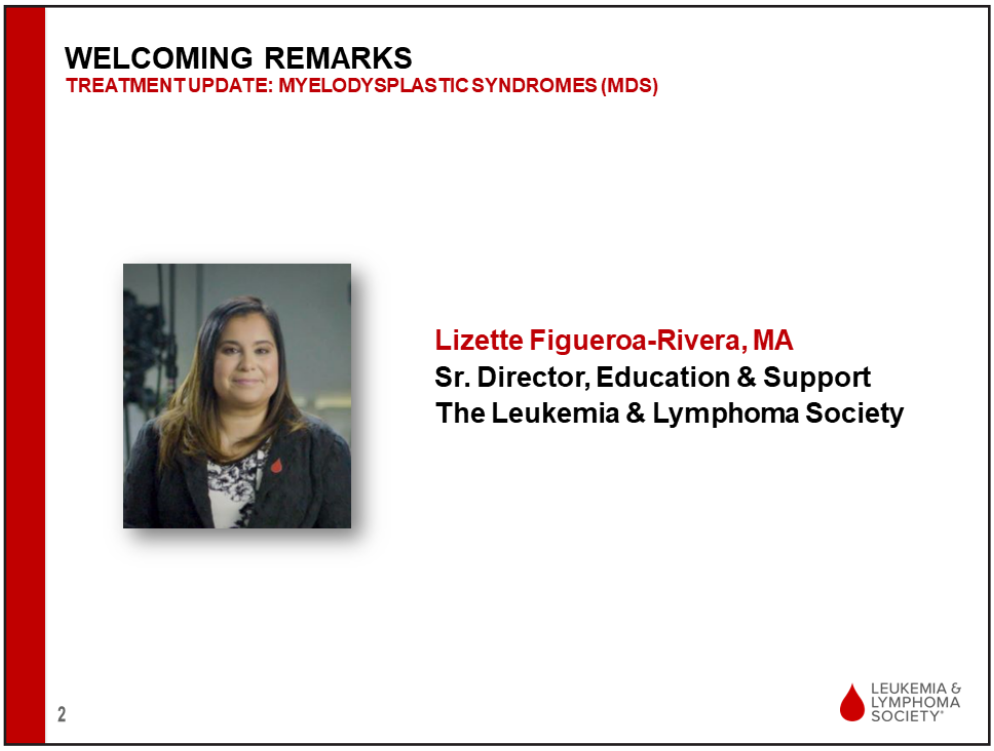
Slide 1: TREATMENT UPDATE: MYELODYSPLASTIC SYNDROMES (MDS)

Greetings, and welcome to Treatment Updates for MDS, a telephone and web education program brought to you by The Leukemia & Lymphoma Society. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you.



Slide 2: WELCOMING REMARKS

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), I would like to welcome all of you. We have over 700 people participating from across the United States, as well as others participating from other countries, including Afghanistan, Canada, Denmark, Ethiopia, Iraq, The Netherlands, and Singapore. Welcome.

With us today we are fortunate to have Dr. Sekeres to provide us with the latest information on myelodysplastic syndromes (MDS) and its current and emerging therapies.

LLS is at the forefront of the fight to cure cancer. As the leading source of free blood cancer information, education, and support for patients, survivors, families, and healthcare professionals, LLS helps you navigate you and your loved one's care through treatment, working to ensure that you will have access to quality, affordable, and coordinated care.

Research will help us achieve an end to cancer. In the meantime, patients and caregivers need help before, during, and after a cancer diagnosis and treatment. Please continue to inform us of what you need during this time and please continue to let us be there for you.

For this program we would like to acknowledge and thank Bristol Myers Squibb and Taiho Oncology for support of this program.

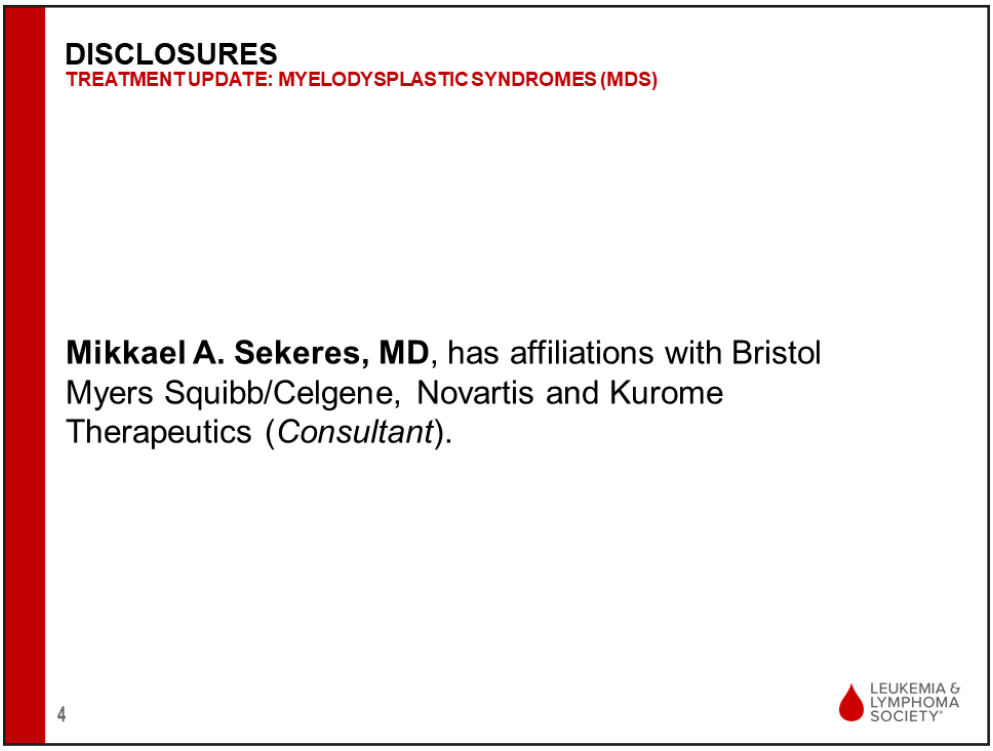
I am now pleased to introduce Dr. Sekeres from the Sylvester Comprehensive Cancer Center at the University of Miami in Miami, FL. Dr. Sekeres, I am privileged to turn the program over to you.

Slide 3: Updates in Myelodysplastic Syndromes

Dr. Mikkael Sekeres:

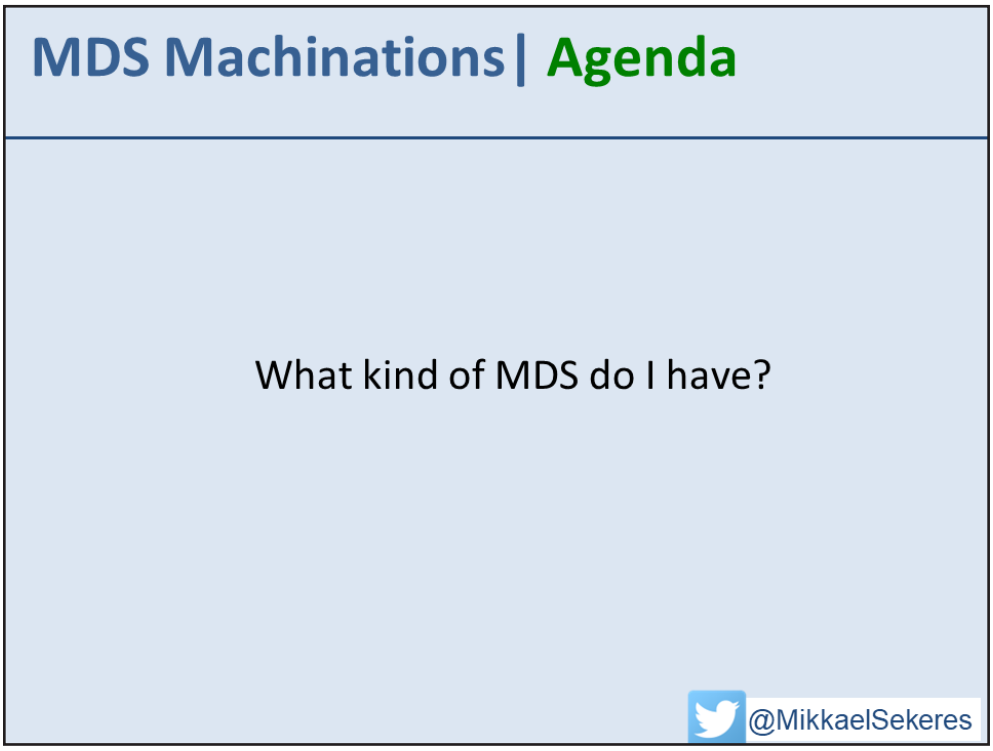
Thank you so much Lizette and what a true privilege it is to be able to talk to you today on behalf of The Leukemia & Lymphoma Society. They are really a marvelous organization and in my years of doing this, I have always found them to put patients first and your needs first beyond anything else.

I will be talking today about updates in myelodysplastic syndromes and I am happy to take questions afterwards.



Slide 4: DISCLOSURES

These are my disclosures.



Slide 5: MDS Machinations | Agenda

I want to start with a basic question. What kind of myelodysplastic syndromes do I have? I will be abbreviating that as MDS during the talk. And… What is myelodysplastic syndromes?

MDS | WHO Classification

2008 Name	Abbrev.	2016 Name	Abbrev.
Refractory cytopenia with unilineage dysplasia	RCUD (includes RA, RN and RT)	**MDS with single lineage dysplasia**	MDS-SLD
Refractory anemia with ring sideroblasts	RARS	**MDS with ring sideroblasts**	MDS-RS
MDS w/ isolated del(5q)	Del(5q)	*unchanged*	*unchanged*
Refractory cytopenia with multilineage dysplasia	RCMD	**MDS with multilineage dysplasia**	MDS-MLD
		(with ring sideroblasts)	MDS-RS-MLD
Refractory anemia with excess blasts, type 1	RAEB-1	**MDS with excess blasts, type 1**	MDS-EB-1
Refractory anemia with excess blasts, type 2	RAEB-2	**MDS with excess blasts, type 2**	MDS-EB-2
MDS, Unclassifiable	MDS-U	*unchanged*	*unchanged*
Refractory cytopenia(s) of childhood	RCC	*unchanged*	*unchanged*

Adapted from Arber et al. *Blood* 2016;127:2391. 6

Slide 6: MDS | WHO Classification

The World Health Organization (WHO) classifies myelodysplastic syndromes just like the World Health Organization has been so involved as we have been thinking about COVID-19 and its variants and its treatments and vaccines to prevent it.

Let's start with what myelodysplastic syndromes is. It is a crazy name, isn't it? Myelodysplastic. That refers to the fact that there are myeloid cells in the bone marrow and they are dysplastic, they are bad-growing. When you look at them under a microscope they look abnormal. So, myelodysplastic actually refers to what a pathologist, a doctor who looks at tissues and cells, is actually seeing under the microscope when examining a bone marrow biopsy or aspirate.

Syndromes, we talk about it that way and we give a plural to it because we recognize that one person's MDS may be very, very different from another person's MDS, so it is really a constellation of different subtypes of diagnoses.

Now, what is going on in the bone marrow when someone has myelodysplastic syndromes, these abnormal cells, these dysplastic bad-growing cells are growing and growing and growing and they are taking up more space in the bone marrow. As they take up more space the normal bone marrow cells start to die out. The normal bone marrow cells are the ones that make the cells in our bloodstreams. They make the red blood cells that bring oxygen to our tissues and when those are low we're anemic, the white blood cells help fight infections, and the platelets help stop bleeding. So, you can imagine as these dysplastic cells are growing and growing and growing in the bone marrow and the normal cells are dying out, the bone marrow, the factory, is not able to make the normal cells that wind up in our bloodstream. And that is why often people who have myelodysplastic syndromes come to a doctor's attention because they have anemia or they have a low platelet count or a low white blood cell count.

Now the different subtypes of myelodysplastic syndromes that the World Health Organization has defined actually reflect what is going on clinically with a patient and what is going on in that person's bone marrow.

For example, one of the categories, the top one, is MDS with single lineage dysplasia. What that means by lineage is one of those 3 lineages of the blood cells, the reds, the whites, or the platelets. So, if somebody has MDS with single lineage dysplasia it means one of those cell lines is affected by the MDS, meaning that person may have an anemia or that person may have a low white blood cell count or a low platelet count, but not 2 or 3 of those.

This diagnosis comes along with a subtype called MDS with ring sideroblasts. What does that mean? Sounds intriguing. When a pathologist is looking at cells under a microscope from the bone marrow, that pathologist will put certain dyes onto those cells and some of those cells will take up the dye and some won't and that is actually how a pathologist can distinguish among different cells.

One type of dye is taken up by the cells and it causes a ring around that cell, just like a ring around Saturn, we call that a ring sideroblast. That becomes important a little bit when we are talking about treatment, because one treatment has been approved by the FDA (Food and Drug Administration) specifically for people who have ring sideroblasts.

And, there is MDS with isolated deletion 5q. That refers to the fact that we all have 23 pairs of chromosomes. They are numbered 1 through 22 and then we have the sex chromosomes, XX for women and XY for men. People who have myelodysplastic syndromes often have an abnormality in one of those chromosomes. That is the genetic material or the DNA within a cell. Most of the time that isn't something that you would pass down to kids or grandkids, it is not like saying, well, I have this genetic display in my chromosome and that means that I have blue eyes and you are going to get blue eyes and my grandson's going to have blue eyes. It is something that arose in the bone marrow to cause the MDS. So, it is most of the time not something that is passed down to kids or grandkids.

In this case, it is MDS that is caused when the leg of chromosome 5 is missing. And that is called deletion 5q. That becomes important because there is another treatment I will talk about that is specifically for people who have the deletion 5q MDS.

