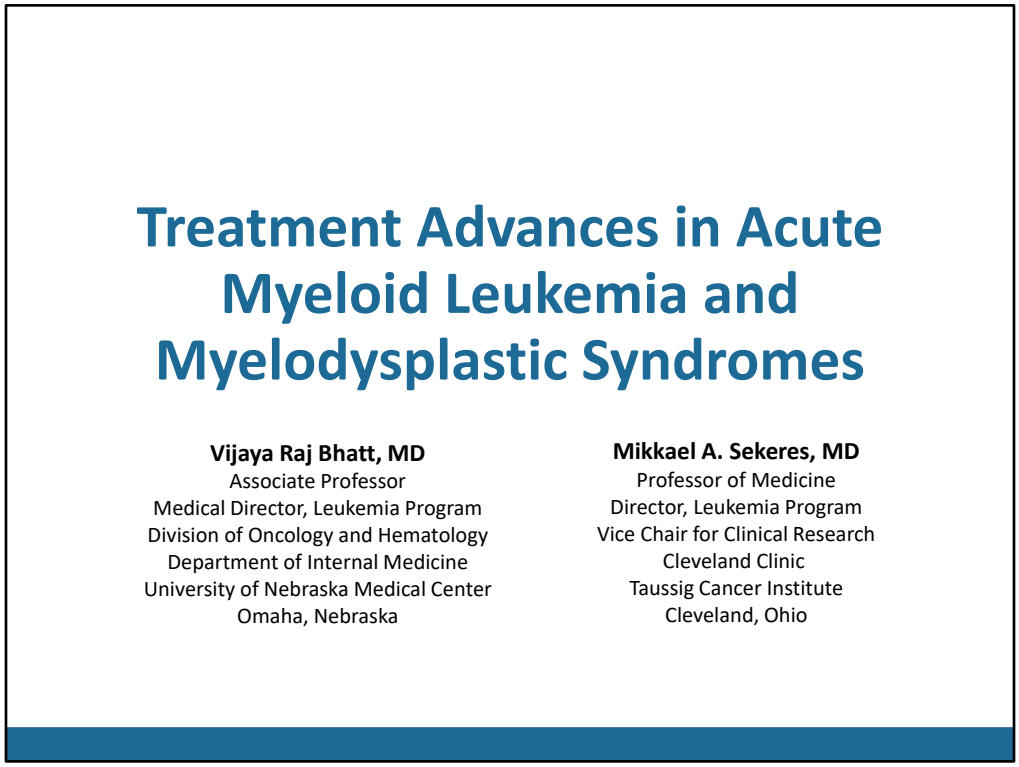
Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes



Hello, I'm Vijaya Bhatt, Medical Director of the Leukemia Program in the Division of Hematology-Oncology at the University of Nebraska Medical Center. Joining me today is Mikkael Sekeres, who is Vice Chair for Clinical Research and Director of Leukemia Program at the Cleveland Clinic.

Faculty Disclosures

- **Dr. Vijaya Bhatt** has received honoraria as a consultant from AbbVie Inc., Agios, Incyte Corporation, Omeros Corporation, Partnership for Health Analytic Research (funded by Jazz), Rigel Pharmaceuticals, Inc., and Takeda Oncology. He has received grant support related to research activities from AbbVie, Incyte, Jazz Pharmaceuticals plc, National Marrow Donor Program, Pfizer Inc., and Tolero Pharmaceuticals. He has also disclosed a financial relationship with Oncoceutics, Inc.
- **Dr. Mikkael Sekeres** has received honoraria related to formal advisory activities from Bristol-Myers Squibb Company and Celgene Corporation – A Bristol-Myers Squibb Company.

These are our disclosures.

Planning Committee Disclosures

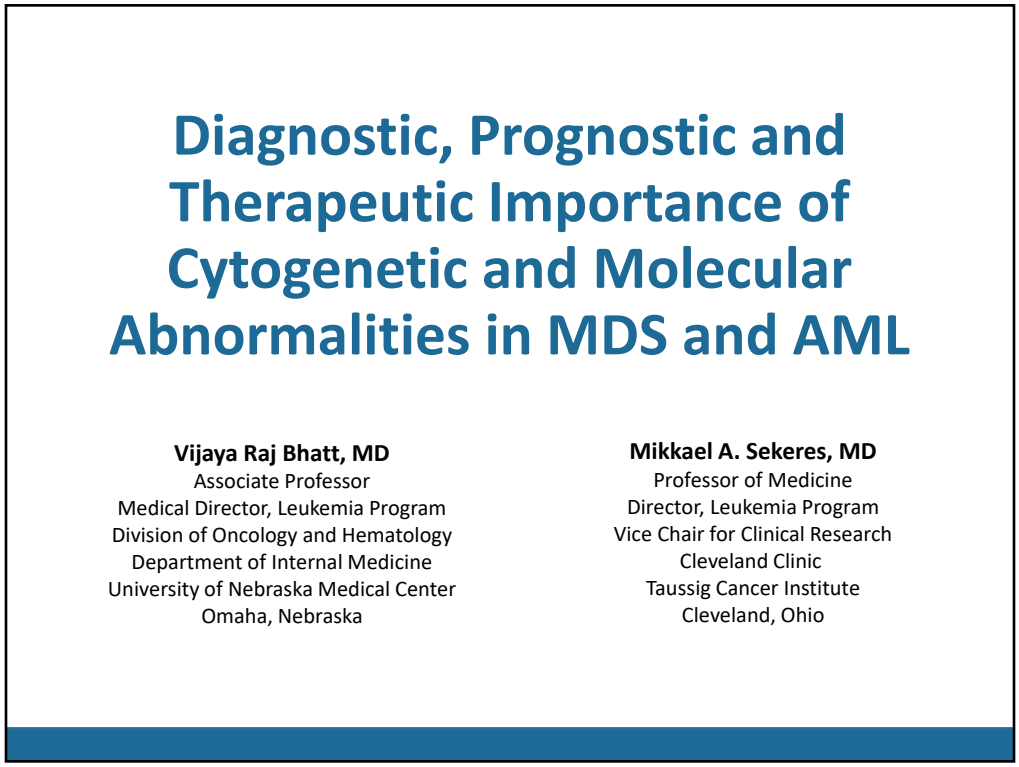
- The individuals listed below from MediCom Worldwide, Inc. reported the following for this activity: Joan Meyer, RN, MHA, Executive Director, Isabelle Vacher, Vice President of Educational Strategy, Wilma Guerra, Program Director, and Andrea Mathis, Project Manager, have no relevant financial relationships
- The individuals listed below from the University of Nebraska Medical Center, Center for Continuing Education and College of Nursing Continuing Education (UNMC) reported the following for this activity: Brenda Ram, CMP, CHCP, Director, Educational Programs, Heidi Keeler, PhD, RN, Director, UNMC College of Nursing Continuing Nursing Education have no relevant financial relationships

These are the disclosures of the planning committee.

Learning Objectives

- Apply updated recommendations for diagnostic and prognostic evaluation of AML and MDS in clinical practice, including optimal use of cytogenetic and molecular testing
- Incorporate new and emerging therapies into the treatment paradigm to provide optimal care for patients with newly diagnosed or relapsed/refractory AML
- Develop individualized treatment plans for patients with AML based on age, risk assessment, and other patient- or disease-related factors
- Manage anemia and other disease-related conditions in elderly patients with MDS

Here are the learning objectives for this presentation.



The recent approval of several novel drugs have improved our treatment options. However, it can be difficult for community hematologists to choose the optimal therapeutic plan for patients with acute myeloid leukemia or myelodysplastic syndrome. We know that treatment should be based on individual patient and disease factors, including the cytogenetic and mutational profiles of the disease.

During this discussion, we'll review the diagnostic and prognostic guidelines, as well as the treatment recommendations for acute myeloid leukemia and myelodysplastic syndrome. I'll begin with a review of the molecular testing recommended for AML.

AML Work-up: ASH-CAP 2017 and NCCN 2020

- Bone marrow core biopsy and aspirate analyses including immunophenotyping and cytochemistry
  - CD33: GO
- Cytogenetic analyses (karyotype + FISH)
- Molecular analyses

Arber DA, et al. *Arch Pathol Lab Med.* 2017;141:1342-1393.; National Comprehensive Cancer Network. NCCN Guidelines®. Acute myeloid leukemia. Version 3.2020 – December 23, 2019. Available at: www.nccn.irg. Accessed August 14, 2020.

The American Society of Hematology and College of American Pathologists 2017 guideline and the NCCN 2020 guidelines recommend the following testing for workup of a patient with acute myeloid leukemia. These include a bone marrow core biopsy and aspirate analysis, including immunophenotyping and cytochemistry for diagnostic purposes. Also, the presence and expression level of CD33 has relevance for use of gemtuzumab. Other recommended testing includes cytogenetic analysis and molecular analysis.

AML Work-up: NCCN 2020

- Molecular analyses (*ASXL1, c-KIT, FLT3* [*ITD* and *TKD*], *NPM1, CEBPA* (biallelic), *IDH1, IDH2, RUNX-1, TP53,* and other mutations)
- Multiplex gene panels and comprehensive NGS

National Comprehensive Cancer Network. NCCN Guidelines®. Acute myeloid leukemia. Version 3.2020 – December 23, 2019. Available at: www.nccn.irg. Accessed August 14, 2020.

The NCCN 2020 guideline recommends either a targeted set of molecular analysis, testing for mutations listed on the slide or a multiplex gene panel or comprehensive next-gen sequence.

AML Work-up: 2017 ELN and NCCN 2020

NCCN[1]

- To appropriately stratify available intensive therapy options, expedite test results of molecular and cytogenetic analyses

ELN[2]

- Results from cytogenetics: preferably within 5 to 7 days
- Results from *NPM1* and *FLT3* mutational screening within 48 to 72 hours, and results from additional molecular genetics within the first treatment cycle

1. National Comprehensive Cancer Network. NCCN Guidelines®. Acute myeloid leukemia. Version 3.2020 – December 23, 2019. Available at: www.nccn.irg. Accessed August 14, 2020. 2. Döhner H, et al. *Blood.* 2017;129(4):424-447.

The 2020 NCCN guideline recommends to expedite test results of molecular and cytogenetic analysis to appropriately stratify available intensive chemotherapy options. The 2017 ELN guideline recommends that results from cytogenetics be available within five to seven days and results from NPM1 and FLT3 mutation be available within 48 to 72 hours.

