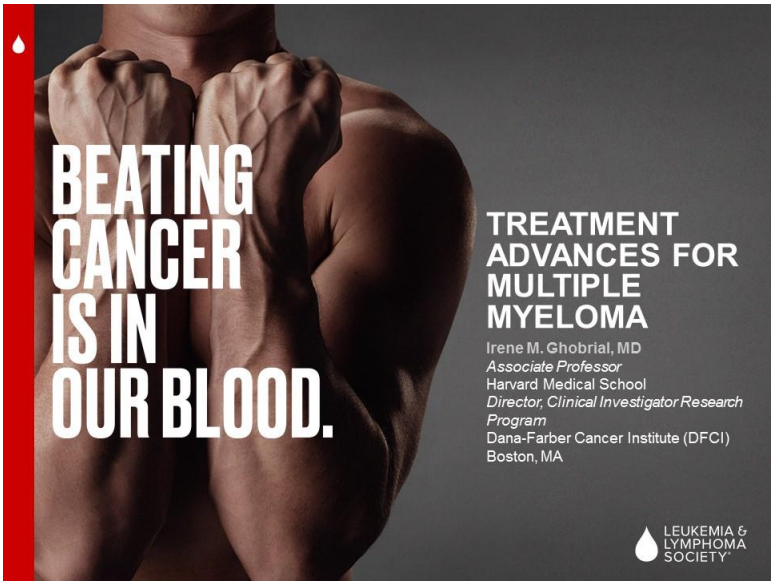
TRANSCRIPT

WELCOME AND INTRODUCTION



Lizette Figueroa-Rivera, MA

Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Irene M. Ghobrial for sharing her time and expertise with us today. We have over 950 people participating in today's program from across the United States and several countries around the world, including Canada and Nigeria. Before we begin, I'd like to introduce Dr. Louis DeGennaro, The Leukemia & Lymphoma Society's President and Chief Executive Officer who will share a few words.

Dr. Louis DeGennaro, PhD

I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society, our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research to advance lifesaving treatments and cures. We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education and support for patients, survivors, caregivers, families and healthcare professionals. We also support blood cancer patients in their local communities through our chapters across the country, and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable and coordinated care. We're committed to working tirelessly toward our mission every single day.

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Today you'll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time, and we appreciate their dedication to supporting our mission, their commitment to caring for patients living with blood cancers. Thank you for joining us.

Lizette Figueroa-Rivera, MA

We would like to acknowledge and thank Amgen, Celgene and Takeda Oncology for support of this program.

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PRESENTATION

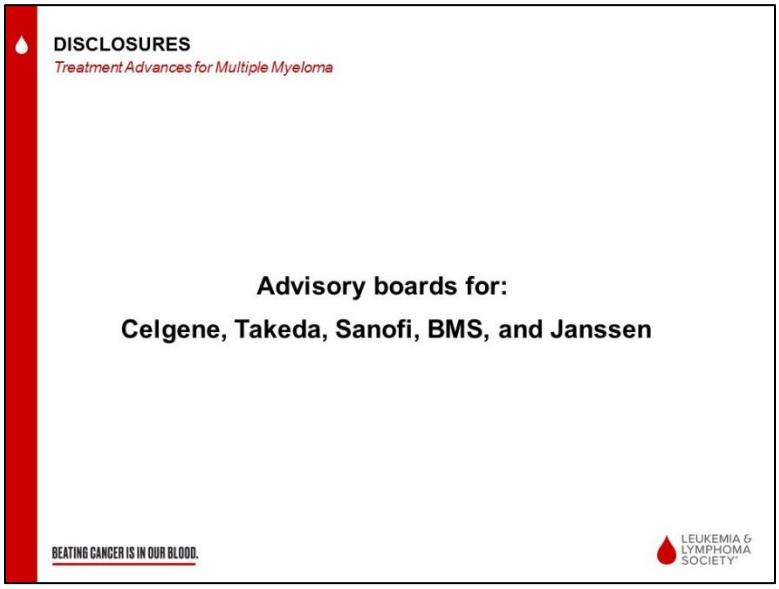
Lizette Figueroa-Rivera, MA

I'm now pleased to introduce Dr. Irene M. Ghobrial, Associate Professor at Harvard Medical School and Director, Clinical Investigator Research Program at Dana-Farber Cancer Institute in Boston, Massachusetts. On behalf of The Leukemia & Lymphoma Society, thank you so much, doctor, for volunteering your time and expertise with us today.

I'm now privileged to turn the program over to you.

Irene M. Ghobrial, MD

Thank you so much; and, again, I want to thank The Leukemia & Lymphoma Society for putting this program together and happy holidays everyone. I'm really excited to be here, especially that it's just before the holidays, so thank you for all of you joining.



And these are my conflicts of interest.

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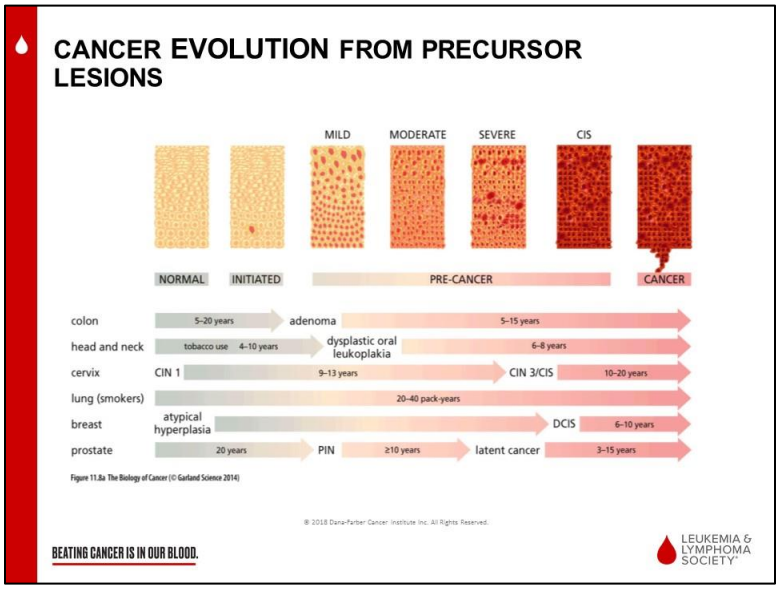

And what I want to do today is take you through some of the work that we're doing on multiple myeloma. And then I know that many of you will have questions, so I'll try my best to finish early so that we have enough time for everyone to have questions and really spend the time discussing your concerns.

Now multiple myeloma, as many of you know, is a very big topic, so I'll try to focus specifically on one area, which is early disease prevention; and this is in the area of monoclonal gammopathy of undetermined significance or MGUS and then smoldering multiple myeloma. It doesn't mean that what I say does not apply to all of you who have actual multiple myeloma or who are on treatment. I'll actually tell you how all of the work we're doing right now applies to many of you. And, also, having your input and having your participation in many of the studies and many of the ideas that we have here.

So, just to take you through the concept of cancer progression, many of you know that as we get older, some of our cells start changing; and they acquire some somatic mutations, which means just changes in the chromosomes or changes in the DNA (deoxyribonucleic acid), and that makes them become cancer-like cells. And this happens in many of us even years before we develop cancer. So, believe it or not, if you have multiple myeloma, you may have had MGUS and smoldering myeloma or even pre-MGUS stage for years and years before you developed multiple myeloma.

And this slide shows you that this is not unique for myeloma. We see that in colon cancer, lung cancer and many other cancers. So, there are years of precancerous lesions before we actually diagnose you with the disease.

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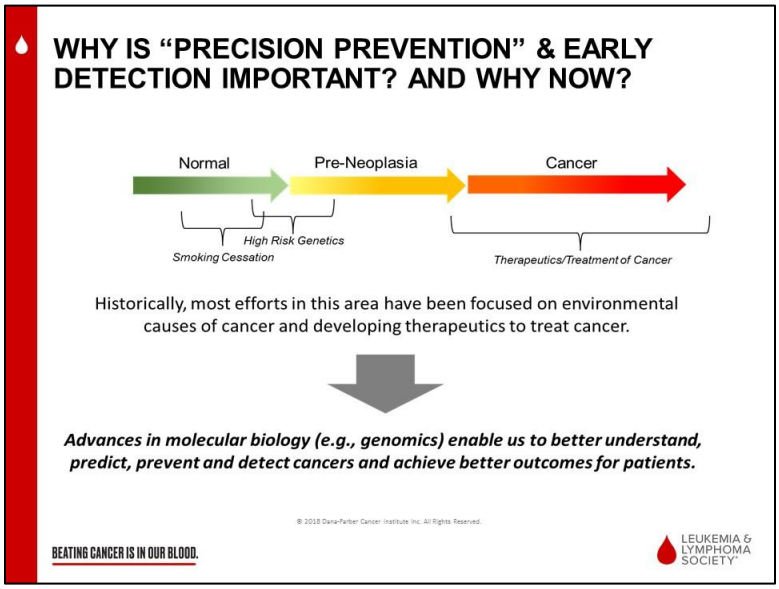

And why is that important? It's important because if we can actually figure out how you have those precancerous lesions, then, guess what, we can potentially eradicate them early; and you don't even develop myeloma. So, think about the concept of instead of waiting until you have cancer and then I treat you, how about we define early on who will have a precancerous lesion and then we prevent it from even going on to develop cancer. So just like vaccines that we have now for infectious diseases, think of prevention as one of the best ways we can cure cancer.

So, this slide shows you that all the work we do in cancer centers and in pharmaceutical companies and all the work we have is treatment of active cancer, treatment of metastatic disease, treatment of myeloma that has already caused for you end-organ damage which means anemia or renal failure or lesions in your bones. Yet, there is so much to be done in early precancerous lesions to potentially prevent it, and this is what we're focusing right now on at Dana-Farber.

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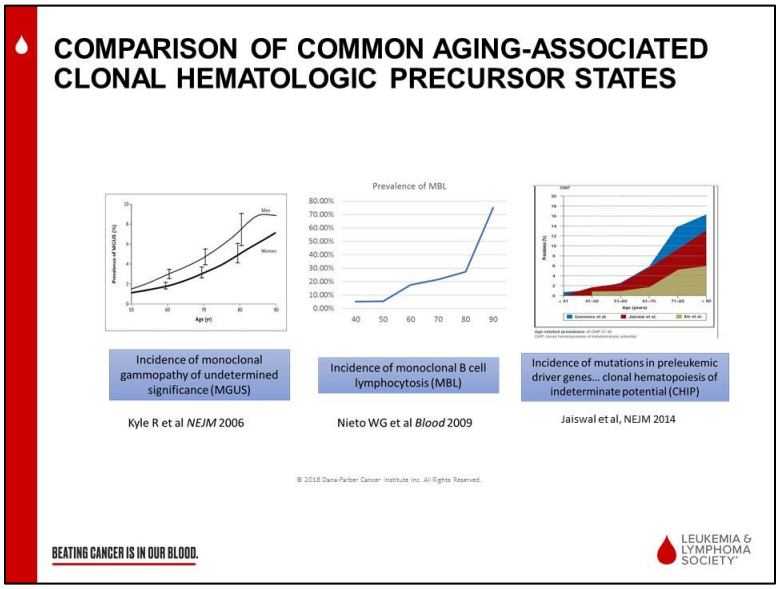
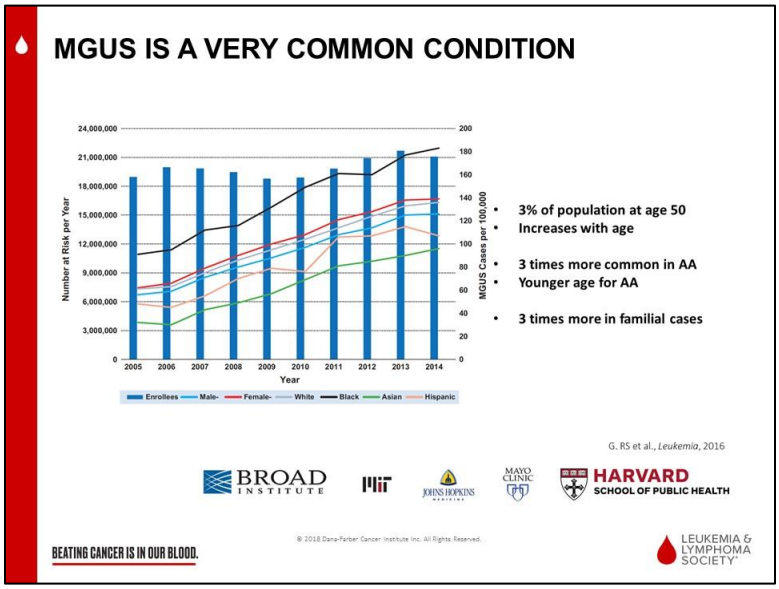


So, I'll give you three examples so that you know that myeloma is not unique in this precancerous lesion. These are three examples of blood cancers that we can actually diagnose with an active test of the precancerous lesions. So, of course, MGUS, as you know very well. There's another one that's pre-CLL or chronic lymphocytic leukemia. It's called MBL (monoclonal B-cell lymphocytosis). And there is another one that's called CHIP, clonal hematopoiesis of indeterminant potential, that happens before we develop leukemia or MDS (myelodysplastic syndrome). So, again, all of the blood cancers have a precancerous lesion, and we can diagnose it by a blood test; and that's so cool and so important for us to know can I potentially be screened for it, and can I identify it early so that by doing that I can prevent this from happening.



So, how often do we see MGUS is important. I just told you that every single one of you who has myeloma likely had MGUS in their lifetime. But we don't go looking for it, so how often do we see this?

And this slide shows you that it's actually a very common disease. In fact, if we just look at the population—if I stick everyone walking down the street today, although it's very cold here in Boston, so we don't have too many people walking out—but if we do, we would find 3% of the population, they have MGUS if they are over the age of 50. So that's a huge number of people walking around with MGUS, and they don't even know about it. And if you're African American or of African origin or if you have a family member who has myeloma or Waldenström or MGUS, you have a three times higher chance of having MGUS when you're walking around. In fact, the African American population, are diagnosed much earlier with MGUS; so, they can develop it at age 40 instead of age 50 with that 3% chance. And then it goes up to 9% chance when you're at age 50. So that's a lot of us walking around completely asymptomatic. We don't know that we have it, and yet we wait until we have fractures or kidney failure and then we go see our doctor.

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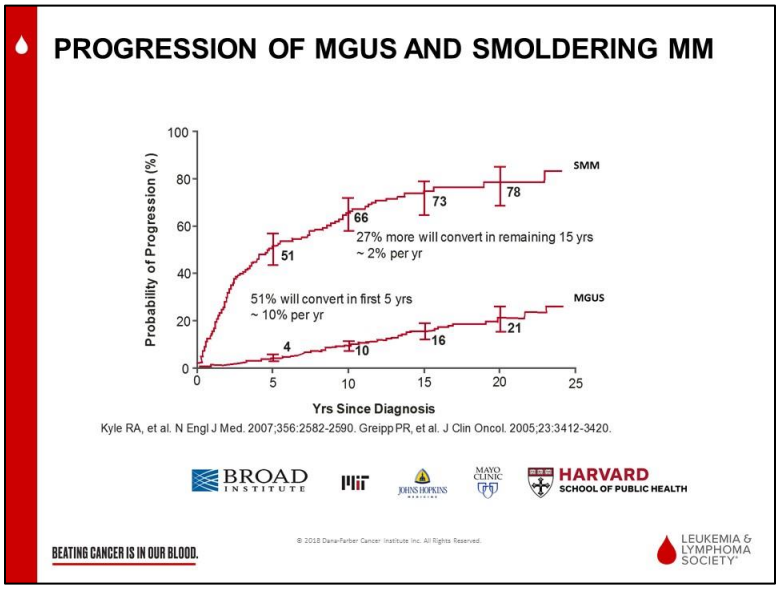

So how often would that go on to develop myeloma? Well, the good news that we have is if you have MGUS and you're on this line, or if you have smoldering myeloma and you're on this line, the chances of progression are not that high. In MGUS, it's about 1% per year. So, every year you have a 99% chance of not developing myeloma but a 1% chance of developing myeloma in this year. And then it goes on and on.

For smoldering myeloma, which is defined by 10% plasma cells, your chances are much higher. It's a 10% chance of progressing to myeloma every year for the first five years; and then it decreases after that. And in some patients, what we call high-risk smoldering myeloma, you have a very high chance of developing end-organ damage, which, again, is the fractures and the anemia within two years. Fifty percent chance of developing those problems within two years of follow-up. And that's very critical because that's a very small window of opportunity for us to do something quickly before you have fractures and before you have anemia and before you have any problems.

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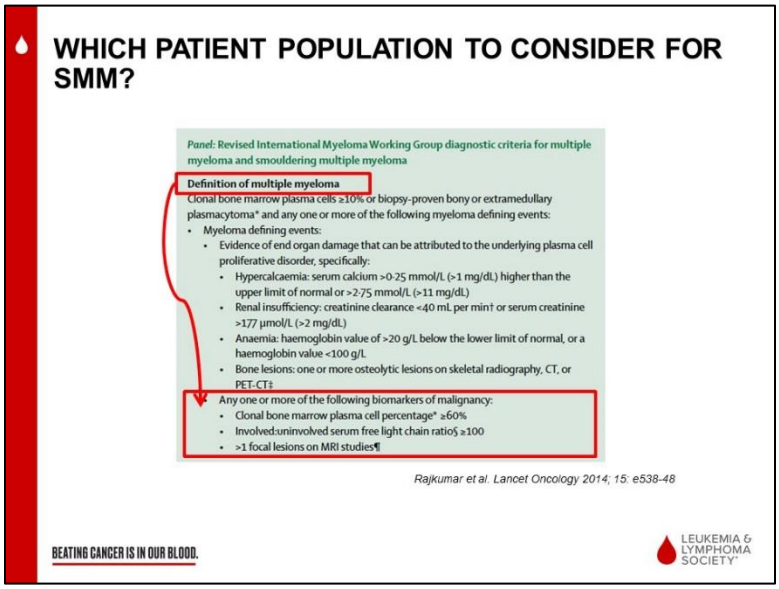


So just for you to know when do we treat you, when we actively say, “Let’s treat you.” Believe it or not, if you have smoldering myeloma and you have 30% plasma cells, but you do not have lesions in your bones or you don’t have anemia, we actually don’t treat you, which that’s the standard of care. We tell you, “Oh, no, wait until you have anemia, bone lytic lesions, hypercalcemia, or renal failure—something called CRAB criteria.