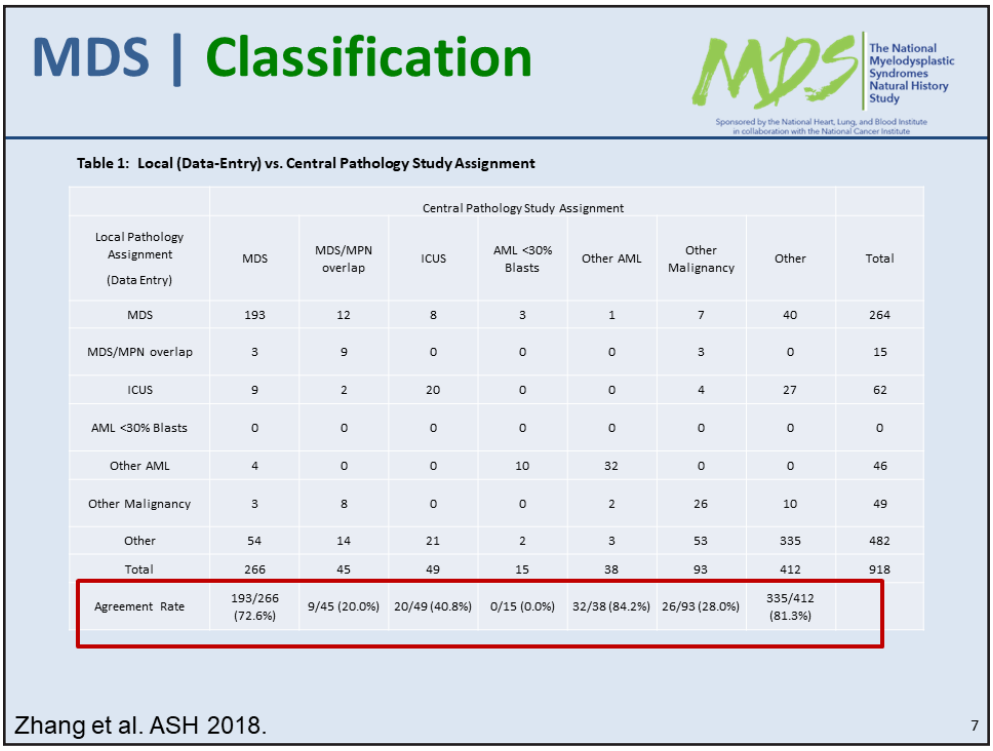
Next, we have MDS with multilineage dysplasia. Above we talked about single lineage dysplasia, now we are talking about multilineage, meaning that a person will have not just an anemia, but an anemia and a low platelet count or an anemia and a low white blood cell count. So, 2 or more abnormalities and this can also include ring sideroblasts.

The next 2 categories are important. Now we are talking about MDS that has excess blasts. Well, what is a blast? A blast is an immature white blood cell. So, full confession here, I have blasts in my bone marrow. I have to, if I eventually want mature white blood cells and a mature immune system. It is normal to have about 1% or 2% blasts in your bone marrow. Once you start to have 5% blasts, we say that is abnormal and that would be somebody who has MDS with excess blasts type 1 with 5% to 9% blasts. That is too many blasts. It is as if you have these immature cells that are accumulating in your bone marrow, imagine again that this is a factory and we have a bunch of kindergarteners or first graders who are running amok in that factory. Those would be like excess blasts. Blasts are the immature white blood cells.

When you have 10% to 19% blasts in the bone marrow, we would say that is MDS with excess blasts type 2. And that is getting awfully close to a diagnosis of acute leukemia. We say that somebody has acute leukemia when he or she has 20% blasts in the bone marrow.

One of our goals in treating MDS is to try to prevent it from going into leukemia, particularly in people who start with excess blasts.

Okay, so that seems pretty straightforward, right? Should be pretty easy for a pathologist to look at a slide of somebody's bone marrow and check the World Health Organization classification and say ah-ha, this is what this person has. Well, it turns out it is actually really tricky to evaluate these bone marrows.



MDS | Classification

The National Myelodysplastic Syndromes Natural History Study
Sponsored by the National Heart, Lung, and Blood Institute in collaboration with the National Cancer Institute

Table 1: Local (Data-Entry) vs. Central Pathology Study Assignment

Local Pathology Assignment (Data Entry)	Central Pathology Study Assignment: MDS	MDS/MPN overlap	ICUS	AML <30% Blasts	Other AML	Other Malignancy	Other	Total
MDS	193	12	8	3	1	7	40	264
MDS/MPN overlap	3	9	0	0	0	3	0	15
ICUS	9	2	20	0	0	4	27	62
AML <30% Blasts	0	0	0	0	0	0	0	0
Other AML	4	0	0	10	32	0	0	46
Other Malignancy	3	8	0	0	2	26	10	49
Other	54	14	21	2	3	53	335	482
Total	266	45	49	15	38	93	412	918
Agreement Rate	193/266 (72.6%)	9/45 (20.0%)	20/49 (40.8%)	0/15 (0.0%)	32/38 (84.2%)	26/93 (28.0%)	335/412 (81.3%)	

Zhang et al. ASH 2018.

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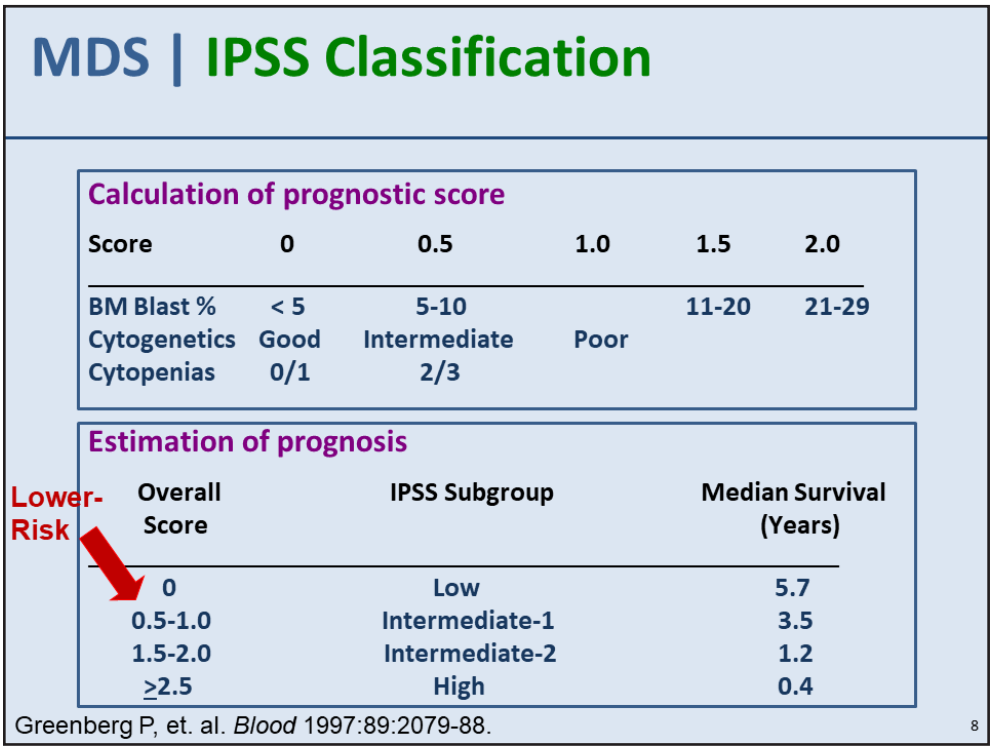
Slide 7: MDS | Classification

This was a study we conducted through the National Institutes of Health (NIH). Within the NIH is a subdivision called the National Heart, Lung and Blood Institute, that is the subdivision, we conducted this study, and it is a really interesting study that we did. We went to a bunch of centers around the country and said if you have a patient you suspect has MDS who hasn't even gotten a diagnosis yet, but you suspect it, please enroll them to the study and we will collect information on their history, their quality of life, and we will actually collect some of their bone marrow samples and we'll do an analysis at our central labs, where we have expert pathologists in MDS to see if they have MDS and if not, what they have.

In the meantime, pathologists who are at the local institution where the person was being seen were also assessing whether or not the person had MDS. And, we did a little study where we looked at the agreement between the local pathologist and our expert central pathologist, and it turns out that they agreed 73% of the time. However, they disagreed 27% of the time, meaning that a local pathologist may have said, this person has MDS and our central pathologist said no, they don't, they have leukemia, or no, they don't have MDS at all, everything is fine.

So, the fact that there was disagreements 27% of the time should give you pause. It gave me pause for sure. And what it told me is just how incredibly important it is to get a second opinion on your MDS diagnosis, not only to hear from somebody who specializes in MDS about the best treatment, but also to get a second opinion on the bone marrow biopsy from an expert pathologist, just to make sure it is truly MDS that you have, and if so, what subtype.



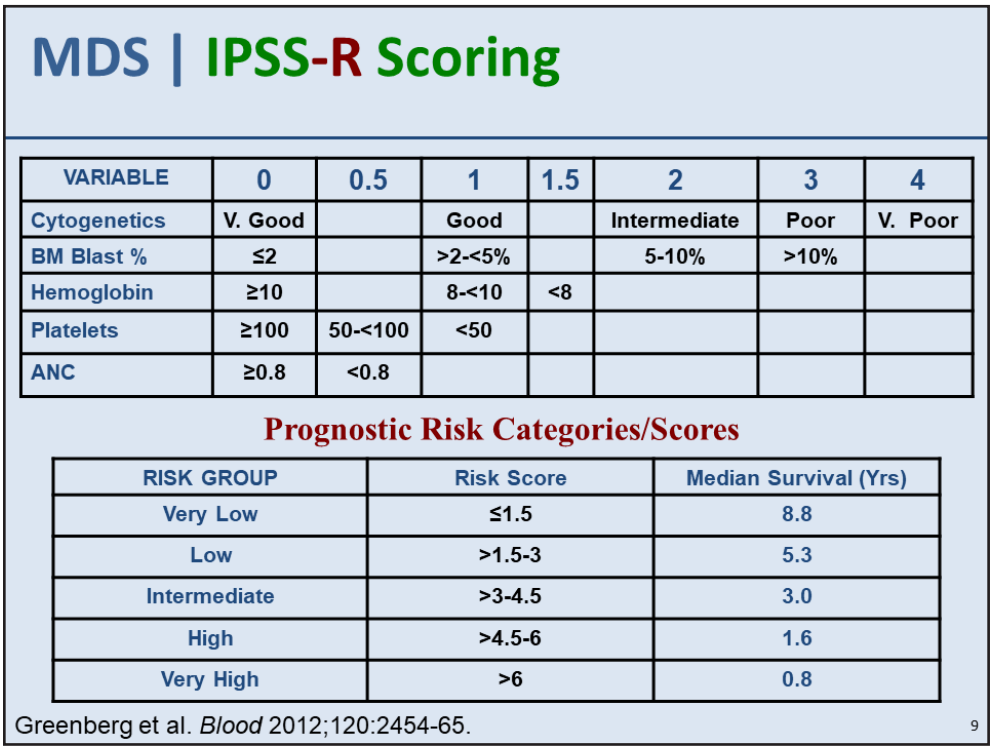
Slide 8: MDS | IPSS Classification

One of the questions my patients often ask me is what stage is my MDS? And a lot of us have friends or family members who have cancers and that person may have a lung cancer and say I am Stage 1, or a person may have breast cancer and say I am Stage 2. So, my patients ask me what stage of MDS do I have?

Well, we don't really stage MDS. Instead, what we use is this very complicated system called the International Prognostic Scoring System (IPSS) to classify MDS based on risk. That is the risk of living a long and happy time or risk of living a short time and risk of the MDS going into acute leukemia. We calculate that risk based on all the tests that we run on every patient who has MDS. We give a point score for the percentage of blasts somebody has in the bone marrow, the more blasts – the higher the score. We give a score based on what we call cytogenetics. Those are chromosome abnormalities in a person's MDS cells and we have classified those into good risk chromosome abnormalities, intermediate, or poor risk chromosome abnormalities, and we base it on the number of cytopenias a person has. In other words, does a person just have a single anemia or does that person have an anemia and a low white blood cell count, or maybe all 3 – anemia, low white blood cell count, and low platelet count? The more of those cytopenias, those low blood counts, the higher the score.

We add these numbers up and then place somebody into an IPSS subgroup, with an estimate of how long that person has to live.

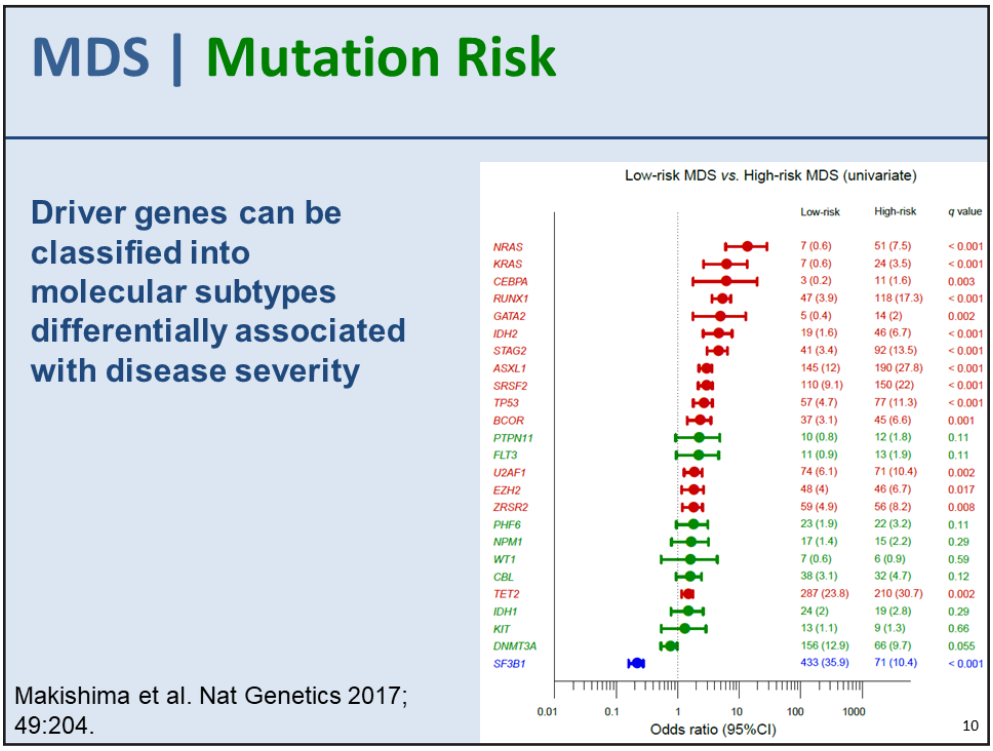
Now I will tell you, this system was published in 1997. It is getting a little bit long in the tooth. And these estimates for survival were only in people who never received a drop of therapy 25 years ago. So, we are not sure how accurate the IPSS still is for estimating survival, but it gives us a good sense of whether somebody falls into one of the lower-risk groups or one of the higher-risk groups. But we recognize that this is a pretty simple way to look at MDS.



Slide 9: MDS | IPSS-R Scoring

So, we revised the IPSS and published this in 2012. (This is getting even more complicated and now I actually have to have this pasted up in my workroom before I go and see my patients.) Now there are a lot more categories for the different sorts of abnormalities that we might find, but they boil down to the same characteristics, whether somebody has very good or good risk chromosomes or poor or very poor risk chromosomes within their MDS cells. Remember, I am not talking about something that has passed down to family members.

