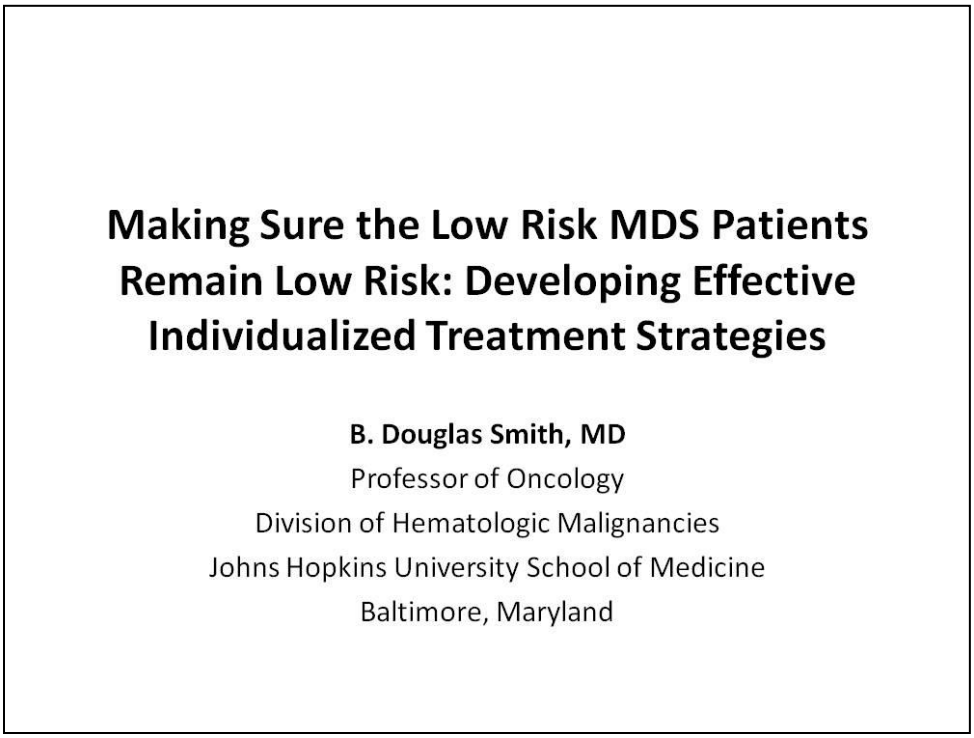
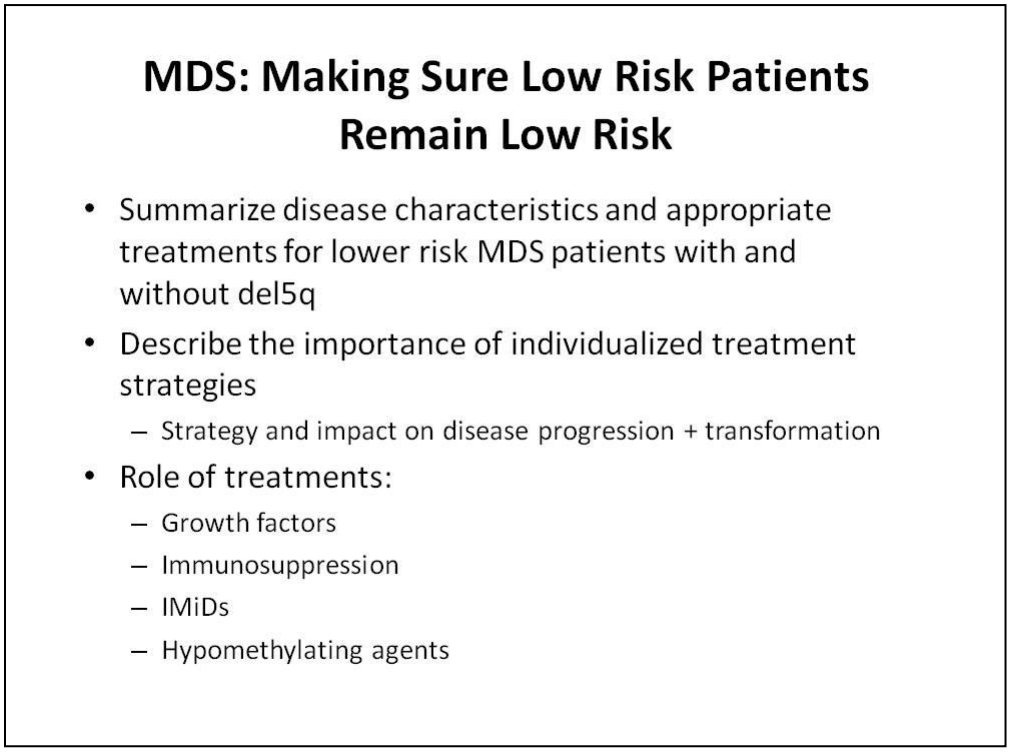
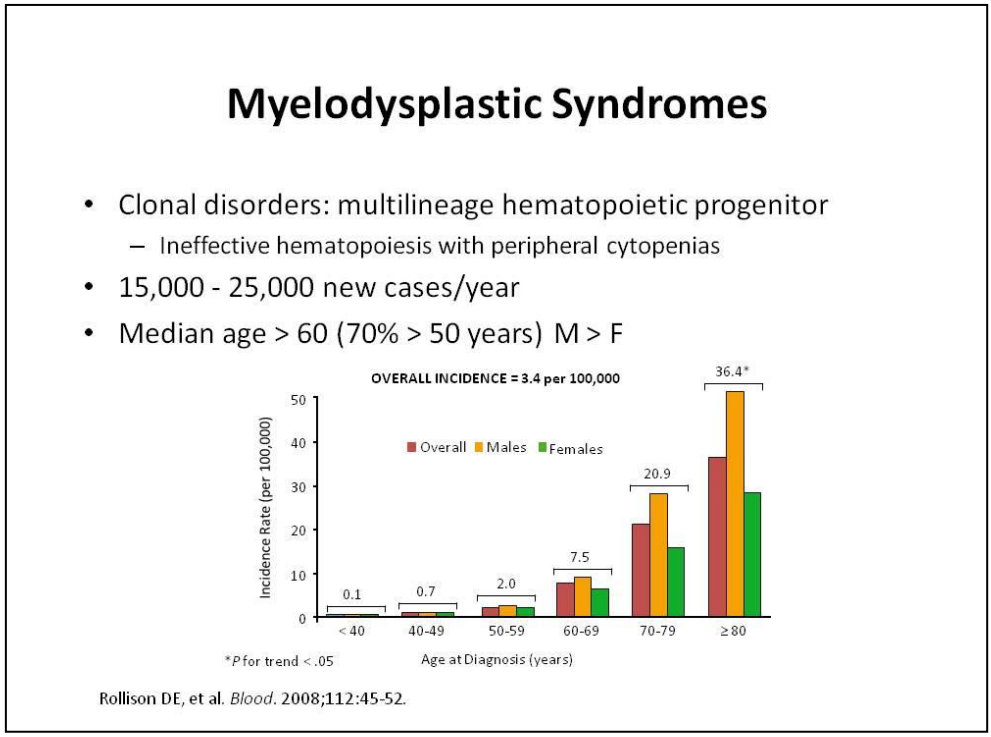


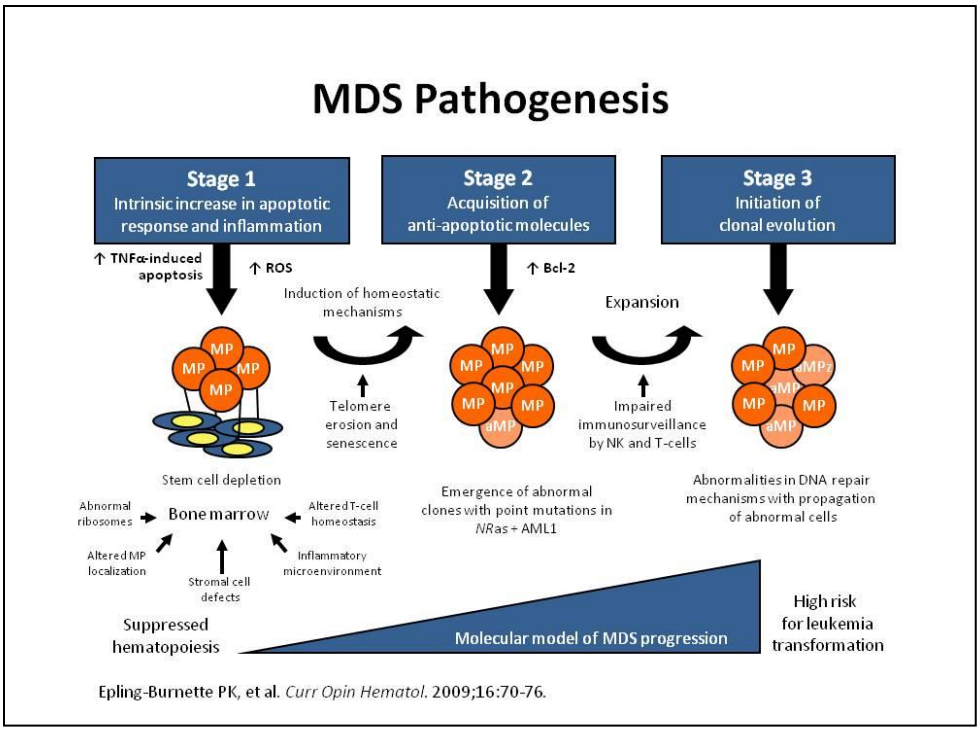
Welcome to *Managing MDS*. My name is Doug Smith, and I am a Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Today, we are going to talk about myelodysplastic syndromes (MDS), and specifically, I want to talk to you about low-risk patients and how to individualize your therapies in hopes of keeping them as low-risk patients.



There are a couple of objectives we want to achieve today. I'm going to summarize the disease characteristics and appropriate therapies for patients with lower risk disease, specifically those with and without 5q deletions. I would like to describe the importance of individualizing therapies and talk to you about strategies that may impact disease progression. Finally, I would like to talk to you about a couple of different treatment practices, namely growth factors, immunosuppressive agents, the IMiDs, and demethylating agents.



As many of you know, myelodysplastic syndromes are clonal bone marrow malignancies that are akin to malignancies of the bone marrow. There are approximately 15,000 to 25,000 new cases each year in the U.S., and these bone marrow failure disorders result in peripheral cytopenias and eventually poor bone marrow function. The median age of this group of patients really closes in on 70, and so, it is important to understand our therapeutic options in this older population. As you can see from the slide, at almost every age group, men outnumber women with this disorder. You can also see from this graph that this is a disease of older patients, and as the population ages, we do expect more and more cases of myelodysplastic syndromes to reveal themselves.