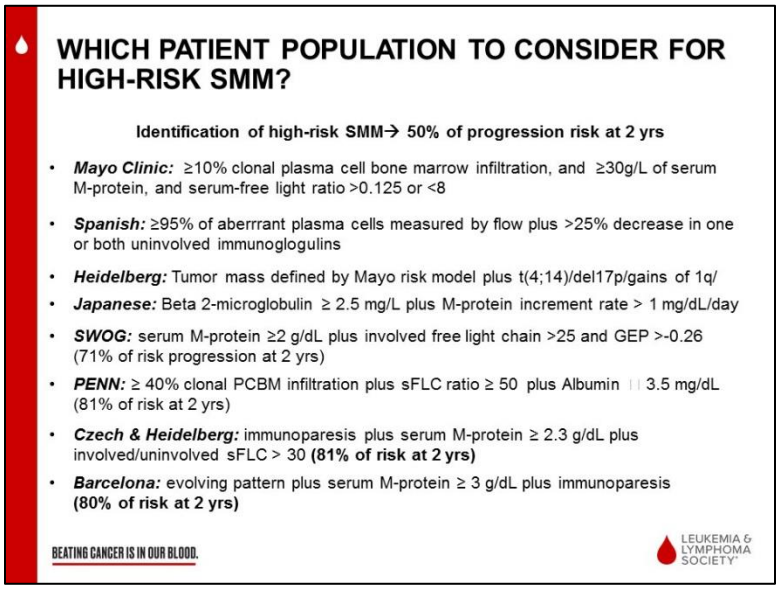
Now we just realized that doesn’t make sense. We’re waiting for people to fall apart and then we treat them. We wait for you to have a fracture in your bones and then we treat you. So, a couple of years ago we said, “Well, why don’t we add a few more criteria so that we’re not waiting for people to really have end-organ damage.” So, we added three things that indicate you are ultra-high risk of developing myeloma, which means you’re really, really going to develop myeloma very soon.

One of them is having 60% cancer cells in your bone marrow. That’s a lot. If we count 100 cells, 60 of them would be bad cells, cancer cells. So that’s already a lot of disease in the bone marrow.

One of them, if we do an MRI (magnetic resonance imaging) or a PET/CT (positron emission tomography/computerized tomography) scan instead of x-rays of the bones, skeletal survey, we find two lesions in your bones, well, that’s already meaning that you have lesions in your bones. We just use a more sensitive test. Instead of using x-rays of the bones, we’re using MRI or PET/CT scan. So that’s an advance that we’ve done.

And then the third one is if you have light chains, which many of you know are a part of the antibody that you secrete from the cancer cells, so if you have a very high level of light chains, over the ratio of 100, it means that you’re likely going to get kidney failure very soon. So, let’s try to treat you before you go into kidney failure and we have you on dialysis.

So, these are the three things we added recently just in case you go to your doctor; and in the old days, you know, a few years ago, they would have said, "No, you have to wait until you have CRAB criteria." Now if they find that you have 60% cancer cells, they might actually treat you early.

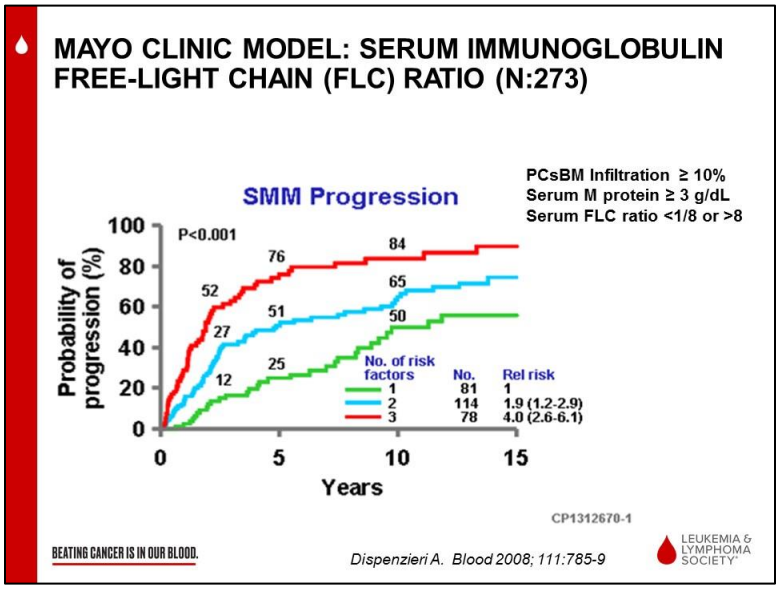


Now that's for active multiple myeloma. And just for everyone to know what does it mean, active myeloma. It's not that it means that suddenly now you develop cancer and before that you did not have cancer. Guess what, every patient who has smoldering myeloma, those cells are already cancer cells. So, the reason why they did not cause damage is several things, either there isn't enough of them or they're not growing fast enough or there's something else going on. And this is the part that we're trying to understand, why would someone who has cancer cells go on to have very fast progressing cells that cause problems and others will take very, very slow time, years and years, before they cause problems.

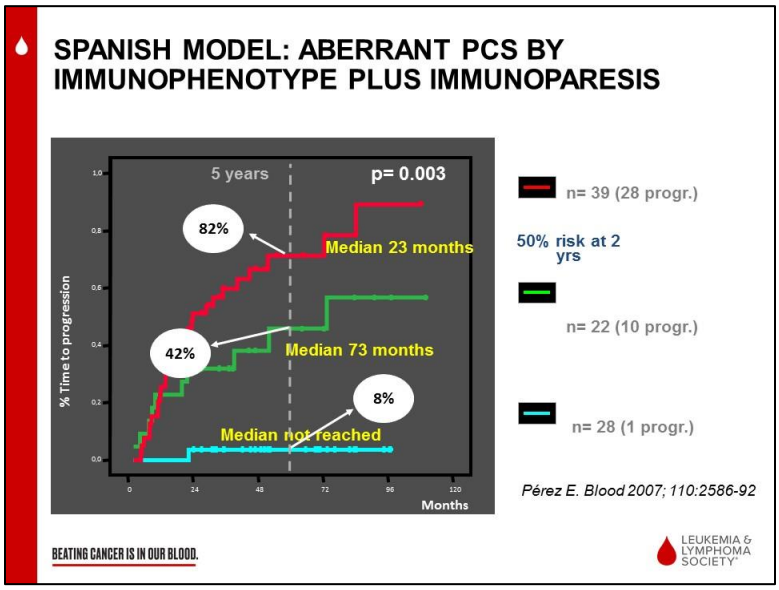
So, we're trying to identify factors that we can predict, with something called biomarkers, so that when I sit with you today and I tell you, "You have smoldering myeloma," and you tell me, "So what is my chance of getting kidney damage, bone lesions, active myeloma? When you tell me that these are the same cancer cells, and I say, "Well, we use certain markers. We use how high is your M spike? How many plasma cells do you have in your bone marrow? How high is your light chain ratio? How fast are those M spikes going up every time we see you?" All of those factors are clinical factors, meaning markers that we can see on the lab values that we see you with, and we put them together to make risk factors or risk criteria so that we can tell you are you high risk or not.

Now you see on this slide that we don't all agree, so the Mayo Clinic doctors do not agree with the Spanish doctors, do not agree with the German doctors and each of us develops basically a different risk criteria to say who's high risk.

And the reason for that is there are no good biomarkers to predict for us who will be high risk.

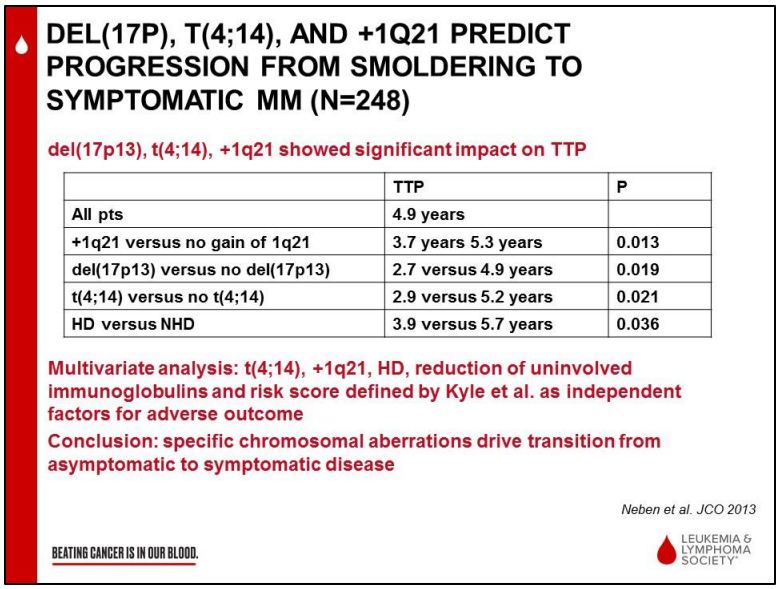


So if you look at the Mayo Clinic criteria, which is this slide, it shows you that indeed we can try and put people into different categories; and some of them who have three numbers, a high light chain, a high M (monoclonal) protein (more than 3 grams) and a high bone marrow (more than 10%), they would progress very fast to active myeloma. While someone who doesn't have all those three would progress much slower to active myeloma.



But if you look at the Spanish criteria, they use something else called flow cytometry which is when we take your bone marrow cells and we put them through a machine that colors them, we can see how many of those cancer cells are in there, inside the bone marrow sample. And if we see a lot of those, then we can say, "Okay, this is likely full of cancer cells that will likely progress."

But, guess what, someone could be high risk on the Spanish criteria but low risk on the Mayo Clinic criteria.



So, overall, those criteria are not perfect because we don't have a good biomarker that really predicts progression.

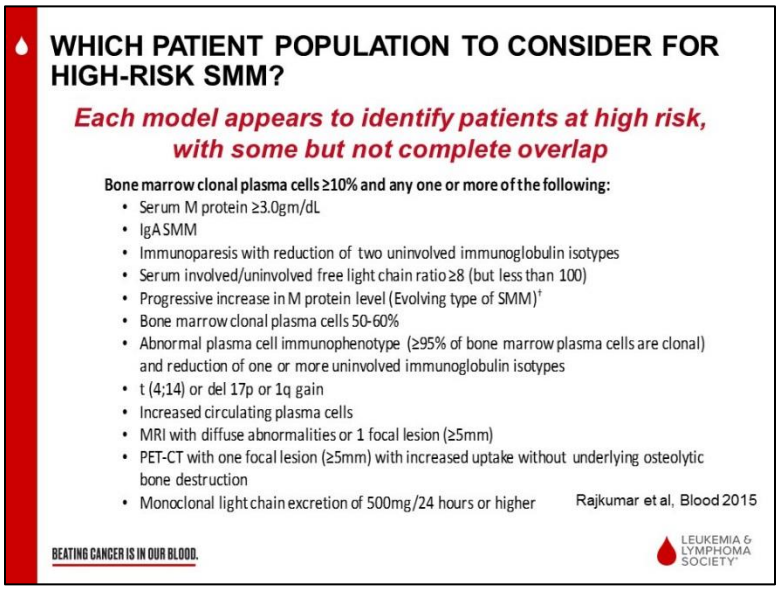
So, we started to say, "Well, how about we look at the cytogenetics, which is the changes in your chromosomes or the changes in your DNA inside your cell. If we see changes that are really bad, that indicates likely those cells behave badly, then this will likely indicate that this smoldering myeloma is going to go to active myeloma very fast.

So, we've looked at certain markers, and many of you are probably very comfortable knowing cytogenetics and FISH (fluorescence in situ hybridization), but I'm happy to answer questions later on if you have questions about this. But, basically, what they mean is when we take your cancer cells from your bone marrow and we look at the pieces of the chromosomes, which is your DNA that's inside your cell, we can actually see that in the cancer cell, unlike a normal cell, your chromosomes are actually not behaving very well. So, either they have small pieces that are cut off; we call those deletion because we removed a piece of your chromosome or they have extra pieces, so instead of having two chromosomes that are a certain number, like 1q, which is a piece of your chromosome 1, you'll have four pieces of that chromosome 1 or five pieces of that chromosome 1. So, this is called gain of 1q, meaning the cancer cells have added extra pieces of that arm of chromosome 1, which is your first chromosome.

Or you can have something called translocation, meaning pieces of one chromosome decided to go to another one. So, chromosome 4 and chromosome 14 decided to take pieces from each other. So now you have a 4;14 translocation. And that's important because suddenly when you have pieces of chromosomes exchanging like this, then we put something that likes to make the cells grow rapidly near another area and now suddenly all those cells keep growing and growing and growing; and your

immune system cannot control them. And no one can control them, and they go out of the way of normal ways of growing, and this is what we call a cancer cell.

So, basically, these are the pieces that we can collect together to say are your cells growing very fast or not.



So, when we look at this, we try to put all of those factors together to say what is high-risk smoldering myeloma, meaning what are the factors that could potentially tell us who is going to progress within two years.

So, these are some of those factors. Again, it's not perfect. It's not complete, and we're still working on this. So, if you are a smoldering myeloma patient, help us understand better why would someone progress and others don't progress by doing more research with us. But this is a list of all those factors, as I've already talked to you about—the Mayo, the Spanish, the chromosomal factors, the evolving, which means every time we see you, your M spike increases. All of these are, indeed, the factors that are causing this progression.

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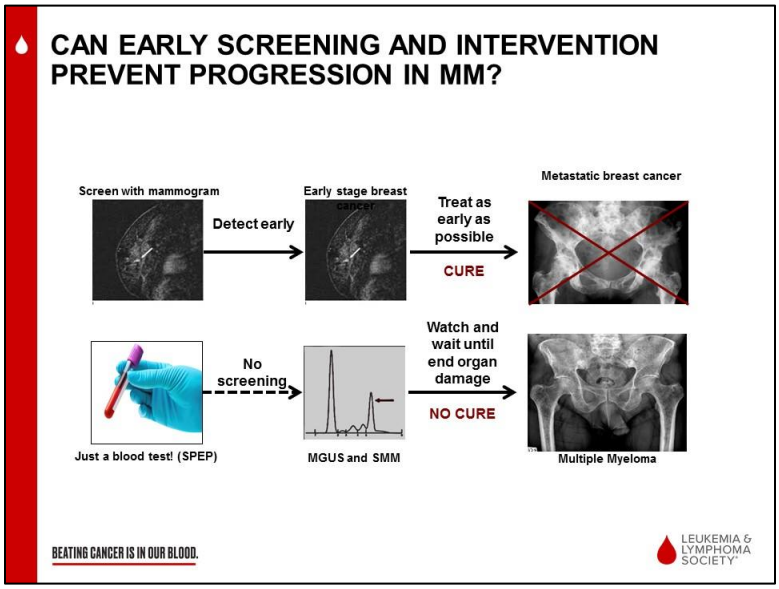
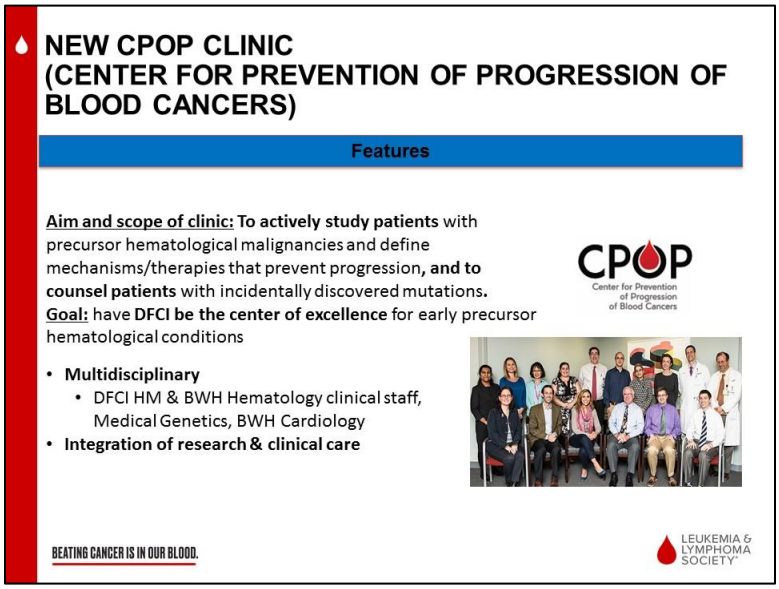


So, the simple thing that we started doing a few years ago was asking a simple question. If you see these days someone who has an early breast cancer or if you're a woman and you're going to your primary care doctor and you're over the age of 40, they will tell you please go do a mammogram because we do screening for breast cancer. If you're a man and you're at the age for a screen for prostate cancer, guess what, they'll tell you please do a PSA (prostate-specific antigen test) because we screen for prostate cancer. But you've never gone to your primary care doctor and he told you, "Guess what, we can take a blood sample from you and screen for myeloma and screen for blood cancers because it's simple, it's easy, and if we get screened for it and can find it early, potentially we can cure it early." And that's the problem, we do not screen for blood cancers.

So here in this slide, you can see that we screen by mammography for breast cancer; and if we detect it early, we remove it and that's it. You don't get breast cancer, or you have a lower chance of getting metastatic cancer. So, we don't wait for you to have metastatic cancer and then we treat you. Yet for myeloma, we do everything the reverse. We don't screen for it, although it's a very simple blood test. It's very sensitive and very specific. And if you have it, if you have smoldering myeloma, we tell you, "Go ahead and watch and wait until you have lesions in your bones, fractures in your bones, anemia, and then I treat you." So, it doesn't make sense that we're treating myeloma at the stage of metastatic disease when we have so much cancer tumor burden inside your bones, inside your bone marrow, that by the time we give you treatment, it may be too late.

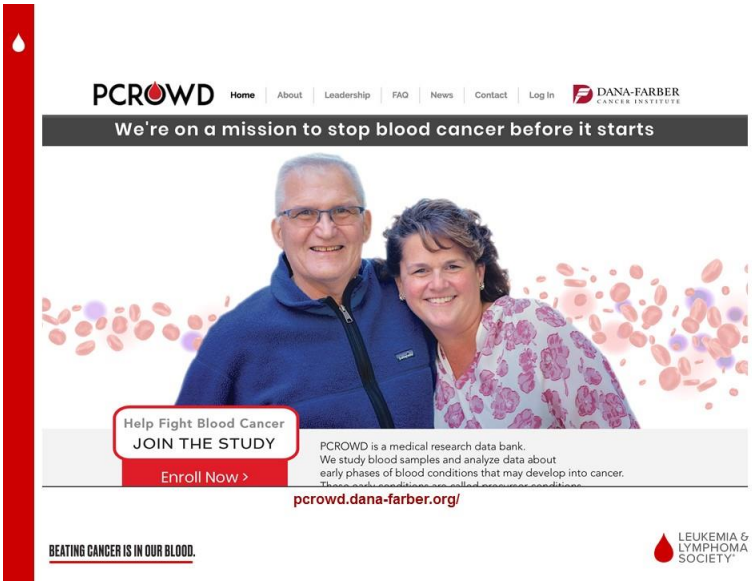
And potentially that may be the problem. We have really good, active therapy for myeloma, but we're not doing a good job of giving it to you early enough so that you can benefit from it early enough.



So, because of that we started a couple of years ago a Center for Prevention of Progression (CPOP). The whole idea is that we will see you early, we'll try to detect who is at high risk of developing myeloma and also treat you early if we need to do that.

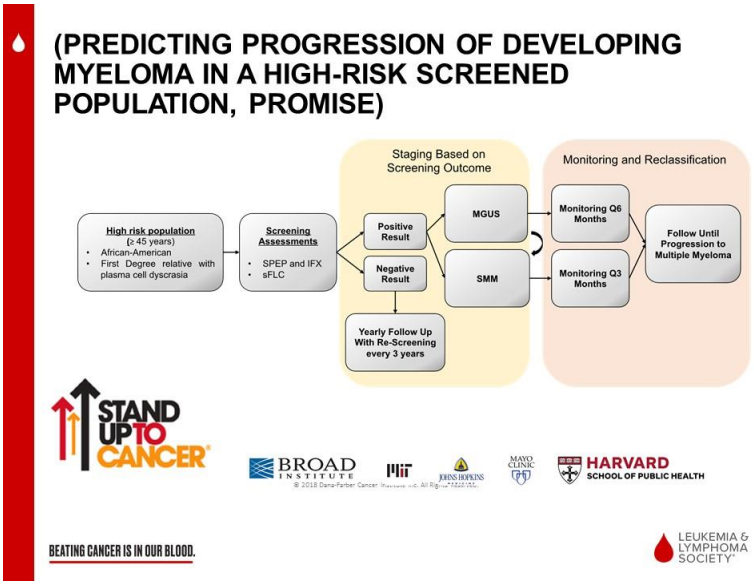
And we don't have to treat everyone, of course, but we're trying to develop therapies to prevent progression in everyone. So, this is just one of those slides that shows you we're not just a group for myeloma. We also have people who we see early CLL (chronic lymphocytic leukemia) and early MDS (myelodysplastic syndromes), and basically everyone involved is revolving around precursor blood cancers. Before you develop an active blood cancer, let's see you.

