Transcript

Slide 1. Welcome & Introductions

Operator:
Greetings and welcome to *Current and Emerging Therapies for Myelodysplastic Syndromes* telephone and web education program. It is now my pleasure to introduce your moderator, Ms. Lizette Figueroa-Rivera. You may begin.

Lizette Figueroa-Rivera:
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I would like to welcome all of you. We have over 400 people participating from across the United States and several countries around the world, including Australia, Canada, Denmark, Italy, Switzerland, and the United Kingdom.

Special thanks to Dr. Mikkael Sekeres for volunteering his time and expertise with us today.

Before we begin I'd like to introduce Meredith Barnhart, Director of The Leukemia & Lymphoma Society's Information Resource Center, who will share a few words. Meredith, please go ahead.

Meredith Barnhart:
Thank you, Lizette. I'd like to add my welcome to the patients, caregivers and healthcare professionals attending the program today.

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. To date we have invested over $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education, and support, and we touch patients and their communities through our 56 chapters across the United States.

LLS also acts as the voice for all blood cancer patients. We advocate for patients, survivors, and their families, helping them navigate their cancer treatment and ensuring that they have access to quality, affordable and coordinated care.

We're fortunate to have our presenter today Dr. Mikkael A. Sekeres, one of our nation's leading experts in myeloma. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to thank him for providing us today with important information on myelodysplastic syndromes.

Thank you all and now I'll turn the program back to Lizette.

Lizette Figueroa-Rivera:
Thank you, Meredith.

Support for this program is provided by The Leukemia & Lymphoma Society in collaboration with the Aplastic Anemia and MDS International Foundation. We would like to acknowledge the Aplastic Anemia and MDS International Foundation, who provided promotional support for this program. They are another patient resource that provides free print materials, regional patient conferences, online education programs and peer-to-peer support. They also have a help line with Information Specialists waiting to answer your questions.

Slide 2: Current and Emerging Therapies for Myelodysplastic Syndromes

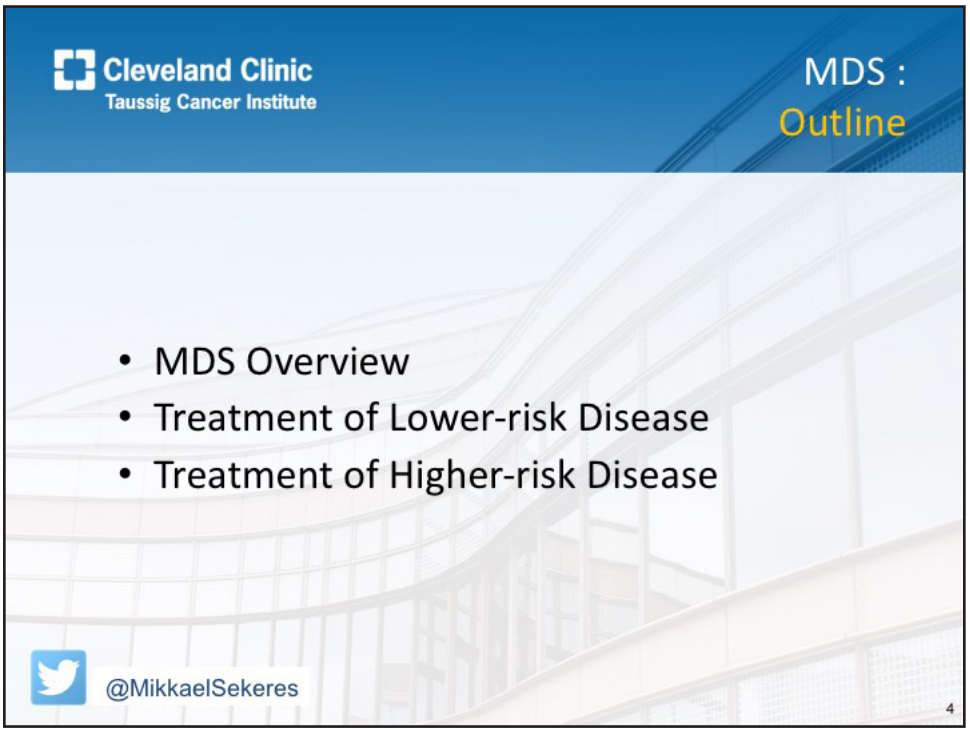
I am now pleased to introduce Dr. Mikkael Sekeres, Professor of Medicine at Cleveland Clinic in Cleveland, Ohio. Dr. Sekeres, I'm privileged to turn the program over to you.

Dr. Mikkael Sekeres:
Thank you so much, everyone. I want to thank everyone who's listening today. It takes a lot to log into one of these webinars or listen by phone and I appreciate your taking the time. I also want to thank The Leukemia & Lymphoma Society and Aplastic Anemia and MDS International Foundation. These are both just fabulous organizations that keep our patients front and center in all of their initiatives, particularly when it comes to educational programming. And I really do appreciate that they make these sorts of programs available to all of our patients.

I am going to talk today about myelodysplastic syndromes.

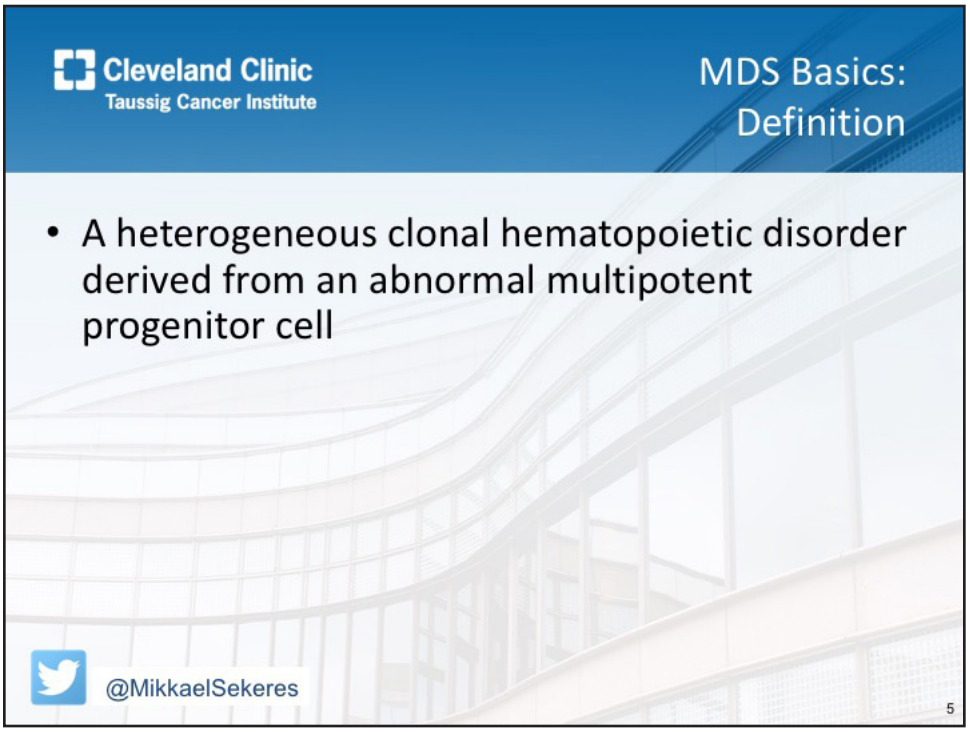
Slide 3: Disclosures

That's the disclosure slide. And now a little bit of an outline.



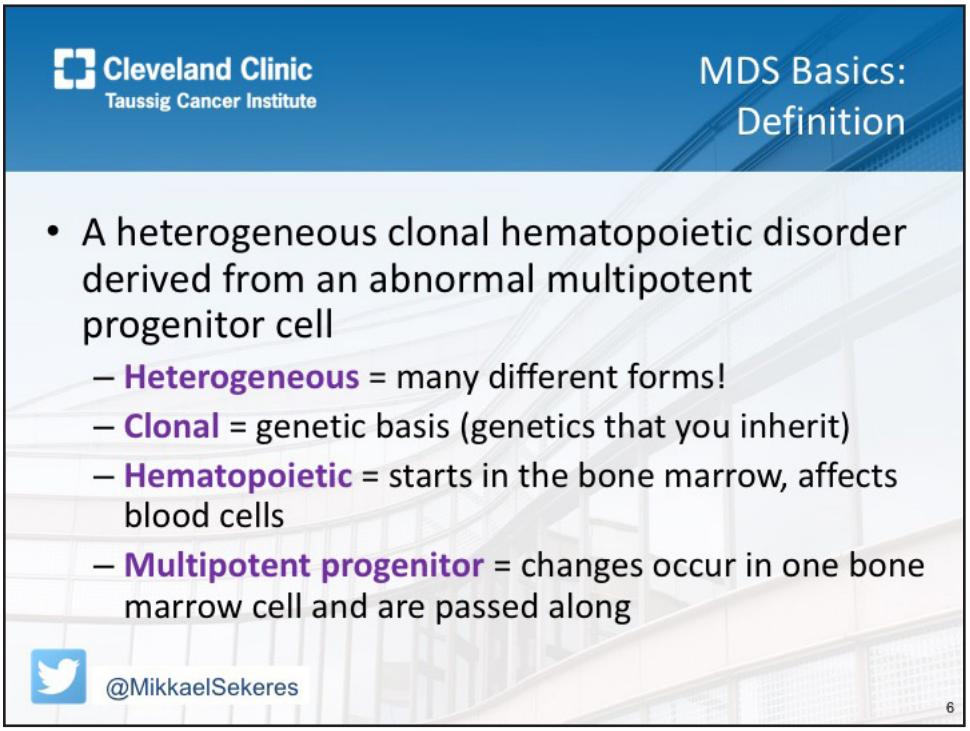
Slide 4: MDS: Outline

I'm going to give an overview of myelodysplastic syndromes to make sure that we are all on the same page in how we talk about these collections of bone marrow disorders. Then I'll talk about treatment of what we consider to be lower risk MDS and finally higher risk MDS.



Slide 5: MDS Basics: Definition

So, the myelodysplastic syndromes are defined as a heterogenous clonal collection of hematopoietic disorders derived from an abnormal multipotent progenitor cell. Now I am embarrassed to say that I have written sentences like that in scientific journals or in textbooks and I find it almost uninterpretable myself.

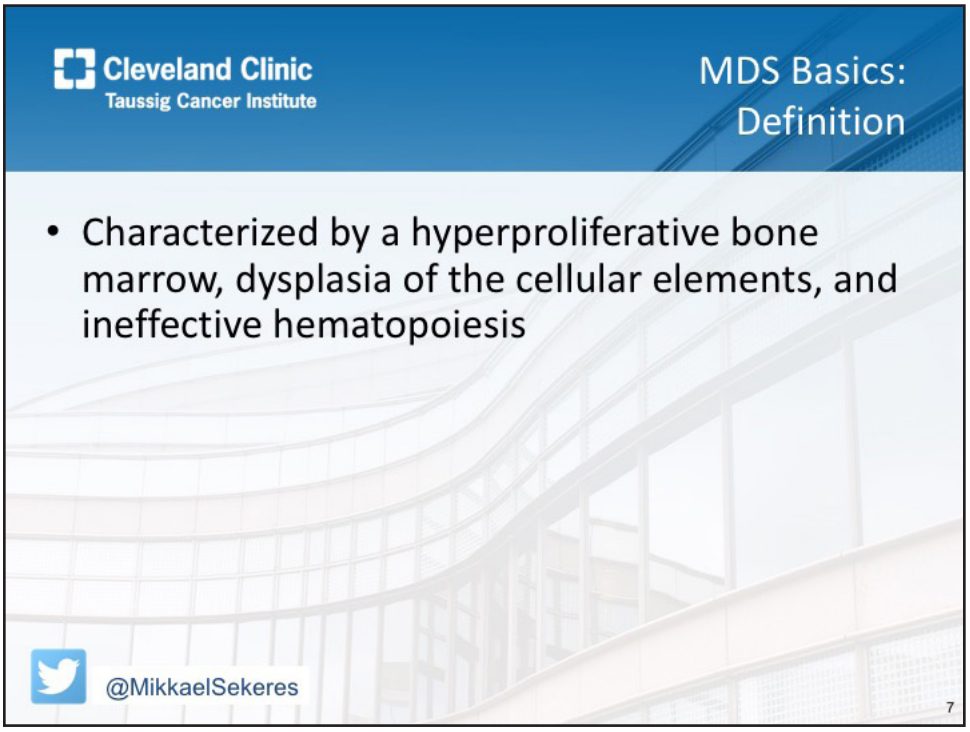


Slide 6: MDS Basics: Definition

So, by heterogeneous we mean that myelodysplastic syndromes take on many different forms and that's why we give it a plural at the end. It's a lot of different disorders that are lumped into this one classification. It's clonal, meaning that it has a

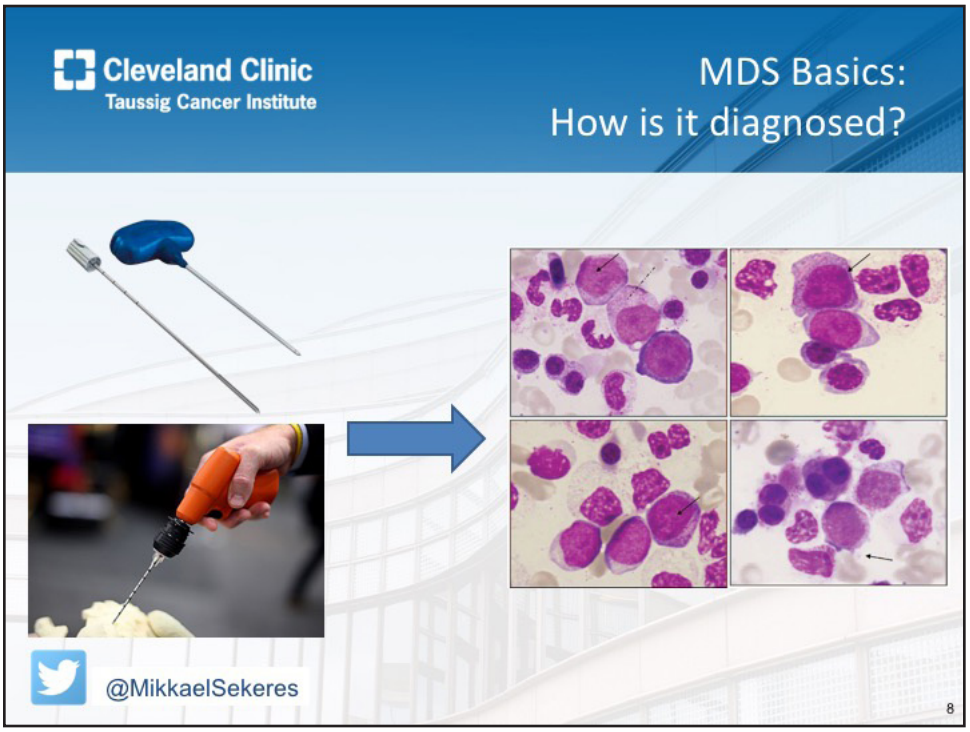
genetic basis. Not genetics that you inherit or that you pass down to your kids or your grandkids. As we age and live a good life, we acquire abnormalities in our genetics, in our DNA. And over time, decades, those genetic abnormalities accumulate and can cause myelodysplastic syndromes.

It's hematopoietic, means it starts in the bone marrow and affects blood cells. And when we talk about a multipotent progenitor cell, we're talking about a bone marrow cell that passes along these abnormalities.



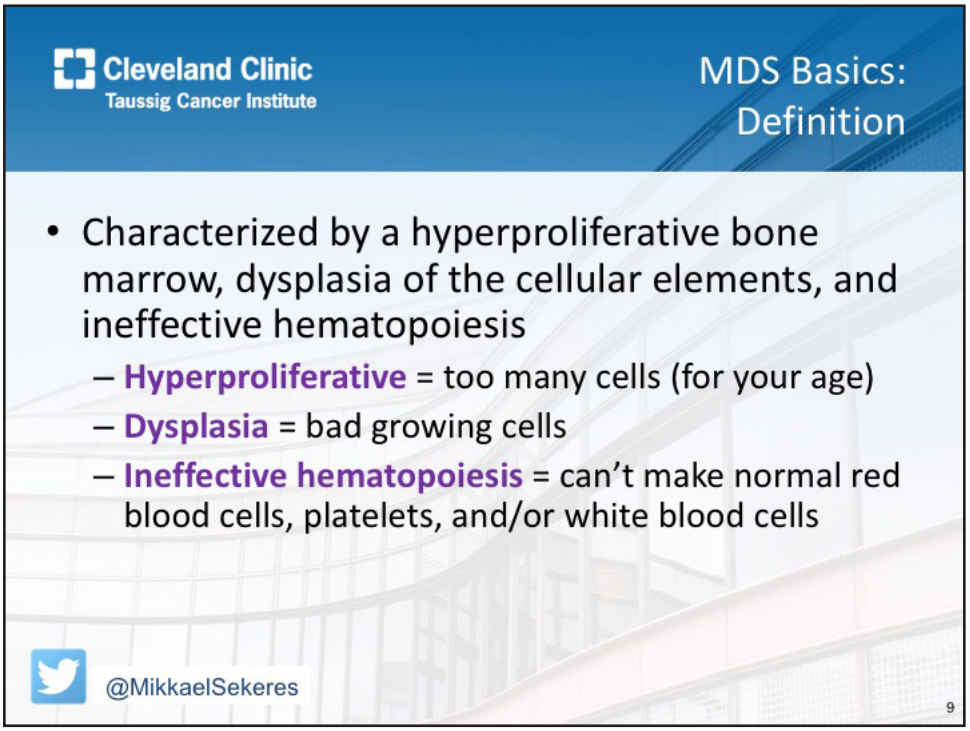
Slide7: MDS Basics: Definition

The second part of the definition, it's characterized by a hyperproliferative bone marrow, dysplasia of the cellular elements, and ineffective hematopoiesis. So what does that mean?



Slide 8: MDS Basics: How is it diagnosed?

So hyperproliferative means that too many cells are growing for your age. When we do a bone marrow biopsy we look under a microscope and we see a bunch of cells, some bone, some air, and you'll excuse the expression, some fat. And in that microscope view our, pathologists quantify what percentage of all of that are cells.

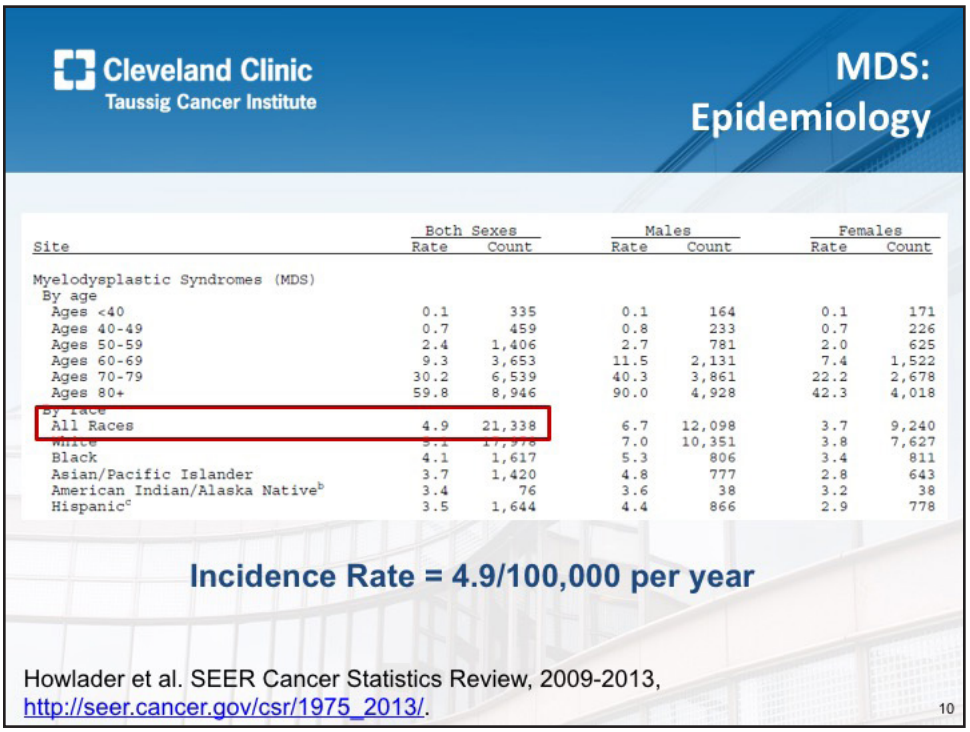


Slide 9: MDS Basics: Definition

The rough calculation is that the percentage of cells should be 100 minus your age. So, if you're 70 years old, we should see about 30% of our view comprised of cells. When we see 60% or 70% cellularity, 70% cells, then we say that it's hyperproliferative.

