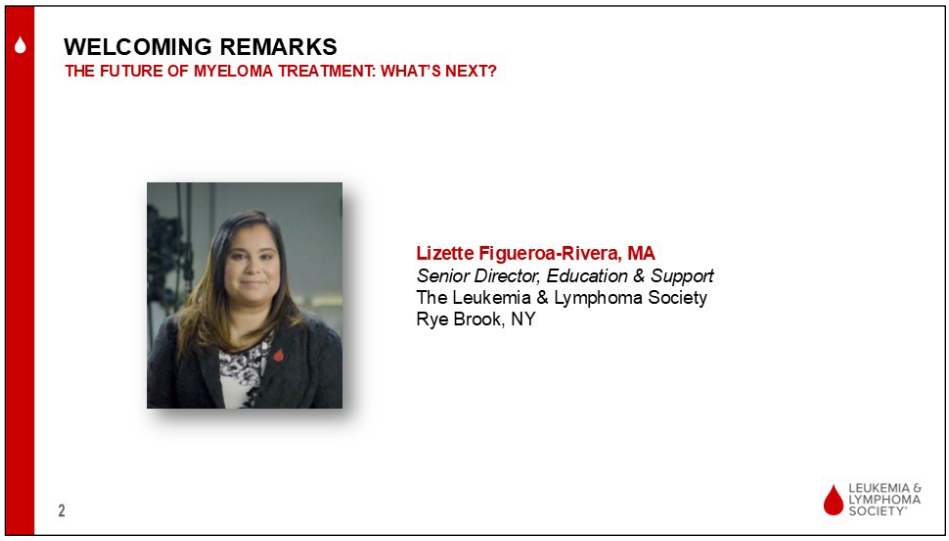
WELCOME AND INTRODUCTION



Lizette Figueroa-Rivera, MA
Hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We are coming to you live from sunny Miami, Florida. Also, a special thanks to Dr. Ola Landgren for volunteering his time and expertise with us today. We also like to thank our in-person audience for joining us today; thank you for being here.

The Leukemia & Lymphoma Society funds leading-edge research for every type of blood cancer. When it comes to cancer, information is power. For many patients and families, coping with a blood cancer diagnosis can be complicated, stressful, and overwhelming. With so much information available online from so many different sources, it could be challenging to know what is accurate or up to date.

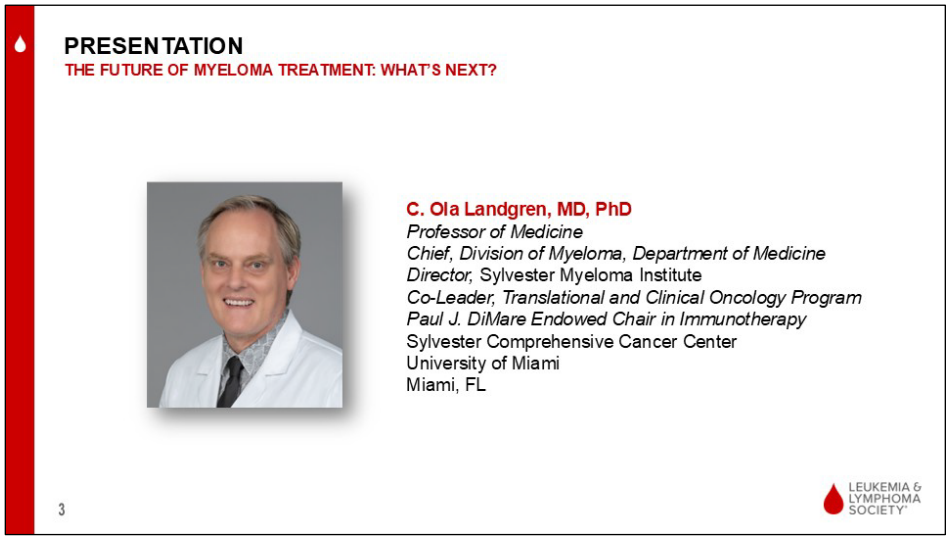
LLS is the leader in free information and comprehensive support for blood cancer patients, families, caregivers, and healthcare professionals. From diagnosis and

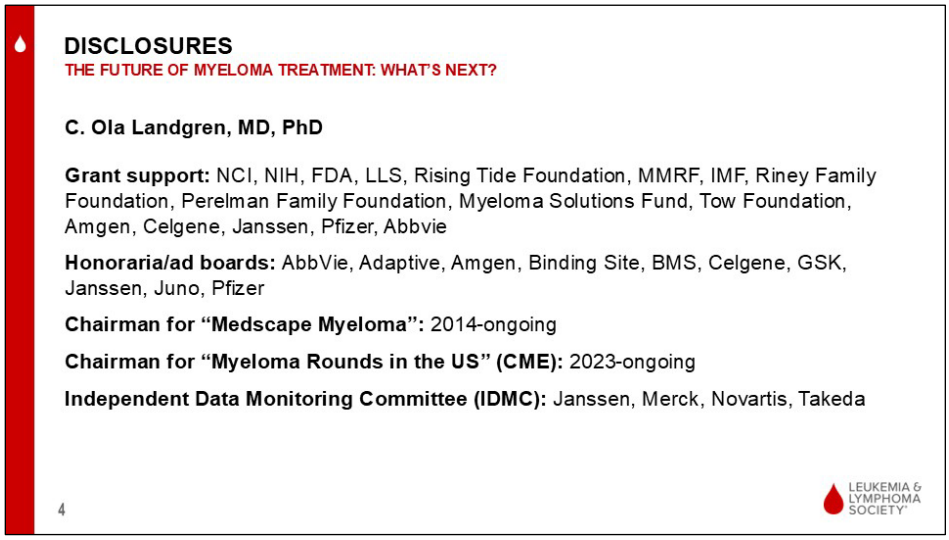
treatment, to remission, survivorship, and ongoing wellness. Let us be here for you during this time, and please continue to let us know what you need from us.

We would like to acknowledge and thank AbbVie Inc., Genentech, a member of the Roche Group, GSK plc, Johnson & Johnson, and Sanofi for their support for today's program, as well as thanks to Sylvester Comprehensive Cancer Center for hosting us today.

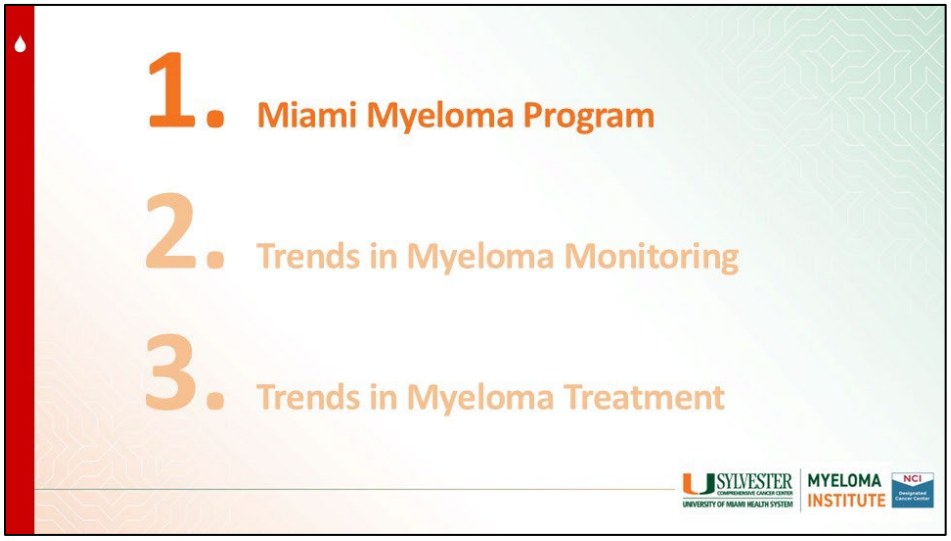
I'm now pleased to introduce Dr. Ola Landgren, Professor of Medicine; Chief of the Myeloma Division and Department of Medicine; Director, Sylvester Myeloma Institute; Co-Leader, Translational and Clinical Oncology Program; and Paul J. DiMare Endowed Chair in Immunotherapy at the Sylvester Comprehensive Cancer Center, University of Miami in Miami, Florida. Dr. Landgren, I'm now privileged to turn the program over to you.

PRESENTATION





C. Ola Landgren, MD, PhD
Thank you very much for those kind introductory words, Lizette. It's really a great honor for me to be here today. I would like to thank The Leukemia & Lymphoma Society for inviting me and for supporting this speaker series. Thank you for everything you do for all our patients and for patients around the United States. That's very, very important work you do. I also would like to thank the audience here in the room for coming, and I would like to thank the audience online. I will do my best to shed light on the topic I was assigned today, which is the future directions of the field.



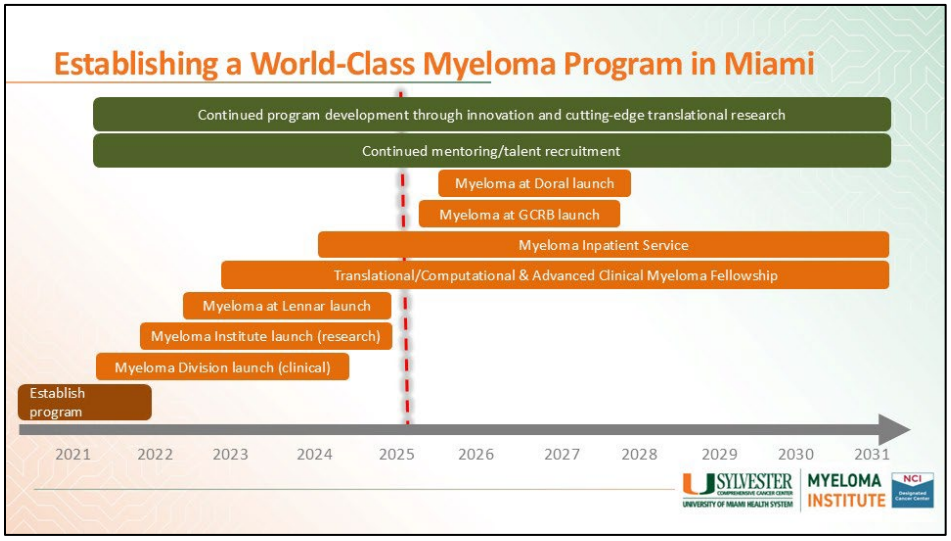
I thought maybe I will give you a brief background of our program here in Miami and then I will turn into two major trends. I will talk about where I see the field going forward in terms of trends for monitoring. I think that's going to be very important in the future; it's been much less important in the past. And then I will talk about treatment. There will be a lot of new drugs. Unfortunately, I will mention a few technical details. I apologize ahead of time if it's too complicated. I'll do my best to try to be more general. If something is too complicated, you can ask me during the Q&A session or you can come up and ask me afterwards and I'll do my best.

I would say that the treatment will change to a very high degree because of all the abilities to monitor. I think in the past this was almost like sending children to school without checking or having any grades or any tests and you just hope for the best. And when the last day at school when they graduate, then you get sort of the full report. That's how the treatment used to be, but with more advanced monitoring, we can monitor things in real time and we can make sure we really stay right on track. This will give us the tools to find a cure for the disease.

I'm convinced that we will establish a cure for multiple myeloma. And I think we already have come to a point where very many patients diagnosed with myeloma will have the same lifespan as a person with the same age and gender. The disease may still be somewhere in the body, but it may not be active, but the lifespan for many patients in 2025 and onwards diagnosed with a disease will not shorten the lifespan. We cannot promise that to every person, and we still don't have an established curative treatment. But, together, the monitoring and the improved treatment will really change this.

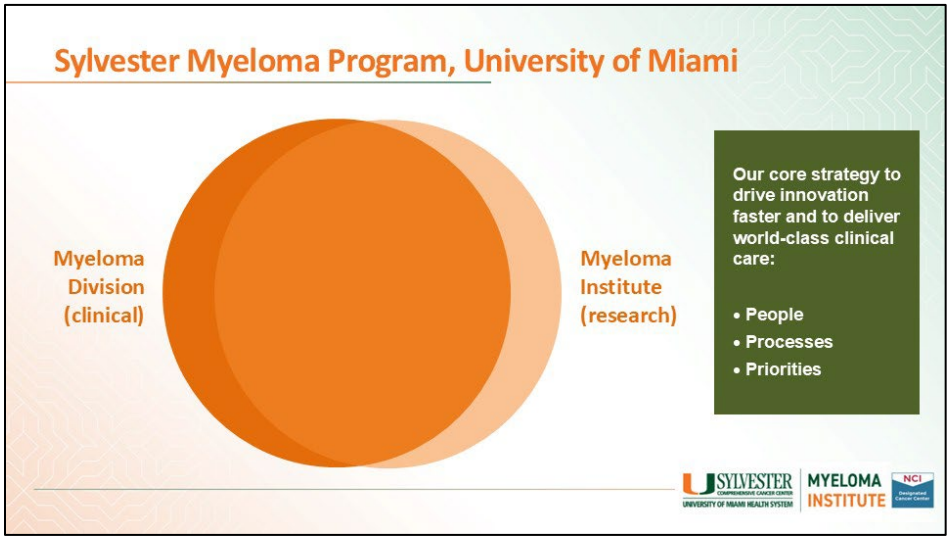
I was born and raised in Sweden, in a university town called Lund, which is from the Middle Age, my high school was from 1085. I started my career at the university there, and I graduated at the Karolinska Institute in Stockholm, Sweden, where I did my MD and PhD and also my fellowship. The Karolinska is a big institution in Northern Europe. It's the home of the Nobel Prize as I'm sure you have heard about. I came 11... Sorry, 21 years ago I came to the National Cancer Institute (NCI) in Washington, D.C., and 11 years ago I moved to Memorial Sloan Kettering in New York. So I spent 10 years in Washington, D.C. and seven years in Sloan Kettering.

I came here in the very end of 2020, and I was employee number four.

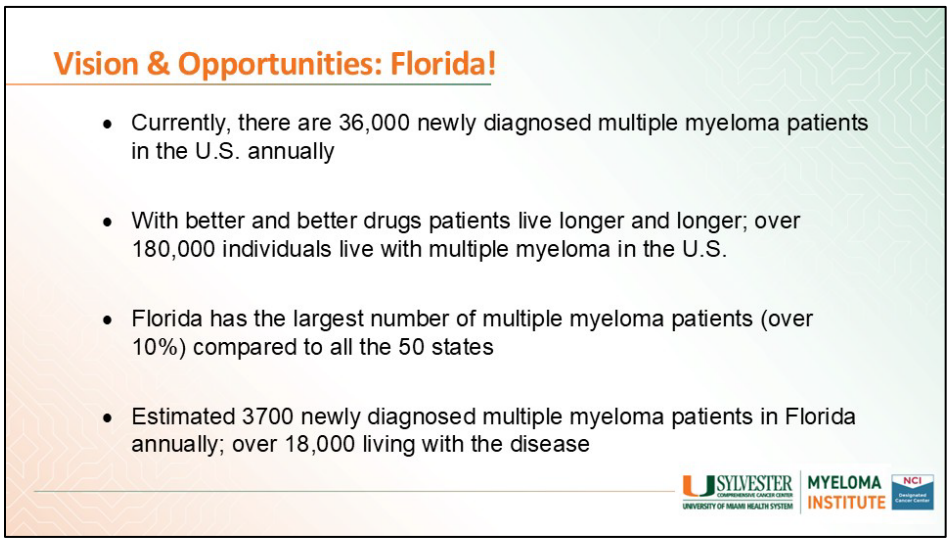


I built an institute for myeloma here together with a lot of friends and colleagues that have come to join us here. We have about 60 people here in Miami working only on multiple myeloma. My mission was to make sure that, within five years, we will be one of the top three programs for multiple myeloma in the United States. And I would say we are right on track for that. I've been here about four years. We have launched an independent division, but importantly we built an institute for myeloma, which holds all the research together. We have launched a presence in Coral Gables, south of Miami, called The Lennar Building. We have opened fellowships that we have created both for clinical training and also translational and clinical oncology. And we also created our own inpatient service.