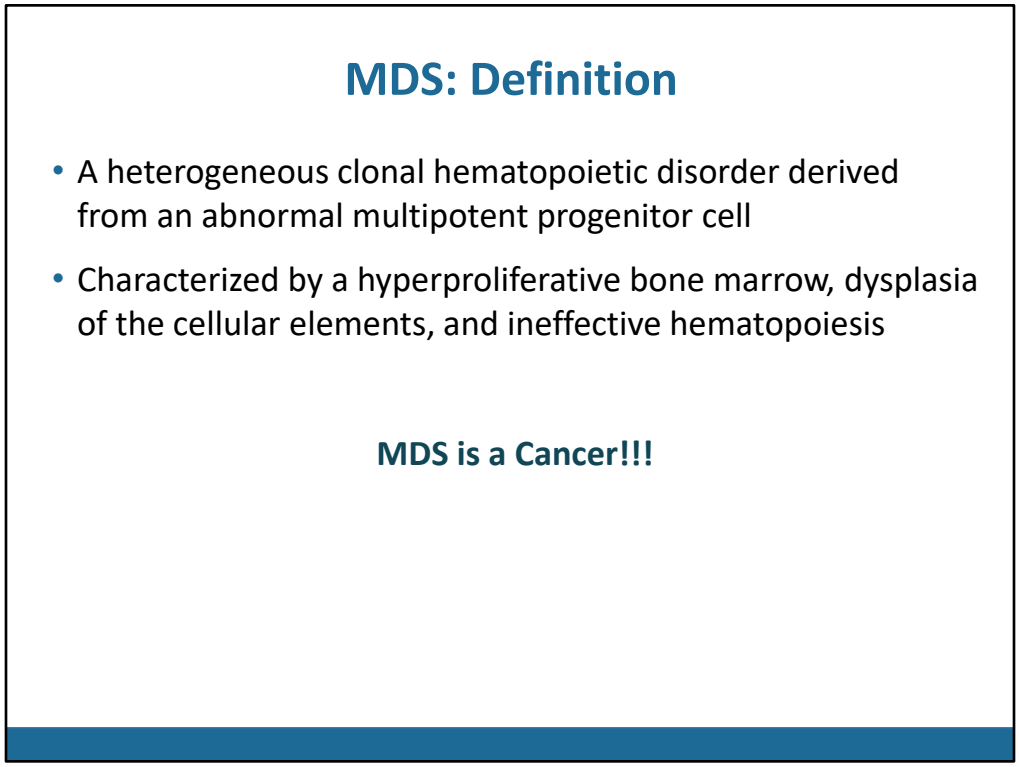
Implications of Genomic Testing

- 2016 WHO classification based on several recurrent cytogenetic abnormalities and mutations[1]
  - AML with mutated *NPM1* or *RUNX1*
  - AML MRC diagnosis based on cytogenetic changes
- 2017 ELN risk categorization[2]
  - *RUNX1, ASXL1,* or *TP53* mutation identify adverse risk
- Therapeutic implications
  - *IDH1, IDH2, FLT3* inhibitors
  - CPX 351 indication for AML MRC

1. Arber DA, et al. *Blood.* 2016;127(20):2391-2405. 2. Döhner H, et al. *Blood.* 2017;129(4):424-447.

What are the implications of genomic testing? The implications are multifold. The 2016 WHO classification of AML is based on several genetic and mutational abnormalities. The 2017 ELN guidelines risk categorization include not only cytogenetic but molecular mutations as well. The recent mutations added in the list include RUNX1, ASXL1 or TP53 mutation, all of which identify adverse-risk AML. Therapeutic implications include use of targeted agents in patients with IDH1, IDH2 or FLT3 mutation. Also, CPX-351 is indicated for a diagnosis of acute myeloid leukemia with myelodysplasia-related changes. The diagnosis of AML-MRC is based on presence of number of cytogenetic changes.

So now we'll focus on the cytogenetic profile and mutational landscape for MDS.



Mikkael Sekeres: Thank you, Dr. Bhatt.

Let's start off with the definition of myelodysplastic syndromes. It's often defined as a heterogeneous collection of clonal hematopoietic disorders derived from an abnormal multipotent progenitor cell characterized by a hyperproliferative bone marrow, dysplasia of the cellular elements, and ineffective myelopoiesis. Now, my dad, who was a newspaper reporter and editor, would have publicly flogged me for writing as convoluted a definition as that, and I'm embarrassed to say that I have written such definitions for review articles or textbook chapters, so let me try to simplify it. MDS is a cancer and it's a cancer that's actually quite similar to acute myeloid leukemia in older adults with a genetic profile that's similar and patients who present with dysplasias similar to AML with a background of dysplasia and profound cytopenias. And like any other type of cancer, it involves too many cells that are growing in the bone marrow, encroaching on the normal bone marrow cellular elements.

MDS: WHO Classification

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

Adapted from Arber DA, et al. *Blood.* 2016;127(20):2391-2405.

The World Health Organization classifies MDS in a way that basically recapitulates what we see clinically. Patients may come to our clinics with an isolated anemia, neutropenia, or thrombocytopenia. Those folks might have MDS with single lineage dysplasia, with or without ring sideroblasts. Ring sideroblasts are important because they're associated with a molecular abnormality typified by a spliceosome mutation, most commonly the SF3B1. Patients may also come to our clinics with multiple cytopenias, so anemia and neutropenia or anemia and thrombocytopenia, and these patients would be classified as having MDS with multilineage dysplasia, once again, with or without ring sideroblasts. Patients may have an isolated deletion 5q abnormality. This is important to identify therapeutically as we do have a drug available to treat this subtype of MDS. And then we have patients who might fall into what we would call higher-risk categories as they start to march towards having acute myeloid leukemia. In other words, those patients with excess blasts. MDS with excess blasts type 1 include those patients who have 5% to 9% blasts in the bone marrow, and excess blasts type 2 includes those patients with 10% to 19% blasts in the bone marrow.

MDS: IPSS-R Cytogenetics

Prognostic Subgroup	Abnormality			Overall Survival		
	Single	Double	Complex	n (%)	Median (months; 95% CI $P < .01$)	HR (95% CI)
Very good	del(11q) −Y	—	—	81 (2.9)	60.8 (50.3 to NR)	0.5 (0.3 to 0.7)+
Good (reference)	Normal del(5q) del(12p) del(20q)	Including del(5q)	—	1809 (65.7)	48.6 (44.6 to 54.3)	1.0 (0.8 to 1.3)
Intermediate	del(7q) +8 i(17q) +19 Any other Independent clones	Any other	—	529 (19.2)	26.0 (22.1 to 31.0)	1.6 (1.4 to 1.8)+
Poor	inv(3)/t(3q)/del(3q) −7	Including −7/del(7q)	3 abn.	148 (5.4)	15.8 (12.0-18.0)	2.6 (2.0 to 3.3)+
Very poor	—	—	> 3 abn.	187 (6.8)	5.9 (4.9 t0 6.9)	4.2 (3.4 to 5.3)+

Schanz J, et al. *J Clin Oncol.* 2012;30(8):820-829.

MDS is complicated genetically, and this risk classification schema that was first published by Julia Schanz, eight years ago, lumps patients with cytogenetic abnormalities into different risk groups. Those patients who have a deletion 11q or a minus Y abnormality would be in the very best risk group cytogenetically with a long median survival, whereas those patients who have either normal deletion 5q, deletion 20q or deletion 12p would be in the second-best category. On the other hand, patients who come in to see us with a paragraph long listing of cytogenetic abnormalities would be in a very poor-risk category, while those who have exactly three abnormalities or abnormalities of chromosome 7 or 3 would be in the penultimate bad-risk category with a median survival that's measured in less than a year and a half.

MDS: IPSS-R Classification

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

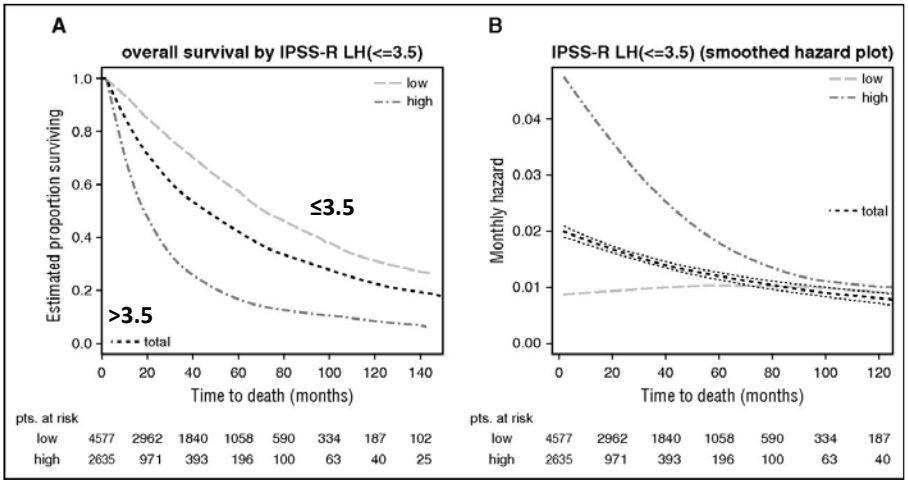
Prognostic Risk Categories/Scores

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

Greenberg PL, et al. *Blood.* 2012;120(12):2454-2465.

That cytogenetic risk classification schema is important to understand because it provided the backbone for the revised International Prognostic Scoring System classification or IPSS-R. This is essentially our default staging system for MDS. Patients who have a very poor cytogenetic risk category, those patients with a paragraph long listing of genetic abnormalities, actually get the highest score on this risk classification scheme, higher even than those patients who have 11% to 19% blasts. The system also gives different scores for degrees of anemia, degrees of thrombocytopenia, and an absolute neutrophil count cutoff. Using the schema and adding up the points, patients are placed into IPSS-R risk groups that range from very low with a median survival that approaches nine years to very high with a median survival that's less than one year.

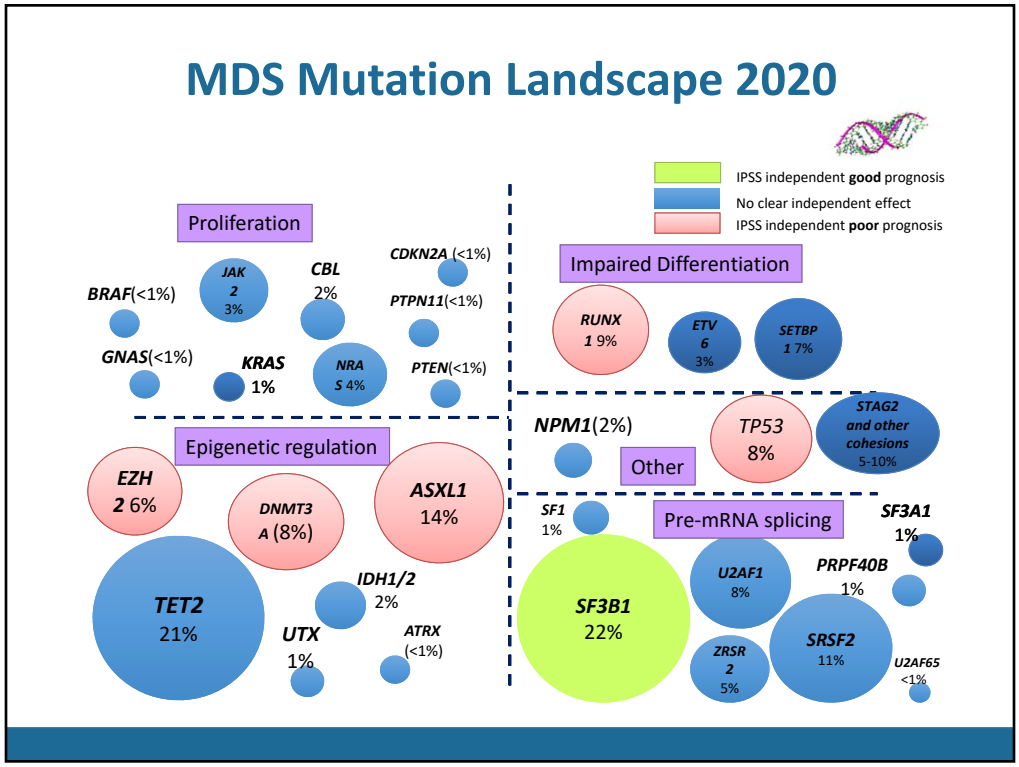
MDS: IPSS-R Classification



Pfeilstocker M, et al. *Blood*. 2016;128(7):902-910.

If you're trying to divide patients into those with lower-risk or higher-risk MDS, which we often do therapeutically, those patients with an IPSS-R score of 3.5 or lower fall into lower-risk categories, whereas those patients with a score that's over 3.5 fall into higher-risk categories.

