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Shifting Paradigms for Assessment and Management of Lower-Risk MDS:

Genomics, Risk Stratification, and Novel Therapies

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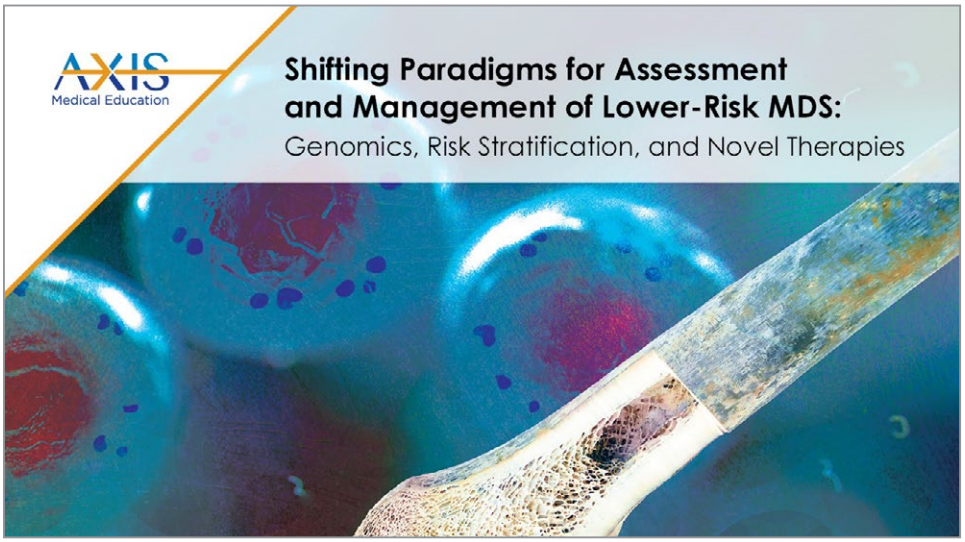
Shifting Paradigms for Assessment and Management of Lower-Risk MDS: Genomics, Risk Stratification, and Novel Therapies

Rami Komrokji, MD, Michael R. Savona, MD and Jamile M. Shammo, MD, FASCP, FACP



Rami Dr. Komrokji, MD: Hello, and welcome to this educational activity entitled *Shifting Paradigms for Assessment and Management of Lower Risk Myelodysplastic Syndromes, Genomics, Risk Stratification, and Novel Therapies*.

I'm Rami Komrokji, Vice Chair of Malignant Hematology Department at Moffitt Cancer Center, joined by two of my dear friends, international experts in MDS, Dr. Jamile Shammo, Professor of Medicine and Pathology at Rush University Medical Center, and Dr. Michael Savona, Chief of Hematology at Vanderbilt University.

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- **Rami Komrokji, MD**, reported a financial interest/relationship or affiliation in the form of *Consultant*: AbbVie; Acceleron Pharma; Bristol-Myers Squibb Co; Celgene Corp; CTI BioPharma Corp; Geron; Innovent; Jazz Pharmaceuticals plc; Novartis Pharmaceuticals Corp; PharmaEssentia; Taiho Pharmaceutical Co, Ltd; and Takeda. *Speaker*: AbbVie, Bristol-Myers Squibb Co, Celgene Corp, Jazz Pharmaceuticals plc, and Servier.
- **Michael R. Savona, MD**, reported a financial interest/relationship or affiliation in the form of *Consultant:* AbbVie; Bristol-Myers Squibb Co; Celgene Corp; CTI BioPharma; Geron; Novartis Pharmaceuticals Corp; Ryvu; Sierra Oncology; Takeda; and TG Therapeutics, Inc. *Research funding:* ALX Oncology; Astex; Incyte; Takeda; and TG Therapeutics, Inc. *Royalty shares:* Boehringer-Ingelheim. *Stocks:* Karyopharm and Ryvu.
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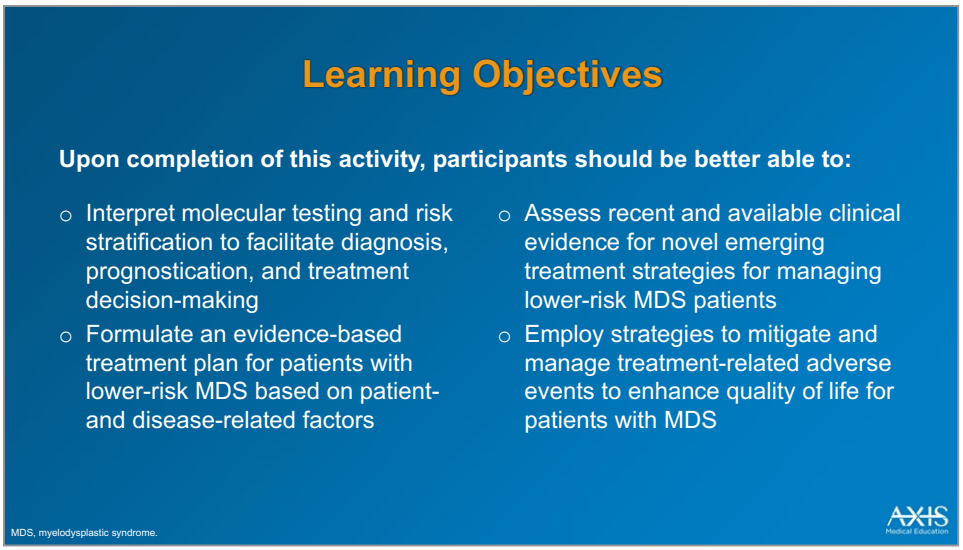
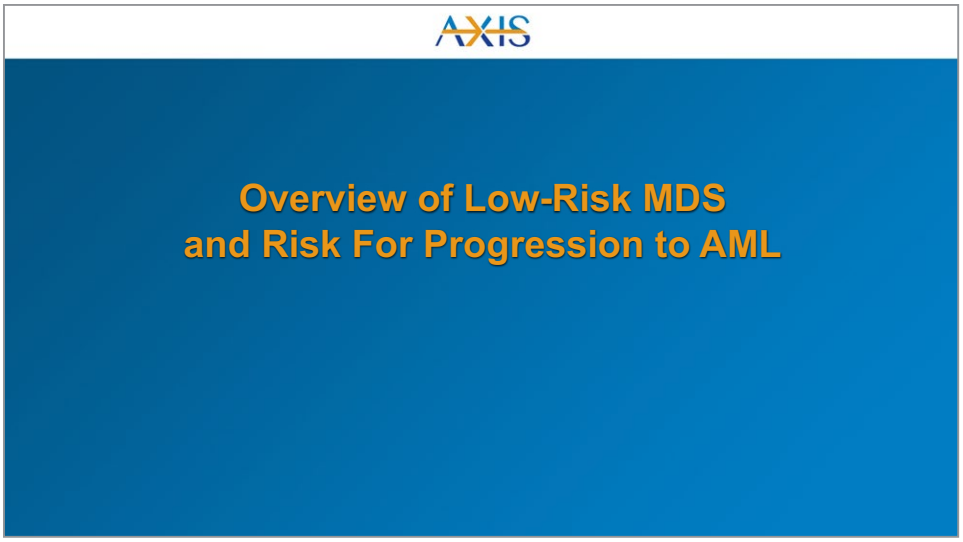


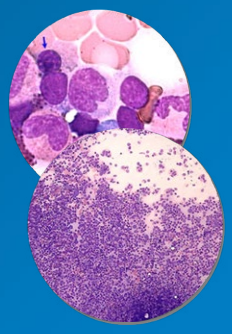
- Today, we're going to be focusing mostly on lower risk MDS, discussing the new advancements and understanding the molecular biology of the disease, the new risk models, and then discussing current available therapies and the novel therapies being introduced in the lower risk MDS.



- I'll start with a brief introduction to this - to set the stage for my colleagues. And then hopefully we'll have a live discussion addressing many of the important clinical aspects of a lower risk MDS.

Myelodysplastic Syndromes

- A group of clonal hematopoietic stem cell disorders characterized by:
  - *Ineffective hematopoiesis/Features of bone marrow failure*
  - *Morphologic dysplasia of hematopoietic lineages*
  - *Acquired cytogenetic abnormalities ~50% of cases*
  - *Clonal hematopoiesis in ~90% of cases*
- Most cases are de novo MDS, a minority are related to toxin exposure (therapy-related)
- Tendency to progress to AML ~ 30% (higher in t-MDS)
- Bone marrow morphology is typically hypercellular for age
- Bone marrow can be hypocellular in ~10% of cases



AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; t-MDS, therapy-related MDS.
Bennett et al. In: Abeloff et al, eds. *Clinical Oncology*. 2004:2849-2881. SEER data. 2000-2009.

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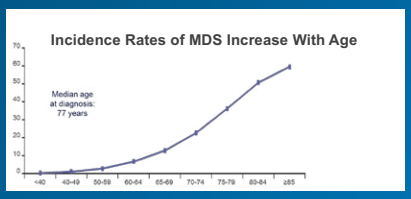
- As you well know, myelodysplastic syndrome are neoplastic stem cell diseases. Those are a spectrum of disease that span from a lower grade to short-term life-threatening diseases. The hallmark of the disease is the presence of dysplasia. In general, around 30% of the patients eventually progress to acute myeloid leukemia. However, unfortunately, majority of the patients die from complications related to the disease, namely the cytopenias.

MDS Epidemiology

- Overall incidence: 3.7-4.8/100,000
- In US: ≈37,000-48,000
- Median age: 70 yrs



More than 86% of patients were diagnosed at age 60 years or older

Epidemiology of Hematologic and Nonhematologic Malignancies in the US (SEER Database, 2016)	Incidence[a]	5-year Overall Survival (2006-2012)
Hematologic malignancies		
Hodgkin lymphoma	2.6	86.2%
MDS	4.5	29%
Myeloma	6.5	48.5%
Leukemia	13.5	59.7%
Non-Hodgkin lymphoma	19.5	70.7%
Selected nonhematologic malignancies		
Lung and bronchus	57.3	17.7%
Colon and rectum	41.0	65.1%
Breast	124.8	89.7%

[a]Age-adjusted incidence rate per 100,000 men and women per year between 2009 and 2013.
MDS, myelodysplastic syndrome.
Zeidan et al. *Blood Rev*. 2019;34:1-15. SEER Cancer Statistics Review, 1975-2016. Ma. *Am J Med*. 2012;125(7 suppl):S2-S5.

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- Myelodysplastic syndrome is probably the most common myeloid disease. The annual incidence in the USA is estimated around 50,000 cases, and the average age is in the 70s. When you put this in comparison to other diseases, the 5-year survival with MDS is unfortunately, as bad as some of the metastatic solid tumors, which is a point we don't think of on a regular basis. I don't think people think of the MDS or the lower risk MDS as a life-threatening disease.

MDS Minimal Diagnostic Criteria

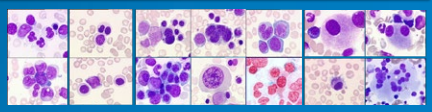
Prerequisite Criteria (Both 1 and 2 must be fulfilled)

1. Cytopenia(s)
   - Hb <10 g/dL, or
   - ANC <1800/μL, or
   - Platelets <100 x 10^9/L
2. EXCLUDE other causes of cytopenias and morphologic changes:
   - Vitamin B12/folate deficiency
   - HIV or other viral infection
   - Copper deficiency
   - Alcohol abuse
   - Medications (esp. methotrexate, azathioprine, recent chemotherapy)
   - Autoimmune conditions (ITP, Felty syndrome, SLE, etc)
   - Hereditary BMF syndromes (Fanconi anemia, etc)
   - Other hematologic disorders (aplastic anemia, LGL disorders, MPN, etc)

MDS Major Criteria

- Dysplasia of at least 10% of cells in one or more major BM lineage(s) (erythroid, neutrophilic, megakaryocytic) or an increase in ring sideroblasts of ≥15% (or ≥5% in the presence of a *SF3B1* mutation)
- An increase in myeloblasts of 5%-19% in dysplastic BM smears or 2%-19% myeloblasts in peripheral blood smears
- An MDS-related (5q-, -7, complex….) karyotype

At least one of these major MDS criteria has to be met (with prerequisite criteria) to arrive at the diagnosis of MDS



ANC, absolute neutrophil count; BM, bone marrow; BMF, bone marrow failure; Hb, hemoglobin; ITP, immune thrombocytopenia; LGL, large granular lymphocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; SLE, systemic lupus erythematosus.
Valent et al. *Oncotarget* 2017;8(43):73483-73500.

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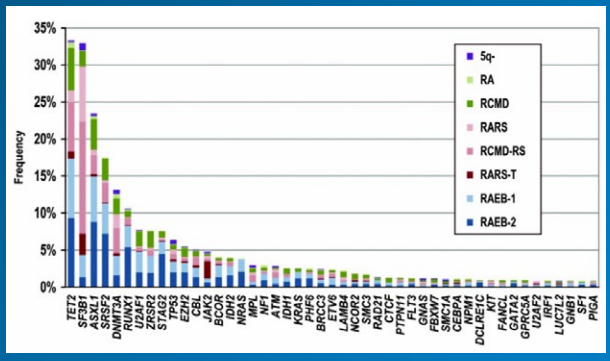
Now, to diagnose MDS, we need to establish presence of cytopenias, low blood count, and then one of certain criteria that are set for diagnosis, either presence of dysplasia, abnormal-looking cells, and it has to be 10% or more of any cell line. And that depends on the pathologist's or hematopathologist's experience, or if there is an increase in the myeloblasts, in the range of 5% to 19%. And there are certain cytogenetic abnormalities that are defining for MDS such as chromosome 5, 7, complex karyotype, etc.

So, diagnosis is usually really the first step and very crucial. There was a paper from our colleagues at MD Anderson looking at discrepancy between a tertiary referral center and MDS and common hem-path reports. And in 15% to 20%, they changed the diagnosis. Establishing the diagnosis is essential and it needs the eyes of an experienced hematopathologist.

MDS Is a Genetic Disease

Recurrent Genetic Mutations in MDS
~89% of patients had a mutation by NGS



MDS, myelodysplastic syndrome; NGS, next-generation sequencing.
Haferlach et al. *Leukemia* 2014;28:241-247.