This next slide is very complicated and outlines the pathophysiology or the pathobiology of myelodysplastic syndromes. I do not think it is important to understand all of the boxes on this slide, but I do think it is important to understand that myelodysplastic syndromes are progressive. They generally get worse over time, and like every other malignancy that we know of, they accumulate genetic mutations

and these genetic mutations result in the disease becoming more aggressive and more advanced.

Myelodysplastic Syndromes

- Clonal disorders: multilineage hematopoietic progenitor
  - Ineffective hematopoiesis with peripheral cytopenias
- 15,000 - 25,000 new cases/year
- Median age > 60 (70% > 50 years) M > F
- Bone marrow failure:
  - Majority succumb from infection or bleeding
  - Transformation to AML in ~ 1 in 3
- Best supportive care has been the standard treatment
  - Count monitoring, growth factors, transfusion support
  - Allo BMT only curative option

What we know is that because of the progressive nature of myelodysplastic syndromes, most patients will end up succumbing to their bone marrow failure disorder. About one in three patients with myelodysplastic syndromes will transition or evolve into an acute myeloid leukemia (AML). Over the past 20 years, the therapies for myelodysplastic syndromes have really evolved tremendously. Initially, we only really had growth factors and transfusions that were supportive in nature to try to keep patients going as long as possible. The extreme therapy that was available included an allogeneic stem cell transplant which we all understand as being highly successful, but unfortunately, it is highly toxic and a lot of our older patients are not good candidates for a transplant.

Low Risk MDS Treatments – 2016

- Best supportive care
  - Growth factor support
  - Transfusions
- Immunosuppression
  - ATG and CSA
- Immunomodulatory
  - Lenalidomide
- DNA methyltransferase inhibitors
  - 5-azacitidine
  - Decitabine

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Myelodysplastic Syndromes. Version 1.2016. Release date: 5/28/2015. *http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf*

However, in the year 2016, there are series of therapies that are available for patients with MDS. Specifically, there are several drugs that have now been approved by the FDA to treat myelodysplastic syndromes. As I have noted on the slide, best supportive care is still the mainstay for treatment of patients with MDS. Immunosuppressive

therapies such as ATG and cyclosporine (CSA) are very important for certain subtypes of myelodysplastic syndromes. Immunomodulatory drugs like the IMiDs, like lenalidomide, are very important drugs, and the hypomethylating agents or the DNA methyltransferase inhibitors, azacitidine and deoxyazacytidine, are again another treatment approach that we can use for patients with myelodysplastic syndromes.

IPSS Is Most Common Tool for Risk Stratification of MDS

	Score Value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Bone marrow blasts	< 5%	5% to 10%	--	11% to 20%	21% to 30%
Karyotype*	Good	Intermediate	Poor	--	--
Cytopenias†	0/1	2/3	--	--	--

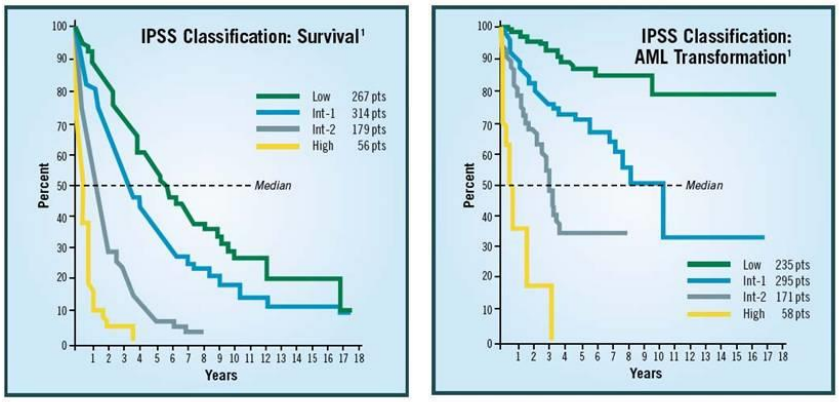
	Total Score					
	0	0.5	1.0	1.5	2.0	≥2.5
Risk	Low	Intermediate I		Intermediate II		High
Median survival, years	5.7	3.5		1.2		0.4

*Good = normal, -Y, del(5q), del(20q); intermediate = other karyotypic abnormalities; poor = complex (≥3 abnormalities) or chromosome 7 abnormalities.
†Hb < 10 g/dL; ANC < 1800/mcL; platelets < 100,000/mcL

Greenberg P, et al. *Blood*. 1997;89:2079-2088.

When we think about MDS and our treatment approaches, it is very important to step back and understand that we have prognostic tools that help us determine whether a patient has a high-risk disease or a lower risk disease. I have shown you the most common and the best known prognostic tool – the International Prognostic Scoring System (IPSS), which uses bone marrow blast percentage, the number of lineages affected by the myelodysplastic syndromes, and the cytogenetic abnormalities to try to determine the likelihood of how well they will do.

Survival and AML Progression IPSS MDS Risk Classification



Higher risk MDS (INT-2, High) is associated with a median survival of 0.4–1.2 years[1]

[1]Greenberg P, et al. *Blood*. 1997;89:2079-2088.

The IPSS was The IPSS was developed in a time when there was no good medical management and no good drugs to treat this disorder. In fact, when we look at survival curves and progression to acute myeloid leukemia curves, we can see that, for those patients with high-risk disease, the outcome is very, very poor - median survival of less than 1/2 year. Whereas, for those with very low risk disease, the median survival is 5 or 6 or almost 7 years in some cases. Likewise, high-risk patients very commonly transition or transform to acute leukemia, whereas low-risk patients almost never do.

If we use the IPSS or a prognostic scoring system as a means to begin to think about our patients, we can then start to think about goals for therapy. Now, what is important to understand is that the vast majority of newly diagnosed patients turn out to be lower risk patients, and what I mean by lower risk,

Treatment Goals in MDS

MDS		
IPSS Score	Risk Group	Median Survival (Years)
0	**Low**	**5.7**
0.5-1	**Int-1**	**3.5**
1.5-2	**Int-2**	**1.2**
> 2	**High**	**0.4**

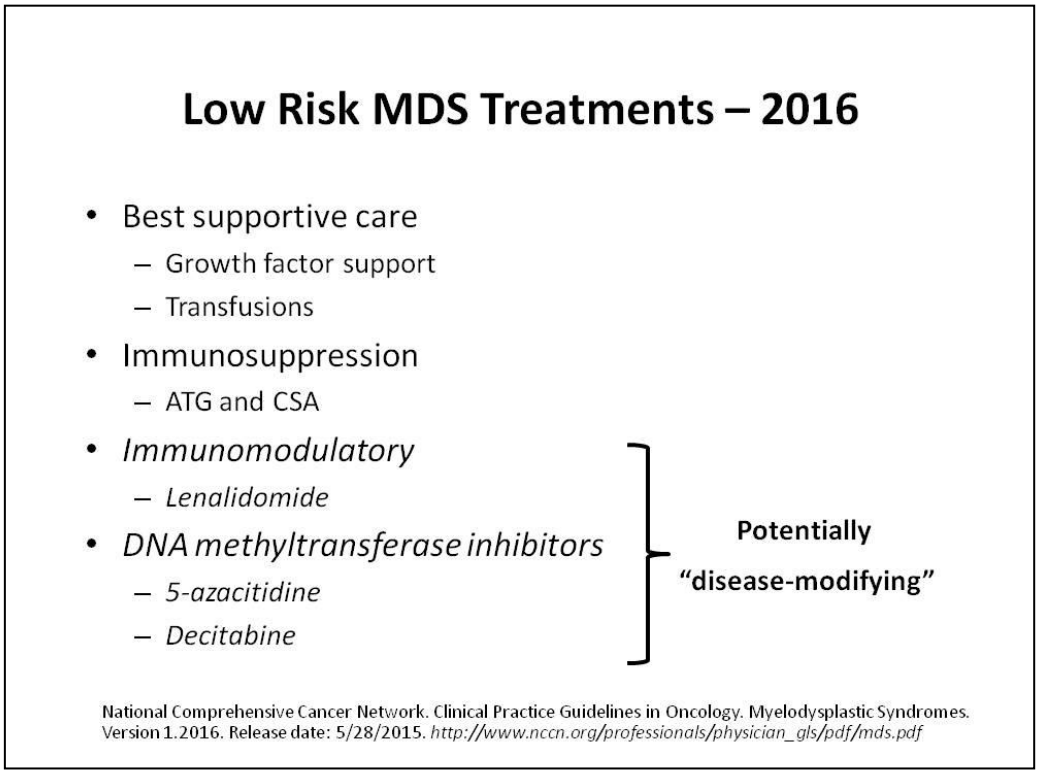
- Most classifications show:
  - Majority (~70-80%) "lower risk" at dx

- Improve marrow function:
  - Lower transfusion needs
  - Decrease impact of MDS on QOL
- Establish careful monitoring plan
- Lower risk of progression

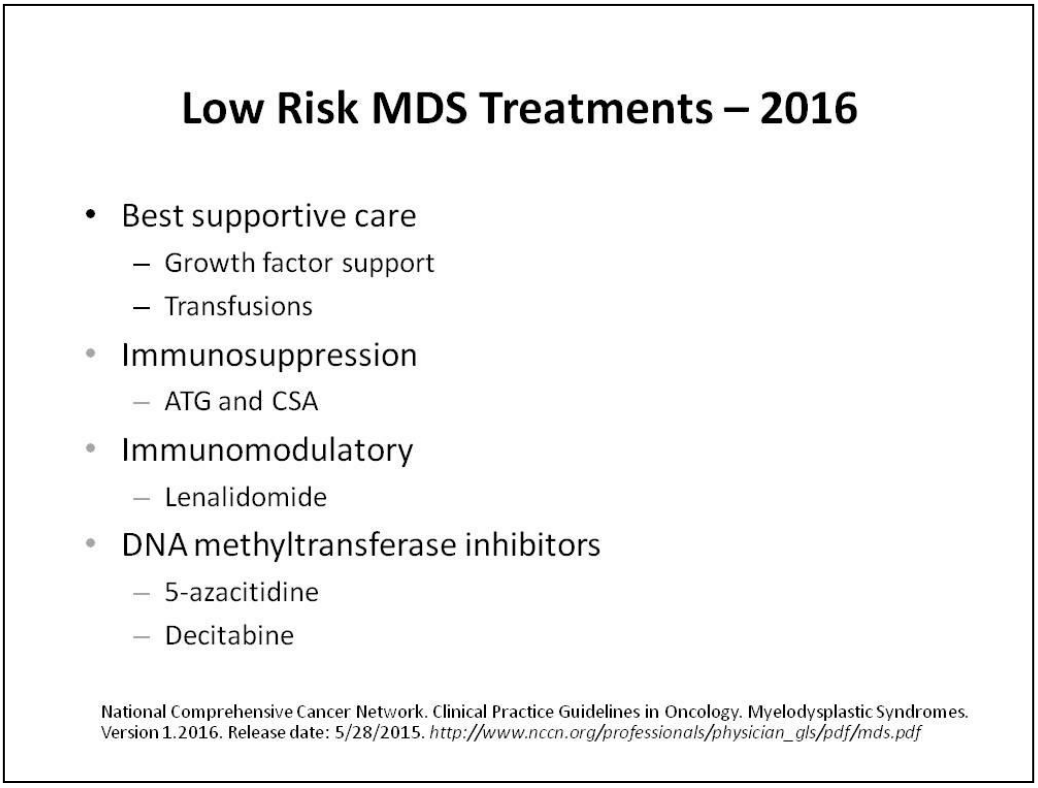
- Stabilize marrow function with trilineage improvement:
  - Lower transfusion needs
  - Lower risk AML transformation
- Move to definitive therapy:
  - Maintenance to maximize benefit
  - Allogeneic stem cell transplant

Greenberg P, et al. *Blood*. 1997;89(6):2079-2088.; Adebonojo SA, et al. *Chest*. 1999;115:1507-1513.