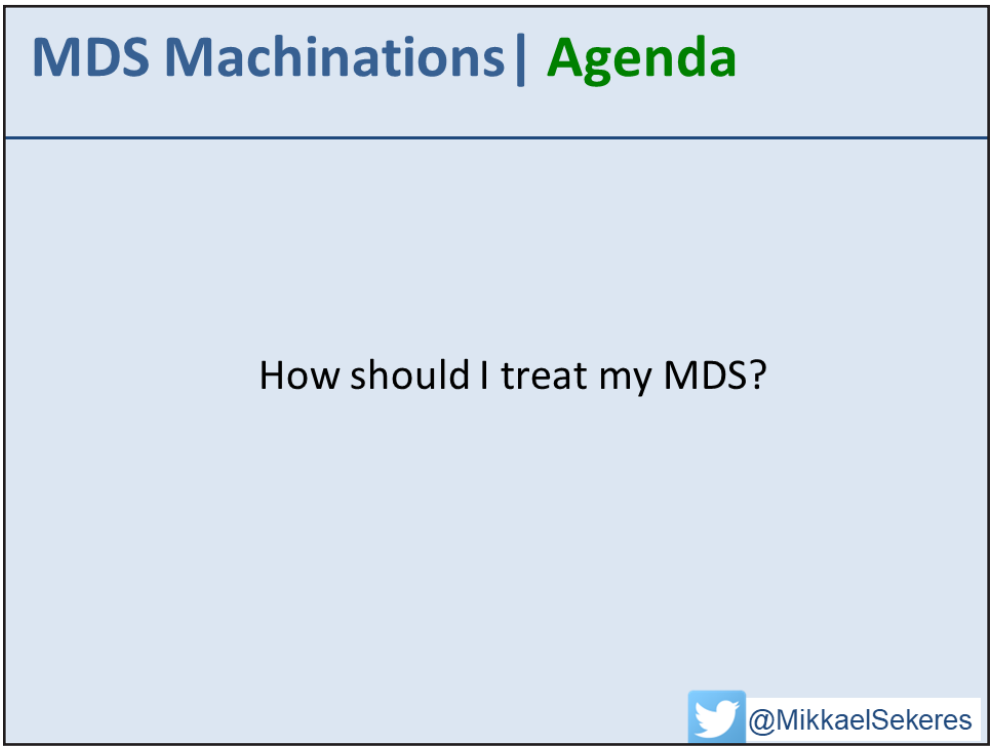
Then a different score depending on the blast percentage a person has in his or her bone marrow and the degree of anemia, low platelet count or low white blood cell count. And then again, we assign a score to that and estimate somebody's prognosis based on it. But again, this was developed in people who never received a drop of therapy, so it is not as accurate once somebody starts to get treated.



Slide 10: MDS | Mutation Risk

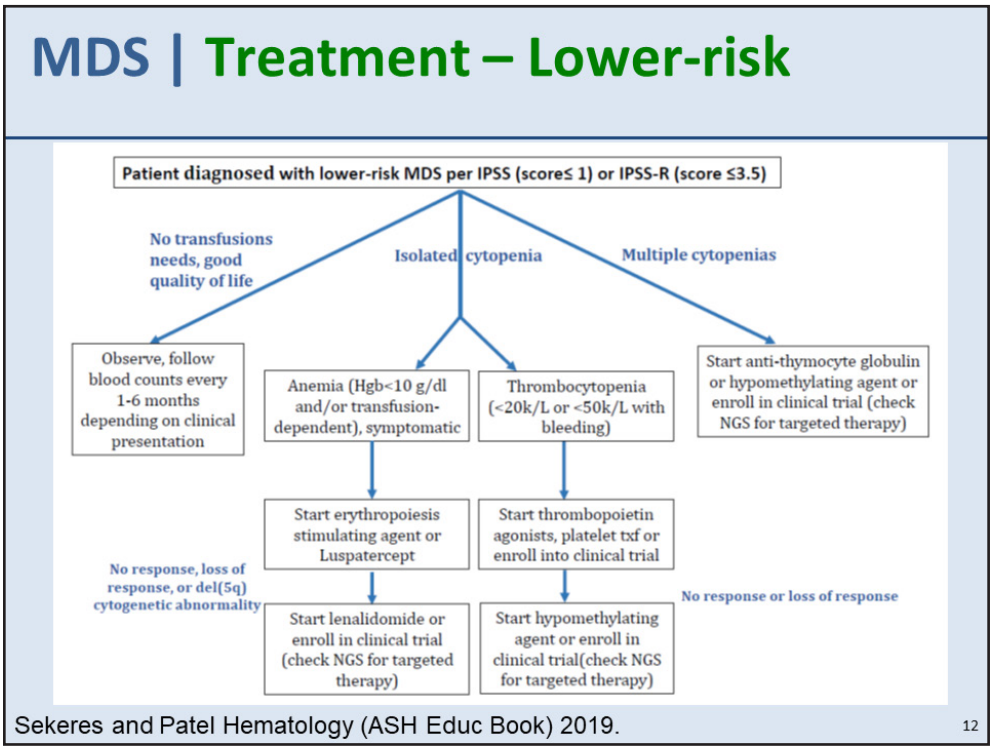
But MDS unfortunately is even more complicated than that. I talked about the chromosomes that we have and how people can have chromosome abnormalities with their MDS. Well, every chromosome we have, remember there are 23 pairs of chromosomes, but we have 30,000 genes in our body, so every one of those chromosomes has hundreds to thousands of genes on it. And you could have an abnormality in a single gene that you can miss if you just look at the broad chromosomes. It is like trying to identify one tree in a forest. We have even more sophisticated technology that is called next generation sequencing (NGS), where we will look for specific gene mutations that we can find on those chromosomes that are commonly associated with myelodysplastic syndromes. These gene mutations tend to be combinations of letters and numbers and make no sense if you try to just read them.

For example, we know that people who have an NRAS or KRAS mutation tend to have a worse prognosis. On the other hand, people who have an SF3B1 mutation, which is associated with those ring sideroblasts we saw from the WHO classification, actually have a very good prognosis. This helps us refine even further how we think about prognosis, survival, and even the therapies that we choose.



Slide 11: MDS Machinations | Agenda

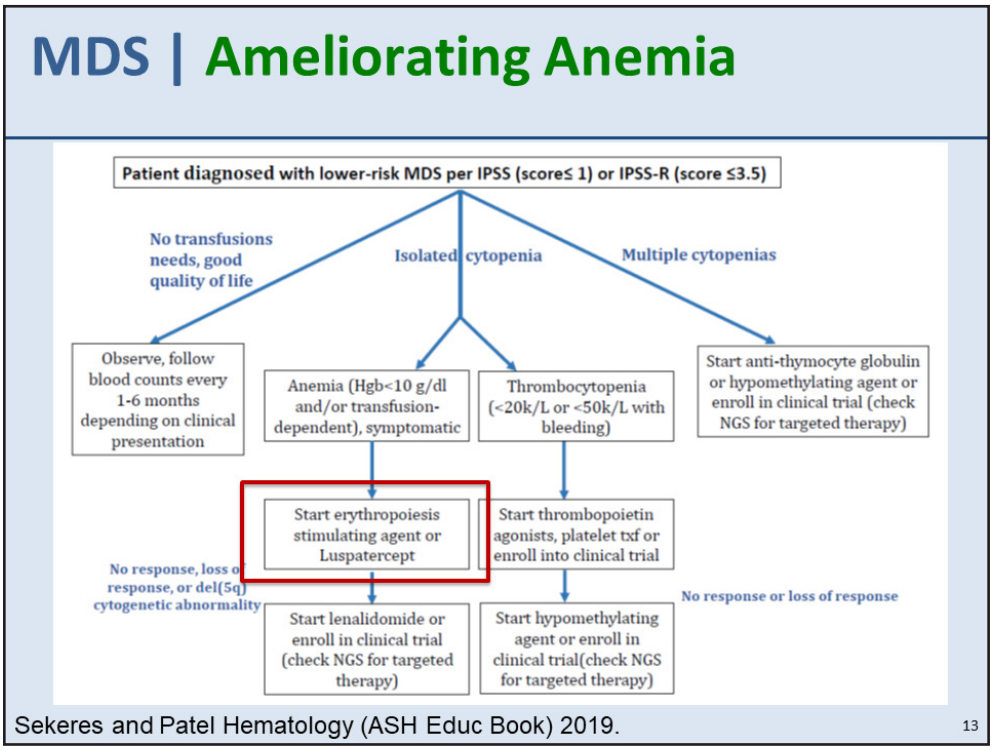
So next question. How should I treat my myelodysplastic syndromes?



Slide 12: MDS | Treatment – Lower-risk

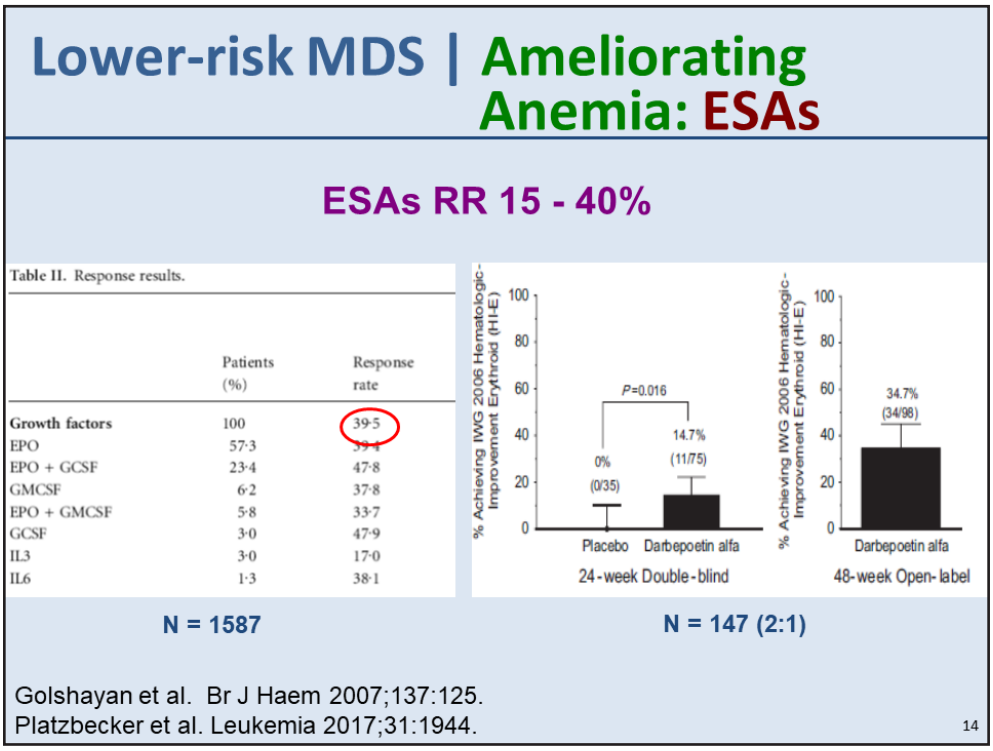
This is an example of an algorithm that we have developed for how we approach treatment of lower-risk MDS. Remember those folks who have relatively good chromosome abnormalities, relatively low blast percentage, and either 1 or 2 cytopenias (low blood counts). On the left hand side of the slide, you can see that some of my patients come to see me and have no transfusion needs, they don't require any blood or platelets, and they've got a good quality of life. One of my patients once referred to this as having mild displeasure syndrome. He didn't like having to fight the traffic to come in and see me, but other than that it really did not affect his life very much. So those are the sorts of folks that I will just follow and see maybe every month or 2 or even every 6 months. I just saw somebody yesterday whom I see about every 6 months for that person's myelodysplastic syndrome, just to monitor the counts.

Then there are people where their predominating problem, the thing that really bugs them, is anemia, a low hemoglobin level. Those are folks in whom we choose certain therapies or people who have a low platelet count, what we call thrombocytopenia, that is really bugging them the most and then we will focus on that abnormality. Finally, there are those folks who have multiple abnormalities that are bothering them. They may have an anemia and a low platelet count and there are different therapies for those. So, let's focus on what those therapies are.



Slide 13: MDS | Ameliorating Anemia

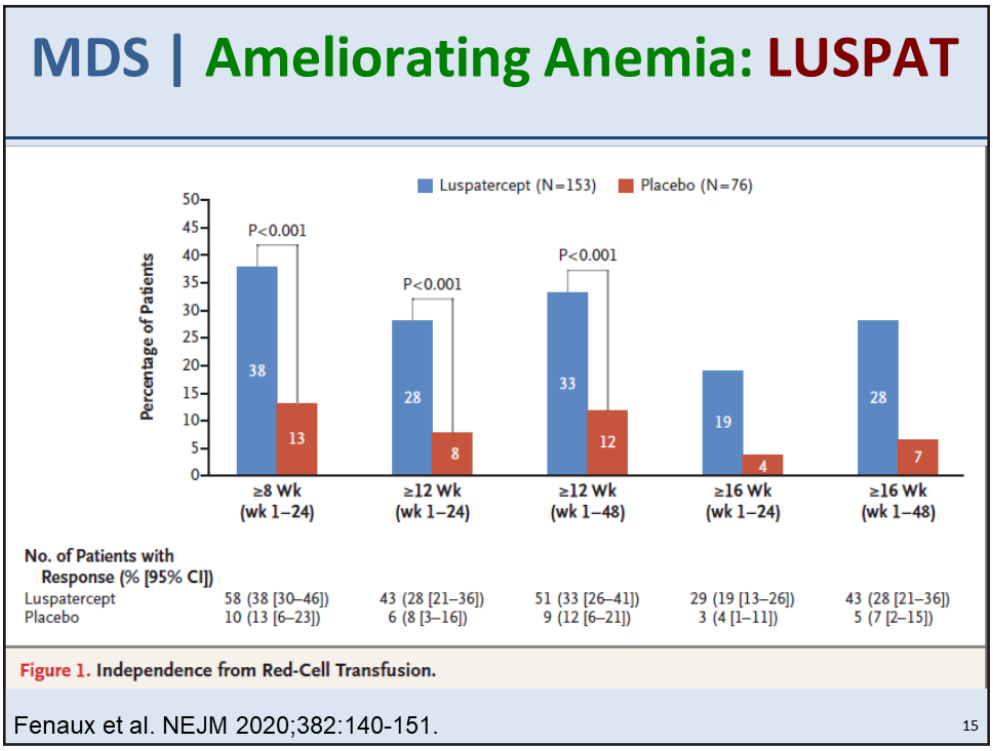
The first, for anemia, we might consider starting what is called an erythropoiesis-stimulating agent or the drug luspatercept (Reblozyl®). What is an erythropoiesis-stimulating agent? That sounds like one of those long medical terms we come up with so nobody can figure out what it is. Those are the growth factors that stimulate the growth of a hormone, EPO (erythropoietin). They are actually EPO themselves, they are a type of hormone that we give to people and that EPO stimulates the remaining normal bone marrow cells to make more red blood cells. It can be drugs like erythropoietin or darbepoetin, which are more commonly called things like Procrit®, Retacrit® (erythropoietin), or Aranesp®.