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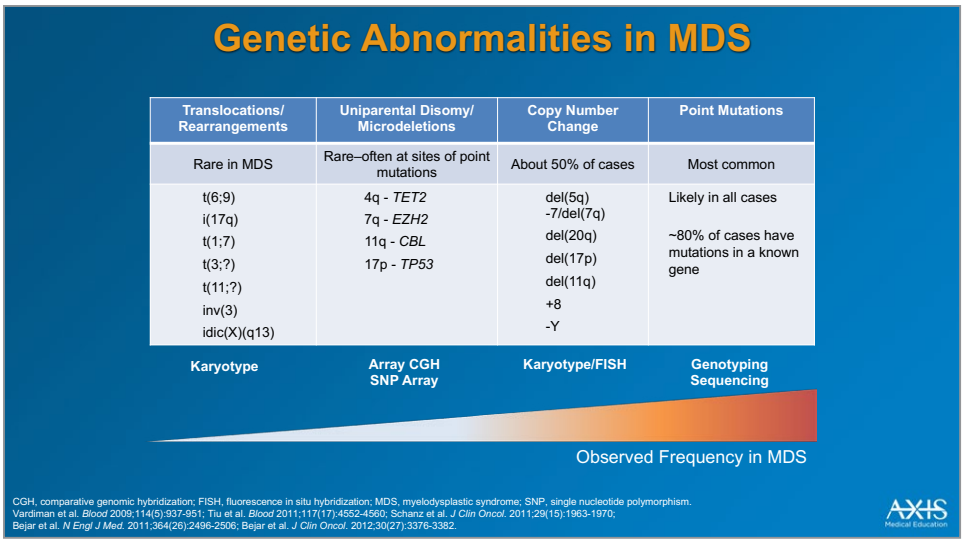
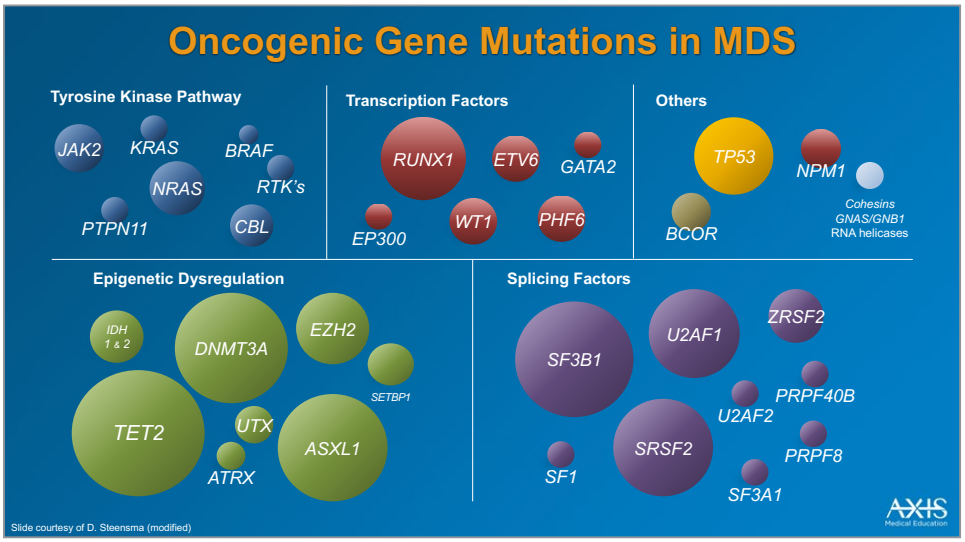
Now, we learned in the last few years that MDS is really a genetic disease. We can identify abnormalities in almost 90% of the patients using conventional cytogenetics as well as next-generation sequencing to identify single somatic mutations. There's obviously an important role for inflammation in MDS. And it's the interplay between those genetics mishappenings, and the inflammation of the underlying biology for the clinical phenotypes and the various heterogeneous presentations we see for MDS.

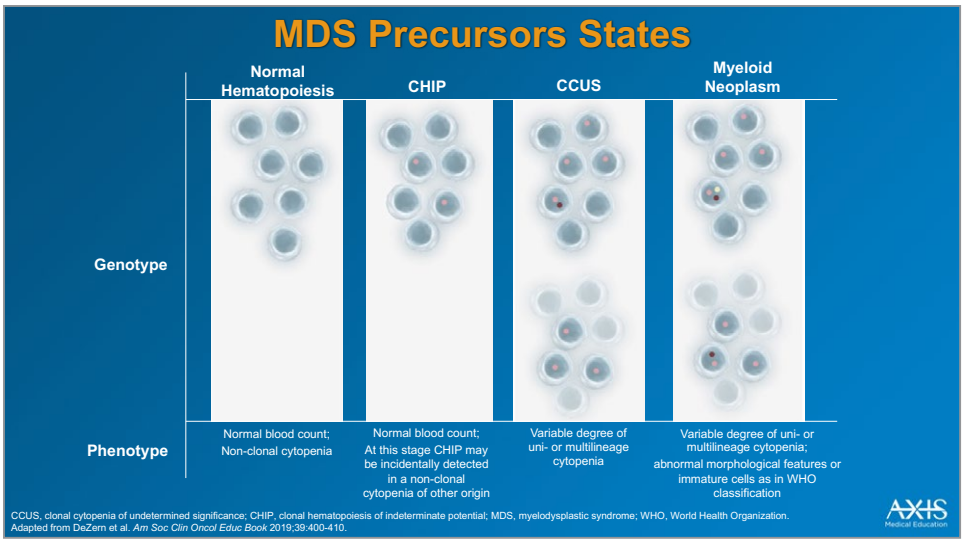


So, for assessment for genetic abnormalities, obviously, conventional cytogenetics or what we refer to as karyotype, or G-banding is still standard of care and part of the assessment. Usually, around 30% to 40% will have an abnormality identified by that. One could use FISH where you have certain probes to detect certain abnormalities. Most places will offer what we call a FISH for MDS that will include deletion 5, 7, 8, 20, etc. FISH is a little bit more sensitive than the cytogenetics. But it's only answering a specific question. In our experience, when we looked at the FISH, it was complementing the cytogenetics only in less than 5% of the cases. So, we currently use FISH only when we don't have mitotic activity.

The other way to evaluate the genetic abnormalities is by integration of next-generation sequencing, where we can identify somatic gene mutations. That's becoming part of the routine assessment, as we will discuss today.

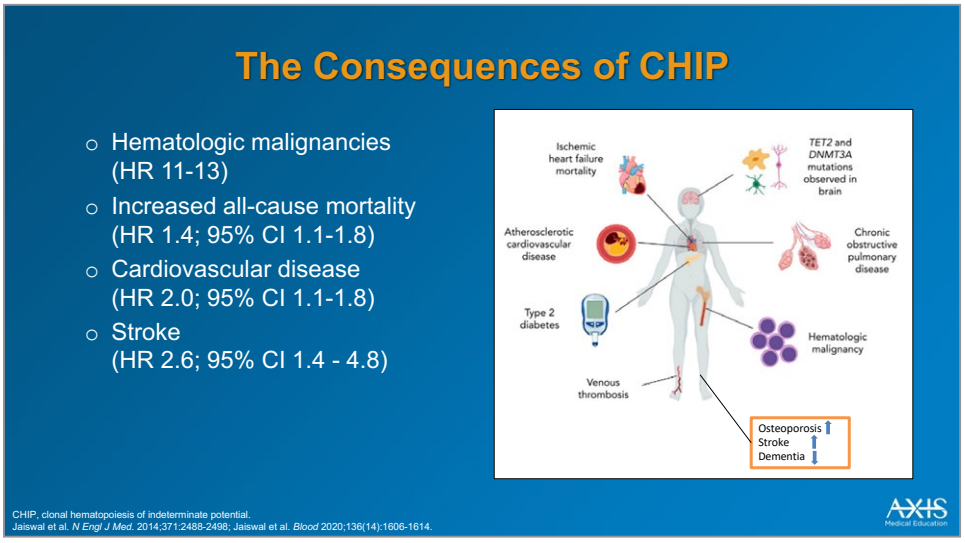


When we look at those abnormalities, they can be lumped into pathways. It turns out that MDS is a disease of epigenetic dysregulation and splicing machinery abnormalities. But there are other mutations as well. Tyrosine kinase pathway tends to be seen more than MDS MPN, p53, always a bad player in any subset.



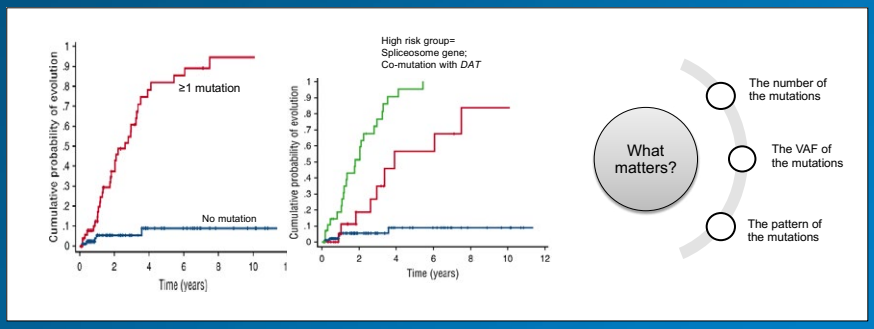
One important advancement is our understanding of the spectrum of this disease. So, now we talk about a spectrum from even before MDS. We have what we call CHIP—clonal hematopoiesis of indeterminate potential. Those are patients that have normal blood counts, we identify a somatic mutation, indicating that some of the hematopoiesis is clonal. Usually, those mutations are at the variant allele frequency of 10% to 20%. We sequence 100 people in above age of 70 without abnormal blood counts, probably 10% to 20% will have that CHIP. Those patients with CHIP are at risk of developing MDS and other hematologic malignancies.

There is also what we call clonal cytopenia of unknown significance. Those patients have low blood count, but there is no dysplasia seen on the bone marrow. The line is really very fine between a clonal cytopenia of unknown significance and lower risk MDS. Those patients typically have similar mutation profile to MDS and based on the number of mutations, the variant allele frequency, the risk of progression to MDS, is way higher than CHIP. We're trying to understand the implication of that.



For example, with CHIP, it's not just the risk of hem malignancies, there is substantial risk of therapy-related myeloid neoplasms if those patients get treatment for solid tumors—increased cardiovascular mortality and other sequelae.

What Is the True Prognosis of CCUS?



CCUS, clonal cytopenia of undetermined significance; *DAT*, *DNMT3A*, *ASXL1*, and *TET2*; VAF, variant allele frequency.
Malcovati et al. *Blood* 2017;129(25):3371-3378.

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- Obviously in CCUS, that's becoming an opportunity for us to see in the future if we can intervene.

MDS WHO 2016 Classification

PB and BM Findings and Cytogenetics of MDS					
Name	**Dysplastic lineages**	**Cytopenias***	**Ring sideroblasts as % of marrow erythroid elements**	**BM and PB blasts**	**Cytogenetics by conventional karyotype analysis**
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15% / <5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15% / <5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15% / ≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15% / ≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except –7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19%, no Auer rods	Any
MDS, unclassifiable (MDS-U)					
with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 x 10^9/L; and absolute neutrophil count, <1.8 x 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 x 10^9/L.
† if *SF3B1* mutation is present.
‡ One percent PB blasts must be recorded on at least 2 separate occasions.
§ Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.
BM, bone marrow; MDS, myelodysplastic syndrome; PB, peripheral blood; WHO, World Health Organization.
Adapted from Arber et al. *Blood* 2016;127:2391.

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- Now, once we establish the diagnosis of MDS, typically hematopathologists will classify the disease. The classification used now is the WHO 2016 classification. But that's all changing. The WHO is coming with the 2022, uh, classification, integrating a lot of the molecular data, and there is the International Classification Consensus. For the first time, we're going to probably have two different classifications. That will be interesting to see how that will evolve. But clearly, all those classifications are starting to recognize the importance of those genetic events in MDS, and potential future treatment based on that. Also recognizing that probably, when the myeloblasts are increased, the line between MDS and AML is also fine.

Faculty Panel Discussion

With that, I will stop and start the discussion around those things. I ask Dr. Shammo to start with walking us through how do you work up patients for MDS? And, how do you integrate all the testing before starting treatment?

Dr. Shammo: Thank you, Rami. That was a beautiful recap of what we know now about MDS and some of the most recent developments in the field. A diagnosis can be rather difficult because of the heterogeneity and because dysplasia is essentially a morphological diagnosis that can be seen in many other situations other than just MDS. Sometimes you find yourself trying to rule out other conditions like viral infections, autoimmunity. That goes into the minimal diagnostic criteria that we need to meet to make a diagnosis of MDS.

For the first time, you see the implementation of some of the molecular discoveries of the recent science that percolated through the, diagnostic criteria of MDS. For example, if you're able to demonstrate the presence of at least 5% of ring sideroblasts together with the presence of SF3B1 mutation, but of course, if you don't do next-generation sequencing, looking for SF3B1 mutation, and your pathologist does not look for or do an iron stain looking for ring sideroblasts, that diagnosis could be entirely missed. You don't have the older definition, dysplasia, defined as more than 15% ring sideroblasts. That's one example. Therefore, it's very important to familiarize ourselves with the most recent diagnostic criteria.

Furthermore, there is some effort to make that diagnosis, even if you don't have ring sideroblasts, and only have confirmation of the presence of SF3B1, because, if you have that clone, it's as if you are demonstrating the presence of this clonal population that in time will only manifest with ring sideroblasts and the ultimate evolution to a clonal disorder, the formation of dysplasia, and, hence, MDS. So, it'll be really interesting—how will that evolve in the new, diagnostic criteria? Or the WHO criteria? And how will the adoption, ultimately, culminate? That's one piece about the diagnosis.

The heterogeneity relative to the molecular landscape is tremendous. It's not just the type of the mutation, it's also the variant allele frequency that we need to pay attention to, and the company with which it keeps. That also is a work in progress.

We are learning more about the therapeutic efficacy of certain agents as it relates to those mutations. Most fascinatingly, what happens when you have clonal hematopoiesis, in terms of cardiac events and thrombotic events? That's the way of the future for us to understand. Is there actually an association between clonal hematopoiesis inflammation and consequences of this, not just for the bone marrow, but for every other organ system? That's yet to come.

You've talked about clonal cytopenias of undetermined significance. I dare to say that the significance is going to be realized soon. It's not just the type of mutation, it's what type of mutation and how—what is the variant allele frequency. And this work has been already done when the Italian group looked at the type of mutations and follow those patients who had ICUS, and demonstrated that those who had high-risk mutations and multiple mutations with a high VAF had a higher risk of evolving into an MDS phenotype and shortened survival with certain types of high-risk mutation. Patients who have SF3B1 definitely had the higher risk of evolving to an MDS phenotype. It's, certainly very interesting. It furthers our understanding to this entity. Whether or not we're going to be implementing those mutations into our risk assessment, I think all of us heard the IPSS Molecular at ASH.

Dr. Komrokji: Thank you. Michael, maybe you can walk us through the testing for somatic mutations. What are the best practices now? What do the national guidelines recommend? And how do you do that in your practice?

Dr. Savona: I think everything that's been said thus far is very helpful in trying to make this diagnosis and showing how next-generation sequencing is really critical. But MDS is a bone marrow failure syndrome that arises from clonal abnormalities, most commonly single nucleotide variants that, unlike a lot of cancers that have hundreds of different genes that are mutated and very low frequency. In MDS, you're really talking about 35 to 55 genes that occupy 95% to 99% of the incidence. It's fairly concise to have a panel that involves most of the genes that are mutated in MDS.

It was the Wild West with next-generation sequencing. Just like most pathologic testing, beyond CLIA approval and validation of a test, there's more acceptance now of certain vendors and academic groups doing tests that include upgrades of new, hotspot mutation areas. It's just common sense, right? In 2015, either you saw a mutation for the first time because only a couple hundred patients or a few thousand patients had ever been genotyped. Now, hundreds

of thousands of patients had been genotyped. So, what was once a variant of undetermined significance, maybe part of the just a rare variant of the normal population, we now know with a little bit more certainty, this is actually associated with disease. That's a work in progress.

We're dealing with this small group of mutated genes where we have more and more information about the recurrent mutations. As Jamile said, the mutations that you see matter, both in MDS proper and in precursor states. I'm sure we'll talk more about both of these things, but I have to say the two biggest innovations or developments in our field in the last several years is the realization that a clonal abnormality occurs, the immune milieu in the marrow changes, and subsequent mutations lead to MDS—the idea of precursor states.

The other idea is that especially young people have constitutional abnormalities that set them up for developing MDS—most commonly are things like DDX41 or RUNX1 mutations that are actually not as uncommon as we once thought in the germline that really predisposes people to developing myelodysplastic syndrome and leukemia. We'll talk more about the latter.