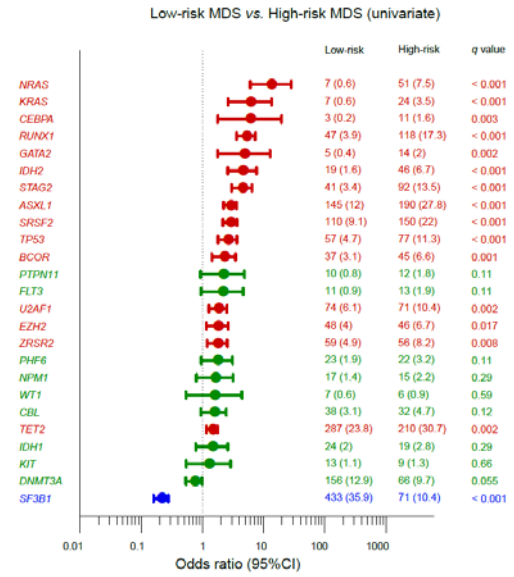
Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes



I mentioned before that MDS is genetically complicated, boy, is it really genetically complicated with a lot of molecular abnormalities that have been tied to MDS. This can roughly be divided into those molecular abnormalities that are proliferation signals, those that are involved in epigenetic regulation, those that are involved in impaired differentiation, and those involved in pre-mRNA splicing, in other words, the spliceosome mutations I refer to earlier that are often associated with ring sideroblasts. There's a final category that includes abnormalities such as TP53, which is a notorious poor-risk marker.

MDS: Mutation Risk

- Driver genes can be classified into molecular subtypes differentially associated with disease severity



Makishima H, et al. *Nat Genetics.* 2017;49(2):204-212.

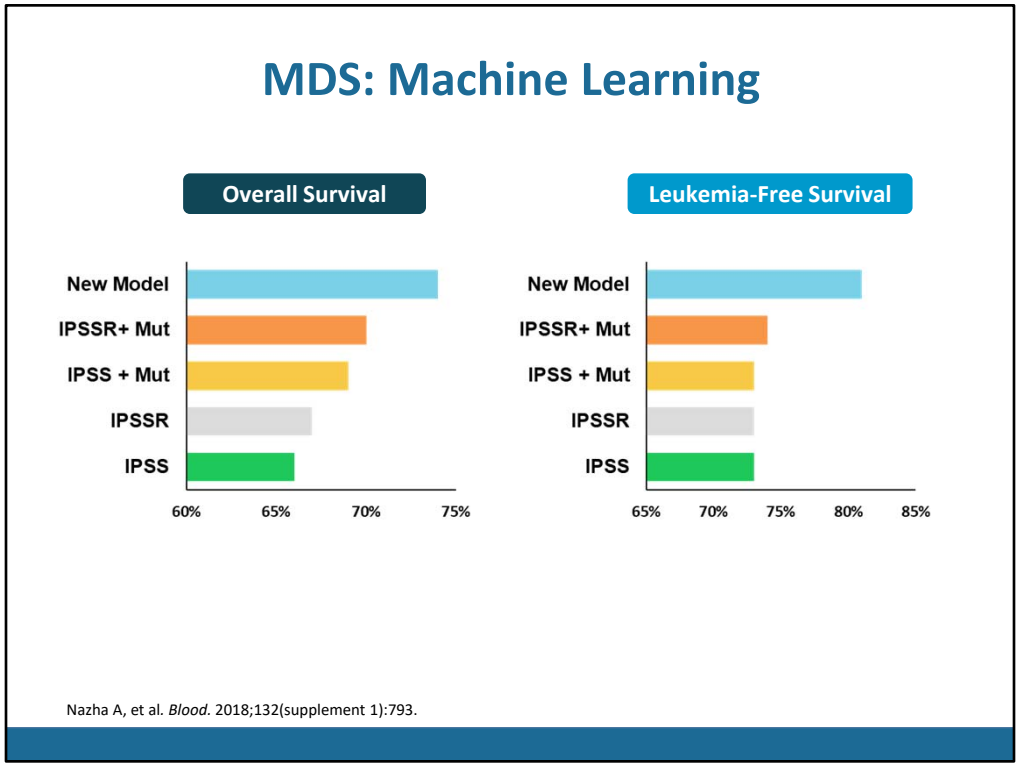
Now with all of these abnormalities, how do we keep straight which are the good risk, which are poor, and which are intermediate? I can make it very simple for you. There's only one good-risk molecular mutation and that's the SF3B1 mutation. Everything else is either intermediate or poor and you won't be surprised to hear that some of the poor-risk abnormalities such as RAS mutations, RUNX1, ASXL1, p53 are some of the same poorest mutations that you'll see in AML.

MDS: Machine Learning

Parameter	Training No. (%)/[range]	Validation No. (%)/[range]	*P Value*
Total	1471	831	
Median age, years	71 [19-99]	69 [4-93]	NS
Clinical Variables			
Median WBC, 10^9/L	4.2 [0.6-82.6]	4 [0.1-25.6]	NS
Median ANC, 10^9/L	2.1 [0-65.1]	2 [0-8.5]	NS
Median Hb, g/dL	9.9 [3.9-15.6]	10 [3.4-17.1]	NS
Median Plts, 10^9/L	120 [4-975]	117 [7-1280]	NS
Median BM blasts %	4 [0-19]	3 [0-19]	NS
2008 WHO Category			
RCMD/RCUD	578 (38)	350 (42)	NS
RARS	209 (11)	128 (15)	
RAEB-1/RAEB-2	573 (37)	302 (36)	
MDS-U	49 (9)	18 (2)	
MDS with del (5q)	62 (5)	33 (4)	

Nazha A, et al. *Blood.* 2018;132(supplement 1):793.

I hate to break it to you, but MDS is even more complicated than that. It turns out that some mutations can co-occur with other mutations, whereas others are mutually exclusive. There's also a hierarchy to mutations in the order in which many of these mutations appear. It gets so complicated that we really need to turn to machine learning algorithms to truly incorporate all of the different risk features, both clinically and genetically, in MDS to determine the true risk that our patients have. This type of approach was undertaken by my junior colleague, Aziz Nazha, where he looked at almost 1500 patients who comprised a training cohort for machine learning, and validated it in a separate cohort of over 800 patients incorporating clinical data as well as genetic data.



When he did this, a new machine learning model was much more accurate and even the IPSS-R when mutations were added to it. In the future, I anticipate we'll be looking at risk in MDS and genetic mutations using these types of machine learning algorithms.

Vijaya Bhatt: There are several challenges that community hematologists may face when incorporating cytogenetic and molecular testing in the management of patients with AML or MDS. Insurance coverage of molecular testing can be a challenge. However, these tests are recommended by several guidelines, as we have discussed, and good documentation of the purpose of testing can help with insurance coverage. The time needed to get the results of cytogenetic and molecular testing is another important barrier. Partnership with academic centers, with availability of enhanced mutation panels can perhaps be helpful.

Mikkael Sekeres: I agree with you with what you've said here. And I'll tell you, it also varies state by state, so something that may be covered in Nebraska may not be covered in Ohio. So it is worthwhile to check it out within your state, and we actually have conversations with our patients about the financial risk of getting next-generation sequencing testing. We like you do recommend it, particularly at diagnosis and at disease evolution, but there is a risk that our patients may be saddled with a $1,000 bill that isn't covered by insurance. I can't emphasize enough, however, how important this is at diagnosis as it does add to prognosis and whether or not we recommend much more aggressive therapies such as hematopoietic cell transplantation and also may open up some actionable lesions that we can target genetically with some of our newer therapies.

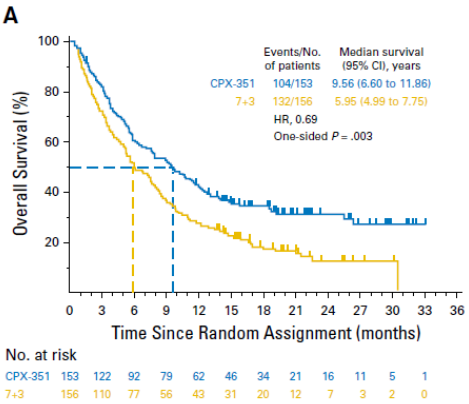
Vijaya Bhatt: Now, I'm going to discuss about treatment landscape for AML focusing on recently approved agents.

Let's start with recently approved drugs that are used as a part of intensive chemotherapy.

Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes

CPX 351

- Liposomal preparation of daunorubicin and cytarabine
- Indication: tAML and AML MRC
- NCCN Category 1 for >60 years, 2A for <60 years

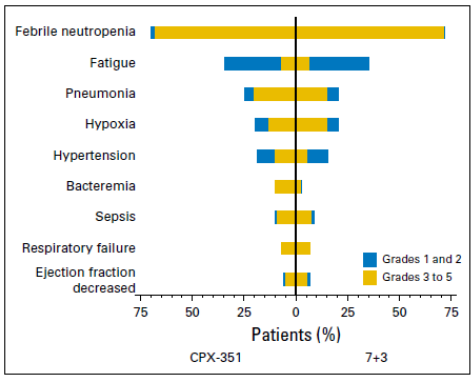


Lancet JE, et al. *J Clin Oncol*. 2018;36(26):2684-2692.

CPX-351 is a liposomal preparation of daunorubicin and cytarabine that is indicated for a diagnosis of treatment-related AML and AML with myelodysplasia-related changes. The approval was based on a randomized phase 3 trial that demonstrated survival benefit over 7+3 in older adults. The NCCN guideline gives a category 1 recommendation for using CPX-351 in older adults with therapy-related AML and AML-MRC, whereas it has a category 2A recommendation for younger patients.

CPX 351

- Toxicities similar to 7+3
- Prolonged cytopenias: consolidation 5 to 8 weeks
- Post-hoc analysis: lower post-transplant mortality due to deeper remission

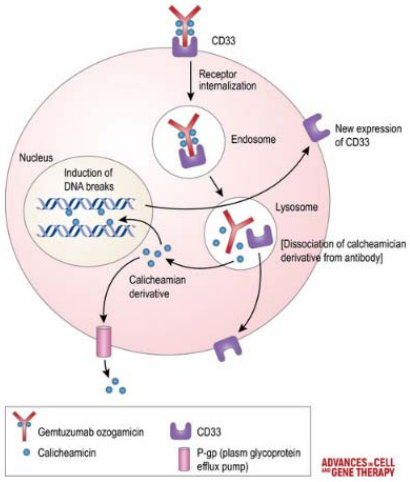


Lancet JE, et al. *J Clin Oncol*. 2018;36(26):2684-2692.

The toxicity profile of CPX-351 is similar to 7+3. We do see prolonged cytopenias which may require consolidation to be delayed to five to eight weeks after induction. A post-hoc analysis demonstrated a lower post-transplant mortality in patients who received CPX-351 compared to 7+3, which is felt to be due to deeper remissions.

Gemtuzumab Ozogamicin

- In combination with 7+3
- Single-agent for initial treatment in older unfit patients
- RR AML

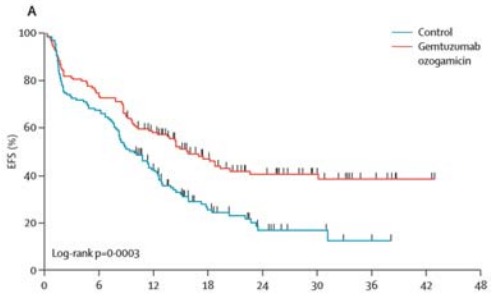


Boddu P, Ravandi F. *Adv Cell Gene Ther.* 2018;1(3):e21.

Gemtuzumab ozogamicin is a CD33 targeted antibody-drug conjugate which received three indications recently, which will be discussed later on.

7+3 +/- Gemtuzumab Ozogamicin

- CD33+
- Core binding factor AML, ie, inv (16) or t(8;21)



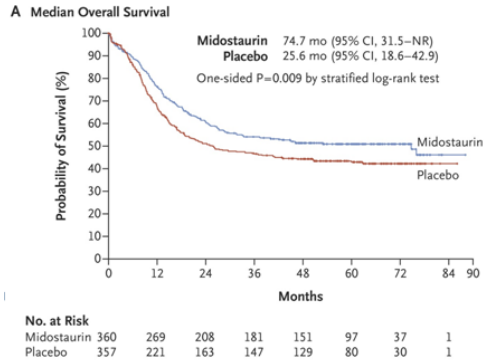
EFS at 2 years: 40.8% vs 17.1%

Castaigne S, et al. *Lancet.* 2012;379(9825):1508-1516.