Slide 14: Lower-risk MDS | Ameliorating Anemia: ESAs

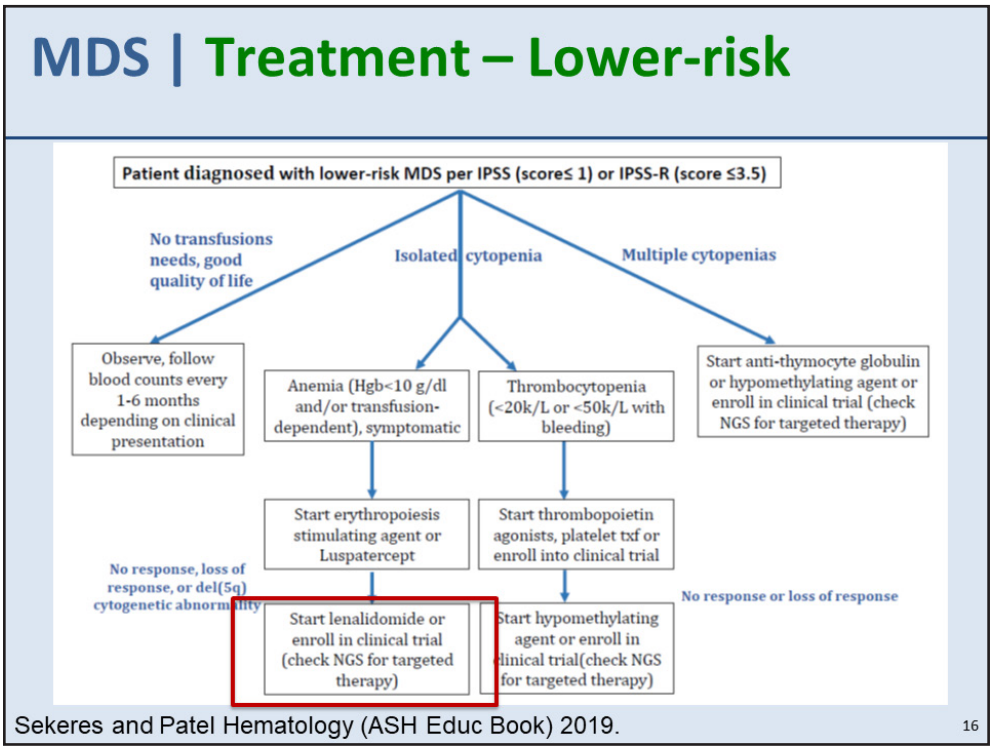
A study we did a few years ago showed that people who have lower-risk MDS, who are treated with one of these growth factors, have a chance of responding, in other words, their hemoglobin improving of about 40%.

There is another study that was recently conducted in Europe that showed that that response rate may be as low as 15%, although over time it seemed to improve to 35%. I will most commonly quote to my patients a chance of getting better with one of these hormones of somewhere around 35% to 40%. And when people get better, on average their hemoglobin improves or they go without transfusions for about a year.



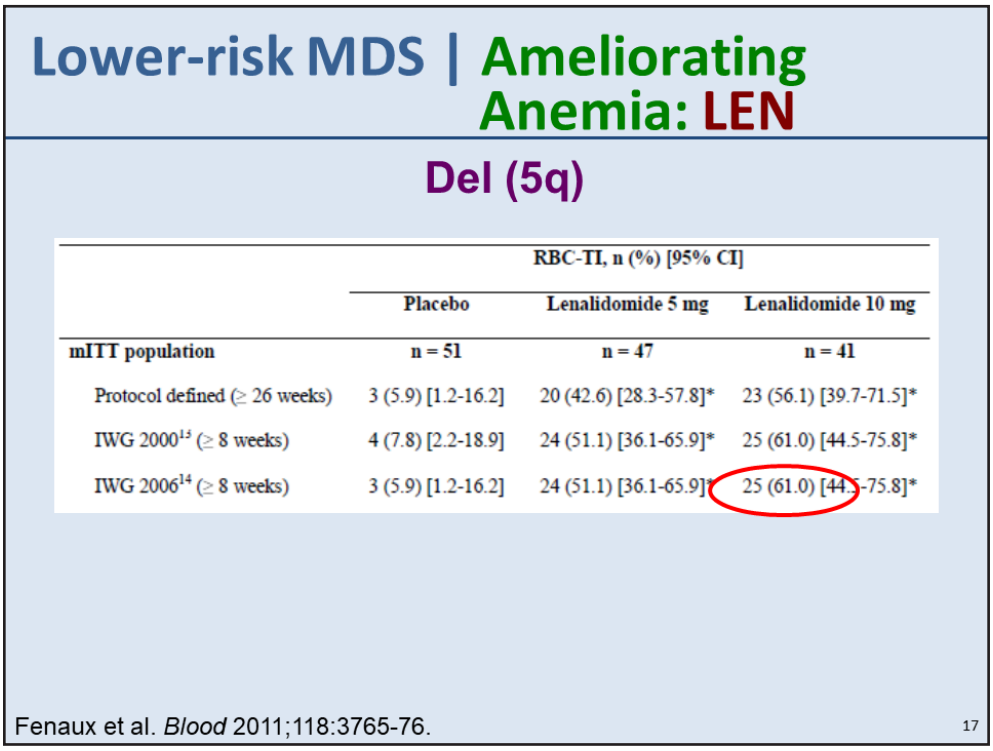
Slide 15: MDS | Ameliorating Anemia: LUSPAT

What about luspatercept? This drug was just approved in 2020 for people who have those ring sideroblasts that I mentioned earlier. In those patients the response rate, in other words the number of people who came onto the study requiring red blood cell transfusions, and then were able to go at least an 8-week period without needing any red blood cell transfusions was 38%. If you are thinking about this in simpler ways, about a little over one-third of patients benefitted from getting the luspatercept. On average when someone benefitted from it, they benefitted for about 32 weeks before the drug started to lose its effect. And this is a shot that people get about every 3 weeks and I think it is a decent option, particularly for those who have ring sideroblasts, which is the on-label indication.



Slide 16: MDS | Treatment – Lower-risk

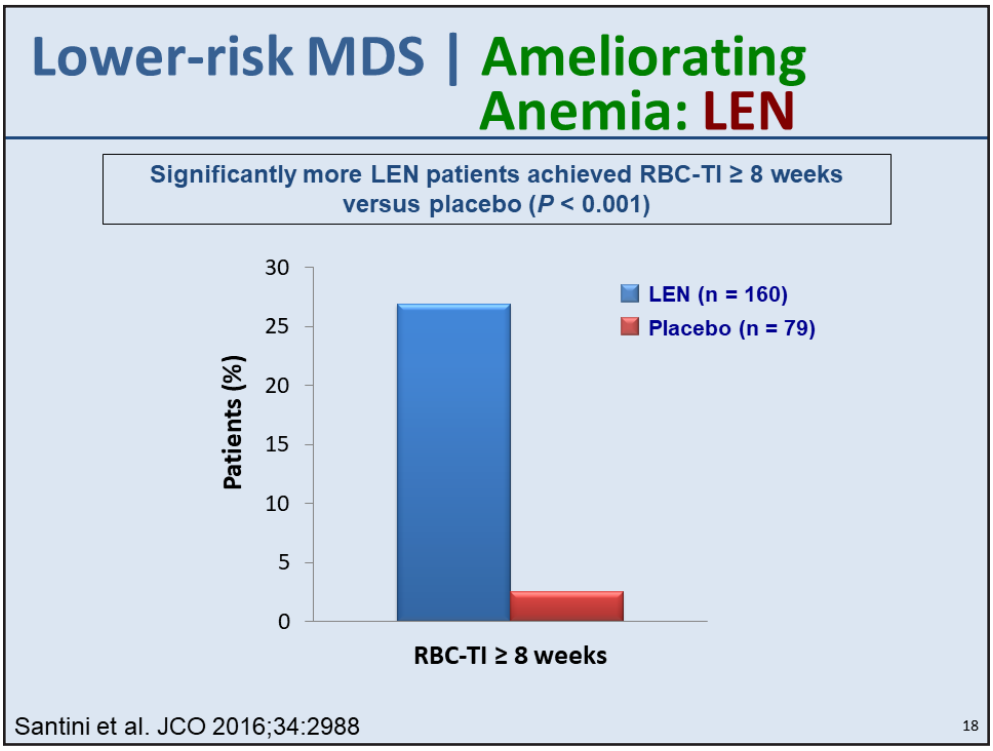
What if somebody actually has that deletion 5q abnormality I was talking about, or that person has already received an erythropoiesis-stimulating agent, that hormone, or luspatercept, and those drugs don't work anymore. Well, then we start to talk about the drug lenalidomide. These are pills, brand name is Revlimid®, and in probably the best study, looking at people who have the deletion 5q abnormality with MDS, the response rate, the period of time of going without a blood transfusion for at least 8 weeks was 61%. That is really good for the drugs that we look at in lower-risk MDS. And that led to the approval of lenalidomide, brand name Revlimid, in Europe. It had already been approved in the United States.



Slide 17: Lower-risk MDS | Ameliorating Anemia: LEN

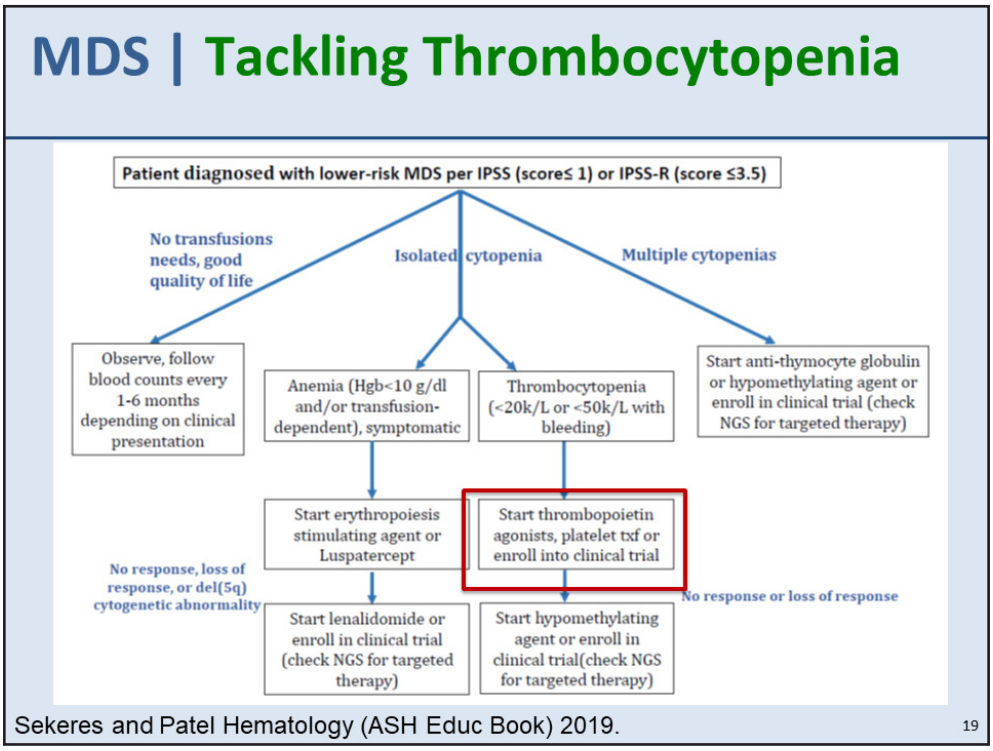
If I were listening to this and I heard that, I would say great, but only about 10% to 15% of people with MDS have that deletion 5q abnormality. What about the rest of us? Lenalidomide was also explored in people who didn't have the deletion 5q abnormality with lower-risk MDS and the response rate was about 27%, so now we would be talking about one-quarter of people who get better to the drug and the response duration was very similar to what we saw with that luspatercept earlier at about 32 weeks on average. I do think this is an option for my patients on-label when they have the deletion 5q and in those patients the response duration was over 2 years. It works really really well for those patients.

Or, off-label for my patients who don't have the deletion 5q abnormality in whom the response rate, so the percentage of people who get better and duration were more modest.



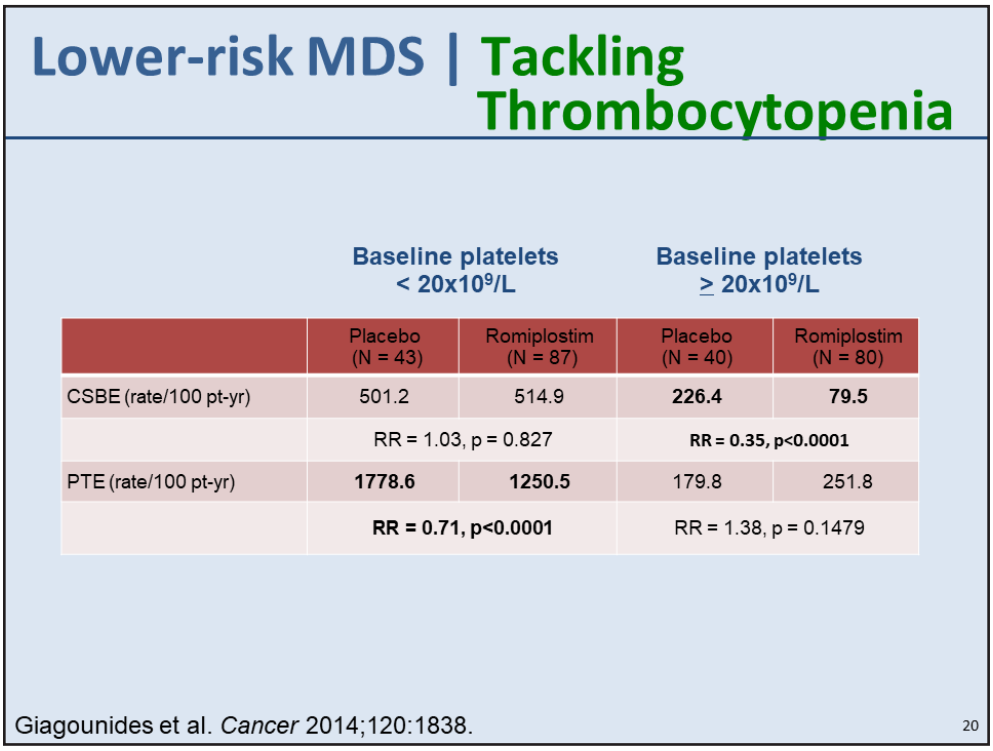
Slide 18: Lower-risk MDS | Ameliorating Anemia: LEN

What if the predominating problem is a low platelet count with MDS? Well, with lower-risk MDS we would then start to think about what I refer to as thrombopoietin agonists (one of those long names again). Think of these as growth factors or hormones and instead of stimulating the red blood cells, they stimulate the platelets or the precursors of the platelets in the bone marrow. There are 2 major brands of this that are available in the United States. One is referred to as romiplostim or the brand name is Nplate®. The other is eltrombopag, the brand name is Promacta®. These are not approved specifically for MDS. They are approved for a condition in which the immune system attacks the platelets, something called ITP or idiopathic thrombocytopenic purpura. However, they can be used off-label for the treatment of low platelet counts associated with myelodysplastic syndromes because there are a couple of studies that support that use.