In a few months, we're going to open up facilities here in Central Miami in the new research building, called GCRB, which is the Griffin Cancer Research Building. We are also opening up in Doral and, in a few months after that, we are also going to open in Aventura. We are here to stay, we do not want to go away ever. We will always be here to help patients here in Miami, and we help patients around the country who want to come here and see us.



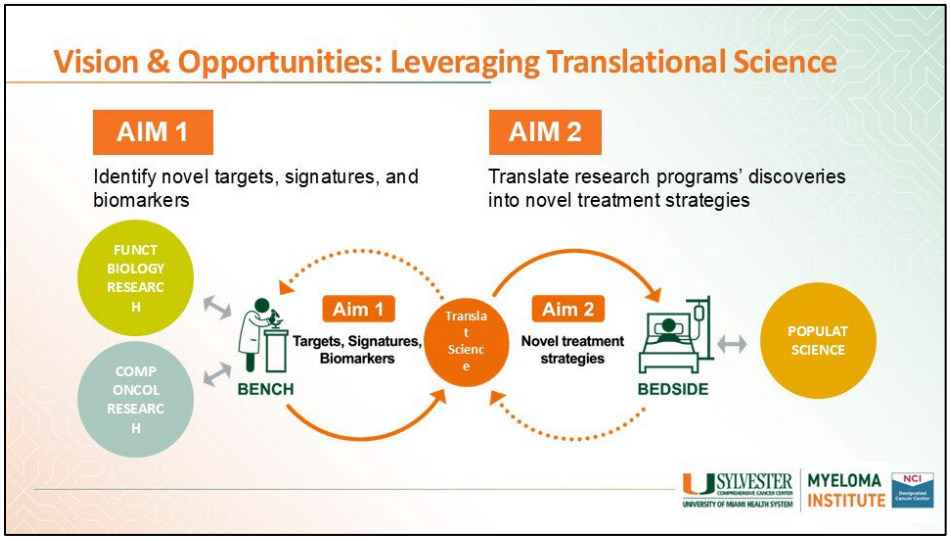
Why do we have a division? Why do we have an institute? I mentioned the division is part of it, but the institute is really what holds all the research together, and that's how we can build into the future. So we can continue to recruit top talent, we can build our processes, and we can make sure that we have the priorities set to only deliver what the patient needs. That is really why we are here.



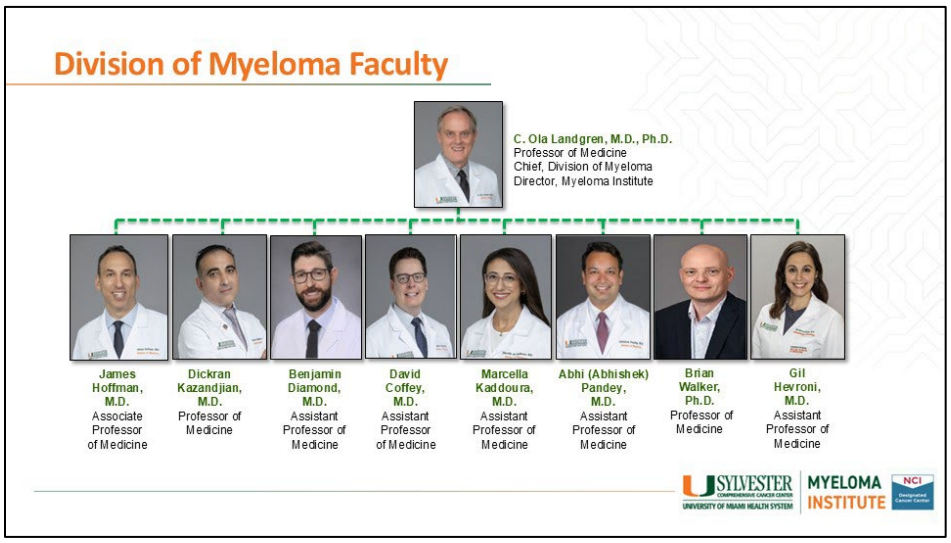
In the United States, there are about 36,000 patients diagnosed every year with multiple myeloma. When I was in fellowship, the survival was only one or two years from diagnosis. And I have seen how this disease has really changed. I mentioned that many patients diagnosed in 2024, 2025, or even '23 or '22 or whatever year will probably have the same lifespan as a person with the same age and gender. The difference is that there will have to be monitoring and some form of treatment, at least for the majority.

There are some patients that I have treated and other colleagues have treated, but they have stopped the treatment and the disease has not come back. So, I think we already know that the disease is curable, we just don't have that established cure. But as a consequence of people living longer and longer, there are a lot of people living with myeloma in the U.S. these days, estimated over 180,000 people. And I followed the field for all these years. This year, I'll have been a doctor for 30 years. That number used to be maybe 50,000. And then it was 60,000 and 70,000, now it's 180,000. And that's because we can keep people living longer and longer and many people can have the same lifespan as a person with the same age and gender without the disease.

The number will continue to go up, up, up until we find a cure. And eventually, if we found a cure, that will be 36,000 diagnosed and that will be 36,000 living with the disease because we could cure them all. We are not yet there. Florida has a very high number. We actually have the highest number of patients with myeloma out of all 50 U.S. states. We estimate there are 3,700 people living with myeloma here in Florida. Excuse me—there are 3,700 diagnosed with myeloma and 18,000 living with the disease here in Florida. None of us in the Myeloma Institute want anyone to be diagnosed with myeloma, obviously. But we want to help patients that have the disease and we want to continue to push the envelope and we want to be able to see if we can find a cure for the disease.

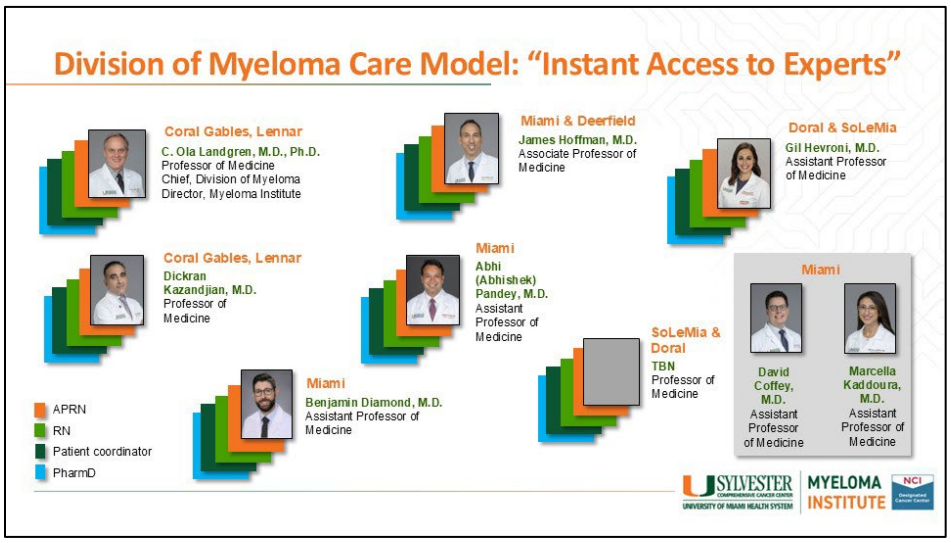


The aim of our program is to identify what's called targets, signatures, and biomarkers. And that all means testing. We also want to translate the research into new treatments. So we want to push the envelope both for testing and for treatment. And together we think that that's the way where we can deliver the best.



I mentioned I was employee number four. One of the three employees that were here before I came a little bit more than four years ago was Dr. Hoffman on the lower left. Dr. Hoffman was trained initially at Sloan Kettering in New York where he did his fellowship.

I used to be the chief of the Myeloma Program at Sloan Kettering for many years before I came here. Dr. Kazandjian used to be the Chief of the Myeloma Program at the NIH (National Institutes of Health) in Washington D.C. Dr. Diamond was a fellow at Sloan Kettering. Dr. Coffey was a fellow and attending at Fred Hutch Cancer Center. Dr. Marcella Kaddoura was a fellow and attending at the Mayo Clinic. Dr. Abhi Pandey was a fellow, he did his residency at NYU in New York, and he was in Colorado. Dr. Brian Walker, he's a wet lab scientist, he was trained at the Imperial College in London, UK, and he's one of the leaders in genomic research and he just joined us about a week ago. And Gil Hevroni, she's originally from Boston, she's graduating from her fellowship, and she's joining us here after the summer. We continue to recruit a lot of talent. And, next time I see you, I will show you more names. I am already negotiating with a lot more doctors coming here.

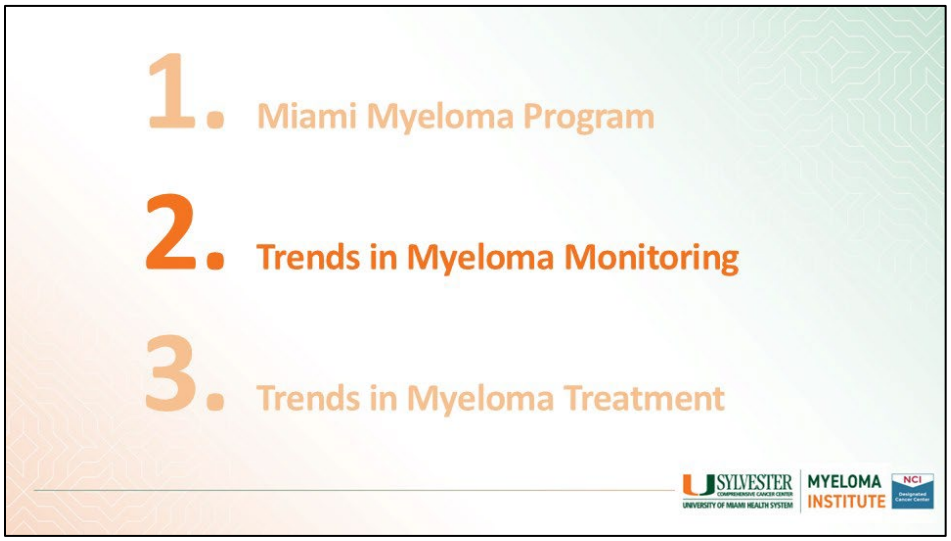


For every doctor, we hire a nurse, we hire a patient coordinator, and we also hire support from pharmacy. We also have social workers. I learned this the hard way when I worked at Sloan Kettering. This is how Sloan Kettering built a model. They have a doctor with a nurse and a patient coordinator and a nurse practitioner and pharmacy support. When the volume grows, you hire a new team. And you can hire another team, and another team, and another team, and another team, and another team. So building it this way means that you will never jeopardize the quality. You can build the same exact quality in every piece. You build the processes, you have a very small number of people involved knowing exactly how to do the job instead of having a big group of people where people don't really know how to get the work done.

So you build a very, very, very tight ship with very tight ropes. And that's what we are doing. And we were actually reviewed last week by the university, and we were 99% accurate for quality. And I said, "I apologize, it's not 100%, but I'll try to do that next time."

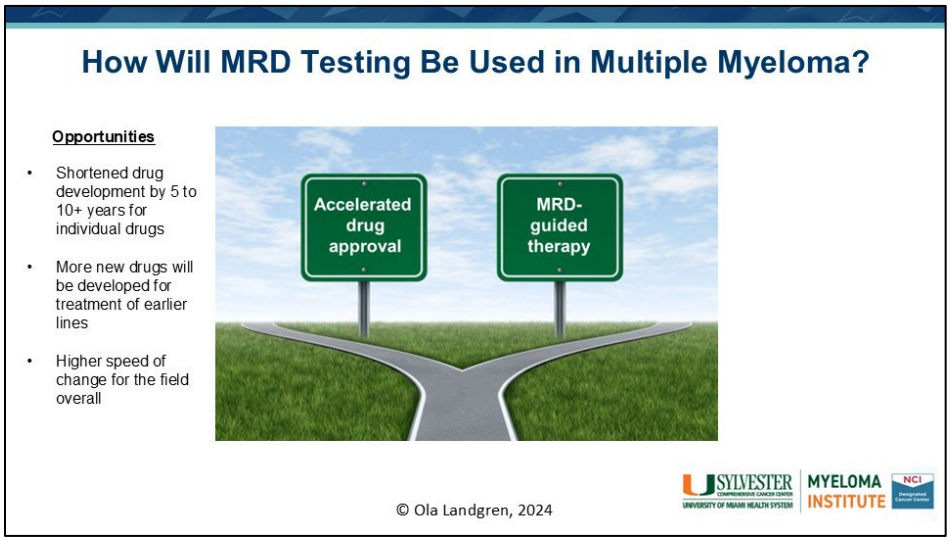
We also have two doctors, Drs. Coffey and Kaddoura, that are located only in the hospital in Miami, and the reason they do so is because they spend a lot of their time in the research lab. But all the doctors on our team are involved in research, either in a laboratory, or in clinical research, or in computational research–that's a requirement when we hire people here. We have to be able to advance the field to drive things forward and to understand the details of what it takes to really build into the future.

The last few slides I show are about the program and then I'm going to turn into talking about the new methods that I think we will see coming. We are building a lot of new facilities around Miami. And every location will have our institute's presence, the exact 99.9% quality. And we will provide all the excellent care in every location.



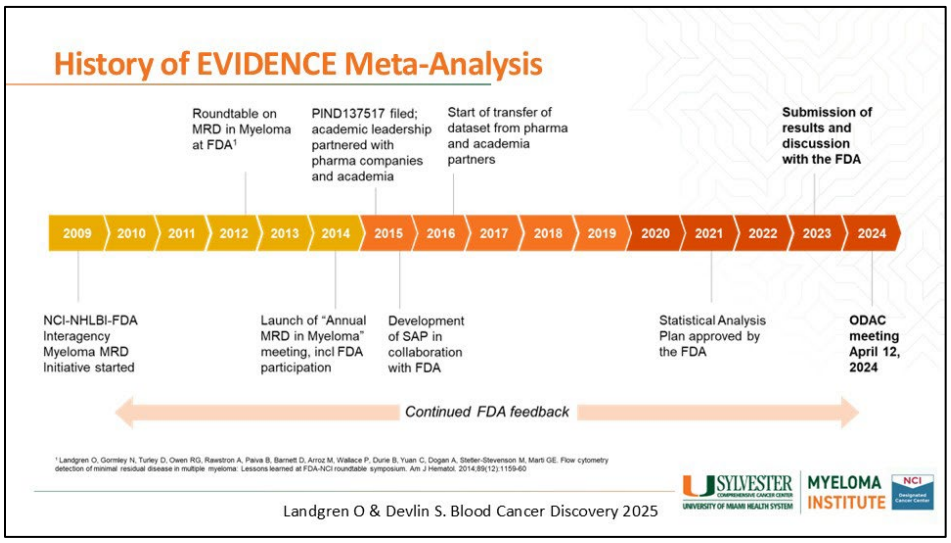
So we'll now turn to talking about monitoring. I think this is a very, very important field where the field has not really spent so much time in the past. One thing that's been very close to my heart has been minimal residual disease (MRD) testing. That means that you look for those last C cells. And to me, this was very obvious a long time ago, when I thought about the fact that if we don't check if there are cells left, we will never be able to find a cure for the disease. And we will also never be able to optimize the outcome. And we will be stuck with treating all the patients the same way. But if we actually could check and see if there are any cells left and we don't find any, maybe that's the time where we could maybe step down the intensity of the treatment, and we could start thinking about curative approaches.

Also, if God forbid someone has been tested and there are increasing numbers with these sensitive tools, maybe that's a much better time to think about changing the treatment instead of waiting for the patient to get sick again. It's all about optimizing the patient outcome – that was the driver for me thinking about this.