Dysplasia, if you break up the word, means bad growing cells. And ineffective hematopoiesis means your bone marrow can't make the normal red blood cells, platelets, and/or white blood cells that it's supposed to.

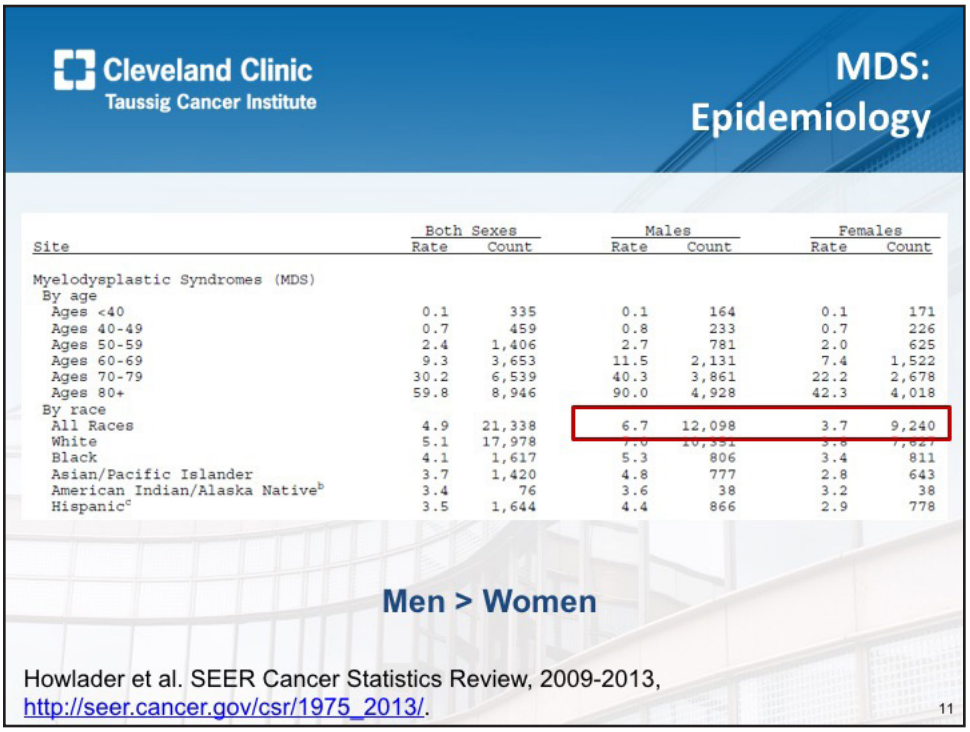
So, some of the background for MDS. You briefly saw earlier a photo of how MDS is diagnosed. It's diagnosed with a bone marrow biopsy. I'm sure a lot of you on the call are familiar with that procedure. Sometimes that's a big long needle that's inserted into the back of your hips. If you ever rest your hands on your haunches, it's just a little bit below that. Or sometimes we use a drill to get the bone marrow sample. Both are equally effective at getting a good bone marrow sample. Some of my patients have told me they think the drill is more comfortable, but for those of them who associate the drill with a dentist's office, they find that disconcerting.



Site	Both Sexes Rate	Both Sexes Count	Males Rate	Males Count	Females Rate	Females Count
Myelodysplastic Syndromes (MDS)						
By age						
Ages <40	0.1	335	0.1	164	0.1	171
Ages 40-49	0.7	459	0.8	233	0.7	226
Ages 50-59	2.4	1,406	2.7	781	2.0	625
Ages 60-69	9.3	3,653	11.5	2,131	7.4	1,522
Ages 70-79	30.2	6,539	40.3	3,861	22.2	2,678
Ages 80+	59.8	8,946	90.0	4,928	42.3	4,018
By race						
All Races	4.9	21,338	6.7	12,098	3.7	9,240
White	5.1	17,978	7.0	10,351	3.8	7,627
Black	4.1	1,617	5.3	806	3.4	811
Asian/Pacific Islander	3.7	1,420	4.8	777	2.8	643
American Indian/Alaska Native[b]	3.4	76	3.6	38	3.2	38
Hispanic[c]	3.5	1,644	4.4	866	2.9	778

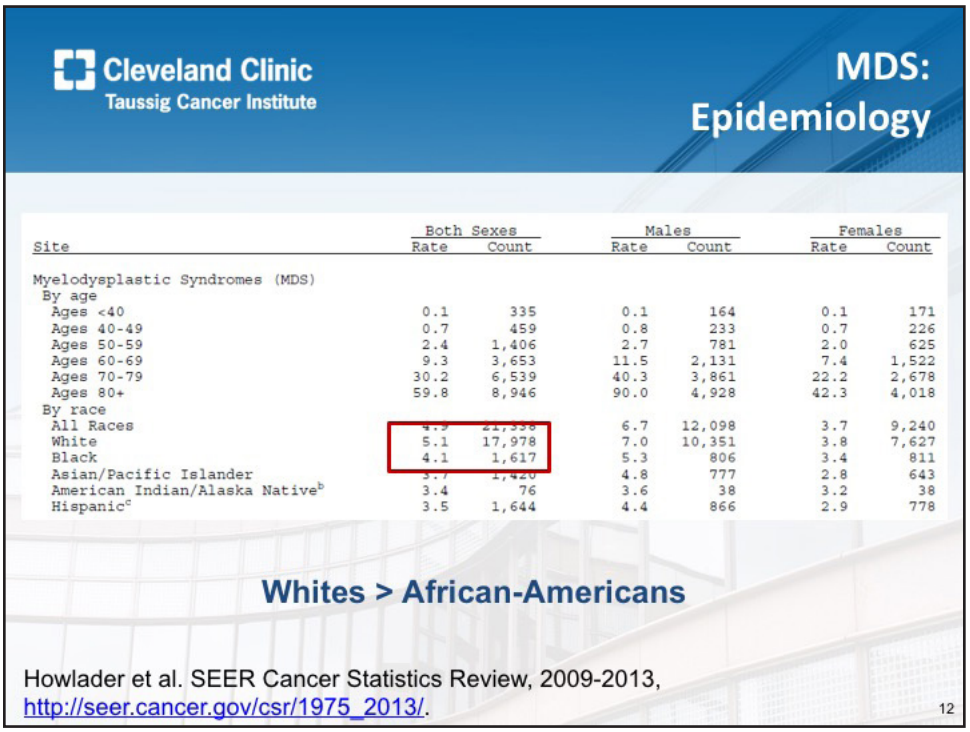
Slide 10: MDS: Epidemiology

Some of the basic epidemiology of myelodysplastic syndromes, it's diagnosed in 4.9 per 100,000 people per year. That roughly translates to about 20,000 new diagnoses in the United States each year. To put that in context, there are 220,000 people diagnosed with prostate cancer each year, 220,000 diagnosed with breast cancer, and about 170,000 diagnosed with lung cancer. So at 20,000 it's not as common as lung cancer, breast cancer or prostate cancer, but it is the most common disorder of the bone marrow.



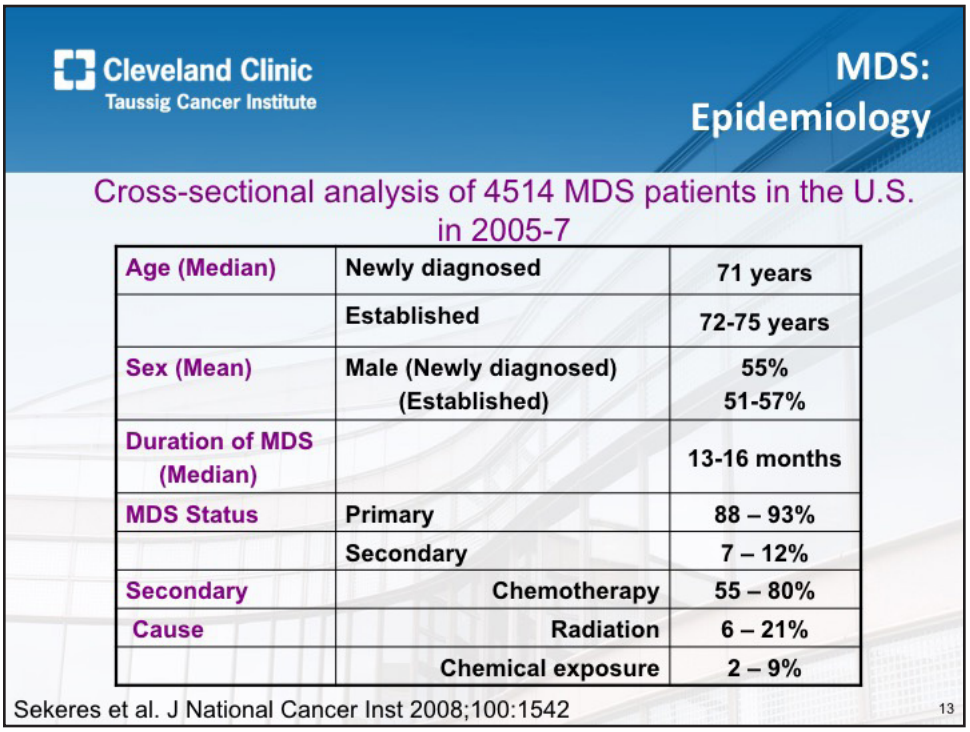
Slide 11: MDS: Epidemiology

Men get it more than women.



Slide 12: MDS: Epidemiology

And white people get it more commonly than African-Americans.

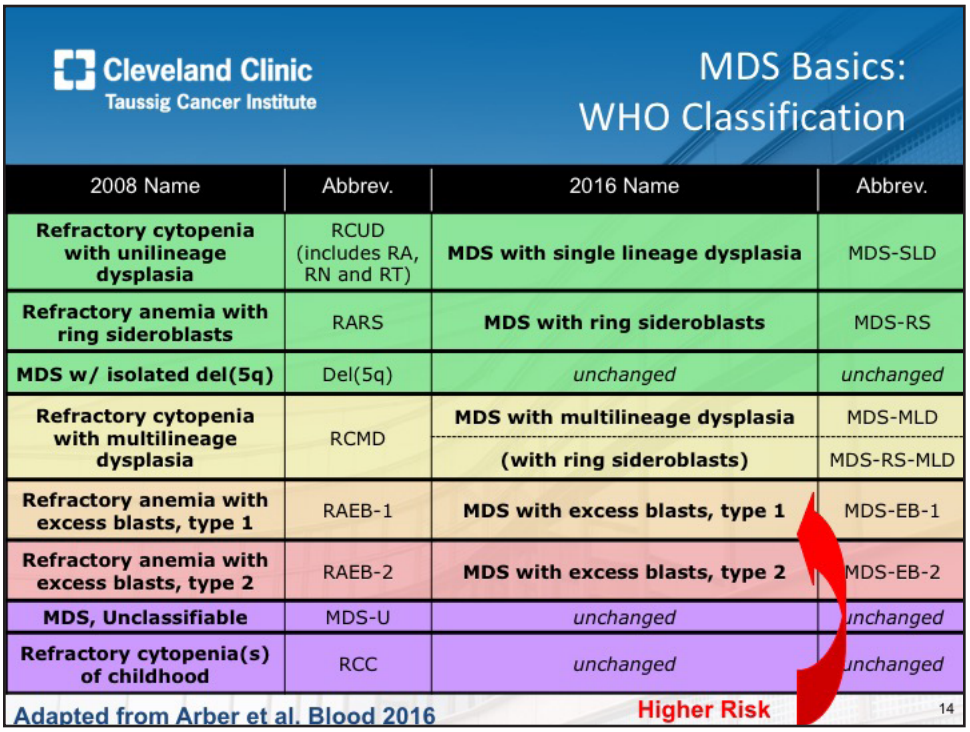


Slide 13: MDS: Epidemiology

Taking a broad view of what myelodysplastic syndromes looks like, the average age at diagnosis is about 71 years old. There's a slight male predominance as I mentioned. About 90% of MDS is what we call primary, meaning it just arose with no kind of trigger. About 10% is secondary, meaning that the MDS arose from some previous insult.

Most of secondary MDS arose because of treatments we give for other cancers. So, when we treat breast cancer with chemotherapy or radiation therapy or lymphoma with radiation therapy or chemotherapy, there is a chance that we may be causing damage to bone marrow cells and that damage may lead to myelodysplastic syndromes.

So, one of the most common questions I get from my patients is what caused my MDS. The answer is, frankly, just dumb luck. It just arose from a lifetime of living and acquiring genetic abnormalities that led to the myelodysplastic syndromes. In a very small percentage of patients is it ever caused by exposure to previous chemotherapy or radiation therapy, and an even smaller percentage of people was it ever caused by environmental exposures.



Slide 14: MDS Basics: WHO Classification

How is MDS classified? Well, the World Health Organization (WHO) is the group that classifies myelodysplastic syndromes, and what they do is break it into a number of different categories. And this looks more complicated than it actually is.

Myelodysplastic syndrome is classified according to whether or not there is a single lineage dysplasia or multilineage dysplasia. Single lineage dysplasia, what that means is one of the cell lines is affected. It could be that somebody has low red blood cells, they're anemic, or low platelets, or low white blood cells. That's all what's referred to as unilineage dysplasia, single lineage dysplasia.

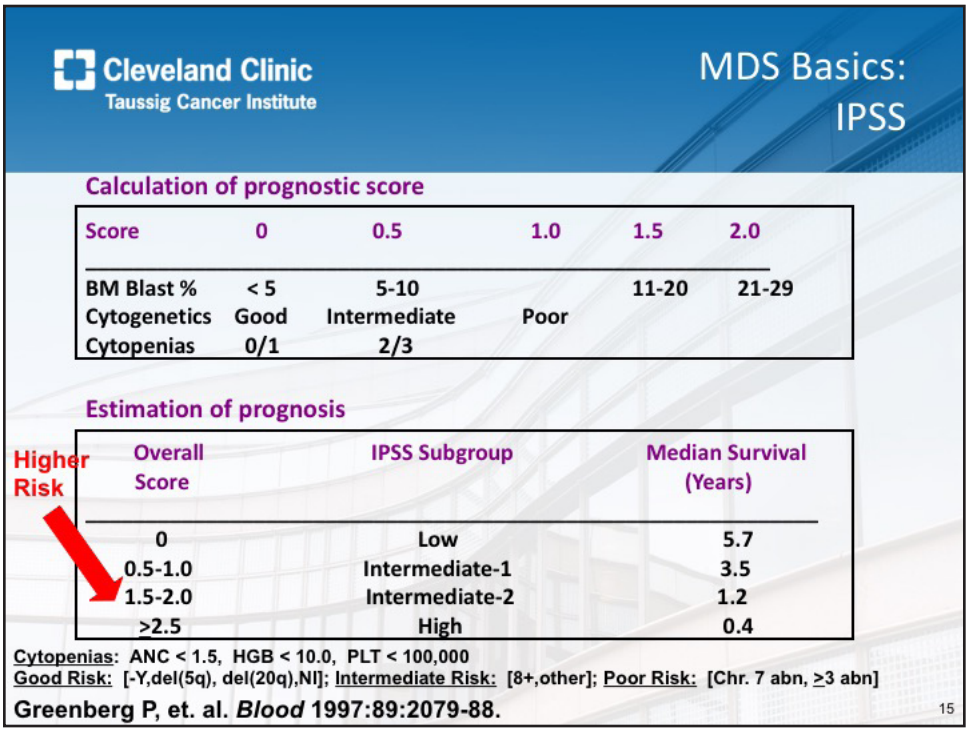
MDS can include refractory anemia with ring sideroblasts. Ring sideroblasts are cells that take up a dye that illuminates actually a very pretty ring around its exterior, or MDS with isolate deletion 5q, it's the genetic abnormality I've talked about before, involves the fifth chromosome.

People can have refractory cytopenia with – MDS with multilineage dysplasia, meaning there are multiple cell lines affected. Somebody may be anemic and have a low platelet count or anemic and have a low white blood cell. Or someone can have what's referred to as refractory anemia with excess blasts.

What are blasts? Blasts are immature white blood cells in the bone marrow. So, everybody on this call right now, including me, has blasts in the bone marrow. I think about them as if you think of cells as becoming more mature and going through elementary school, middle school, high school, and then graduating from the bone marrow to go into the bloodstream, blasts are stuck at the kindergarten stage or first grade stage. They haven't matured to become a high schooler, to go out and make a living. So, we all have blasts, we need them to make those high schoolers to go out and make a living.

It's normal to have fewer than 5% blasts in your bone marrow. Once you have 5% blasts or more, it's considered abnormal. Patients who have the type 1 of excess blasts have between 5 and 9% blasts. Those who have type 2 have between 10 and 19% blasts.

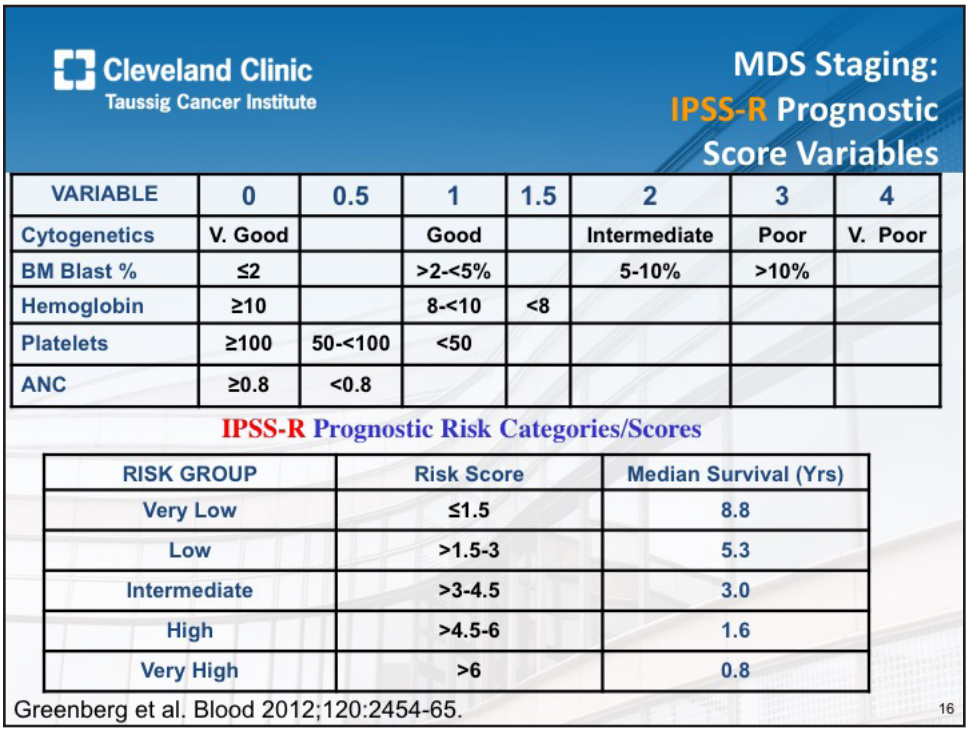
So, if you're trying to simplify this, as I do, you would say that people who have excess blasts have higher risk MDS. Those who have fewer than 5% blasts, the other categories, have lower risk MDS.