With respect to the former, in the precursor states, we've learned that not all mutations are created equal. It matters which gene the mutation's in, it matters how many mutations there are, it matters how many of the cells have the mutation in them and the variant allele frequency, the combination, the interplay between those genes. We're still iteratively improving this understanding. The latest thing is probably an energetic variation where one mutation in the gene is important and one mutation is not, which makes total sense. If you imagine how different genes function and gene products function, if you have a mutation that's in an important binding region versus a mutation that's way downstream, for example, they may have great difference of importance on the impact of the disease.

I think that one of the key questions that Rami was asking about—what's the nuts and bolts of doing next-generation sequencing? We're going to see more insistence from the community and ultimately, regulation around what are the standard common genes and common hotspots that are tested? While it's getting more custom and centralized, there's still quite a bit of variability from different vendors. That's why it's really important to understand the genes that are mutated in this disease and use a trusted vendor that you have a relationship with. Sometimes these things are driven by payers and insurers and makes it complicated. So, it adds a new complication to taking care of these patients for sure.

Dr. Komrokji: I agree. It's fair to say that next-generation sequencing should be part of standard care nowadays. It's important to be cautious on interpreting the results because it needs some expertise. Current national guidelines recommend integrating it at least at the time of diagnosis. Although it's not part of the diagnostic criteria, it's coming soon. It establishes clonal hematopoiesis, as you mentioned. Definitely adds prognostic value, as we will talk about more and more, and therapeutic value.

In our institution, sometimes when disease changes or there is a treatment failure, and we are moving to the next treatment, we reconsider repeating those because every now and then, we'll be able to identify targets.

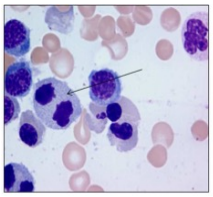
There is no doubt that integration is happening. But your points are very well taken about knowing the lab that you are using, be cautious in interpreting them, as Jamile mentioned—it's not just a mutation, what's the variant allele frequency?

Dr. Savona: I think our practice is very similar to yours. Everyone who comes in with a new diagnosis of MDS needs next-gen sequencing. Everybody who has a real change in the character of the disease, I repeat genetic testing. I often use genetic testing, although this is outside the recommendations in my practice—the recommendations haven't caught up with this kind of thing quite yet. In my practice, I use genetic testing at times where I'm making difficult decisions, when to send someone a stem cell transplant, do they have genetic evolution of the disease? That might be just enough to make that recommendation where I wouldn't otherwise.

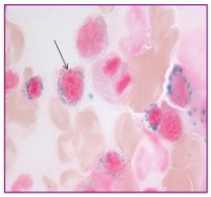
Dr. Komrokji: Absolutely. I'd like to focus a little bit about a unique subset as we are discussing genetic mis-happenings, talking a little bit about MDS with ring sideroblasts. Obviously, this is an entity we knew about many years ago. We understand the strong genotype-phenotype association. MDS with ring sideroblasts is not the most common, maybe 10%, 15% of the cases, but it's one of the most prevalent because those patients have relatively better overall survival, but always have this unmet need of anemia.

Jamile, can you walk us a little bit about what our MDS ring sideroblasts, how we diagnose that, their unique association with SF3B1, and how we are moving into the molecular classification of this entity?

MDS with Ring Sideroblasts



Wright Giemsa stain demonstrating Dyserythropoiesis (arrow)



Prussian blue stain demonstrating Ring sideroblasts (arrow)

- RS are erythroid precursors in which after Prussian blue staining (Perls reaction) there are a minimum of five siderotic granules covering at least a third of the nuclear circumference
- The iron deposited in the perinuclear mitochondria of RS is present in the form of mitochondrial ferritin

MDS, myelodysplastic syndrome; RS, ring sideroblasts.
Patnaik and Tefferi. *Am J Hematol.* 2015;90(6):549-559. © 2015 John Wiley & Sons, Inc.

Dr. Shammo: MDS with ring sideroblasts is a special type of MDS whereby the bone marrow erythroblasts are characterized by the presence of small blue granules that represent mitochondrial ferritin and can be visualized on a Perl stain. Essentially, most of those cases are characterized by the presence of spliceosomal mutation, known as *SF3B1*.

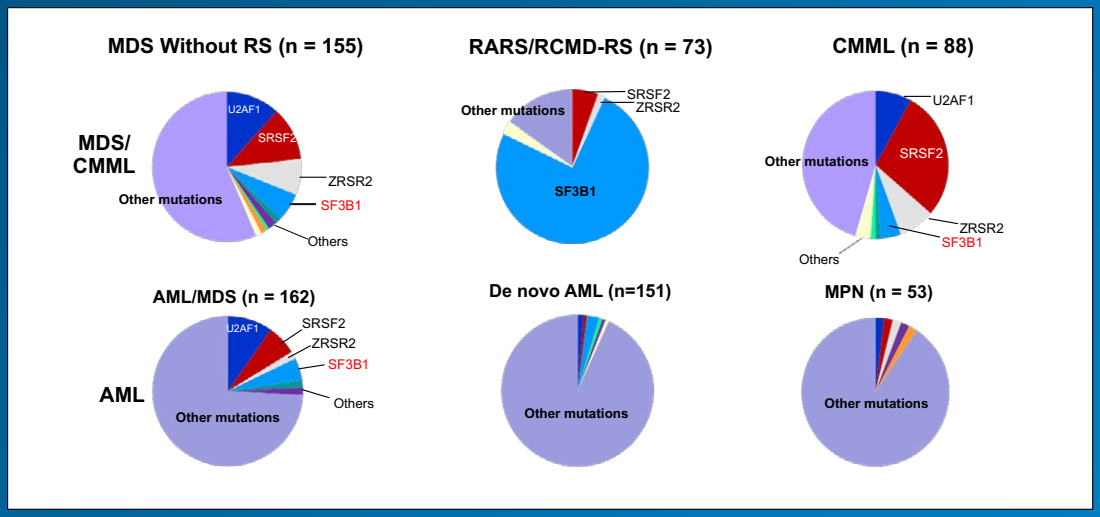
RS and *SF3B1*

- *SF3B1* mutations can be seen in ~80% of RARS cases, with the percentage of BM RS often correlating directly with the *SF3B1* mutant allele burden
- Meayamycin, a pharmacologic inhibitor of SF3B1, can induce RS in healthy in vitro BM cells, and BM RS can be seen in *sf3b1*-heterozygous-knockout mice
- The molecular mechanism behind the development of RS in relation to *SF3B1* mutations is unclear. One hypothesis is that *SF3B1* mutations could alter *ABCB7* gene expression, dysregulating mitochondrial iron homeostasis, resulting in the formation of RS
- *SF3B1* mutations can be seen in a variety of myeloid neoplasms with BM RS such as RARS-T (~80%), RCMD-RS (~30%), PMF~7% , and CMML~6%
- They have also been described in nonmyeloid cancers such as CLL (~15% enriched in patients with del11q) where they are associated with adverse prognosis

BM, bone marrow; CLL, chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; PMF, primary myelofibrosis; RARS, refractory anemia with ring sideroblasts; RARS-T, refractory anemia with ring sideroblasts with thrombocytosis; RCMD, refractory cytopenia with multilineage dysplasia; RS, ring sideroblasts.
Patnaik and Tefferi. *Am J Hematol.* 2015;90(6):549-559.

Of course, there are many other spliceosomal mutations, but the most prevalent, perhaps 80 some percent, is that involving *SF3B1.*

Spliceosome Mutations Are Enriched in MDS



AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RS, ringed sideroblasts.
Yoshida et al. *Nature* 2011;478(7367):64-69.

The majority of that work goes back to 2011, when Yoshida actually performed the initial work on 29 patients where they did whole exome sequencing, which doesn't necessarily pick up the gene rearrangements, but looks at protein abnormalities. Then they found the spliceosomal mutations in a decent number. Then they went ahead and did this work in a much larger patient population, confirming the initial finding and noting that, again, this was a tremendous finding that led to further understanding that those who are not only specific to MDS, certain MDS subtypes, but that they were mutually exclusive, and that they were related to the disease phenotype. For example, later on, we found out that knocking out *SF3B1* mutations in mice does produce the MDS phenotype. As I guess the next question was, well what was that exactly related to? And there's still some speculation as to why does this mutation that relates to alteration in splicing, the premessenger RNA leads to inability to utilize the RNA that gets stuck in in the mitochondria in the form of mitochondrial ferritin? It's not exactly clear, but there's some suggestion that perhaps there may be some downregulation of some gene that has also been implicated in hereditary sideroblastic anemia.

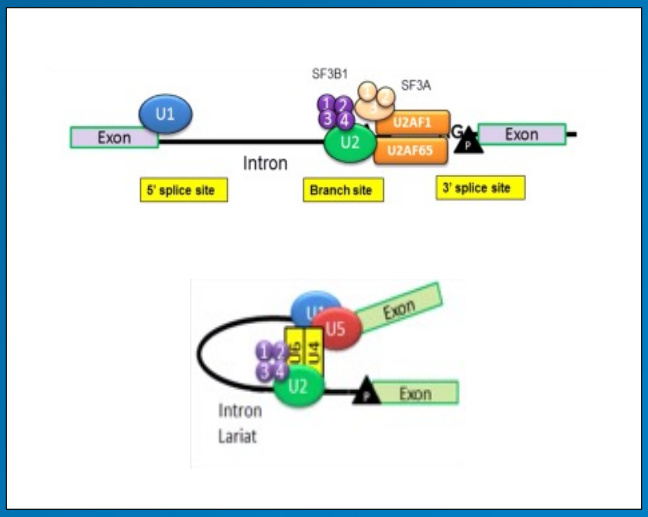
There's some very fascinating basic science that's going on in that area. The bottom line—this is something that we can certainly look for by next-generation sequencing. It does have some prognostic implications in that patients who have *SF3B1* seem to have a very good prognosis.

Dr. Komrokji: Absolutely. It's always a fascinating entity or subtype of MDS. I always tell my fellows to remember that not every ring sideroblast is MDS. As you alluded, there's the three forms—copper deficiency, if no somatic mutations, always look for copper deficiency with ring sideroblasts. It can be seen in other situations as well. And as you mentioned, the strong association with *SF3B1*, its subtype characterized by this ineffective hematopoiesis. A relatively favorable outcome, but this transfusion-dependent anemia over time. That's all shifting more to a molecular-based classification. We had a paper earlier, talking about *SF3B1* subtype proposal that's probably going to be adopted in the 2022 classification by the WHO.

Michael, can you walk us a little bit through that *SF3B*1 proposal as an entity and the details of that?

SF3B1

- SF3 splicing factors help tether the U2 snRNP to the pre-mRNA
  - These factors play an additional role in the formation of the intermolecular helix between the 5' end of U2 and the 3' end of U6 snRNAs
- **Splicing Factor 3 Binding Partner 1 – SF3B1** (155kDa) is one of the seven SF3 spliceosome-associated proteins that are incorporated into the spliceosome during the assembly of the pre-splicing complex and become part of the U2 snRNP
- Most mutations in *SF3B1* are **heterozygous** substitutions and tend to cluster in exons 12–16 of the gene (chromosome 2q33.1)
- The *SF3B1* K700E mutation usually accounts for 50% of the variants, with additional codons such as 666, 662, 622, and 625 acting as hot spot sites



snRNP, small nuclear Ribonucleoproteins.
Patnaik and Tefferi. *Am J Hematol*. 2015;90(6):549-559. © 2015 John Wiley & Sons, Inc.

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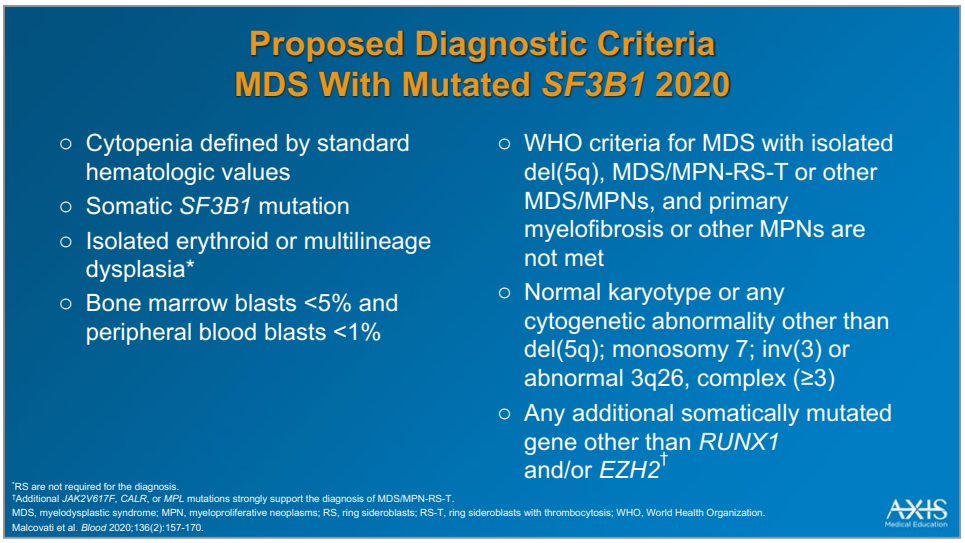
Dr. Savona: *SF3B1* is a fascinating entity. Because we now have therapy that can target some of these *SF3B1*-mutated MDS cases, it's important to identify it, because it is, in the presence of ring sideroblasts indicative of a disease. There is a movement to reclassify *SF3B1*-specific mutant cases with a lower amount of ring sideroblasts. And there are some who believe, in our community, that *SF3B1*-mutant disease is sufficient for the diagnosis of MDS.

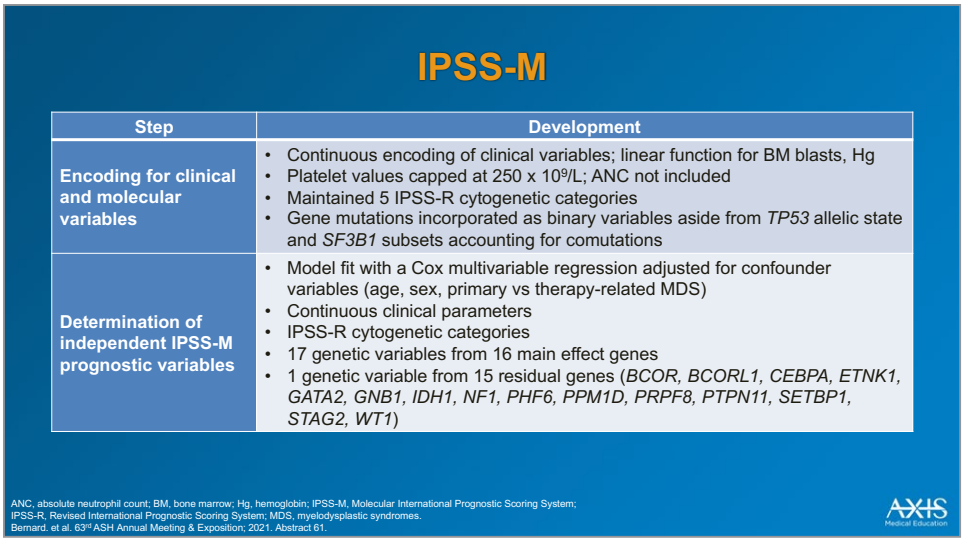
I think *SF3B1* is fascinating mutation in that it's actually associated with good risk in MDS. There are about 10% to 15% of patients with *SF3B1* who actually have a pretty poor risk disease and are co-mutated with *TP53*. But for the most part, *SF3B1* mutations associated with very good risk.