People think about and talk about MRD and they talk about many different things along these lines, but I would say that there are two major themes. One is to use this MRD, or minimal residual disease testing, to think about how you can develop drugs faster, that is, an accelerated drug approval. For every patient, this is very, very important. Because it's hard to develop drugs – I will show that on the following slides – if you don't have a good surrogate endpoint such as MRD. The other thing is MRD-guided treatment. Can you use the results from MRD to change the treatment for the individual patient? And I will tell you exactly what this means. It may sound a little bit abstract.

Let's start on the left. The accelerated drug approval means that you can shorten the time window that it takes to develop a new drug. And if you can do that, there will be many more drugs of course, developed faster for patients. Patient can get access to the new drugs much, much faster. And we will see a much higher speed of change in the field overall. So the field needs to really be on top of the game. That's exactly why we are building the program we do, where we try to have these very, very focused small cells of doctors, nurses, nurse practitioners, and pharmacists supported by the research group. So we can always be on top of the game.



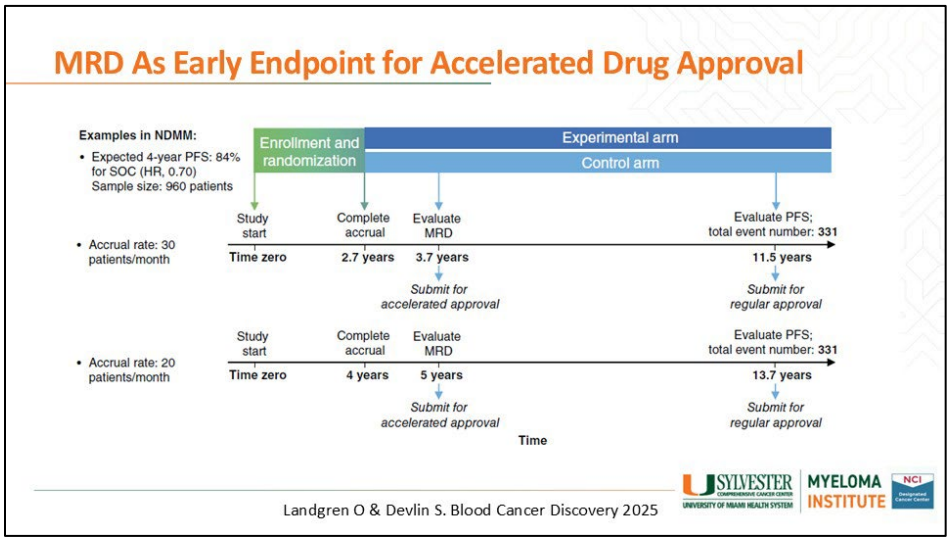
I started working on MRD in myeloma in 2009. It takes a very stubborn person to do this. Last year, I was invited to the FDA (U.S. Food and Drug Administration) to present the results. So that was only 15 years of work. Long story short, on this slide, on the left, I used to work at the NCI for 10 years. I came there in 2004 and I left in 2014. In 2009, I formed together with some colleagues at the NCI, the FDA, and NHLBI (The National Heart, Lung, and Blood Institute), an Interagency Myeloma MRD Initiative. We worked on that for a few years. In 2012, we set up a roundtable at the FDA site in Silver Spring, Maryland. Between 2009 and 2012, we worked regularly in Bethesda, Maryland at the NCI. In 2012, we had a roundtable, and we presented everything we had done and showed a lot of people. We invited patient organizations, academia, and we had representations from obviously, the federal government, from the NCI, NHLBI, and the FDA. And we also had some drug companies were also allowed to listen to what we were thinking.

We were thinking if you could use MRD as a tool to see if a drug is successful, if it works, that those results could be generated much, much quicker versus just waiting for many years to see how good the drug really is. You could get the approval by using this test, the MRD test. In 2014, we then went ahead and we launched an MRD Myeloma Meeting that we had in New York. In 2014 I was recruited to Memorial Sloan Kettering Cancer Center in New York City and we had that meeting in the summer of 2014. My thinking was, even if we do everything right, coming to the FDA in the end, they're probably going to say, "It looks right, but the other people don't agree." So it's like raising a family. If the whole family does not agree, it's going to be hard to convince people in the end. So I thought, "Let's just invite everybody."

So we invited people to come to New York and we had it once a year, every spring we had it there. And when I came here to Florida in 2020, we moved it here. So this is now a Myeloma Meeting for MRD; it's the 11th year we will have had it. We're going to have it in April, I have it on my very last slide, I'll show you. Anyway, I filed something called an IND (investigational new drug application), PIND (pre-IND) to the FDA, allowing me to formally request the federal government to review all the data. Then we developed a statistical analysis plan. We started transferring data. I asked every company, "Can you share your original data with us?" And that was very hard. All the lawyers got involved from all the

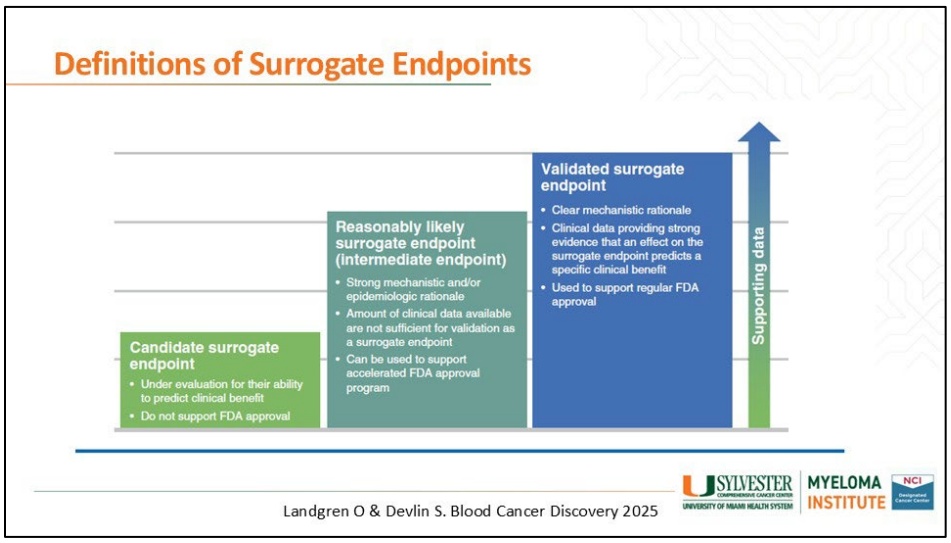
companies, and I was the point person for negotiation with every company. Eventually, I got every dataset, took a long time. And, in 2021, the FDA finally approved the project. And in '23 we submitted the data. And in April of 2024, we were invited to ODAC (Oncologic Drugs Advisory Committee).

In parallel with this, after we had this roundtable in 2012, there was another group that we had invited to be part of it or people we had invited, but they decided to start their own program instead. They developed another project and they worked in parallel. There were two projects working in parallel. Which is sort of the beauty of life, there are different ways of doing things. Both the groups were invited to ODAC in April.

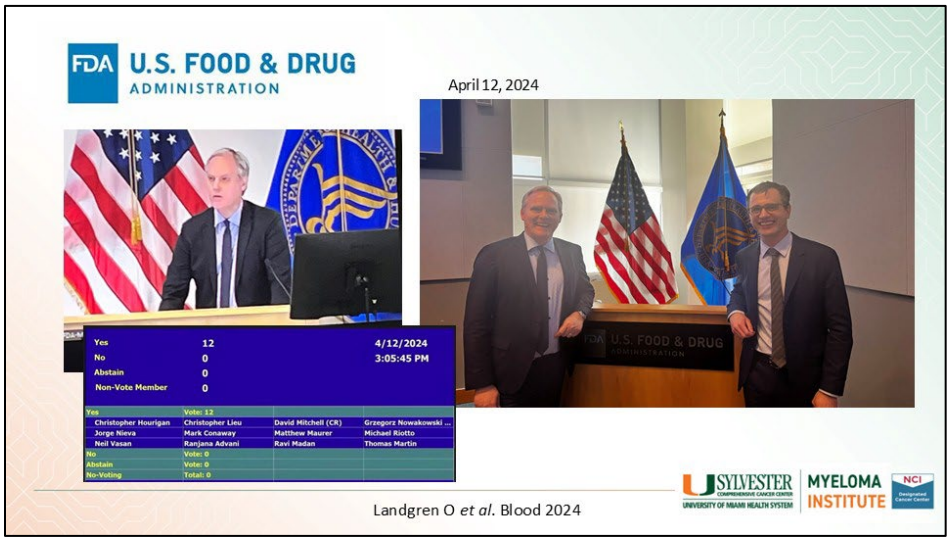


What this is all about is, if you look from left to right, when a new drug is being developed for the treatment of myeloma, you typically, as a company, would be tasked to do a randomized study to show that the new drug is better than the old drug. They have to randomize patients between the two arms. But if you have a lot of patients that need to be randomized, that takes a lot of time. So if you're able to enroll 30 patients per month, that's a lot of patients going on the trial. With the appropriate sample size, it could take almost three years or 2.7 years as you can see on the top.

What I showed with my project and our project was that, if you check for these MRD tests one year after, which is 3.7 years, that will give you the results that you otherwise could wait for 11.5 years from a clinical follow-up to get. So if you wait for 11.5 years, you see that the new drug is better, if it truly is better, but the test would give you the results after one year after randomization. You could get it approved after 3.7 instead of 11.5 years. And if you cannot enroll 30 patients, if you only enroll 20 patients per month, you see that we are now talking even more years. So we basically saved 10 years to get drugs approved. This is what a patient needs.

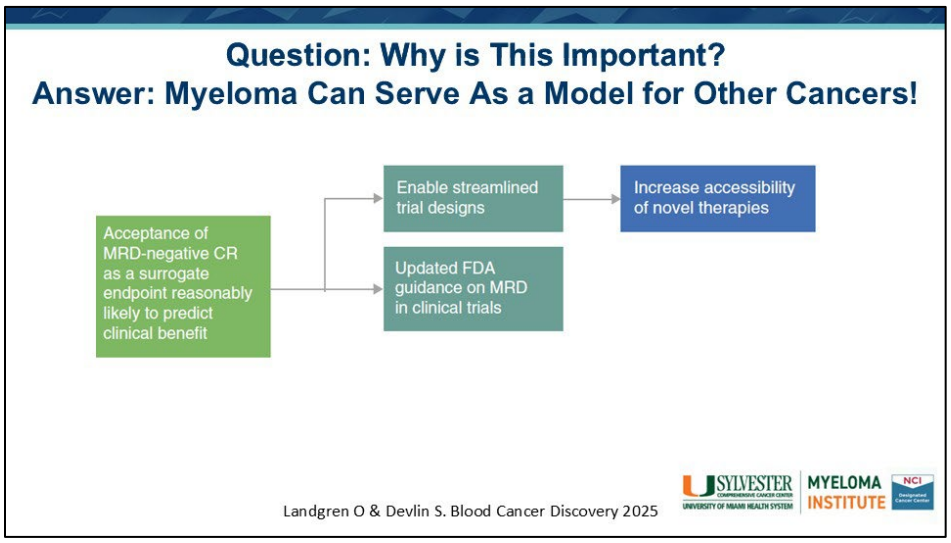


After being grilled for six hours in a courtroom style, showing the FDA that MRD is good enough to be an intermediate endpoint,

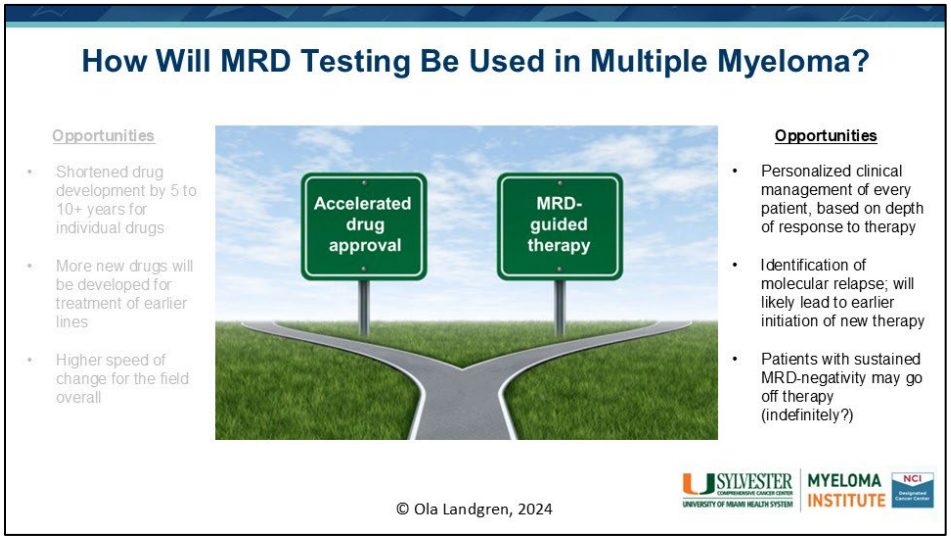


they voted 12-0 yes. So, we walked out of the FDA with this, and this was really, really a great moment.

Our presentation was followed by the other group I mentioned, the I2 group, and the FDA voted on the two groups together. They took into account all the data we had generated, the methods, all the results, and the other group's, their methods and the results. This is published in a journal called *Blood Cancer Discovery*, and it was published in January of this year, 2025. It's actually available for free if anyone is interested in looking and reading about how this happened.



I would say this is a huge step forward for patients with myeloma, because it gives access to drugs 10 years faster than it otherwise would take. You couldn't wait that long. I would also say that in the absence of that, that will be a huge repellent for any company to develop a drug because when they develop drugs, if the patent time runs out before the trial is done, there's no incentive of doing it. So, this was completely necessary to go forward for the field. But also, this is important because this could actually change it for all the other cancers. This could actually serve as a model potentially to speed up drug development for any cancer medicine in the U.S. A lot of work needs to be done. You cannot just assume that because myeloma now has it that the other diseases could do it also. Someone needs to do all the work, but instead of doing 15 years, maybe they could do it in five years or something like that, because now the path is already sort of paved out there.

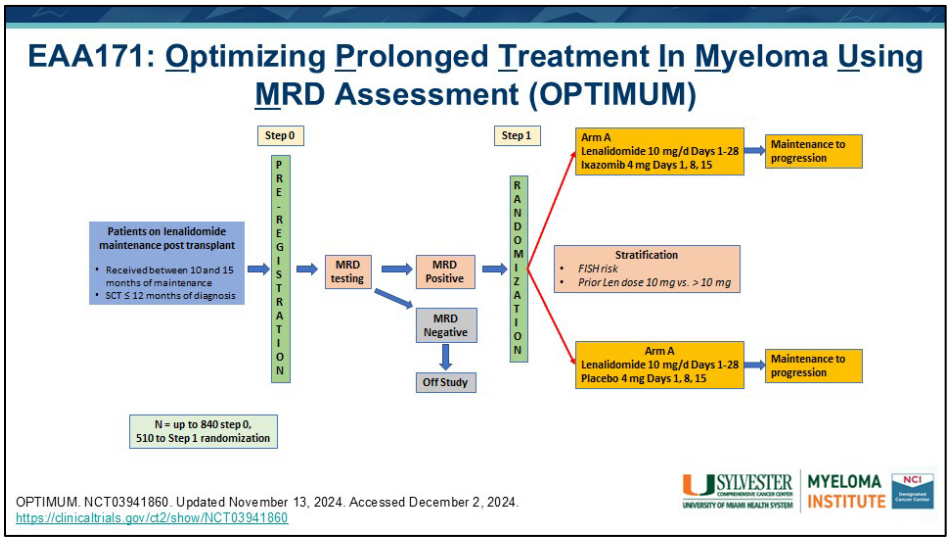


I mentioned also MRD-guided treatment. That's also very, very important. So, MRD-guided treatment means that you can personalize the treatment. When a patient comes

to the doctor's office, usually doctors that don't do research, they will read guidelines and they will just follow these guidelines. If the guidelines say give six months of treatment, the doctor will do that. If it says give 12 months of treatment, the doctor would do that. But let's say that there is a patient that has no detectable disease after a quicker period of time, a shorter period of time. Do you really need to give 12 months? Could you do fewer months? We don't really know, but there is emerging data indicating that if there is no disease, that maybe you don't need to go all the way.