Slide 15: MDS Basics: IPSS

But MDS is a little more complicated than that. So, we don't have a formal staging system for MDS. You may have friends who have breast cancer or lung cancer and they say, oh, I'm stage 2 or I'm stage 3 or 4. With MDS we don't have staging, but our default staging system is the International Prognostic Scoring System (IPSS). And what it does is assign a score for the blast percentage that you have in your bone marrow, the gene abnormalities that I talked about earlier, those chromosomes that are abnormal, and those fall into three different risk groups of good, intermediate, or poor, and the number of cell lines that are affected by MDS, what we refer to as cytopenias, and that can be one cell line affected, maybe it's just an isolated anemia, or three cell lines affected. Maybe somebody has an anemia and a low platelet count and a low white blood cell count.

We then add up the scores from this system to place people into a category within the IPSS of low, intermediate 1, intermediate 2, or high. The higher your score, the higher risk your MDS is. And by higher risk I mean the more likely the MDS is to evolve into something more serious, such as acute myeloid leukemia.



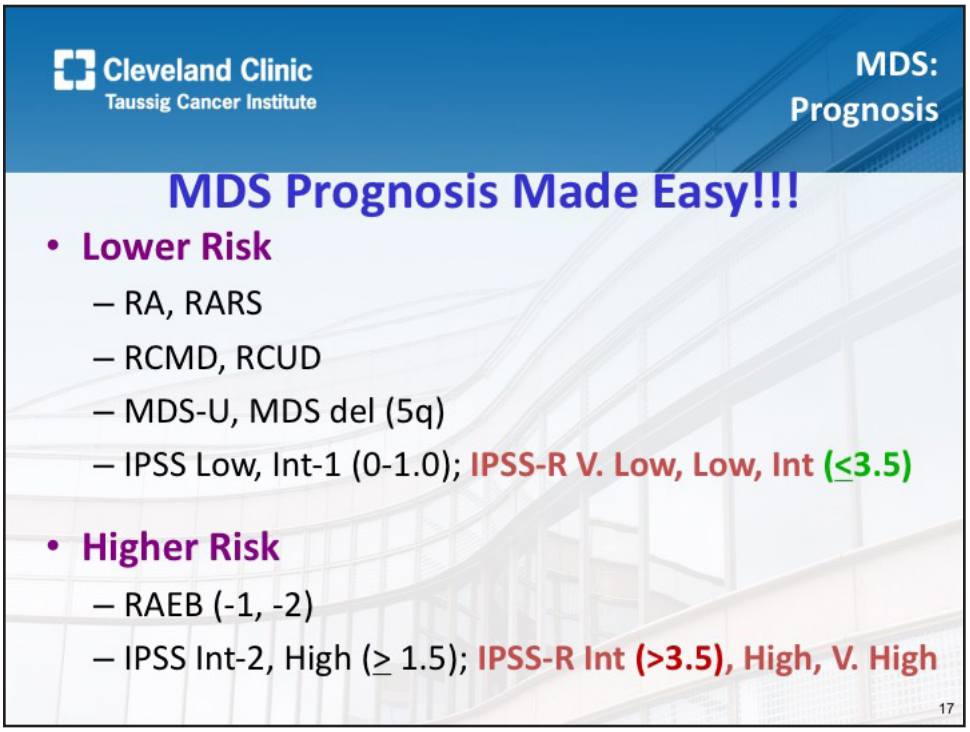
VARIABLE	0	0.5	1	1.5	2	3	4
Cytogenetics	V. Good		Good		Intermediate	Poor	V. Poor
BM Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

RISK GROUP	Risk Score	Median Survival (Yrs)
Very Low	≤1.5	8.8
Low	>1.5-3	5.3
Intermediate	>3-4.5	3.0
High	>4.5-6	1.6
Very High	>6	0.8

Slide 16: MDS Staging: IPSS-R Prognostic Score Variables

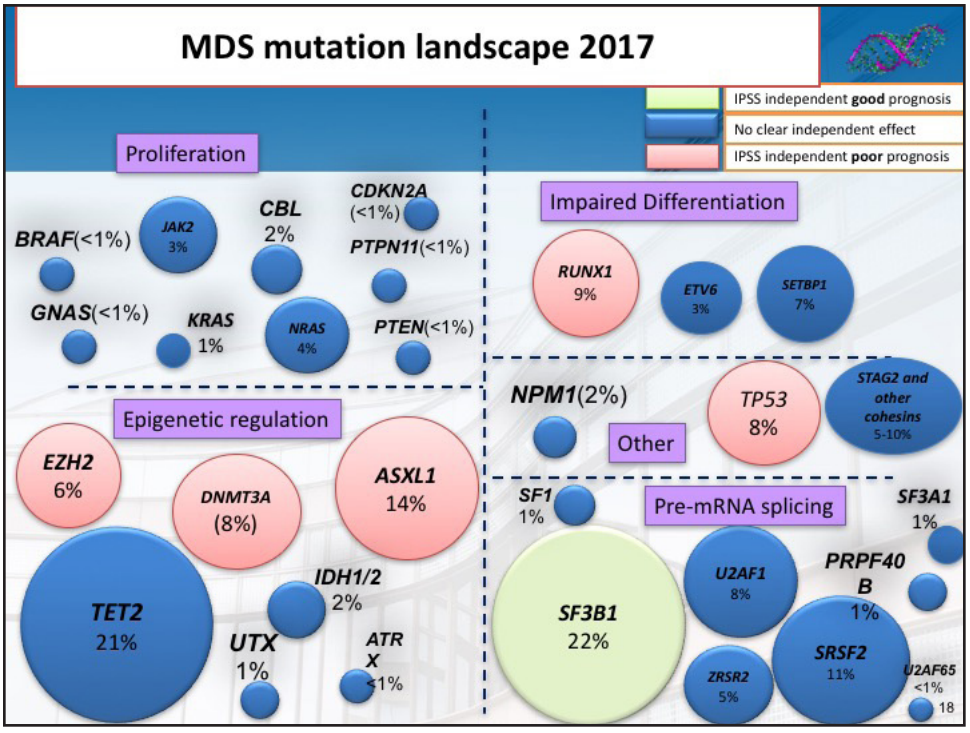
Now unfortunately, MDS is even more complicated than that, so there's a revised system that's been developed to figure out prognosis in MDS. In other words, the stage that we work with. Now I certainly can't memorize something as complicated as this and I have it put up on the wall in my work room when I'm seeing patients. To simplify it, what I can say is that the cytogenetics, those genes or chromosomes that are abnormal, are now divided into five separate categories of risk. And then there's different point scores for the blast percentage, the hemoglobin – in other words, the degree of anemia – the platelet count and how low the white blood cell count is and neutrophil count. And that yields a score which in turn results in a prediction of how long somebody's going to live with his or her MDS.

When you're looking at these survival estimates, from these prognostic systems, I'd like everyone to keep something in mind. These don't necessarily have anything to do with reality of how people are treated for their MDS in this day and age. To develop these systems, what centers were asked to do was to provide information about patients who were never treated for their MDS. So, as we have therapies that are altering the natural history of MDS, how long people live with it, these systems really aren't as accurate at predicting how long someone's going to live, but they are good at distinguishing whether somebody has lower risk MDS or higher risk MDS.



Slide 17: MDS: Prognosis

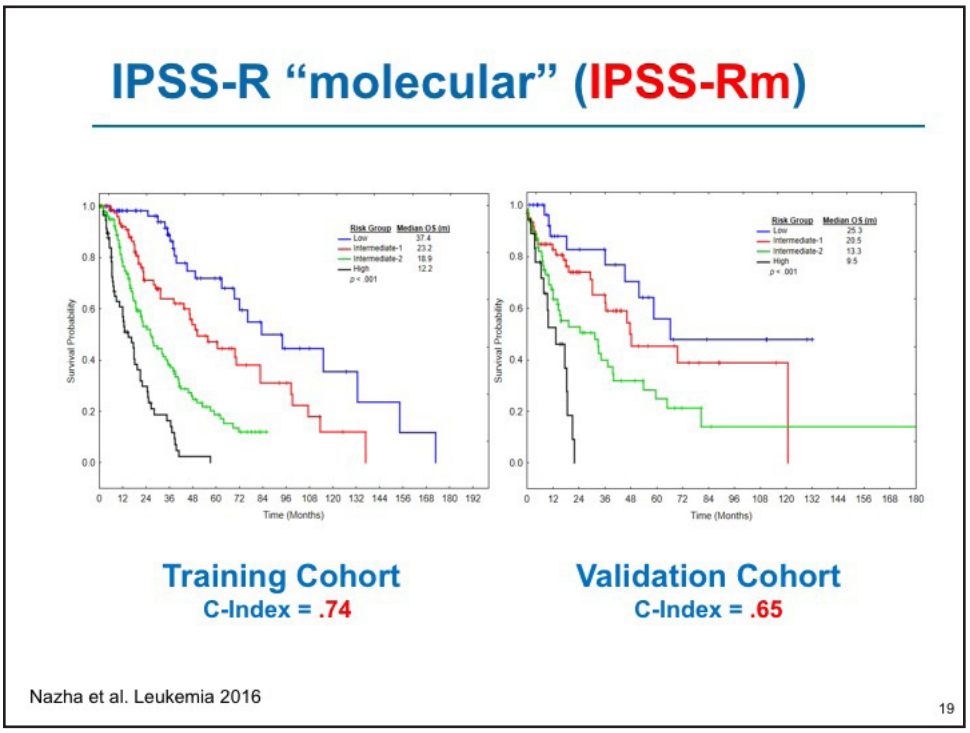
So, this is my slide where I try to sum everything up that I've just said. And I'm sorry for taking so much time to go over this, but please understand that trying to figure out a prognosis of MDS also determines not only how long you'll be living with your MDS, but also what therapies will be recommended for your MDS. And this is how we divide it into lower risk disease or higher risk disease.



Slide 18: MDS Mutation Landscape 2017

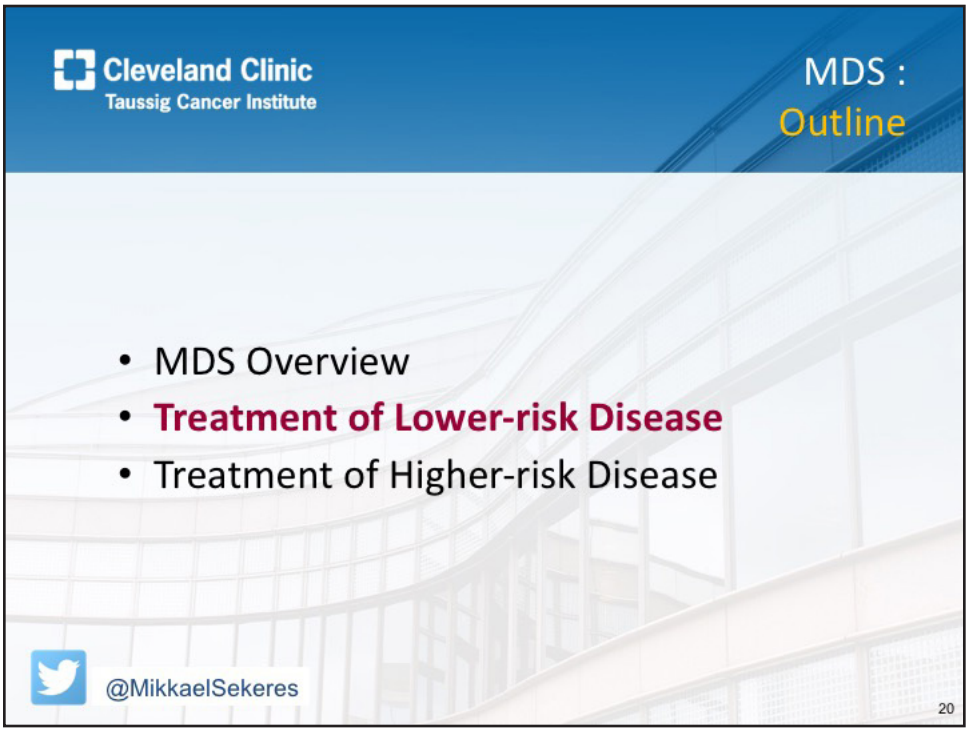
Now I put just this one slide up. When I talked before about the genes that – the genetic abnormalities that you acquire over the course of a lifetime, this is an example of those types of genetic abnormalities that are seen within MDS. It's very, very complicated and there are a lot of them. You can see that there are some, those big circles, that are very common in MDS. Things like TET2 or SF3B1. And then there are things that are very uncommon in MDS, like the UTX abnormality.

Increasingly, people are having their genetics analyzed and these genetics are then being incorporated into some of these prognostic systems that I just showed you, to be even more precise about what therapies might work and how long someone's going to live with his or her MDS.



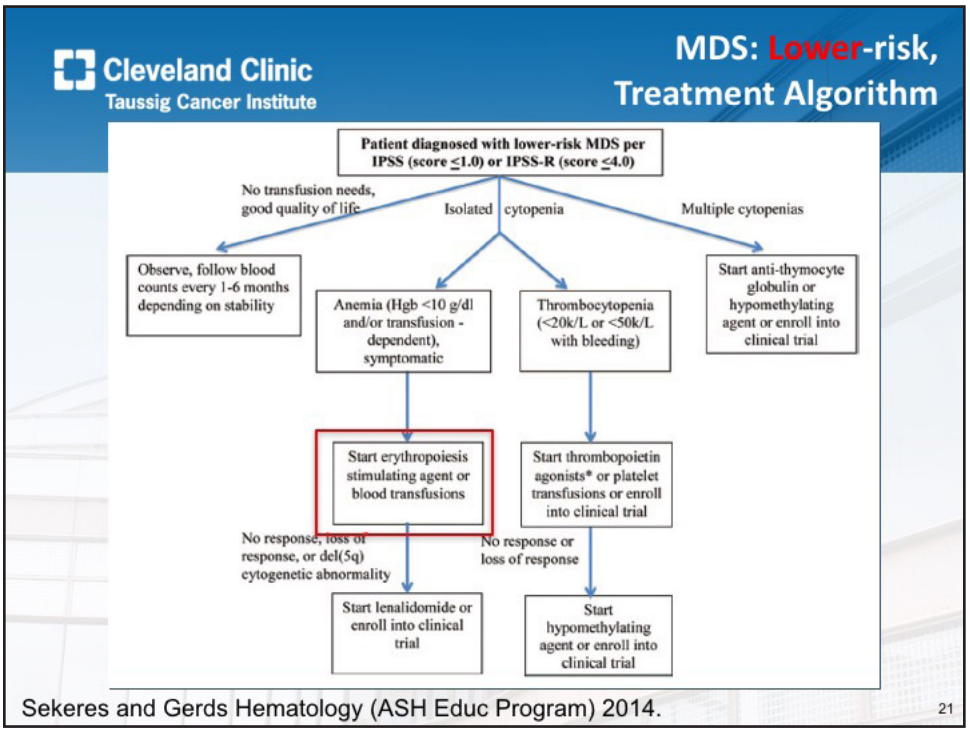
Slide 19: IPSS-R "molecular" (IPSS-Rm)

So, in this slide you can see how this is one example of how these genetic abnormalities are being incorporated into the revised IPSS system that I showed you earlier, and are making it more accurate.



Slide 20: MDS: Outline

So, let's talk about how we treat lower risk disease.



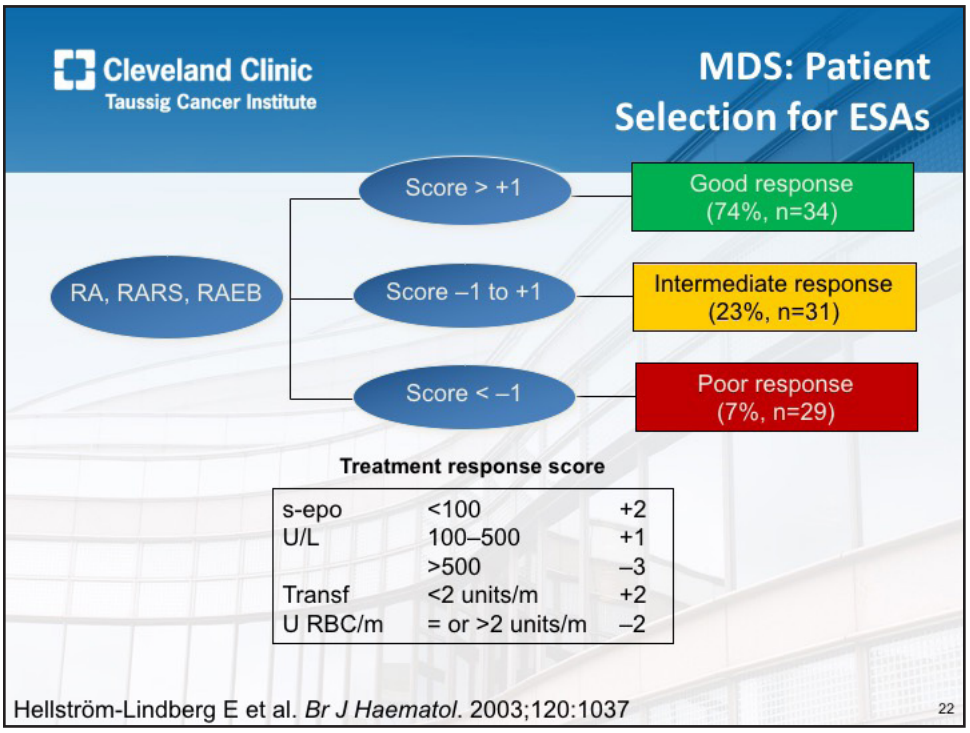
Slide 21: MDS: Lower-risk, Treatment Algorithm

We determine what therapy somebody's going to receive by what that person's blood counts look like. So, I have some patients who don't require any transfusions and have a very good quality of life. One of my patients once referred to that type of MDS as having mild displeasure syndrome. It's displeasing to him to have to drive into Cleveland every few months

to see me and have his blood counts checked, but otherwise it doesn't affect his life very much. For those folks, we don't offer any therapies. We just monitor the blood counts and make sure they don't get worse.

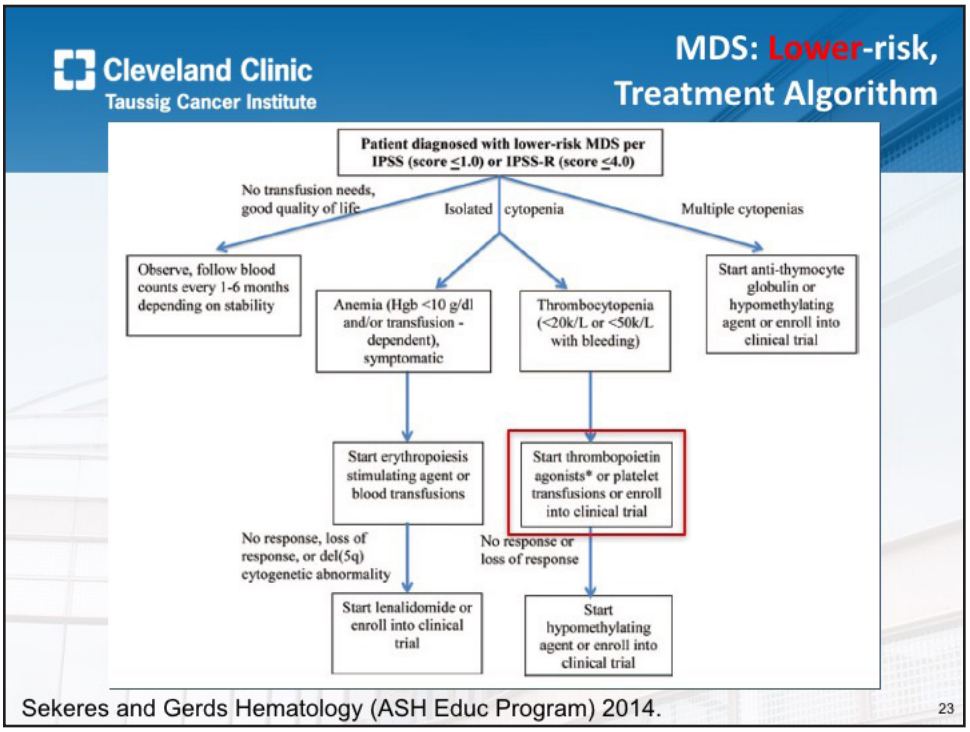
We have treatment approaches for people who have anemia, who have a low platelet count, thrombocytopenia, or for people who have multiple cytopenias, who might have anemia and thrombocytopenia, or anemia and a low white blood cell count, and offer different types of therapies, depending on how many blood counts are affected.