An interesting molecular epidemiology finding is in the last several years, we've discovered that in pre–MDS precursor states, CHIP and CCUS, *SF3B1* mutations much more likely lead to disease. So remember, that CCUS is very common. There are probably hundreds of thousands of patients with CCUS, but many of those patients never develop MDS at all. And the ones that do seem to be enriched for *SF3B1*, which turns out to be the less risky mutation when you actually have MDS.



Dr. Komrokji: Absolutely. We're learning a lot about the proposal for *SF3B1* as unique entity is probably going to be adopted in the criteria set. it was absence of complex karyotype, no increased blasts, and certain co-mutations, such as *RUNX1, EZH2*, rarely *TP53*, will not have the same good prognostic value.

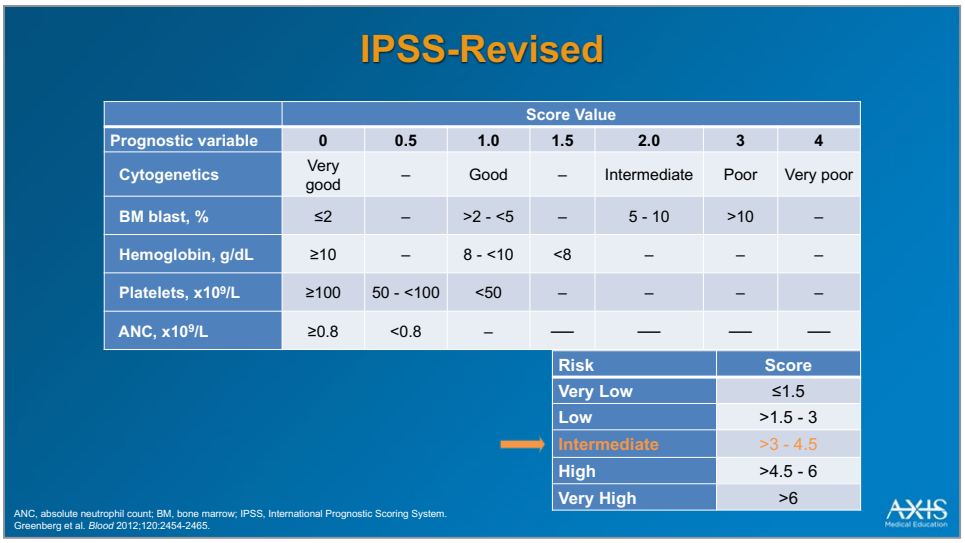
It's very obvious that we spend a lot of time in establishing the diagnosis, getting the molecular testing. Although the classification is important, and in cases like deletion 5q and *SF3B1*, we have targeted therapy.



The crucial step is really the risk stratification. We've historically used the IPSS Revised Version most recently to risk-stratify patients. And the goal at the end is having patients into two groups, either a lower risk, where we manage stepwise, elevated cytopenias, or a higher risk that we are entertaining allogeneic stem cell transplant or trying to intervene to improve survival.

Where we are moving now is definitely integrating molecular. As we already briefly mentioned, there is now a new, modern IPSS-M, the molecular international prognostic scoring system that was presented at the American Society of Hematology and just published in *The New England Journal of Medicine*.

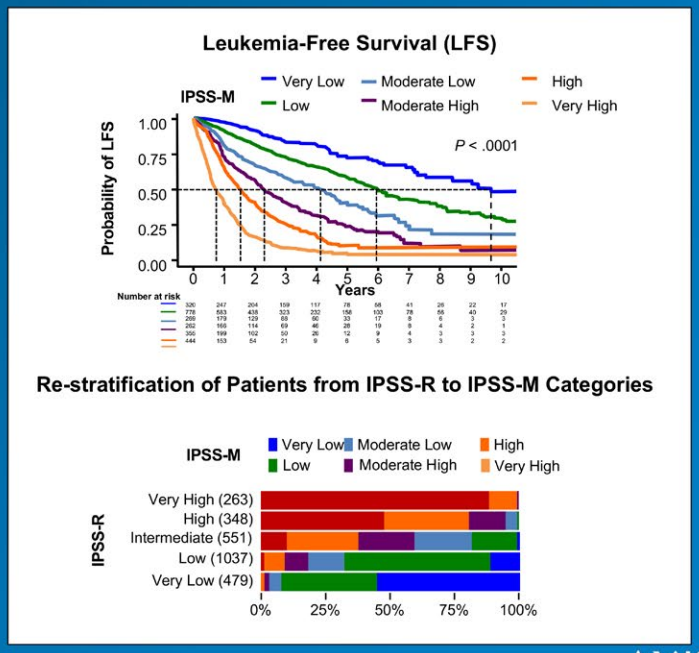
Jamile, can you tell us a little bit more about this IPSS-M? How does it differ from the revised IPSS?



Dr. Shammo: The IPSS-molecular was an endeavor to combine clinical data with molecular data to come up with a scoring system that encompasses all of the above, to provide a better estimation of overall survival in leukemic evolution, and to help us as practitioners take care of MDS to overcome some of the heterogeneity and understand where to place those mutations that we all know figure into the prognosis. Granted, this is a very complex disease and a complex endeavor to begin with. Fortunately, there is a calculator that we can use. I just received a link to a molecular calculator to this particular scoring system. Hopefully, it'll be somewhat easier to do.

Molecular IPSS for MDS

- Diagnostic MDS samples from 2,957 patients with less than 20% blasts and white blood cell count below 13x10^9/L were profiled for mutations in 156 driver genes (discovery cohort)
- Candidate target risk variables consisted of blood counts, blasts, cytogenetics and gene mutations, while patient age, sex and MDS type (de novo or not) were treated as confounders
- 46% (n = 1,223) of patients were re-stratified
- 7% (n = 196) of patients were re-stratified by more than one strata



IPSS, International Prognostic Scoring System; IPSS-M, Molecular IPSS; IPSS-R, Revised IPSS; MDS, myelodysplastic syndrome.
Bernard et al. 63rd ASH Annual Meeting & Exposition; 2021. Abstract 61.

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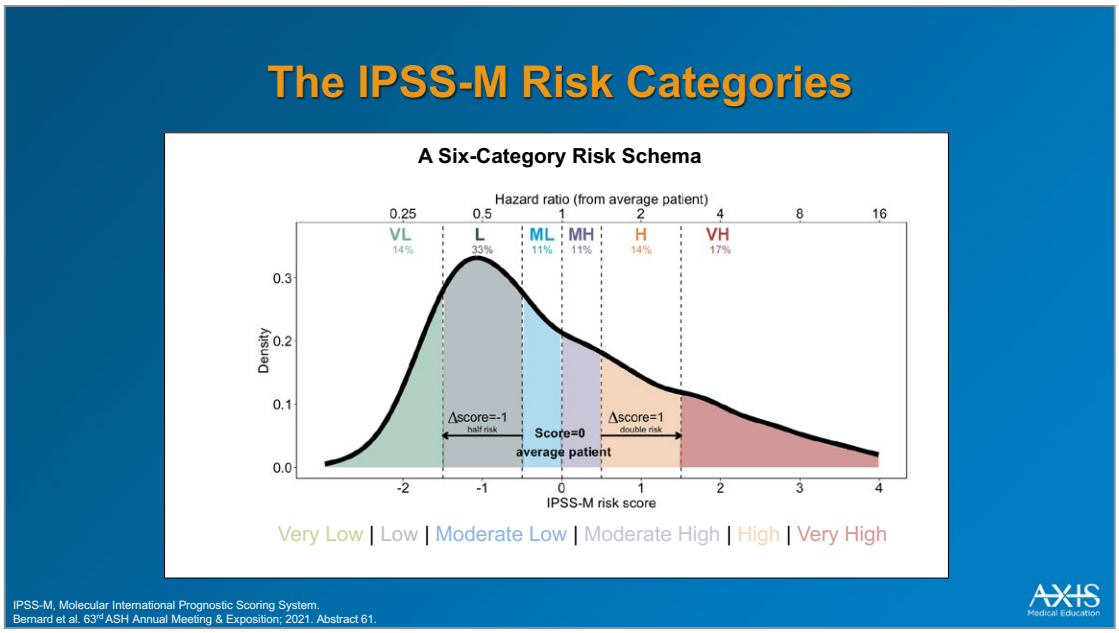
How they did this is that they had a discovery cohort, some very large number in the thousands, and then a validation cohort. They adjusted for certain variables, and then they incorporated various genes, and then they came up with a score, and they have six groups, instead of the five that we have with the IPSS. In their hands, it appears that this is better than the IPSS. It has somewhat of more discerning capabilities. When I look at it, if you look at the very low, low end intermediate, reclassification of the IPSS-R, you can see like a Technicolor, right, of the reclassification of what you found in the IPSS if you were to apply the IPSS-M, telling you that maybe you are up risking some of those patients that were considered an intermediate, and now they are either high or very high, which you would like to know because you probably would consider them for transplantation. This was already validated in a validation cohort.

It'll be really interesting if this is going to be something that the practitioners will utilize. I certainly would use it in concordance with the IPSS-R to get a handle on this. I'd be curious to hear what you guys think about this. I mean, certainly we need a tool to put this forth to utilize it in clinical practice.



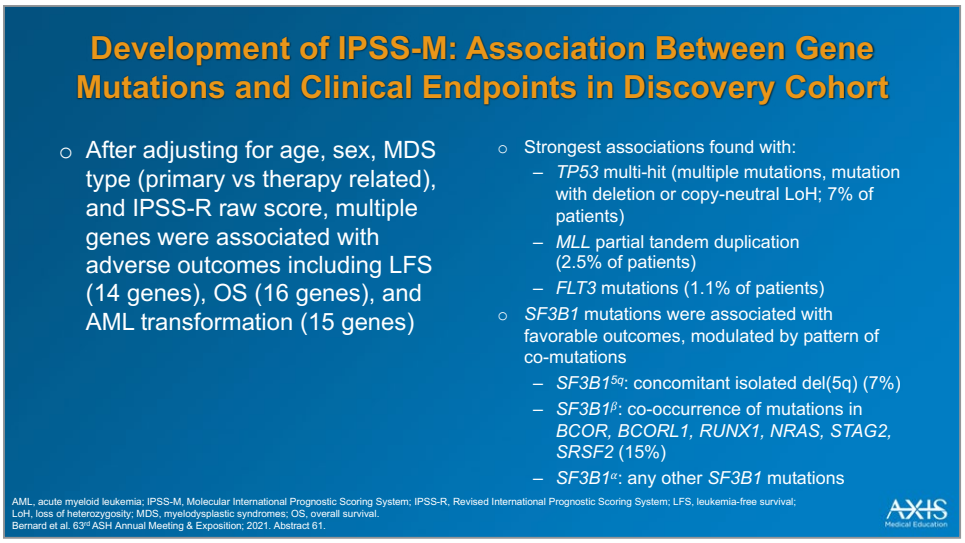
Dr. Savona: I think that risk stratification is something Rami spent a career working on and I'm sure he's got thoughts on how important this is. But it's a work in progress, right? And I think as wonderful as our IPSS-M is, in some ways, we're learning that it's already outdated. So, it's binary, you have a mutation, or you don't. But we know it matters, how much of the mutation you have, and the co-mutational status. And it may not even matter energetically. But that's okay, because the C index, the accuracy of prediction with the IPSS-M exceeds what we already have. And if you go to MDS-risk-model.com, you can actually put in test cases in the model. What you'll find is just as Jamile said, patients who are intermediate risk in IPSS are recategorized, not infrequently to a different risk category with IPSS-M based solely on the presence of single nucleotide variants.

This is important because it edifies why we do next-generation sequencing, and it shows how important those next-generation sequencing results will be because it's the difference between someone going to transplant or not going to transplant.

In my clinical practice, I was beta-testing this risk model for quite some time, and I found it really changed how you look at cases. I took all the lower risk cases, and looked at their genetic sequencing, and saw how that changed their risk score in IPSS-M, and really opened my mind to think—perhaps this might be a patient I would consider transplant earlier, given the risk associated with those mutations.

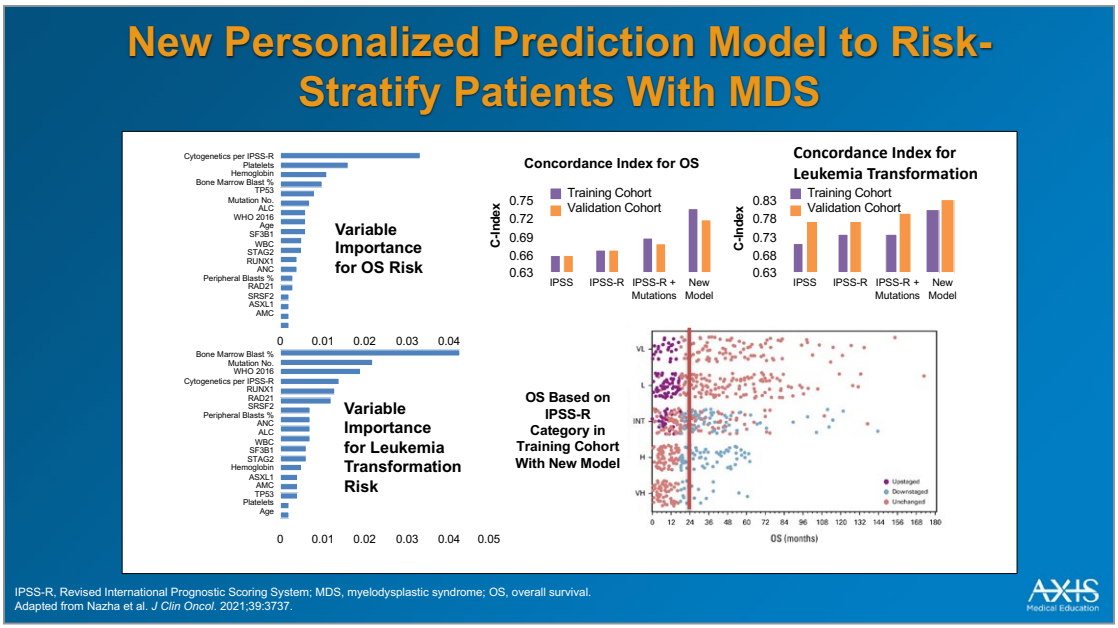
I really do think it's going to be adapted. It's always a work in progress over time. It becomes a bioinformatics problem, right? It's not just 3,000 patients in a model testing the binary presence of gene or not gene, but is there a mutation allele burden or a mutation location within the gene itself that is more important than another mutation in the same gene? That's clearly the case. It's going to take years before we figure out, exactly how to further improve upon this. So, this is really an accomplishment by the IWGPM and certainly helps us do a better job of stratifying patients who come through the door.

Dr. Komrokji: Absolutely. The main point is, as Michael alluded, that is it perfect—probably not. And there are going to be future versions, but it definitely refines the revised IPSS. I think the risk models are always dependent on our therapeutics and how effective. Just to give an idea for the audience, the IPSS-M retains all the clinical variables from the IPSS-R, except the neutropenia, and then adds data from 17 genetic variables, and then one genetic variable from other 15 genes. So, it's really pretty comprehensive for the abnormalities. It's based on leukemia-free survival.



- We learned that not the most common abnormalities, but things like a *FLT3* mutation, or another mutation they described and the *MLL* gene as a partial tandem duplication in 2% of the patients are very important and have strong association with outcome. As we've known for a while now, the presence of a biallelic or multi-hit *TP53* is one of the most important prognostic factors.