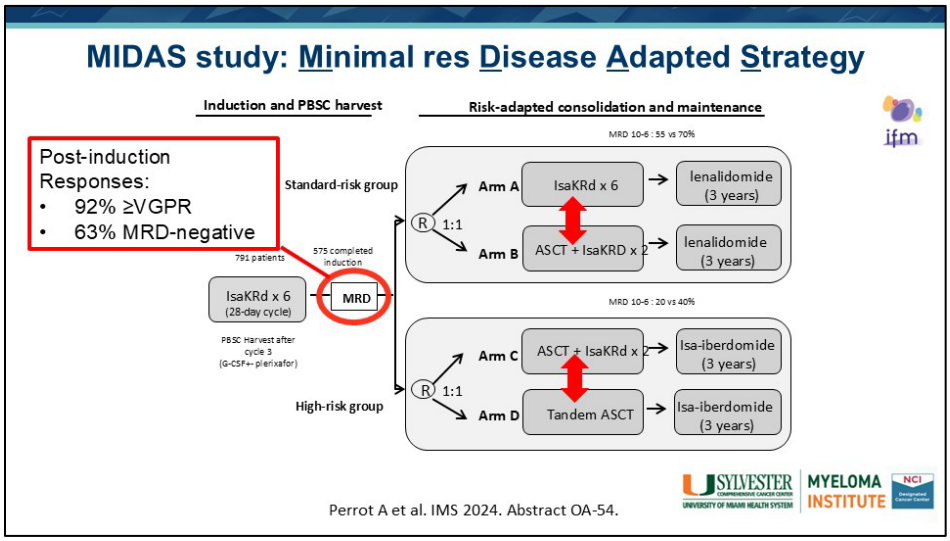
In myeloma, do you need to transplant every patient? That's a question a lot of people have asked, including myself. And I don't think you need to do that if you can achieve no detectable disease with a modern treatment. I should say that that remains a controversial topic, and there is a difference of opinion, and I do respect that people have different opinions. But there is emerging data showing that if you reach a point where you have no detectable disease, if you get one therapy or the other, what really matters is that there is no detectable disease. You don't have to give every patient the same treatment. To identify the disease, if it comes back after we have treated, the molecular relapse is also something that's important.

Can you continue to monitor MRD negativity over time, what's called sustained MRD negativity? Could patients even go off that therapy if they're tested and they are negative, negative? And they stop that and they're negative, negative, negative, has this patient being cured? I would think so. There will be new guidelines. We have worked on this in the myeloma field.

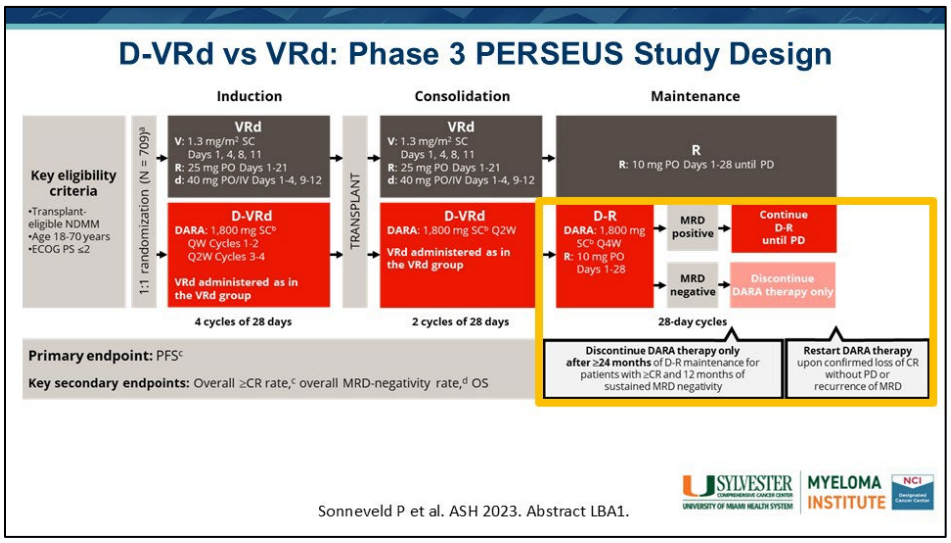


There is something called The International Myeloma Working Group® (IMWG). I became a member many years ago of that and we worked probably for over 20 years trying to form guidelines around the world. We had a meeting in November last year, where we, for the first time, could agree to put the word finding a cure with measurements with MRD. It has not yet been published, but the draft is circulating among the people that were at the meeting and probably patients that are MRD negative for five years after they have stopped therapy. That will probably be the future definition for this new guideline.

Here's an example of a study, a lot of details. I will walk you through the key pieces here. These are patients that have been treated. This is a clinical trial developed by one of the external groups. But the point here is, patients are treated with combination therapy. They go on maintenance therapy on the left in the blue. They are transplanted, they go to maintenance. Then it says step zero, they register and then they're tested for MRD. If the patient is MRD negative, they are not on the study. But if they're positive, they can then be randomized to Arm A on the top there, step one, to lenalidomide with ixazomib. Or they can be randomized down to the other Arm, it's lenalidomide with placebo. This study is really trying to see if you do lenalidomide with ixazomib, or just lenalidomide. Do you need to have two drugs or is one drug good enough?

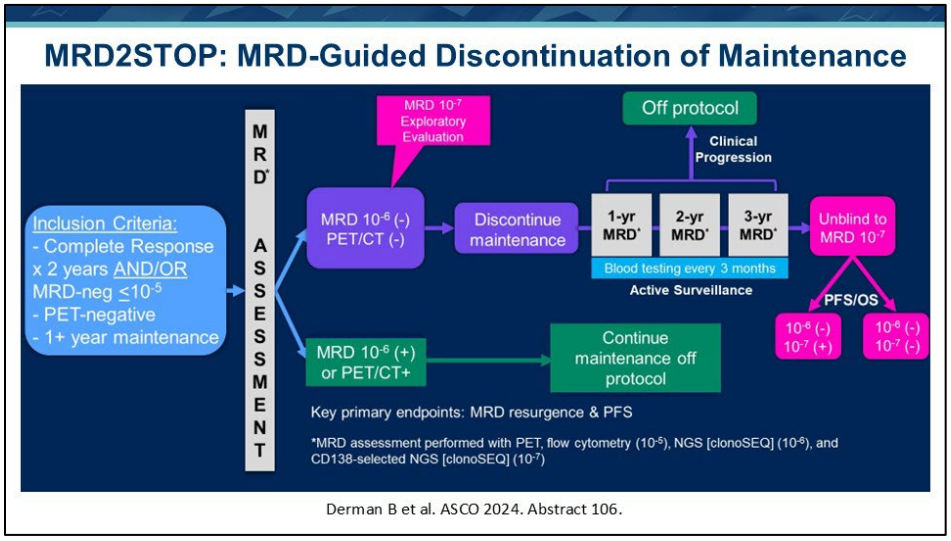


Another example of a study... These are just examples of how people are thinking about using MRD. This is from the French group. They have patients that are treated with combination therapy. Then after six cycles of combination therapy, they're tested for MRD. Then they are randomized if they are what they call standard-risk with FISH (fluorescence in situ hybridization) testing. They can be randomized to Arm A or Arm B (that's on the top), either more combination therapy followed by maintenance, and lenalidomide, or they go to transplant with more combination therapy and then lenalidomide. So, here, the idea the French group has is, if you have standard-risk disease, which is the vast majority of patients, can you just get rid of the transplants in half the patients? That's what this study is designed to test. But the French, they like to do transplants. So, for the patient they call high risk, they do either one transplant or two transplants. But, in the future, it may be that they will even include high-risk patients if the treatment gets better. So, this is just an example.



Sonneveld P et al. ASH 2023. Abstract LBA1.

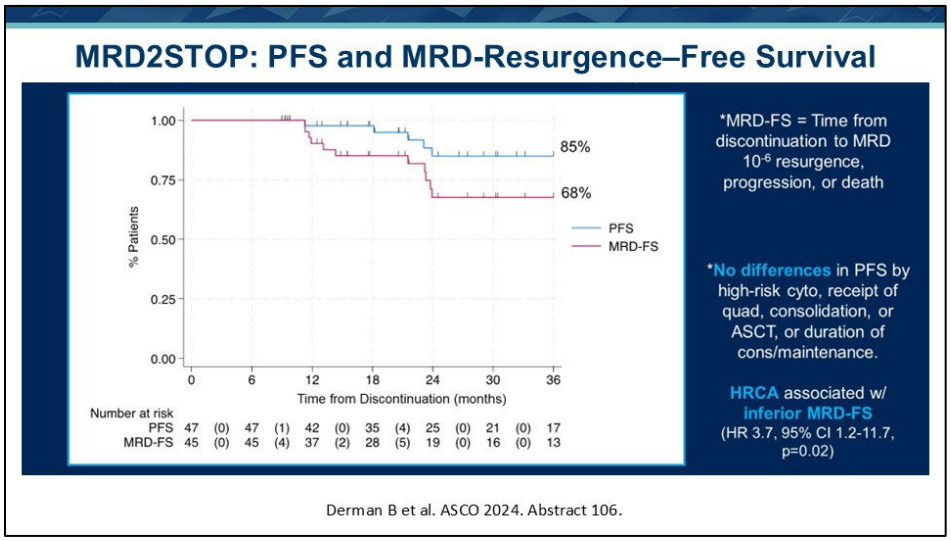
Another study that was published in January last year is this study called PERSEUS. They also used MRD to make treatment decisions. Patients were treated with daratumumab with bortezomib lenalidomide, dexamethasone versus bortezomib, lenalidomide, dexamethasone. It's a randomized study. They were transplanted and then they got maintenance therapy. Those patients that got maintenance with daratumumab and lenalidomide, if they remained free from disease for two years, if they were MRD negative, they stopped the daratumumab. The daratumumab was really driven by the MRD results. MRD was really changing the treatment.



Derman B et al. ASCO 2024. Abstract 106.

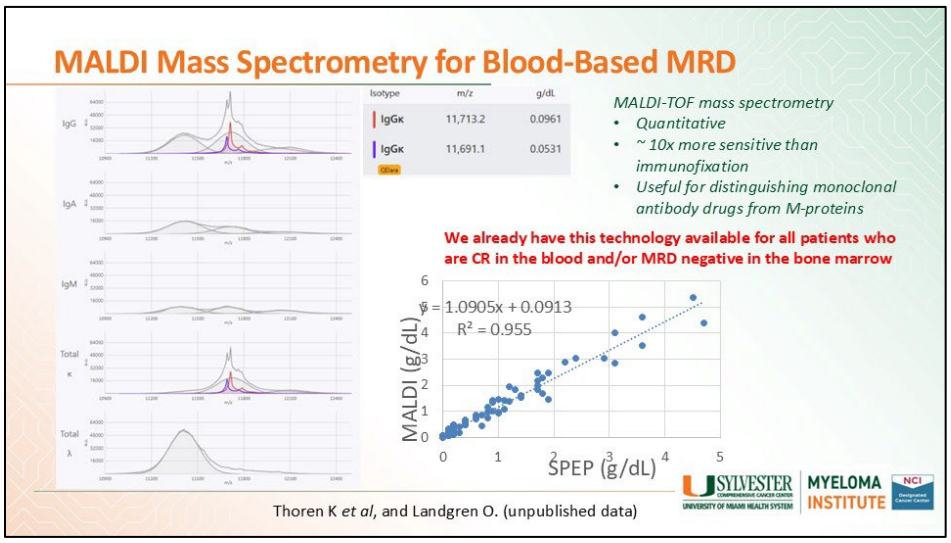
Here's another colorful slide from Chicago. They also designed the study. They had patients that had been treated with the therapy that the doctors have given. They come to them on the left, they have been in remission for two years and/or they are MRD negative. They have done PET/CT (positron emission tomography/computed tomography) that's negative, and they have one or more years of maintenance therapy. Then they test them for MRD in the purple box. And if that test is negative and the PET

scan is negative, they stop the maintenance therapy. They don't continue any lenalidomide. Then they test them year one, two, and three. And if they're three years out, they're tested even more to see if they can really find any disease. And for patients that are positive in green, they continue with maintenance.



What they have plotted out here are patients that went off therapy in blue; 85% of patients three years later had not had the disease coming back. So, I guess, it depends on is it half full or half empty? I would say this is very, very encouraging results. If you expect 100% of patients being free from disease, that would be great, but I think still 85% three years out is pretty amazing. So, out of 100 patients treated, if you stop the therapy three years later, 85 of them have still no active disease. It also shows in red that, if you use these MRD tools, that 68% of patients still have no detectable disease. So, that's about seven in 10 patients have no detectable disease three years later.

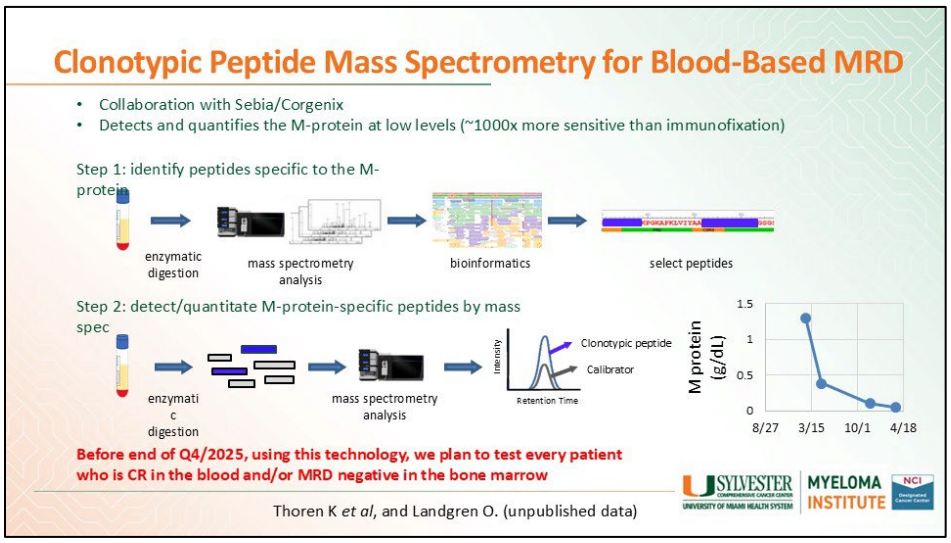
We don't know what's going to happen here. Will this study eventually show after four, and five, and six, and seven years, that there will be patient that will stay completely free from disease forever? I would think so. I have patients I followed for 10, 15, or more years that have been off therapy, patients I used to treat at the NIH that have been off therapy for over 10 or 15 years by now, and they had no detectable disease. I assume that these patients are cured; I think this study and many other studies will show the same.



Where I see the field going forward will be blood-based tests for MRD. To do bone marrow biopsies to look for residual disease, that's the best we have, but that's also an invasive test. It's painful for the patient, it's complicated, and it can just not be done over and over again. It's too much. We have worked on something called MALDI-MS (Matrix-Assisted Laser Desorption/Ionization mass spectrometry). The Mayo Clinic has worked on this and there are other groups as well. We have shown that this technology is over maybe 10 to 50 times more sensitive than conventional blood tests. This is a test we could do, say, once every three months and make sure there is no returning disease in the blood instead of doing biopsies over and over again.