The gemtuzumab is approved in combination with 7+3 based on a randomized trial that demonstrated superior event-free survival compared to 7+3 alone. Patients with high expression of CD33 and patients with core-binding factor AML derive the most benefit from addition of gemtuzumab.

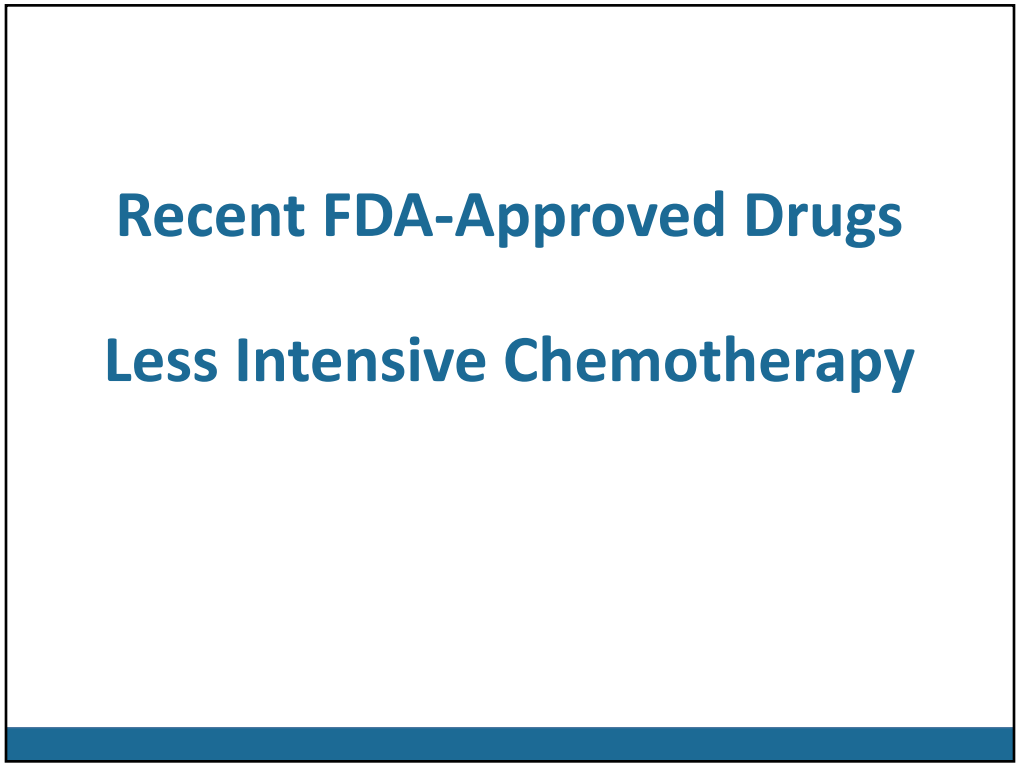
7+3 +/-Midostaurin

- Phase 3 trial: <60 years
- Phase 2 trial: all ages
- FLT3 ITD and TKD
- Approved: all ages



Stone RM, et al. *N Engl J Med.* 2017;377(5):454-464.

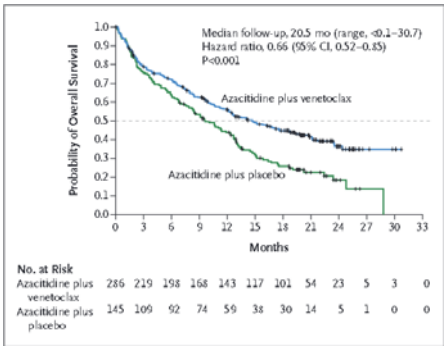
Midostaurin is a FLT3 inhibitor that received FDA approval for patients with FLT3-ITD or FLT3-TKD-mutated AML based on a phase 3 randomized trial that demonstrated superior overall survival compared to patients who were treated with 7+3 alone. Another phase 2 trial was performed that included not only younger patients but also older patients as well.



Now, let's discuss recently approved drugs that are utilized as a part of less intensive chemotherapy.

Venetoclax in Combination with HMA or LDAC

- Promotes apoptosis
- Indication: older, unfit patients



DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

Venetoclax is a BCL2 inhibitor that is combined with hypomethylating agent on low-dose cytarabine. It is approved for older adults who are unfit for intensive chemotherapy. The approval was initially based on early phase trials. However, at this point, phase 3 randomized trial data published in the *New England Journal of Medicine* and *Blood* demonstrating superior survival with venetoclax and azacitidine over azacitidine plus placebo.

Venetoclax in Combination with HMA or LDAC

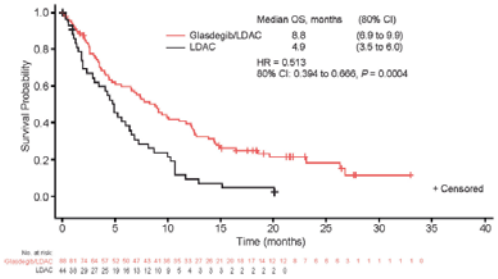
- Myelosuppression and infection duration/ dose adjustment
- Interaction with azoles
- IDH1/IDH2: better responses
- FLT3/RAS pathway, monocytic-resistance

Pei S. *Cancer Discov.* 2020;10(4):536-551.; DiNardo CD, et al. *Blood.* 2020;135(11):791-803.; DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

Some of the common toxicities that can happen with venetoclax combination include myelosuppression and risk of infection that requires adjustment of duration or dose of venetoclax. Venetoclax has significant drug-drug interaction with azole antifungal requiring dose reduction. Some studies indicate patients with IDH1 or IDH2-mutated AML may respond better with venetoclax-based regimen and there are indications that FLT3 or RAS pathway mutation as well as monocytic lineage are associated with resistance.

Glasdegib in Combination with LDAC

- Hedgehog pathway inhibitor
- Indication: older unfit AML
- QT prolongation

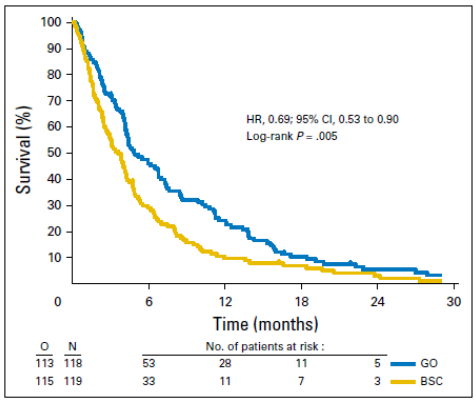


Cortes JE, et al. *Leukemia*. 2019;33(2):379-389.

Glasdegib is a hedgehog pathway inhibitor that is indicated for older patients who are unfit for intensive chemotherapy. It is used in combination with low-dose cytarabine. The approval was based on a randomized controlled trial that demonstrated survival benefit over low-dose cytarabine alone.

Gemtuzumab Ozogamicin Single-agent vs BSC

- High CD33 expression status
- Favorable/intermediate cytogenetic risk profile
- Women



OS at 1 year: 24.3% vs 9.7%

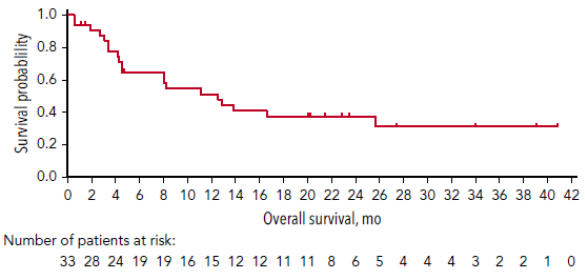
Amadori S, et al. *J Clin Oncol.* 2016;34(9):972-979.

The other indication for gemtuzumab include used as a single-agent treatment for older patients who are unfit for intensive chemotherapy. The approval was based on a randomized phase 3 trial that demonstrated survival over best supportive care. Patients who have high CD33 expression presents with favorable- or intermediate- cytogenetic risk profile and women are a subgroup of patients who have better outcome with monotherapy with gemtuzumab.

Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes

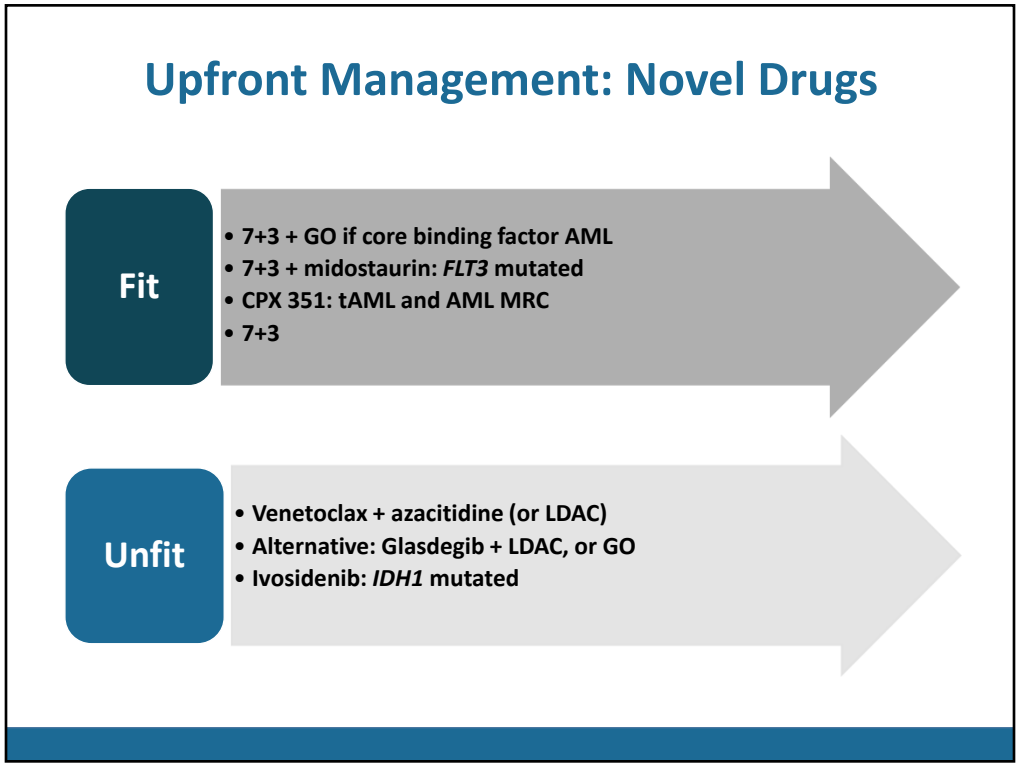
Ivosidenib Upfront

- IDH1 inhibitor
- CR/CRh 42%
- 61% in remission at 1 year
- 43% transfusion independent
- Median overall survival 12.6 months



Roboz GJ, et al. *Blood.* 2020;135(7):463-471.

Ivosidenib is an IDH1 inhibitor that was recently approved for use as a monotherapy for newly diagnosed AML with IDH1 mutation. Treatment with ivosidenib can result in a complete remission rate of about 42% which can be sustained and leads to transfusion independence. Median overall survival in the clinical trial was about 12 months.