Slide 19: MDS | Tackling Thrombocytopenia

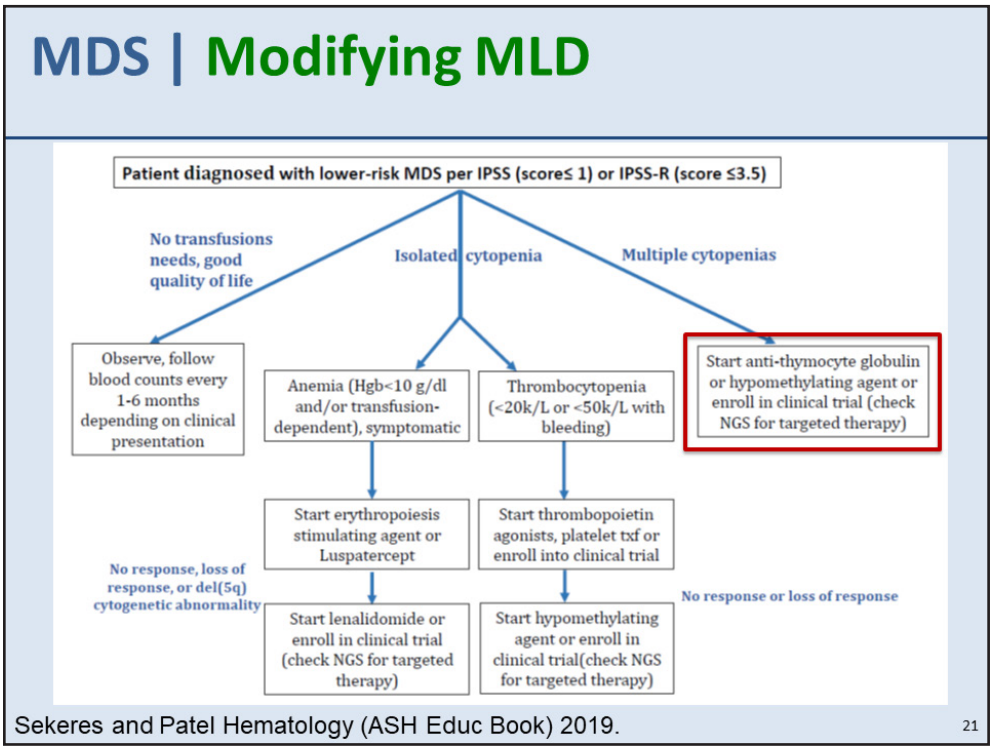
This is one of those studies. In this study about 40% of patients who were treated with romiplostim got better. In other words, their platelet count improved to the drug, compared to those folks who got placebo.



Slide 20: Lower-risk MDS | Tackling Thrombocytopenia

And on this slide, this is how complicated this gets, success was defined as an improvement in CSBE (clinically significant bleeding events). In other words, did somebody have a major bleed, not just my gums were bleeding a little bit after I brushed my teeth, but they had a bad nosebleed or blood from their GI tract. And, it turns out that those who received the drug romiplostim, the brand name Nplate, those clinically significant bleeding events occurred about 80 times compared to 226 times for those patients who didn't receive the drug. So that was an improvement.

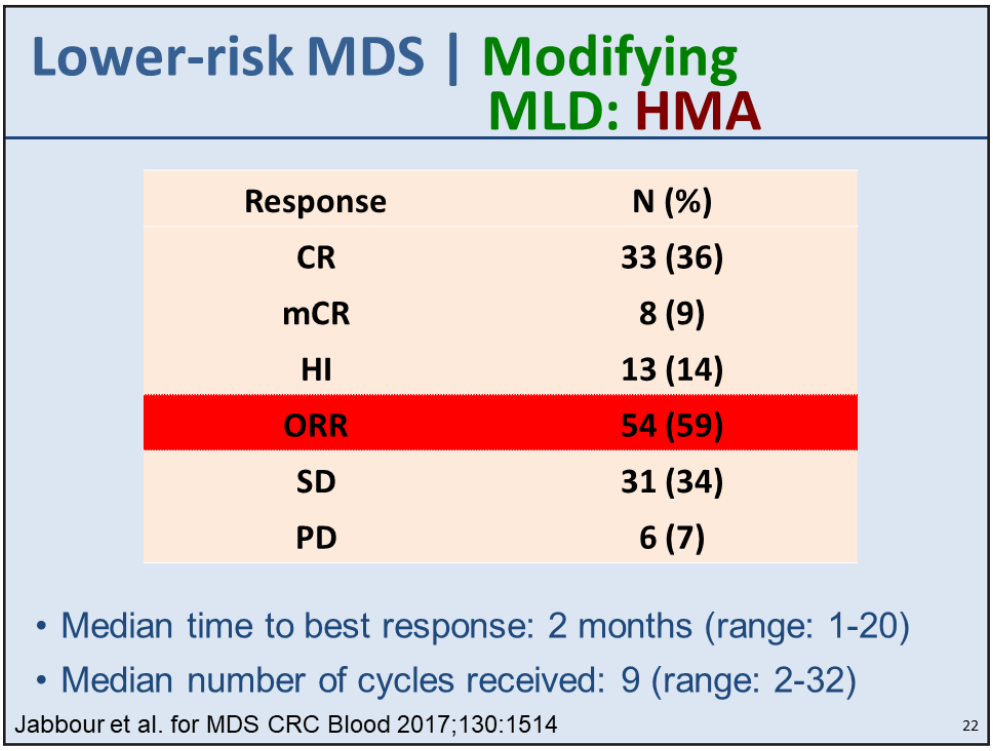
Also, those who got the drug, when you focus on PTEs, platelet transfusion events, how often did they need to receive a transfusion of platelets, that occurred much less frequently for those who got romiplostim versus those who received placebo.



Slide 21: MDS | Modifying MLD

I do think this is an acceptable off-label use of one of these drugs. The caution I will give you, however, is that these drugs should never, never, never be given to folks who have MDS with excess blasts. It turns out that blasts have receptors on them, that this hormone can trigger. People can have an increase in blast percentages if they receive the romiplostim, brand name Nplate, or the eltrombopag, brand name Promacta. So, we stay away from these drugs in people who have excess blasts.

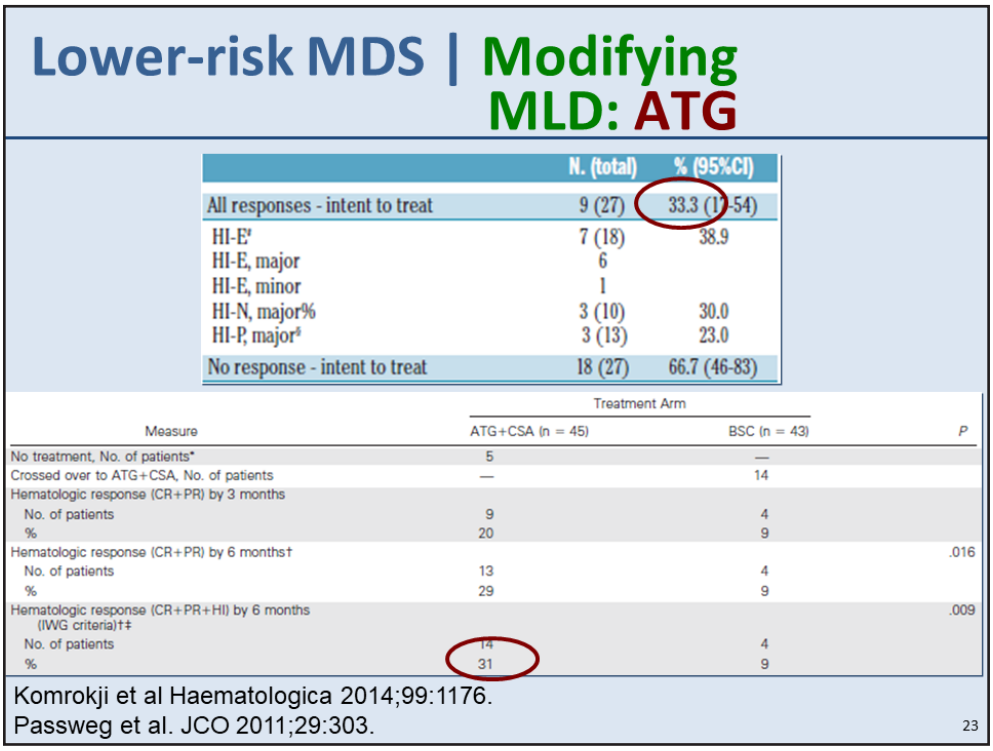
What about folks who have multiple cytopenias? They will have anemia and a low white blood cell count or anemia and a low platelet count. Then we think about a couple of different types of treatments we can use.



Slide 22: Lower-risk MDS | Modifying MLD: HMA

The first are drugs that are referred to as HMAs, hypomethylating agents. This includes drugs I am going to talk a little bit more about in a second, that include zacytidine, brand name Vidaza®, decitabine, brand name Dacogen®, or there is a new pill version of decitabine that is a combination of decitabine and cedazuridine (Inqovi®). We did a study looking at using these drugs, not in patients with higher-risk MDS but in lower-risk MDS and giving these drugs for a shorter period of time. You can imagine, this is a study that we conducted without any support from a pharmaceutical company because what drug company in their right mind would want to fund a study showing that giving less of their drug is actually better? But what we found is that in patients who have lower-risk MDS, less is more. We found that those who received only 3 days of the Vidaza instead of the product label 7 days, or 3 days of the decitabine, brand name Dacogen, where ordinarily we would give it for 5 days, had an overall response rate at 59%. Typically, we would have expected an overall response rate of only 35%, so this was much better and it lasted for longer, for about a year and a half. So, my standard approach to treating somebody with lower-risk MDS who has more than one blood count abnormality, is to use 3 days of azacitidine, brand name Vidaza, or 3 days of decitabine, brand name Dacogen.

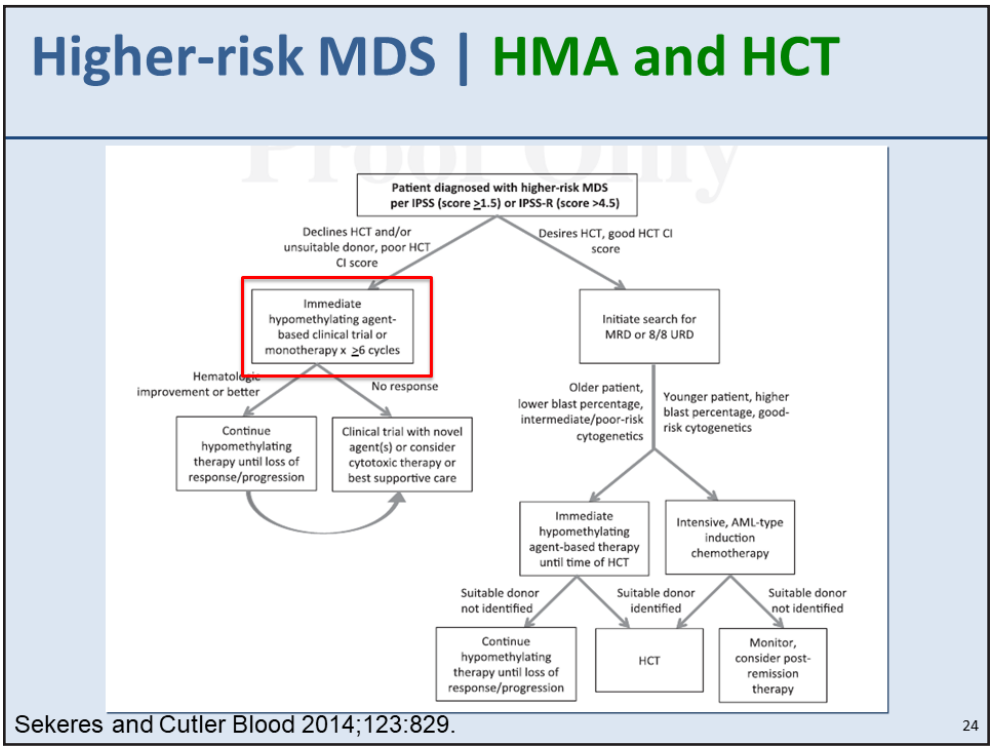
One other approach we can take is to actually combat back the immune system. There is a theory in MDS that some MDS subtypes actually arise because the immune system by accident attacks the bone marrow cells. And if we can stop the immune system from doing that, the bone marrow cells will actually start to flourish and produce the normal blood cells that they should.



Slide 23: Lower-risk MDS | Modifying MLD: ATG

There are a couple of studies that have used a drug called ATG, antithymocyte globulin, that basically stops the immune system in its tracks. And stops the immune system from attacking the bone marrow. In both of these studies, the ATG works about one-third of the time. The top study was conducted in the United States, the bottom study was conducted in Europe.

The duration of response was about a year to a year and a half. The bad news is you have to go into the hospital to get 4 days of the ATG, because people can have bad allergic reactions to it. The good news is, it is kind of one and done. You go into the hospital for 4 days and then you take a pill, a low-dose cyclosporine (various brands), which also helps suppress the immune system and you have basically taken care of it for a while. It works one-third of the time. I do reserve this for my patients who have multiple cytopenias, so a bunch of blood counts that are low and who have already received a hypomethylating agent, the azacitidine or decitabine, and it has not worked for them or it has stopped working.