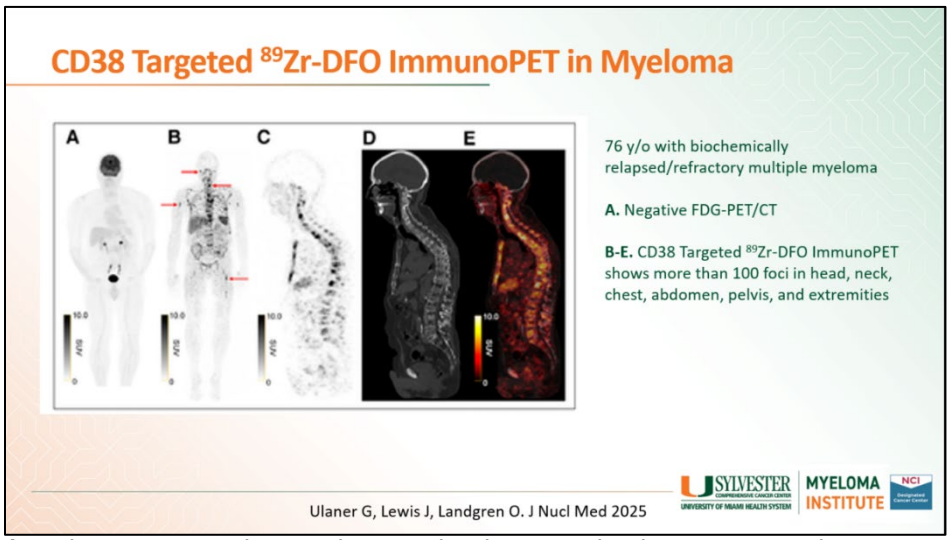
If someone were to stop therapy, if we check with this type of test, and the test remains negative, that could also be a segue towards showing that the person will not have the disease returning in the long term. This technology is much better than conventional technologies, but it has technical limitations in the sense that, in our blood, we have a lot of other proteins. The biggest protein we have in our blood is called albumin. It is an important protein that carries a lot of things the body needs to transport around in the blood. We also have regular immunoglobulins. Immunoglobulin G (IgG) is the biggest of those. It's the highest concentration. And we have IgA (immunoglobin A), and IgM (immunoglobin M) and other proteins as well.

When you run these type of tests, when you're looking to see if there is myeloma left, yes or no, you have to make sure that you measure the right protein. All those background proteins sometimes make these tests a little bit hard to interpret.



For that reason, there's another type of technology called clonotypic peptides. Basically what this technology does is that it uses the sequence for the patient's disease, and the sequence from the DNA will tell which proteins the sequence actually leads to. The cells make proteins based on the sequence. So, if you have the sequence, you can figure out exactly what proteins to look for, or these peptides. That means that you look for specific peptides. You don't just look for any protein, which I showed on the previous slide.

This test is probably a thousand times more sensitive than any of the existing technologies. We have already set up this in our lab here in Miami, but we are working to calibrate it. We think by the end of this year, or early next year, that we will be able to do this. These two types of tests, we have spent a lot of time and effort setting up. The first test we already have. So, any patient that comes here, we can test with that technology. And we can also do this in some patients, but we are trying to scale this up.

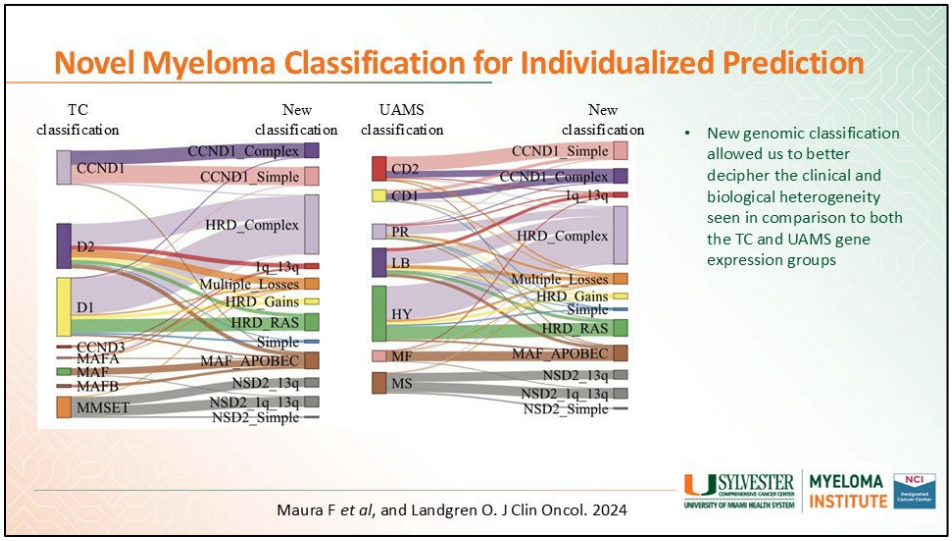


Another area we have also worked on, and other groups also, is to see, could you use antibodies to take pictures? Here's a patient that's 76 years old where the M-spike and

the light chain started to rise. So, that looks like there was a relapse. But as you can see here on the slide, panel A is negative with a traditional regular PET/CT. There is no disease. Completely negative. What we did was that we have taken a very small amount of antibody, labeled it with zirconium-89. We have done something called DFO (deferoxamine) chelator linkage. Then we label that with zirconium-89. So, with a very small amount of this antibody injected, we can now see if the antibody binds to any residual disease. And, if it does, the zirconium-89 can be detected in the camera. So, many times you hear about targeted therapy, but what I'm talking about here is targeted imaging, targeted tracking of disease. What we show here is that there are 100 areas that light up. This is the same patient just a few days after with this other technology.

The standard technology with FDG-PET (fluorodeoxyglucose-positron emission tomography) said negative, but the new technology showed over 100 areas. If we had known that in every patient, we would not stop the therapy. And now we did this, so we now didn't stop the therapy. But imagine if you do that for every patient, if you could advance the field to have much better resolution, that would make a huge difference.

We have a study that's going here. If there are any patients interested, we have probably another 10 or so slots available. It would be a visit here to get a brief injection and then we take images.

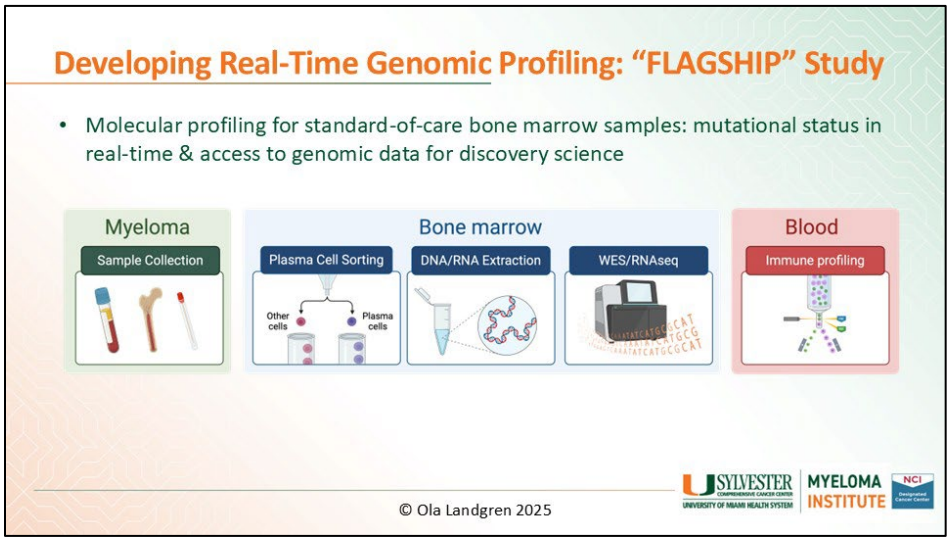


The field for sequencing has been going for a long time, and myeloma is basically put into different subgroups. In lay terms, we talk about standard risk or high risk. But in more research settings, we talk about many more subgroups. This is sort of a complicated picture. I just put it there to illustrate the fact that it's complicated.

There are two panels as you see, one on the left and one in the middle there. The one on the left, it says, "TC classification." And then you move to the right, it says, "UAMS (University of Arkansas for Medical Sciences) classification." Those are the two classifications that are in the textbook for how myeloma subgroups work. But, having been in the field for a long time, and many others as well, we know that patients that are labeled in one of these subgroups, if you treat them all the same way, they don't have the same prognosis. So, that tells us that these subgroups are probably not right. If we

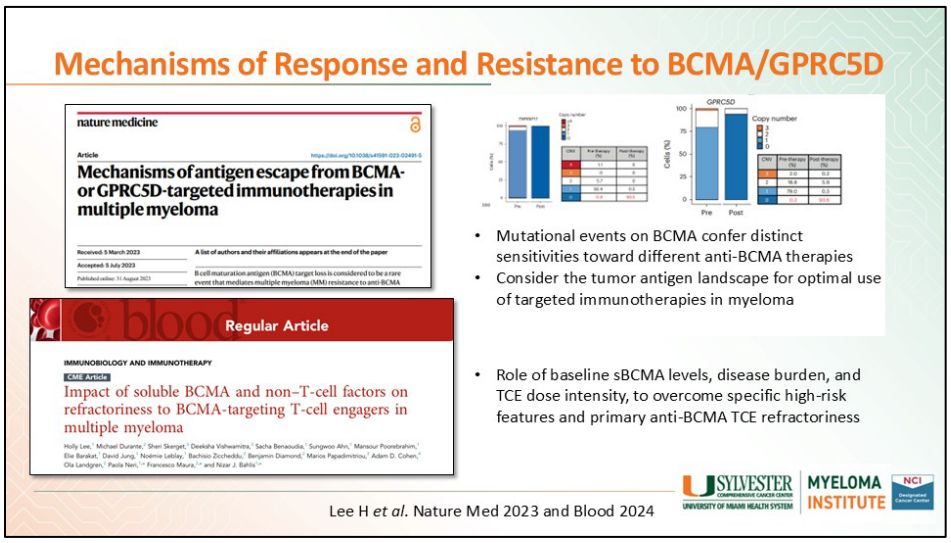
say that every patient in a subgroup is that unique subgroup, and we treat them the same way, you would expect the outcome to be the same, but it's not. That's because the subgroups are not perfect. There are a lot of errors.

So, what we have done is that we have worked to see if we can improve and put patients in new subgroups. We have played with this with over 2,000 cases. And as you can imagine when you do these types of projects, the people that wrote the old classification, they don't like it. So, one of the first thing we did was to make sure that they were collaborators in this project, so we could publish it together. And that's how research goes, like life in general.

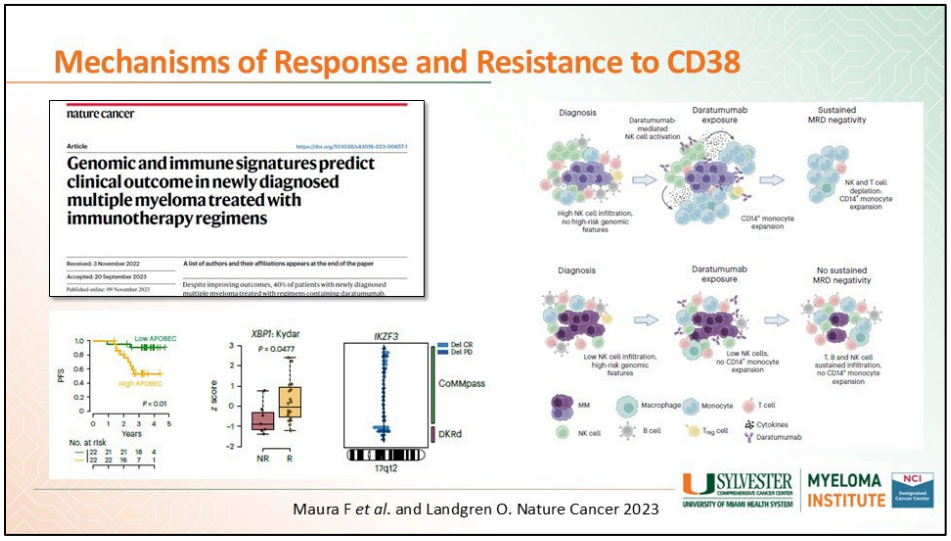


What I also thought about a lot is, as much as we learn these things and we do all these things, if we cannot scale this up for patients in general, it doesn't really matter if we know how these subgroups should be done. If patients are going to continue to be tested with FISH and cytogenetics, it won't change anything. What really needs to happen is that the field needs to move from black-and-white TV into color TV, into high-definition TV. FISH and cytogenetics is like black-and-white TV. We already have technologies that can deliver high-resolution color TV.

We decided to start a study called the FLAGSHIP study, and we are profiling patients here in Miami, and there are other groups doing similar things as well. Basically, what we do is that we do a regular bone marrow biopsy when the appropriate time to do a biopsy is, say, at diagnosis. Then, if the patient agrees, we can split the sample, half goes to FISH and cytogenetics and half goes to the FLAGSHIP study. Then we can run very sophisticated testing to see what we find in the disease cells. We do what's called transcriptomics and we do sequencing out of the disease. We already know, I can tell you we have not published this yet, but you can capture instead of 20 markers that you do with FISH, you can capture 5,000 markers or more with this technology. So, there is much, much more information, and you're going to be much more accurate in your prediction.

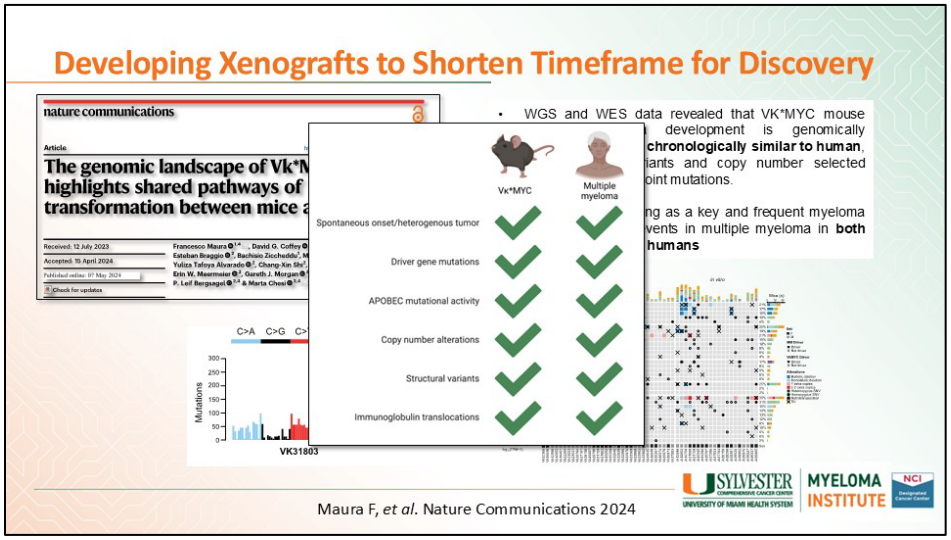


Some of these slides have a lot of technical details, so you don't have to pay attention to all the words. I will try to walk you through briefly. When you use the new bispecific antibodies, there are two types of targets. One is called BCMA (B-cell maturation antigen) and the other one is called GPRC5D. When you use these drugs, they usually work very, very well, but there could be situations when the drugs don't work. Why is that? In the past, people didn't really know. So, what we and others have worked on is to try to understand if there could be some genetic explanation. What we and others have found together is that the cells could turn off some of those genes that are responsible for expressing the target on the surface of the disease cells. Specifically, you can have biallelic losses of the target genes. We have also spent a lot of time, we recruited Damian Green from the Hutch also to come here from Seattle, from the Fred Hutch Cancer Center to join us. He's now our new Chief for the Cell Therapy and Transplant Service. We are very close collaborators. Damian and I are also very good personal friends. We worked for a long time together. Damian has shown that, in many patients, that are something called soluble BCMA in the blood, and BCMA is the target for a lot of the CAR T cells and also for many of the bispecific antibodies. But if a patient has a lot of BCMA floating around in the blood, the drug may bind to that instead of going after the disease cells. And Damian has shown how these things work, and we are continuing to evaluate and build on this.