We're physically going to be starting that clinic in January, so before that, each of us in our department, myeloma department, MDS; but actually, next year, 2019, in a few weeks, we will all be sitting together in the same place. So, if you have an early MGUS and an early MBL (monoclonal B-cell lymphocytosis) for something that can happen in some patients, we will actually be seeing you, two physicians at the same time, and asking the question of what is going on in that bone marrow. So, again, let your family members, let everyone know about this because this is the first time that a cancer center specifically focuses on prevention and early detection of blood cancers.



And then once we found it, well not everyone wants to fly to Boston or drive to Boston. How about opening this to everyone around the world? So, we created something called Precursor Crowd (PCROWD). So instead of crowd sourcing for money, we're crowd sourcing for patients. And we're basically telling you we are empowering you as a patient to really have an active participation in research, to be part of this actively. So, if you live in Arkansas, in Alabama, in San Francisco, it doesn't matter. You can go online, on this website, pcrowd.dana-farber.org. You register, you sign a consent on your own. You don't need a doctor in between you and your research, and we send you a kit. And that kit, you take it to your doctor whenever you're going next time, they put the blood in it, or if you're going for a bone marrow biopsy, they'll stick a little bit extra fluid for us, and you ship it to us. And with that in mind, you are actively participating and understanding better who will progress and who will not. So, it's as simple as being part of a study across the nation, and we actually opened it internationally now so that everyone can really be part of it. I heard that there are people from Canada and from Nigeria, so that's wonderful, and we want to have more and more international people with us.

And I can tell you that when we started this study two years ago, we got so many people excited about it; and we have now over 1,500 participants of this, and we want to grow it more and more. The only way we can understand better who would progress and who will not is by having thousands and thousands of participants saying, "Yes, put me on this so that I know my answer in the future, so that I know whether I will be progressing or not in my lifetime."

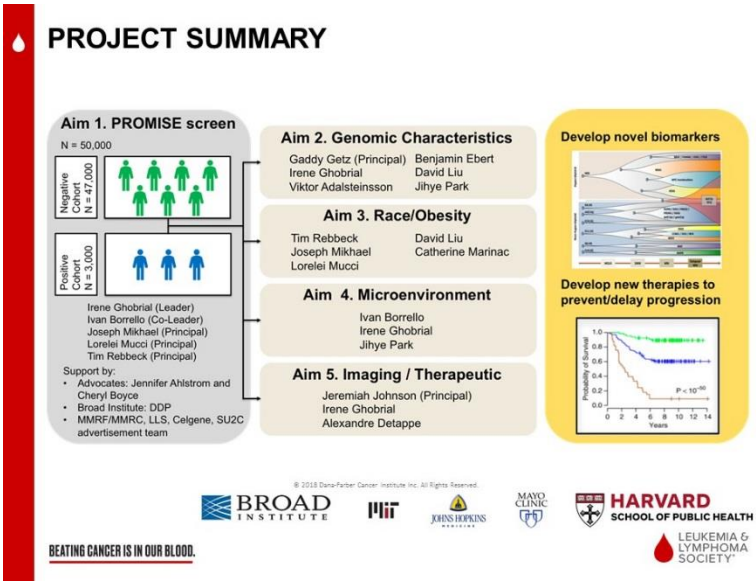


So, then the other question that we started recently, and this is in collaboration with Stand Up To Cancer but also in collaboration with The Leukemia & Lymphoma Society is asking the question should I screen for blood cancer. So, I just told you we don't have a blood screening test. We never screen for it. We screen for mammography and all of the other cancers. So, we started saying, "You know what, enough is enough. We're going to start screening for blood cancers." So, we started a PROMISE study (www.promisestudy.org), and this PROMISE study is screening for the first time for multiple myeloma. We're screening high-risk individuals, meaning people who are at high risk of developing myeloma. So, these are either African American over the age of 45 or first-degree relative of someone who has a plasma cell dyscrasia, dyscrasia meaning myeloma, Waldenström and so on.

And then, again, it's all online. You send us the blood sample, and we will check if you have an M spike or not. And we expect a very small number to have M spikes, but if you do have it, it's good to know that you have something as early as this time point. So as early as ten years, 15 years before you develop the cancer, you get to know that you have this potential for developing a precancerous lesion. And if we detect it early, can we prevent it from even going on to myeloma.

And it's an important question of do I want to know early or not. Yet, for all the other cancers, you probably would say yes. Please tell me when it's only 10 cells or 20 cells. Don't tell me when it's thousands and thousands of cells, and it's eating up my organs. So, let's do that also for blood cancers. Let's try and detect this early so that we can potentially completely get rid of it instead of waiting for you to have fractures and then it may be too late for us to treat you.

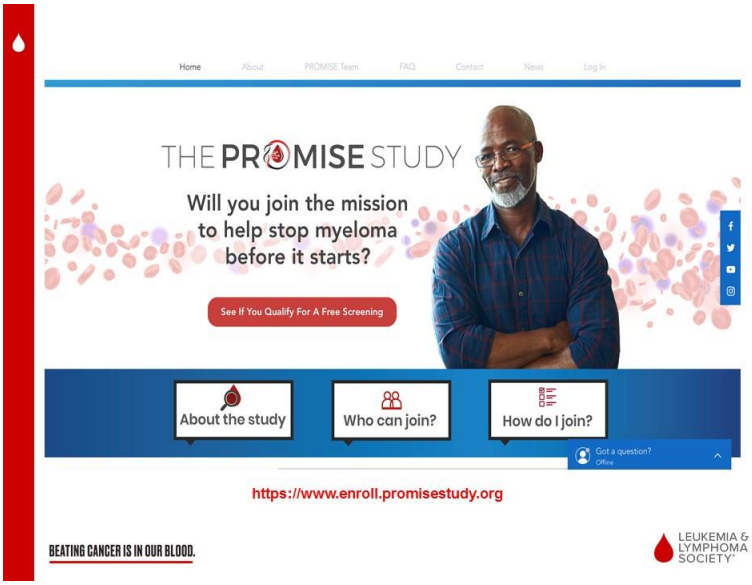
So, we will follow very carefully everyone who is diagnosed with MGUS or smoldering myeloma, and we would offer you, of course, options of clinical trials and options of intervention early, especially if you have high risk of disease.



So here is, again, the options of treatment that we will be doing; but mostly it will be actually research questions asking why would someone progress to multiple myeloma. And these are questions to understand at the DNA level, questions to understand why an African American or a relative of someone who has myeloma would have a higher chance. Why would someone who's obese or someone who was taking certain medications would have a higher or lower chance of developing myeloma. And then whether your immune cells are the bad players here. So, you may have the same cancer cells between two different people, but one of you, your immune system is not working very well; and that's the person who goes on to develop myeloma.

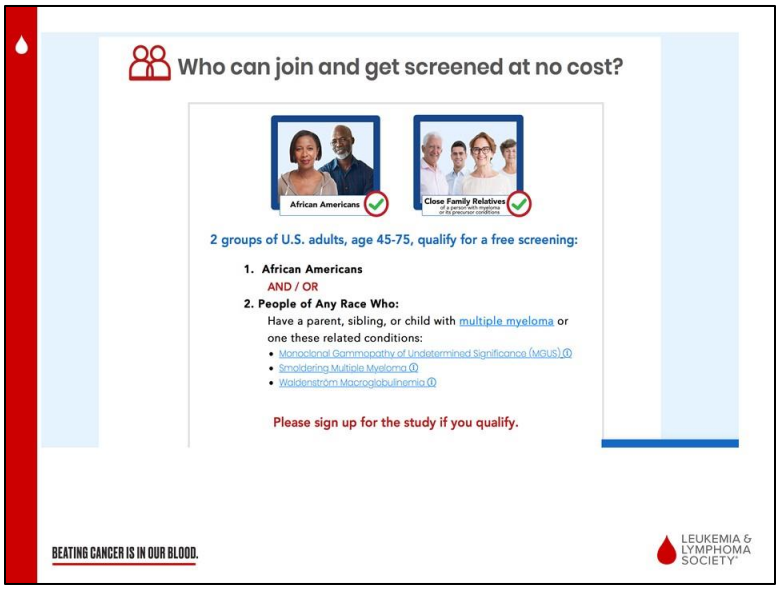
And we're also developing new ways to detect it early by better imaging modalities. So instead of using an MRI or x-rays of the bones, we're trying to develop new ways of detecting you early.

And this is, again, a collaboration between so many people, including, of course, LLS as well as many other sites including the Broad Institute, the School of Public Health and so on.

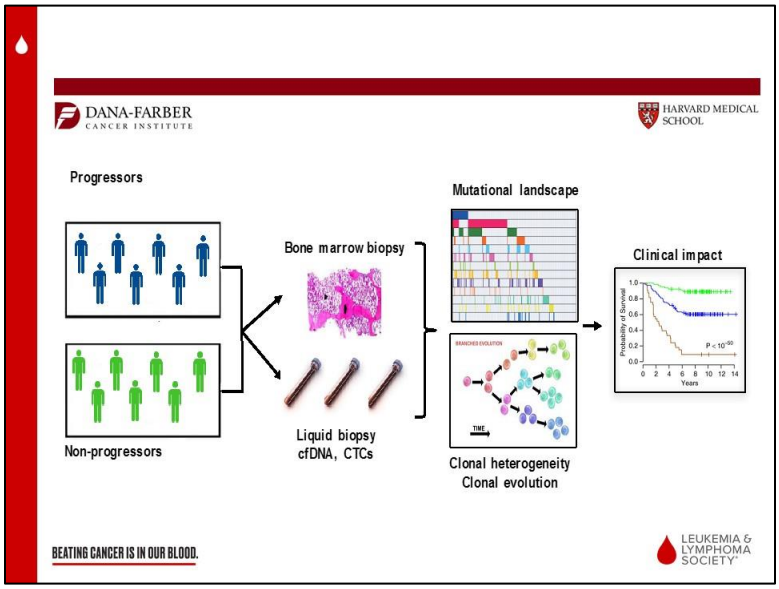


This is our website, and you can see here this is the promisestudy.org. So, you can go and enroll at promisestudy.org or if you just type in your Google search, promisestudy.org, you will actually find it. And, again, the same idea. You can screen online. You do not need a physician between you and the research, and we will have you get a kit. We will send you the kit online. It will be sent to you at your house, and you can take that kit to any local Quest or phlebotomy area. So any of your places that you go to for getting blood drawn or if you have a Quest Diagnostic site and we will give you the link

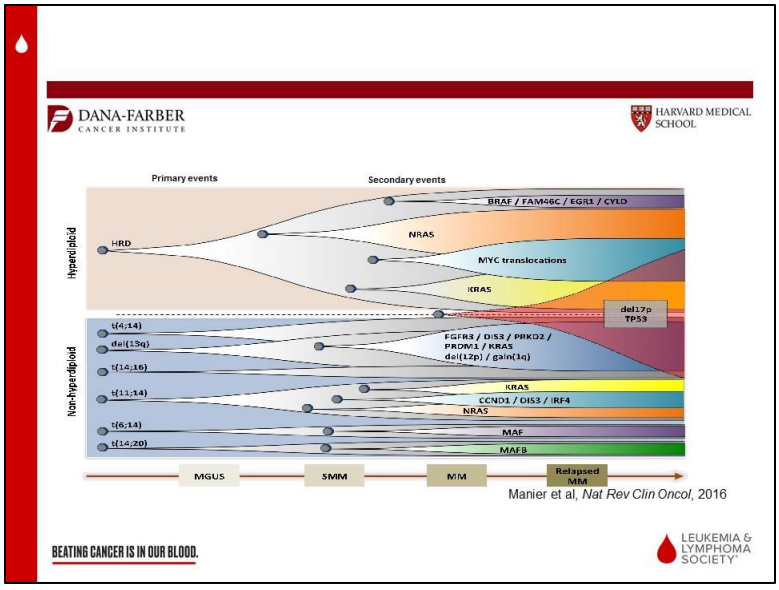
for that, you can go get there the blood test done; and then we will call you if it's positive or we will email you if it's negative, and then we will go from there.



And this is just to show you the website and the inclusion and exclusion criteria, meaning if you're an adult and you're between the age of 45 and 75, either you're African American or, and of course, and, if you have a family member who has multiple myeloma or Waldenström or MGUS or smoldering. So, again, most of you who are online now, likely you have a family member, a brother, a sister, a father, or a daughter who has this potential of knowing whether they, indeed, have MGUS and whether we can prevent it early from going on to develop myeloma.



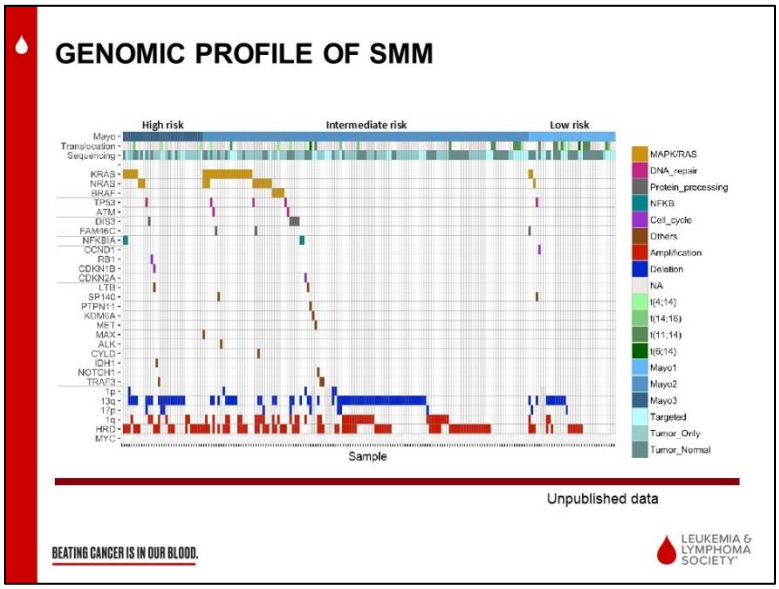
So, the question is, what are we doing with all those samples? Many of you will tell me, “You take my blood and you don’t tell me what you’re doing.” So, here’s what we’re doing. We’re taking all of those samples, bone marrows and blood, and we’re trying to define, instead of those markers that I told you early on that are not very predictive, let’s define markers that are predictive. Let’s actually define what are the changes in your DNA, what are the changes in your immune cells that can predict better in your case whether you would progress or not?



So, the first thing we do is we take your cancer cell, even if there are small numbers of cells, and we do something called next-generation sequencing. What does that mean? It means that instead of looking at big pieces of chromosomes, like I told you earlier, we actually look at every single

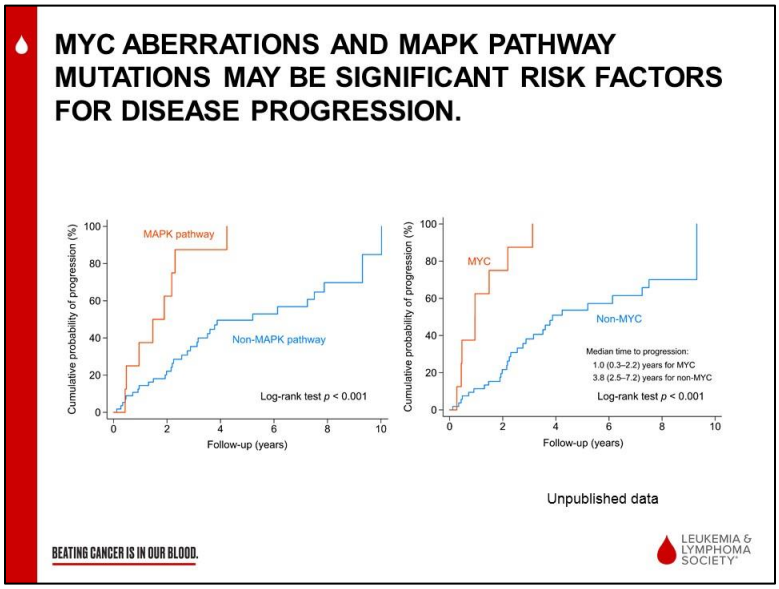
sequence of your DNA and we actually can tell if one of them just changed a little bit, even one tiny single nucleotide changed. We can tell if that got mutated or not.

So, if you can think about it, this is a huge advantage compared to looking at big pieces of chromosomes because we can miss it when it's big pieces like this because we're only detecting big pieces. But small little changes we would not detect them otherwise. Now we can detect them, and we can tell you if you have a mutation that will predict for you to have progression or not. And, indeed, this is what we did.

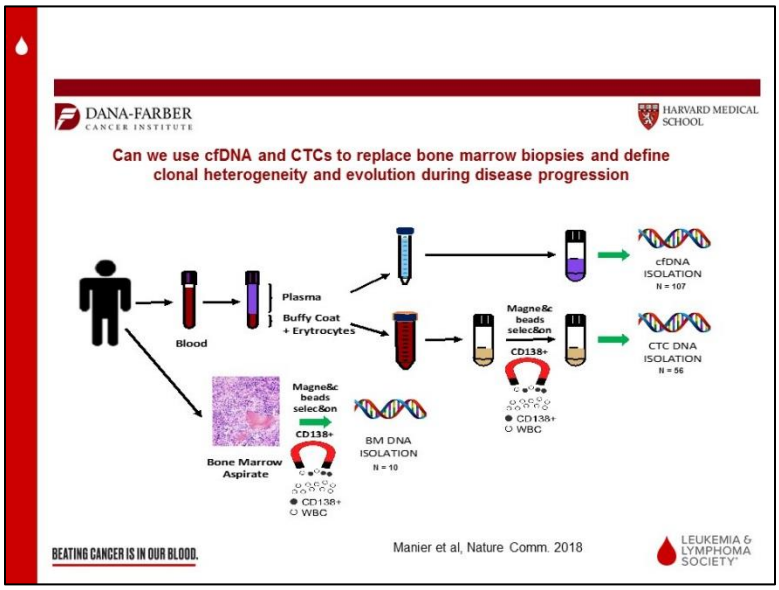


So, again, those blue and red lines here do not mean much to you; but it indicates that every single sample that we took from patients who have smoldering multiple myeloma, we looked if they have certain mutations, as I said. So, these are small, tiny changes in your DNA; and we found, indeed, that actually many of you have small tiny changes in your DNA while otherwise your doctor would have told you, "No, your normal cytogenetics. No, you don't have any problems. Well, guess what, you may actually have small changes in your DNA that we could not detect by the current lab testing that we do.