For lower risk disease, most people have anemia and our first approach to treating people is to use what's called an erythropoiesis stimulating agent, drugs like erythropoietin, Procrit®, or darbepoetin, Aranesp®.



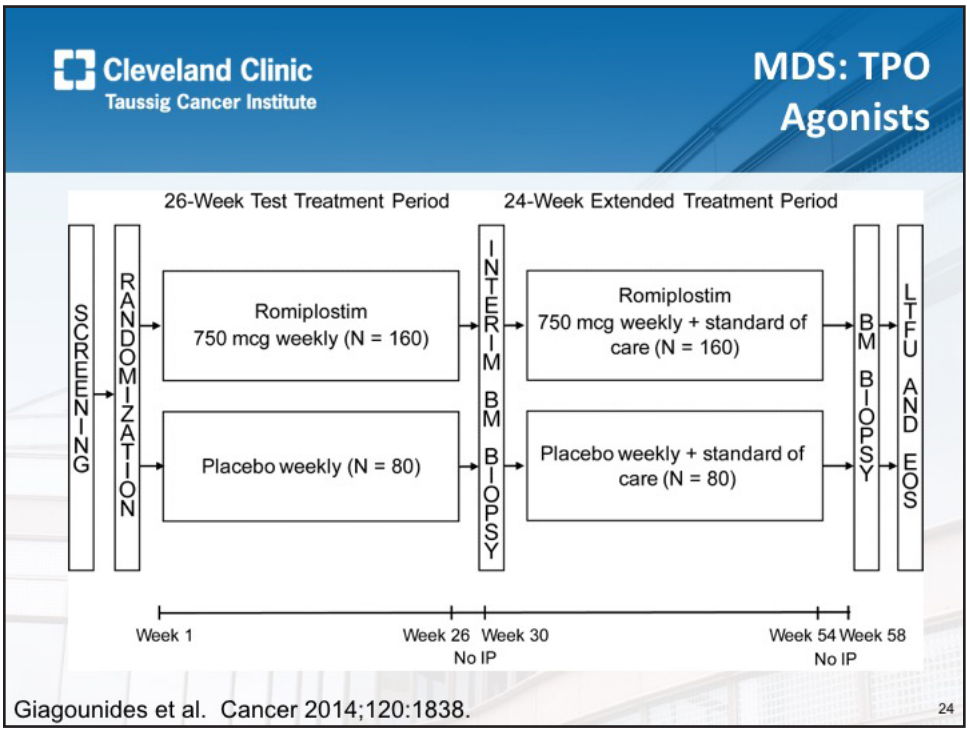
Slide 22: MDS: Patient Selection for ESAs

How do we know who's going to do well with these drugs? Well, what we do when a patient comes to my office, I will check a lab value called the erythropoietin level in that person's bloodstream. That's the measurement of a hormone. And I will assess how frequently a person is already receiving blood transfusions. If my patient has a low erythropoietin level in the bloodstream and doesn't require transfusions yet, the likelihood that that person is going to have anemia that improves with giving erythropoietin is high, 74%. On the other hand, if I have a patient who has a high erythropoietin level already walking through the door, and is already dependent on red blood cell transfusions, the likelihood that my giving erythropoietin is going to make that person's anemia improve, is very low, only 7%.



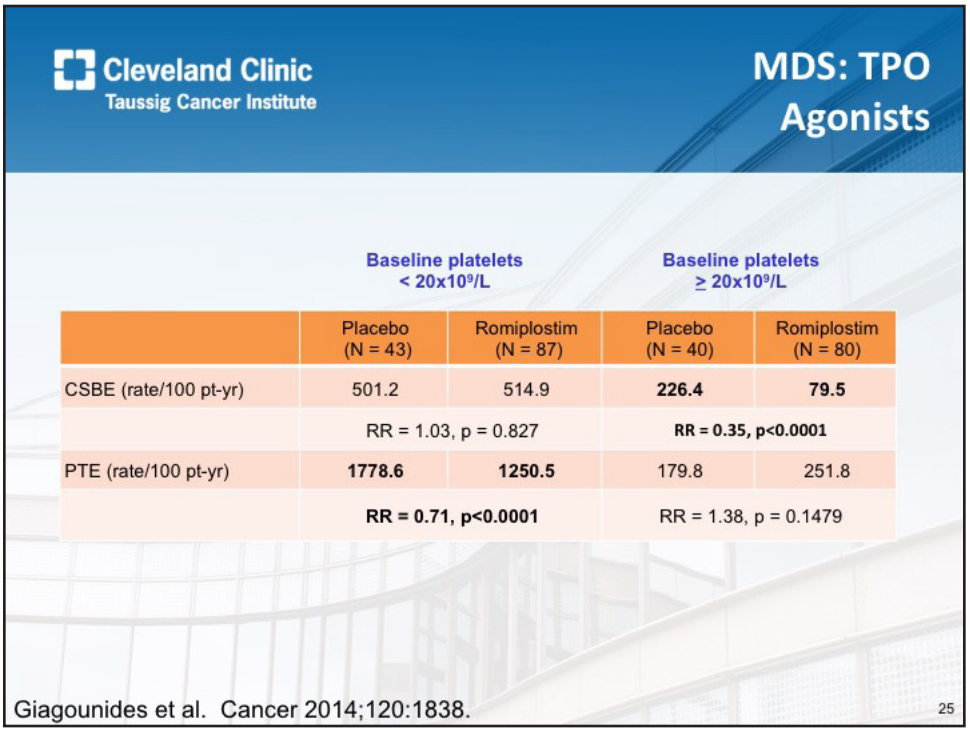
Slide 23: MDS: Lower-risk, Treatment Algorithm

So, what about somebody who has a low platelet count? What kind of therapy do we offer that person?



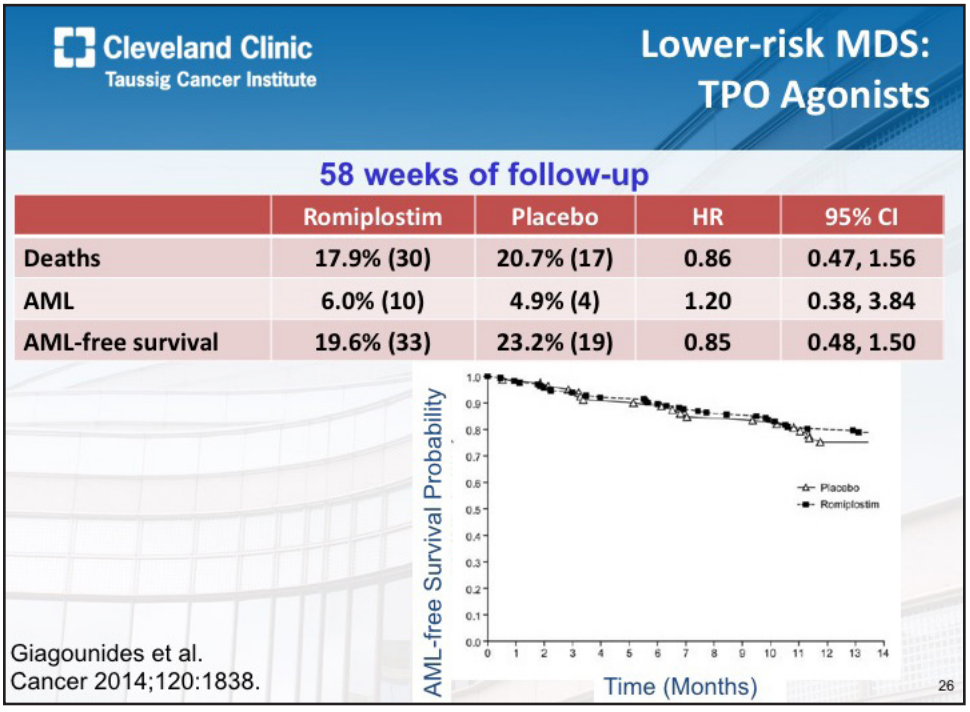
Slide 24: MDS: TPO Agonists

There was a study that randomized people to getting the drug romiplostim, also known as Nplate®, or placebo, and followed over time, whether or not people's platelets got better. Romiplostim is a hormone that stimulates the bone marrow cells that make platelets, to make more platelets.



Slide 25: MDS: TPO Agonists

In this study whether or not the drug works was assessed with two different factors. One was – you'll see the abbreviation CSBE, that means clinically significant bleeding event – so if someone has a really bad nosebleed or has internal bleeding, and whether or not the drug reduced that. And what this study found is that in those patients who came onto the study, who had already had a history of having bleeding events, romiplostim significantly reduced the number of those clinically significant bleeding events. For those patients who were already dependent on platelet transfusions, the drug also reduced the number of platelet transfusion events significantly. So, it looked at first blush as if this drug really did work for people who had a low platelet count.

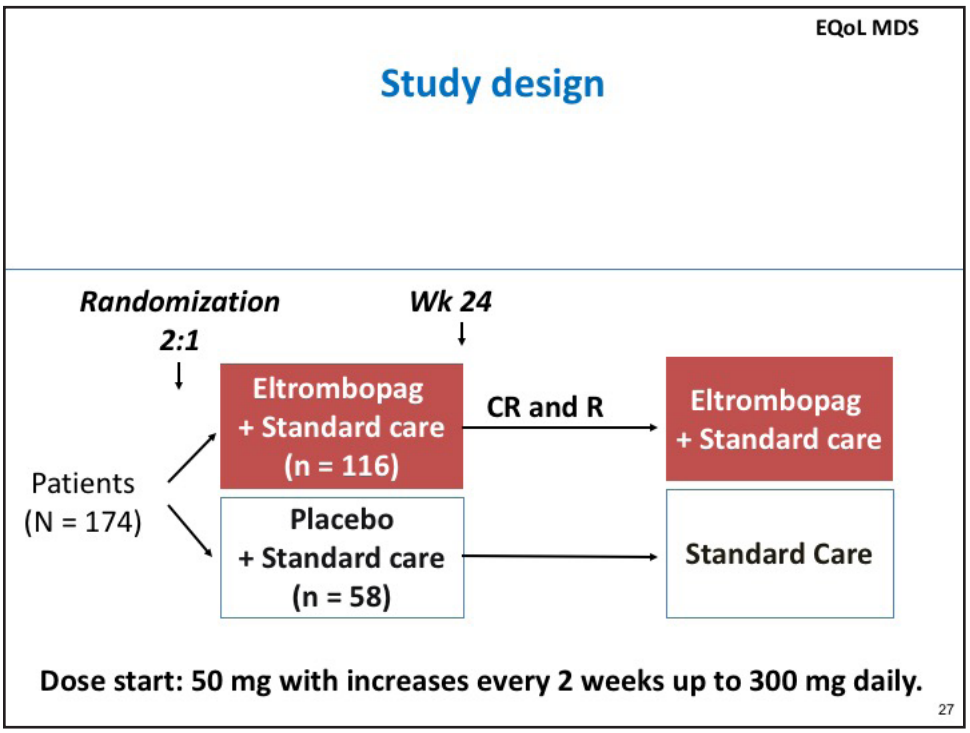


Slide 26: Lower-risk MDS: TPO Agonists

However, there's unfortunately a however with this study, and that is that patients who were enrolled to the study who already had excess blasts – remember we talked about those blasts, those immature white blood cells – in those patient's blasts have a receptor for this hormone. So, when you give this hormone to people who have excess blasts, those blasts increase in number. And increasing blasts is not a good thing. It can mean that your MDS is becoming more higher risk or it can mean that the MDS is converting into a leukemia. And unfortunately, it was found that those patients who received the drug, who had excess blasts to start with, had an increase in those blasts.

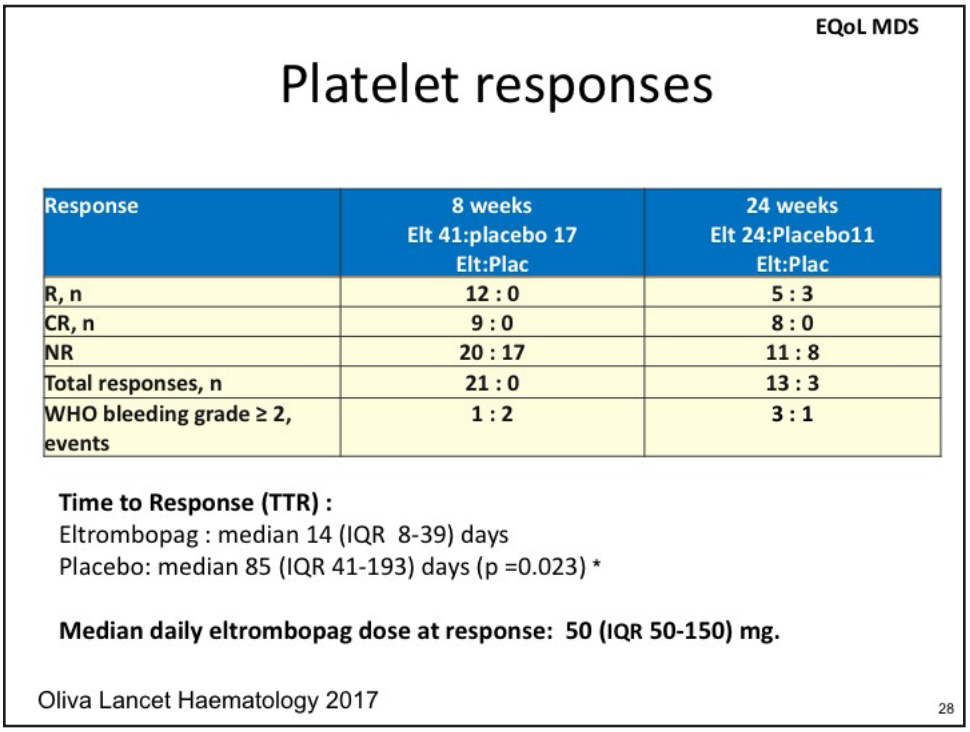
As a result, the study was stopped prematurely and it was examined over time for whether or not the drug romiplostim really did increase the likelihood that people would develop leukemia or not, compared to placebo. Over a long period of time it was found that the rates of developing leukemia were actually similar between romiplostim and placebo. However, because the study was stopped early and because there is a risk that this drug can convert people who have excess blasts into leukemia, the drug did not get FDA approval for the treatment of MDS.

So, it is available, it is FDA approved for the treatment of people who have an immune attack on their platelets, something that's called idiopathic thrombocytopenic purpura (ITP), and people who have MDS can get the drug, just off-label. So, this is an off-label indication and I do administer this to some of my patients, but you can be sure I don't dare give a drop of this drug to any of my patients who have excess blasts.



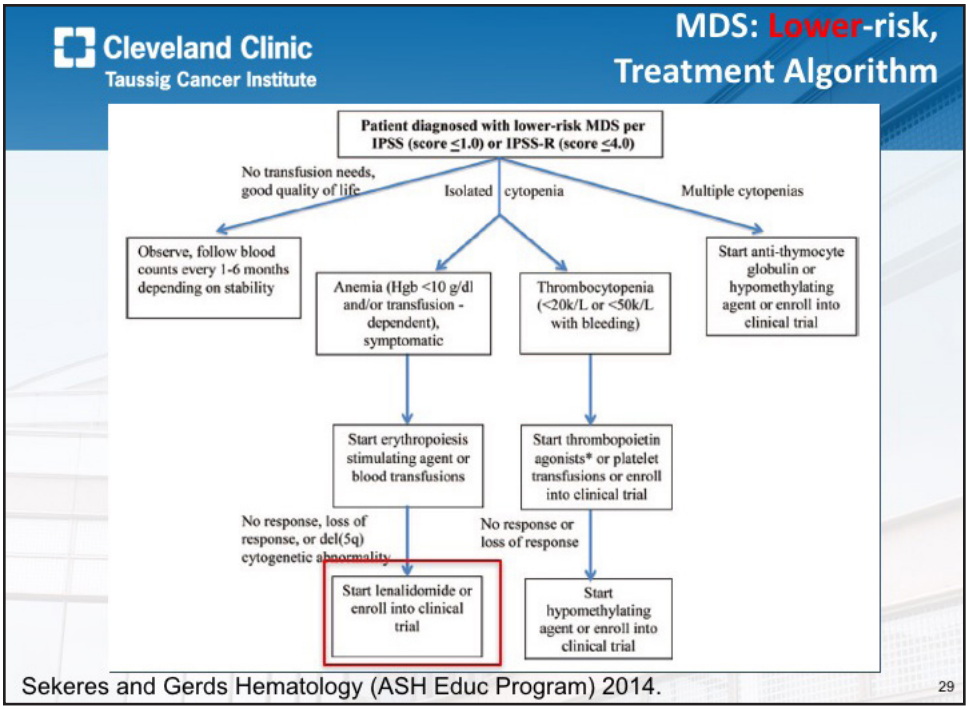
Slide 27: Study Design

So, there's a new drug called eltrombopag, that also is FDA approved for the treatment of people who have an immune attack on their platelets. This was also studied in a clinical trial where patients were randomized to getting the drug eltrombopag, or they were randomized to receiving placebo.



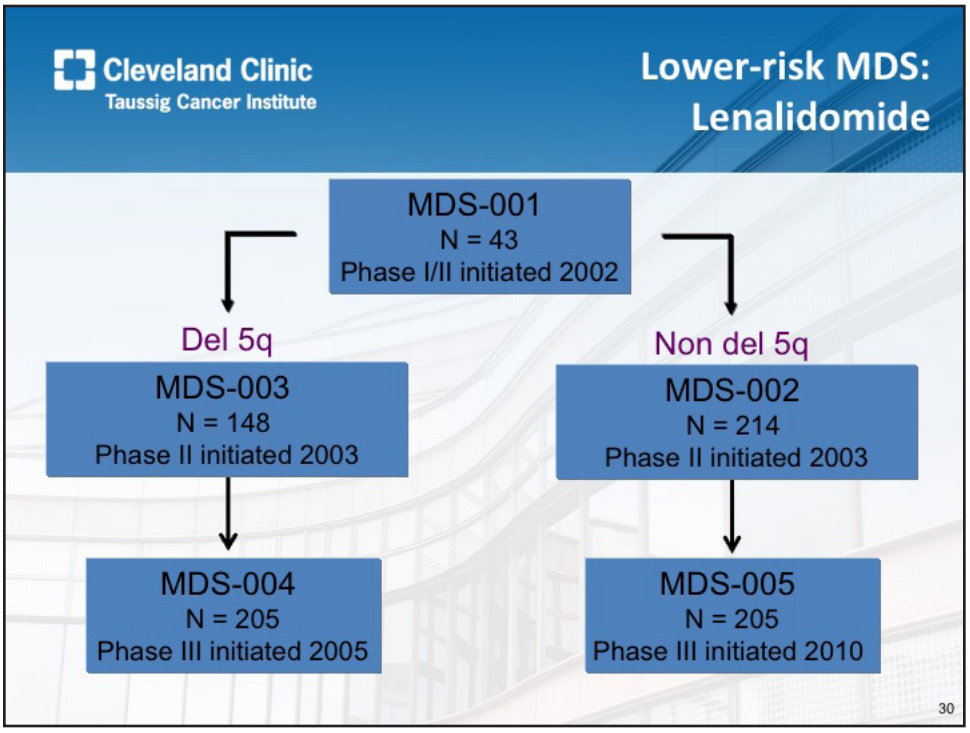
Slide 28: Platelet responses

And in this study, which was conducted in Europe, people who received the eltrombopag were more likely to have improvement of their platelet counts or reduction in their platelet transfusion needs than people who received placebo. So once again it seemed to work about as well as the romiplostim, that I just talked about. But again, I would never give this to anybody who had excess blasts.