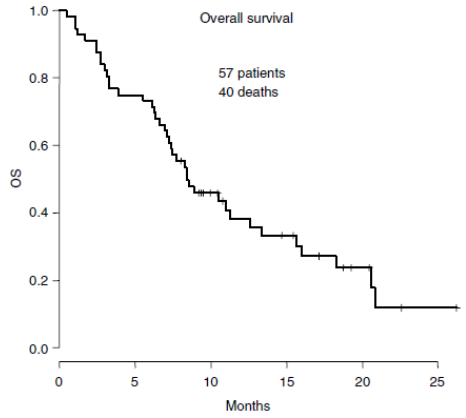


To summarize, how do we utilize novel drugs in upfront management of acute myeloid leukemia? First, we have to determine whether a patient is fit or unfit for intensive chemotherapy. Fit older adults or younger adults can be treated with 7+3 in combination with gemtuzumab if they have core-binding factor AML. For patients with FLT3-mutated AML, midostaurin is combined with 7+3. Patients with treatment-related AML or AML with myelodysplasia-related changes, CPX-351 is recommended. Other patients can be treated with 7+3. Unfit patients, the treatment options include venetoclax in combination with azacitidine or even low-dose cytarabine, glasdegib in combination with low-dose cytarabine, or gemtuzumab. Patients who are unfit for intensive chemotherapy and have IDH1-mutated AML can be treated with ivosidenib.

Now let's discuss recently approved drugs for relapsed/refractory AML.

Gemtuzumab Ozogamicin Single-agent for RR AML

- 26% CR, 7% CRp
- Median OS 8.4 months



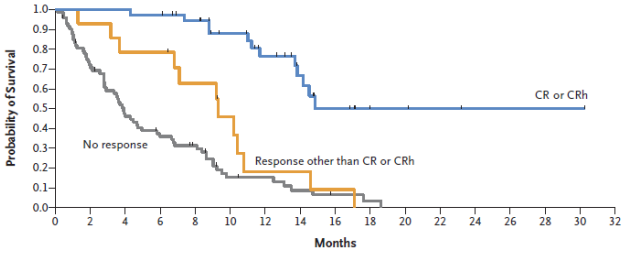
Taskin A-L, et al. *Leukemia.* 20017;21(1):66-71.

Gemtuzumab is also approved as a single agent treatment for relapsed/refractory AML based on a single-arm trial where complete remission rate was about 30% and it resulted in a median overall survival of about eight months.

Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes

Ivosidenib: RR AML

- ORR 42%
- DOR 6.5 months
- 35% transfusion independence
- Median OS 8.8



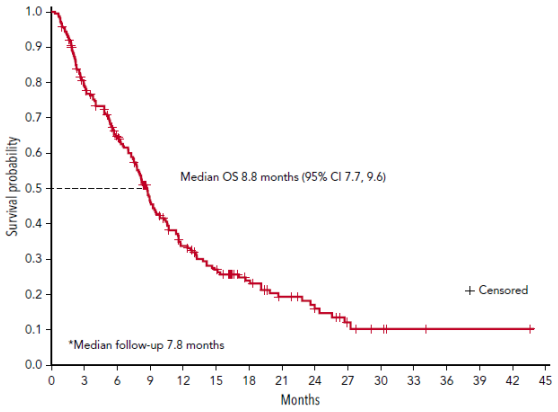
DiNardo CD, et al. *N Engl J Med.* 2018;378(25):2386-2398.

Ivosidenib is an IDH1 inhibitor that is approved for initial treatment of older adults with AML who are unfit for intensive chemotherapy. It results in a complete remission rate of about 42% that can correlate with transfusion independence and it results in a median overall survival of about a year.

Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes

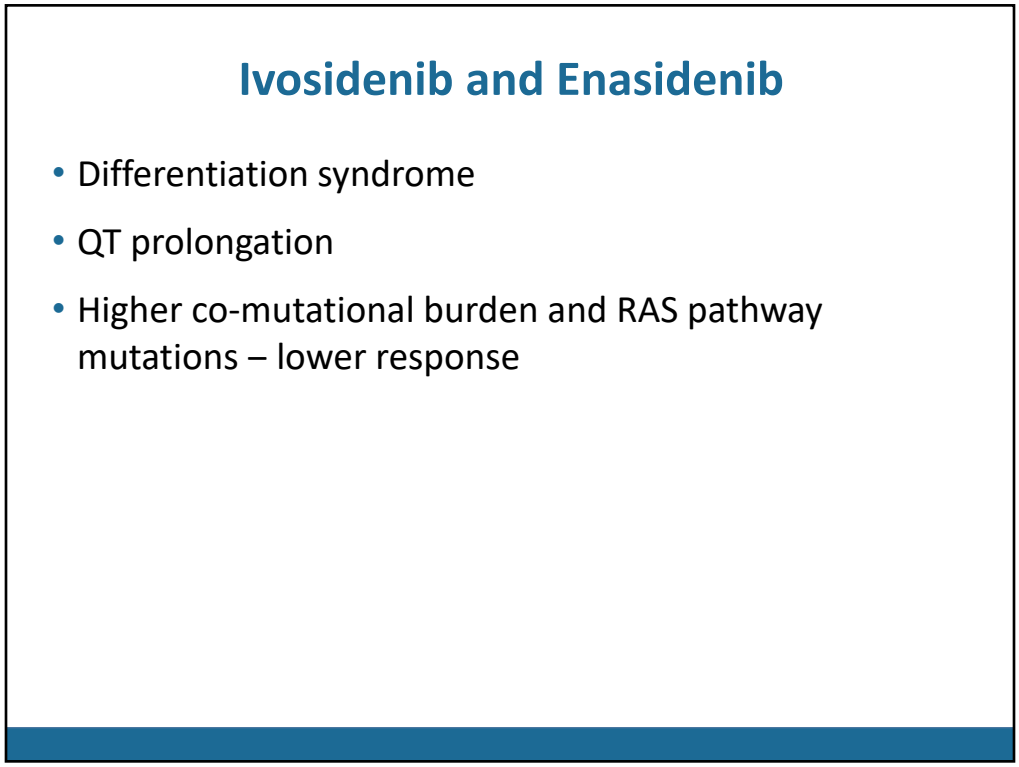
Enasidenib

- IDH2 inhibitor
- Indication: RR AML
- ORR 39%
- DOR 5.6 months
- >40% transfusion independence
- Median OS 8.8



Stein EM, et al. *Blood.* 2019;133(7):676-687.

Enasidenib is an IDH2 inhibitor approved for patients with relapsed/refractory AML with IDH2 mutation. This results in an overall response rate of 39%, which can lead to transfusion independence and a median overall survival of about eight months.

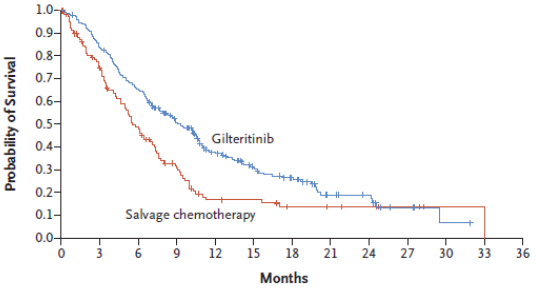


Both ivosidenib and enasidenib can be associated with differentiation syndrome, so it's important to carefully monitor for differentiation syndrome and treat it with steroid and drug cessation as appropriate. Both of these agents can be associated with QT prolongation and studies have demonstrated that higher co-mutational burden and RAS pathway mutations can be associated with lower response rate to these agents.

Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes

Gilteritinib vs Chemotherapy

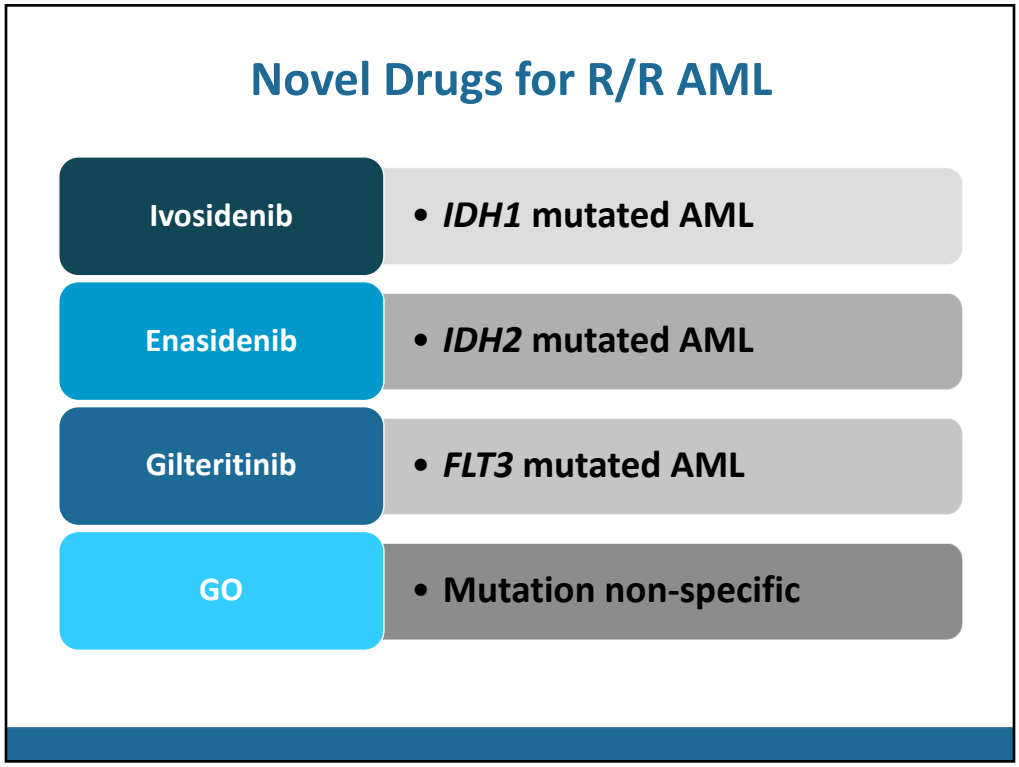
- FLT3 inhibitor
- Indication: RR AML
- Interaction with posa/vori
- QT prolongation



CR/CRp 34% vs 15%
1-year OS 37% vs ~17%

Perl AE, et al. *N Engl J Med.* 2019;381(18):1728-1740.

Gilteritinib is a potent FLT3 inhibitor that is approved for relapsed/refractory AML with FLT3 mutation based on a phase 3 randomized controlled trial that demonstrated higher overall survival over cytotoxic salvage chemotherapy. Gilteritinib does have interaction with posaconazole or voriconazole and it can cause QT prolongation requiring EKG monitoring.



To summarize, how should we use novel drugs for relapsed/refractory AML? For patients with IDH1-mutated AML, ivosidenib can be used. Enasidenib is approved for IDH2-mutated AML. Gilteritinib is approved for FLT3-mutated AML. All of these oral agents can be better tolerated compared to cytotoxic chemotherapy, and gemtuzumab can be utilized regardless of mutation.