TRANSCRIPT



And we also found that, indeed, if we take some of those markers, something called MYC amplification or something called MAP kinase mutations, which are KRAS, NRAS, and BRAF, and we see if patients progress rapidly or not, in fact, they can predict very nicely for us if someone will progress to myeloma or not. So that's the first time in our lifetime that we can discover that indeed if we do next-generation sequencing on your sample, we can predict better if you are going to progress to myeloma. And we're working now to put that as a panel that we can clinically have available for people in the future so that you go get your blood test or bone marrow test and get to know if you have those changes or not.



The other thing we discovered is people do not like bone marrow biopsies, and if we want to do testing frequently and we want to understand better what's going on with you, then we should start looking at the blood, so using the blood biopsy instead of the bone marrow biopsy.

And here what we asked is several things. One is can we use your blood instead of your bone marrow so that in the future you don't have to go for a bone marrow biopsy, which is exciting. I'm sure a lot of you would say yes. And, two, can I potentially understand better what are the changes in your chromosomes or in your DNA that can reflect all of the changes that happen in your bone marrow. Remember, when you take a bone marrow biopsy, you're taking it only from one place—from your hip area. And it's only one tiny piece of bone marrow that we take. So, it may not reflect all of the changes that happen everywhere else in your bone marrow. So, if you have a change that happened in your backbones and I did not see that because I'm only taking a hip bone biopsy, then I'm missing potentially very important changes that can predict response or resistance to therapy. But the blood could be a perfect place where everything goes into the blood, and by taking a blood sample we can predict better what happens for you.

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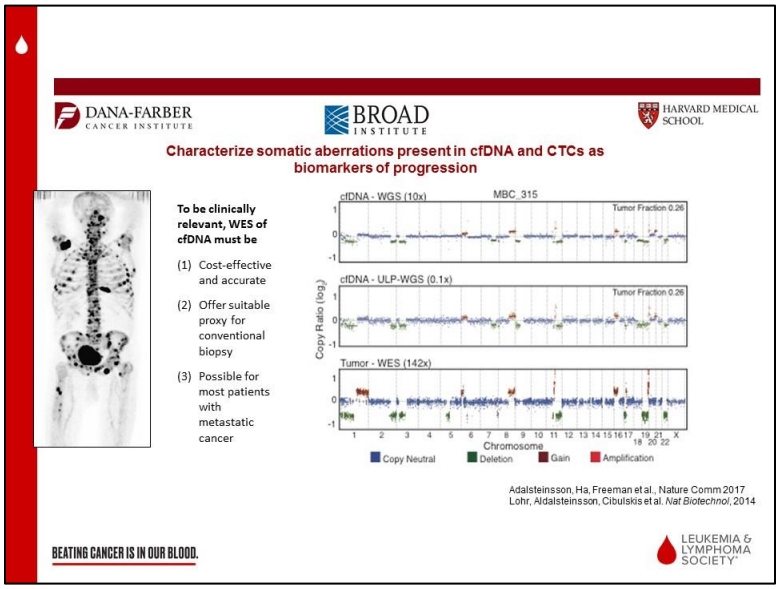

So, this is what we did. We took blood samples from people, and we did something that's as cheap as $20 per sample, something called ultra-low-pass whole genome sequencing, big long name which just tells us that we can detect if you have bad cancer cell DNA inside your blood. And if it's at 3%, only 3% of your DNA that's in your blood is bad cancer cell DNA, we can actually sequence that and discover what's going on with you.

And here's a slide that shows you that if you have MGUS, you have a little bit of that DNA. If you have myeloma, you have a lot of that DNA showing up in your blood. So already by doing this blood sample testing, we can predict potentially who has active myeloma and who is going to progress to myeloma by taking your blood sample.

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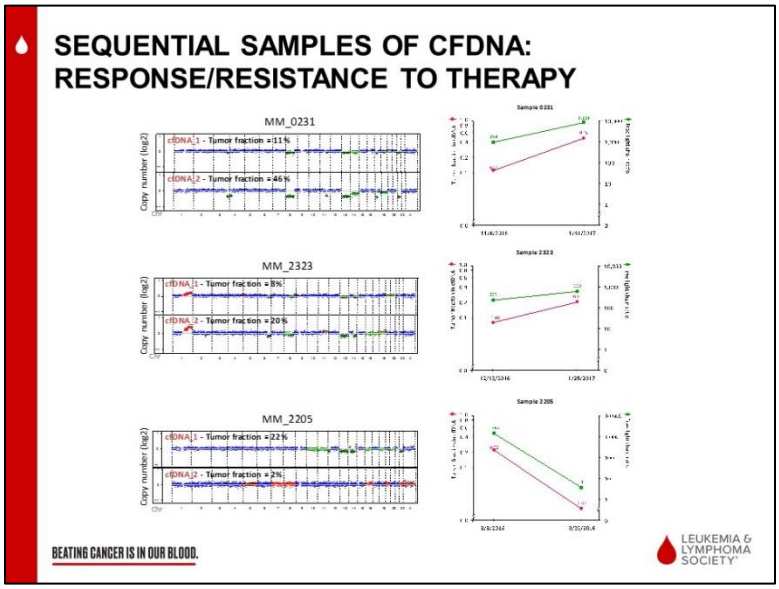
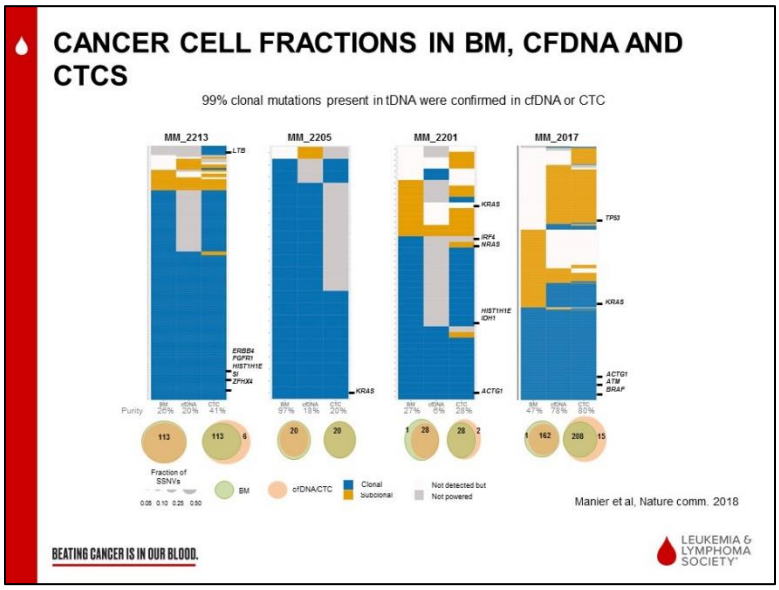


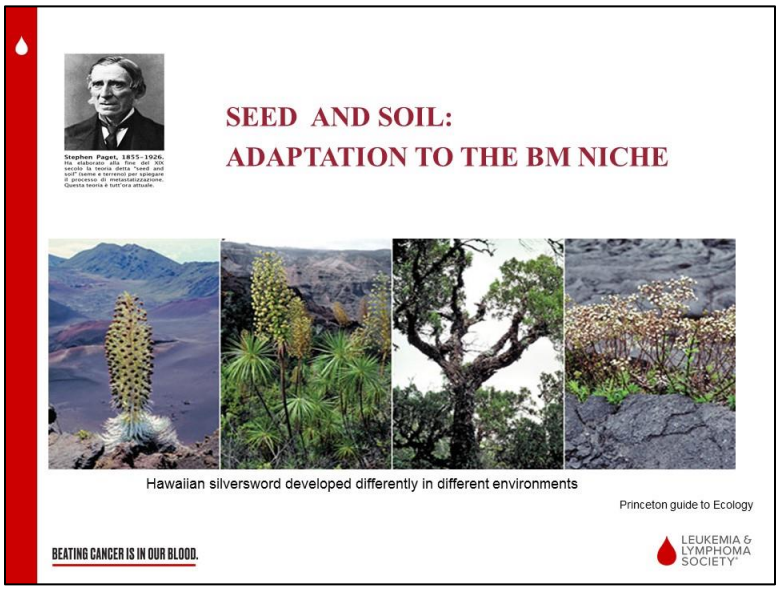
We can also predict in this slide if you are going to respond or not respond to therapy. So, you can see here the two lines, the green and red lines, this is someone who is not responding to therapy. While the ones that are going down, these are the people who are responding to therapy, so already showing you that we can predict response and resistance to therapy by doing this new DNA test in the blood.



And when we compared the blood versus bone marrow versus cells that are circulating in your blood, we call it circulating tumor cells, we found that indeed you can detect every single change that happened in your bone marrow, which is the blue areas here. We can see them in all areas—in your bone marrow; in your circulating free DNA, which is your blood sample; and in your circulating tumor cells or CTCs, which is the cells that like to circulate or go around in your blood.

TRANSCRIPT

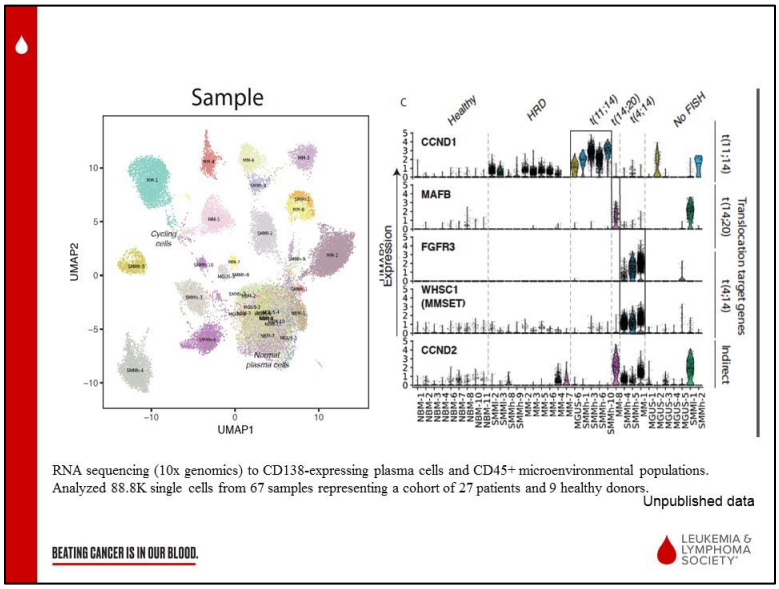
So that's the first sign that for the first time we can take a blood sample and tell you what's going on in your bone marrow. And we're actively working right now to try and develop this as a test that you can go and get it ordered by your doctor, a preapproved test. But also, something that can predict for you progression and also response to therapy in the future.



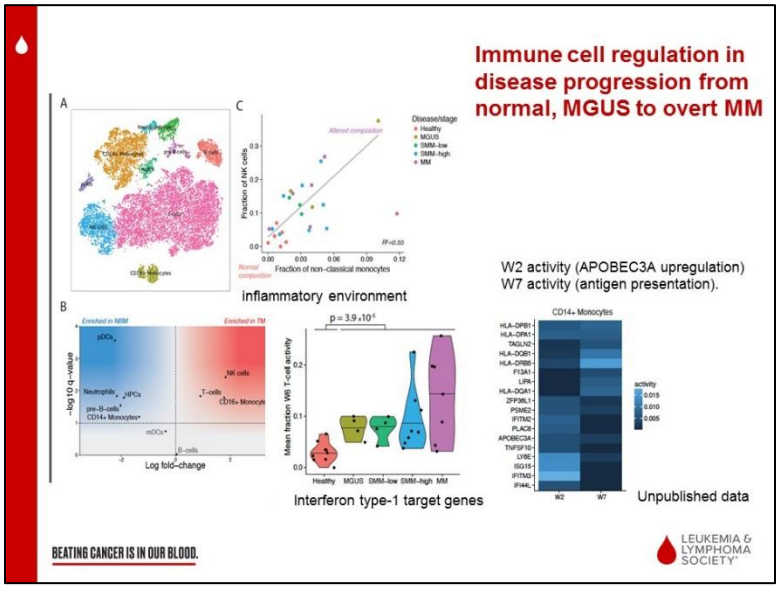
Now this was all about the cancer cells, but I told you earlier what about the environment? What happens to immune cells? Maybe two people have the exact same cancer cells; but one of them will progress and the other will not progress. So, what is going on?

And this shows you something called the Seed and Soil Hypothesis. So, these are seeds, Hawaiian silversword seeds that if you put them in different environments, they would grow into completely different types of plants. And that's exactly what happens in our own environment. If you put cancer cells inside the bone marrow of someone who has a very good immune system, well, it can kill those cancer cells because it can detect it. If you have a bad immune system or bad changes in your bone marrow or inflammation or something else is going on, then those cells will thrive and will grow and will cause myeloma to happen.

TRANSCRIPT



So we started doing something called single-cell RNA (ribonucleic acid) sequencing, meaning we take every single cell in your bone marrow and actually look at it as a single cell so that we can understand better what's going on with all of those tiny little changes and can we understand better which are the bad cells, which are the bad immune cells here, and which ones are the good immune cells and how do they protect you from going on?



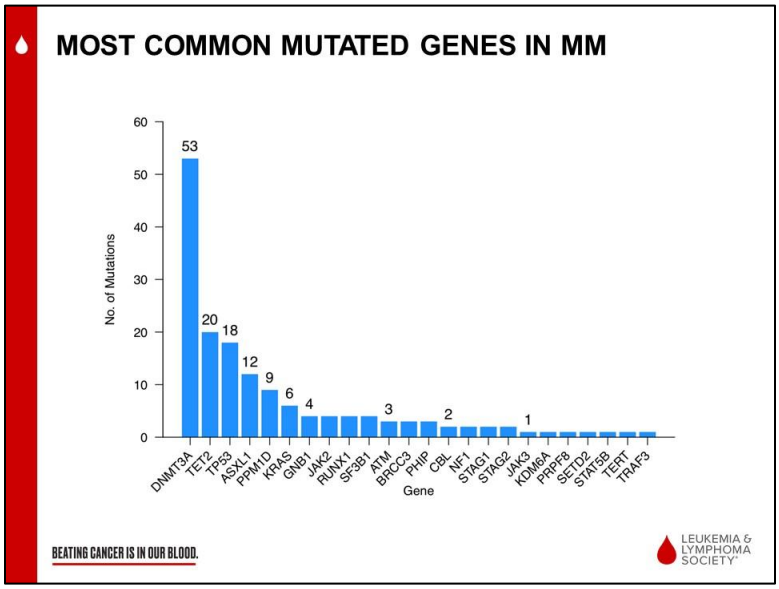
So, this is just a high level. So, again, it's a lot of research information; so, you guys are all going to be very good in understanding lab research. But this is taking all those tiny little cells, so each dot here in those colors are actually a single cell, with changes in the gene level of each of those cells. So, tons and tons of information that tells us that indeed your immune system is already in bad shape at the early stage, even before we diagnose you with multiple myeloma. And it tells us that sometimes

the NK cells (natural killer) or the T-cells, which are types of immune cells, can keep going up higher and higher and getting worse and worse as you progress from MGUS to myeloma.

So why is this important? It's important because by understanding this, we can actually develop therapy to make your immune system active again. The biggest thing that we've had as a cancer therapy over the last five years has been something called immunotherapy, meaning we can develop therapy to activate your immune system; and this is exactly what we're trying to do now is we look at this and try to say who will benefit from immunotherapy early on at the stage of MGUS or smoldering myeloma.

And then in this slide and, again, I'm giving you a lot of information here.

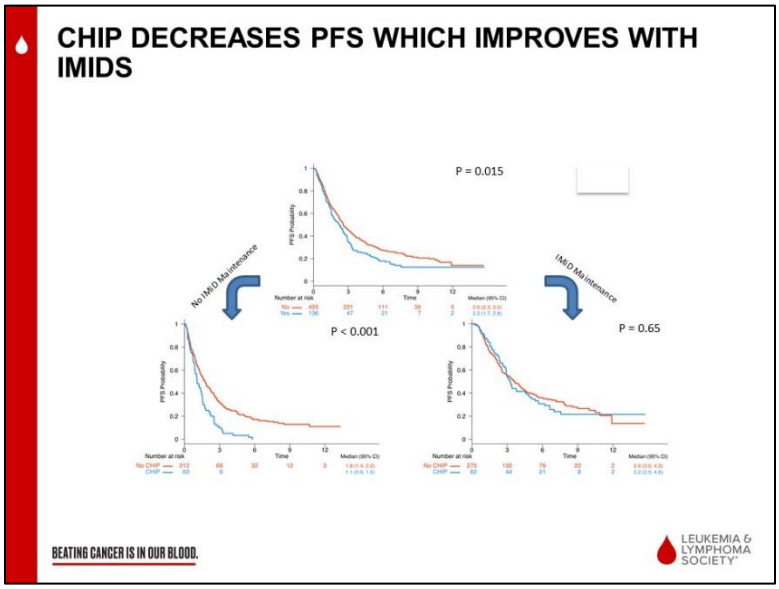
TRANSCRIPT



In this ASH, which is American Society of Hematology [Annual Meeting], a few weeks ago we presented the first work that we've had on something called CHIP, which is clonal hematopoiesis of indeterminant potential.

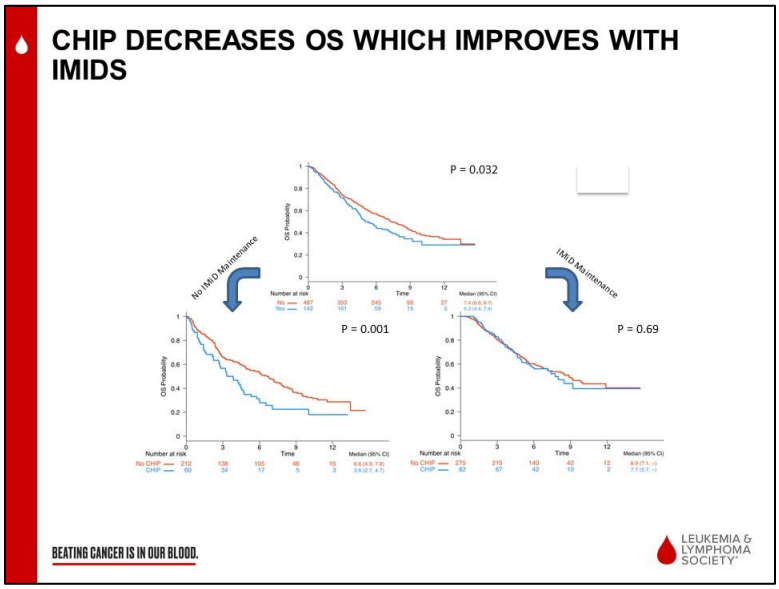
Big long name which is basically the MGUS of leukemia or MDS. An early change in your stem cells that can happen in many of us, even at the stage of MGUS and smoldering. But here in this study what we did is we took 600 people who went on and received stem-cell transplant, so in multiple myeloma we all or most of us will get a transplant, so we collect your stem cells.

Well, the leftover stem cells, we took a little piece of it, and we asked the question, "Do you have changes in your stem cells? Are your stem cells already bad when you start with it so when we give them back to you there is already a problem. And, guess what? We found 20% of everyone who has myeloma already has changes in their stem cells that are bad. So, they already had those changes, either because of aging or because of another problem. We don't know, but you had damage in your stem cells to start with. It's not from the chemotherapy. It happens even before the chemotherapy.