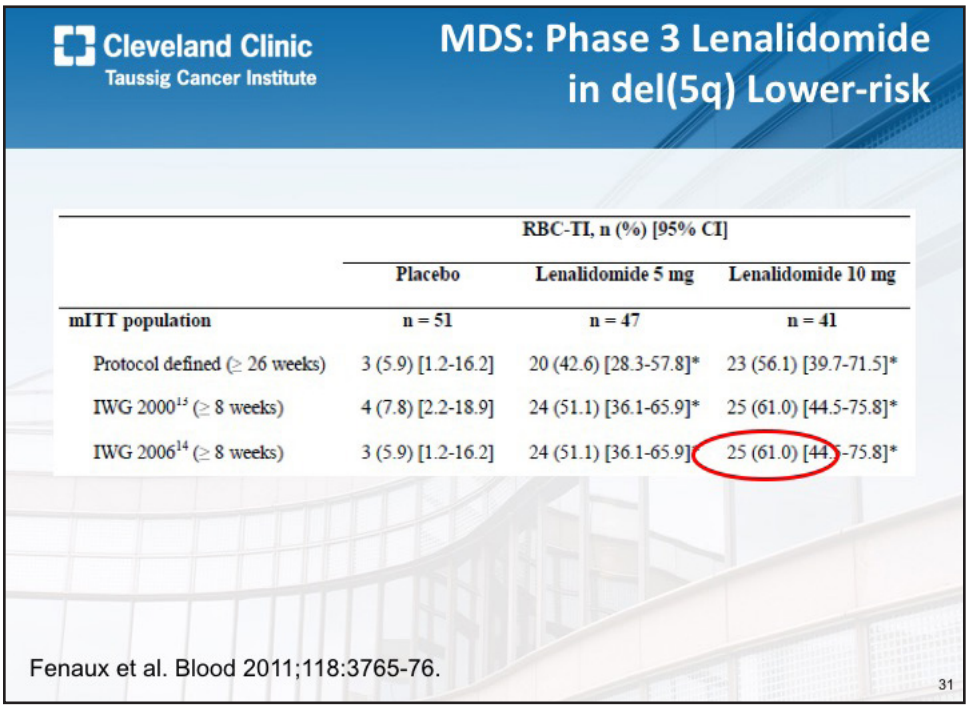
Slide 29: MDS: Lower-risk, Treatment Algorithm

So, what about patients who have that chromosome 5 abnormality that I talked about earlier? Well, the drug that's approved to treat these folks is called lenalidomide or Revlimid®.



Slide 30: Lower-risk MDS; Lenalidomide

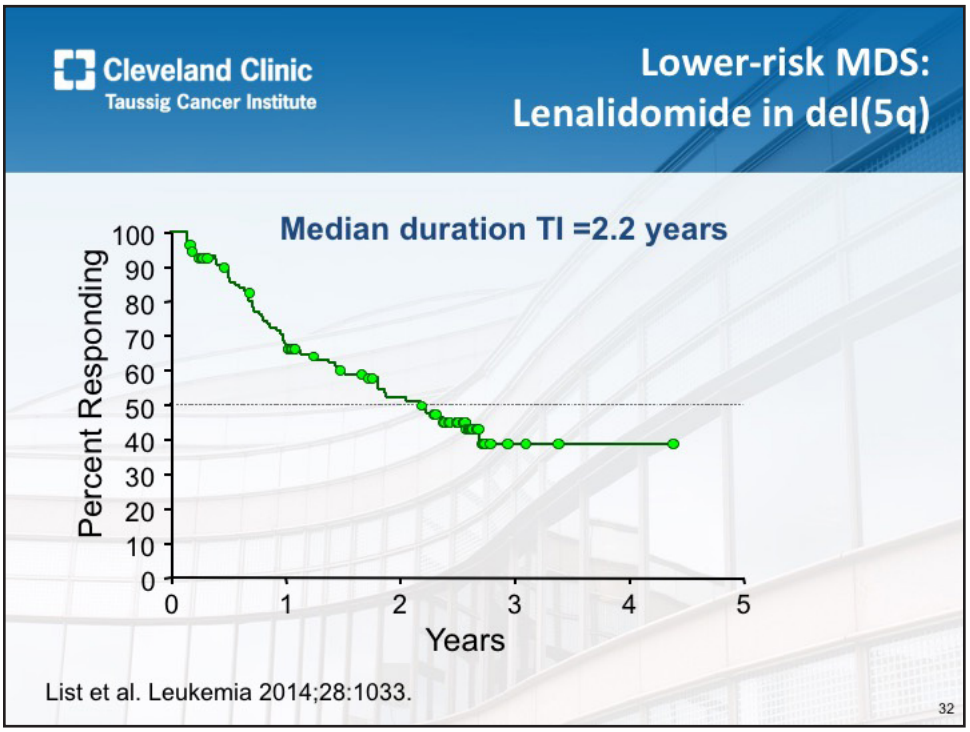
Lenalidomide has been explored in five studies. About half the studies only enrolled patients who have that chromosome 5 abnormality and about half of them enrolled patients who have lower risk MDS, but don't have that chromosome 5 abnormality.



Slide 31: MDS: Phase 3 Lenalidomide in del(5q) Lower-risk

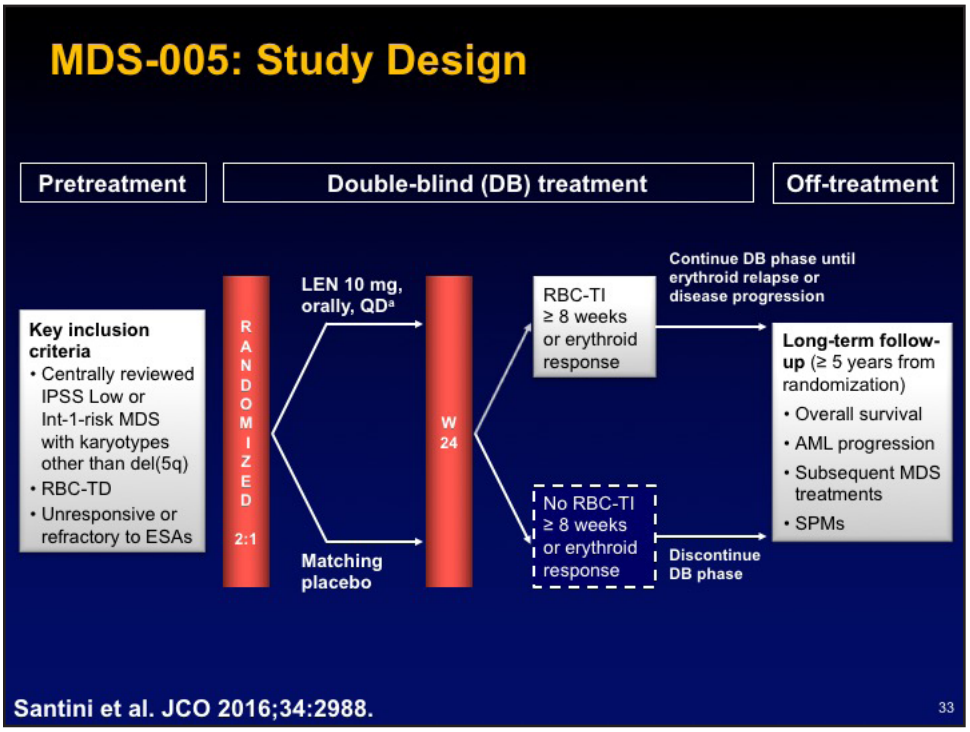
In patients who have that chromosome 5 abnormality, this drug works about two-thirds of the time. Sixty-one percent of patients had an improvement in their anemia or were previously dependent on blood transfusions and didn't need those

transfusions any more, compared to those who got placebo. That was a big deal. That's considered a very good response rate for a drug in MDS.



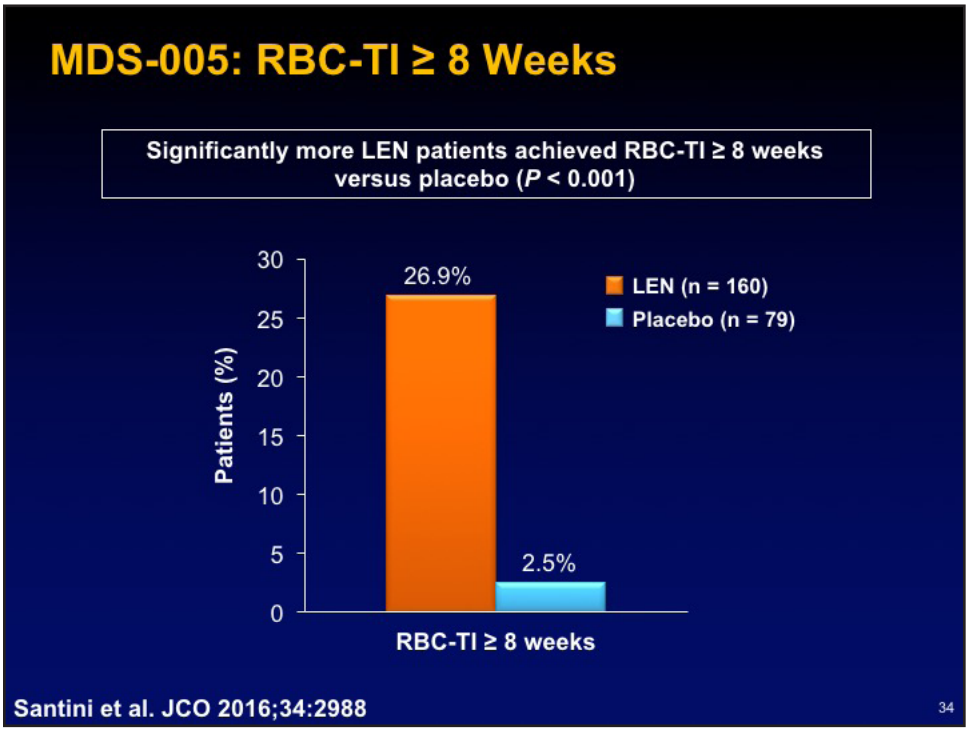
Slide 32: Lower-risk MDS: Lenalidomide in del(5q)

And those who did get better to the drug, who did respond to it, had a response that lasted on average over two years. Once again that's a very good response to a drug, and that's why this drug was approved for people who have the chromosome 5 abnormality with lower risk MDS.



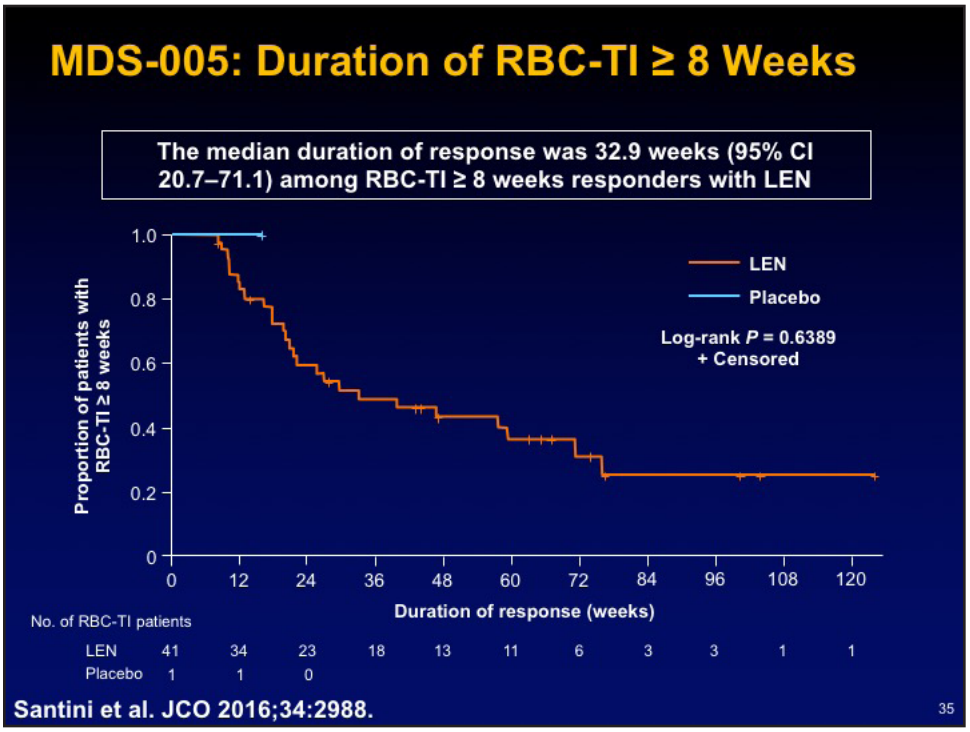
Slide 33: MDS-005: Study Design

In patients who don't have that chromosome 5 abnormality, but have lower risk MDS, there was also a randomized study that was conducted in which patients received either the drug lenalidomide or placebo.



Slide 34: MDS-005: RBC-TI ≥ 8 Weeks

And in truth, people who received the drug lenalidomide were more likely to have an improvement of their anemia and to no longer require blood transfusions than those who didn't get the drug. But now you'll notice that that response rate, which was 61% for patients who have the chromosome 5 abnormality, was only 27% in this study, for those who don't have that chromosome 5 abnormality.

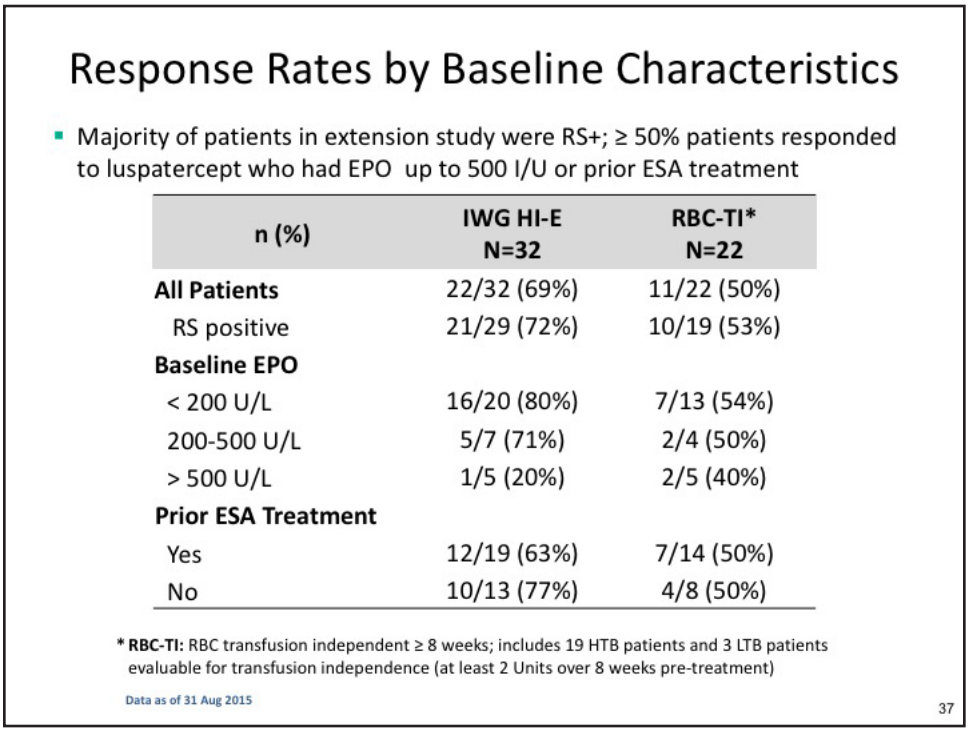


Slide 35: MDS-005: Duration of RBC-TI ≥ 8 Weeks

The duration of response, remember, it was over two years for those patients who had that chromosome 5 abnormality. For those who don't have the abnormality it was 33 weeks. So, I do use lenalidomide for my patients who have chromosome 5 abnormalities, and also for those who don't have chromosome 5 abnormalities, but the responses – the likelihood that somebody's going to get better to this drug is much more modest in those who don't have the chromosome 5 abnormality.

Slide 36: Abstract # 92 Luspatercept Treatment Leads to Long Term Increases in Hemoglobin and Reductions in Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelsdysplastic Syndromes (MDS): Preliminary Results from the Phase 2 PACE-MDS Extension Study

So, what's new coming down the pike for people who have anemia with MDS? Well, this drug luspatercept, I think is probably the next drug that has the best chance of getting approved by the FDA for anemia associated with myelodysplastic syndromes.



Response Rates by Baseline Characteristics

- Majority of patients in extension study were RS+; ≥ 50% patients responded to luspatercept who had EPO up to 500 I/U or prior ESA treatment

n (%)	IWG HI-E N=32	RBC-TI* N=22
All Patients	22/32 (69%)	11/22 (50%)
RS positive	21/29 (72%)	10/19 (53%)
Baseline EPO		
< 200 U/L	16/20 (80%)	7/13 (54%)
200-500 U/L	5/7 (71%)	2/4 (50%)
> 500 U/L	1/5 (20%)	2/5 (40%)
Prior ESA Treatment		
Yes	12/19 (63%)	7/14 (50%)
No	10/13 (77%)	4/8 (50%)

* **RBC-TI:** RBC transfusion independent ≥ 8 weeks; includes 19 HTB patients and 3 LTB patients evaluable for transfusion independence (at least 2 Units over 8 weeks pre-treatment)

Data as of 31 Aug 2015

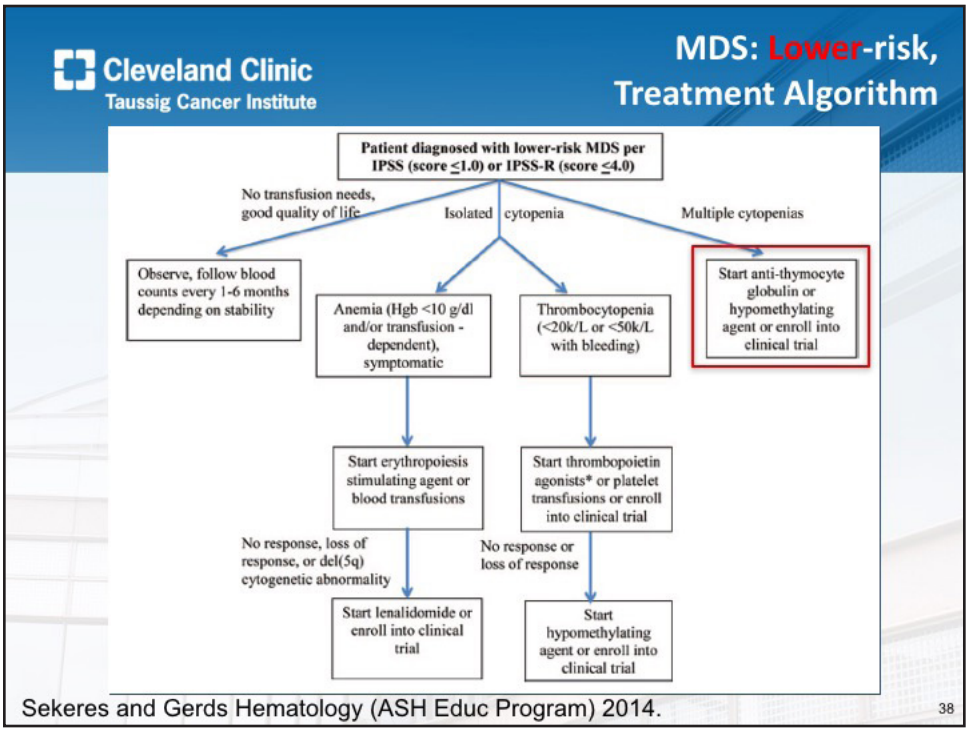
37

Slide 37: Response Rates by Baseline Characteristics

In this study – there were two studies that were conducted, one in Europe and one in the United States. The one in the United States was with a drug called sotatercept, which is very similar to luspatercept. The one in Europe was with luspatercept. The drug that's moving forward in MDS is the luspatercept. And in this study, you can see that those – in the study patients were not randomized, so everybody got the drug, and you can see that the overall response rate for patients was 69% with 50% of patients who previously depended on receiving red blood cell transfusions, no longer needing those red blood cell transfusions.