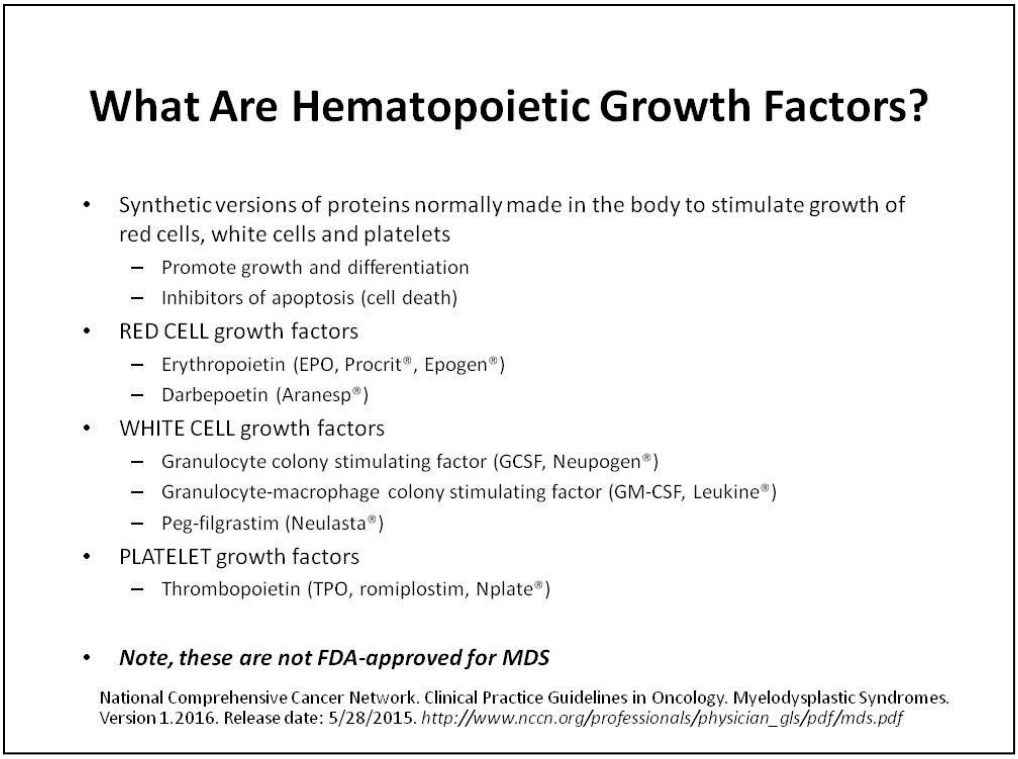
specifically, is a low risk or intermediate-1 by the IPSS scoring system. And when I think about these patients, I think the goals of our therapy are really to improve the bone marrow function, lower transfusion needs, and really decrease the impact that myelodysplastic syndromes have on the patient's quality of life (QOL). This is very important, as one of the goals of therapy is to establish a good careful monitoring plan, and to do everything that we can to prevent progression of the disease. In higher risk patients, who end up having a very poor prognosis, the goals of therapy are very different. One needs to work very hard to stabilize the bone marrow function for the patient and do everything that they can to move that patient into a therapy for long-term management. Some patients are candidates for allogeneic stem cell transplant. The majority of those who go to stem cell transplant are really in the high-risk group of patients.



Going back to the slide looking at the therapies that are available for patients with low-risk disease, I will block them into two separate groups. I will talk about each therapy individually, but I want to note conceptually when I think of supportive care I think of things like transfusions, growth factor support, and immunosuppressive agents such as ATG and cyclosporine. But when I think of some of the medications that we have available to treat low-risk MDS, like the IMiDs and the DNA methyltransferase inhibitors, I think of these drugs as potentially being able to alter the disease biology. And if they are used properly, the hope would be that one would hold off progression, hold off a bone marrow failure state, and really impact the patient's overall survival.

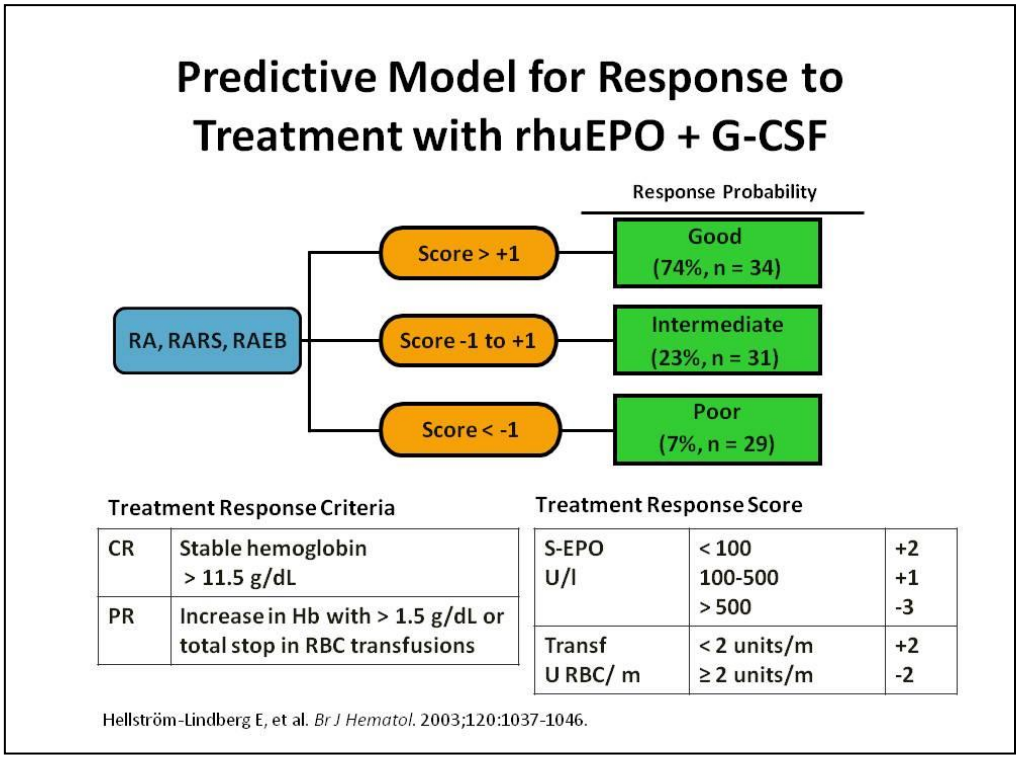


Let's go through these one by one and talk briefly about them. Best supportive care, namely growth factor support and transfusions The vast majority of patients with myelodysplastic syndromes will eventually require transfusion support, either red blood cell transfusion support or platelet transfusion support.

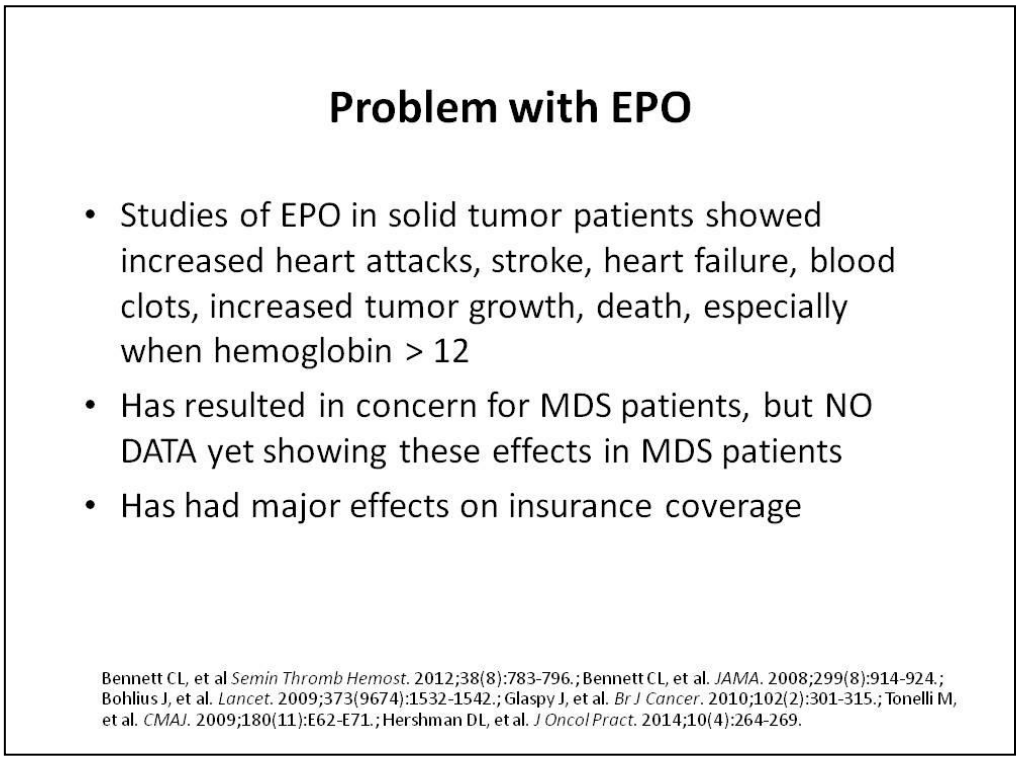


And what we know is that the bone marrow is sent signals by naturally occurring proteins in the body that drive the production of the white blood cells, red blood cells, and the platelets, and that hematopoietic growth factors are simply synthetic versions of these proteins that are administered to patients to try to drive and improve their bone marrow function. We have growth factors for red blood cells, white blood cells, and more recently, we have been studying growth factors to improve