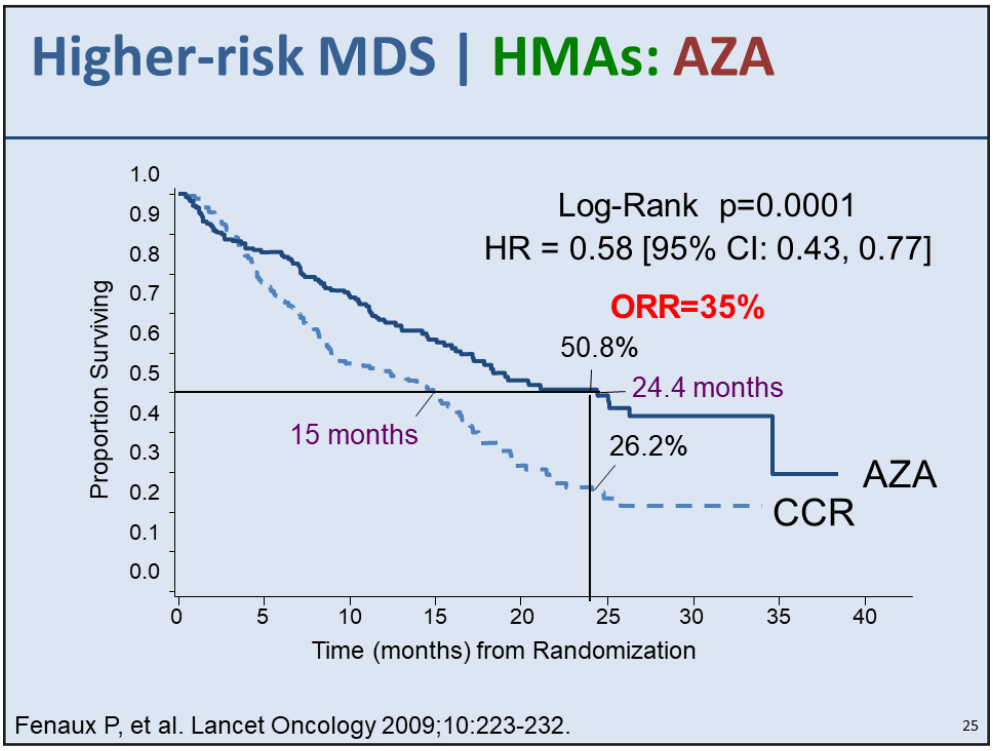


Slide 24: Higher-risk MDS | HMA and HCT

Okay, so let's switch to people who have higher-risk MDS. This is again one of those treatment algorithms that actually we wrote 8 years ago, but it has not changed very much.

For people with higher-risk MDS, we will often talk very early about whether or not they would benefit from a bone marrow transplant, where we give drugs to eliminate bone marrow cells from the bone marrow, and then replace those cells with a transfusion of somebody else's healthy bone marrow. That healthy bone marrow then takes up residence in the bones and starts to hopefully produce normal healthy blood cells.

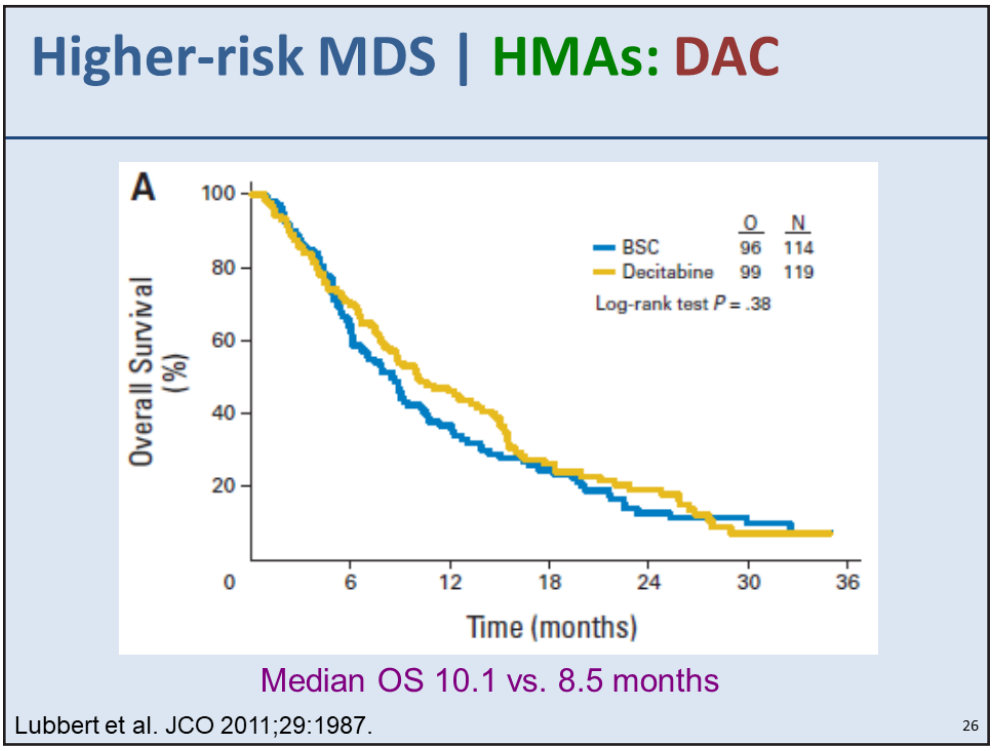
One approach we take is to talk about bone marrow transplant from the very beginning of somebody's diagnosis and while we are doing that we will start to treat them with hypomethylating agents. As I mentioned before, there are 3 of them, and I am going to talk about them right now.



Slide 25: Higher-risk MDS | HMAs: AZA

The first drug is called azacitidine, brand name Vidaza. In this study, patients were randomized to receive the azacitidine or conventional care regimens. Now conventional care regimens, 60% of them consisted of people receiving best supportive care, so just transfusions or antibiotics as they needed them, but no active therapy for their MDS, or they received chemotherapy as if they had acute leukemia and were being treated for that. And, in this study people who received the azacitidine (Vidaza), lived an average of 2 years, compared to 15 months for those who received the conventional care regimens. This was a significant difference. This was a really big deal because it was the first study that showed a survival advantage for any drug that we use to treat MDS compared to anything else.

I will tell you over time that we have found the survival to drugs like azacitidine or decitabine to be more modest than that 24 months. I am very comfortable in saying that treatment with azacitidine or decitabine is beneficial to my patients. And with the azacitidine, it can prolong their lives.



Slide 26: Higher-risk MDS | HMAs: DAC

The second drug I am going to discuss is the decitabine that I mentioned. This was also looked at in a trial in which people with higher-risk MDS were randomized to receive decitabine or best supportive care. Now in this study, for very strange reasons, there was no survival advantage for those who received decitabine versus those who received best supportive care. In other words, transfusions, antibiotics, but no active therapy for their MDS.

But there are a bunch of us in the MDS community who believe that this was a flawed study. The decitabine was given in the wrong dose, the wrong way, and the wrong regimen. And the patients enrolled to this study were very different than the ones enrolled to the azacitidine study.

Follow-up studies have compared decitabine to azacitidine in population registries and have found absolutely no difference between the two in terms of how long somebody lives.

We feel pretty comfortable in the interchange between decitabine and azacitidine, so if you are on decitabine, brand name Dacogen, don't worry, we think it works just as well as the azacitidine, brand name Vidaza. I will tell you that my personal practice is to treat people with the azacitidine, brand name Vidaza, because of the previous slide I showed with the survival advantage, and because I think they tolerate it a little bit better.

Higher-risk MDS | HMAs: DAC/CED

Oral Cedazuridine/Decitabine Phase 2 In Int-1, Int-2, High, CMML

Type of response	Phase 2 overall (N=80)	
	n (%)	95% CI
CR	17 (21)	13, 32
PR	0	
mCR	18 (22)	14, 33
With HI	6 (7)	3, 16
HI	13 (16)	9, 26
HI-E	8 (10)	4, 19
HI-N	2 (2)	0, 9
HI-P	11 (14)	7, 23
Overall response (CR + PR + mCR + HI)	48 (60)	48, 71
No response	32 (40)	29, 52

Garcia-Manero et al. *Blood* 2020

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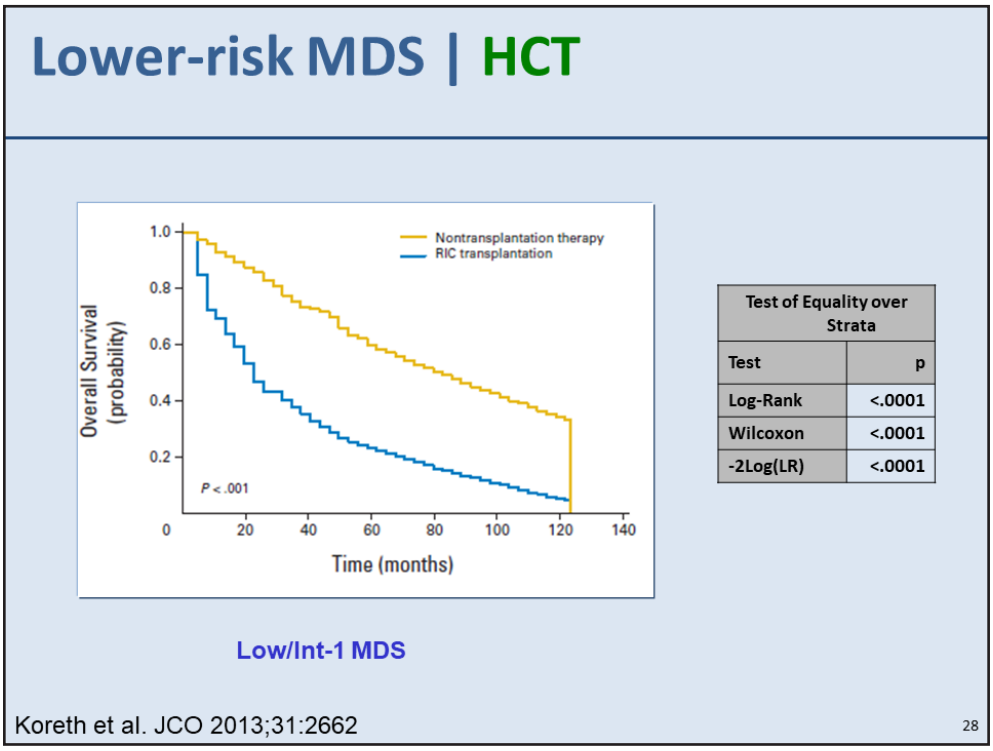
Slide 27: Higher-risk MDS | HMAs: DAC/CED

I told you there was a third kid on the block now and that is a pill form of decitabine combined with something called cedazuridine and that cedazuridine actually prevents the decitabine from being broken down in the stomach's acid. It is a way that it can be given in pill form.

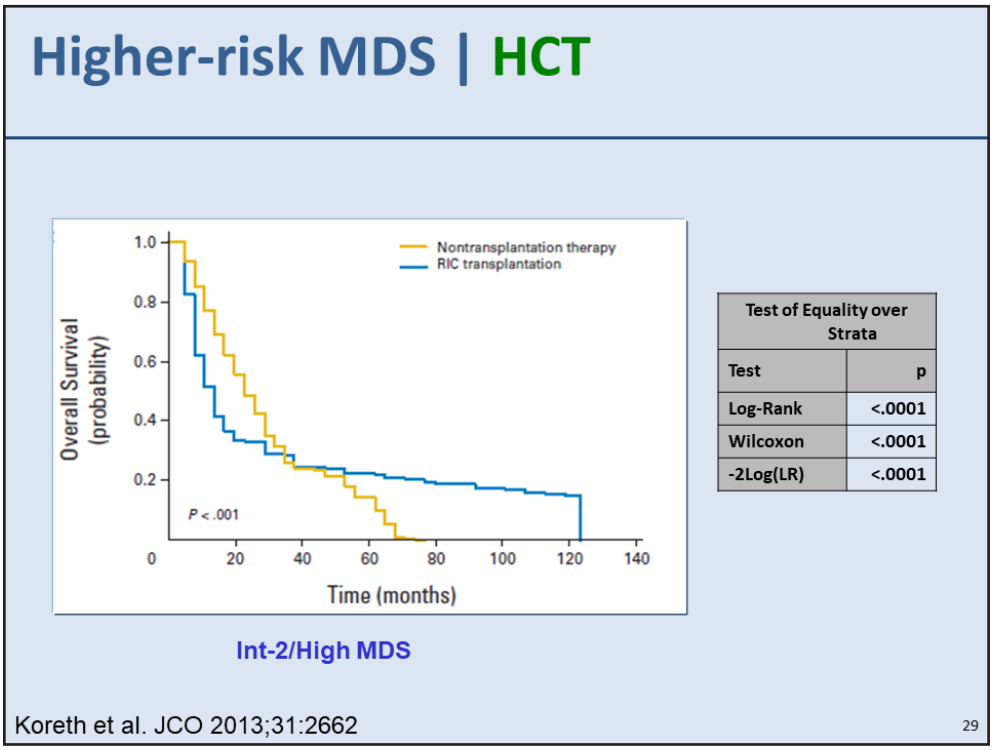
What we see from this study when we look at the various definitions of response here, those patients who received the oral version of the decitabine seemed to have about the same response rate as if they had received the IV decitabine. The pills seem to work about as well as the IV. We do not have any head-to-head comparison because this was actually enough data to convince the FDA to approve the decitabine in a pill form.



Slide 28: Lower-risk MDS | HCT

I mentioned transplant to you earlier and I am showing something that is called a survival curve. If you look at it, it starts out at 1.0. That means 100% of people are alive when the study was started. And then on the bottom axis of the graph, you will see is time denoted in months: 20 months, 40 months, 60 months, 80 months, 100 months. When you look at a survival curve like this you always want to be on the top curve. That means people are living longer when they receive a certain treatment.

For lower-risk MDS, for people who have lower-risk MDS, we don't talk about transplant up front because guess what, that top line, that yellow curve, represents people who received drug therapy and not a transplant. The bottom line are those people who received a transplant. People live longer if they don't receive a bone marrow transplant at diagnosis with lower-risk MDS. We usually reserve transplant for this group after they have been treated with all the therapies I just mentioned, the therapies may have worked for a while and then stopped working and/or my patients cycle through it, and they are left with few other options. At that point, that is when transplant is really ideal for my patients with lower-risk MDS.