  On the other hand, as we were discussing *SF3B1*, we learned that *SF3B*1 co-mutations can affect the outcome. So again, things like *RUNX1*, *EXH2*, and other mutations will not have the same favorable communications with *SF3B1*. And very interestingly, the coexistence of the deletion 5q with *SF3B1*, as well, was not associated with good outcome.



It's a web-based calculator. It accounts even if some variants are missing. We're going to be seeing more and more use for it. But I totally agree with Michael, I think it's not the last step, it's just a step forward in our risk assessment.

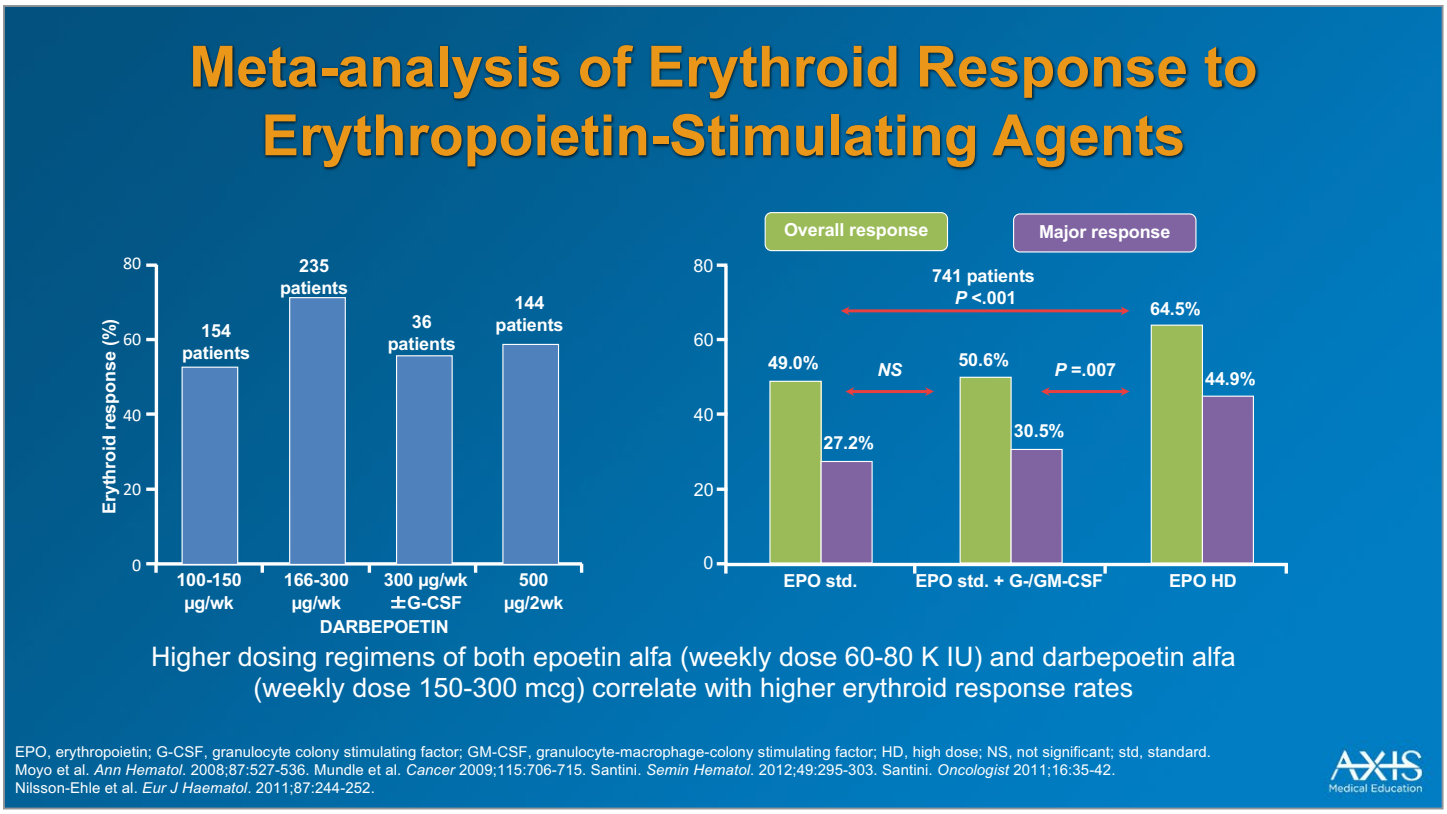
Dr. Savona: So Rami, the point you made about the *MLL* and the *FLT3*-ITD, and the *TP53*, I'd just like to comment on that briefly. So, specifically, the *FLT3* and the *MLL*, these are really rare in MDS, and they usually represent MDS in transformation. The fact that these came across as the single, biggest risk, mutations that we saw, is in itself a positive control, right? So we have positive controls that showed us what we already believed, with *TP53* biallelics with *MLL* with *FLT3*, and with this *SF3B1* with respect to good risk. Then we got the further stratification of those combinatorial mutations with *SF3B1*, which will be really helpful in the future.

Dr. Komrokji: Absolutely. We should probably move to talking about some of the treatments. We will focus today on the lower risk MDS. We spend a lot of time thinking about making sure we have the right diagnosis and risk stratification, and then we will put those patients in this bucket of what we call lower risk. This is a particular area that I've been interested in in the recent years looking at the outcome for those patients. We found that maybe 30% of those patients eventually will progress. Some of the mutations that even Michael just alluded are probably in transition, things like IDH1, IDH2. But majority of those patients actually stay in that lower risk state.

However, unfortunately, more than half of them probably die from complications of the cytopenia. When we look at national registries, we see that even patients with moderate anemia are not treated in the lower risk. In most of the lower risk, the main issue of treating anemia, we could come back and talk a little bit more about isolated neutropenia or thrombocytopenia—those are less often in the lower risk. But in most of the cases, we are treating anemia. So, our first treatment had been always the erythroid-stimulating agents.

Jamile, talk us a little bit through how do you decide that this patient is a good candidate? When do you start? How long do you keep it? And what's really an ESA failure?

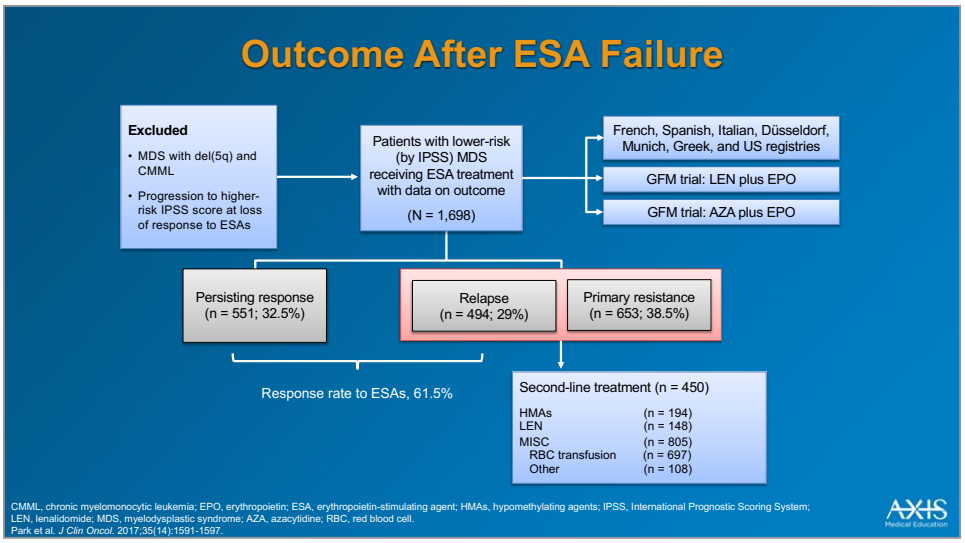
Dr. Shammo: Patients who have MDS generally will present with anemia to begin with. Those who may not be transfusion dependent will ultimately require transfusion, only a matter of time. It is essential that whenever a diagnosis is made, for us to obtain baseline serum EPO level. This should be done before a transfusion has taken place. I find that to be sometimes a missing piece. It's difficult to interpret the level after transfusion. So that needs to be done prior to transfusion.



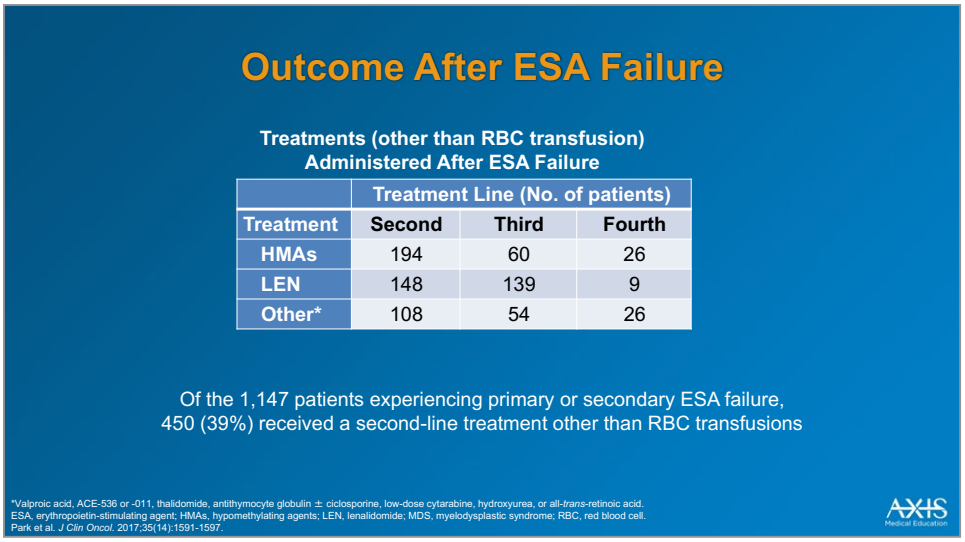
So why? Well, because EPO level is extremely helpful in understanding what the likelihood of a response may be. There's data from the Nordic group that dates many years back, suggesting that any level below 500 will portend a response in that analysis from three studies—people who have a level below 100 had the best response, which is on the order of 75%, between 100 to 500, is perhaps 23%. And then, above 500, is negligible.

More data recently suggests that perhaps we should adopt below 200, because that seems to be a much more reasonable cutoff. We don't have any data between 200 and 500. The lower the level, the higher the response rate. And be that as it may, you could give the patient a trial between 8 to 12 weeks of either a formulation of ESAs, plus-minus G-CSF. And there used to be data adding Neupogen or granulocyte-stimulating factor to patients who have ring sideroblasts, at least according to NICE data, from UK. And again, you could add perhaps 4 weeks to that.

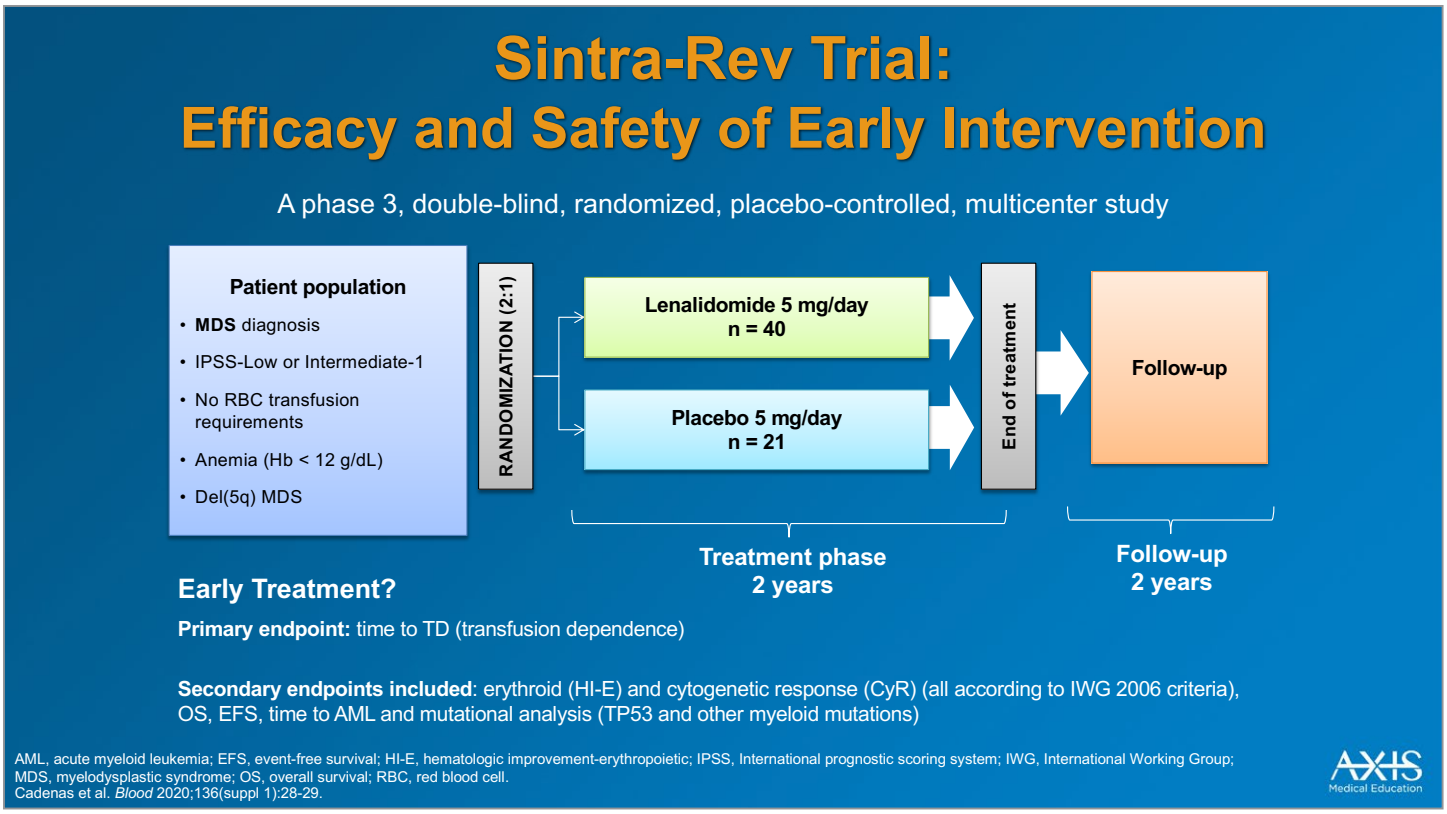
In 8 to 12 weeks, you'll be able to identify whether your patient is a responder or not. The higher the dose of the ESAs, the better the response. It has been shown with multiple meta-analyses of various trials, so we don't have to deliver. But the point is that if the patient continues to be transfusion dependent, despite those escalation, despite giving it a fair shake, or if they have a baseline EPO level of over 500, then I think we need to think about an alternative.



Dr. Komrokji: Absolutely. If you look at the data, probably the responses are seen in the range of 40% to 50% failure is inevitable of the ESAs. Sometimes we see a lot of unnecessary continuation or somebody getting blood transfusions every 2 weeks, but they're still on an ESA, and with the thinking that that's minimizing transfusions. That's a clear ESA failure.



I struggle sometimes with somebody's hemoglobin staying stable, not going up. But, once you tried 8 to 12 weeks, and if there is really no clear response, one should move to the next step.



So, if patients have deletion 5q, lenalidomide had been our standard of care for many years. For patients that are transfusion dependent, I think there had been recent interesting data with the Sintra-REV study.