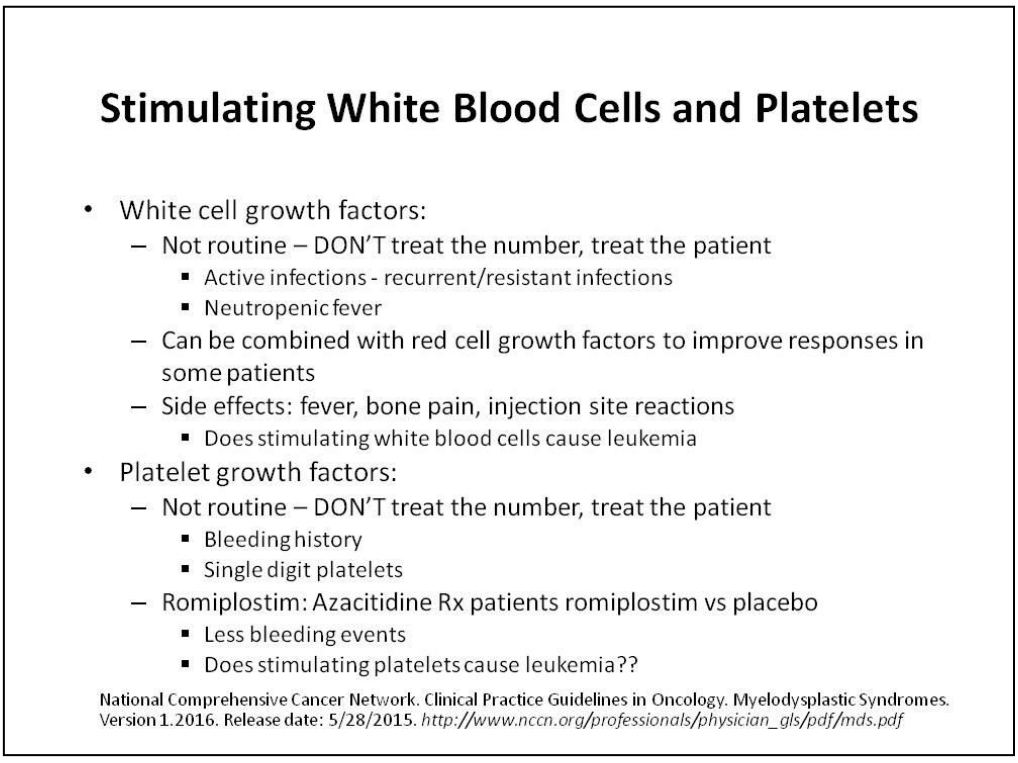
platelet count. It's important to recognize that, while these drugs are very, very important and they are very, very effective at driving red cell, white cell, or platelet growth, none of them are FDA approved in the setting of myelodysplasia.



We do use these drugs commonly in MDS. When we look at erythropoietin-stimulating agents (ESAs) as the most commonly used growth factor for MDS, there are models that we can use to help sort out whether a patient is likely to respond to a drug like ESA or not. Here is a very simple model, namely the patient's own endogenous erythropoietin level. If this level is low, there is very good chance that patients will respond to adding some erythropoietin back. The number of transfusions patients have needed, again, is very important in determining whether they are likely to respond to an ESA, and using this model, you can see that there are some patients that you will use erythropoietin for who will have a very, very low chance of responding. For the most part, we do not use erythropoietin in those patients. However, in the group with the higher scores, who are most likely to respond to these drugs, this is a very common way that we would try to improve people's bone marrow function.

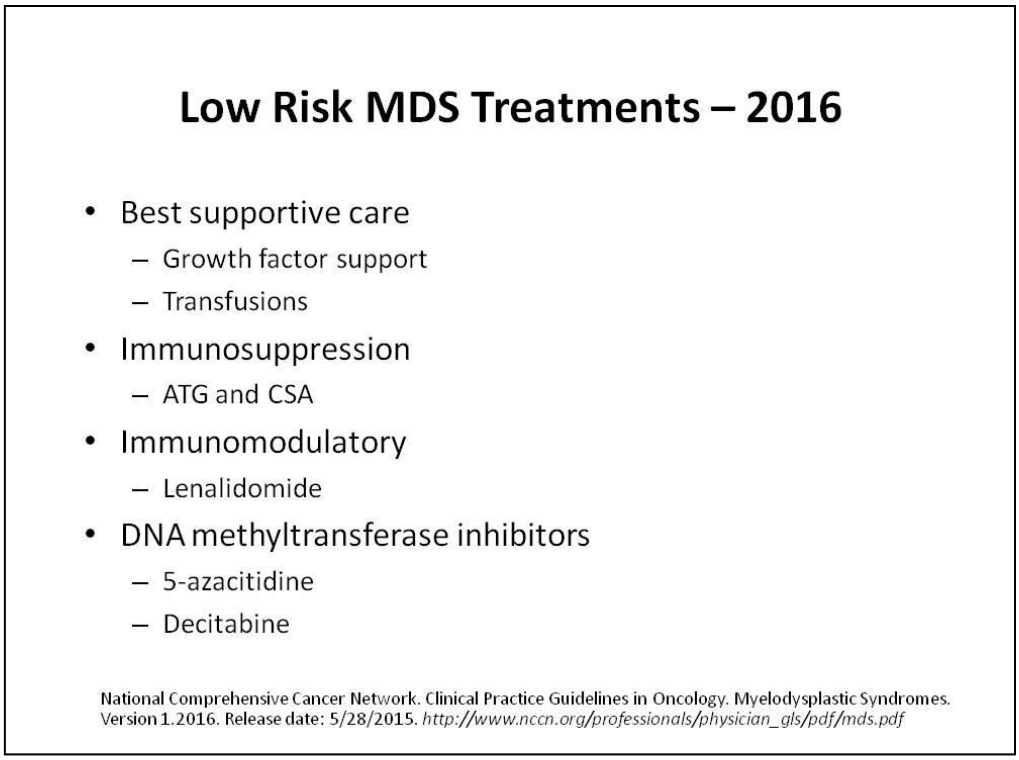


There are problems with erythropoietin. Clinicians need to be aware that in several solid tumor studies, these drugs have been associated with worse outcomes for patients. Specifically, efforts to drive the red cell count too high have not been associated with improved outcomes. In fact, it has been shown to have worse outcomes for patients with head and neck cancers and certain other tumor types where this has been studied.



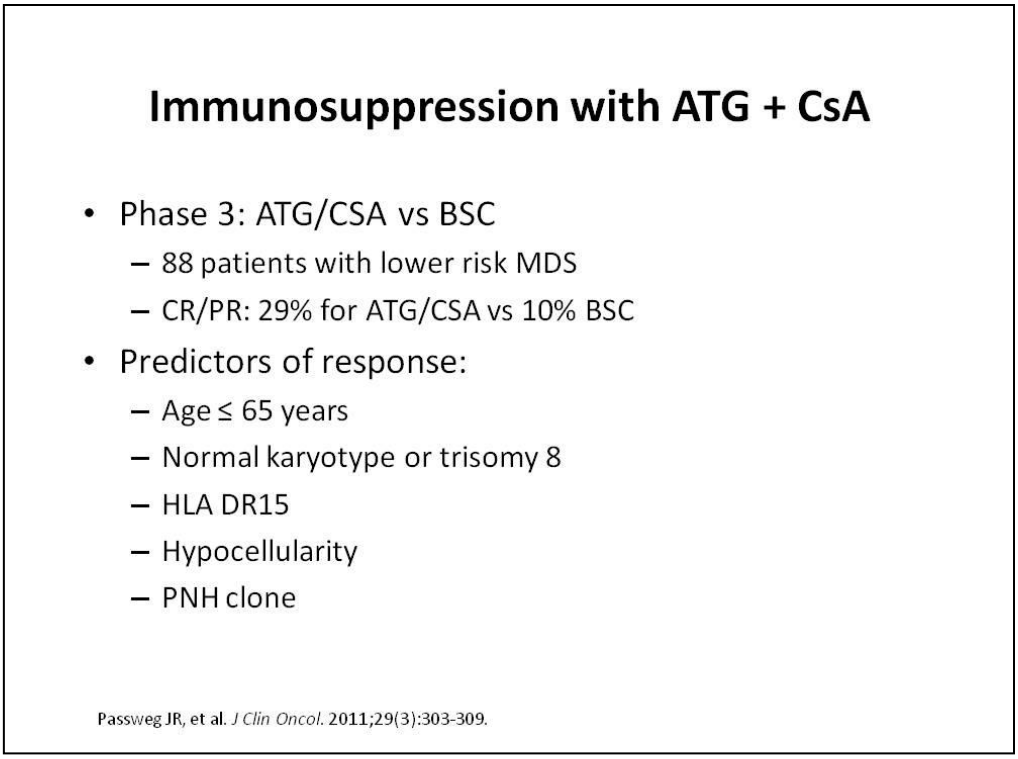
White blood cells and platelet growth factors again are commonly used in patients with myelodysplasia. I have come to a very simple rule that I do not treat a number, but rather, I treat a symptom. For patients having difficulty with recurrent infections, and often have low blood white blood cell counts, I will periodically use the white cell growth factors to try to improve the bone marrow function and make that number better. Same with platelets, if the patient is persistently low or is refractory to

transfusions and has bleeding problems, I think it is not unreasonable to consider using a drug to stimulate the platelet growth to try to keep the patients out of that danger zone. Again, I remind people these are not approved for this indication, but are clinically effective and can be used in the right setting.



What about immuno-suppressive agents? We have known for a long time that there are forms of myelodysplastic syndromes that seem to involve the immune system, an overactive immune system, and using drugs that suppress the immune system have been effective at normalizing the bone marrow function. The most famous combination is antithymocyte globulin, or ATG, and cyclosporine A (CSA).

And here, I will show results from a phase III study. The study looked at 88 patients, which is not a large number for a typical solid tumor phase III study, but for this rare form of myelodysplasia, which is manifested by a hypocellular marrow, they looked at 88 patients. And they saw that, compared to best supportive care, ATG and



cyclosporine resulted in remission rates of up to 30%. There were predictors that suggested which groups may or may not respond. Importantly, this therapeutic strategy is often used for patients that have hypocellular forms of myelodysplastic syndromes, and there are certain HLA types like DR15, which predict a better response to immunosuppressive therapies.