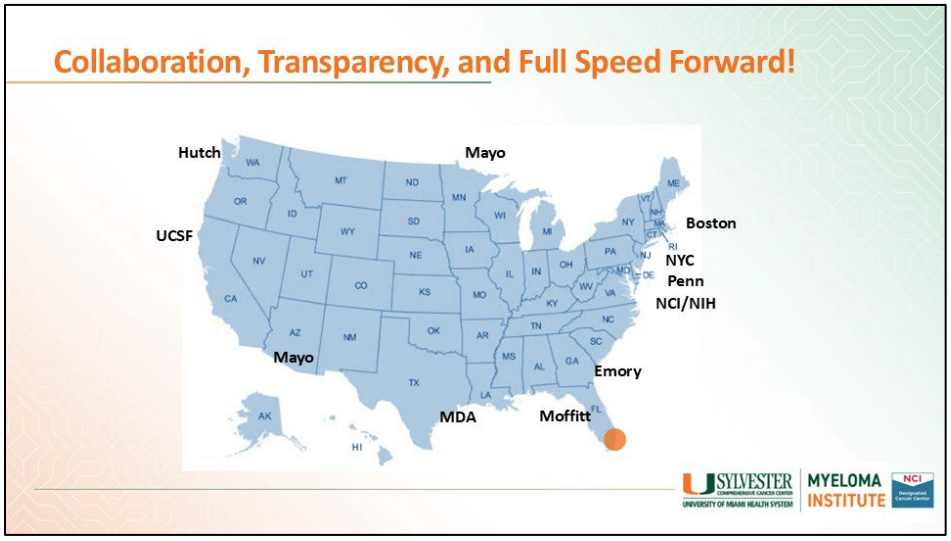
We are also trying to profile the disease cells, as well as the cells in the microenvironment. What has been more and more apparent from research, that we and others have done, is how the immune system plays a very important role. When you treat the patient, the disease cells may have certain configurations that make the cells more stubborn or harder to treat, but also the immune system plays an important role. We and others have shown that there could be alterations in T cells, and B cells and what's called NK (natural killer) cells that play a role for how the prognosis could go when you use combination therapies.

I just showed you some of these examples of things that we do in our laboratory. When a patient participates in our clinical trials, if the patient gives us permission, we would collect the samples and try to drill down to the absolute details of why it does or does not work, so we can try to overcome that in that individual or other patients.

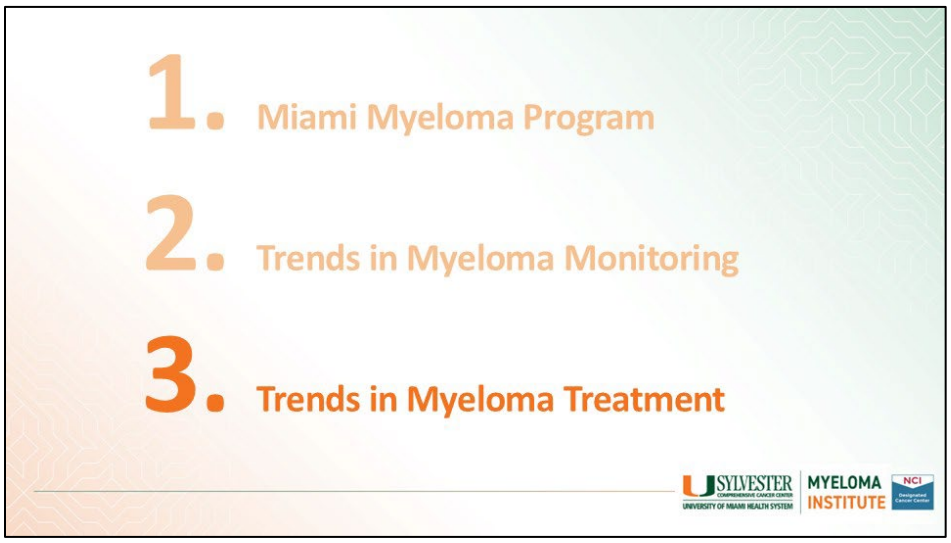


Lastly, we are not only studying in the patients. We are also working on what's called xenografts, or mouse models. And what's very important is that the lifespan for a human being is so long, so we would all retire before the experiments are done if we study someone for so long that it takes to develop the disease. But the mice, they have maybe only, say, nine or 12 months for the experiment to read out. We will actually be able to do very many more experiments. What we have found is that the models we use, called the Vk*MYC model is very, very similar to what we see in the patients.

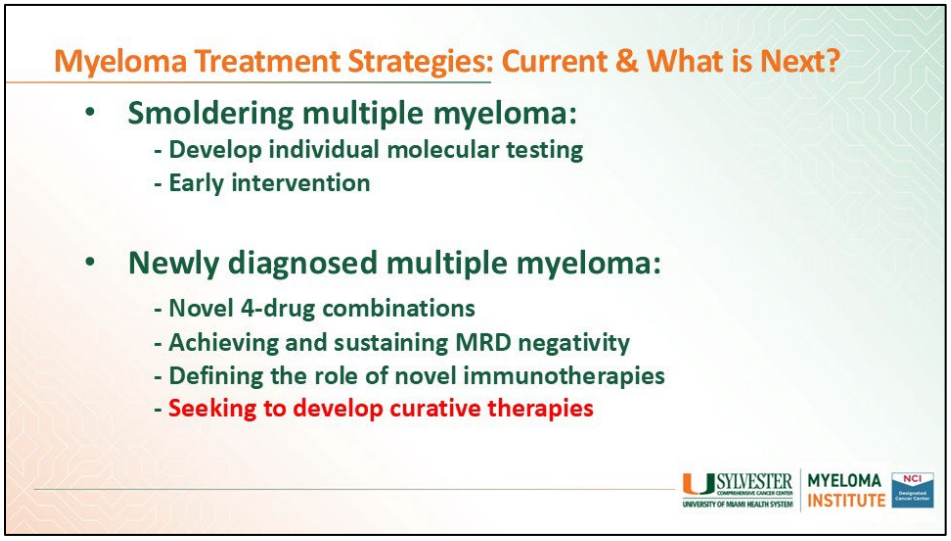
Brian Walker, who joined us about a week ago, I mentioned in the beginning, he's one of the world leaders in developing xenografts in myeloma. So, that really closes the loop. We have a very strong discovery lab with computational oncology. We are now establishing a big wet lab with epigenetics and xenografts, and we are recruiting even more people coming here soon. And we have a very strong translational program with clinical trials.



I think the only way forward is collaboration, is transparency, and full speed forward. Working with others, and share the data, and try to find people that are honest and want to continue to work, and help and drive the field forward. We are all working for the patients.



The trends I see in treatment are several.



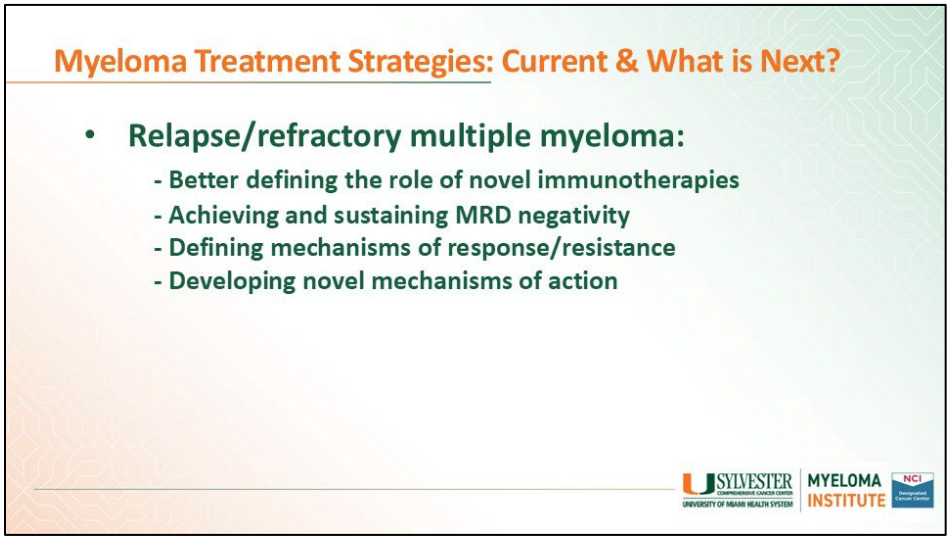
Smoldering myeloma was proposed in 1980 as a precursor condition. It was proposed based on six patients that didn't have multiple myeloma, but they didn't fit the bill with a monoclonal gammopathy, or MGUS. These six patients had been followed for five or more years and none of them had developed myeloma. So, the conclusion was, don't do anything. But we have learned over the years that many patients with smoldering myeloma, they will develop myeloma. While many, they actually will not develop myeloma.

We currently don't have an accurate test to say who is going to progress and who is not. That is something that needs to happen next. And I think this spring, most likely the FDA will approve the first treatment for smoldering myeloma. This could be the first treatment worldwide for smoldering myeloma. This is daratumumab that has now been tested versus doing nothing in a very large randomized trial showing that daratumumab can

really delay the disease from coming back. And there's an indication that lifespan could also be longer. The therapy with daratumumab will not eradicate the disease. It will not formally cure the patients, but for many patients may be holding the disease away, could be the right way to go for smoldering myeloma. I think there will be many trials that will look into full eradication of the disease. We have trials here as well. We are using daratumumab with bispecific antibodies. We give an injection once a month. So, we have open studies for that as well.

I think for newly diagnosed myeloma, the field has come a very long way, but there's still more work to do. We have now novel four-drug combinations with proteasome inhibitors, immunomodulatory drugs, antibodies, and steroids. Patients can be treated without getting any chemotherapy, just immunotherapy of small molecules–amazing therapies. Patients can have probably the same lifespan as someone who doesn't have the disease with the same age and gender. Even without transplants, many patients can have this.

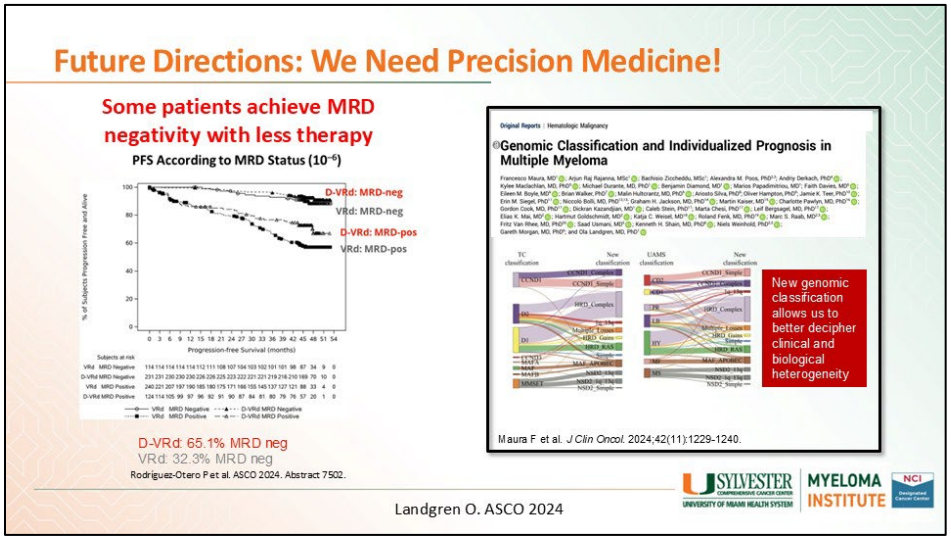
I think the field is now gearing towards achieving and sustaining MRD negativity in more and more patients. And I tried to spend a lot of time talking about technologies; we need better technologies to check in the blood for patients. There is a lot of work going on right now trying to better define the role of the new immunotherapies. The new bispecific antibodies are coming into the newly diagnosed space. They're currently only approved for patients who have relapsed multiple times, but there are already studies evaluating it. We are going to open here in Miami soon a bispecific antibody trial also for newly diagnosed patients. I think putting all the pieces together with all the tests, with all the new drugs, and MRD as a regulatory approval endpoint for accelerated approval, we can actually develop curative therapies for myeloma. That's never happened before. I'm really very excited about it, and I think we will make it. I'm convinced we'll make it.



Relapsed/refractory disease (if the disease comes back) unfortunately still is the case for the majority of patients. In the vast majority of patients, the patient feels very, very well. But it could just be a blood test indicating there is a little bit of protein in the blood. The patient feels great, it is a doctor that sees the relapse. We pick it up very early. I think with the new technologies, we could even pick up earlier than that, and I think we will probably see changes integrating new technology with new interventions. I think, in this

space, better defining the role of novel immunotherapies is something that we will see. I think we already see you can achieve and sustain MRD negativity. You can have MRD negativity in very high rates of patients if you use modern combination therapies or modern immunotherapies in the relapsed/refractory space as well. That will be more and more focused on defining the mechanism of response and resistance. That's what I showed on my prior slides when I talked about how you can dissect the cells and the immune system.

If we can understand why a therapy works in one patient but not in the other, that gives us really a clue how to approach individual patients and how to change the treatment. We will also continue together with the other groups to develop novel mechanisms of action. These are basically new classes of drugs. Until we have a cure for the disease, this remains a very important task. If we have a patient running out of options, we need to have new options through new mechanisms of action.



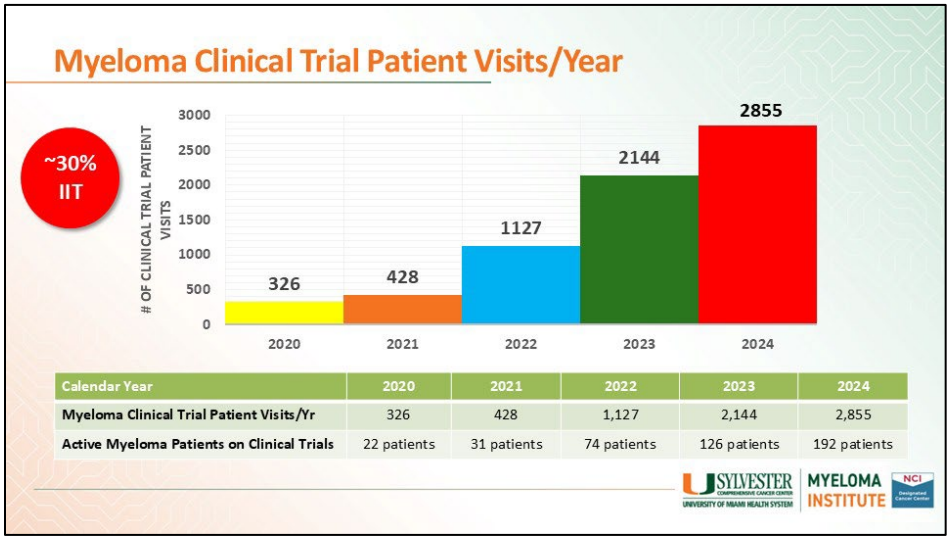
Life is not fair. We know that some patients can have a very good response with less therapy. What these curves show here on the top it says D-VRd (daratumumab, bortezomib, lenalidomide, dexamethasone), MRD negative, and it says VRd (bortezomib, lenalidomide, dexamethasone), MRD negative. That means that patients are treated with four drugs, the D-VRd, or three drugs, the VRd. Both those categories are MRD negative, and they have the same prognosis.

How could that be that some patients get four drugs and some do three drugs, and they have the same prognosis? It's probably because the disease is not the same in every patient. When we do these advanced tests I was talking about, I mentioned we could see over 5,000 alterations in a given patient. If we do many patients, although there are thousands of alterations in a given patient, they are not the same in every patient. There are some of them that are commonalities, but there is also a big variety. We need to be much better at defining high-risk disease. Right now, the definition for high-risk disease is not good.