Jamile, can you tell us a little bit more about the earlier use of lenalidomide in deletion 5q?

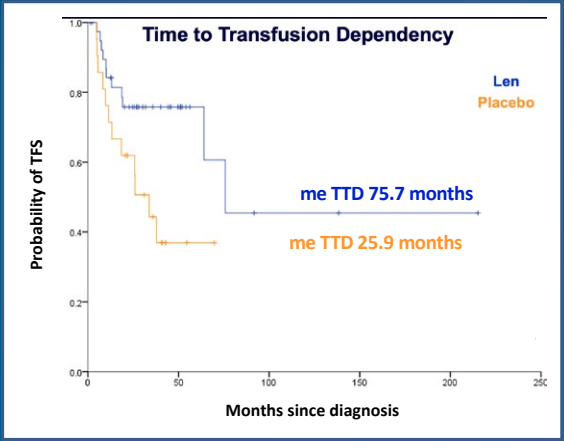
Dr. Shammo: The Sintra-Rev trial is practically designed because a lot of my patients who have MDS with del 5 would be denied lenalidomide until they are transfusion dependent. I don't think that that is a reasonable assumption, because someone who may have a hemoglobin of 9.5 would definitely benefit from a disease-modifying agent and perhaps improvement of the hemoglobin.

So, this trial is a phase 3 double-blind, randomized, placebo-controlled multicenter study taking patients who have a diagnosis of low or INT-1 disease, they're not necessarily transfusion dependent, their hemoglobin could be below 12 grams and have a diagnosis of del 5q, and exploring the notion of earlier versus late treatment. So randomizing patients to 5 milligrams daily versus placebo and then following those patients for about 2 years and then for another 2 years.

The primary endpoint in this situation is time to transfusion dependency, how long does it take those patients to ultimately develop transfusion dependence. And course, there are many other secondary time points included in that, cytogenetic response. For patients who may have *TP53* from the get go, what happens to this leukemia evolution, etc.

Sintra-Rev Trial: Efficacy and Safety Profiles of Early Intervention

Early treatment in anemic non-TD patients



Patient characteristics:

- 82% females; median age 72 years (range 37-89); median time since diagnosis 3.6 months; median Hb at inclusion 9.8 g/dL (7.1-11.7 g/dL); and 93% of patients had isolated del(5q)

Lenalidomide versus placebo:

- Low doses delay TTD (75.7 vs 25.9 months; $P = .021$)
- ER in 72.5% vs 0.0% of patients ($P < .001$)
- Cytogenetic responses in 80% vs 4.8% ($P < .001$)

Tolerability:

- The number of adverse events reported within both treatment arms were not significantly different
- Lenalidomide had a manageable safety profile

Author's conclusions:

- Low dose lenalidomide (5 mg) in anemic non-TD low-risk MDS del(5q) patients prolongs the period of time to TD, improves Hb levels and induces clonal responses

ER, erythroid response; Hb, hemoglobin; Len, lenalidomide; MDS, myelodysplastic syndrome; TD, transfusion dependent; TTD, time to transfusion dependence; ER, erythroid response.
Cadenas et al. *Blood* 2020;136(suppl 1):28-29.

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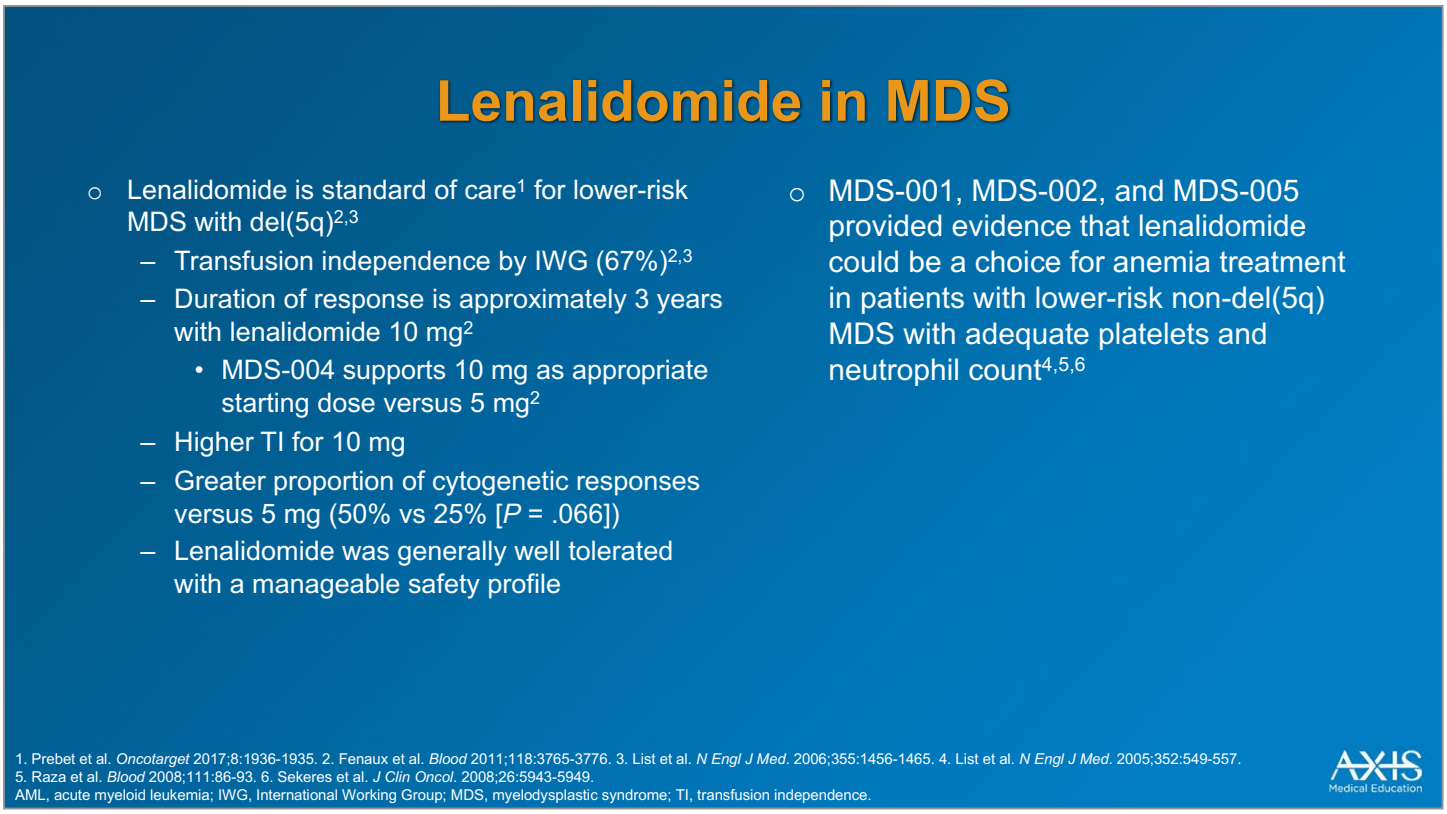
What's interesting is to see that the median hemoglobin at inclusion for those patients vary, anywhere 7 to 11.7 grams. The median was about 9.8. So, we're not talking about people who have very high hemoglobin; some were definitely anemic at the time of inclusion. What was interesting is to see that the time to transfusion dependence was triple that in people treated versus those that weren't.

It's an interesting concept in that if you treated patients earlier, you would delay their transition dependency. It's something that might resonate hugely with patients—you don't want to get to the point where you are sitting in the infusion suite receiving blood over 2 and 3 hours or what have you and would impact somebody's quality of life.

If I'm a patient, I would be in favor of getting treated so that I don't end up with this outcome that is transfusion. That was statistically significant. The most biologically relevant piece to this is in what happens to leukemic evolution, what happens to subclones that come with this, or if someone has *TP53*, what is the impact of earlier treatment on that? That we don't have yet. So more to come.

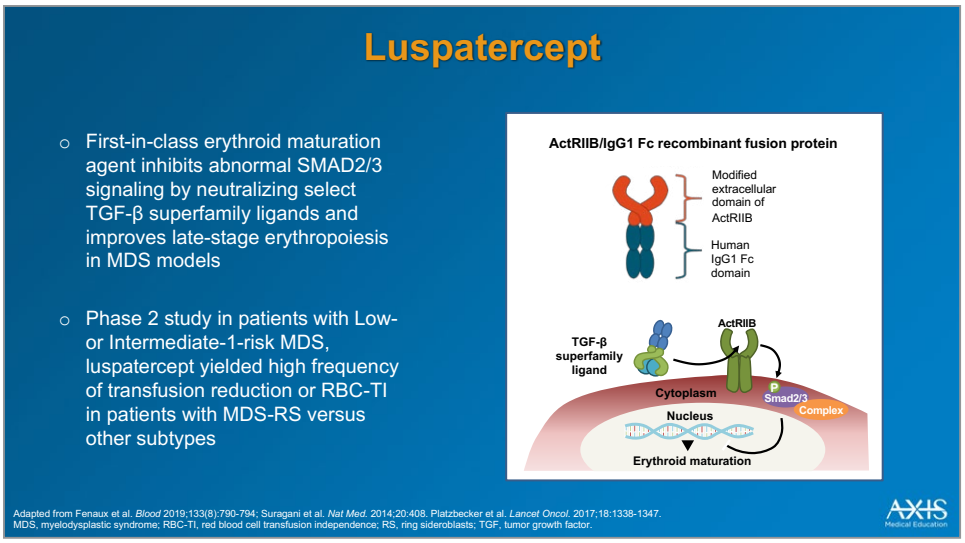


Dr. Komrokji: Absolutely, I think lenalidomide is very active in del 5q. It was really interesting to see how a lower dose only for 2 years produced that benefit, challenging, you know, our primary endpoints in lower risk MDS of always being the transfusion independency, but rather as we get more and more active therapies to go for, time to transfusion or free transfusion durations.

So, if patients got ESA, del 5q gets lenalidomide; if patients have MDS with ring sideroblasts nowadays, we have a treatment—luspatercept. This is the first drug approved in 10 years in MDS.

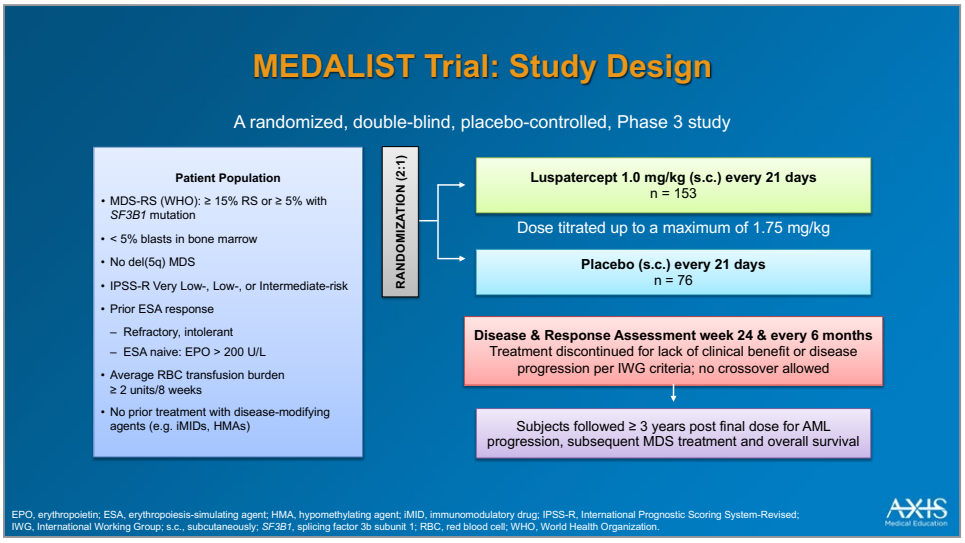
Michael, can you tell us a little bit about luspatercept, its mechanism of action? Summarizing a little bit also the clinical data and your experience using it?

Dr. Savona: Of course. I think the lower risk MDS has gotten confusing. It used to be—we had EPO and we had a couple of different ESAs to offer and then we had lenalidomide. And lenalidomide was largely in the del 5qs. Now we have luspatercept and a variety of new TGF beta ligand traps that are coming down the pike as potential treatments for low-risk MDS.



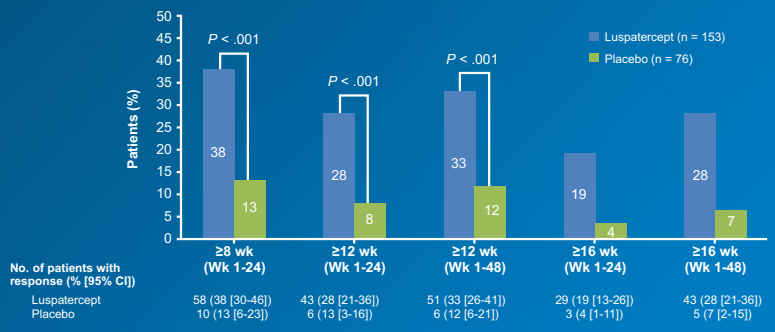
- Luspatercept and sotatercept were co-developed, and luspatercept was the one that was moved forward in phase 3 study and ultimately approved. This drug is not exactly a TGF beta ligand trap, but acts like one. It is IgG-1 and FC recombinant fusion protein, active in R2B and IgG-1 that traps, the TGF beta superfamily ligand, which is Smad2/3 signaling. Ultimately, it blocks the negative regulator of late-stage erythropoiesis. By this double-negative locking the inhibitor of late-stage erythropoiesis, you get later erythro differentiation and production of red cells.

  It's important to know that luspatercept was first tested in a variety of low-risk and intermediate-risk MDS patients and had a reduction in transfusions and transfusion independence across the board. In the phase 3 study, the patients with ring sideroblasts are the ones studied.



- So, the phase 3 MEDALIST trial basically was a 2 to 1 study that randomized patients 2 to 1 to placebo or luspatercept infusion every 21 days. It was for patients with ring sideroblasts or with at least 5% ring sideroblasts and *SF3B1*, or 15% ring sideroblasts.

MEDALIST: Red Cell Transfusion Independence with Luspatercept in MDS-RS



MDS-RS, myelodysplastic syndrome with ring sideroblasts.
Fenaux et al. *N Engl J Med.* 2020;382:140-151.

- This was a positive study across the board, revealing that improvement in transfusion independence, revealing a hematologic improvement - a bump in hemoglobin in patients who did respond.

MEDALIST: RBC-TI ≥8 Weeks

RBC-TI ≥ 8 Weeks Over the Entire Treatment Period	Luspatercept (n = 153)	Placebo (n = 76)	Luspatercept Minus Placebo	
			OR (95%CI)*	*P**
Average baseline RBC transfusion requirement, n/N (%)				
≥ 6 U/8 weeks	14/66 (21.2)	2/33 (6.1)	4.17 (0.89–19.60)	.0547
≥ 4 to < 6 U/8 weeks	20/41 (48.8)	2/23 (8.7)	10.00 (2.07-48.28)	.0013
< 4 U/8 weeks	39/46 (84.8)	8/20 (40.0)	8.36 (2.51-27.83)	.0002

More luspatercept-treated patients achieved RBC-TI ≥ 8 weeks over the entire treatment period compared with those receiving placebo, regardless of baseline transfusion burden

*Determined using a Cochran-Mantel-Haenszel test.
OR, overall response; RBC-TI, red blood cell transfusion independence.
Fenaux et al. *N Engl J Med.* 2020;382:140-151.