Low Risk MDS Treatments – 2016

- Best supportive care
  - Growth factor support
  - Transfusions
- Immunosuppression
  - ATG and CSA
- *Immunomodulatory*
  - *Lenalidomide*
- *DNA methyltransferase inhibitors*
  - *5-azacitidine*
  - *Decitabine*

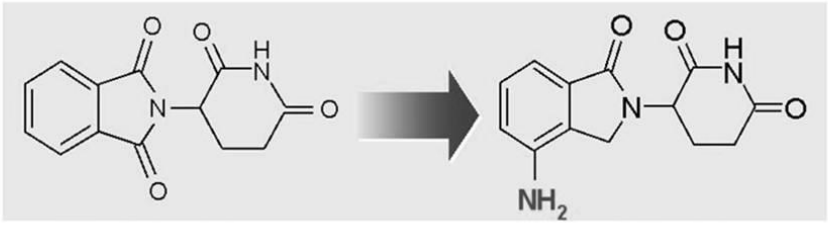
Potentially "disease-modifying"

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Myelodysplastic Syndromes. Version 1.2016. Release date: 5/28/2015. *http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf*

When I think about the last two treatment approaches that remain, the IMiDs and demethylating drugs, I do like to think of these as potentially disease-modifying drugs.

First, lenalidomide is an IMiD. Lenalidomide is a really important drug for the treatment of myelodysplastic syndromes, and specifically, it is interesting because we are not 100% sure how it works. It does modulate T-cells. It affects their proliferation, their growth, and their production of cytokines. However, it is also an anti-angiogenesis factor. It is a cousin of the drug thalidomide, which we know is a very good inhibitor of new blood vessel growth.

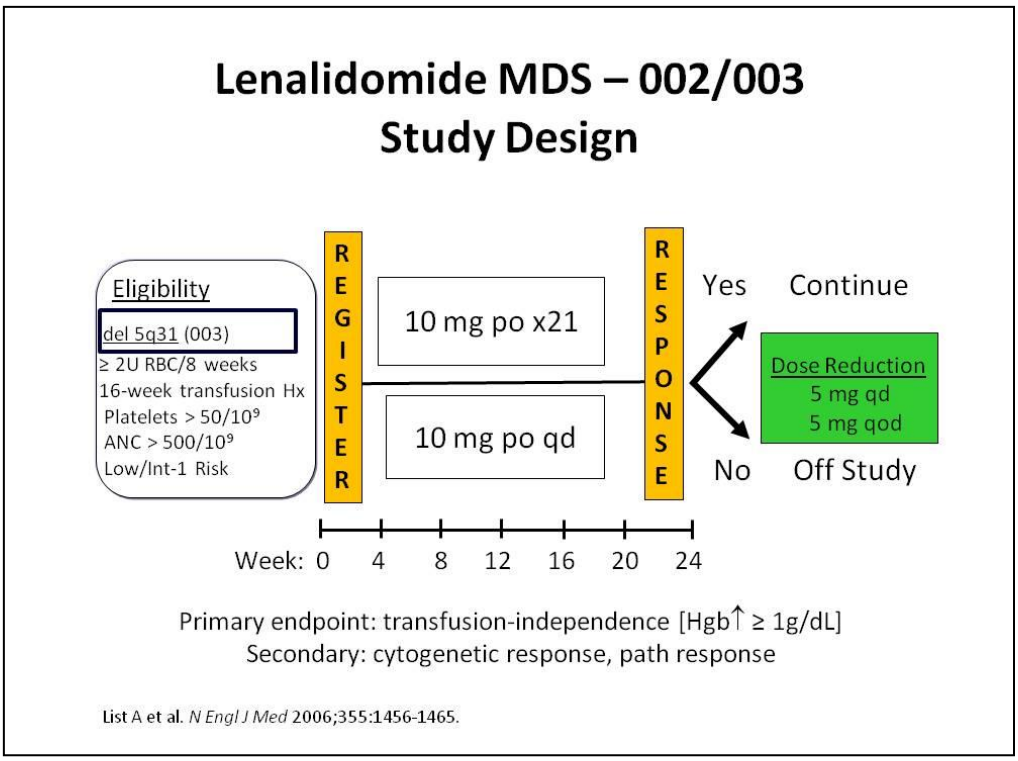
Lenalidomide: Pharmacologic Evolution



Thalidomide Lenalidomide

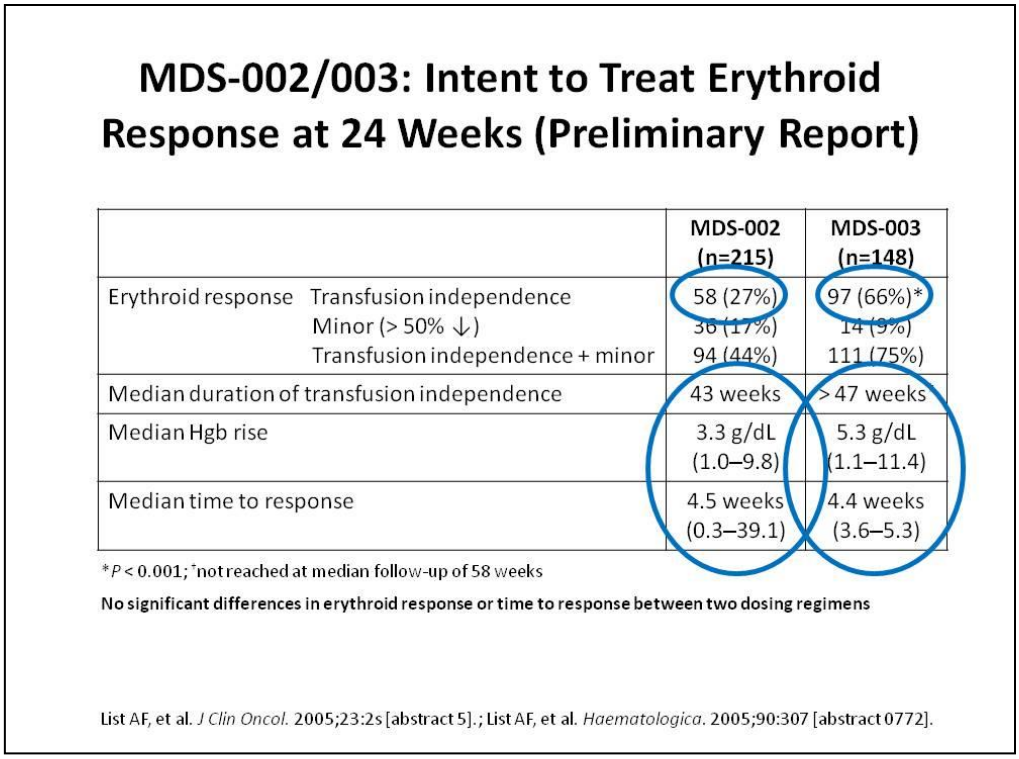
- More "potent" immunomodulator than thalidomide
  - Up to 50,000 times more potent inhibitor of TNFα
  - ↑ stimulation of T-cell proliferation, IL-2 and IFNγ production
- Anti-angiogenesis impact

Bartlett JB, et al *Nat Rev Cancer.* 2004;4:314.; Sterling D. *Semin Oncol.* 2001;28:602.

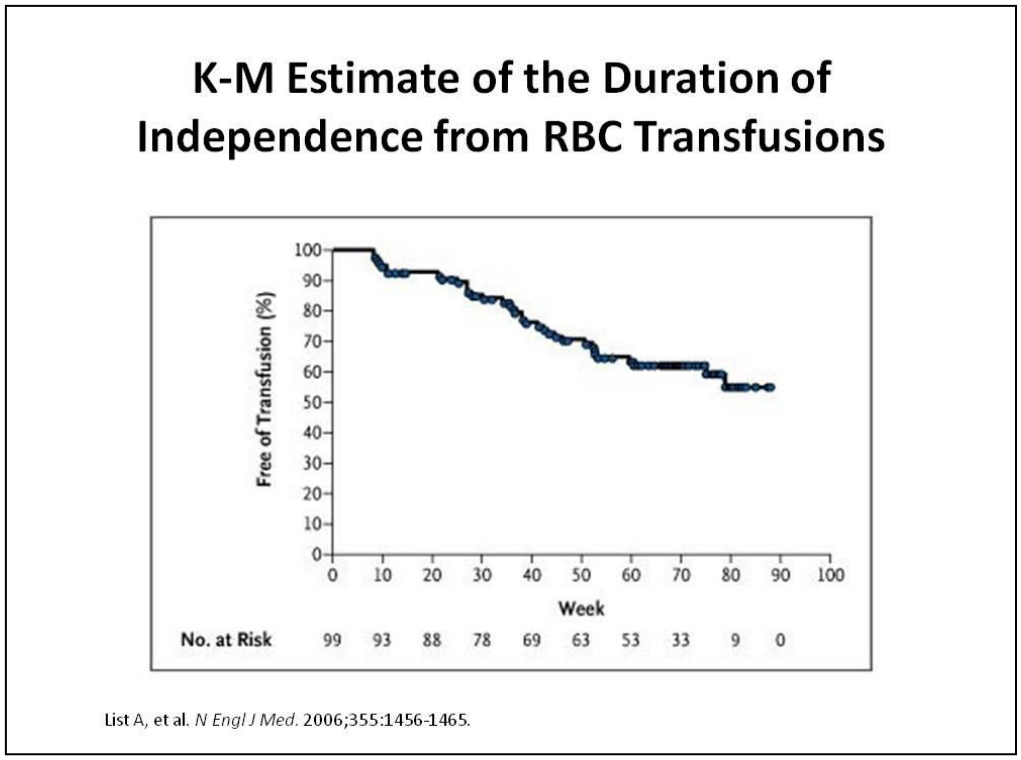


Lenalidomide has been studied in lower risk patients, namely patients with red cell transfusion needs. Lenalidomide or the IMiD family is really good at improving erythropoiesis and affects red blood cell counts more than it does the other lineages. This is a study schema from a two-arm study looking at lenalidomide as a single agent, and specifically, it is important to understand that all the patients had to have low-risk disease by the IPSS criteria. They had to have fairly preserved platelets, and they had to have relatively few transfusion needs. Ultimately, there were two arms, one arm that focused on patients with the deletion 5q, which is a well-known factor that predicts responsiveness to lenalidomide, as well as the second arm, for patients with low risk that did not have to have the 5q deletion. The plan randomized patients between 10 mg of the drug every day or 10 mg 21 out of every 28-day cycles.

And what they found looking at the two different groups is that patients who had the 5q deletion had an incredible response rate, with over 66% becoming transfusion-independent. This happened very quickly, with a median time to the response of about 4-1/2



weeks. Patients with low-risk disease but without the 5q- also had a very nice response, with 25% of them becoming transfusion-independent, also very, very quickly. So, the effectiveness of this drug had really not been seen before in patients with low-risk disease and the ability to make people transfusion-independent was a very, very powerful clinical outcome.



What you can see in this survival curve, a Kaplan-Meier estimate, is how long people remained transfusion-independent, and again, this goes out: the median time is beyond 1-1/2 years. And ultimately, what we discovered is that those patients who respond nicely to lenalidomide are often able to have very prolonged responses, but over time, as one might expect, the responses become fewer and fewer.