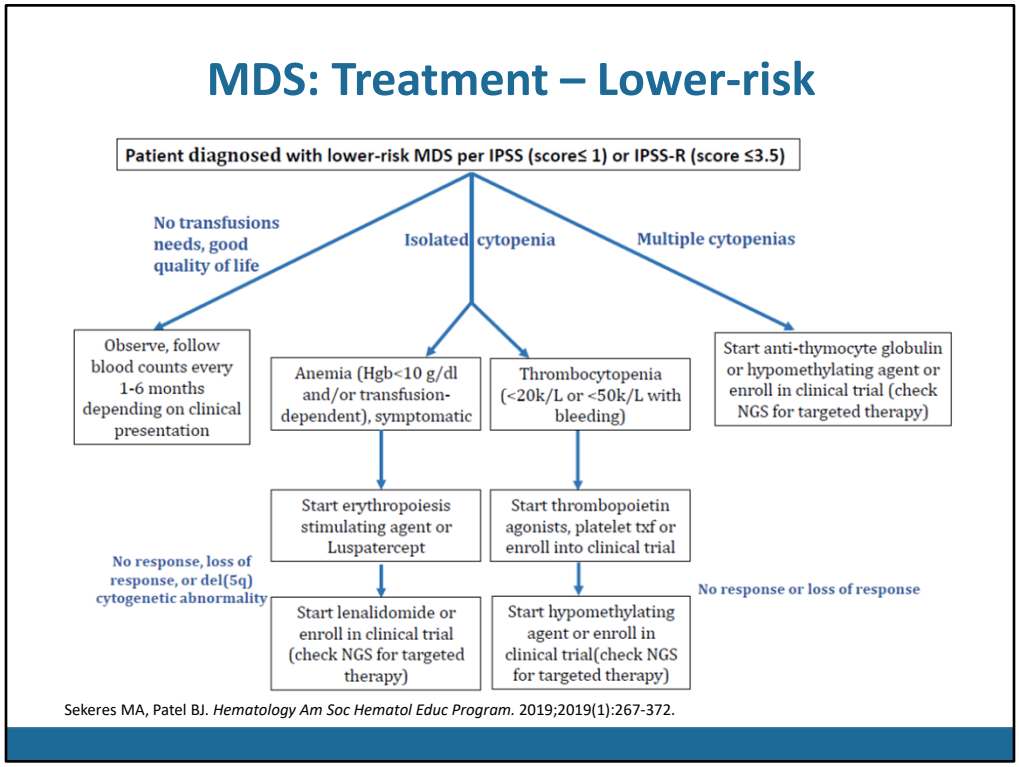
Treatment for RR AML: NCCN 2020

- Clinical trial
- Targeted therapy: ivosidenib, enasidenib, gilteritinib, GO
- Cytotoxic therapy, eg, CLAG or FLAG +/-Ida, HiDAC, EC+/-mitoxantrone
- Ven-based, HMA (less aggressive)

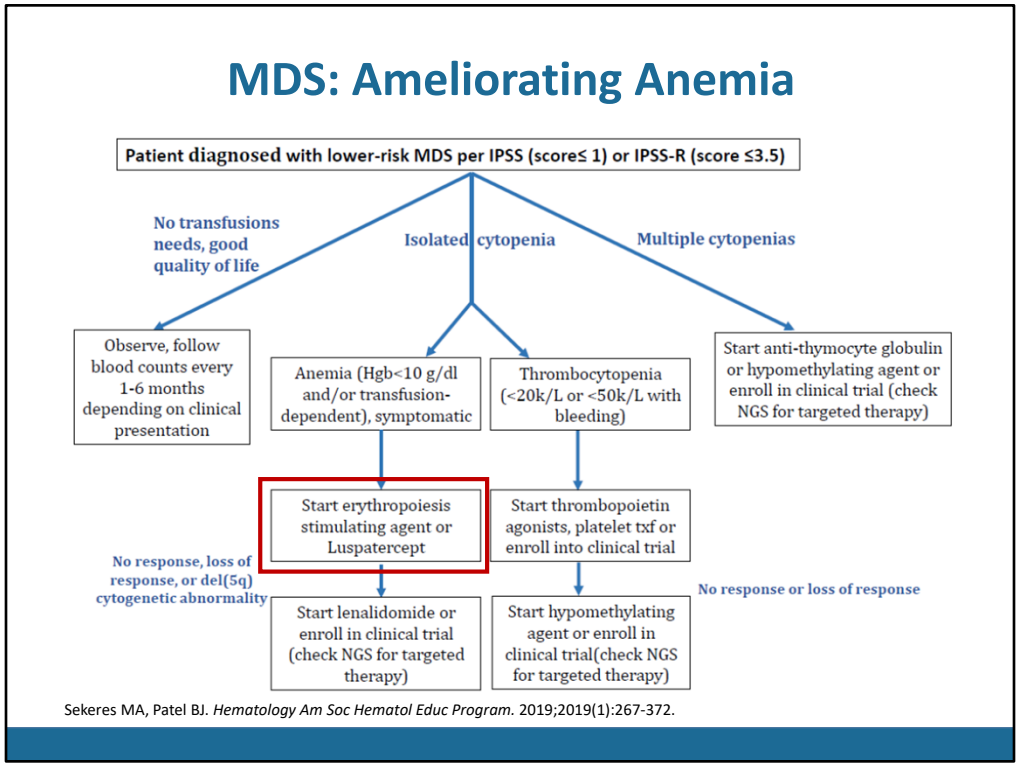
In addition to these newly approved agents, there are cytotoxic chemotherapy that can be utilized and clinical trials certainly is an important option for relapsed/refractory AML.

Now, Dr. Sekeres is going to discuss about treatment landscape for MDS.

Mikkael Sekeres: Thank you so much, Dr. Bhatt.



Let's talk about lower-risk MDS to start with. Recall that those are the folks who have a score of 3.5 or lower on the revised IPSS. We tend to treat these patients according to the cytopenias that are predominating when they first come to see us. On the left-hand side of this slide, you'll see a patient who has no transfusion needs, a good quality of life, something that one of my patients once referred to as having mild displeasure syndrome. He didn't like to fight the traffic to come into Cleveland to see me every few months, but other than that MDS wasn't really affecting his quality of life. For that sort of patient, we would just follow them regularly without any type of treatment. Then we have patients for whom anemia is the predominating cytopenia, thrombocytopenia predominates or multiple cytopenias are the problem.



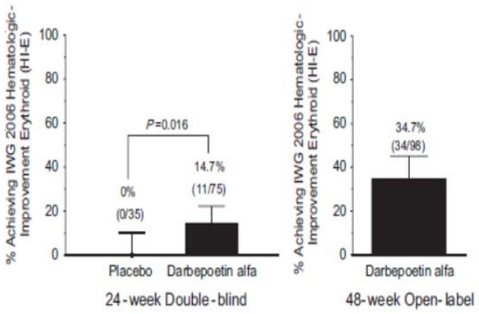
Let's start with those patients who have anemia, the most commonly used drug in this patient class are erythropoiesis stimulating agents.

MDS: Ameliorating Anemia – ESAs

ESAs RR 15 - 40%

Table II. Response results.

	Patients (%)	Response rate
Growth factors	100	39·5
EPO	57·3	39·4
EPO + GCSF	23·4	47·8
GMCSF	6·2	37·8
EPO + GMCSF	5·8	33·7
GCSF	3·0	47·9
IL3	3·0	17·0
IL6	1·3	38·1

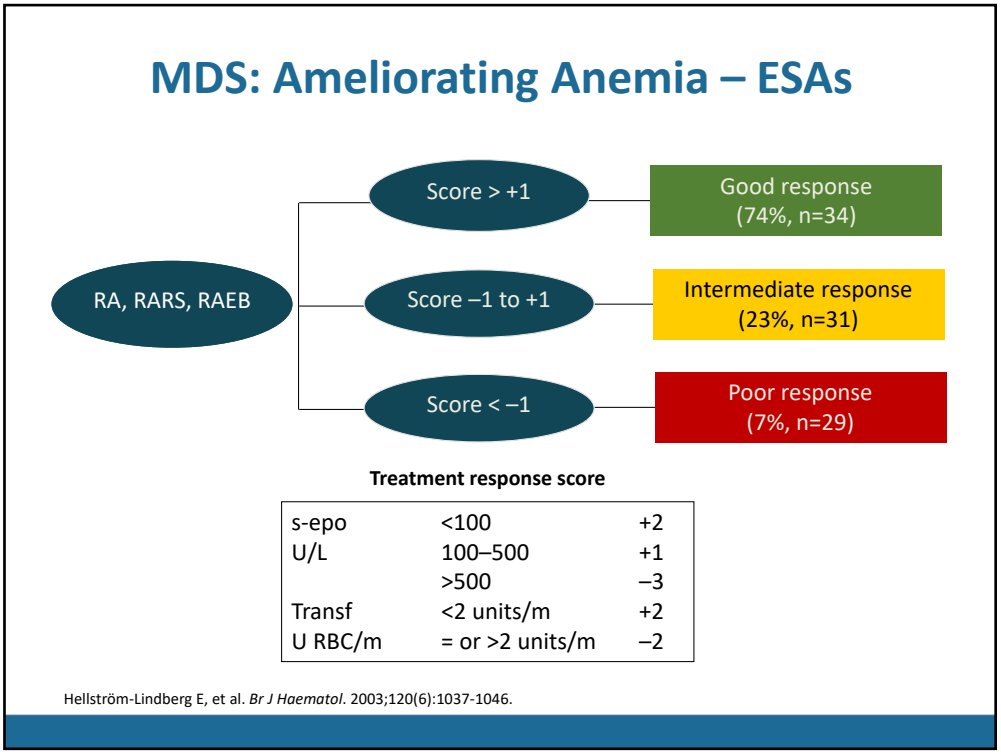


N = 1587

N = 147 (2:1)

Golshayan A-R, et al. *Br J Haematol.* 2007;137(2):125-132.; Platzbecker U, et al. *Leukemia.* 2017;31(9):1944-1950.

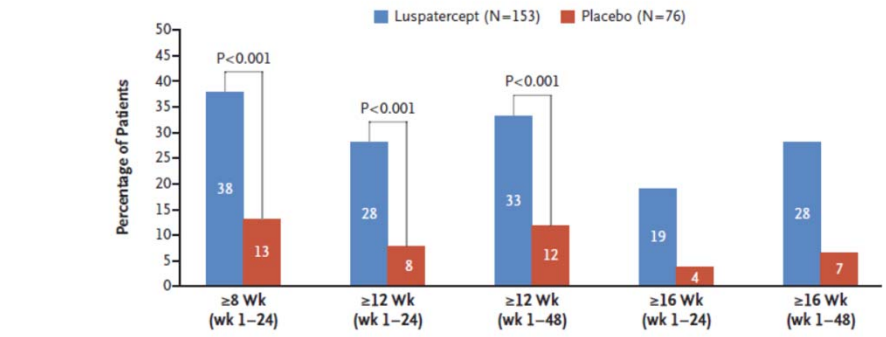
Now, there have been a variety of studies looking at ESAs in patients who have lower-risk MDS. In a meta-analysis that we published over a decade ago, we looked at 20 years of published literature in lower-risk MDS and standardized response criteria. When we did this, we found a response rate of about 40% for ESAs in the treatment of patients with lower-risk MDS. More recently, there was a randomized study of darbepoetin, a long-acting ESA, versus placebo in patients treated in Europe. During the initial 24-week double-blind portion of the study, the response rate to darbepoetin was only 15%. However, with longer follow-up that response rate rose to about 35%, so I usually cite to my patients the chance of responding to an ESA is somewhere between 15% and 40%.



Who's more likely to respond? Well, this should be clinically and intuitively fairly obvious. When a patient comes into our clinic and already has a serum EPO level that's in the hundreds or even thousands, and is already requiring red blood cell transfusions regularly, the likelihood that giving even more EPO to that patient is going to help is quite low at less than 10%. On the other hand, a patient who comes into our clinic who has a low serum EPO level, and for MDS low is often defined as less than 100 and hasn't yet started to require transfusions. In that person, the likelihood that he or she is going to respond to an ESA is much higher at almost 75%.

Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes

MDS: Ameliorating Anemia – LUSPAT



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

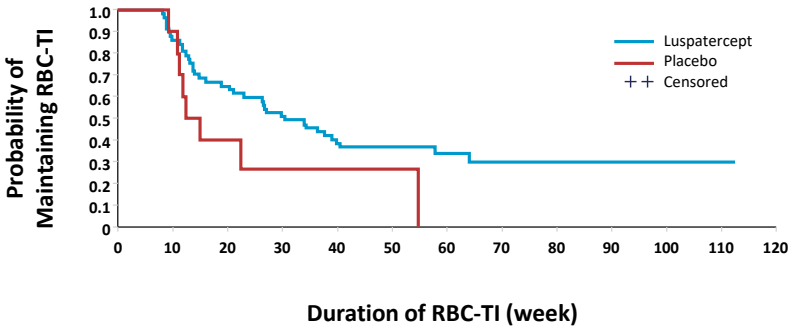
Figure 1. Independence from Red-Cell Transfusion.