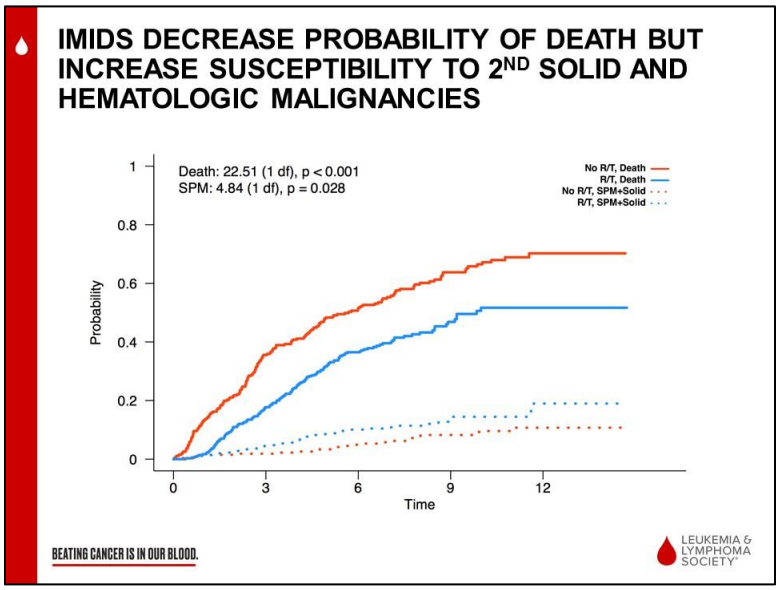


And we know that if you have this damage, if you get a stem cell transplant, then you're having this high dose chemotherapy that can make those stem cells get damaged further; and potentially you can develop now MDS or leukemia, something we call secondary leukemia.

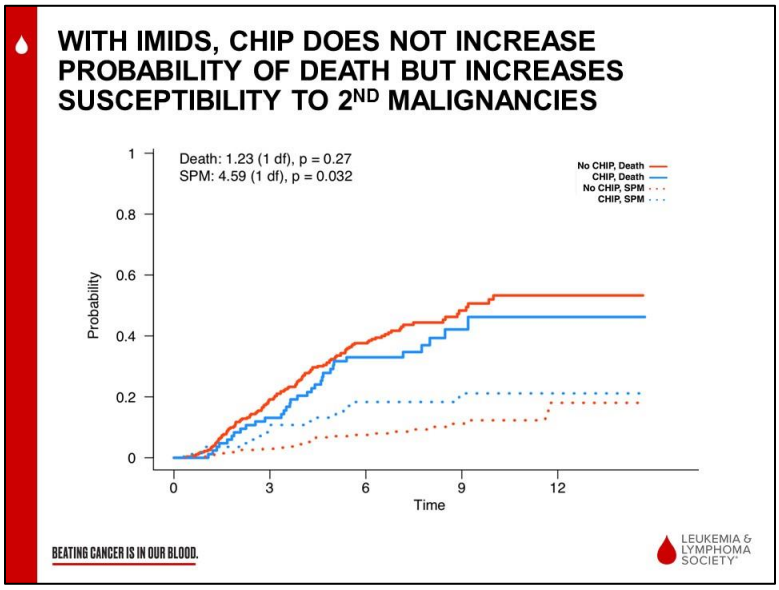
But what we found also, which was very interesting, is if you go on maintenance therapy with lenalidomide, which is Revlimid®. You actually benefit from that, and it prevents that survival problem from happening.



So, it actually can prevent the changes that occur with the stem cells, and it improves the progression-free survival, meaning preventing progression of myeloma when you are on an immunomodulator like Revlimid or thalidomide. And the same for overall survival.

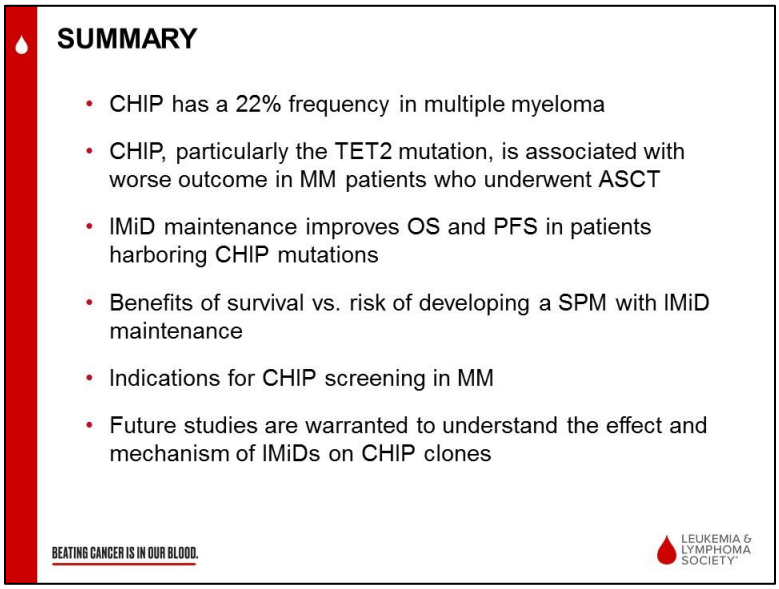


So, if you're going to get transplant, it's a good idea to get Revlimid or thalidomide. And if you already have those CHIP mutations, it may not be a good idea to get the stem cell transplant. And in the future, after we validate the study in a larger number of people, we may actually start saying, "Let's check for those stem cell mutations first." And if they are positive, maybe we don't want to give you this high dose of chemotherapy. Maybe we want to go in a different route. While if you don't have those problems, then potentially we can give you the transplant.

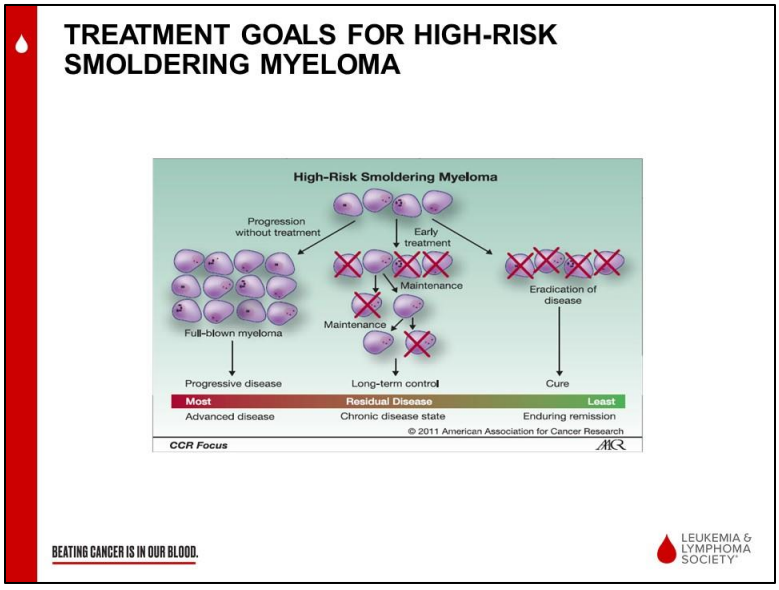


So that may change completely the way we think of how we transplant people and who do we transplant. And if we transplant you, making sure that we give you maintenance therapy and not leave you without it. Again, this is a huge area of interest for us. Now we do not yet apply this to the

clinical care, so don't go tomorrow to ask your doctor about CHIP mutations because they would not know what you're talking about. We're just trying to understand this better. And once we have a better sense, then we could potentially change the guideline of how we transplant patients.

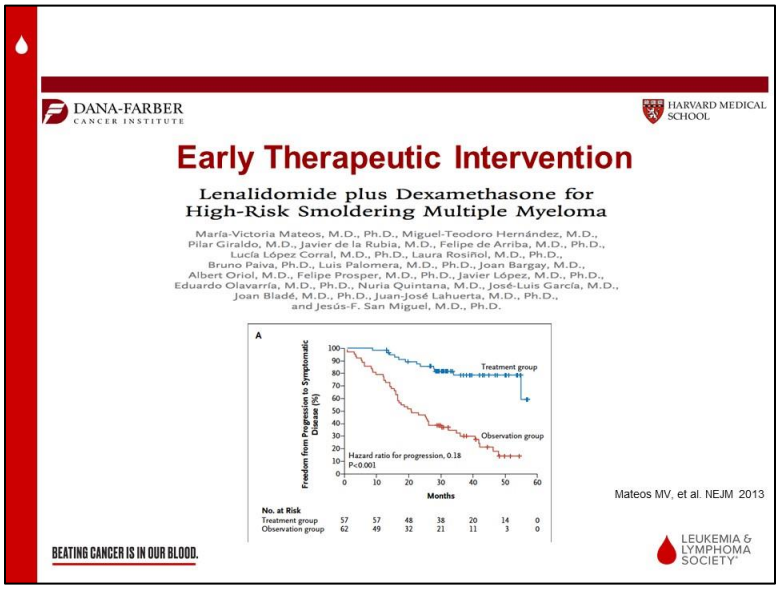


But just for you to know that stem cell damage can happen early on and can explain potentially why some people develop leukemia or MDS post-transplant in multiple myeloma.

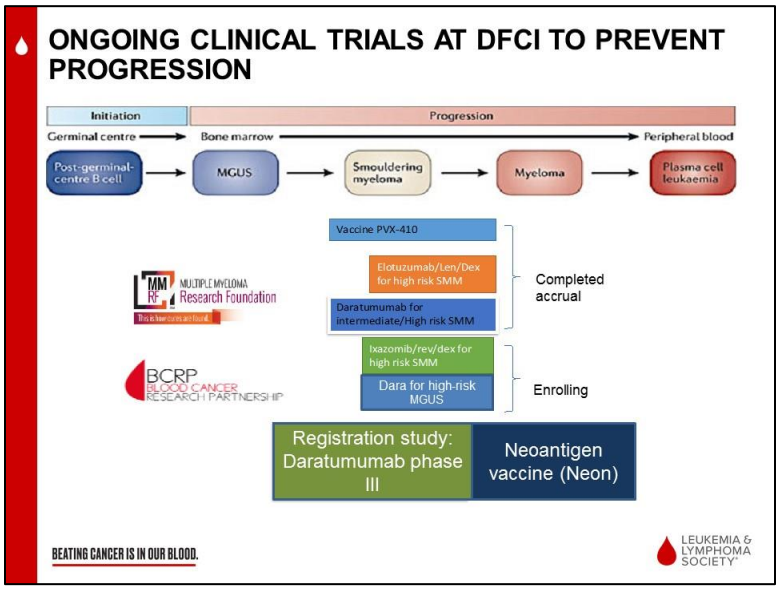


And then I'll finish in the last few slides with how do we treat high-risk smoldering myeloma? So, I just told you earlier on that we want to prevent it by early therapeutic intervention. So, think about it, you have all those cancer cells; and they keep growing and growing until you develop myeloma or active disease. We could potentially eradicate them early on and potentially cure myeloma early.

TRANSCRIPT

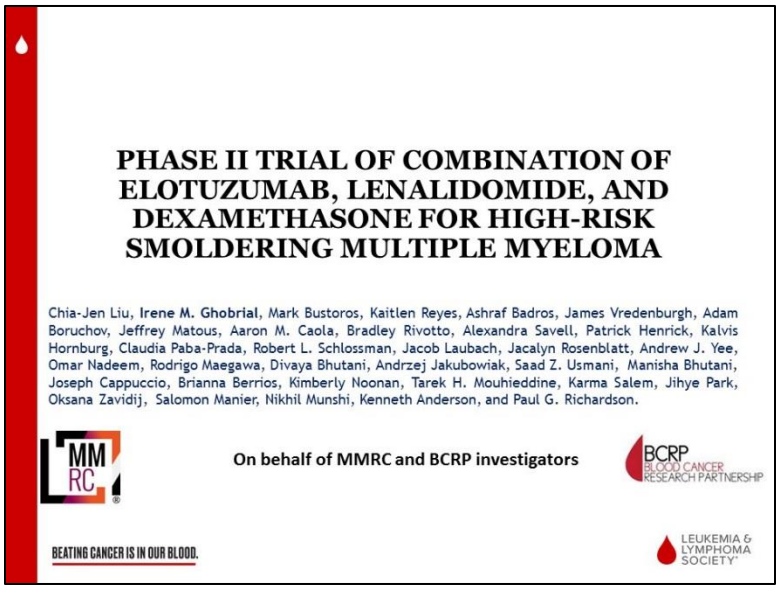


And the first potential idea that this would work was done by the Spanish group, something called lenalidomide and dexamethasone or Revlimid and dex (dexamethasone) versus observation, which is doing nothing. And, indeed, they found, like you see in the blue line, that people who receive treatment, Revlimid and dex, actually did much better and lived much longer compared to people who did nothing at all and just watched and waited until they developed myeloma.



So that made us think, okay, let's start thinking of early intervention and early treatment, specifically for high-risk smoldering myeloma. So, this is a slide showing you all the trials that either are ongoing right now at Dana-Farber or have completed accrual, meaning that closed already but we're looking at follow-up of those people or things that we would open in the future. And you can see we have lots and lots of options, so call us any time if you have questions. We have antibodies, we have oral

therapies, we have vaccine therapies, we have everything that could potentially prevent disease progression in our patients.



And I'll give you data from two examples of two clinical trials, and some of you are actually participants probably who have been on the trials, so I want to thank you all, anyone who's on the line who has been a participant on a clinical trial. Thank you for doing that.

So, this is one of the phase II trials where we tested an antibody called elotuzumab which goes and activates NK cells along with the Revlimid and dexamethasone that I told you already is a treatment for myeloma.

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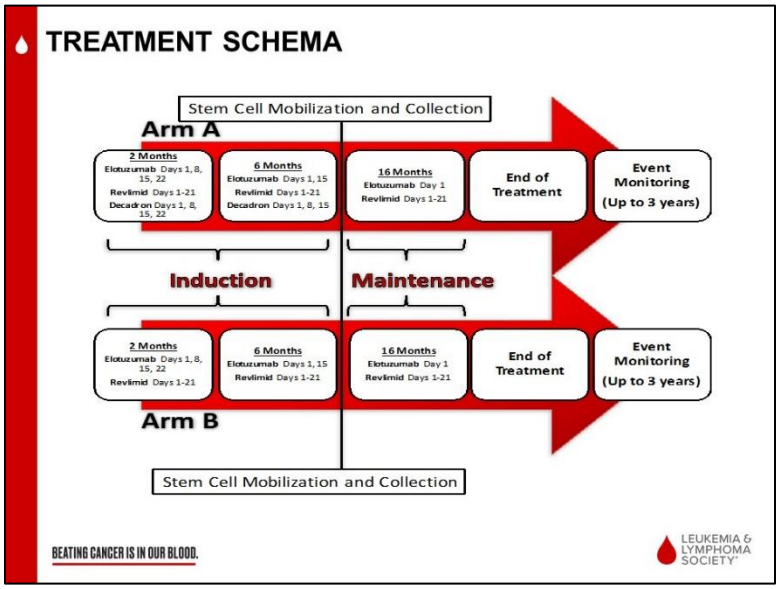
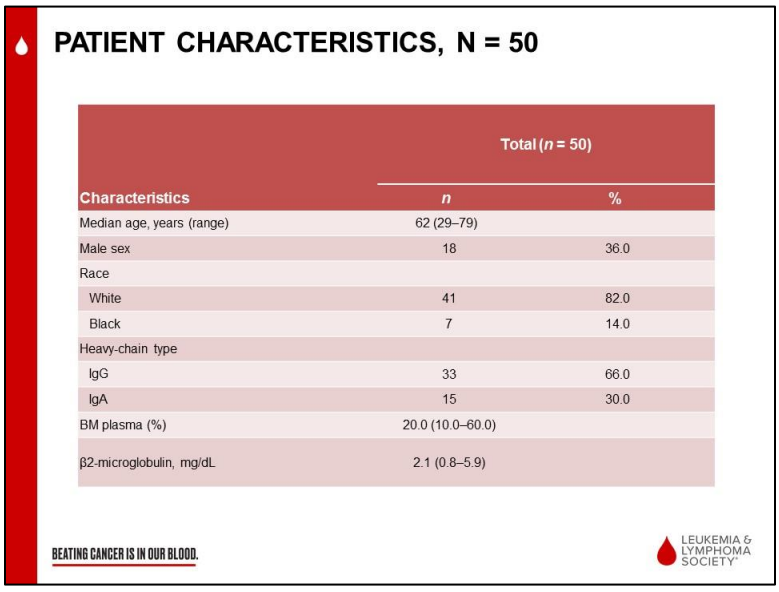
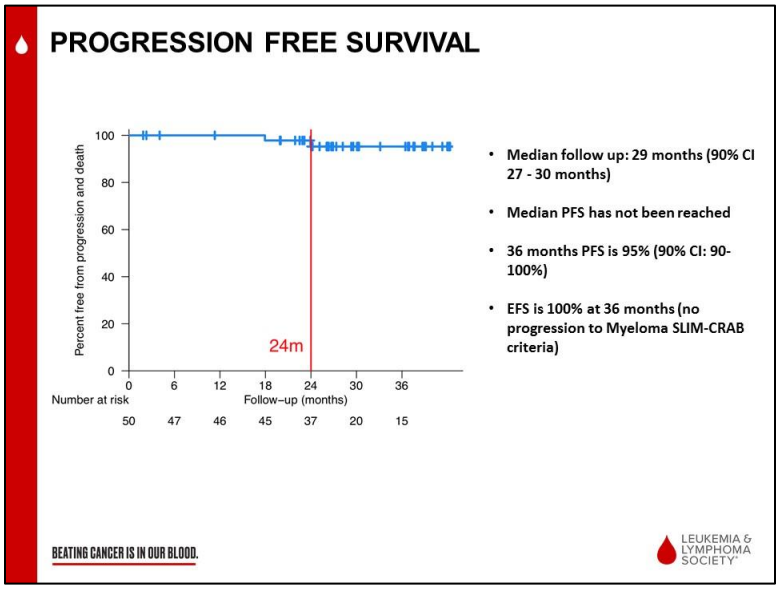


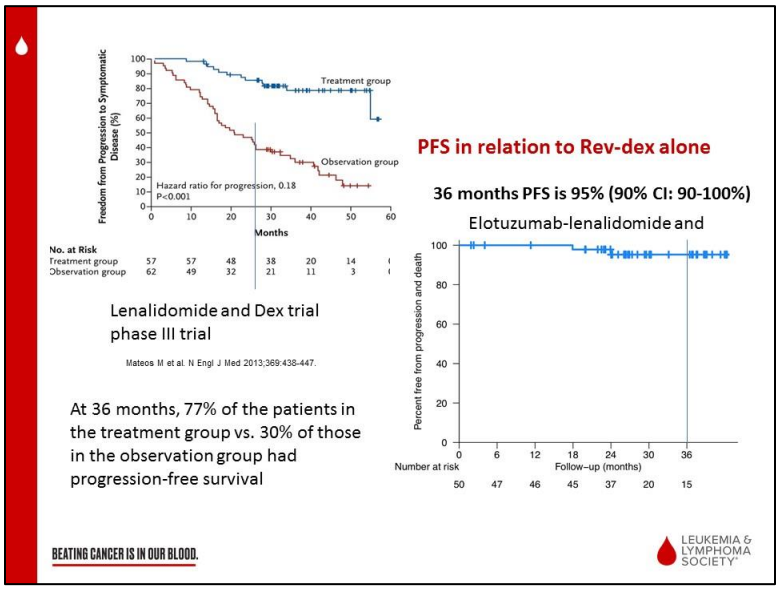
And this is just showing you that we treat for six months, and then we collect stem cells for everyone so that you have them nicely collected already for you. And then we treat you for maintenance therapy.