I envision with better understanding of how the disease works, integrated with more sophisticated testing and access to better drugs, we can do individualized management

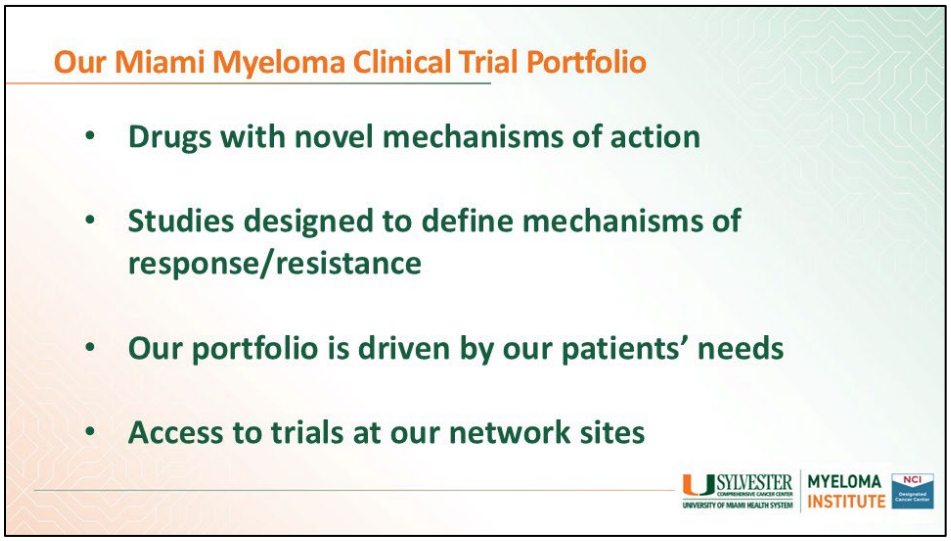
of patients and that could be a way to seek curative strategies for individual patients. We published this paper about a year ago in the *Journal of Clinical Oncology* showing how this could be done. We use, I'm sure you all know, ChatGPT. We developed a ChatGPT for myeloma where you can ask the system questions. I have these and those changes based on what the model sees, which would be the preferred treatment strategies. I think we will see more and more of this going forward. This is not final what I mentioned to you, but I think we are seeing more and more steps in this direction.

The last few things I want to mention to you is the importance of the clinical trials. Clinical trials are here for patients. Patients are not here for clinical trials. That has to be very clear. The trials give access to drugs that are not yet FDA approved. If someone is looking for something that's on a trial, that could be a way to get access.

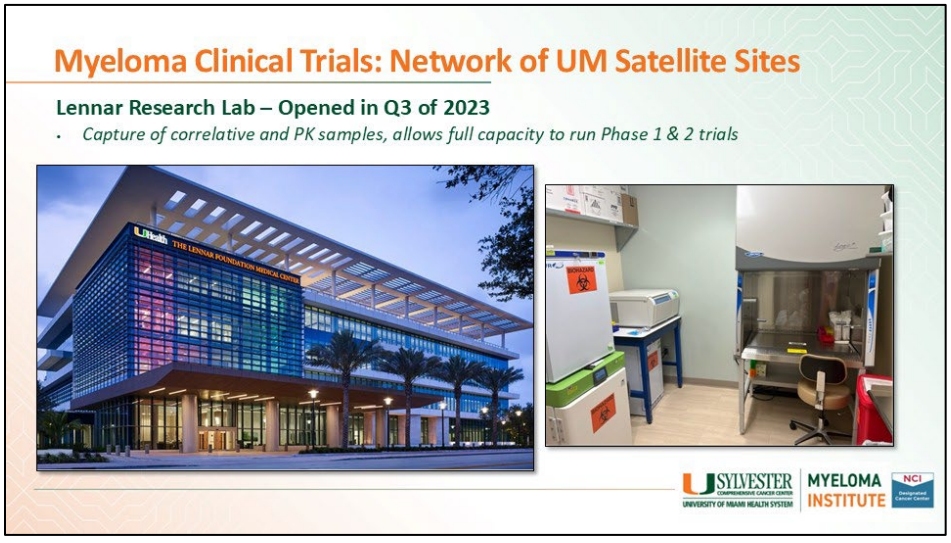


When I came here, there were not very many patients. There were 20 or so patients on clinical trials for myeloma and we now have almost tenfold increased this. We're going to

continue to grow these very, very fast. Thirty percent (30%) of these studies we have open are written by ourselves, and our portfolio is built on the following paradigm.



We look for drugs with novel mechanisms of action. Patients that have run out of options elsewhere can come here, and we have other mechanisms of action that are not FDA approved. We will continue to do this. We will also have studies that are designed to define the mechanisms of response and resistance, so we can learn how to overcome resistance and how we can help individual patients. We look very carefully at our patient population coming here, what the actual needs are. If there are a lot of patients say with kidney failure, we will develop drugs that can be given safely to patients with kidney failure if other drugs are not available, for example, or patients that have other types of limitations or certain needs. That's how we build it. And I also mentioned that we set up our clinical program to provide access. That is very important for clinical trials.
When I came here, I was here in Miami practicing, and I lived in the Coral Gables Pinecrest area, south of the city myself.



In this building there was no way to do the clinical trial. So I moved my clinic there because I knew that I am going to ask for it till we have it. In about four months, we set up a lab, and the lab doesn't have to be that big. We have the culture hood, we have the centrifuge, we have the freezer and refrigerators. And thanks to these very small investments, we can actually do any trial in Coral Gables. We have now replicated this system.

We are not only bringing the standard of care to where the patients live, we also bring out the trials where the patients live, because the traffic here in Miami can be pretty crazy and I'm sure it's the same in many other big cities. And these are things I learned the hard way when I was in New York. We have to build it where the patients live.

I want to end my talk by saying that since we came here we have been very happy to collaborate also with a lot of others. We partnered this February with the very successful Lymphoma, Leukemia & Myeloma conference in New York. They celebrate their 25th anniversary this fall in New York City. And this winter in February, the inaugural winter symposium for this successful conference started here in Miami. And we are very happy to be partners together with the LLM program, the Sylvester Cancer Center is partnering.

We also are the host for the International Myeloma Workshop, and that's going to happen not too many days from today at the Intercontinental Hotel here in Miami.

The last example I will give is, as I mentioned, the myeloma MRD meeting. We moved that from New York City down here to Miami when I came here and now it's going to be the 11th year we have this, and this actually is open for both doctors and patients/caregivers. But we will broadcast it, and it will be available for free to watch for anyone who is interested. We will talk about all the latest strategies, how to track MRD with new technologies, and how the new treatments are panning out. We will have patient representatives that will be legislators also for how to design the studies. And there will be discussions also by people that are developing the new clinical trials. We are very excited about this meeting.

I initially started this meeting, I mentioned, in 2014, and I said to the FDA, "I'm going to have this meeting every year until you approve MRD as a regulatory endpoint." And they

approved it last year. This will be a new version of the meeting because we already delivered that. This will be the first year after the approval from ODAC.

This is the last slide I have, and I thank you so much for your attention and I'm happy to take any questions you may have. Thank you.

Lizette Figueroa-Rivera, MA
Thank you so much, Dr. Landgren, for volunteering your time with us today and discussing myeloma and all the advancements in treatments. As the doctor mentioned, it's time for our question-and-answer portion of our program.

The first question, Doctor. Deborah is asking, "While in remission from myeloma, what would the difference be between choosing standard maintenance therapy or monitoring the disease with labs every three months and bone marrow biopsy once a year?"

C. Ola Landgren, MD, PhD
That's a very good question. I will repeat it. If you have received combination therapy and you're wondering, "Shall I go on maintenance with lenalidomide or shall I just stop the treatment and do monitoring?" I think the standard of care in the United States, at this time, is to do lenalidomide maintenance. If I think about how the field has moved back and forth, and also thinking about how the field has been different across the different regions in the world. In Europe for a long time, where I came from, it used to be no maintenance therapy, and it was basically because of restriction of access. Over time, the European paradigm was to do one year and then many studies for two years, and all the American studies showed superiority that the disease stayed away longer if you do maintenance therapy.

The American studies were always considered to be superior for that reason. But I mentioned in my presentation that life is not fair. Some patients have a very good outcome with less therapy. There are patients that go off therapy that do very well. I think it's probably fair to say that if you go on it or you go off it, you're probably going to have the same lifespan. But really what we are talking about is that the duration of the disease staying away may be statistically longer if you stay on it. But if you have side effects, quality of life also has to be weighted in there. I think that if you can be tested in a safe way and you choose to go off, I don't think that that's necessarily wrong. There is no right and wrong, really.

Lizette Figueroa-Rivera, MA
Thank you, Doctor. We'll take the next question from the telephone audience please.

Mark from California:
Okay, if you're on Tecvayli®, which is a BCMA-directed BiTE (bispecific T-cell engager), if that peters out, should you have another BiTE with a different target or should you get a CAR T with a different target?

C. Ola Landgren, MD, PhD
That's a very good question. I repeat the question with my words, "If someone is on a treatment with a bispecific monoclonal antibody that binds to BCMA, if that were to stop working, would it be wise to go to another BCMA-targeted bispecific antibody, or CAR-T cell with BCMA as a target, or would it be better to go to another mechanism of action, a drug with another target?" I think the short answer is that, statistically speaking, it's better to go to something with a different target because these drugs, if they stop working, one of the reasons they stop working is because the myeloma cells, they stop having the BCMA on their surface.

If you switch from one drug to the other that goes after BCMA, you may still be in a situation where the drug doesn't work, you switch from one drug to the other. But the somewhat longer answer is that that's a simplification of what I just said. The cells don't lose the whole BCMA. And, in fact, the drugs don't just randomly grab to BCMA. The drugs, they bind to certain binding domains that are small proteins that are located on BCMA, the BCMA receptor. If you develop resistance to one drug, it could be because those small proteins that that drug binds to may no longer be expressed. But that could be a drug that is a BCMA drug that actually is designed to bind to certain other small proteins. That may still work.

If you listen to my talk, I talked about the importance of testing. With more sophisticated tests, it would be possible to see if the targets are still there for a list of drugs. But right now, we don't have those tests. But if you could have a test, I could see if the binding domain for another BCMA antibody, if those are still expressed, you could safely go to it, but right now you don't know. You're basically taking a risk. If you, on a probability note, choose, you probably go to something with another target. But could you go back and pick another drug for the same target? You could probably do that. I would for the short term do another target. Sorry for the long answer, but that's a difficult question you asked.

Lizette Figueroa-Rivera, MA
Thank you, and our next question comes from Steve who's joining us in person. Steve is asking about CAR T-cell therapy expansion. "Some products in clinical trials claim rapid expansion in the body instead of waiting weeks for re-engineering in the lab. What are your thoughts on this?"

C. Ola Landgren, MD, PhD
CAR T cells with rapid expansion or not rapid expansion, what that refers to is that... what is a CAR T cell? A CAR T cell is a technology where you take out T cells typically from the same person who's going to get the T cells back. That's what we call an autologous T cell. But you could also have from donors, you could have someone who donated their T cells. That would be an allogeneic CAR T-cell product. For myeloma, right now we don't have any FDA-approved allogeneic, they are autologous from the same person. The question refers to when you give those T cells back to the person where they came from, do they become more and more and more? Should they wipe out the myeloma? Does that happen faster or slower? There are all different drugs that do that job differently. And there is also the dimension of how long do they actually stay in the body? Can they continue to clean up and remove myeloma?

I am not really sure how to answer the question. I can just say that there are only two FDA-approved products that go for the same target. They behave actually quite similarly, but also not very similarly. They are not similar in the sense of the side effects kicking in. One of them, the side effects come after usually 24 hours while the other one takes about a week. I think the biological properties are very different. I don't think we know at this point if this is important, if it's fast or slow as a general rule. These are areas where we are still doing research.

Lizette Figueroa-Rivera, MA
Thank you for the question. Sharon is asking, "What is the most successful number of medications to slow down the myeloma cells? Three, four, or less? Why are there more drugs than less for medication for myeloma?"

C. Ola Landgren, MD, PhD
Which is the most successful number of drugs? I think it depends on what drugs we are talking about. I don't think that there is like a general rule that the more you do is always the best because if the drugs are not that good, obviously that's not going to be the case. But if you look at the drugs that are modern drugs, the immunomodulatory drugs and steroids, they used to be standard over 20 years ago. Then there was the addition of a proteasome inhibitor. So, two became three. In the past few years, it's been more and more common to add an antibody CD38-targeted antibody. Four has been better than three, but does that mean that five will be better than four? I don't know. I think it's very

possible that even three could be equally good to four. It may be even better if you could swap some of the existing drugs in that mix for some other drug. And there are studies that are designed to look into that as we speak. I think as a general rule, more is not always better if you have really good drugs. And I think transplant is another example. Do you need to transplant every patient? I think the answer is no. But could you transplant every patient? Yes, certainly if they are fit and they want to do that. That's another example. And the same question could be asked also for CAR T cells. Is that always the right thing? Probably not, but I think the future with more and more available options, the future will be options. That's what the myeloma field is going—options.

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

Joannette from New York
Yes. I wanted to know. I have no antibodies. Will I get my antibodies back or how does that work?

C. Ola Landgren, MD, PhD
The question is, "You don't have any antibodies. Will they get back?" I assume that you are talking about IgG levels, is that right? Or you're talking about disease antibodies?

Joannette from New York
IgG.

Dr. Ola Landgren MD, PhD
IgG. The body makes immunoglobulins. In a very simple way, the immune system is made up by two major dimensions: one is the cellular side, and the other one is called the humoral side. The cellular side includes a range of different types of white cells. When we do blood tests, we call it white cells, but there are many different types of white cells. One of the types of white cells we're particularly interested in are the neutrophils. We want them to always be over 1.0 or higher. That's the cellular side. The humoral side is the making of immunoglobulins. IgG in reality is the one we want to make sure it has sufficient levels. The textbook would say that a healthy 25-year-old person would have somewhere between 600 and 1,600 grams per deciliter of immunoglobulin G in the blood. But if you treat with the drugs that we use, they can get rid of the myeloma cells, but side effects of the new drugs we have is that they can also kill healthy plasma cells. And they are the cells that make the immunoglobulins, including immunoglobulin G.

Very commonly do we see that the IgG levels go down as we treat the patient with the new drugs. That's a side effect of the medication. Now if the textbook says that it should be 600 to 1,600 grams per deciliter, when should we start worrying and what do we need to do? The field has not really known about this for a long, long time because the drugs used to not be so good and now they are better and better and we see more and more of these side effects. I would say that in the past 10 years we have seen with daratumumab and other antibodies that IgG goes down. If you go under 600, you go 500, you go 400, usually nothing happens.

That seems to be quite safe for the majority of patients. But I have seen patients that have been 200 or even 100 where they have developed more severe infections. Not every person, but there is a higher risk that that could happen. If you start going that low, I would give immunoglobulin IgG also called IVIG, intravenous immunoglobulin G. What

we have learned the hard way as a field is that, with the bispecific antibodies, this phenomena is even more common. You can see much deeper suppressions of IgG. It can go from normal levels to very low in quick time. And that usually seems to increase the risk for quite severe infections. If we treat someone with a bispecific antibody, we want to keep the IgG levels over 400. And the same is also true with cell therapy. If we give CAR T cells, we want the IgG levels to be over 400 and that's very important.

Lastly, I should say, if you step back on the treatment, if you give it a bispecific once a week, and then you give it every other week, and then say you give it once a month, or if you were treated with a CAR T cell in the beginning, it's low. And if you give IVIG once a month, after a while the body will recover. The same is true with the other antibodies as well, that if you give it less often over time, you usually find sort of a sweet spot where the body can maintain the levels.

Lizette Figueroa-Rivera, MA
And we have Jeff in person asking, "Is myeloma inherited?" And I have Yvonne asking on the web, "Currently, is there a genetic test that relatives of patient survivors can take to know their susceptibility of having myeloma?"

C. Ola Landgren, MD, PhD
So the first question, is it genetically inherited, is there a known gene? The answer is, "No." I would say, for the most part, the reason why myeloma happens is largely unknown. There are some risk factors. I've been involved in studies over the years, and I've found together with others that Agent Orange could play a role. Also, I worked when I was at the NCI, pesticide application when I was in New York with the first responders from the World Trade Center, and there have been other studies looking at other things as well. So there are some risk factors that have been proposed, but most people have not been exposed to these things and still a lot of people are diagnosed. So, for that reason, it's correct to say that the reason is largely unknown.