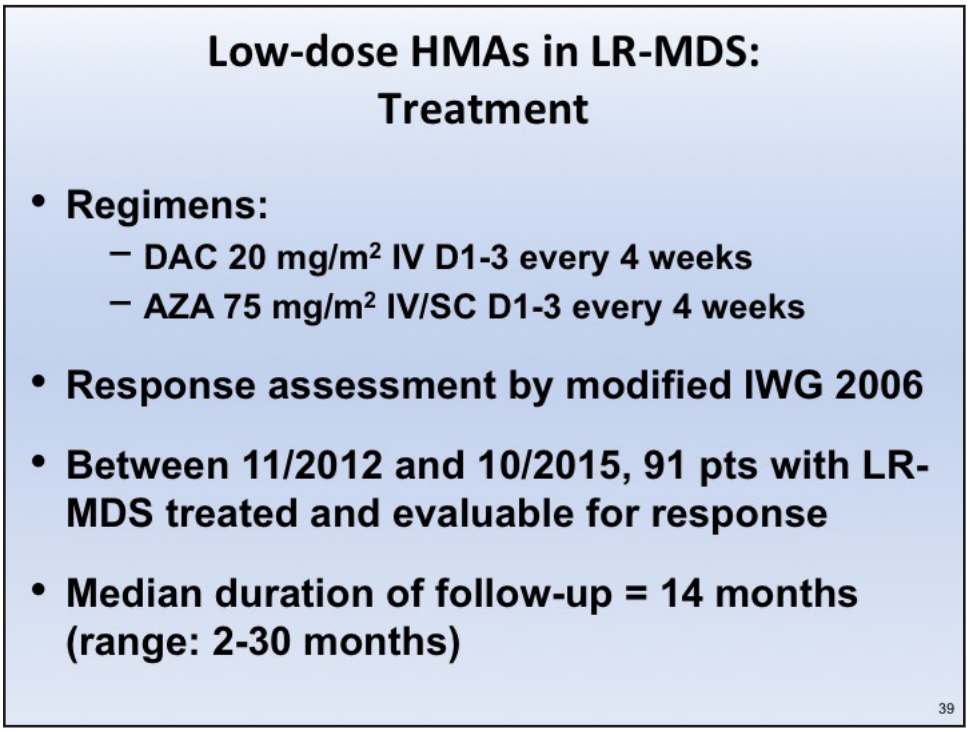
This drug worked particularly well in people who had the ring sideroblast MDS. Remember when I described that earlier, that stain that's taken up by the bone marrow cells. For whatever reason, we're not sure why, this drug really worked in those patients.

So, the study that's open right now is a randomized study, it's international, we have it open here in Cleveland, where people are getting luspatercept or placebo, if they have the ring sideroblast MDS.



Slide 38: MDS: Lower-risk, Treatment Algorithm

So, what about patients with lower risk MDS who have multiple cells that are affected by the MDS? In other words, they have anemia and thrombocytopenia or anemia and neutropenia.

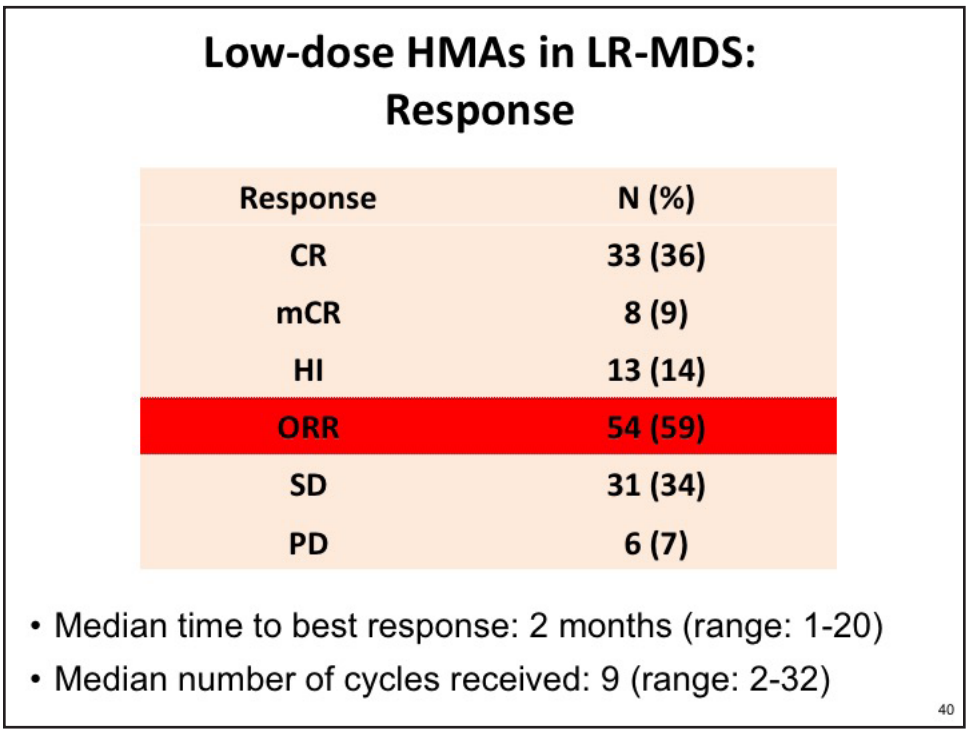


Slide 39: Low-dose HMAs in LR-MDS: Treatment

There are two drugs that are already approved for the treatment of MDS, that are used predominantly for people who have higher risk disease, and those are azacitidine and decitabine, also known as Vidaza® or Dacogen®.

We participated in a study where we did the unthinkable. We lowered the doses of these drugs and gave them to patients who had lower risk MDS. And you can imagine this is not a study that was supported by a pharmaceutical company, because what drug company would pay to have a study that shows that giving less of their drug is a good thing? Well, as a matter of fact, it may be a good thing, particularly for people with lower risk MDS.

We gave the decitabine, instead of giving it over five days, over three days, every four weeks, and the azacitidine we gave instead of over seven days, we gave it over three days, every four weeks.

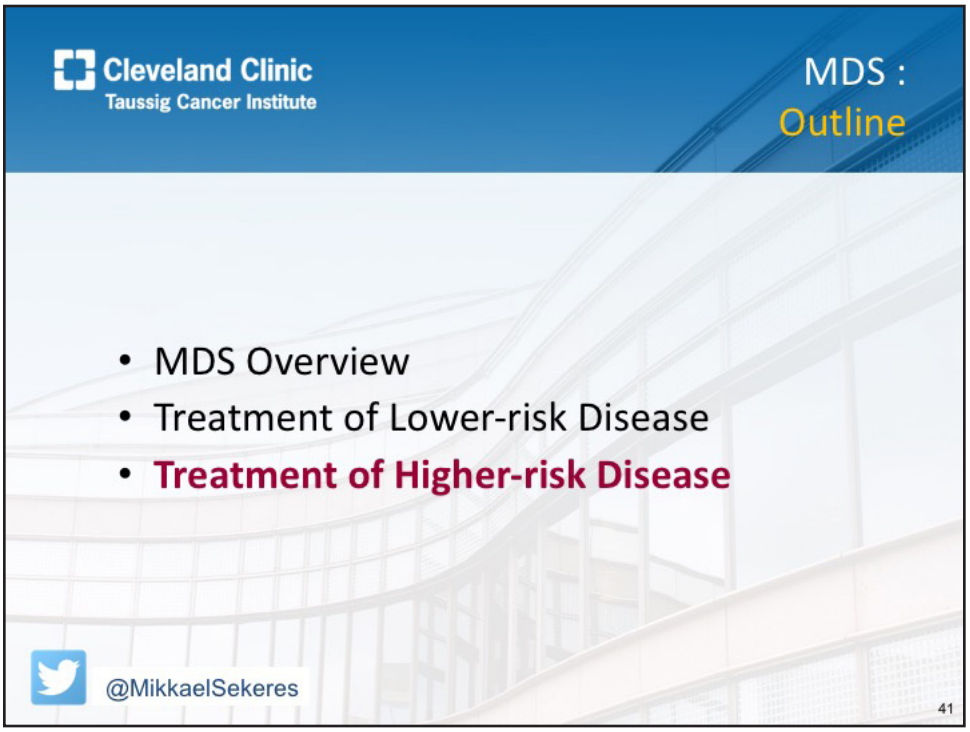


Slide 40: Low-dose HMAs in LR-MDS: Response

And what we found was that the overall response rate was actually quite impressive and at least equal to what we would have expected if we had given the full dose of these drugs in people who have lower risk MDS.

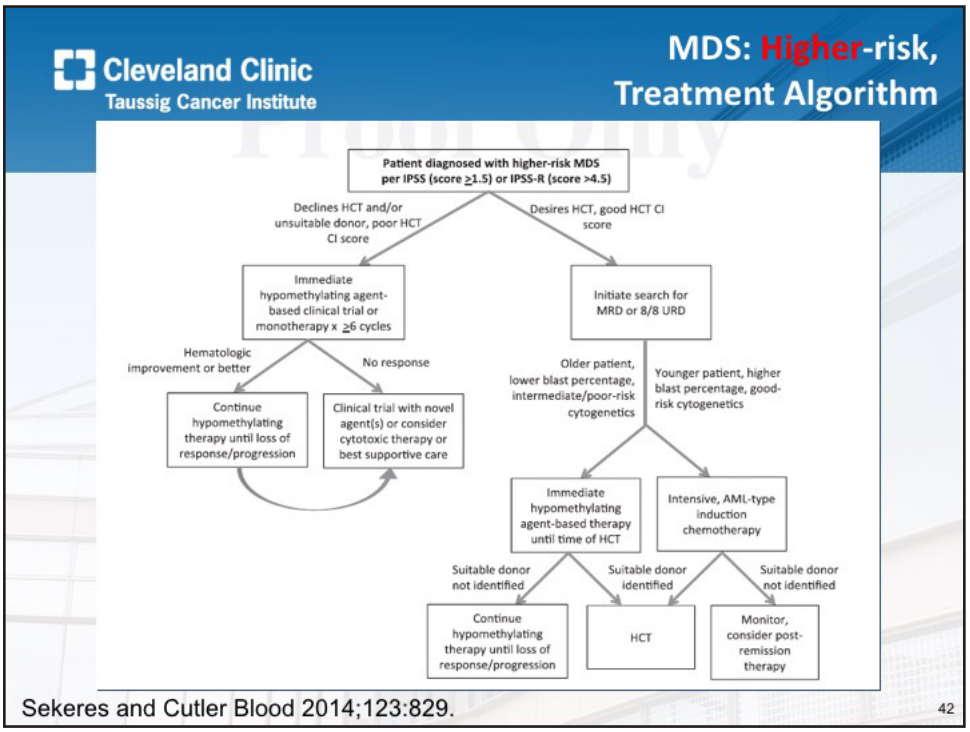
The overall response rate was almost 60%. So, in other words, almost 60% of people had their MDS get better in some way with lower doses of these drugs.

So, we're continuing to explore this in a randomized study, but it may be that with lower risk MDS less is actually more. It may be better to give less of these drugs than we've been giving in the past.



Slide 41: MDS: Outline

So, I'm going to switch over to talking about how we treat higher risk MDS.

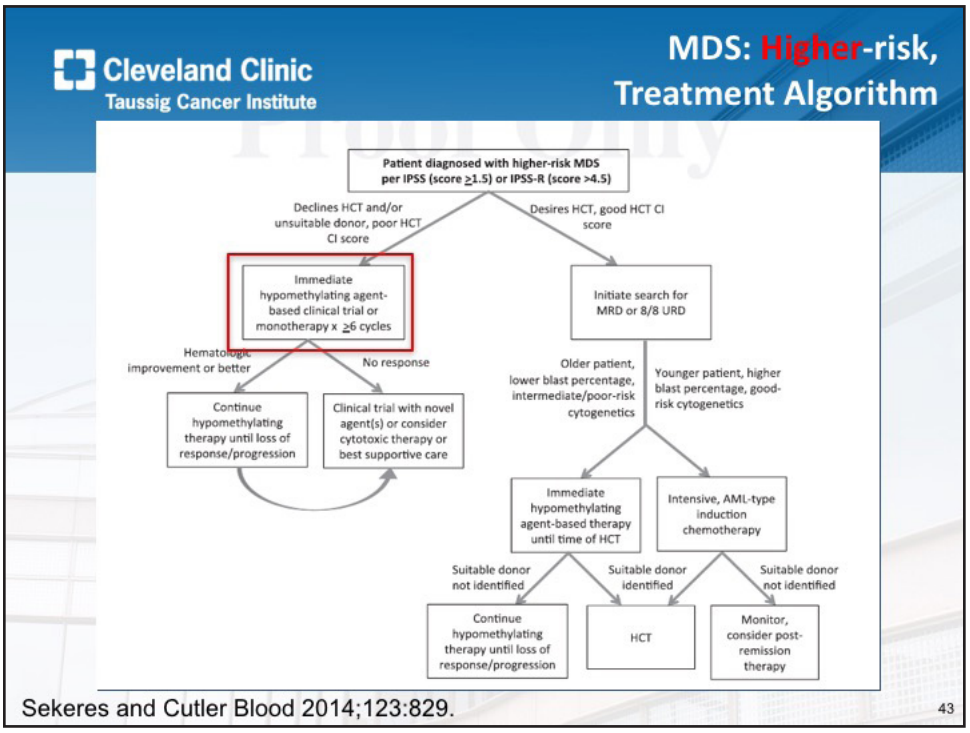


Slide 42: MDS: Higher-risk, Treatment Algorithm

Now with higher risk MDS, and we define this kind of the way I told you about earlier here, by using the IPSS or the IPSS-R. We would define somebody as having higher risk disease with higher scores in the IPSS or the IPSS-R, and we divide the approach into this – to treating people with higher risk MDS, by whether or not a bone marrow transplant would be a good thing for that person.

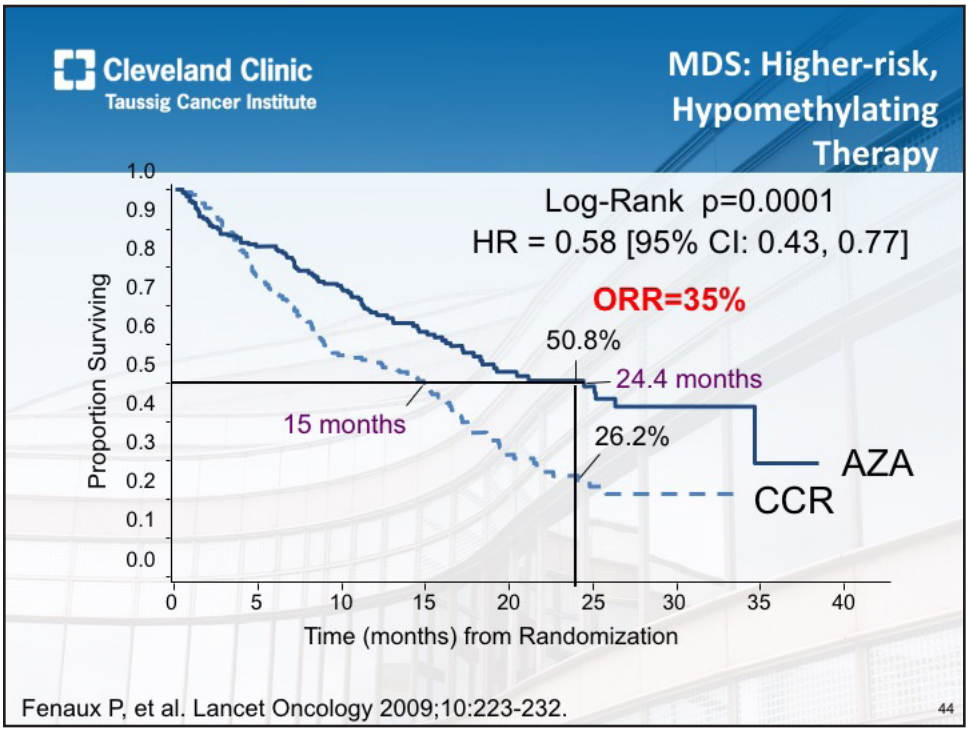
On the one hand, we have people who may decline a transplant, who may say thanks, but no thanks to the idea of getting a bone marrow transplant, or that person has an unsuitable donor, we can't find someone to donate a bone marrow to that person, or that person may have a lot of other illnesses. If you have someone who is older, let's say 80, 85 years old, who also has severe heart disease, then that person would never survive a transplant and therefore transplant's not a good option for that person.

In those folks, our approach is to start what we call a hypomethylating agent. That's the azacitidine or decitabine I just talked about. Or we may have somebody who does desire a transplant and doesn't have a lot of other illnesses, and may be relatively younger, maybe 60 or 65 years old. That person might be a good candidate for a transplant.



Slide 43: MDS: Higher-risk, Treatment Algorithm

I'm going to focus first on those people for whom we would treat them immediately with one of these drugs, one of these hypomethylating agents.

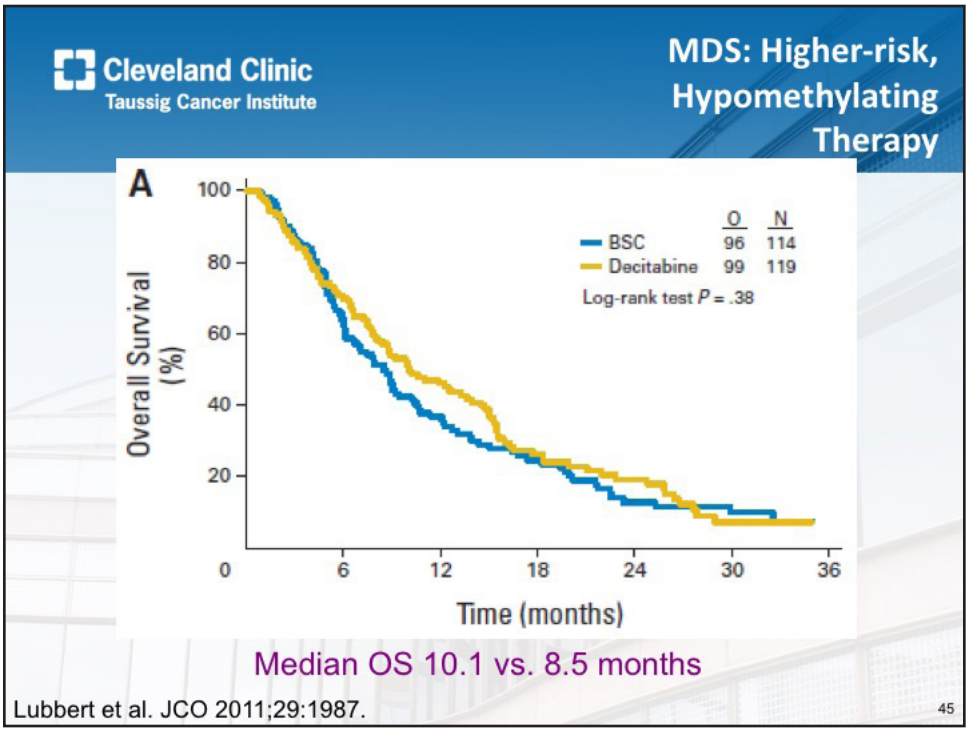


Slide 44: MDS: Higher-risk, Hypermethylating Therapy

We have one study in all of MDS that has shown a survival advantage for a drug used to treat MDS, and that's this study. Patients on this study had higher risk MDS and were randomized to receiving azacitidine, AZA, or conventional care regimens, in other words, either best supportive care, just getting transfusions, no active therapy, low doses of chemotherapy or high doses of chemotherapy. And about 60% of people on that conventional care regimen arm received just transfusions, no active therapy for their MDS.