And what we found is in 50 people who were enrolled on this study, many of them were actually very young, as young as 29, and some of them as old as 79. So, we welcome everyone, and everyone potentially can benefit from the treatment.

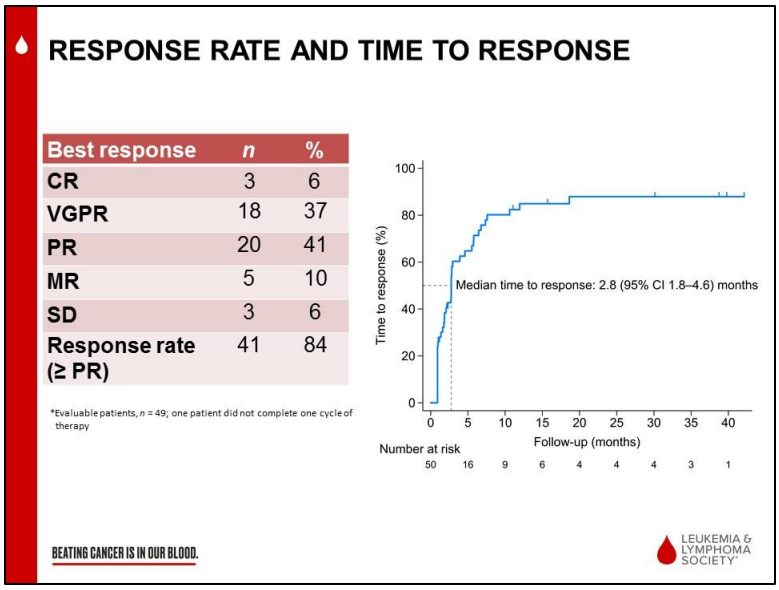


And we found that, indeed, if we want to delay progression, which is basically at two years, would we delay progression to myeloma or not? The answer was yes. Even at the three years' follow-up, we only found two people who were not able to prevent progression in them, and this is because they had other complications—heart attacks and diabetes and problems with infection because of the diabetes.

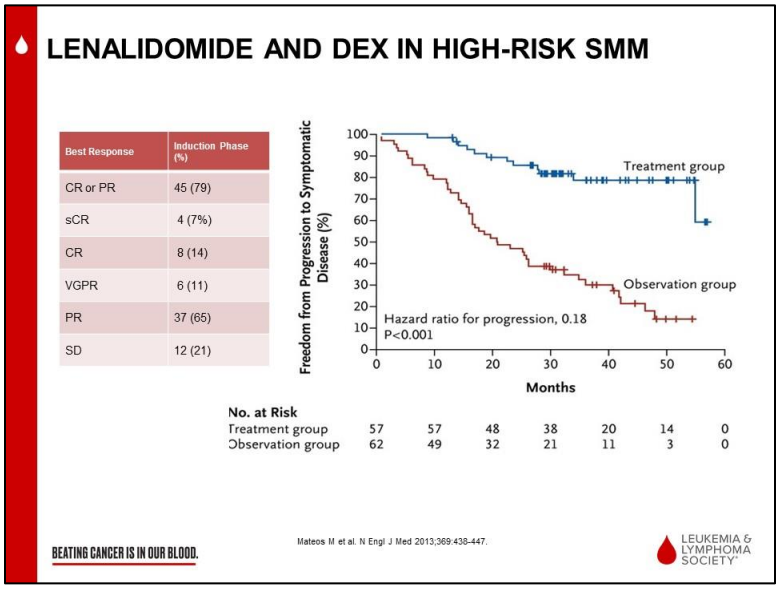


But if you just look at that, you can see that elotuzumab, Rev (Revlimid) and dex, the people on it did much better; and at three years, they were even better than, of course, the observation group, which is the red color in that line or even the prior treatment group in the Spanish study, which is the Revlimid and dex. So, by the three-drug combination, we're doing an outstanding job in really

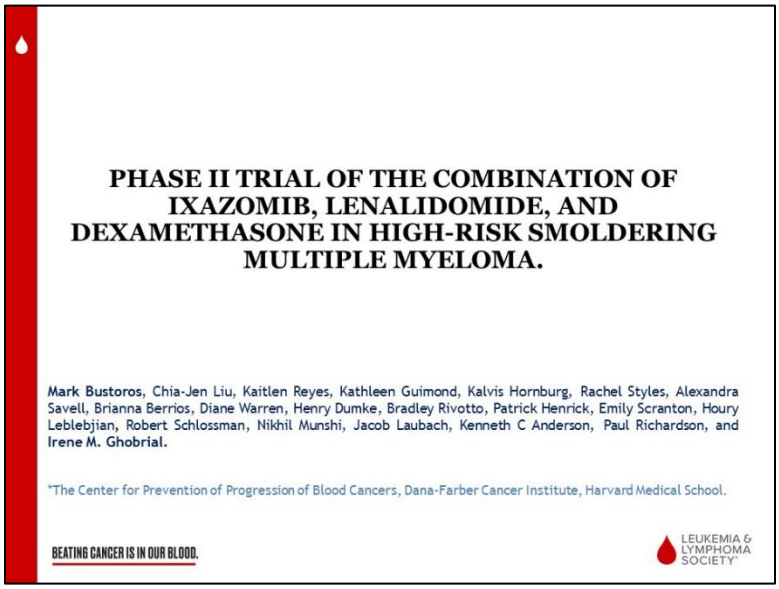
preventing progression, at least at three years' timepoint; and we're hoping to even see longer follow-up for these patients.



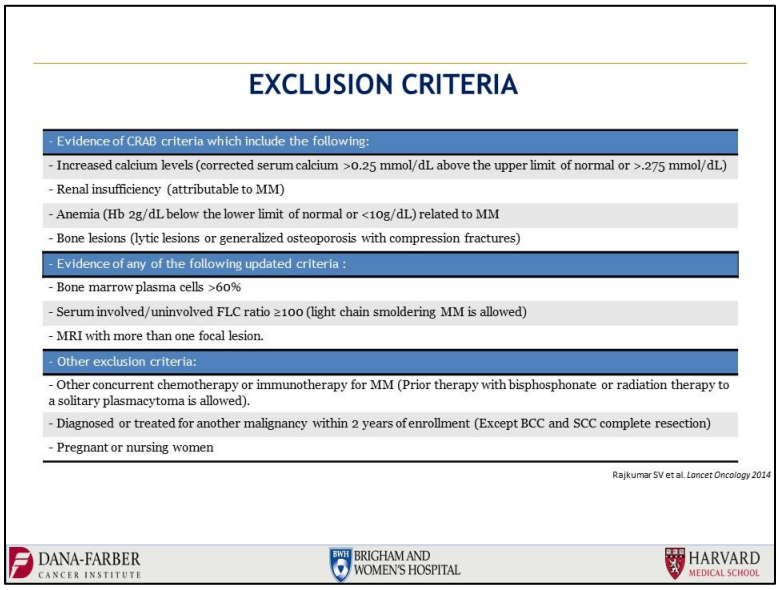
This is just showing you the response rate, and 84% of the patients had a 50% reduction.



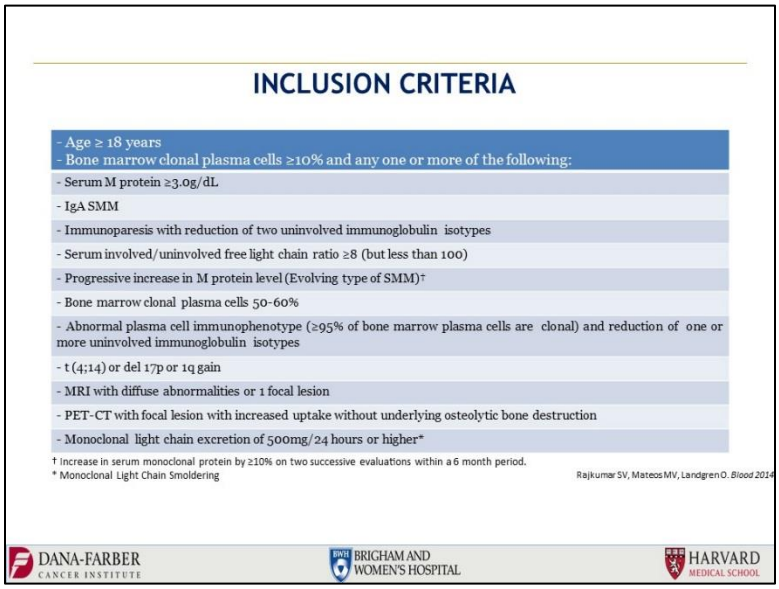
Almost 100% of the patients had some response, which means either a minimal response or a partial response or a complete remission.



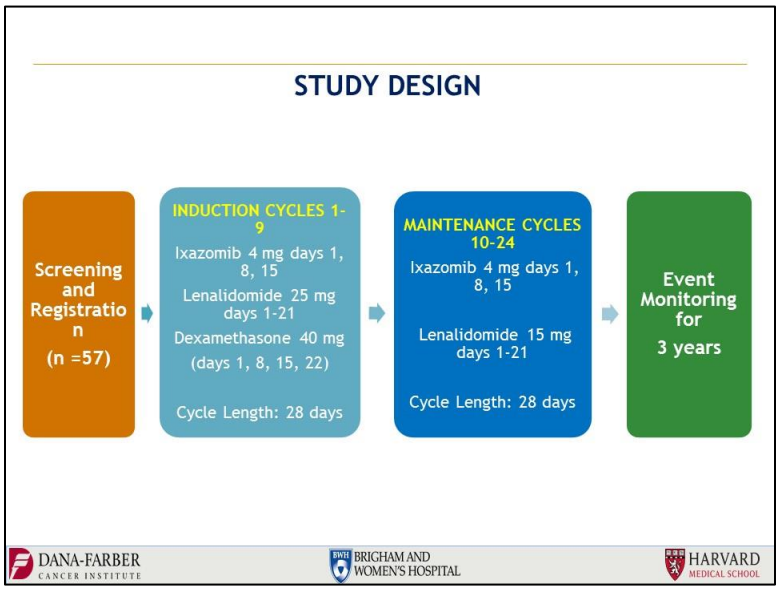
The other study that I'll talk to you about is three oral drugs, ixazomib, lenalidomide, and dexamethasone. This study is still ongoing, so we haven't finished it yet.



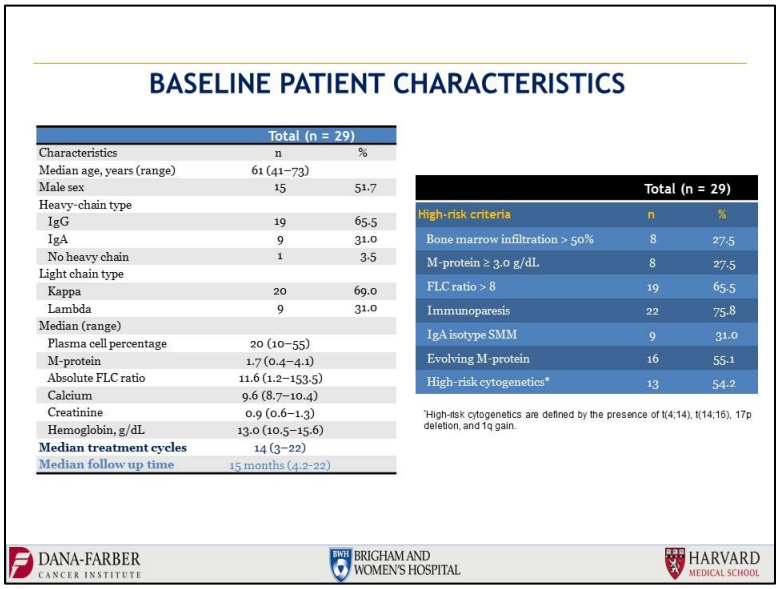
But we showed the data on the first 29 patients, and I know that many of you are interested to know what are the results on this study.



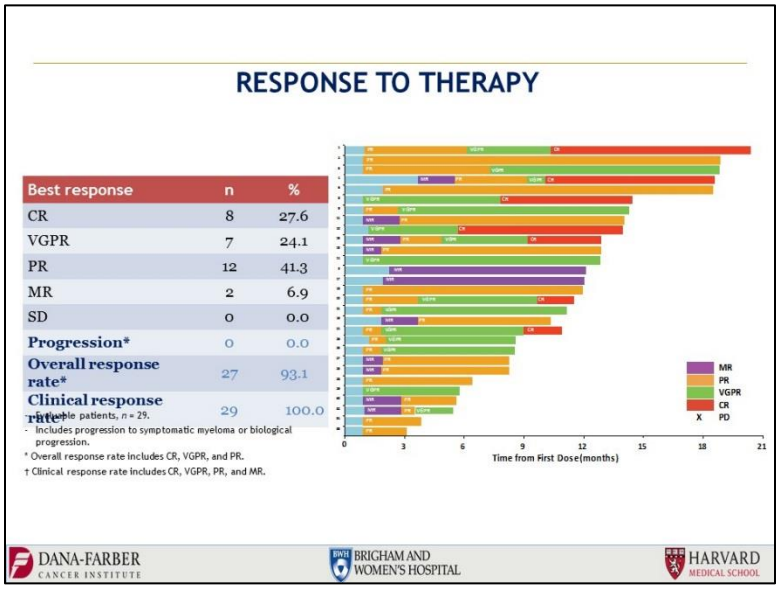
So, this is inclusion and exclusion criteria, meaning who is allowed to go on it and who is not; and basically, we're saying we don't want people who have active myeloma, but we want people who have high-risk smoldering myeloma, and these are the criteria.



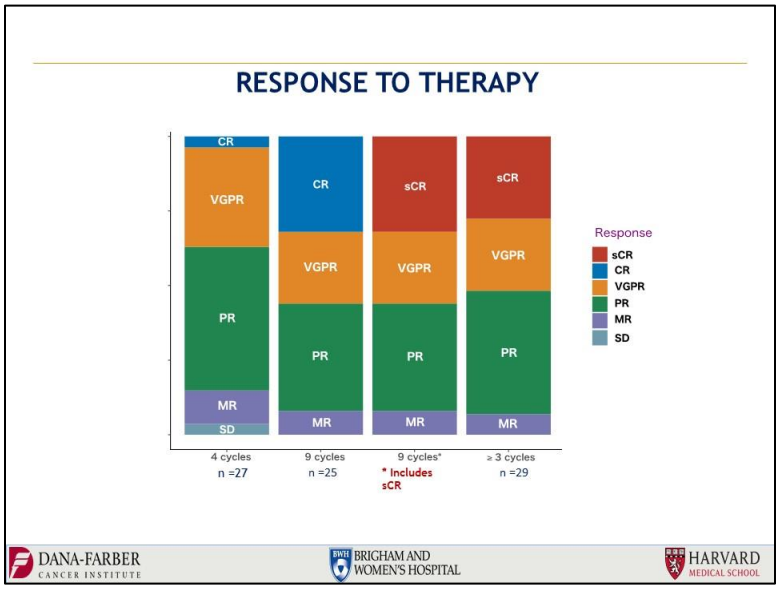
And we treat those patients, and we're still ongoing in treating patients with the three-drug combination, all oral. Then we do stem cell collection. Then we give you maintenance therapy, meaning no more steroids, just a lower dose of the ixazomib, lenalidomide for two years' treatment total, and then we continue follow-up.



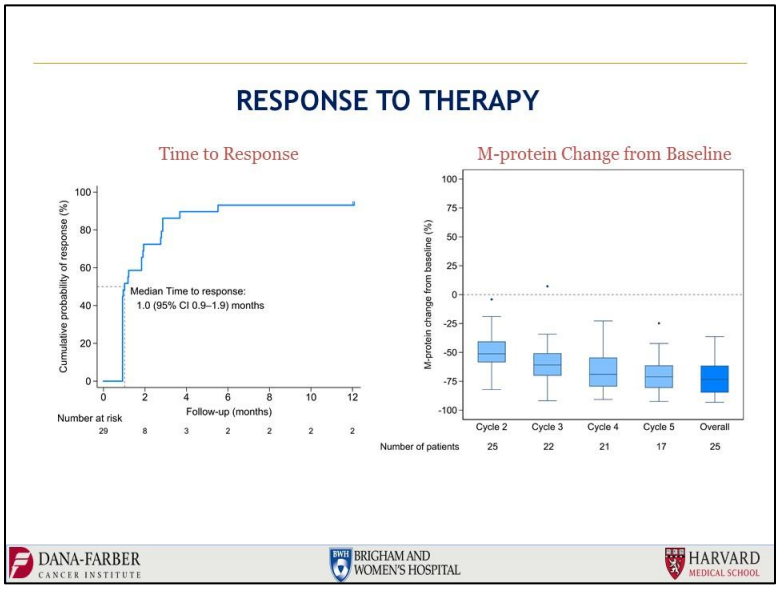
And, again, this is the data on the first 29 patients on this study, and you can see that many of them had very high plasma cells or cancer cells in their bone marrow, up to 55%. Some of them were young, as young as 40, as old as 73, and, again, many different types—IgG or IgA, having chain, light chain, and so on.



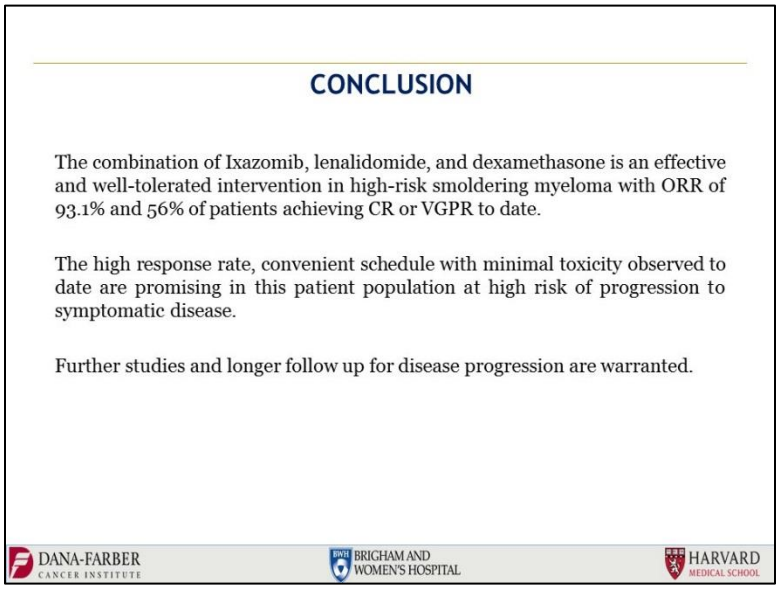
And you can see here that 100% of the patients responded to therapy. Every person has responded to therapy. And if we look at if they had a deep remission, meaning complete remission, you have 27% of them. Very good partial remission, which is 90% reduction, another 25% of the patients.



So more than half of the patients had a very deep remission, and we're trying to see if these patients are the ones who had something called MRD-(minimal residual disease) negative, meaning potentially, they could be cured, but we don't know that until we follow them for years and years.



So, again, very exciting to see with a three-pill drug combination we can have such a high response rate. And it happens very fast. Within the first month we start seeing people respond to this treatment.