Also say that myeloma, if you look at a number of cases, it is a rare disease. There are about six individuals per 100,000. So that's considered to be a rare disease. When I was at the NCI, we used databases from Scandinavia, where I come from in Europe, and we had access to the whole population of Sweden and the whole population of Denmark. And, at the time, we looked to see if there were patterns of familial aggregation. And we actually found that there are more cases in families. But, if myeloma happens in 6 per 100,000 in family members, that risk was maybe 10 in 100,000. So we're still talking about very, very rare numbers. It's very rare. Families don't only share the genes, they also share the environment and behaviors and everything we do and eat and so forth. So, we still don't know why that is. There is no genetic test that has been found to link with the onset of disease.

The last thing I could say along these lines is that, if someone wants to know if they have any increased risk, that is true whether they have a family member or not or if they're exposed to some of these things I mentioned or not. If you do blood tests, you can check with SPEP (serum protein electrophoresis), immunofixation, and kappa/lambda light chains and see if you have abnormal proteins. If you do, you could fulfill the diagnostic criteria for MGUS (Monoclonal Gammopathy of Undetermined Significance), a monoclonal gammopathy.

There is currently not yet a guideline saying that screening is recommended, but there is a large screening study where I'm the co-PI (principal investigator) for in Iceland led by Sigurður Kristinsson, who used to be actually my PhD student over 20 years ago. He's now the boss of the program there. He runs a big program. We have found that, by monitoring people and following them, that you can see sooner if someone is progressing into myeloma so you can avoid a lot of the complications. But the final results have not yet been published. So until then, there is not yet a screening recommendation in print. But I think there probably will be in the future for select groups in particular high-risk groups.

Lizette Figueroa-Rivera, MA
I have a lot of questions in regards to neuropathy. Judy's asking, "Are there any advances for relieving pain associated with myeloma as well as neuropathy?"

C. Ola Landgren, MD, PhD
If there are advances? Well, I think that, importantly, figuring out what the reasons are is always important. If you know the problem, you are more likely to be able to fix it. And that could be some patients that have underlying other processes. There is something called light chain amyloidosis or AL amyloidosis to make sure that that's not a condition that's going on. That is luckily a quite rare condition. But to rule that out is important and that can be done by doing some additional blood testing. There's something called troponin T or NT-proBNP testing, looking at some of the other labs and also making a careful exam of the patient. And that can be additional tests that can be done as well.

Neuropathy for the vast majority of cases is not due to that, but that just should be checked and ruled out. I think there is a higher risk for neuropathy. We don't really know. I think it probably is due to some antibodies that are made by the plasma cells that we just don't have the right test to figure out yet. So, that could happen both in MGUS, smoldering myeloma, or a patient with new diagnosis of myeloma.

Then of course there are drugs that can lead to it. Velcade or bortezomib can cause a lot of neuropathy. We have used a lot of carfilzomib for those reasons because it doesn't have those side effects. The older drugs like thalidomide or so could also do it and that could be other drugs as well. Lastly, there are other conditions that can happen. Say someone developed diabetes, that can also lead to that type of nerve sensation alterations or B12, B6 vitamin changes or thyroid or other things. So to just make sure that all the symptoms are not due to another comorbidity that could be easily fixed.

Lizette Figueroa-Rivera, MA
Thank you. And the next question, Terry is asking, "Do you think CAR T should come before stem cell transplantation? I was reading about patients not responding as well to CAR T if they have had a prior transplant."

C. Ola Landgren, MD, PhD
There was a presentation at the American Society of Hematology—the ASH meeting—in San Diego in December this past year. That was from the Mass General in Boston. They have looked at patients that got CAR T cell with a prior transplant versus not. They showed that the patient with a prior transplant, the CAR T cells work much less well. They argued exactly what was asked here that maybe you shouldn't do a transplant because that would decrease the risk for CAR T cell working. That's one study. It's not a randomized study, and you could argue back and forth about what that really means. I

don't have the details of the study, it was just a presentation at this meeting I mentioned. That's where those results come from.

Now the other question is, is it better with a CAR T cell and then transplant? How usually the answer to those types of questions are being addressed is by randomized studies. There are actually randomized studies that have been developed and ongoing. They're not yet done or finished these studies. But one of them is that you have combination therapy and then patients are randomized to either CAR T cell or transplant to see which has the long-term benefit, which is better. There are also studies that are used in combination therapy without transplant, but CAR T cell is compared to continued maintenance therapy with more drugs. So trying to see if CAR T cell could play a role.

But there are also studies that are looking at bispecific antibodies. We have, just for example, a study here in Miami where we give an antibody with a bispecific antibody once a week for four months instead of a transplant. So far, those results are amazing. So could CAR T cell be one? Maybe. Could bispecific be one? Maybe. Could be other. We don't know. Maybe.

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

Joe from Maryland
Thank you. With the current state of the affairs in the United States, with a lot of economic upheaval aimed at various health and medical institutions such as the FDA, how is this going to affect you and others in terms of drug development, novel biomarkers, and anything else that's going to help you find a way to make myeloma disappear?

C. Ola Landgren, MD, PhD
Yeah, that's a very difficult question. I'm not sure I know the exact answer. Maybe my answer is that there are always changes, and the way we run our programs is that we are trying to look from our experience in the past. I think the financial situation right now, when it comes to grants from the federal government, looks less good. But we also standing on the legs of... we have foundations that we are applying for grants at those. We also have philanthropic donors that have provided us with funds.

We try to sort of over time to risk spread our programs. I think our program overall is in very, very good shape and our mission has not changed and will not change. We are here to provide care, the best possible care, for all the myeloma patients here in Miami. We also have a program to find a cure for the disease. There are things we cannot really control, but I think everything goes also in a pendulum when it comes to those things you bring up.

Lizette Figueroa-Rivera, MA
Thank you doctor. Next question comes from Graceann. Graceann is asking, "Please advise on the word 'remission' when discussing a myeloma patient. It's my understanding that remission is not possible."

C. Ola Landgren, MD, PhD
Well, remission is definitely possible, and these are words, and a long time ago people had their own way of defining these things. It made it very difficult to compare different

studies. I remember when I worked in Washington, D.C. or in Bethesda, Maryland at the NCI, there was a meeting in 2005 and a meeting happened in D.C., where all the stakeholders came together and agreed to have one way of defining these things so we could compare different studies with each other. This was a big step forward. The definition was that if the protein in the blood, the monoclonal protein, is zero, and if the light chains have been found to be abnormal to begin with, that they also normalized, that that would be the first piece in the puzzle. Then the second piece in the puzzle was to do a bone marrow biopsy and make sure that there are no residual myeloma cells using standard workup. That would be the definition of complete remission or complete response or CR. This has many different names, but it is the same thing. That is still the guideline.

What we learned over the years, and I remember when I worked at the NIH, was that many patients could achieve remission. I remember we saw more and more patients, so I was thinking, if the game is just about achieving remission, we can almost stop developing things because most of our patients 20 years ago, 15 years ago, were in remission when I was at the NCI. So I was wondering if we don't develop better tools, it's not going to be meaningful to try to improve things. So we developed the MRD tools. What we saw was that, in many patients that were in remission, in many of them there were still residual disease cells when we looked deeper and some of them there were not.

When we followed them over time, we saw that the ones that we couldn't find any residual disease cells, that they had the best prognosis. It makes sense if there is no disease, that would be the better outcome. This is really how my interest in MRD started. I started seeing these things.

So, coming back to your question, remission, can you define that in myeloma? Yes, in newly diagnosed myeloma, I would say in our clinics between 95% and 98% of our patients are in remission after we have treated them with our drugs. We have probably at least 70% of our patients being minimal residual disease negative, which is one step beyond remission. So remission is sort of with a standard test, and then if you apply the minimal residual disease testing beyond that, that that's a higher degree of negativity for no detectable disease.

Lizette Figueroa-Rivera, MA
Thank you. And our next question comes from Edward. Edward is asking, "What are the side effects of bone strengtheners?"

C. Ola Landgren, MD, PhD
Bone strengtheners are typically of the class bisphosphonates. Bisphosphonates can be actually quite toxic. Many patients have told me that, when they have been treated for myeloma, that the drugs were not that toxic. It was quite low side-effect impact with the combination therapies we have done. While the bone strengtheners, many patients have told me was like getting flu every time you got these medications. That's what I heard from many patients. Not every patient, but many patients have told me that.

There are also bone strengtheners that are of another class, called rank ligand inhibitors (RANKL). It's doing similar things but it's using different approaches to achieve the same thing, to reverse the buildup of the bone versus the breakdown of the bone, to make the bone stronger. Different patients will respond differently. I think, importantly, there are

guidelines showing that you should not have bone strengtheners for longer than two years. If you get combination therapy in a newly diagnosed patient, you can do it once a month, but you can also go to every three months because they last for a very long time. The half-life is very long. So you could get once a month for a while and then do every three months, but with a total of a two-year window to stop it.

Lastly, I want to say that there are controversial topics everywhere, including here. So one controversial topic is do you really need to give these bone strengtheners for every patient? I think the answer is probably, "No." When I was in New York, I made very good friends with all the other institutions in New York, with Mount Sinai, NYU, Columbia, and Cornell. We met very regularly for dinner, with the leaders of the programs. We asked each other questions that you couldn't find anywhere else. One time I remember I asked at one of these dinners, "Do you guys give these bone strengtheners for patients who have no disease?" And everyone looked at me and no one wanted to answer because the guideline said, "Yes." Then one of my colleagues said, "I don't." And then all the others said, "I don't do that either." I said, "I'm glad you told me that because I don't do it as well." A lot of things are not always the way the guidelines are written. I think if there is no myeloma in the body, what are we trying to prevent?

Because the myeloma in the bone marrow leads to the bone surrounding the bone marrow being weakened. But if you can treat with effective drugs and the patient is MRD negative, the bone will heal usually by itself. And these drugs can also cause side effects in terms of renal failure. There's a small proportion of patients that have poor dental status that could develop something called osteonecrosis of the jaw (ONJ). Where there could be big, big problems in the mouth that could turn into chronic problems. So, there are a lot of differences in opinion. I'm not saying what other people should do. I can share my perspective and I can share the guideline. The guidelines say give it once a month to every three months for a total of two years. In my practice, if a patient complains about side effects, I usually stop it. I, many times, don't even give it, because if I get rid of the disease very quickly with the new drugs, I don't think there's such a big problem. If someone has a lot of disease and there are issues with the skeleton, I may give it, but I've really changed my perspective on this over time.

Lizette Figueroa-Rivera, MA
And our last question today, I know that you mentioned ChatGPT, which utilizes artificial intelligence. And Judy's asking, "What part of artificial intelligence is currently playing a role in myeloma research? Or, what could AI, the role of AI, be expected to play in the future for myeloma?"

C. Ola Landgren, MD, PhD
I could answer the question in couple of different ways. The first may be a silly way of answering, saying, "I'm not going to hire Dr. Google or Dr. ChatGPT because they do a lot of mistakes." So that would be sort of the silly way of answering it. But maybe the less silly way of answering it is to say that we actually use a lot of ChatGPT and many other tools in our research because we do a lot of complicated analysis with a lot of data points. So, say we have a tissue, we sequence, we DNA or RNA, we even have just pictures. We try to understand and analyze the pictures or the sequences or things like that, proteins in relation to some form of outcome. There are so many different ways you can do it. We build in computer programs. We have a very strong computational oncology program, probably one of the strongest in the country. Probably one of the strongest in the world for myeloma, we have here in Miami. We are not only one. There

are also good programs, for example, in Boston and elsewhere, but we have a very strong program. In those programs, including ours, we can use these tools. We can develop code to analyze data and we can then post that data into the system and say, "Can you help me and see if you can improve the code?" And the computer will come back with pretty creative answers. It's almost like sitting next to a very smart PhD student, but it's your computer. If you ask a lot of questions, if you ask 20 questions, maybe 18 of them come back like, "Wow." But if you don't know the two that are wrong, if you follow everything, that's why you start doing mistakes.

We take someone who is really skilled knowing how to handle it, but you can actually work with a computer. You can also ask the computer, "What is this?" The computer will say, "It's that." Then you can say, "How did you know that?" Then it would show you where it was looking and then you start looking there. And I wouldn't look there myself. "Oh, maybe that's important to look there." So, you can use it in ways that can really leverage things. So, I think we will use more and more of these tools, but I don't think we... we are not going to hire them in the clinic, that's for sure.

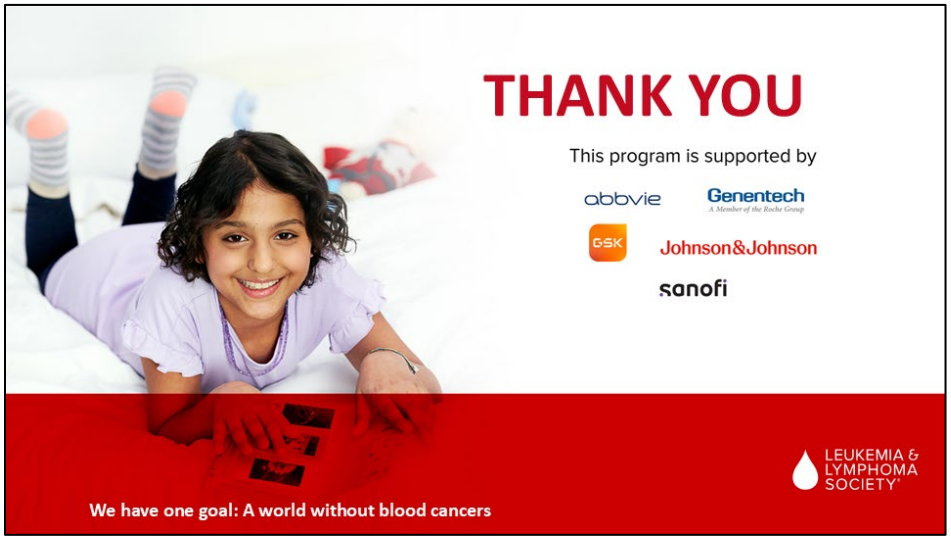
Lizette Figueroa-Rivera, MA
Well, thank you so much Dr. Landgren for this very informative presentation. Thank you.

C. Ola Landgren, MD, PhD
Thank you. Thank you very, very much. Thank you so much.

Lizette Figueroa-Rivera, MA
If we were not able to get to your question today, please call us at The Leukemia & Lymphoma Society. We have Information Specialists that can speak to you from 9:00 AM to 9:00 PM Eastern Time. Or you can reach us by email at LLS.org/ContactUs. You can call us at 1-800-955-4572. And also, patients as well as caregivers can schedule a free personalized nutrition consultation with our dietitians, and you could reach them at LLS.org/Consult.

We also have nurse navigators in our clinical trial support center that are available to assist you in finding any available clinical trials to see if a clinical trial is appropriate for you. For more information about our nurse navigators, you can contact them at LLS.org/Navigation.

LLS offers a variety of education and support resources, including online chats, which are free live forums that are moderated by oncology social workers. We also offer free educational videos and podcasts, and you can see Dr. Landgren on some of our videos. And The Leukemia & Lymphoma Society also offers financial assistance to help individuals with blood cancer. And for more information on our financial assistance programs, you can contact LLS.org/Finances. Please note that also continuing education credit is not being offered for this program for healthcare professionals.



Again, thank you so much, Dr. Landgren, for sharing your knowledge with us today. And thank you for being here and for all that you do for all of your patients as well as The Leukemia & Lymphoma Society. We're honored to be here with you today.

And, again, we'd like to acknowledge and thank AbbVie Inc., Genentech, a member of the Roche Group, GSK plc, Johnson & Johnson, and Sanofi for their support for today's program.

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