In this study, as I said, there was a survival advantage for patients who received the Vidaza. The average survival of somebody who receives the Vidaza was about two years, compared to 15 months for those who were randomized to receive the conventional care regimens. And that was a significant difference.

So azacitidine is approved for MDS. We use it for higher risk MDS. And the label now contains information about a survival advantage for people who have higher risk MDS.

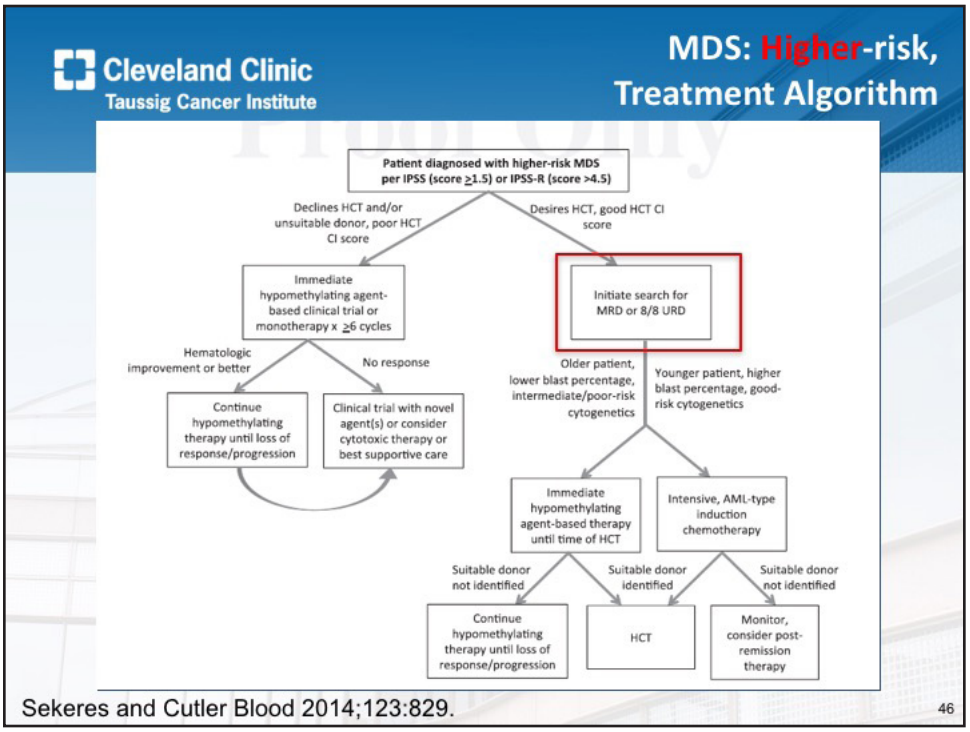


Slide 45: MDS: Higher-risk, Hypomethylating Therapy

Decitabine is a little more complicated. You know, those of us who do this for a living really do believe that decitabine and azacitidine are almost identical drugs and they should work the same way. Unfortunately, the clinical trials were designed differently, so in a study that randomized higher risk MDS patients in Europe to receiving decitabine or best supportive care, there was no difference in overall survival. At ten months for decitabine versus eight and a half months for best supportive care. So it wasn't a significant difference.

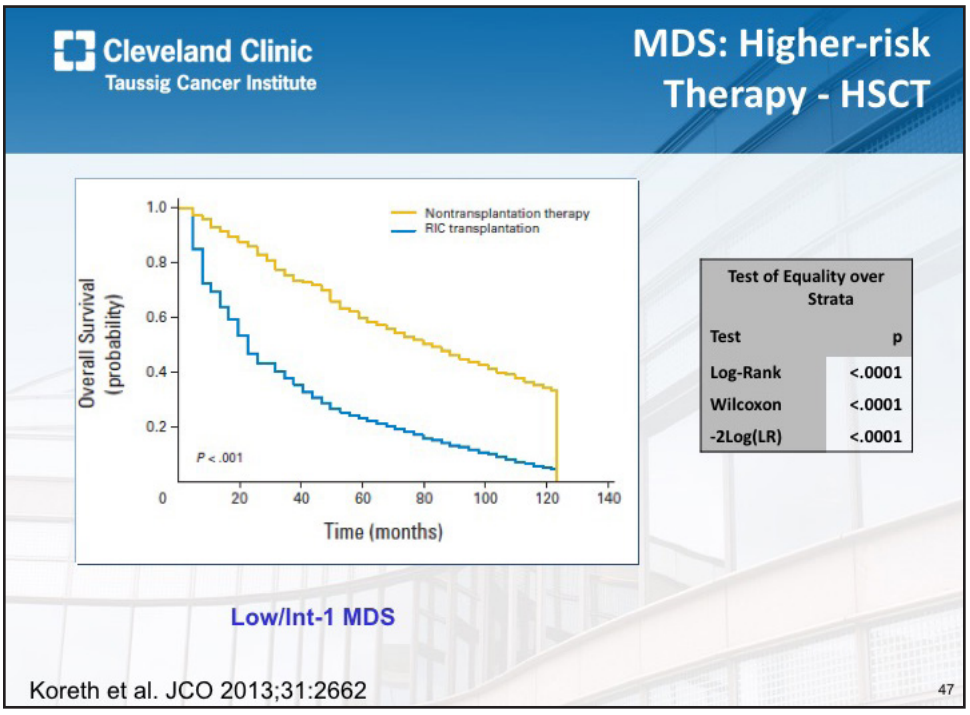
So why is it that that happened? Well, these were different trials and they must have enrolled different patients. If your control arm in this study lived for eight and a half months and your control arm in the azacitidine study lived for 15 months, these had to have been people who had a different type of MDS.

So, do I think these drugs are probably similar? I do. But when I talk to my patients and say I have a survival advantage for azacitidine but not for decitabine, you can imagine which drug they choose.



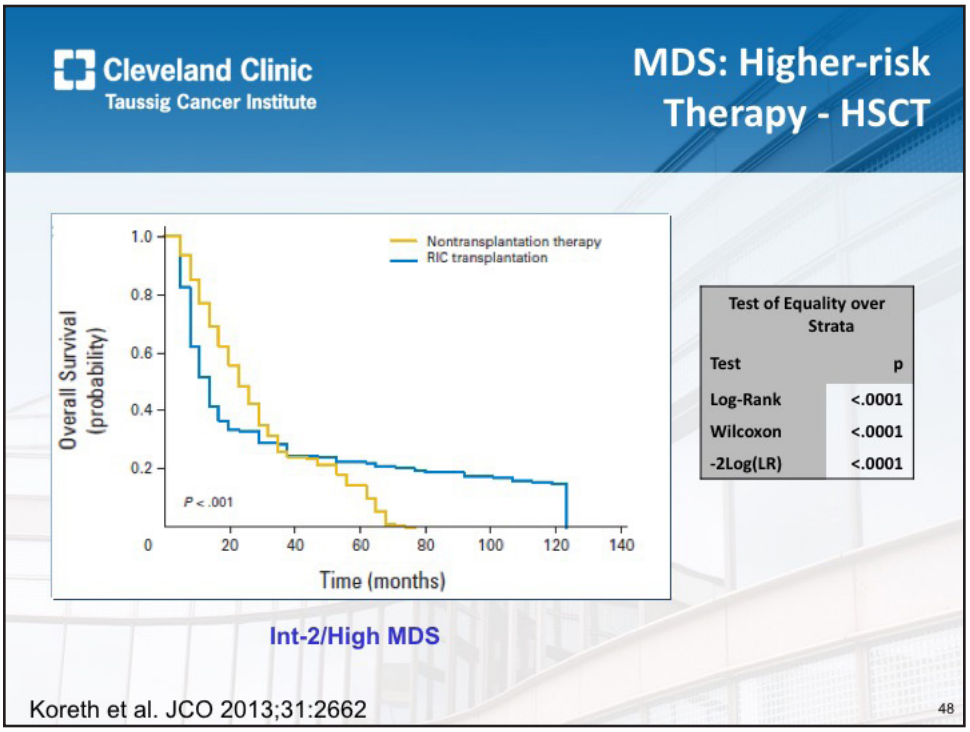
Slide 46: MDS: Higher-risk, Treatment Algorithm

So, let's focus now on bone marrow transplant.



Slide 47: Higher-risk Therapy - HSCT

I have a discussion about bone marrow transplant with every one of my patients who has higher risk MDS, almost the moment that that person walks in the door. For somebody who has lower risk MDS, there actually is not an advantage to doing a bone marrow transplant. And on this slide what we're showing is that the yellow line, the non-transplant therapy, people who were treated with erythropoietin or lenalidomide, actually live longer than those with lower risk MDS who were transplanted.



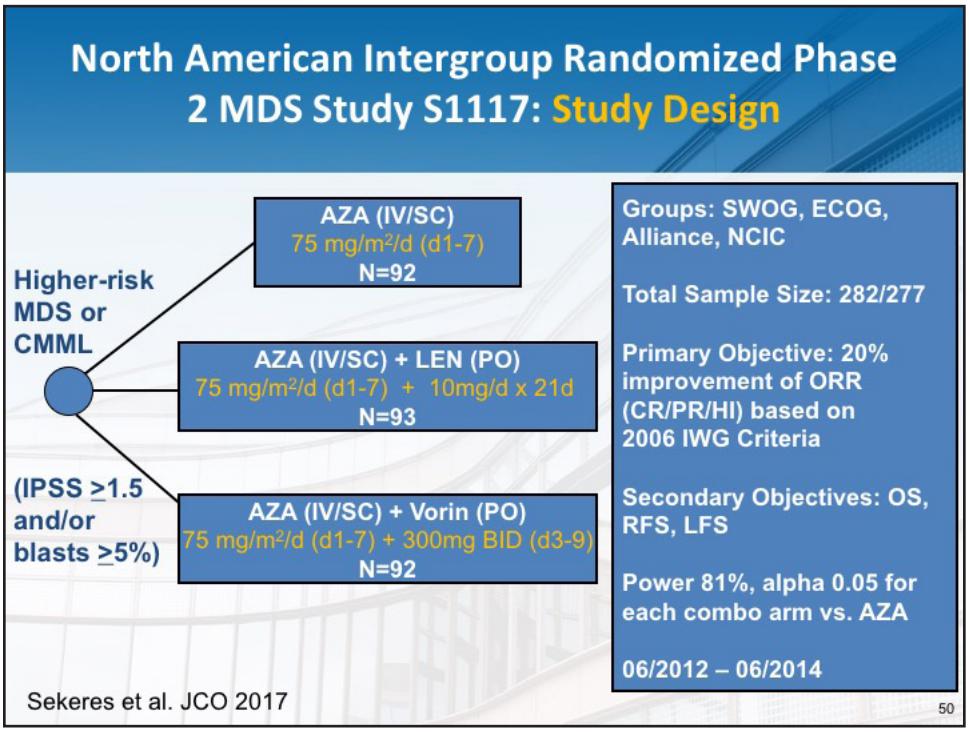
Slide 48: MDS: Higher-risk Therapy - HSCT

On the other hand, for people with higher risk MDS, eventually they live longer if they receive a transplant earlier, compared to those who don't receive a transplant. You can see that those curves cross. What that means is that the transplant itself, as I said before, is no walk in the park. There are people who die from receiving a bone marrow transplant. So, the curves cross because there are people dying from the transplant early on, but eventually those who survive the transplant do live longer than those who receive drugs as their therapy.

So, I do recommend transplant to my patients with higher risk MDS. It is our only curative therapy for MDS. But as I said, it's not a walk in the park and does carry with it a lot of side effects.

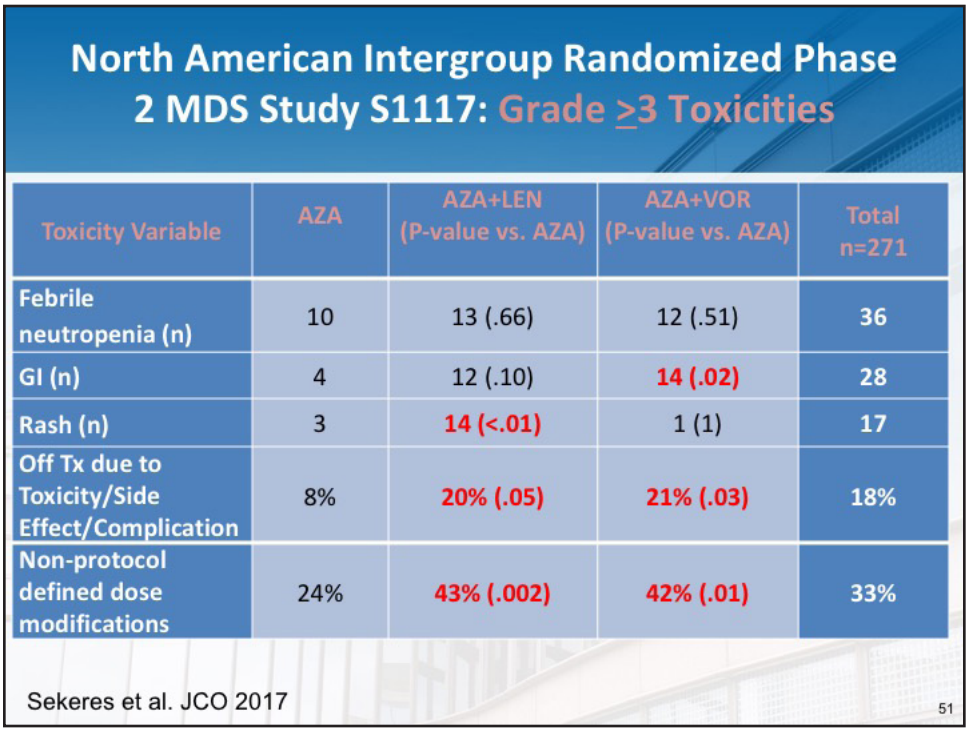
Slide 49: Higher-risk MDS

So, what happens when we add drugs together? And this has kind of been the latest approaches to treating MDS in people who have higher risk MDS.



Slide 50: North American Intergroup Randomized Phase 2 MDS Study S1117: Study Design

This study is the largest MDS study ever conducted in North America. And in it people were randomized to receiving azacitidine, the Vidaza on its own, azacitidine combined with lenalidomide or Revlimid, or azacitidine combined with a drug called vorinostat, which helps the azacitidine to work. Total of 277 patients were enrolled on this study.



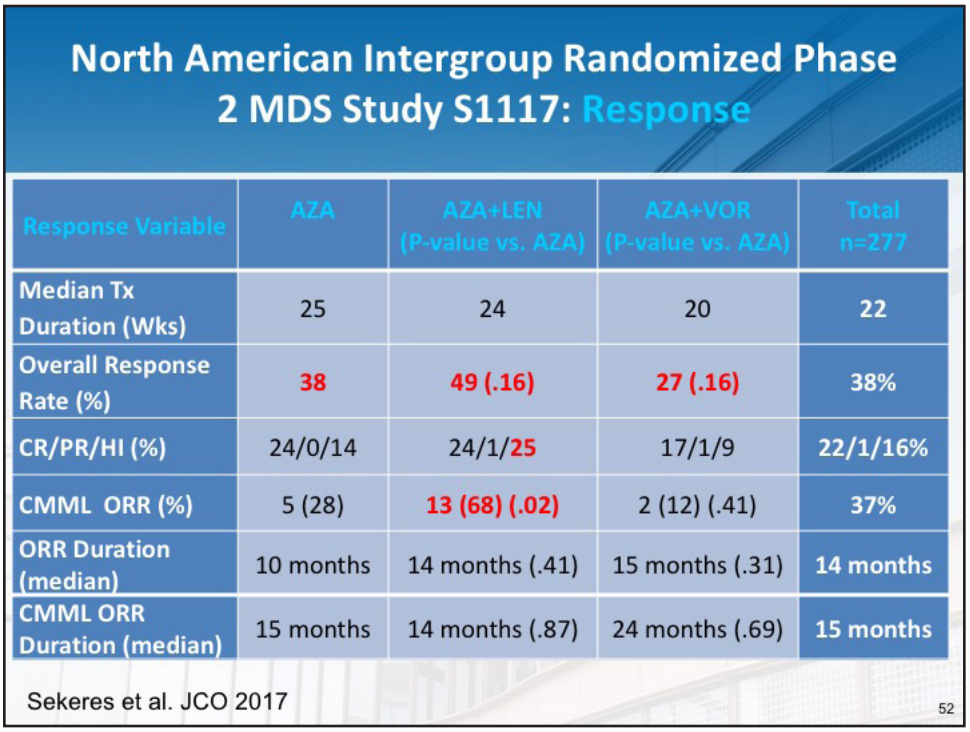
Slide 51: North American Intergroup Randomized Phase 2 MDS Study S1117: Grade ≥3 Toxicities

In this study, the side effects to these various treatment approaches were pretty similar. Similar rates of people developed a fever in the setting of a low white blood cell count. People who received the azacitidine and vorinostat were more likely to have gastrointestinal side effects. And those who got the azacitidine and the lenalidomide were more likely to develop rash.

But one thing that really concerned us as we analyzed these data, when we looked at how many people came off of therapy because of toxicities or side effects, those rates were much higher in the combination arms than they were in the azacitidine alone arm, despite the fact that the toxicities of these drugs that we measured seemed pretty similar.

When we then looked at what percentage of patients underwent non-protocol-defined dose modifications, in other words they had their doses lowered, when the study didn't say to lower the dose, that was also significantly higher in the combination arms than it was in the azacitidine only arm.