So, again, an exciting time for us to see that potentially something as simple as three oral drugs could give us this high response rate with more than 50% of the patients having deep remission, meaning complete remission and very good partial remission.

So, I'll stop here. I know I speak very, very fast; but I wanted to make sure that you have time for questions, for thinking about what are the things we want to think of, and trying to understand better what do you want to do, and what are the potential options for people in the future for multiple myeloma.

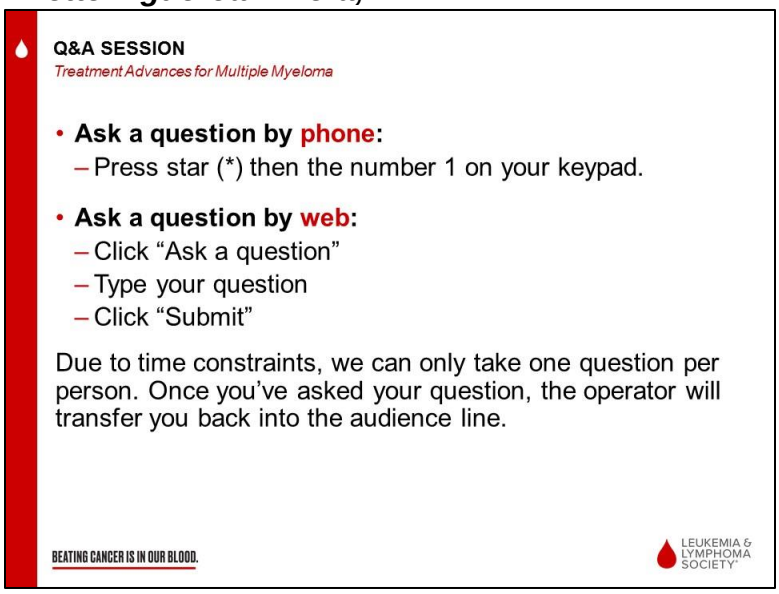
So, I'll say thank you again.

Lizette Figueroa-Rivera, MA

Well thank you so much, Dr. Ghobrial for volunteering your time with us today to update us on the current advances in myeloma.

QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA



It's now time for the Question & Answer portion of our program.

Lizette Figueroa-Rivera, MA

We'll take the first question from our Web audience. Doctor, Kim is asking if patients with active myeloma can also submit samples as well as to predict progression and/or high-risk components of the myeloma as it would be very valuable for patients to know.

Irene M. Ghobrial, MD

Yes, absolutely, but not through the PROMISE study. So, the MMRF (Multiple Myeloma Research Foundation) has been doing a study called CoMMpass℠, and then they've launched another study called Myeloma Cloud (MMRF Curecloud™) and we collaborate very closely with the MMRF. It's still in the first steps of launching it, so stay tuned. And everyone can submit samples, and I think the Myeloma Cloud, which is through MMRF will be something important to help you understand that.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from our Web audience. Don is asking, "Can multiple myeloma morph into other kinds of cancer?"

Irene M. Ghobrial, MD

Usually not. We've seen some patients with myeloma who have also amyloidosis or myeloma who progressed to something called plasma cell leukemia. So, these are the same steps of the same type of plasma cells but just different behavior, but it's not a different cancer completely.

Lizette Figueroa-Rivera, MA

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

Operator

Thank you. Our first call is from Richard from New Jersey. Please state your question. Your line is now live.

Richard from New Jersey

My question is I have stem cells stored, and can I request my doctor to check the stored stem cells for mutations in DNA?

Irene M. Ghobrial, MD

That's a great question. Unfortunately, not yet. Once we have this data validated in a large cohort, we will have this available for everyone on how to test for those CHIP mutations. It's not a test that's available clinically yet everywhere.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from the Web audience. Doctor, Brian is asking how to deal with extreme neuropathy after usual drugs have been tried and have had no response.

Irene M. Ghobrial, MD

Yes, it's a great question. It depends on the cause of the neuropathy. So, of course, we want to make sure this patient does not have amyloidosis or POEMS or Waldenström or anti-MAG antibodies. If it's caused really by Velcade® (bortezomib) or thalidomide. So, there is a lot to be checked first. And then we usually work with our neurology colleagues very closely so that we can understand what's causing the neuropathy and then how we can treat it effectively after that.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Patricia from Tennessee. Patricia, please state your question? Your line is now live.

Patricia from Tennessee

Yes, I had seen you one time in Boston. I now live in Tennessee. I was first diagnosed with Waldenströms macroglobulinemia and then also non-Hodgkin's lymphoma and now I'm being told I have multiple myeloma. I'm being told that through my blood samples of the IgM and so forth. But my question would be I seem to be falling apart, my bones. I don't know if this is part of it or not. And I've been treated with two different kinds of chemo. But right now, I'm supposedly in remission.

Irene M. Ghobrial, MD

So that's wonderful that you're in remission. Again, it's very hard to comment on the phone on different diagnosis, but, again, it's hard to know whether indeed the diagnosis originally was really Waldenström or it was an IgM myeloma. But, again, it sounds like your doctors have done the right thing and have given you the right medication. So, congratulations on that.

Lizette Figueroa-Rivera, MA

Thank you for the question. And the next question, doctor, you had mentioned plasma cell leukemia, and Denise is asking, "How is plasma cell leukemia related to myeloma and is it treated the same way?"

Irene M. Ghobrial, MD

Great question. So, plasma cell leukemia is basically a lot of the plasma cells or the cancer cells that start circulating in the blood instead of just sitting inside your bone marrow. So, most patients with multiple myeloma, believe it or not, have small numbers of cells circulating in the blood, but we don't usually detect it regularly. But if they start increasing more and more and more, then we call it plasma cell leukemia, which just means cells are circulating in your blood. So, it's not that different than regular myeloma other than it's probably more aggressive and we need to treat it more radically. We usually use combinations of chemotherapy. Of course, it depends on the stage, have you received treatment before or not, but we usually use a three-four drug regimen to try and get rid of those cells, but also, of course, getting rid of the bone marrow cells because they're the source of those cells going into your blood.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Solomon from California. Solomon, please state your question. Your line is now live.

Solomon from California

I'm asking, I'd like to join the research and I didn't get a phone number?

Irene M. Ghobrial, MD

Oh, that's wonderful. So, it depends. If you want to join the PCrowd, if you have MGUS or smoldering myeloma, you join the PCrowd, P-C-R-O-W-D. And, again, if you just Google Search Dana-Farber and PCrowd, you'll find our website. If you're looking to join the PROMISE study or if your family members are interested in the PROMISE study, then it's promisestudy.org. Again, we can maybe communicate that information back to The Leukemia & Lymphoma Society and have it available to everyone.

Lizette Figueroa-Rivera, MA

Yes, and you can also call an Information Specialist here at The Leukemia & Lymphoma Society. And I am going to say the phone number directly to the PROMISE study after the Question & Answer session.

Doctor, the next question comes from Gwen, "Can you discuss the new treatments for people with active multiple myeloma?" I know that you were just at the American Society of Hematology [Annual] Meeting, and I know that there's a lot of excitement with multiple myeloma treatments.

Irene M. Ghobrial, MD

Yes, absolutely. And we always have a new change and a new modality. Right now, what we were using is three-drug combination therapies, so an immunomodulator, a proteasome inhibitor, and dexamethasone for upfront therapy. Now we're starting to say likely we will be adding a fourth drug like an antibody daratumumab to the combination of therapy. So that was one of the big things that we were talking about in ASH this year.

For the relapsed setting, there's a lot of new drug therapies that we're thinking of. One of them is immunotherapy like CAR (chimeric antigen receptor) T therapy. So that's an immunotherapy to try and activate T-cells to go and attack cancer cells. And there were a lot of studies about that that were very, very promising. This is more for the relapsed setting.

And then there are new drugs, something called venetoclax and other ones like bispecific antibodies. A lot of new things coming along so that we can use them for the treatment of myeloma.

Lizette Figueroa-Rivera, MA

Thank you. And on the same lines, Maurice is asking how effective is immunotherapy? He started on elotuzumab, which is Empliciti™ and was told that there's an 85% success rate. Is that so?

Irene M. Ghobrial, MD

Elotuzumab is a great drug and, again, when used in combination with thalidomide and dex or pomalidomide and dex, it gives us a very high response rate. That does not mean that you personally would respond to it. So, again, in general, we look at numbers of people and their response rate, but we cannot predict for an individual whether they will respond or not.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Janelle from South Dakota. Janelle, please state your question. Your line is now live.

Janelle from South Dakota

When a person goes into remission, some doctors feel that I guess you can perhaps go off your drug, your chemo drug and others think you should continue, do it on an ongoing basis. If you do continue with Revlimid and dexamethasone, can you reduce the amount of Revlimid, the milligrams of Revlimid that you take in terms of an ongoing therapy?

Irene M. Ghobrial, MD

Yes, absolutely. So, in maintenance therapy, we usually remove the dexamethasone and we give a lower dose of Revlimid, 15 milligrams or even 10 or 5 milligrams of Revlimid. So, yes, we do reduce it when we go on maintenance therapy. In general, we do like to have maintenance therapy in multiple myeloma. Some of the data shown in ASH this year we are even considering ixazomib, which is an oral proteasome inhibitor, as also maintenance. So there has been multiple studies that show that maintenance therapy has benefits for patients with multiple myeloma.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Geraldine. Geraldine is preparing for her stem cell transplant later this month and would like to know what her main concern should be and what questions are appropriate to ask her doctor pertaining to her transplant.

Irene M. Ghobrial, MD

Yes, that's a great question. Being your own advocate and knowing exactly what to expect is very important. I think just having a good knowledge of what to expect – what are the side effects, how long will you be in the hospital, how long it will take you to recover and get back to work or to feeling normal – are all questions. I'm sure there are either LLS or MMRF or IMF (International Myeloma Foundation) commonly asked questions as well as your doctor will give you a lot of information. We usually here at Dana-Farber spend a couple of hours just going through the teaching session of expecting transplant and what to expect from it.

Lizette Figueroa-Rivera, MA

Thank you. And, yes, we do have a list of questions to ask your physician. And at the end of the Q&A session, I will also give the number to our Information Specialists that can provide that to you.

Our next question coming from the telephone, please.

Operator

Our next call is from Ralph from California. Ralph, please state your question. Your line is now live.

Ralph from California

Hey, doctor, we're told that myeloma can be induced by a weird list of modern irritants like radiation, Agent Orange, contaminated polio vaccines, whatnot. Can you get a researcher like yourself or maybe the LLS folks to do a broad survey of the tens of thousands of patients with myeloma and maybe get a simpler list of say correlated factors, maybe not causes, but things like something we could, like, foods, insect bites, chemicals, mold, lack of sleep or those kinds of things? Look back a century or two in history and say if maybe some of the pneumonia deaths were actually end-stage myeloma and what kind of exposures they had so we cannot further irritate our immune system hoping to slow progression or relapse.

Irene M. Ghobrial, MD

Yes, it's a great question. And, you're right, they may not be causative, but eventually correlating with increased progression or faster progression or changing your environment. And the problem is some of those studies are very hard to do because it needs thousands and thousands of patients because of potential problems with deciding whether this is, indeed, correlating with it or not as you know.

So, some of the questionnaires that we send to people either through the PCrowd or the PROMISE study are actually asking you questions of environmental exposure, of medications, of other things, of obesity because, believe it or not, obesity is linked to inflammation and potentially progression; of medications like aspirin or metformin because maybe those will decrease risk of progression. So, we have long questionnaires.

So, if you get one of those questionnaires, don't get tired of us asking you again and again have you been exposed to this or that or this or that. It's because we want to actually understand that better.

Lizette Figueroa-Rivera, MA

Thank you. That was a very interesting question. And Mary is asking, "What is the best way to monitor treatment effectiveness for completely non-secretory patients?"

Irene M. Ghobrial, MD

Yes, that's a hard one. So, we usually, unfortunately, do either imaging by PET scan or MRI and see if we have something to follow or by bone marrow biopsies because we don't have any other good measure.

Lizette Figueroa-Rivera, MA

Thank you. That is a difficult question. And the next question is coming from Michael. Michael is asking, "How long can one stay on maintenance therapy when managing multiple myeloma?"

Irene M. Ghobrial, MD

Yes, it's controversial. There are some studies that say maybe a couple of years is enough. There are other studies that are ongoing for a very long time. We don't really have a good sense when to stop. We're doing current studies now where we ask the question if you are MRD negative for a long time, let's say one year, can we stop safely maintenance therapy and hope that indeed this is a cure? So, we don't have a good answer yet. We're hoping that will happen in the future.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Nancy from Idaho. Nancy, please state your question. Your line is now live.

Nancy from Idaho

Yes. You mentioned how genetics might play a part in multiple myeloma. And I'm wondering if you have any idea of the percentage of time that genetics do play a part. Is there a good chance that multiple myeloma patients' son or daughter will get multiple myeloma?

Irene M. Ghobrial, MD

Yes, great question. So, we don't know that it's an inherited disease, but potentially we inherit a susceptibility gene, meaning it's not like breast cancer where strong family history happens, although

we've seen family histories where every generation there is a person who has myeloma or MGUS. So, these are the ones that we're sequencing their gene line to really understand do they have an inherited gene. But in most other cases, we don't see that strong of a correlation. So maybe they inherit something that makes them susceptible to develop myeloma or something else that weakens the immune system. And we're trying to understand that through the PROMISE study. So, by having 50,000 individuals, and that's why I'm saying please enroll on it because it's the only way we can answer all those questions, then we can understand family members and why are they susceptible for this.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from the Web. Marie is saying that she's regarded as smoldering myeloma, but her last urine in November showed protein present. What does this mean in terms of the progression of the myeloma and the state of her kidneys? None of her other labs have changed.

Irene M. Ghobrial, MD

Yes, the presence of protein in the urine does not mean anything because all of the light chains and the monoclonal protein get excreted in the urine at the end of the day. So, it just means that the light chains that you have are going out in the urine. It does not change your staging.

Lizette Figueroa-Rivera, MA

Thank you. And Suzanne is saying that she has high-risk smoldering multiple myeloma and is asking how long might it be before the three-pill protocol you discussed might be available for smoldering?

Irene M. Ghobrial, MD

So, I would encourage her to either come and see us for a consult and we can discuss it because we have that trial available in other sites, not just at Dana-Farber, or look up www.clinicaltrials.gov and see all the clinical trials available. Right now, there is no standard of care for treatment of smoldering myeloma. It's all on clinical trials until something gets approved.

Lizette Figueroa-Rivera, MA

Thank you. And Batina is asking about treatment advances without dex for people who have myeloma but are not in remission and have decided against transplant.

Irene M. Ghobrial, MD

Yes. Great question. There are lots and lots of options even without transplant, including antibodies, of course, like daratumumab, elotuzumab, new monoclonal antibodies that are coming along. If someone has 11;14 translocation, venetoclax. So, there is a lot of options coming out and, again, discussing it specifically with your doctor.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Robert from Maryland. Robert, please state your question. Your line is now live.

Robert from Maryland

You indicated, or you stated, that one has a 1% chance of developing multiple myeloma each year after the diagnosis of MGUS. Is there any data that shows the longer you don't move into multiple myeloma that 1% chance goes down?

Irene M. Ghobrial, MD

No. Interestingly, it keeps on 1% per year. So that shows you that in the 10 years, 20 years after, there's still a very high chance of progressing to myeloma.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from the Web. Patricia is asking, "What are the signs to look for that the maintenance medication isn't working anymore?"

Irene M. Ghobrial, MD

So, in general, we consider it progression when the monoclonal protein keeps going up, and we consider it response when the monoclonal protein goes down, whether it's the M spike or the light chains. And stable disease means it's fluctuating within that same area where it was. Again, there are specific numbers that we use, 50% reduction, 25% increase, and so on but, in general, we use your monoclonal protein, which is either your M spike or your light chains to measure your disease.

Lizette Figueroa-Rivera, MA

Thank you. And Linda is asking, "How often should FISH testing be done?"

Irene M. Ghobrial, MD

Yes, great question. I would advocate every time people get a bone marrow biopsy because things change. So, in the old days, we used to say, "Well, it's good enough to have it the very first time and that's it." Unfortunately, we know that that's not correct. Things do change. Something called clonal evolution. So, after treatment, you may actually have new completely different FISH changes, and these may actually tell us which therapy to use in the future. So, I would consider doing FISH and cytogenetics every time.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Phyllis. Phyllis is asking, "When treated for an additional type of cancer other than multiple myeloma, can different chemotherapies or radiation affect the myeloma?"

Irene M. Ghobrial, MD

Great question. It depends, of course, on the treatment options and whether they are effective for myeloma or not.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Nicole from Pennsylvania. Nicole, please state your question. Your line is now live.

Nicole from Pennsylvania

Yes. My question is I've had smoldering myeloma for six and a half years. Was on Revlimid, did well, M protein is ugh. I think the last time I had a bone marrow biopsy it was like maybe 1. Every time I get my blood drawn my M protein is like 0.3. It has now reached like 0.6. So, my question is I know the next time that I go I'm going to have to go and get a biopsy and all of that probably in January. But I know my doctor always asks me, "Have you fallen? Have you fallen?" And I always, "No, haven't fallen." But I actually did fall maybe about a month ago. And as I was listening to this program, I was looking in my phonebook to call over to my doctor's office. Just we had like a little light snow and I fell. So, when the doctors do ask, like, "Have you fallen?" with the smoldering myeloma, what does that mean? Does that mean if you fall, that you have a possibility of like injuring something else related to smoldering myeloma?

Irene M. Ghobrial, MD

Yes, great question. I think your doctor is asking you, "Have you fallen?" because he's worried about fractures of the bones, which means that you now develop active myeloma. Remember, I said there is four criteria that we use for myeloma. One of them is bone fractures.

Well, what usually happens is people don't fracture their bones like this on their own. It would be a minor fall. You just fell off from something or on the stairs or just when you're walking. And for a normal person, this should not cause a fracture of your bones. For someone who has weak bones because of myeloma, this could cause a major fracture. So, he's probably just worried about just making sure that your bones are healthy and there's nothing that has happened recently.

Lizette Figueroa-Rivera, MA

Thank you and thank you for the question. The next question is coming from Ellen. Ellen is asking, "How important is the bone marrow biopsy for a relapsed patient if all indicators are within normal limits and the patient has no other issues? Tolerating maintenance drugs well after second stem cell transplant. And is a 24-hour urine collection necessary?"

Irene M. Ghobrial, MD

Great question. So, we do bone marrow biopsies only if we're thinking someone is in a complete remission and we want to prove it, or someone is progressing, and we want to prove it, but you don't have to routinely do bone marrow biopsies all the time.

As far as 24-hour urine, it's a great point. Everyone hates collecting that big jug of urine and then you leave it on the train or on the bus or you're flying through the airport and they tell you "Check it" and all of this that happens with 24-hour jugs. We think that likely the light chain, the serum-free light chain can reflect exactly what happens in the urine. So, in the future, most likely, we will stop collecting those jugs of urine from you.

Lizette Figueroa-Rivera, MA

Thank you. The next question comes from Beth. Beth is asking, "What type of test gives you MRD (minimal residual disease) negative results?"

Irene M. Ghobrial, MD

Yes. There are two different tests that we use for MRD. One of them is done mainly in Europe by the Spanish, which is a flow cytometry. So, we don't do that one here routinely. The other one is a sequencing study, which is done by a company called Adaptive. And this is a kit that basically we order, and we send your sample to the company and it gets us the MRD data.