MEDALIST: Safety

TEAE of any grade, %	Luspatercept (n = 153)	Placebo (n = 76)
Fatigue	27	13
Diarrhea	22	9
Asthenia	20	12
Nausea*	20	8
Dizziness	20	5
Back pain*	19	7
Cough	18	13
Peripheral edema	16	17
Headache	16	7
Dyspnea*	15	7
Bronchitis	11	1
Constipation	11	9
UTI	11	5
Injury, poisoning, or procedural complication: fall	10	12

TEAE, %	Luspatercept (n = 153)	Placebo (n = 76)
Patients with ≥ 1 TEAE	98.0	92.1
≥ 1 serious TEAE	31.4	30.3
≥ 1 Grade 3/4 TEAE	42.5	44.7
TEAEs leading to death	3.3	5.3
TEAE causing discontinuation	8.5	7.0

- 4 patients progressed to AML
  - 3 in luspatercept arm, 1 in placebo arm
- Most common grade 3/4 TEAEs in luspatercept arm:
  - Anemia (6.5%); fatigue (4.6%); fall (4.6%)
- Any grade ≥3 AE suspected as being related to treatment resulted in a dose delay until the AE was resolved to grade ≤1 or baseline
  - Treatment was then resumed, but with a 25% dose reduction
  - Treatment was discontinued if a patient had ≥2 dose reductions due to suspected related AEs
- FDA-approved with a warning for hypertension
  - Monitor BP; initiate anti-hypertensive treatment if necessary

*At least one serious adverse event occurred: nausea (in one patient receiving luspatercept), back pain (in three receiving luspatercept), dyspnea (in one receiving luspatercept), bronchitis (in one receiving luspatercept), and urinary tract infection (in one receiving placebo).
AML, acute myeloid leukemia; BP, blood pressure; TEAE, treatment-emergent adverse event; UTI, urinary tract infection.
Fenaux et al. *N Engl J Med.* 2020;382:140-151.

AXIS Medical Education

It's, for the most part, really well tolerated. About 40% of the patients that were on the study developed profound fatigue. Most of that went away if they were able to stay on the treatment. That's pretty similar to the experience I've had in the clinic. I have had patients who've had so much fatigue, they refuse to stay on the drug. But if I can get them through a cycle or two, I usually don't see too much fatigue. It's a little strange, reports of neuropathy pleural effusions, and diarrhea, asthenia in the clinical trial were higher than what we expect in the placebo side. I haven't seen a lot of that myself, but I've seen a little of it. The drug definitely adds to our arsenal.

When can you use luspatercept beyond ring sideroblasts? We use it in MDS with ring sideroblasts, we use it and overlap MDS MPN, with ring sideroblasts in thrombocytosis. But, off label should we be using it in lower risk MDS? That's being explored on the COMMANDS trial, which will look at all other types of low-risk MDS that might benefit. What we're going to find is that there's a place for this drug and drugs like it, in lower risk MDS. The new challenge will be sequencing them properly with other things we have available like ESAs and lenalidomide.

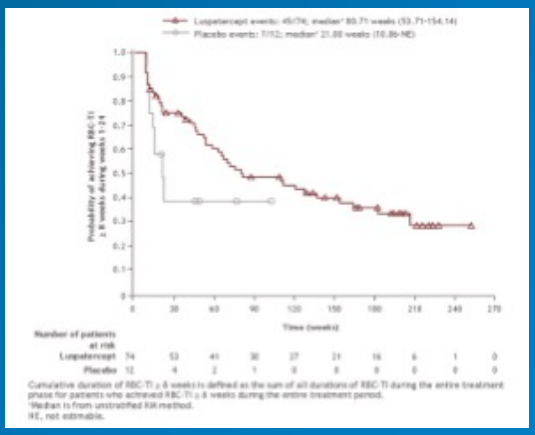
Dr. Komrokji: Absolutely. So obviously, luspatercept is currently approved for patients with ring sideroblasts. In the study, the transfusion burden was the most important predictor of response, which we see also in real life. The key clinical messages is this is an injection every 3 weeks, one needs to escalate the dose, especially among patients that are heavily transfusion dependent, that was devised, using 6 units every 8 weeks, and giving the drug some time to assess if there's a response.

MEDALIST: Long-Term Response

RBC-TI ≥ 8 weeks and ≥ 16 weeks during the entire treatment period

	Luspatercept (n = 153)	Placebo (n = 76)
Achievement of RBC-T1 ≥ 8 weeks		
Patient, n (%) 95% CI	74 (48.4) 40.22-56.58	12 (15.8) 8.43-25.96
Common risk difference in response rate, % (95% CI)	32.95 (22.07-43.83)	
OR (95% CI)	6.12 (2.91-12.87)	
P	<.0001	
Achievement of RBC-T1 ≥ 16 weeks		
Patient, n (%) 95% CI	48 (31.4) 24.9-39.39	6 (7.9) 2.95-16.40
Common risk difference in response rate, % (95% CI)	23.37 (14.05-32.68)	
OR (95% CI)	5.90 (2.34-14.90)	
P	<.0001	

Cumulative duration of RBC-TI ≥ 8 weeks during the entire treatment period for patients who achieved RBC-TI ≥ 8 weeks during the entire treatment period



- Patients receiving luspatercept experienced an extended period of RBC-TI compared with those randomized to placebo throughout the entire treatment period
- Patients randomized to luspatercept who achieved RBC-TI ≥8 weeks during the entire treatment period experienced durable clinical responses, with a median cumulative duration of RBC-TI response of approximately 20 months

OR, overall response; RBC-TI, red blood cell transfusion independence.
Fenaux et al. *J Clin Oncol*. 2022;40(suppl 16):7056.

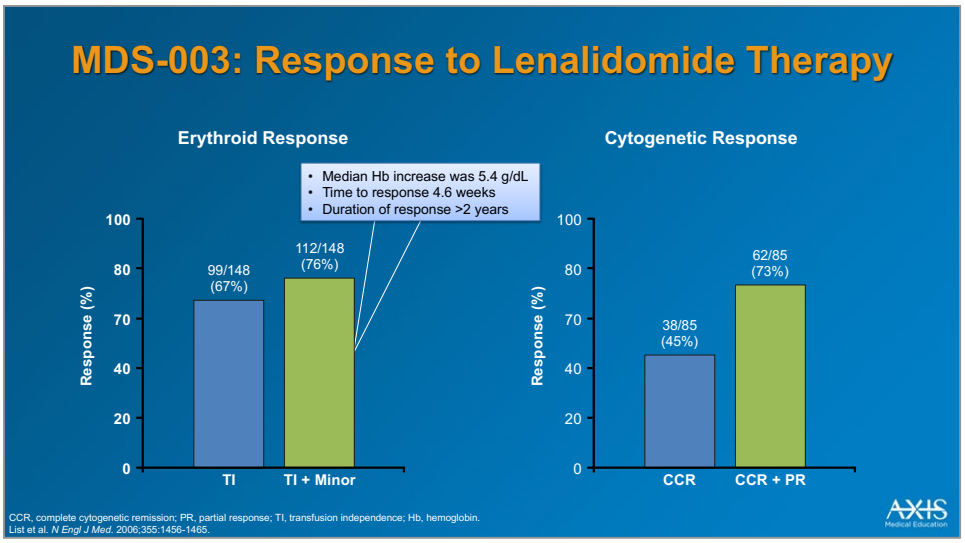
AXIS Medical Education

So, at past ASCO and the EHA meetings, we heard updates on the luspatercept with the longer-term use, where almost 40% plus of the patients achieved the endpoint. When you look at the transfusion independency, the duration can exceed a year with luspatercept use. There were cases where patients needed blood transfusion occasionally, but with the adjustment of the dose, the median duration is around 80 weeks with luspatercept. So, this is reflective of the longer-term data.

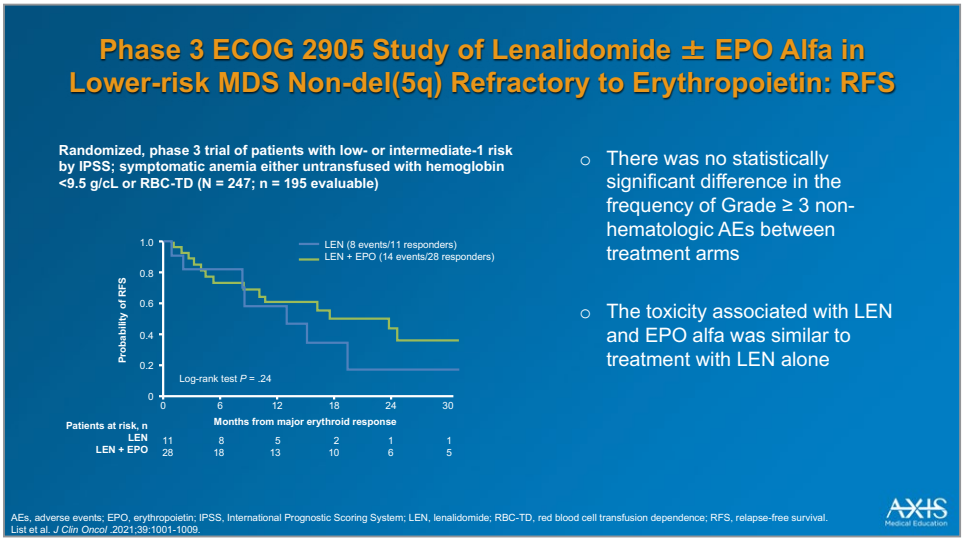
The key message again is the appropriate identification of patients, maybe introducing the treatment earlier because the most predictive of response is the magnitude of transfusion or the transfusion burden, which could reflect the biology but also an opportunity to intervene earlier and the maximization of the dose. Many of the patients that are transfusion dependent, especially if it's heavy transfusion dependency, will need to go to the 1.75 milligram per kilogram dose, which is the highest dose. That was also published by Dr. Uwe Platzbecker, looking at that majority of the patients needed the increase in dosing if they were heavily transfusion dependent.

Fatigue is a phenomenon we see in the first couple of months, some GI toxicity, edema. But all over, less than 5% of the patients discontinue. As you alluded, the research side is extending beyond the MDS ring sideroblasts. The COMMANDS study is looking at comparing it to ESA upfront. There are studies looking at combinations with lenalidomide with ESA and so forth.

So, we covered upfront ESA, deletion 5q get lenalidomide. MDS with ring sideroblasts get luspatercept. Then you get to the rest, garden variety of the lower risk, non-del 5, non-ring sideroblast. We have a few options that, Jamile, can you tell us about lenalidomide use in non-del 5q in that group?



Dr. Shammo: Yes. As I'm sure everyone knows, this has already been explored with the MDS-003, and the response to lenalidomide in the 002 study, which evaluated the same drug in the non-del 5 population, was more modest. One of 4 patients attained transfusion independence. So, it is possible to achieve up to perhaps 40% erythroid response.

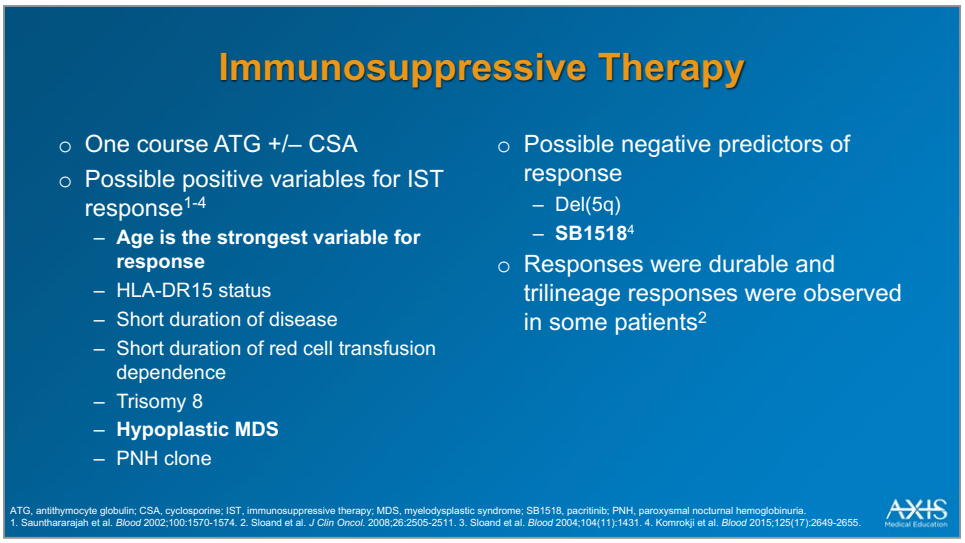


There was an ECOG study. Dr. List I believe reported on that, there was a European trial that combined EPO with lenalidomide in the non-del 5 and demonstrated that the combination actually performs better than lenalidomide alone.

So I think it's certainly reasonable to consider the combination in someone who may have preserved hematological parameters other than the hemoglobin because clearly that's why you are utilizing it to improve the anemia. So in someone who may have reserved platelet count, neutrophil count, I feel comfortable using the combination to achieve potential hematological improvement or transfusion independence.

Dr. Komrokji: Absolutely. It's reasonable to use it in patients that are purely anemic. If patients have concomitant thrombocytopenia, neutropenia, even if they're not severe, probably that group is not going to respond to lenalidomide in the non-del 5q setting particularly.

Now, when we see patients having some concomitant thrombocytopenia and neutropenia, options become limited. Again, not necessarily that those are severe or needing intervention, but their presence could affect our choice of therapy.



I always like to think of immunosuppressive therapy in younger patients. This is always underutilized option. It's one of the few that can get your trilineage responses. If somebody's young, responses can exceed 40% or 50%. In our patients, less than 60, particularly if they have pancytopenias, we tend to think of ATG.

But in reality for the majority of the rest of the patients if they have concomitant thrombocytopenia or neutropenia, our mainstay, or after failure of the other therapies we discussed, still remains using hypomethylating agents, which is available in the USA, interestingly not out of the USA.

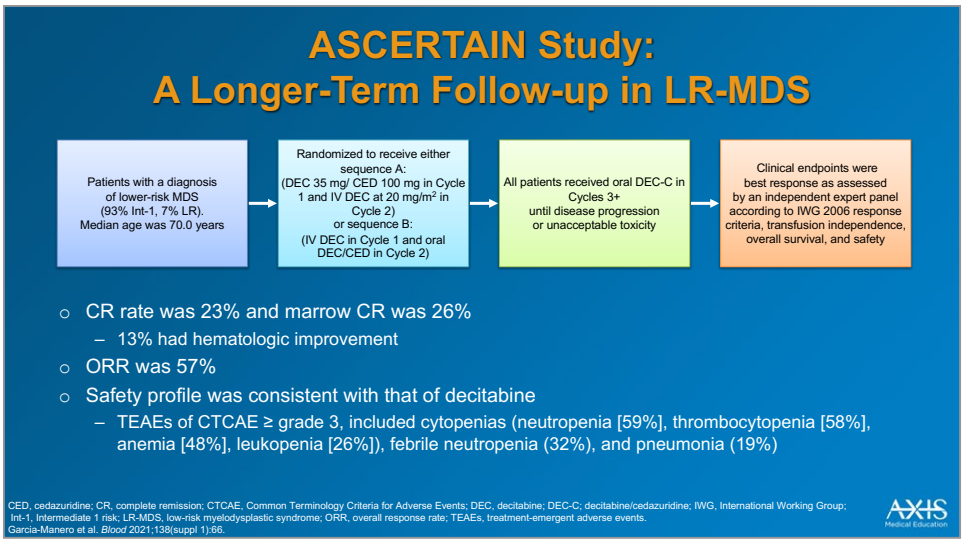
Faculty Panel Discussion

So Michael, maybe you can walk us a bit through use of hypomethylating agents, also telling us a little bit more about the oral formulations. You've been on the front end, developing those presented data on oral hypomethylating agents. Walk us through hypomethylating agents used in lower risk MDS.