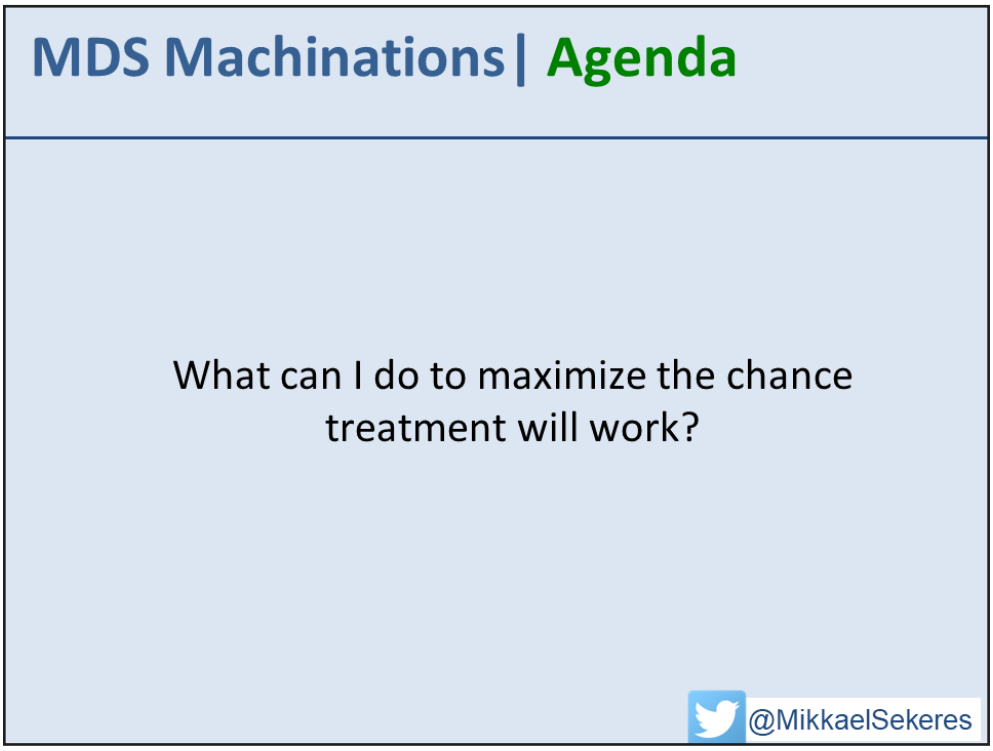
Test of Equality over Strata	
Test	p
Log-Rank	<.0001
Wilcoxon	<.0001
-2Log(LR)	<.0001

Slide 29: Higher-risk MDS | HCT

For higher-risk MDS, the story is different and a little more confusing. Once again that line you are seeing that is yellow are people who did not receive a transplant. The blue line are people who did receive a transplant. You will see that eventually the blue line is higher than the yellow line, meaning those who received a transplant live longer than those who don't. But it takes a little while for that blue line to eventually triumph because there are side effects to getting the transplant and some of those side effects include people dying from the transplant itself.

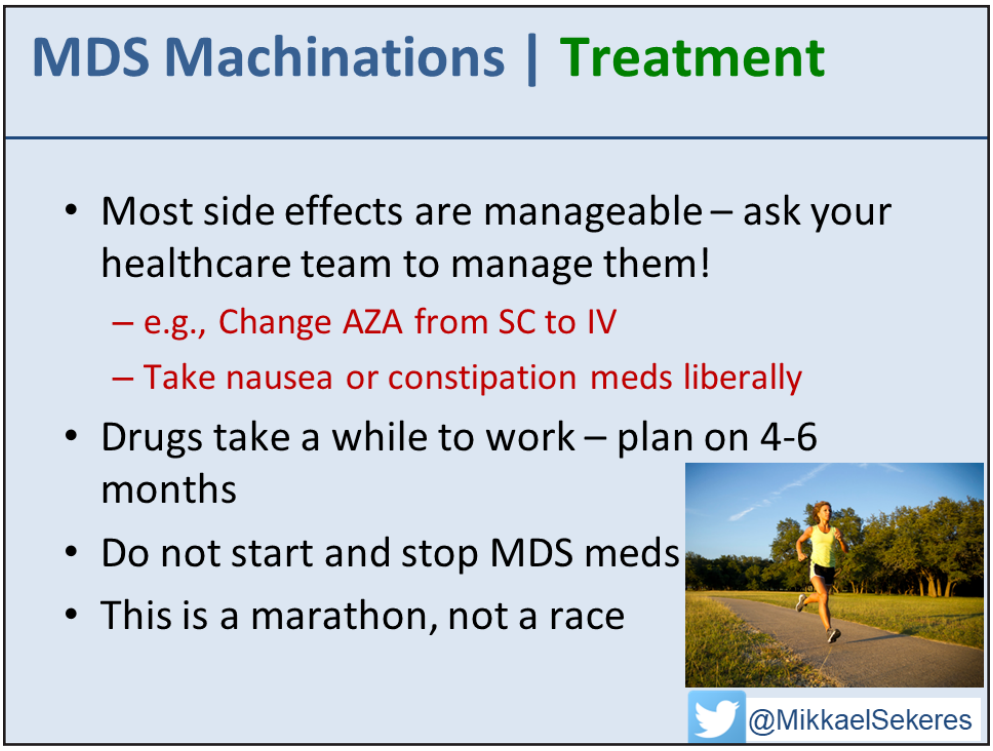
I do talk about transplant at diagnosis for my patients with higher-risk MDS and ask them to consider it and I refer them to a transplanter. I myself don't do bone marrow transplants. So, when I refer someone to a transplant, it is with a pure heart.

Because I do think eventually there is a chance that people will live longer and in fact transplant is the only cure for MDS. If I have a patient who wants to be very aggressive about his or her MDS and is willing to go through pretty aggressive therapy, then I will 100% support them in pursuing their transplant.



Slide 30: MDS Machinations| Agenda

What can I do to maximize the chance that treatment will work?



Slide 31: MDS Machinations | Treatment

My top message with this is that most side effects are manageable, most side effects to these drugs we can find a way to make them tolerable or eliminate them. I beg you to ask your healthcare team to manage them. This is not something that you should have to figure out on your own.

I have some patients who get an injection of the azacitidine, the Vidaza, underneath their skin and they get terrible rashes from it and it burns and they don't like it. Well, we can then switch to the injections to giving them intravenously. The drug works just as well and it is much more tolerable.

Or, we can start to prescribe medicines to help with nausea or medicines to help with constipation, to get folks through it. I have some patients who get constipated when they get treated with, for example, the azacitidine, and they drink a lot of fluids the weekend before they start and they are fine. Sometimes we can find pretty easy and palatable solutions to help manage this.

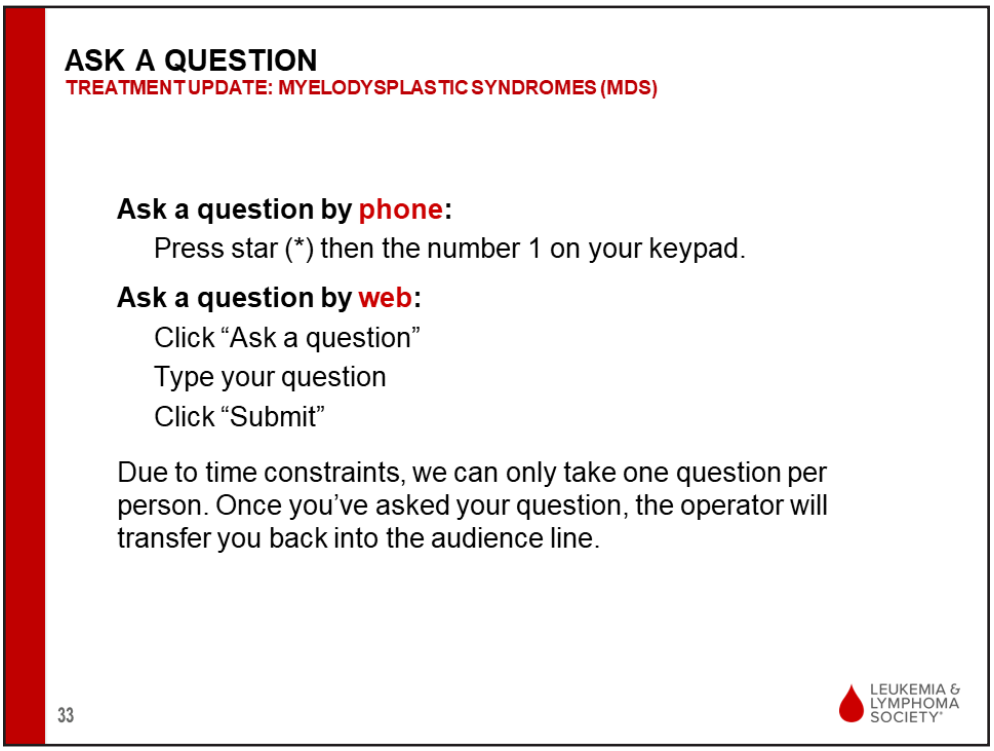
Drugs take a while to work. Whenever you start a drug, plan on taking 4 to 6 months to see whether or not it works. Stopping after 1 or 2 courses of therapy, you - I say you, but really not you, your doctor - may have shot you in the foot. Because these drugs – remember MDS take a while to arise – it's going to take a while to get rid of as well. I always have a contract with my patients about staying on a drug for 4 to 6 months before we declare victory or defeat.

Don't start and stop MDS medications. That is how MDS becomes resistant to drugs. Once you start on it, keep going.

And this is a marathon, not a race. Particularly with lower-risk MDS. Remember most of the drugs I showed you work about one-quarter to one-third of the time. That means that we are going to have to try 3 or 4 drugs before we find one that works. So, we cycle through them. We will go on that walk right along with you.

Slide 32: Thanks!!!

I want to thank all of you for listening. I am so happy with my move from snowy Cleveland to sunny Miami and I will be the first to admit that is a very unfair picture of Cleveland, but it shows the dramatic effect. I am happy to take questions at the end of this. We will hand it back to Lizzette.



Slide 33: ASK A QUESTION

Ms. Figueroa-Rivera:

Thank you so much Dr. Sekeres, thank you for the presentation. And as Dr. Sekeres mentioned, it is now time for the question-and-answer portion of our program.

Ms. Figueroa-Rivera:

We will start with the web audience. Doctor, Amy asks… What levels of dysplasia is considered MDS and not *de novo* AML?

Dr. Sekeres:

That is a great question. By definition myelodysplastic syndrome is a percent of dysplasia in one cell line. In other words, in the bone marrow 10% of the primordial red blood cells have to be dysplastic or 10% of the primordial white blood cells or 10% of the early platelets. There is no distinction with acute myeloid leukemia and in fact there is a WHO category for acute myeloid leukemia with a background of dysplasia. The dysplasia itself does not distinguish myelodysplastic syndrome from leukemia, it is the blast percentage. Remember, 19% blasts or lower is MDS, 20% blasts or higher is acute myeloid leukemia.

Ms. Figueroa-Rivera:

Thank you. And along that line, Sarah is asking… What is the difference between MDS and MPNs, which are myeloproliferative neoplasms?

Dr. Sekeres:

Another fabulous question. You know, they are on a continuum and there is a WHO category that is MDS/MPN overlap, for people who have some component of their bone marrow that has myelodysplastic syndrome, and the other component that has myeloproliferative neoplasms. In general, what I would say is that myelodysplastic syndrome by definition has to have that dysplasia, that dysplastic component. Myeloproliferative neoplasms don't, they involve cells that are growing very quickly, they are proliferating. So, when we look at the cellularity in a bone marrow, it is often elevated for somebody who has myelodysplastic syndrome because these dysplastic cells are growing a lot. Maybe in a 70 year old I should see about 30% cellularity. We say it is roughly 100 minus a person's age, so I should see 30% cells in a microscope view. With MDS, I might see 60% cells. With a myeloproliferative neoplasm, I will often see 90% cells. So, it is cell growth, cell proliferating, as opposed to cell dysplasia, bad growth.

Ms. Figueroa-Rivera:

Thank you. We will take the next question from the telephone audience, please.

Operator:

We will hear from Karen in New York. Please go ahead.

Karen:

Thank you, Doctor. Just a quick question. In your knowledge, my husband was on Zarxio® and Procrit for two and a half years, was diagnosed with congestive heart failure after receiving the COVID vaccines. Since then, none of the medicines that have been tried are able to raise his hemo [hemoglobin]. Is there any correlation that you know of between heart meds and medicines for MDS? Thank you.

Dr. Sekeres:

That is another fabulous question. Heart medicines themselves shouldn't affect MDS. It shouldn't cause MDS or make MDS worse. What there may be, remember I showed those genetic mutations where we look at the specific genes that are abnormal in MDS that are on the chromosomes? Remember the chromosomes have a total of 30,000 genes across 23 pairs. We look for these very specific gene mutations that we find in myelodysplastic syndrome.

There was a study that was done a few years ago that showed that people who do not even have a diagnosis of myelodysplastic syndrome, but have some of these mutations, are more likely to develop myelodysplastic syndrome, but surprisingly were more likely to develop heart disease. And in fact, having one of these mutations is more of a risk factor for developing heart disease than a high cholesterol level.

We discovered that there is this link between heart disease and myelodysplastic syndrome probably because of the inflammation around heart disease and there is an argument that there is a similar inflammation around myelodysplastic syndromes and they are both caused by one of these gene mutations.

So, I wonder if in this case, and kind of broadening it to the whole audience, it is not surprising to hear similar diagnoses – the same person having heart disease and myelodysplastic syndrome because we think there may be a common cause to it. But, heart disease medicines don't cause myelodysplastic syndromes.

One thing I have found with heart medicines in my patients is that they can cause fatigue. It is very hard for me to distinguish in my patients if fatigue is due to some degree of anemia or is it due to a heart medicine that somebody is on.

Ms. Figueroa-Rivera:

Well, thank you for that question. Since you mentioned fatigue Doctor, Linda is asking… How to deal with fatigue as well as loss of appetite?

Dr. Sekeres:
That's a good one. Both of those things can arise from anemia. The best answer to that is to get blood transfusions if you need them and try to find a therapy that works. Easy for me to say, right? But it means cycling through therapies. If you are on a drug like one of the erythropoiesis-stimulating agents, remember that erythropoietin or darbepoetin, those hormone shots, sometimes healthcare providers can't think of a next option so they just keep you on the same drug long term. I have had patients who are on those drugs for like 5 years, 6 years, and they are getting a blood transfusion every month. Well, the drug is not working.

One approach to that is if you have persistent anemia and it is causing things like fatigue and a low appetite, stop the drug and go onto another drug. And if your doctor can't come up with an option for what another drug might be, go get a second opinion, to be honest.

That may be oversimplifying things. Some of my patients can also have fatigue from just having myelodysplastic syndrome itself. There is this whole theory that the myelodysplastic cells release chemicals that also cause normal bone marrow cells to die off, but also can make you feel not so good. That can include fatigue and not wanting to eat very much. So once again, the answer to that is to treat the myelodysplastic syndrome, try to reduce it more so that they are not producing these chemicals that lead to these symptoms.

Finally, what I would say is, I am a huge fan of consulting nutritionists or dietitians for thinking about diet. One thing my patients will sometimes tell me is that when they are getting some of the drugs I use, like the azacitidine, their sense of taste changes. And not in a way they can really put their finger on. The best I can come up with is that my patients who get drugs like that, where their sense of taste changes, become almost like toddlers, you know how toddlers want foods based on texture more than on taste. My patients get very sensitive to texture of foods. And for example, I have patients who will binge on moist foods or wet foods like melons. I had one patient who loved lo mein because of the greasy noodles, he loved the texture of it.

So, going to a nutritionist or a dietitian can help with food choice. And I will throw in that nugget also, that your sense of taste may change and experiment with different types of food.

Ms. Figueroa-Rivera:

Thank you so much. And I know that you did mention the EPOs. Ron is asking… If they can possibly cause secondary myelofibrosis?