Fenaux P, et al. *N Engl J Med.* 2020;382(2):140-151.

Now, there's a new drug that was just approved by the FDA in 2020 to treat patients who have lower-risk MDS with ring sideroblasts who are transfusion dependent who have already been exposed to an ESA or for whom an ESA is unlikely to work, and that drug is luspatercept. It works on SMAD2/3 signaling at late stages of erythropoiesis. And in a randomized study in which patients received luspatercept or placebo, the transfusion independence response rate was 38% for those receiving luspatercept versus 13% for those receiving placebo. Now, the primary outcome of this study was 8 weeks of transfusion independence. When that's actually extended to 12 weeks or 16 weeks, which we think is more clinically meaningful to patients, the response rate does drop down to 33% for 12 weeks or 28% for 16 weeks, still meaningful, though, in this patient population.

MDS: Ameliorating Anemia – LUSPAT

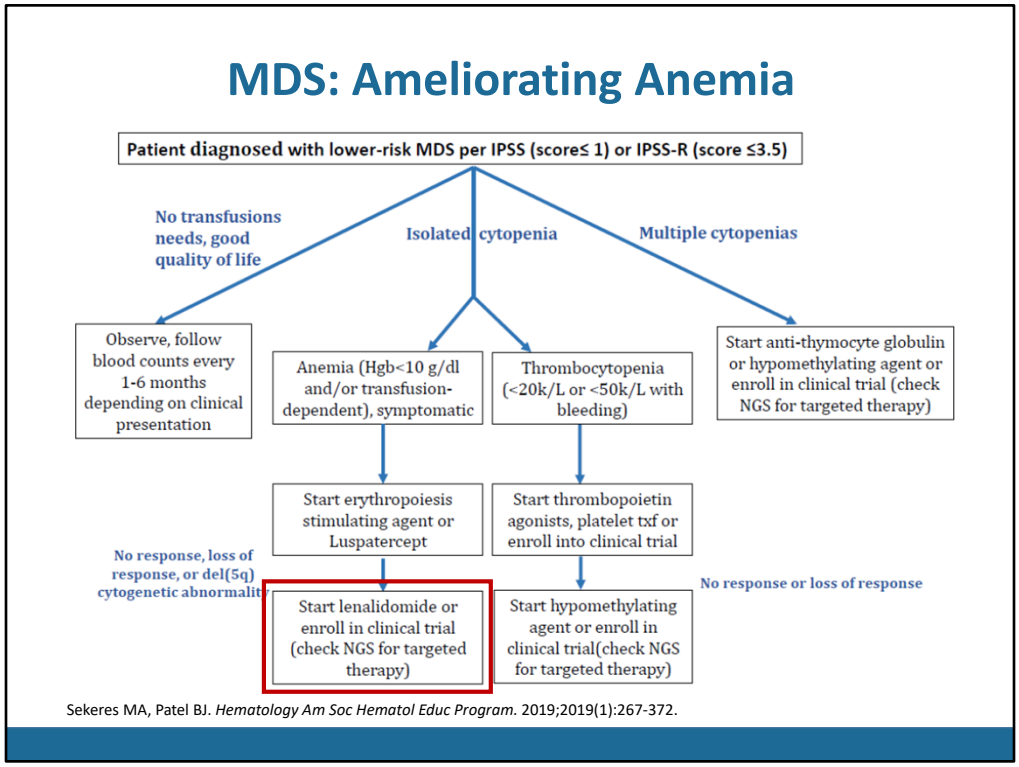
Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)



Fenaux P, et al. *N Engl J Med.* 2020;382(2):140-151.

The median response duration was about 31 weeks for those patients receiving luspatercept versus almost 14 weeks for those who received placebo.

Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes



Sekeres MA, Patel BJ. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):267-372.

For patients who've already been exposed to an ESA or luspatercept and particularly for those patients who have a deletion 5q abnormality, we would consider the drug lenalidomide

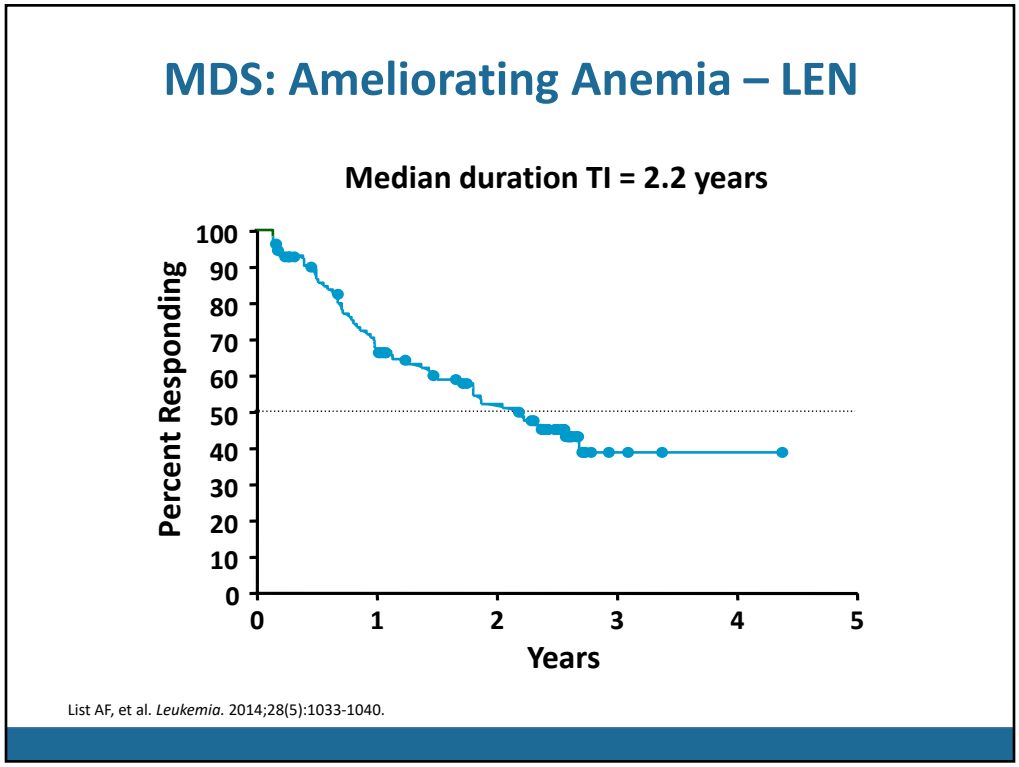
MDS: Ameliorating Anemia – LEN

	RBC-TI, n (%) [95% CI]		
	Placebo	Lenalidomide 5 mg	Lenalidomide 10 mg
mITT population	**n = 51**	**n = 47**	**n = 41**
Protocol defined (≥26 weeks)	3 (5.9) [1.2-16.2]	20 (42.6) [28.3-57.8]*	23 (56.1) [39.7-71.5]*
IWG 2000 (≥8 weeks)	4 (7.8) [2.2-18.9]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*
IWG 2006 (≥8 weeks)	3 (5.9) [1.2-16.2]	24 (51.1) [36.1-65.9]*	25 (61.0) [44.5-75.8]*

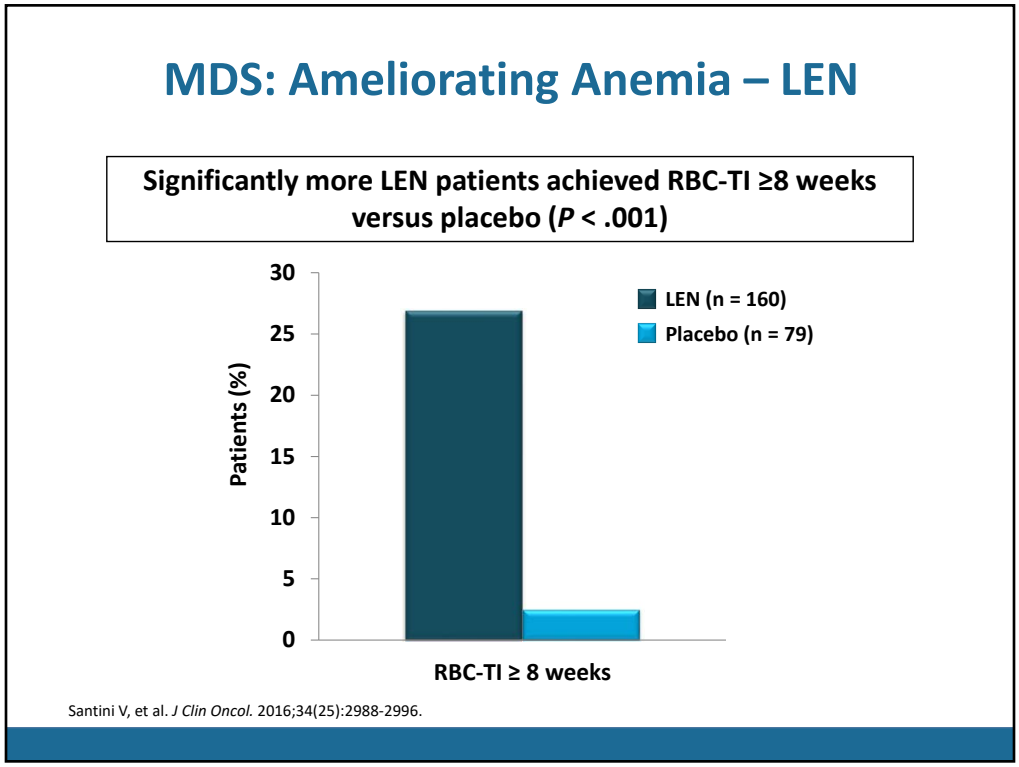
*$P < .001$ versus placebo

Fenaux P, et al. *Blood.* 2011;118(14):3765-3776.; Cheson BD, et al. *Blood*. 2000;96(12):3671-3674.; Cheson BD, et al. *Blood*. 2006;108(2):419-425.;

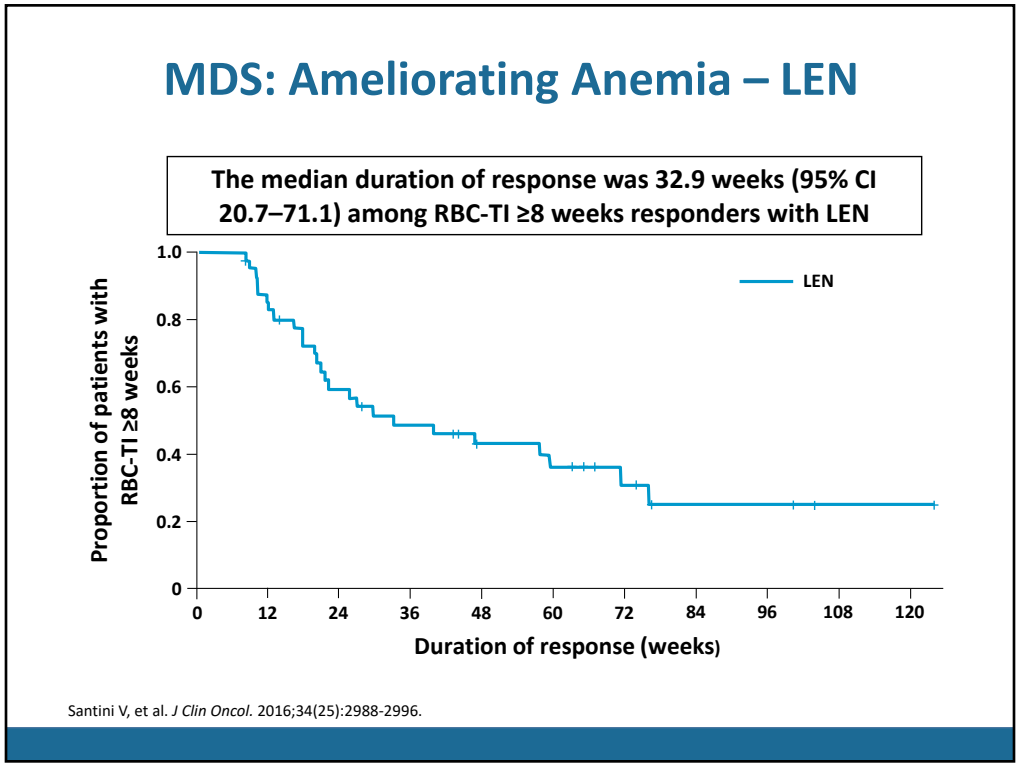
In patients who have a deletion 5q abnormality who were packed red blood cell transfusion dependent, the response rate to lenalidomide where responses to find is transfusion independence was 61% in a randomized study that was conducted in Europe. That's quite high for a lower-risk MDS population where typical response rates are around 30% like we saw with luspatercept.