Dr. Savona: Sure. DNA methyltransferase inhibitors, or hypomethylating agents, are really the backbone of therapy for MDS since 2001. The AZA-001 study, which led to the approval of azacitidine in patients with MDS and CMML. It's clear that patients need disease modification when they have increased blasts. It's always trickier and lower risk disease. And the way I like to think about this, EPO and luspatercept, we're not sure yet, but we think luspatercept and EPO are both non–disease-modifying, that is, it doesn't change the trajectory of the clonal disease, it's more of a symptom control, phenotype improvement. That remains to be determined yet on luspatercept, but we think that's the case. Lenalidomide has some disease-modifying activity.

In patients who have non-del 5q disease, if you have bilineage cytopenias that are getting the patient into trouble, that can still be low risk by IPSS-R or by IPSS-M, if they don't have a lot of mutations on their NGS. They may be good candidates for treatment with the DNMTi and ASTX727 or DEC-C, it has a few names, is the combination of decitabine at the standard dose in an oral form given together with cedazuridine, which is an cytidine deaminase inhibitor which prohibits the drug from being metabolized on first pass in the gut and the liver, leading to pharmacokinetic equivalence to the parenteral dose of decitabine. This is only available for decitabine right now in the United States and Canada and soon Europe, but the same idea is being tested with oral azacitidine plus cedazuridine, and that's currently in phase 1 study.

The use of an oral inhibitor opens up the door to easier combination. And, you know at lower doses—metronomic dosing of lower risk MDS, which is certainly been explored for a long time .We know there's a dose-dependent effect on hypomethylation with DNMTIs, and the idea that you could have a lower risk disease and maybe cause less cytotoxicity and less disease-associated cytopenias, but may get more hypomethylation and reversal of genetic pathology and improvement in counts is something that people are wanting to explore.



The ASCERTAIN study in which we studied patients who were intermediate 1, intermediate 2, and high risk, with the ASTX727 DEC-C combination included quite a few patients with intermediate 1 disease, and a very small number of lower risk patients as the idea was to follow the label for decitabine for inclusion criteria.

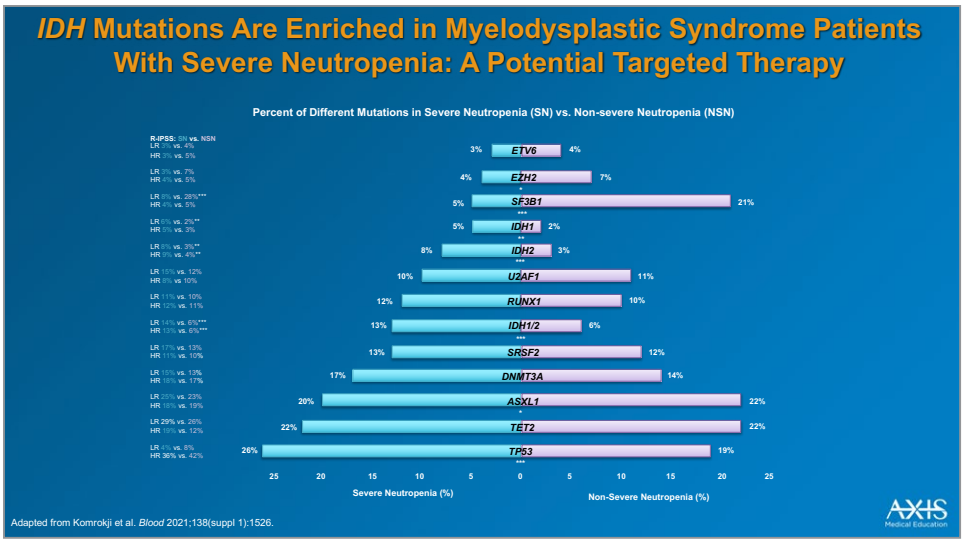
But, this drug, and any of the DNA methyltransferase inhibitors, could be used when patients get into trouble with more than just anemia. Anemia and thrombocytopenia, anemia and neutropenia and, of course, neutropenia risk is a function of how deep the neutropenia is, and/or don't respond to growth factors. I typically don't use a lot of growth factors in patients who have any kind of proliferative component to their disease, because there is a theoretic risk there of transformation. But patients who have no proliferative or very low proliferative risk, single mutated *SF3B1*, less than 5% blasts, who develop a subsequent neutropenia, there might be an opportunity to get a benefit out of growth factors. But for the others, I like the idea of being able to use DNA methyltransferase inhibitors. An important message for practitioners is to understand that the label for decitabine and DEC-C is 5 days, the 20 milligrams per meter squared over the oral equivalent, cedazuridine. Or the azacitidine over 7 days, 75 milligrams per meter squared. We don't have an oral equivalent yet for the parenteral azacitidine. But, either of these, the parenteral or the oral, can be dosed-down. We often dose-down patients from 5 days of ASTX727 or DEC-C to 4 days or even 3 days and space out their treatment by weeks.

There aren't a lot of patients that remain on a standard 5 days of treatment, every month, every 28 days for a long time. Most people do need dose adjustments. And patients with higher blasts, you want to make sure that you're appropriately treating the patient to disease reduced prior to transplant, lower risk patients, we need to be even more sensitive and careful that we don't put them at higher risk of neutropenic fever and an earlier death by overtrading and causing deeper cytopenias.

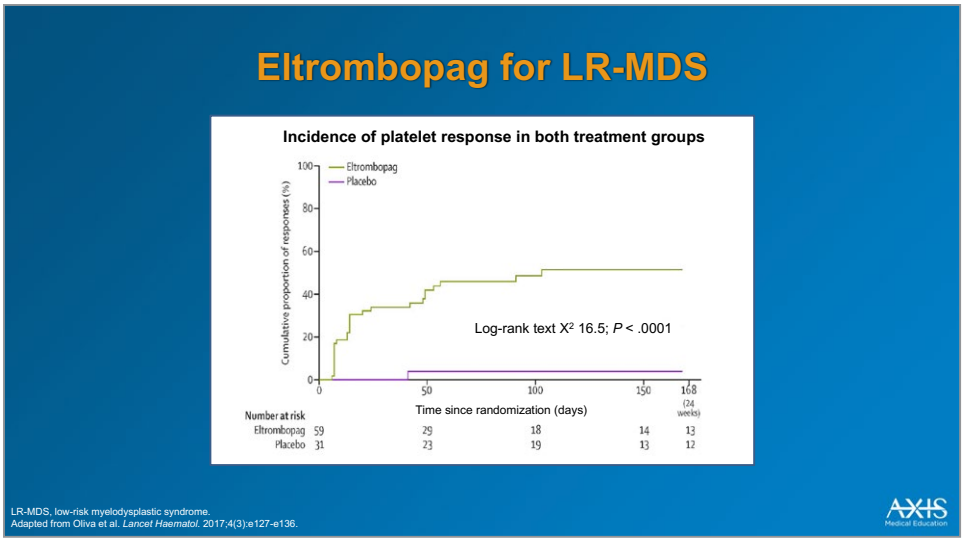
Dr. Komrokji: Absolutely. I think the appeal of the oral hypomethylating agents is the ease for the patients. There are some issues sometimes with a copayment in real life. But I think we are testing those in attenuated dosing in lower risk. In standard requires the monitoring at the beginning but is definitely a step forward. Hopefully we'll have more and more of a total oral therapy for our MDS patients.

You alluded to the neutropenia and thrombocytopenia. As we talked at the beginning, there is only a small subset of lower risk MDS patients that will have either isolated neutropenia or isolated thrombocytopenia. In our practice, we share your concerns about liberal use of G-CSF. There had been no studies to show survival advantage.

So, if patients have isolated neutropenia without recurrent infections, we observe. Even with hypomethylating agents, the responses are probably in the range of 20% to 25%.



- There had been some interest recently looking at IDH inhibitors that seems to be enriched in patients with neutropenia. Similar with thrombocytopenia, hypomethylating agents are probably the only active agents. Younger patients can get ATG cyclosporine.



- There is some data on eltrombopag single agent use or romiplostim in patients with isolated thrombocytopenia. And with a long follow-up and reasonable responses.

Faculty Panel Discussion

We are also having newer and exciting drugs being tested in lower risk MDS. Jamile, tell us a little bit about imetelstat, roxadustat, IDH inhibitors in lower risk MDS?

Dr. Shammo: It's really interesting. Suddenly, we have this plethora of novel agents that you can explore. The data look really interesting. For imetelstat, for example, they're looking at the exact same population that would not be responders to ESAs—either have failed it or have an EPO level above 500. The transfusion independence rate of about 40% is rather remarkable. But, we have to wait for the phase 3 clinical trial data. So, it's being explored also in MPNs, and so not just in MDS, so safety and additional data will be really needed.

Roxadustat is a hypoxia-inducible factor inhibitor, which basically promotes the production of erythropoietin, and is already approved in China for the treatment of renal failure, which is what we use here, not necessarily roxadustat, but ESAs in people who have kidney failure, is another agent that is being explored for the treatment of anemia in MDS.

You already mentioned eltrombopag, that's another agent that could be utilized.

All of a sudden, we have various novel agents that could be used. And we are awaiting results of many other phase 3 trials that will hopefully give us more agents to use in this heterogeneous and difficult-to-treat patient population.

Dr. Savona: I think heterogeneity speaks to some of the difficulty with drug development in MDS. We've had a lot of very promising phase 1 and phase 2 data with novel agents, the APR 246, pevonedistat. And you know, you go to phase 3 study, and these things don't seem to pan out. I tend to believe that this is likely a function of patient selection that we're missing. It probably is a subset of MDS patients.

As both of you have illustrated so well, today, this is a very heterogeneous disease. The idea that you can develop one drug to treat all patients with disease is a little bit naive and banking on the experience we've had with azanucleosides, where 60% of patients get some response and a quarter of them get complete response. Well, that's better than nothing across the board, but we really have to do better.

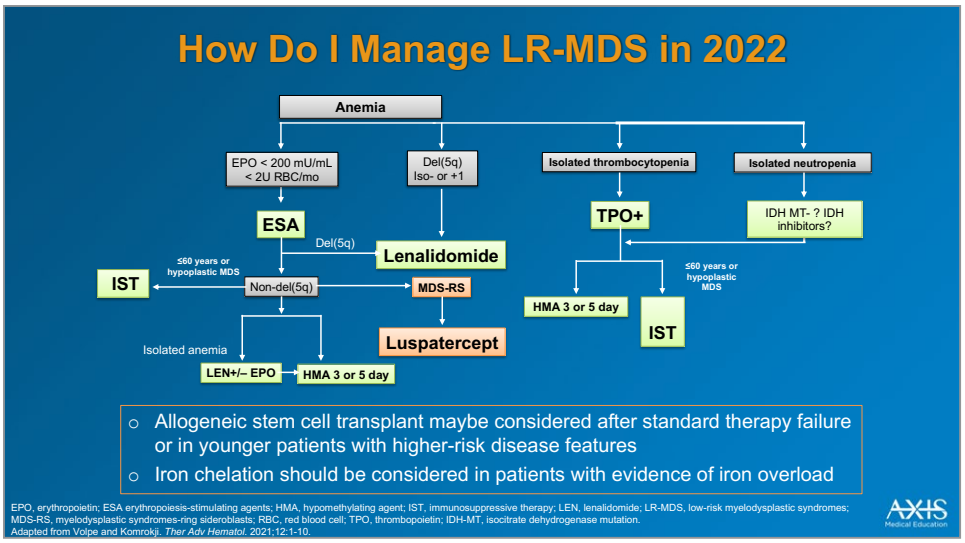
You mentioned IDH inhibitors, Rami. If you have an *IDH* mutation MDS, by all means, together with DNMTis is a good combination. It's just so rare in MDS. And then when you see them, they're almost always a function of a pre-leukemic state approach, because they're a proliferative gene. I find that IDH inhibitors are not so useful in MDS, because you just don't have a lot of those patients before they have AML.

But, in patients with transforming disease or those rare patients you get, it's a fine agent used in combination with azanucleosides. The use of venetoclax in these patients is something else that will be explored, just like that's moved from AML toward MDS in other high-blasts MDS. In lower risk disease, that probably has less of a role.

Dr. Komrokji: Absolutely. I was alluding more to the severe neutropenia patients. We presented some data looking at those patients that actually have higher rate of the *IDH* mutations. But your point is well taken, typically associated with a higher risk, like 5%, 10%. But when you look at the severe neutropenia patients, isolated neutropenia, those IDH1, IDH2 can be enriched, so it could be a potential target.

The French group presented data on both IDH1 and IDH2 in MDS, three separate cohorts, upfront higher risk, HMA failure higher rates, but there was a cohort after ESA failure in the lower risk, and again, showing activity.

To your point, all of this is pointing exactly to what you said. It's so naive to think of treating all lower risk with the same. with things like ESA, HMA, they may have universal mechanism of action, but we really have to go down and know the substance of the disease. I think ineffective hematopoiesis mechanism is different among those groups. And we should target that.



- It's very clear from our discussion today that the evolution of our understanding of the disease, the importance of molecular data, spending time on risk stratification, and now even the landscape for lower risk and 2022 have several options that are tailored based on the disease. So, deletion 5q get lenalidomide, MDS with ring sideroblasts luspatercept, hypomethylating agents for patients with concomitant cytopenias or higher risk feature, immunosuppressive therapy for younger patients. There may be an oral for TPO stimulants and isolated thrombocytopenia, etc. that's where we are going to divide patients into homogeneous groups based on the underlying biology of the ineffective hematopoiesis and target that.

Always it's a pleasure talking to you. And it's always a learning experience for me. Any final comments, Michael or Jamile?

Dr. Savona: This has been very enjoyable, Rami. I appreciate the opportunity. I agree. I always learn from both of you. To me, the main take-home points for low-risk MDS would be that, number one, there's myriad choices. We have a lot more available for low-risk MDS. And number two, it's a lot more complicated because the disease is very heterogeneous. And then, allogeneic stem cell transplant people say, 'Oh, low-risk disease, you don't need stem cell transplant.' I'd be careful with that because a lot of patients with low-risk disease at diagnosis become refractory to all this low-risk treatment and they're still only 60 years old. And they will ultimately succumb to iron overload and from transfusions, they have low quality of life; stem cell transplant should be always considered in those situations.

Dr. Komrokji: Absolutely. Thank you for bringing that up. Because it was on my mind to bring that there is room for allogeneic stem cell transplant after failure of current therapies, younger patients, higher risk disease features as we incorporate more of those molecule-based models. I think your point is very well taken.

Jamile, any final thoughts?

Dr. Shammo: Thank you. Rami. This was a fantastic discussion. After years of taking care of MDS patients, low-risk MDS is emerging to be the most difficult group of patients to take care of—for me, anyway. Because for high-risk, we have more delineated, this is what you do. But for low-risk, it's becoming more like hairsplitting, what to do with this group of patients. But hopefully, it will be a little bit easier with more options to come.

Dr. Komrokji: Absolutely. I'd like to thank our audience for hanging around with us, listening to all those developments in lower risk MDS. Thank you for participating in this activity. And see you next time.

Dr. Shammo: Thank you.

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