Lizette Figueroa-Rivera, MA

And MRD is minimal residual disease. How important is that in myeloma right now, doctor?

Irene M. Ghobrial, MD

It's a very important test. In fact, the FDA just approved it for us as a test for myeloma, which is very important. That means that if you're in a complete remission, you likely still have thousands and thousands of cells in your bone marrow. So complete remission may not be enough anymore for us to say indeed you have a deep, deep remission. And we know that the deeper we get, the likelier chance that you will have longer remission and potentially a cure. So MRD is basically trying to count even if it's a small number of cells. So, one in a million we can detect. And this is why it's important now to start thinking of doing MRD. It's not available everywhere yet, but now that the study has been

approved by the FDA, insurances are starting to pay for it. You'll find it being ordered by many physicians as we go along.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call comes from Steve from New York. Steve, please state your question. Your line is now live.

Steve from New York

Hi. Okay, I'm a multiple myeloma patient. I was diagnosed in 2011. Had a stem cell, chemo and radiation stem cell treatment in 2012 and was in remission for about four years and now have a low level, which is being maintained. But what I'm wondering is in the mention of I think it was the PROMISE study qualified people for that included relatives of a person with multiple myeloma. Would that include children in the ages of in the low 30s, low to mid-30s ages?

Irene M. Ghobrial, MD

No, they have to be 45 or higher. So, brothers, sisters.

Steve from New York

Okay, so it's both. Not just relatives.

Irene M. Ghobrial, MD

Exactly, any relative, first degree relative as long as they're over the age of 45. But thank you for asking and encourage all your family members.

Steve from New York

Okay, thanks. Okay, thank you.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Estella. Estella asks, "I'd appreciate knowing the current thinking on using Zometa® (zolendronate) as a maintenance therapy. I've been on Zometa on and off for some time now. Are there any new alternative drugs for myeloma maintenance purposes?"

Irene M. Ghobrial, MD

Yes, great question. We're starting now not to use maintenance for years and years because Zometa can inhibit your osteoclasts so much that we start having actually fractures from lack of turnover of the bones. So, there is data, and, again, it's very hard to do long-term studies of maintenance that indicate potentially we don't need it that much. In general, we think that Zometa is important for early when you're diagnosed with myeloma. We're starting to say that there is data that says every three months instead of every month is actually useful. And we need two or three years at the most. If you're in a complete remission, you may not need it that much anymore, but people who have active disease we restart them on therapy again. So, if they relapse, we restart them on it again.

There are new drugs RANK (receptor activator of NF-kappa B) ligand inhibitors and others, DKK1 inhibitors and all of that. The long-term follow-up that we've had with Zometa makes us still interested in using it. If you have renal failure, then we start thinking of other options or alternative options that would give us the same benefit but not any better survival compared to Zometa.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Donald. Donald is asking about the combination of Pomalyst® (pomalidomide), dex and Ninlaro® (ixazomib) if there's any data in regard to this combination.

Irene M. Ghobrial, MD

Pomalyst, dex and Ninlaro. So, yes, of course, there is data, and we use it a lot in the relapsed/refractory setting. I don't know if it's published or not. There should be some publications on it, but, absolutely, we can use ixa-pom-dex (ixazomib-pomalidomide-dexamethasone).

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from William from New Jersey. William, please state your question. Your line is now live.

William from New Jersey

Doctor, you mentioned neuropathy as a result of Velcade. And I've been on Darzalex® now for five months, and my neuropathy it started when I was diagnosed in May of going from smoldering to active myeloma. Will that neuropathy ever decrease going forward or am I stuck at this level forever?

Irene M. Ghobrial, MD

So Darzalex, which is daratumumab, usually does not cause neuropathy. So, I would wonder if there is an underlying cause for your neuropathy. And, again, we do a workup for amyloidosis, POEMS, other potential causes for neuropathy in your case.

William from New Jersey

And so, should that be done by a neurologist or can my oncologist?

Irene M. Ghobrial, MD

Yes, or your oncologist.

William from New Jersey

Okay, I'll ask him that. Thank you.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Nancy. Nancy is asking about, "Any interaction of green vegetables with certain chemo drugs or anything in regard to nutrition that people should avoid while on some of the medications for myeloma?"

Irene M. Ghobrial, MD

Yes. We've known about green tea, for example, or high doses of vitamin C with Velcade could have interaction. So just let your doctor know if you're taking other medications or herbal things before you start chemotherapy and just let them know so that they can see if there are interactions between them.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Danita. Danita asks, "Do you hear of many patients complaining of their bones popping or clicking with Revlimid maintenance?"

Irene M. Ghobrial, MD

I have not heard of that complaint, but I'll look for it now as you said it. But, no, usually we don't have popping or clicking. That usually means cartilage problems, so that's likely your joints rather than your actual bones. So, see if you have some arthritis and maybe you would benefit from just further investigation into that.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call comes from Elise from Texas. Elise, please state your question. Your line is now live.

Elise from Texas.

Yes. Doctor, I have multiple myeloma. I've stopped and stayed off of all of my drugs. I got mad for about two years, and I had a tooth pulled and had a hemorrhage. And now the dentist knew that I had had cancer from their examination. So, I went back to my oncologist and been put back on a regimen. But I was wondering how important is diet? And I'm taking dexa[methasone] something and one other drug called Adriamycin® (doxorubicin). And I had a body scan for my bones, but since then, that was about I'd say a month ago, and he hadn't brought it up on the full body scan. So, I'm going to ask him about what happened or what was shown up. So, what do you recommend? I'm pretty hard headed too.

Irene M. Ghobrial, MD

So, I would say, again, for diet, we do not have any specific diet recommendations. For body scan or bone scans, we usually don't do imaging unless, again, we're starting you on a new treatment; we're looking for response or we're looking for progression. But we don't have to do a lot of imaging. And usually it's either skeletal surveys, which are body X-rays or better, of course, PET/CT scans or MRIs. Usually we follow your monoclonal protein in the blood. But, again, depending on the cases, some people don't secrete that much and that's why they need body scans.

So, again, yes, definitely talk to your doctor about your specific follow-up of your treatment, but there are no specific recommendations for diet other than just a good healthy diet.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Dean. Dean is asking how to recognize what chemo is causing what side effect.

Irene M. Ghobrial, MD

Yes. So, there is a list of potential side effects. As you talk to your doctor and you start a new therapy, I'm sure they will discuss with you potential side effects. And usually we give our patients also all of the other lists of side effects, the rare ones. You can find them online. I'm sure on LLS and MMRF [Websites] there are all the medications with their side effects. And, of course, ask your doctor.

Lizette Figueroa-Rivera, MA

Yes. Definitely. And we'll take the next question from our telephone audience, please.

Operator

Our next call is from Francis from Oregon. Francis, please state your question. Your line is now live.

Francis from Oregon

Yes. I'm 89 years old, and I get frustrated because all the discussions I ever hear relate to people younger than that. and I wonder am I too old to qualify for studies? What does an older person do?

Irene M. Ghobrial, MD

So, I'm so glad that you asked this question, and congratulations for an amazing life. And absolutely not, we do not disqualify patients based on age. In fact, we do not have an upper limit for age on any of our trials. And I can tell you when I was in a meeting with the FDA recently because stem cell transplant used to have an age limit. We used to say at age 65 or 70. And they actually said, "Stop having ageism." And now that we're in the era of no sexism and no this and no that, this is the era of saying no ageism. So absolutely not. We never say no to anyone who's doing well and healthy and is 89 or 90 or older. Just talk to your doctor about qualifications.

Lizette Figueroa-Rivera, MA

Thank you. And our next question from Robert. "I'm in posttransplant remission from myeloma, and my maintenance therapy is Revlimid and prednisone. What's your opinion of using prednisone instead of dexamethasone?"

Irene M. Ghobrial, MD

Yes. It's a great point. I don't usually add any steroids in the maintenance therapy. So, again, I'm not sure why your doctor is adding it. Could be just to prevent some of the side effects but maybe talk to your doctor about it.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Patricia from Tennessee. Patricia, please state your question. Your line is now live.

Patricia from Tennessee

Yes. I am on or I had been on Rituxan® (rituximab) and Velcade with Privigen® (immune globulin intravenous) given in between. Does that sound like a good regimen to you?

Irene M. Ghobrial, MD

So that's for Waldenström probably because of the Rituxan part. So, again, it's hard to know which regimen is for which disease, but maybe discussing that specifically for your doctor is the best option.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Bridget. Bridget is asking, "What is the relationship between multiple myeloma and heavy chain disease and the treatment relationship?"

Irene M. Ghobrial, MD

Yes. So just heavy chain disease in a specific organ could be related to multiple myeloma. It depends, of course, on what's going on and making sure that there is no other complication and what is exactly going on. Is it the heavy chain deposition? Do you have also myeloma or not? So, I think this is also very specific question with specific discussion with your physician.

Lizette Figueroa-Rivera, MA

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

Operator

Our next question is from Joe from Florida. Joe, please state your question. Your line is now live.

Joe from Florida

My question is I have been diagnosed since last year, 2017, I guess. And they gave me massive doses of radiation in my right chest because they said that's where the myeloma was presenting. And I constantly have pain in my right chest. Could this be caused by the radiation itself or is it part of the myeloma or what? Because in my particular case, I'm on my third oncologist in a year. The other two left for greener pastures, and I don't know if they've lost continuity or not.

Irene M. Ghobrial, MD

Yes, great question. So, again, it's hard to know because it could be pleurisy, it could be inflammation, it could be radiation-induced pain. Again, talking to your doctor specifically about that would be very important and seeing maybe a pain doctor to see if they can help with the management. And I agree having continuity of care with one specific doctor for long-term follow-up is very important.

Lizette Figueroa-Rivera, MA

Thank you, and Jim is asking, "What are the current prospects for relapse and for overall survival for someone who's been in complete remission for five plus years after an autologous stem cell transplant?"

Irene M. Ghobrial, MD

So, congratulations! It's wonderful, of course, to be years and years in complete remission. However, there is still a very small chance that relapse can happen. So, again, continuously seeing your doctor and having close observation is very important.

Lizette Figueroa-Rivera, MA

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

Operator

Our next call is from Sharon from New York. Sharon, please state your question. Your line is now live.

Sharon from New York

Oh hello. Years ago, I had had my thyroid out. They thought it was precancerous cells. And it turns out it wasn't, but ever since then, which was 11 years ago, I ended up neuropathy in my face. So, I'm on gabapentin. So recently I was at a dermatologist. I actually went for like a mole on my leg, and I just happened to ask her. I said, "Listen, I'm getting old and weathered. If I had Botox® (botulinum), would that be a problem on smoldering multiple myeloma?" Now years ago, I was told the Botox might actually help my facial pain. Is there any contraindication of not having Botox with smoldering multiple myeloma? I know the question's kind of out there, but I just thought I'd ask.

Irene M. Ghobrial, MD

Yes, I don't know that there is any contraindication. I mean Botox is a localized, you know, something on the nerve. And I don't know that it would have any effect on systemic issues with smoldering myeloma.

Lizette Figueroa-Rivera, MA

Thank you. And the next question comes from Dante. Dante is asking, "In regard to the symptoms that Revlimid is no longer functioning, I understand the protein change, which I monitor every three months with my doctor, but are there any physical symptoms that would be apparent?

Irene M. Ghobrial, MD

So, the hope is, of course, you don't wait until you have physical symptoms of progression but rather just watching carefully with the monoclonal protein, because we don't want to have anemia and then you have fatigue and tiredness or bone fractures or anything like that. We want to catch it early when your monoclonal protein is going up.

Lizette Figueroa-Rivera, MA

Thank you. And our next question, "How old do children need to be to take the blood test?" I think you addressed this that for this study over 45. But we have been seeing a lot more patients that are younger and younger in age with myeloma here that are contacting us at The Leukemia & Lymphoma Society. Have you also been seeing that, younger patients with multiple myeloma?

Irene M. Ghobrial, MD

So, it's correct we do see young patients. Again, it could be a bias of big cancer centers. So, when someone is very young, they probably would go to a cancer center or they would probably call the LLS. But I don't think that we are now diagnosing myeloma at a younger age in general. I think there's always extremes. In general, myeloma is on the older side when we look at the medians and average, but there are always extremes of young and very old. And we are definitely trying to understand better why myeloma would happen in someone very, very young at age 20 or even younger at age 18 and so on. But these are rare cases. These are not the most common cases.

The PROMISE study, because we're screening a large population, we cannot be looking for the small one event here and there. We're looking for high percentages could be positive. More than 9% or so are potentially positive, although we powered it to be around 6%. So that's why we're screening at age 45.

Lizette Figueroa-Rivera, MA

Thank you. And we'll take another question from a caller, please.

Operator

Our next call is from Linda from California. Linda, please state your question. Your line is now live.

Linda from California

Hi, I'm a stem cell transplant survivor of ten years. And I was diagnosed with multiple myeloma in 2007. And I was in the original EVOLUTION trial. And all of a sudden, numbers are coming back up a little bit. And my doctor at UCSF (University of California, San Francisco) is prescribing Revlimid, dexamethasone, and Cytoxan® (cyclophosphamide) and that was the EVOLUTION plus Velcade. I would love to hear your opinion on that. And the numbers for my myeloma were originally seen in 1991 prior to my breast cancer in 1999.

Irene M. Ghobrial, MD

Yes. So, again, I'm impressed with the long-term follow-up, the long remission. I'm sorry that your disease is coming back after years and years of remission. And this is a very good regimen, and I'm hoping you're going to have a good response again for a long time.

Lizette Figueroa-Rivera, MA

Thank you. And, doctor, I just wanted to ask you following this American Society of Hematology meeting that has just occurred at the beginning of the month, what you were most excited about for newer myeloma treatments.

Irene M. Ghobrial, MD

Yes. I think there is a lot of excitement now of longer remission, of immunotherapy. Like I said, the CAR T therapies are starting to show more and more promising results and potentially newer generations of them. New generations of antibodies, BCMA (B-cell maturation agent)-specific antibodies, whether they are conjugated to a toxin or whether they're bispecific, is a new thing. We're starting to see more novel agents like venetoclax and others. These are being used. Or MCL1 inhibitors. All of these are in clinical trials now.

Again, I'm excited about the smoldering myeloma trials that we showed because we're demonstrating that, indeed, it can make a benefit for us

And, of course, on the sequencing side or the lab side, more and more studies are showing us that, indeed, we can detect small changes in disease and this can predict progression or can predict resistance. So that the future we do something called precision medicine. We don't treat everyone with the same three drugs or four drugs. We start really taking your own sample and finding the right combination of therapy that would work for you.

In the future, all newly diagnosed patients we will be likely using four-drug regimens, not three. And then, again, remission is longer and longer, especially in MRD negative disease patients. And we're hoping myeloma will potentially be a very long remission with many, many years of excellent response and potentially even cure this in early therapeutic intervention.

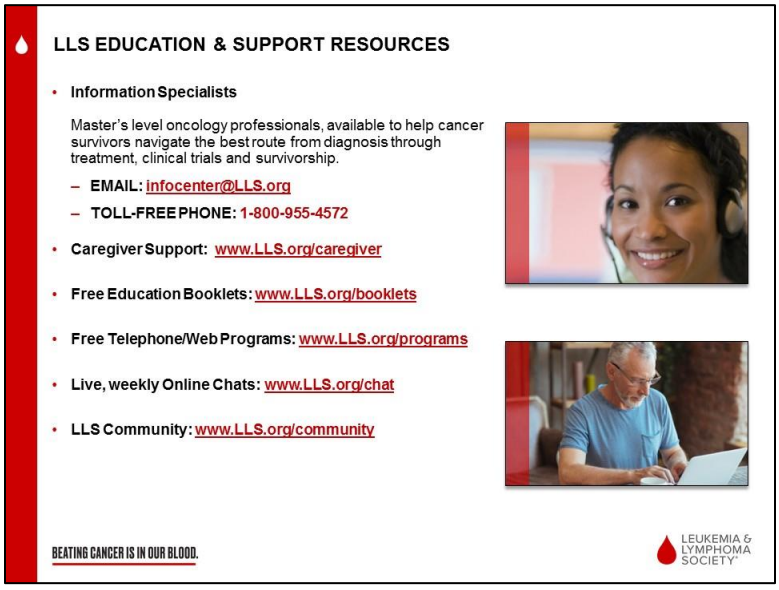
Lizette Figueroa-Rivera, MA

I know we're all happy to see all of the advances that are coming in for myeloma.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA

Dr. Ghobrial, thank you so much for your continued dedication to patients, and thanks so much for providing us with this very important information today.



And if we were not able to get to your question today, please call The Leukemia & Lymphoma Society Information Specialists at 1-800-955-4572. And Information Specialists are available to talk to you from 9 AM to 9 PM Eastern time. You can also reach us by email at infocenter@LLS.org.

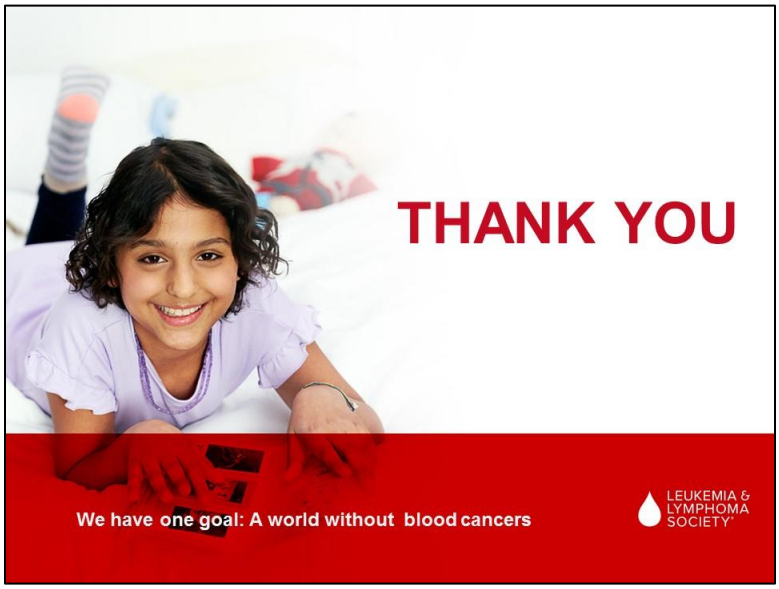
We can provide information about treatment, including clinical trials or answer other questions you may have about support, including questions about financial assistance for treatment. And The Leukemia & Lymphoma Society Patient Aid Program does provide financial assistance to blood cancer patients. And eligible patients will receive $100 stipend. And you can learn more about that at www.LLS.org/finances.

TRANSCRIPT

And as Dr. Ghobrial mentioned, the goal of the PROMISE study is to increase early detection of myeloma precursor conditions in order to develop new therapies that prevent disease progression and improve survival. So, to learn more about this study, as well as how your first-line relative can join, you can call area code 617-582-8544 and that's directly to the PROMISE study. As Dr. Ghobrial mentioned, you can also visit www.promisestudy.org. Again, their phone number directly is 617-582-8544.

Again, we'd like to acknowledge and thank Amgen, Celgene, and Takeda Oncology for partnering with us to support this program. And thank you so much, Dr. Ghobrial, for sharing your knowledge with us today.

TRANSCRIPT



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

Irene M. Ghobrial, MD

Yes, thank you again, and Happy Holidays everyone.