Dr. Sekeres:

That is a fabulous question. Let me back up a little bit. The EPOs we are talking about, those erythropoiesis-stimulating agents. We have all sorts of different abbreviations for them, so I abbreviate them ESAs, but EPO is fine because it is short for erythropoietin or darbepoetin, the brand names remember are going to be things like Procrit, Retacrit, or Aranesp.

These are hormones, like I said, that stimulate the remaining normal bone marrow cells to work better, to produce more normal cells. I haven't seen much on them causing myelofibrosis. It is possible that you may have started out with a myelodysplastic syndrome and remember how I said earlier there can be an overlap diagnosis, myelodysplastic syndrome and then a myeloproliferative neoplasm, an MDS/MPN category, it is actually defined by the World Health Organization. Part of MPN, I talked earlier about a bone marrow that had 90% cells in it, you can also develop fibrosis with it. So it may be that what you have is an MDS that is now evolving into an overlap disorder where there is also the

fibrosis.

There is a story, not about EPO causing fibrosis, but about TPO, those thrombopoietin drugs I mentioned earlier, the ones that stimulate platelet growth, and that story is in patients who have the autoimmune disorder where they chew up their own platelets, that ITP, idiopathic thrombocytopenic purpura. And in those patients who are treated with the drugs like eltrombopag or romiplostim, the Promacta or Nplate, there is a story about myelofibrosis occurring. So not with the EPO drugs but with the TPO drugs, the thrombopoietin agonists, the romiplostim and eltrombopag.

Ms. Figueroa-Rivera:

Thank you so much. We will take the next question from our telephone audience please.

Operator:

We will hear from Irene in Utah. Please go ahead, your line is open.

Irene:

Hi Doc, thank you for taking my call. I am an 80-year-old person and I have had 5q minus since I turned 62, which they said was very young to have myelodysplastic syndrome. I have been on Revlimid® all these years, which was wonderful up to about 6 months ago, and I have had problems with my blood cells dropping, my neutrophils are very low, I have had 3 units of blood since January. And I wondered, I had taken a drug called Inqovi®, I do not know if you know anything about that. But it seemed to lower my cells. I wondered if you could tell me something about this.

Dr. Sekeres:

Sure. Let me start out with congratulating you on having such phenomenal success with lenalidomide, brand name Revlimid. If I am doing my math right, you have been on it for 18 years at 2022, that takes us back to 2004, which means I think you may have gotten before it was even FDA approved, because it wasn't approved in 2004, which is amazing. So that is just incredible.

But it is not curative, as you are pointing out, so at a certain point the lenalidomide or Revlimid will stop working. Depending on your blood count abnormalities, you can go on one of the hypomethylating agents. Inqovi is the brand name for that pill, the decitabine and the cedazuridine. I think that is a perfectly reasonable option to try after being treated with the lenalidomide or the Revlimid. I would use it more for people who have more than one cell line that is affected, so not just anemia, but anemia and a low platelet count or anemia and a low white blood cell count. Another thing to consider if it is just an isolated anemia that you have is to think about the luspatercept. It may be used off-label, you would have to look into that, depending on whether or not you have ring sideroblasts.

But yes, eventually all of these drugs will stop working and then we start the cycle, we start to go through other drugs and see if we can find another one that works just as well and it sounds like that is what you are doing.

Ms. Figueroa-Rivera:

Thank you so much for the question. We have a few questions Doctor in regard to transplant. Warren is asking… Is stem cell transplant and bone marrow transplant the same and do we have folks asking if MDS would come back after transplant?

Dr. Sekeres:

Both great questions. Colloquially, kind of informally, we will interchange bone marrow transplant and stem cell transplant and it really means the same thing. It is getting cells from another person's bone marrow and then collecting them, cleaning them and transfusing them into another person, and hoping that they will then set up residence in the bone marrow and start to make normal blood cells again.

Technically, stem cells – when you are collecting bone marrow cells from another person you can do it one of two ways. You can either do something like a bone marrow biopsy in that person, but instead of one bone marrow biopsy you are doing about 40 bone marrow biopsies to collect enough of those cells. That is often done under anesthesia. Or, you can give a person drugs to cause that person to send bone marrow cells out into the bloodstream and then the bloodstream is pheresed, it is basically collected from the bloodstream itself without a bone marrow biopsy. But it is the same cells, either way they are from the bone marrow itself. That is the distinction between the two.

In terms of MDS coming back after a bone marrow transplant, yes, that is possible. The bone marrow transplant may fail. There are a lot of different percentages that are quoted to people about the chance that a bone marrow transplant will work, the chance that the MDS will come back, the chance that a person will suffer harm from the transplant or even die. Most commonly, I have seen numbers that are around 40% to 50% chance that the bone marrow transplant will work, 20% chance that somebody will suffer significant harm or even death, and that puts us about 30% to 40% chance that the MDS will actually come back and the transplant was not successful.

Ms. Figueroa-Rivera:

Thank you, Doctor. We have a question from Nadine. Nadine is asking… Can you please discuss targeted personalized CAR-T cell therapy for MDS and also where are we with CRISPR (Chimeric Antigen Receptor T-cell Therapy) and (Clustered Regularly Interspaced Short Palindromic Repeats) gene editing for MDS?

Dr. Sekeres:

Yes, I can tell that you must do a lot of reading because that is pretty sophisticated stuff. Those are both still in a research phase with MDS. We are not even close to having those as part of our standard therapies yet.

CAR-Ts are really fascinating. Imagine a person who has a type of cancer and let's say it is leukemia, and that person has active leukemia, it hasn't gone into remission, it is flowing in their bloodstream, and then you take some of those leukemia cells out of the person's bloodstream, along with some of that person's white blood cells, and you put them outside of the body into like a test tube and you grow the white blood cells, particularly those that seem to form around those leukemia cells and get rid of them. Because remember, eventually if prompted the right way our immune system has the potential of getting rid of cancer. So, you are prompting the immune system, the part of the immune system that can configure to that cancer to grow, grow, grow, grow, grow, so you have instead of a couple of soldiers, an army of those white blood cells, configured specifically for that cancer, and then you reinfuse them into a person's body and you say okay, go get rid of what is there.

It is pretty remarkable technology. And, it has been successful in people who have lymphomas and in people who have acute lymphoblastic leukemia, so notice that lymph that I keep mentioning. We talked about myelodysplastic syndrome and the myeloid cells in the bone marrow, that represents half the cells in the bone marrow. The other half of the white blood cells are lymphoma cells, lymphoid cells.

CAR-T really works for lymphoid cells, lymphoma cells. It doesn't work for myeloid cells. You can find CAR-T studies that will enroll people who have acute myeloid leukemia or myelodysplastic syndromes, but unfortunately, they really haven't worked well.

CRISPR technology is where we take a cell, we alter the genetics in the cell, we fix the mutations, the things that are wrong, and then we put that into a virus and reinfect a person with it and you get that fixed DNA now incorporated into a person's cells and hopefully get rid of certain conditions. It has worked with things like sickle cell anemia, it has worked with very rare genetic disorders, where there is a single abnormality that's caused the disorder. With myelodysplastic syndrome I think it has potential, but it is going to be hard. Because myelodysplastic syndrome isn't a single genetic abnormality that caused the myelodysplastic syndrome, it is often 3 or 4 abnormalities that have caused it.

Ms. Figueroa-Rivera:

Thank you. Our last question today is from Lorraine. Is there research targeting the specific genetic mutations in MDS? And I'm also interested in, doctor, what you're excited about with the recent research in MDS?

Dr. Sekeres:

Yes, great questions. There are a couple of drugs that are approved for the treatment of acute myeloid leukemia that target something called an IDH (isocitrate dehydrogenase) abnormality. Remember those mutations I said were a bunch of letters and numbers, so there are 2 mutations, one that is called IDH-1 and another called IDH-2. And there are 2 drugs already approved by the FDA for people who have leukemia with these mutations. Well, it turns out these drugs also work in people with myelodysplastic syndrome, who have these mutations. I will use these drugs off-label in my patients with MDS, who have one of these mutations. I will often save it for after I have tried a hypomethylating agent like azacitidine or decitabine in them and that drug has stopped working, then I will use one of the IDH inhibitors.

I am very excited about that and I remain excited about combinations of drugs and their potential for working in people who have higher-risk MDS. Azacitidine or decitabine plus something else, and there are a number of trials looking at these sorts of combinations right now, including combined with the drug venetoclax (Venclexta®) or combined with the drug sabatolimab or with another drug called magrolimab.

Ms. Figueroa-Rivera:

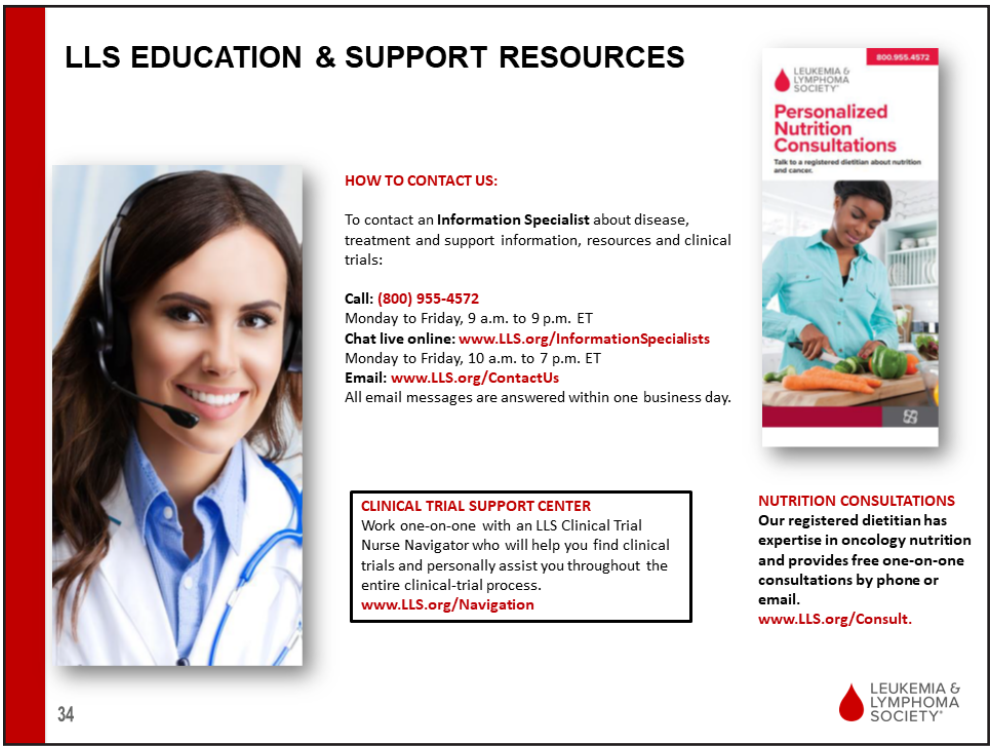
It is really great to know that so much is happening in the MDS space and different treatments for MDS, newer combinations and hopefully newer treatments that have a better quality of life associated with them, right, Doctor? Less side effects.

Dr. Sekeres:

Yes, absolutely.

Ms. Figueroa-Rivera:

Well, thank you so much Lorraine, that was our final question today, and thank you so much Dr. Sekeres for volunteering your time and expertise with us today, especially during these busy times.



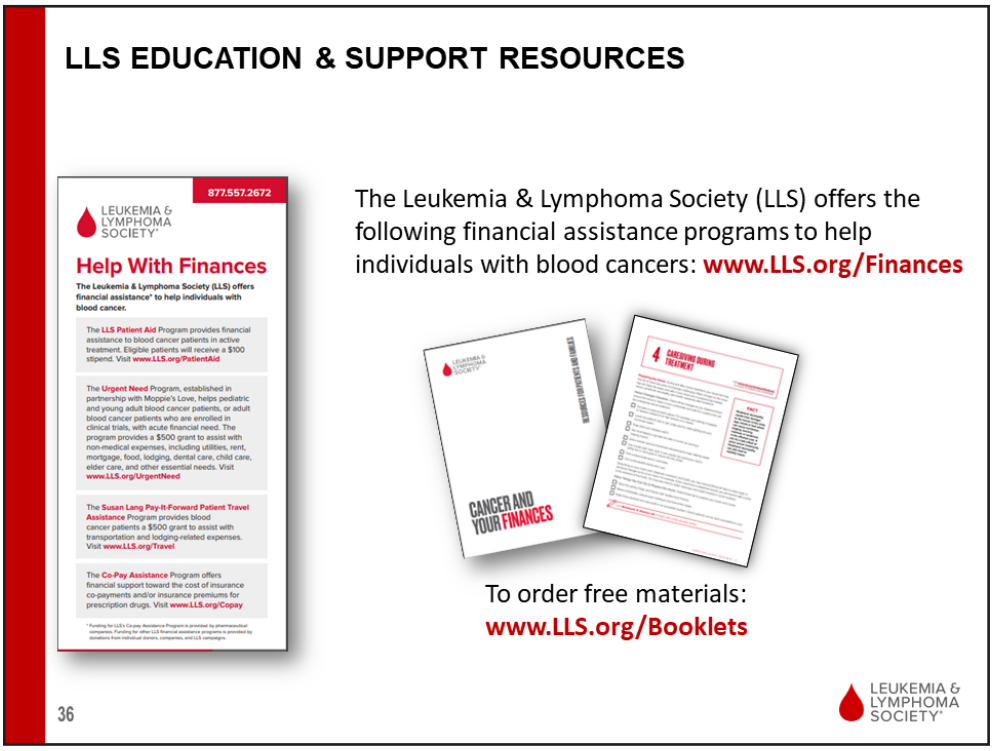
Slide 34: LLS EDUCATION & SUPPORT RESOURCES

If we were not able to get your question answered today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572. We're there from 9 AM to 9 PM Eastern Time, or you can reach us by e-mail at LLS.org/ContactUs. Information Specialists are available to answer your questions about treatment including clinical trials and answer other questions you may have about support, including financial assistance for treatment.

We also have a Clinical Trial Support Center, where Clinical Trial Nurse Navigators are nurses with expertise in blood cancers and they can assist you with finding out if a clinical trial is right for you, and they can be found at LLS.org/Navigation. And, as Dr. Sekeres mentioned the importance of nutrition, LLS does have free nutrition consults to assist patients and caregivers. You can visit LLS.org/Nutrition for more information.

Slide 35: LLS EDUCATION & SUPPORT RESOURCES

As a reminder, you can download and print the slides as well as listen to the audio and view the program on our website LLS.org/Programs.



Slide 36: LLS EDUCATION & SUPPORT RESOURCES

Again, we would like to acknowledge and thank Bristol Myers Squibb and Taiho Oncology for their support of this program.

Slide 37: THANK YOU

Again, Dr. Sekeres, thank you so much 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.