One thing that needs to be noted is that lenalidomide is an orally available drug and patients take it at home. It has a pretty significant impact on the remaining bone marrow function, and one needs to be aware that the most common early side effect is really cytopenias. In fact, in early clinical trials looking at lenalidomide, some studies show that up to 80% of patients needed to be dose-reduced in the early going in order

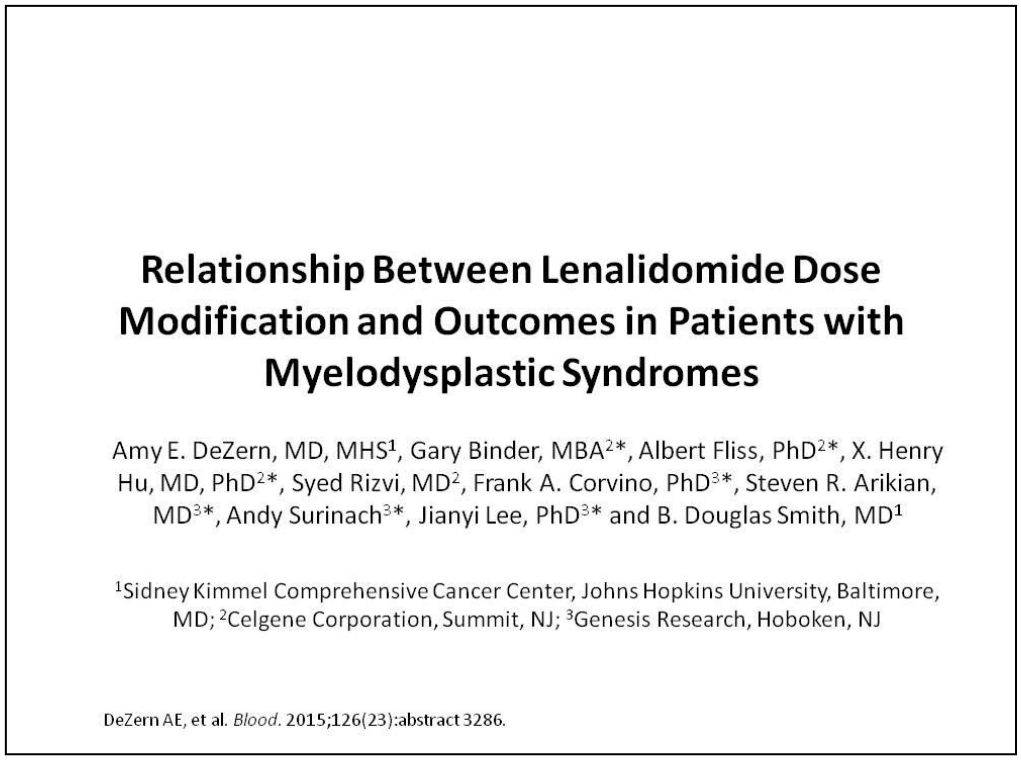
Most Frequently Observed Hematological Adverse Events: del 5q MDS Safety Data

N=148	ALL Grades	Grade 3/4
Neutropenia	58.8%	53.4%
Thrombocytopenia	61.5%	50.0%
Anemia NOS	11.5%	6.1%
Leukopenia NOS	8.1%	5.4%

- Grade 3/4 febrile neutropenia reported in 4.1% (6/148) of MDS patients
- In registration trial, G-CSFs were permitted for patients who developed neutropenia or fever in association with neutropenia
- Patients may require the use of blood product support and/or growth factors

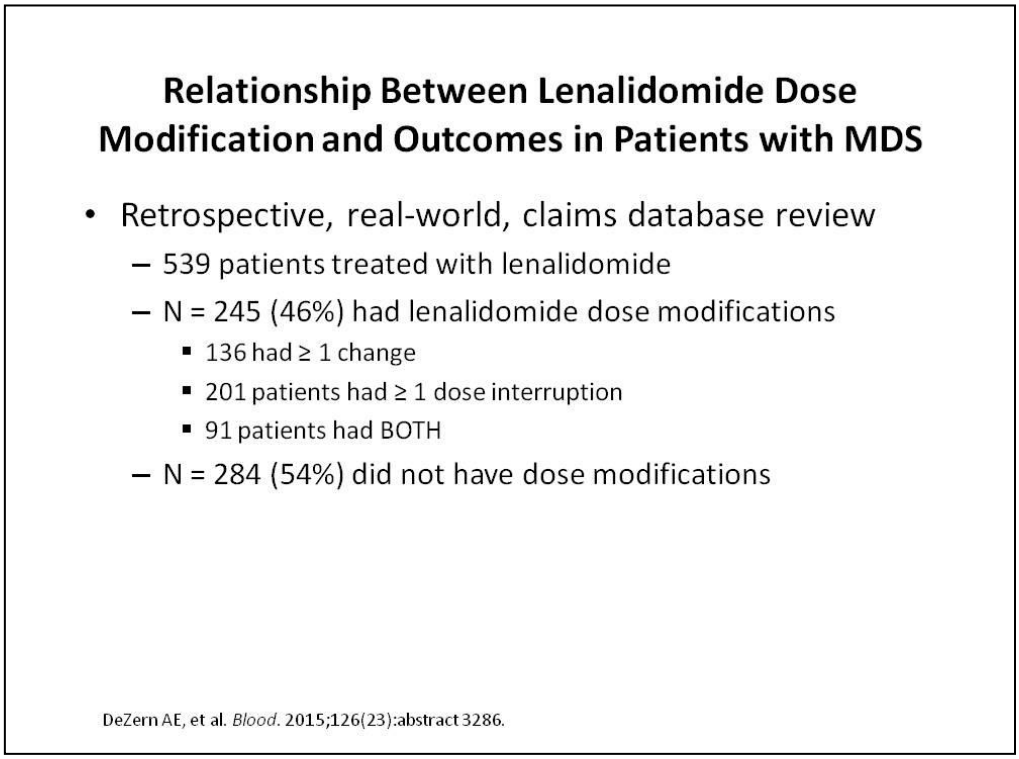
List A, et al. *N Engl J Med.* 2006;355:1456-1465.

to avoid significant and troubling cytopenias. So, when one treats a patient with lenalidomide, one also has to keep in the back of the mind that transfusions and cytopenias are important side effects of this drug.

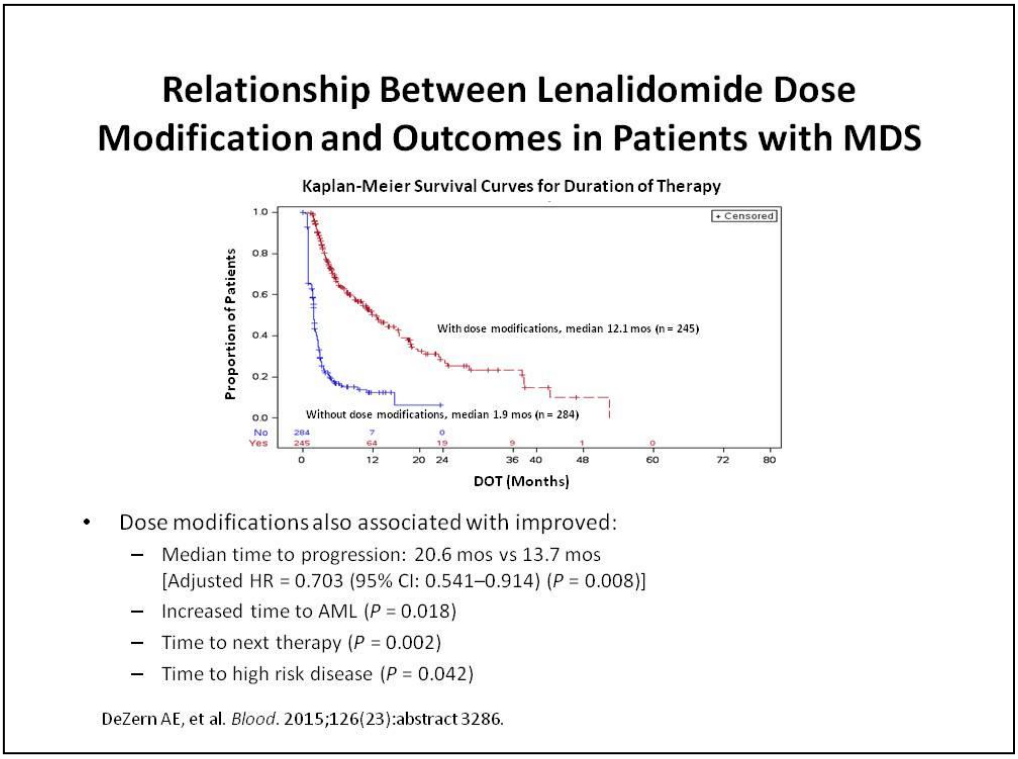


I had the opportunity to work with a couple of my colleagues, as well as a database team, to look backwards retrospectively and try to understand how we could maximize lenalidomide's effect through dosing manipulation.

The study really looked retrospectively at real-world outcomes of patients who were treated with lenalidomide. We looked at the database, and we basically asked the question, how many of those patients needed to be dose-modified? And when patients were dose-modified, was there a difference in outcomes between those we stopped the drug in, those we lowered the dose



of the drug in, or those we were able to continue on and manage?. You can see that we looked at almost 540 patients to try to do this analysis.



I will show you an important curve, and this curve basically says that, when we looked at those patients in whom we stopped the treatment because of cytopenias and compared them to patients whose physicians chose to modify the dose of lenalidomide, these two groups had distinctly different outcomes. Not only was the relationship between the duration of therapy extended, but, for patients in whom the dose of lenalidomide was modified, there was an improved time to transformation to leukemia, a longer time to the next planned therapy, and a longer time to transition to a higher risk disease. What my colleagues and I have taken from this retrospective look at real-world data is that physicians who manipulate the dose of lenalidomide have an opportunity to not only keep their patients on the drug longer, but to get some clinical benefit from that: namely patients do better, they remain on therapy a lot longer, and the likelihood of them transitioning to higher risk disease or acute leukemia is lower. For that reason, we have come to understand that drugs like lenalidomide appear to alter disease biology, and using good clinical strategies to maintain the right patients on trial seems to be important thing for outcome.