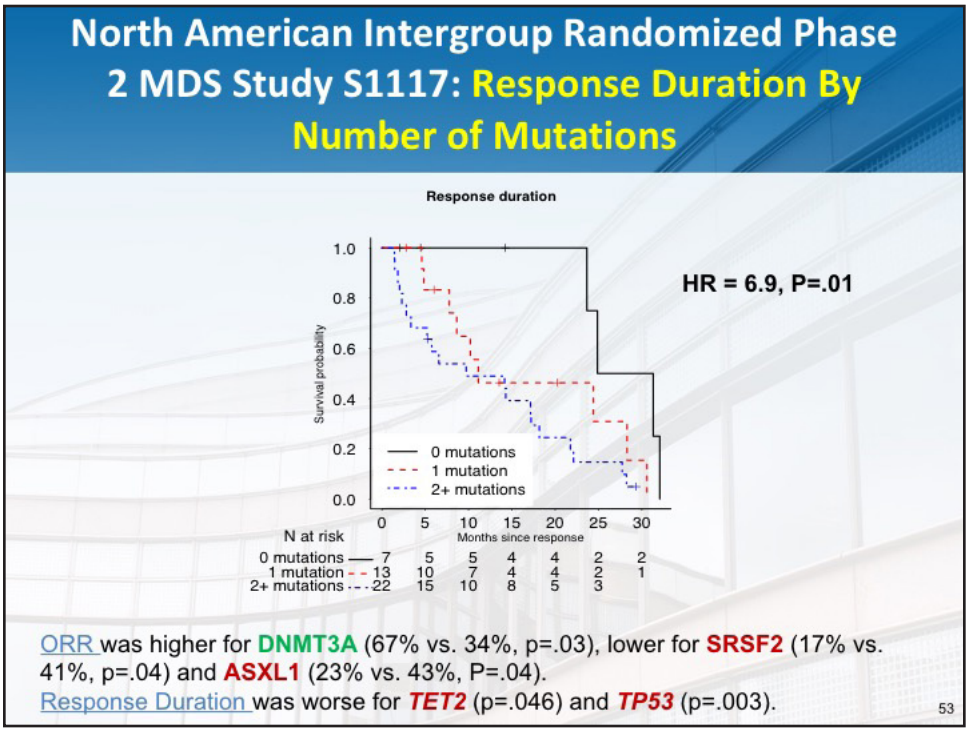
What this told us was that probably people were having their doses lowered or they were stopped from their drugs prematurely. They weren't taking the combination drugs for long enough. Meaning their doctors were taking them off of these drugs too early. And that probably affected how well the combinations of drugs worked.



Slide 52: North American Intergroup Randomized Phase 2 MDS Study S1117: Responses

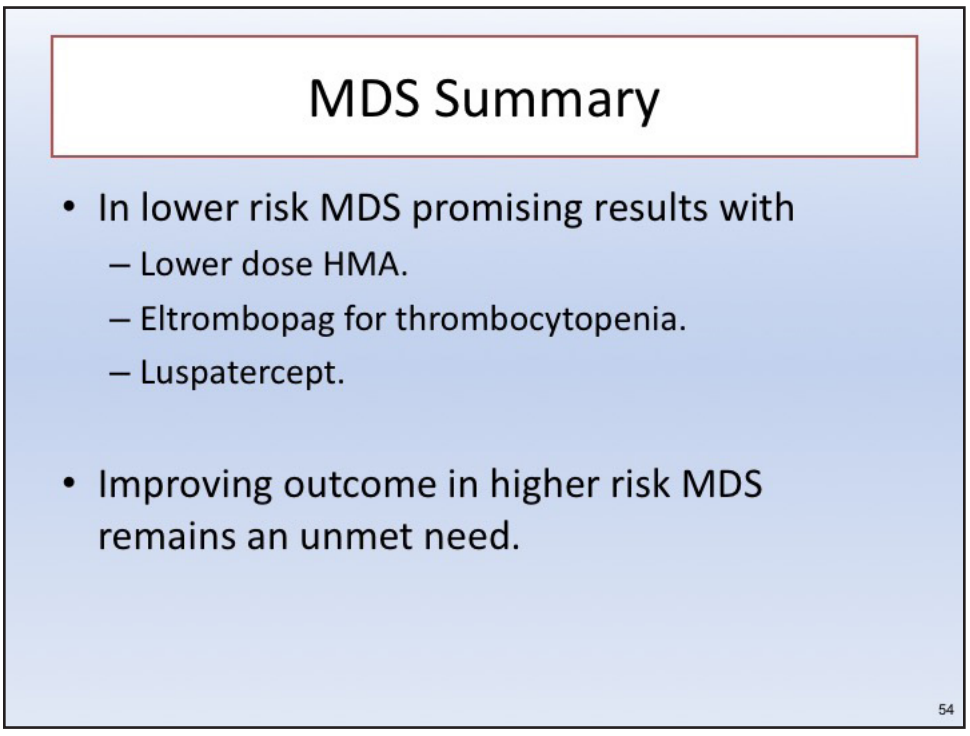
So then when we looked at the results of this study and we looked at the overall response rates, sure enough the overall response rate was higher in patients who got the azacitidine and the lenalidomide at 49%, so almost half of the patients got better, compared to 38% for the azacitidine, and only 27% for the azacitidine and vorinostat. But it wasn't significantly higher. And probably the reason for that is people were discontinued from their drug too early.

For those patients who had chronic myelomonocytic leukemia, CMML, which is a type of MDS, the combination of azacitidine and lenalidomide really did seem to work better, with a response rate of 68%. So, two-thirds of people got better. Compared to 28% for the azacitidine alone.



Slide 53: North American Intergroup Randomized Phase 2 MDS Study S1117: Response Duration by Number of Mutations

So, then you'll see these mutations coming out here. I put this up here not because there's a major take-home message here, but just so that you can see that we're starting to look at these genetic abnormalities and whether or not these drugs are going to work for people. And it turns out when you have a lot more of these abnormalities, these types of drugs don't work as well for you.



Slide 54: MDS Summary

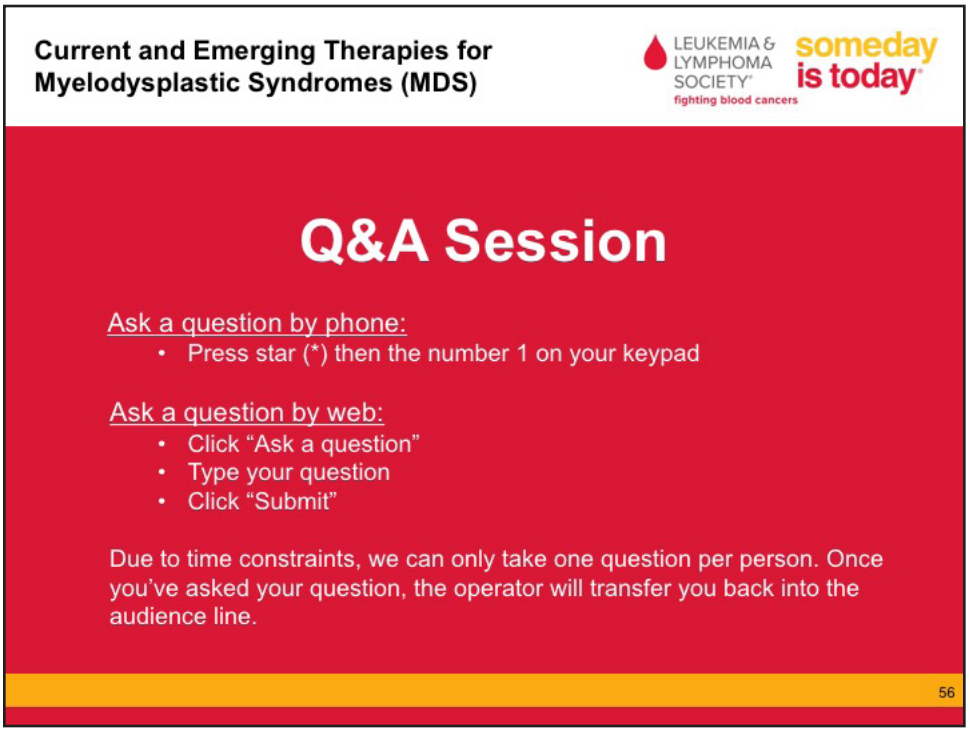
So, to try to wrap all of this up, in lower risk MDS we're seeing promising results with lower doses of the hypomethylating agents, azacitidine and decitabine. We now have another drug, eltrombopag for patients who have low platelet counts. And we have a drug luspatercept which is in advanced trials and may be the next drug approved for the FDA.

We're seeing an improved outcome in higher risk MDS, but it still remains an unmet need. We still need to work harder on the appropriate combinations of drugs for higher risk MDS, or in keeping people on those drugs for longer.

Slide 55: Thanks to You and LLS!

So, I want to thank all of you and The Leukemia & Lymphoma Society and the Aplastic Anemia and MDS Foundation for tuning in today. I always like to thank all of the folks who contribute to our leukemia and MDS program at Cleveland Clinic. And most of all our patients, who are just so wonderful and keep us in this every single day to try to make these therapies even better.

Thanks again.



Slide 56: Q&A Session

Lizette Figueroa-Rivera:
Thank you so much, Dr. Sekeres, for your clear presentation. It is now time for our question and answer portion of our program.

And we'll take the first question from our web audience.

Doctor, Jean, Michael and William are asking about iron overload from frequent transfusions. They're asking if it could be prevented or how it is treated.

Dr. Mikkael Sekeres:
That's a fabulous question and it's one of my favorite questions, but it involves a little bit of a soapbox, so I'm going to ask your apologies ahead of time.

People who receive multiple blood transfusions are at risk of getting iron overload because blood contains iron. This is a terrible consequence of a lifetime of blood transfusions for kids who have thalassemia or sickle cell disease. And these kids, after decades of transfusions, do acquire an iron overload syndrome, where iron deposits in organs like the heart or the liver or even some glands and causes them illness as a result of it. These kids can develop heart failure from this, for example, or liver failure.

For somebody who has MDS, which is diagnosed at age – on the average, as you saw, at age 70 – the number of transfusions that person is going to receive in their lifetime, for the most part, there are some exceptions, for the most part won't be enough to cause enough iron overload to then cause end-organ damage.

We are all exposed to a pretty aggressive marketing campaign by a company that makes an iron-lowering agent, and therefore all become worried about iron overload. I'll be honest. I would love for my 70 year olds to live three, four or five decades and then be at risk of developing these conditions where their organs may fail. But in truth, people don't live to be 120 years old.

So, I de-emphasize the use of these iron-lowering agents and ask my patients instead to focus on therapies that really work to help make their MDS better.

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

Operator:
Our next question comes from Mary Lou from Houston, Texas. Please state your question.

Mary Lou:
I understand Gleevec® is also used now for MDS. What do you think – or it used to be used or has been or does – they do use it in CML, but now they're using it in MDS – what does the doctor think of that one?

Dr. Mikkael Sekeres:
Great. Thank you for your question. As you mentioned, Gleevec or imatinib, has been FDA approved for the treatment of chronic myeloid leukemia, CML, since 2001, and is one of the greatest success stories we have in cancer therapy. That pill was actually on the cover of *Time* magazine, if you can imagine that a pill would be on the cover of *Time* magazine.

There was a recent report in one of our major journals, the *New England Journal of Medicine*, showing that people with CML, who were treated with that drug, have a life expectancy that's probably pretty similar to people who don't even have that type of leukemia. It's really remarkable.

Its efficacy in conditions like myelodysplastic syndrome, however, are really pretty limited. It has been looked at in people who have leukemia as a maintenance strategy, or in people who have a very specific genetic abnormality associated with their leukemia, and it seems to help those people, but not as dramatically as it does those folks who have chronic myeloid leukemia. So, these other studies were looked at in acute myeloid leukemia. Within myelodysplastic syndromes, it really has a very limited applicability.

There are folks who have a rare genetic abnormality who have that chronic myelomonocytic leukemia (CMML), so not chronic myeloid leukemia, but chronic myelomonocytic leukemia, who do benefit from the Gleevec.

Lizette Figueroa-Rivera:
Thank you, Doctor.

And we'll take the next question from our web audience. William asks what are the long-term effects on the immune system for MDS patients?

Dr. Mikkael Sekeres:
Yeah, another fabulous question. There is a weird kind of relationship between the immune system and MDS. There was a study that came out of Sweden that looked at people who had autoimmune conditions, so things like rheumatoid arthritis or lupus or Crohn's, and their risk of developing bone marrow conditions like myelodysplastic syndromes, and it turns out it is much higher.

With myelodysplastic syndromes, it depends on which of your cells is being affected in the bone marrow. If it's just your red blood cells and you're anemic, then your immune system may be normal. If it's just the platelets and you have a low platelet count, then once again your immune system may be normal. But if the myelodysplastic syndrome is starting to affect the white blood cells, and particularly what are called the neutrophils within the white blood cells, then you will be more prone to infections and that can worsen over time.

So, I ask my patients to engage in the sort of behavior that I do when I'm in the hospital, to try to avoid infections. Frequent handwashing. You may walk around with a bottle of that Purell® alcohol stuff. And be conscious of when you've just touched another person, and when you need to wash your hands or use that Purell stuff.

So, I kind of joke with my patients, that they should become a little bit like Howard Hughes, but not too much, in being attentive to germs. That's more appropriate advice for my patients with low white blood cell counts. But if your white blood

count and your neutrophils are normal, then I really don't think you're at an increased risk of infection.

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

Operator:
Yes, of course. Our next question comes from Steven from New Jersey. Please state your question.

Steven:
Hello, Dr. Sekeres. I've been reading about alternative Vitamin K2/T3 combination, sometime also in conjunction with Vitamin A and C. But mainly on the K2 and T3. Very low toxicity. Sort of frowned upon by the regular medical profession. Although some MDs have participated in studies. There was one in Japan. Forget whether it was five year – 5,000 participants or 9,000. Another one in Europe, which was supposedly up to 24,000 participants. Wondering what your feelings are about those particular studies and treatments.

Dr. Mikkael Sekeres:
Yeah, thanks for your question. So, you've highlighted one of the – boy, I guess I'd call it a tension that we have in practicing traditional Western medicine, versus the use of either Eastern medicines or in vitamin supplementation or homeopathy or a lot of other approaches.

So, in Western medicine, the way I was trained was to follow well-designed clinical trials and, you know, let the best drug win, and to be rigorous about those sort of outcomes and endpoints and what we consider to be a meaningful outcome as well.

The use of what are sometimes called alternative or complementary medicines doesn't necessarily ascribe to that scientific approach to judging whether or not a drug works. So, I certainly respect alternative approaches and support my patients when they want to pursue alternative approaches, but I can't give a clear stamp of approval because most of the time these alternative approaches haven't been subjected to the types of studies that I rely on in making my recommendations.

I will say there is some noise in the field about some of these genetic abnormalities that I talked about, may – have been shown in some preliminary, you know, mouse studies or basic science studies, to be susceptible to certain vitamin approaches. Things like Vitamin C, like you mentioned, or ascorbic acid.

So, I think there's more to come on that. I think you will start to see some clinical trials, where they're incorporating vitamins into the regimen to see if there's some particular benefit. If you feel as if you want to use these sorts of medicines, my advice to you would be to let your doctor know, and again, with my patients I don't prohibit them from doing it, but I can't give them a clear stamp of approval either.

Lizette Figueroa-Rivera:
Thank you, Doctor.

And our next question comes from Marilyn. She asks about the impact of chromosome 7 deletion with TP53 mutation on the disease, and how to decide when or if to begin treatment or a clinical trial.

Dr. Mikkael Sekeres:
Boy, it's a tough question and it's a really good one. When we talk about the good risk, intermediate risk and poor risk genetic abnormalities or chromosome abnormalities in these prognostic systems, chromosome 7 abnormalities are considered a poor risk.

Now TP53 or p53 are one of those genes that I showed. If you remember the slide I showed with all the bubbles on it, with the different types of – how complex MDS is with its genetic abnormalities, that TP53 is one of those bubbles and it's often associated with chromosome 17. It's also considered a poor risk for MDS. And we struggle with what to do with folks who have these abnormalities.

There seems to be some indication that treatment with azacitidine or decitabine seems to work preferentially well in patients who have the p53 abnormality. Now if you have a p53 abnormality and a high blast percentage, and a chromosome 7 abnormality, gee, that's considered high risk MDS and that's the sort of person for whom I would consider a bone marrow transplant.

If you have a chromosome 7 abnormality and your blood counts are perfectly normal and you don't have excess blasts, boy, that's really, really tricky. It's hard for us to recommend a bone marrow transplant in somebody like that. But we'd probably do our homework in assessing whether or not an available donor was around, and move pretty quickly towards a transplant, if we saw those blood counts start to slip.

Lizette Figueroa-Rivera:
Thank you, Doctor.

And Jennifer asks our last question today. She thinks that she's the third in her family to have MDS, and if you know if there are any studies regarding genetics in MDS.

Dr. Mikkael Sekeres:
Yeah, boy, I'm sorry to hear that, that you have MDS, that seems to run in your family.

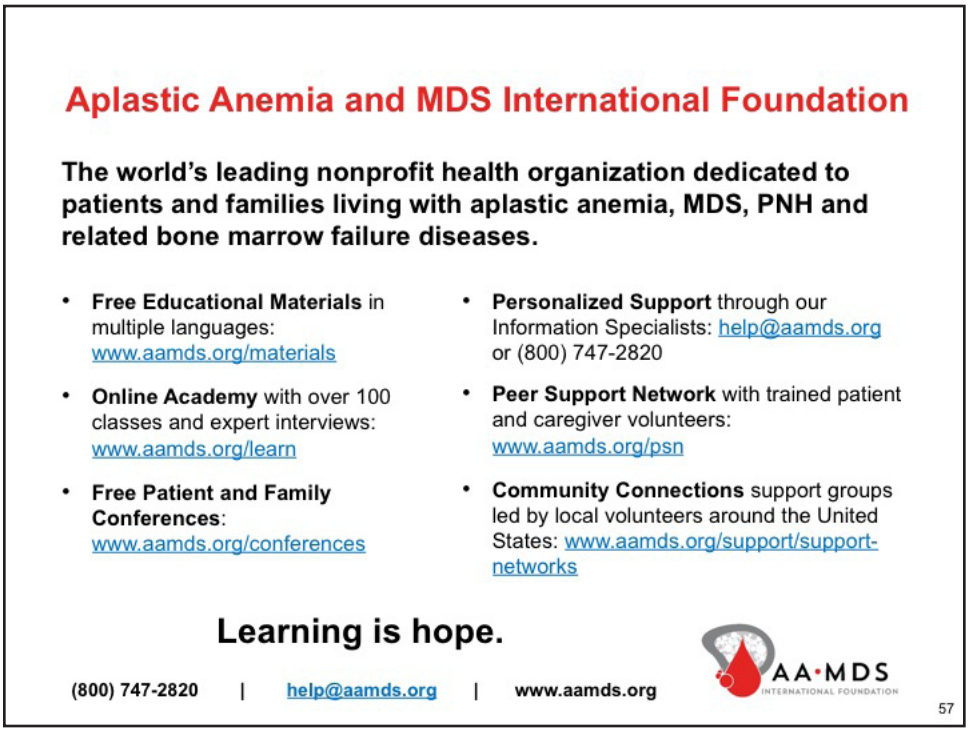
If you're anywhere near Cleveland we're happy to see you or your family members here to discuss it in a little more detail.

To try to broaden this discussion a little bit, there are rare, rare, rare family syndromes in which there's a lot of MDS. We described one of those families here in Cleveland, where it started with a pair of twins who had MDS and their dad had died of leukemia. And when we explored it we found that they had an abnormality, it has a funny name to it, it's called a DDX41 abnormality that ran in their family. When we presented this information at one of our international meetings, colleagues from Germany and Japan came up to us and said, hey, we think we have families like that, too. And we combined all of this information into a scientific paper. So this is now a recognized family syndrome of MDS.

There are some other abnormalities that do run in families, again, rarely and so rarely that you can actually name which country that family lives.

If you feel as if that is something that is occurring within your family, I do encourage you, if you're near Cleveland come on down, we'd love to see you. There's also a group at the University of Chicago who's studying family syndromes of MDS.

Lizette Figueroa-Rivera:
That's very interesting, and thank you, Jennifer, for your question.



Slide 57: Aplastic Anemia and MDS International Foundation

Thank you also, Dr. Sekeres, for your continued dedication to patients.

For those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

Slide 58: Support Resources

If we weren't able to get to your question today, call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or you can also reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

As a reminder, you can download and print the slides, as well as listen to the audio of today's program from our website, at www.LLS.org/programs.

Dr. Sekeres, thank you again for volunteering your time with us today.

And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us.

Goodbye and we wish you well.