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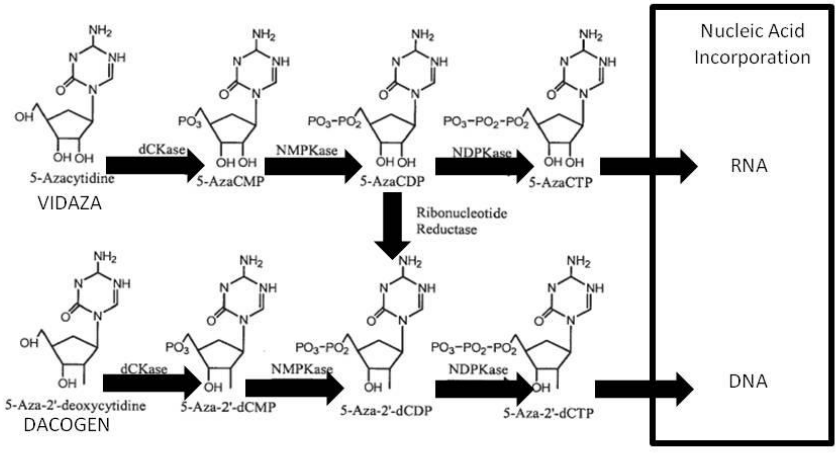
Finally, I would like to turn my attention to the hypomethylating drugs or the DNA methyltransferase inhibitors, namely 5-azacitidine and decitabine. Again, I view these drugs as potentially disease-modifying, and if we use them correctly, the goal will be to maintain disease stability in patients longer.

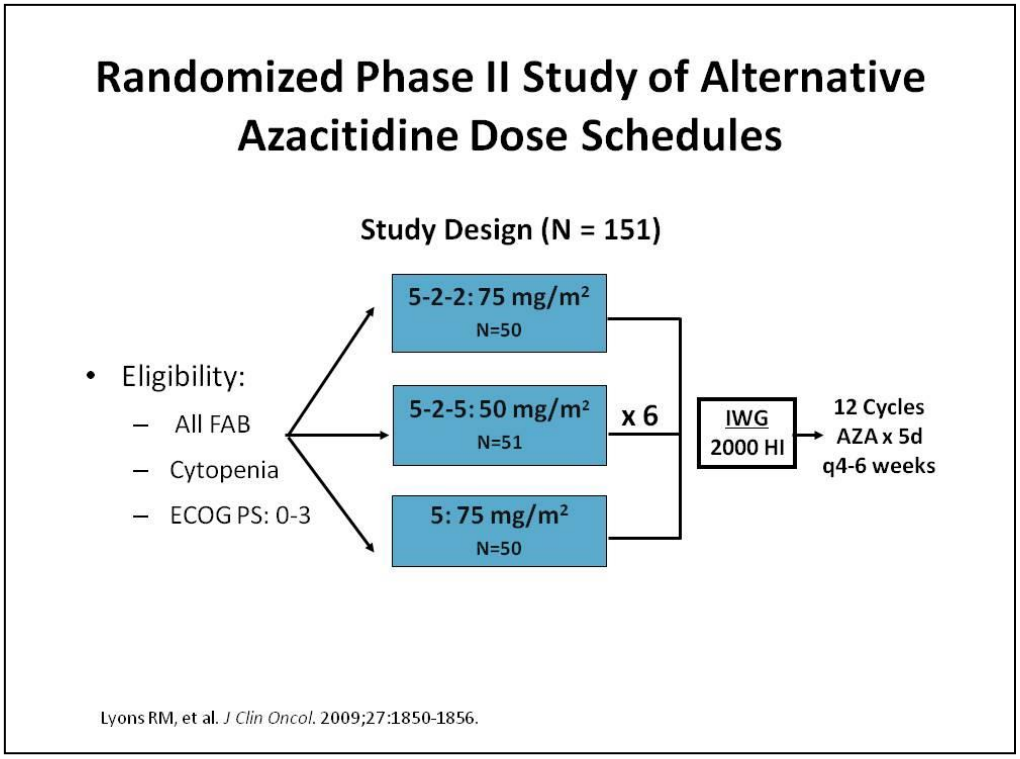
Hypomethylating Agents
Structural Differences



MOA – differentiation by normalizing gene expression thru epigenetic modifications

Kuykendall JR. *Ann Pharmacother.* 2005:39:1700-1709.; Meletis J, et al. *Med Sci Monit.* 2006;12(9):RA194-206.

Hypomethylating drugs have been studied for over two decades now, and the drugs shown here are really cousins of each other, based on similar chemical structures. One is called 5-azacitidine, and the other one is called deoxy-5-azacitidine, and you can see that the decitabine chemical structure is missing a hydroxyl group. And what is important to understand is that, while the mechanism of action of these drugs is not completely understood, they seem to work by differentiating cells over time, and they do this through normalization of gene expression in the MDS cells.



Now, these drugs have classically been used for patients with high-risk myelodysplastic syndromes. However, there was a very, very nice study looking at different ways to use these drugs to try to improve patients with transfusion needs, and these patients were not required to be high-risk patients. They just were required to need transfusions to be on the study, and there were three different arms planned for this. This is using the drug azacitidine where the patients could receive the drug 5 days in a row, take the weekend off, and receive 2 more days of the drug the following week. This repeated every 28 days. One could take a lower dose of the drug daily for 5 days, take the weekend off, and treat for 5 more days, or use the standard dose of the drug 75 mg/m^2 5 days in a row and call it a day. The goal of this was to see who we could improve blood counts in, who we could improve transfusion needs, by using treatment schedules that were conducive to outpatient management. As you know, that the original dosing for 5-azacytidine was 7 days in a row, which is not necessarily convenient for outpatient care.

Alternate AzaC Dose Schedule Study:
Frequency of Major HI in Evaluable Patients (N = 139)

Lineage HI in Evaluable Patients,* n (%)	5-2-2 (n = 50)	5-2-5 (n = 51)	5d (n = 50)
Erythroid$_{Ma}$	19/43 (44)	19/43 (44)	20/44 (46)
RBC-TI	**12/24 (50)**	**12/22 (55)**	**15/25 (64)**
Platelet$_{Ma}$	12/28 (43)	8/30 (27)	11/22 (50)
Any HI	22/50 (44)	23/51 (45)	28/50 (56)
Neutrophil$_{Ma}$	4/23 (17)	4/23 (17)	9/24 (38)
Heme AEs > Grade 3	**33/50 (66)**	**24/48 (50)**	**17/50 (34)**
AE Tx delay	**34/50 (68)**	**30/48 (63)**	**17/50 (34)**

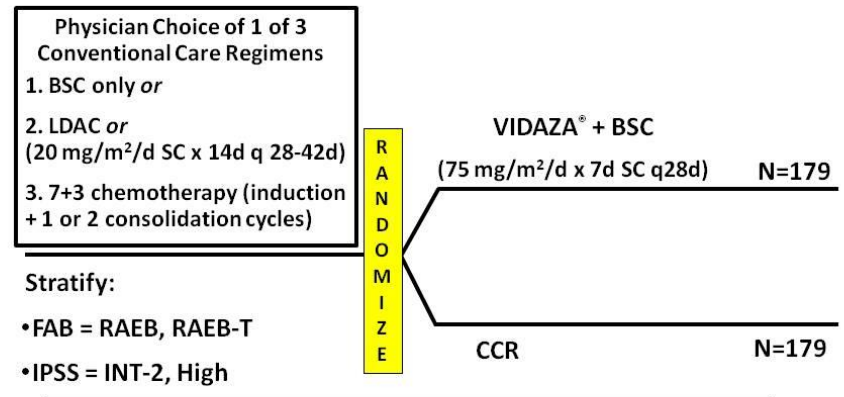
*IWG 2000 criteria

Lyons RM, et al. *J Clin Oncol*. 2009;27:1850-1856.

I will show you a very busy table which shows the improvement in blood counts with each of the schedules, and one can note a couple of important things. Number one, there were erythroid, platelet and neutrophil improvements seen in all study schedules. But what really seemed to stand out is that at least half the patients in each of the groups became transfusion-independent using one of the schedules. The 5-day schedule, which was a 75 mg/m^2 of the azacitidine given daily for 5 days, seemed to do the best as far as transfusion independent, but the groups were not big enough to prove that this was a statistically different amount. Suffice it to say that the demethylating drugs can impact both red cells, white cells and platelet counts, but when you are looking to try to improve transfusion needs, these are very effective drugs in patients who require red cell transfusion.

Now, I mention to you that these drugs might be disease- or biology-modifying drugs, and where I get this notion is really from the AZA-001 study. This is a fairly complicated study done in higher risk patients. The study was really designed to pit standard treatments versus azacitidine in a randomized trial, and the idea was that physicians could pick what they would consider standard for their practice, either

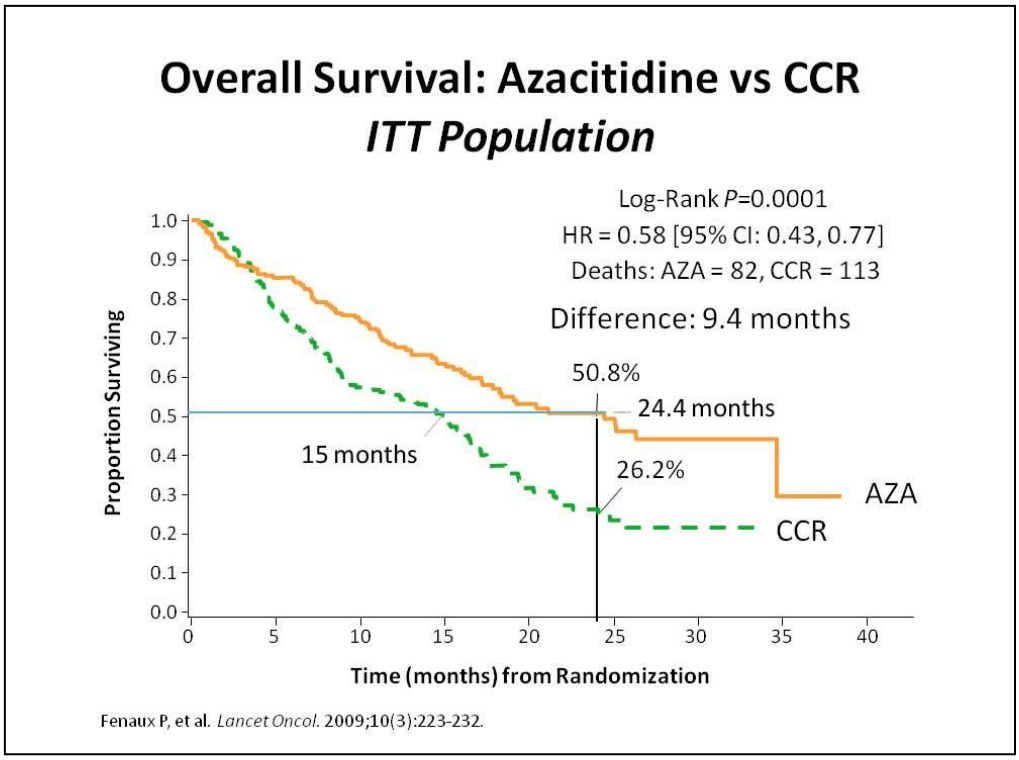
AZA-001: Trial Design



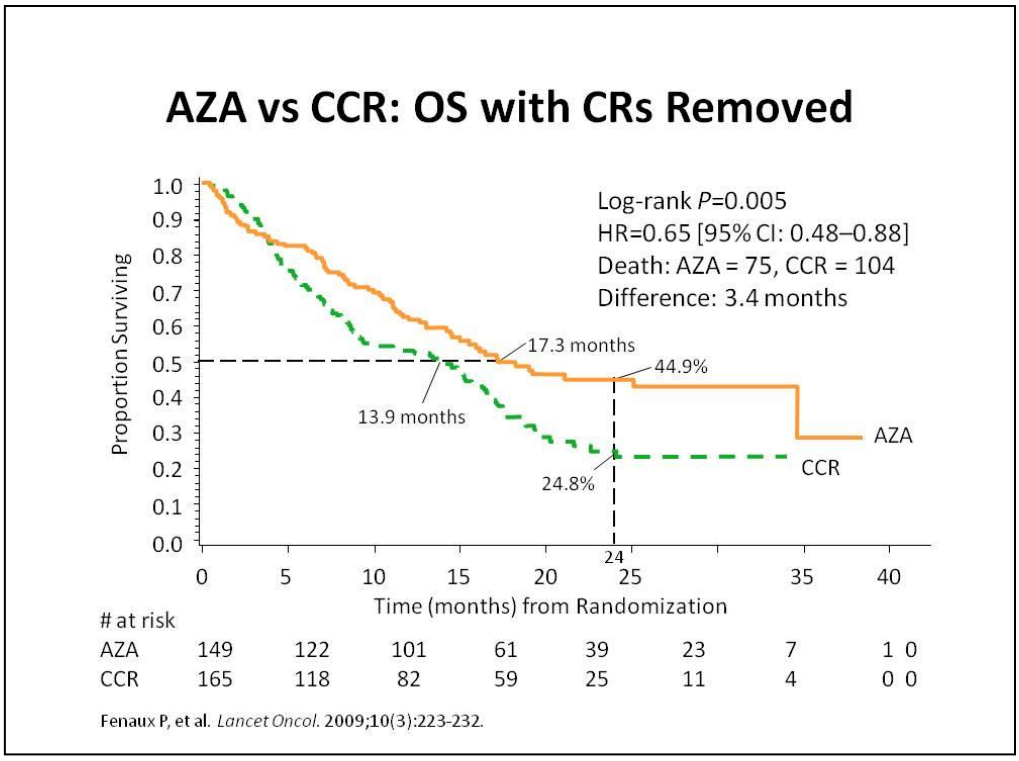
AML=acute myeloid leukemia; BSC=best supportive care; CCR=conventional care regimen; IPSS=International Prognostic Scoring System; LDAC=low-dose Ara-C

Fenaux P, et al. *Lancet Oncol*. 2009;10(3):223-232.

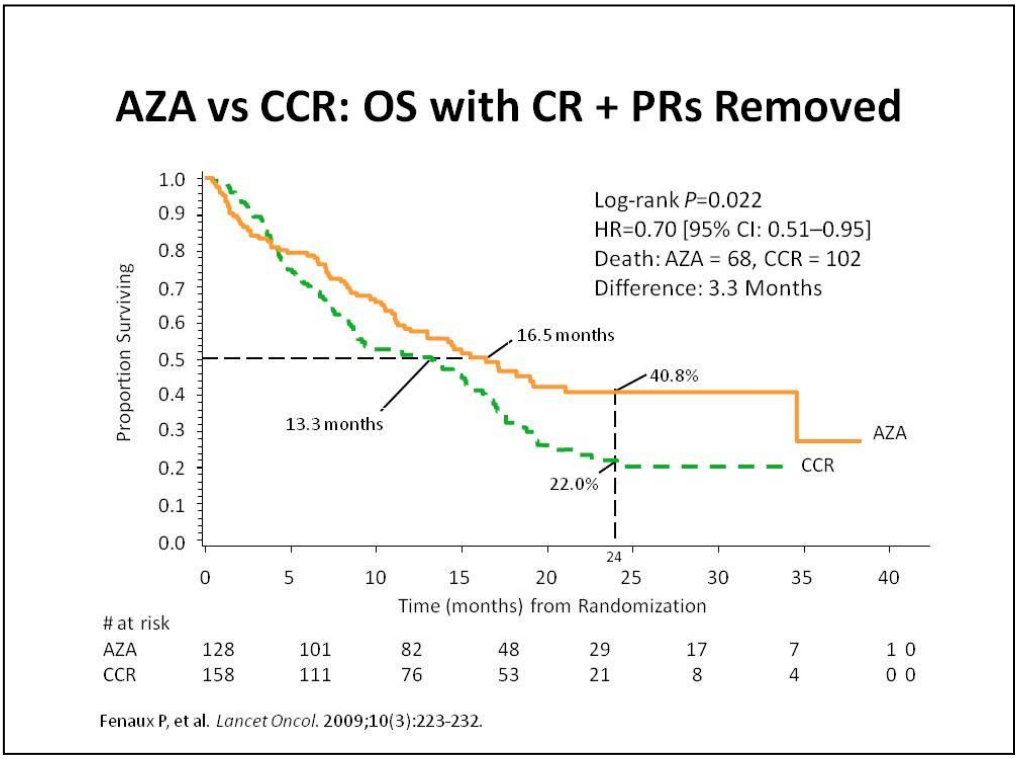
supportive care, low doses of Ara-C, or traditional Ara-C given in combination with an anthracycline, like you were treating a patient with acute leukemia. And whatever predetermined standard treatment was then randomized against azacitidine, and you can see this is very large randomized study of high-risk MDS patients, about 180 patients per arm.



What the study found was that, when they looked at the survival outcomes for patients who were randomized to azacitidine compared to one of the other standard treatment arms, patients actually did better, survived longer when they were randomized to the 5-azacytidine arm. Here, you can see at 2 years, there was a near doubling of survival. One of the criticisms of the study was that most of the patients received best supportive care as the doctor's/physician's choice, and so, most of the time, the randomization took place of azacitidine versus a best supportive care. So, it would not be hard to expect azacitidine to beat standard of care. However, they did a post-study analysis, which looked specifically removing the best responders.

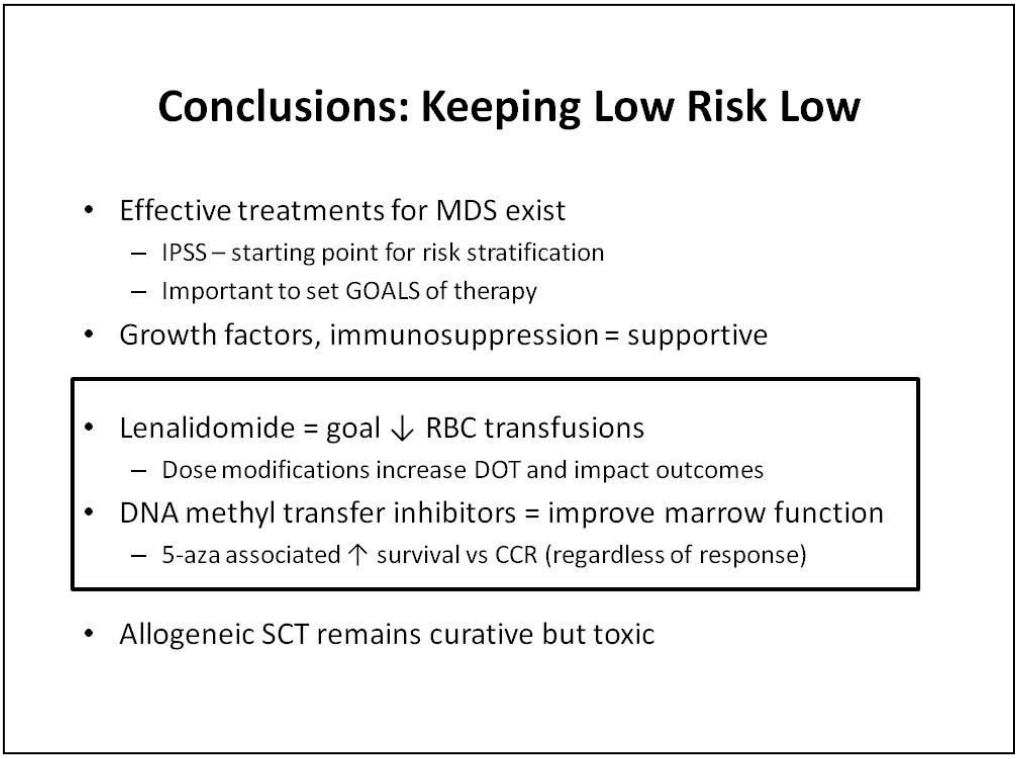


Here you can see survival curves where they have taken out anybody that has achieved a complete remission, and again, if you look at 2 years, you can see a near doubling of survival.



If you take out even patients with complete remissions and partial remissions, so the best responders in each arm, to really try to level the play in field between the best supportive care patients and the azacitidine patients, it turns out that you still get a nearly doubling of 2-year survival. This again led many of the investigators and many of the clinicians who use this class of drugs often to understand and believe that these agents, the demethylating drugs, are somehow changing disease biology; these patients not only survive better, but even those patients who are not achieving a traditional complete or partial response appear to be living longer than those patients who are treated with either best supportive care or traditional chemotherapy-based regimens.

So again, the thinking is that, some of the therapies that we are using are supportive in nature, but there are others that may change the biology and really impact patient survival.



In conclusion, when one thinks about myelodysplastic syndromes and specifically patients with a low IPSS score, or low-risk MDS, the important factor is to try to keep them in the low-risk disease group. In the year 2016, we have effective therapies. We use the IPSS to help us stratify patients to identify who needs immediate therapy, who needs support and who has goals of just trying to maintain disease stability. Ultimately, I think growth factors and immunosuppressive agents do play a role in treating myelodysplastic syndromes. I think they are very, very good supports. Allogeneic transplant, although we did not speak about it much today, I think it does play an important role for patients. Typically, we reserve the use of allogeneic stem cell transplant for patients with higher risk disease or patients progressing out of lower risk disease. If one thinks about the therapies that we use to try to maintain patients in low-risk disease status, I specifically think about the IMiDs like lenalidomide. The goal is to improve transfusions, and if you are smart, dose-modify when you can. Ultimately, we think that more patients will benefit from longer duration of therapy, with a reduced likelihood of transforming to acute leukemia. With drugs like azacitidine and decitabine, again, it is very important that not only do these drugs improve bone marrow function, but they have been shown to improve survival even in the setting where a complete response was not seen.

Thank you for viewing this activity. As you will note, there are additional resources available and other educational activities at *ManagingMDS.com*, and I thank you for your attention.