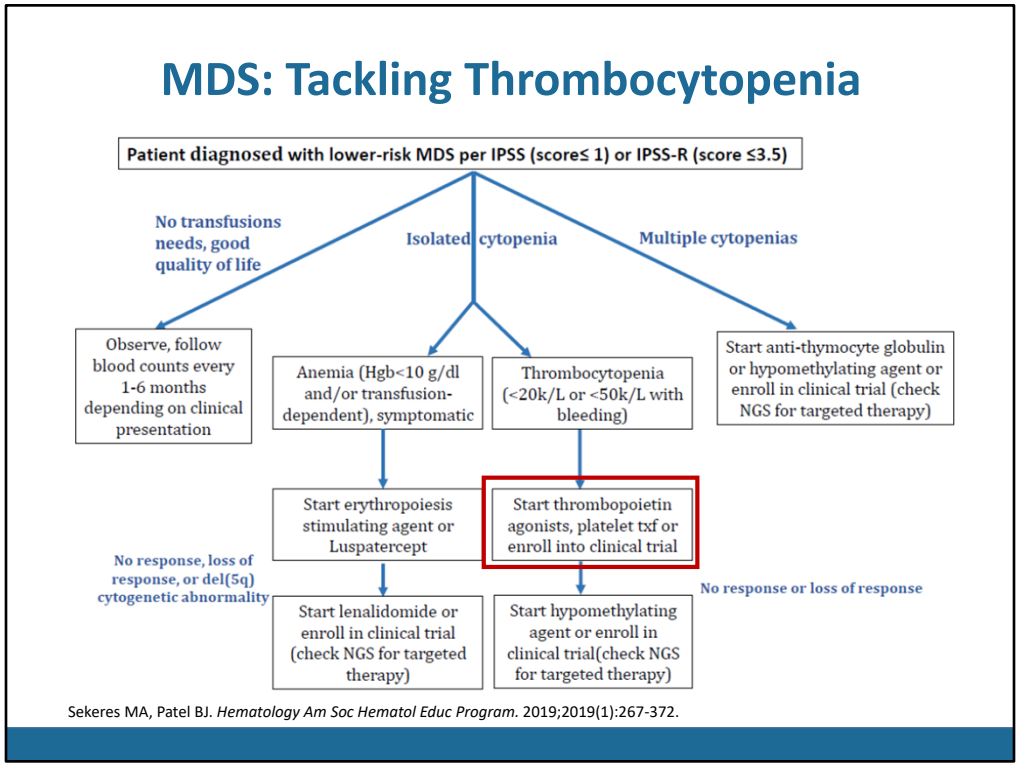
The response duration was a median of 2.2 years in these patients which is also quite long in a lower-risk MDS population.



Now if lenalidomide is used off-label in the United States for a non-deletion 5q transfusion dependent lower-risk MDS population, the response rate is more modest at 27%, which starts to become kind of similar to what we saw with luspatercept in those patients with lower-risk MDS who had ring sideroblasts.

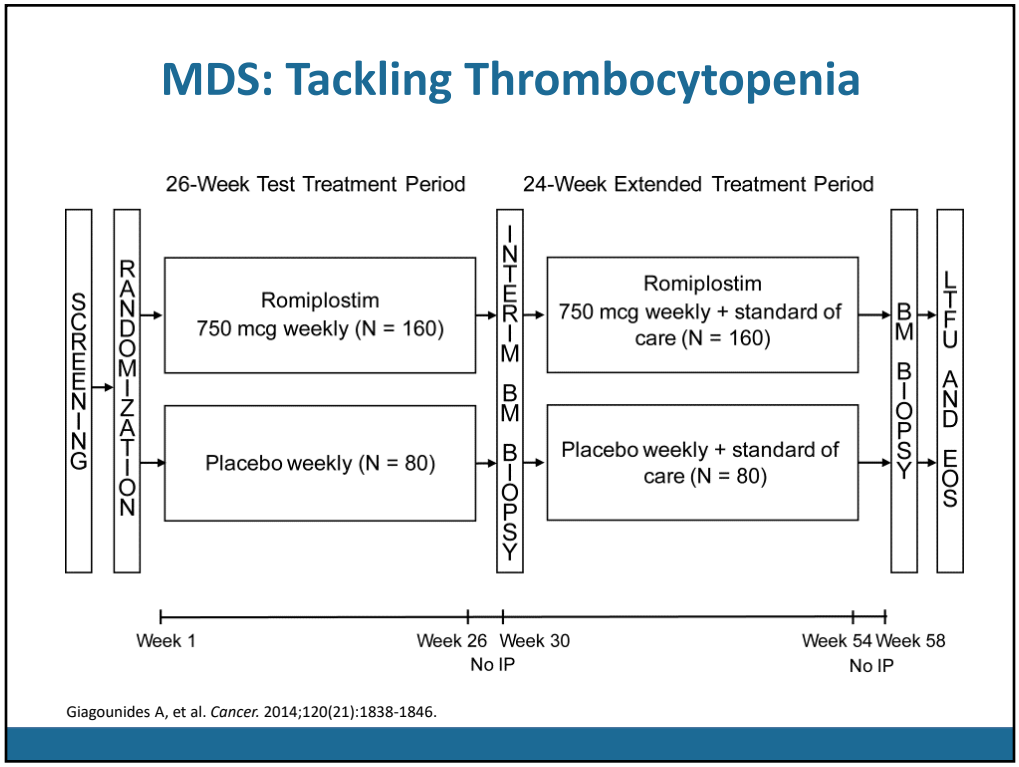


The response duration was also quite similar to what we saw with luspatercept at a median of 33 weeks.



Sekeres MA, Patel BJ. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):267-372.

What about those patients for whom the predominating cytopenia is thrombocytopenia? Well, in these patients, we might consider TPO mimetics such as romiplostim or eltrombopag.



The largest and what I think is the best designed study looking at these agents is this one published by Ari Giagounides in 2014. Patients with lower-risk MDS who had thrombocytopenia were randomized to receive romiplostim or placebo and followed over time.

MDS: Tackling Thrombocytopenia

	Baseline platelets <20 x 10^9/L		Baseline platelets ≥20 x 10^9/L	
	Placebo (N = 43)	Romiplostim (N = 87)	Placebo (N = 40)	Romiplostim (N = 80)
CSBE (rate/100 pt-yr)	501.2	514.9	**226.4**	**79.5**
	RR = 1.03, *P* = .827		**RR = 0.35, *P* < .0001**	
PTE (rate/100 pt-yr)	**1778.6**	**1250.5**	179.8	251.8
	RR = 0.71, *P* < .0001		RR = 1.38, *P* = .1479	

Giagounides A, et al. *Cancer.* 2014;120(21):1838-1846.

Now the primary endpoints of this study were actually met. Those patients who entered this study with fewer than 20,000 platelets, who were already dependent on platelet transfusions, had a platelet transfusion event rate that was significantly lower when they received romiplostim versus placebo. On the other hand, patients who came into the study with a platelet count of between 20,000 and 50,000, but had had clinically significant bleeding events, had fewer of those events when they were treated with romiplostim versus placebo.

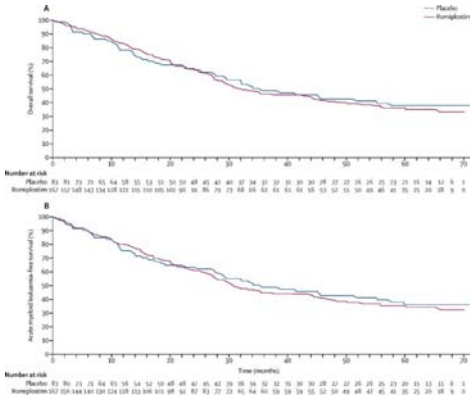
MDS: Tackling Thrombocytopenia

	Romiplostim	Placebo	HR	95% CI
Deaths	17.9% (30)	20.7% (17)	0.86	0.47, 1.56
AML	6.0% (10)	4.9% (4)	1.20	0.38, 3.84
AML-free survival	19.6% (33)	23.2% (19)	0.85	0.48, 1.50

5 years of follow-up

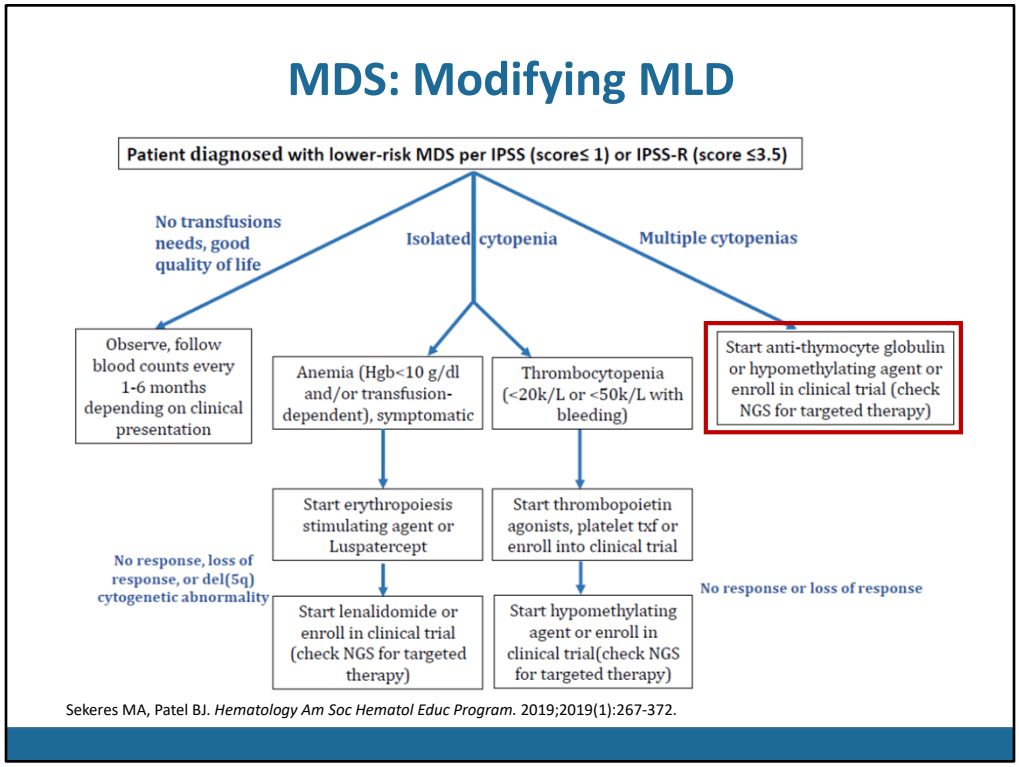
OS

LFS



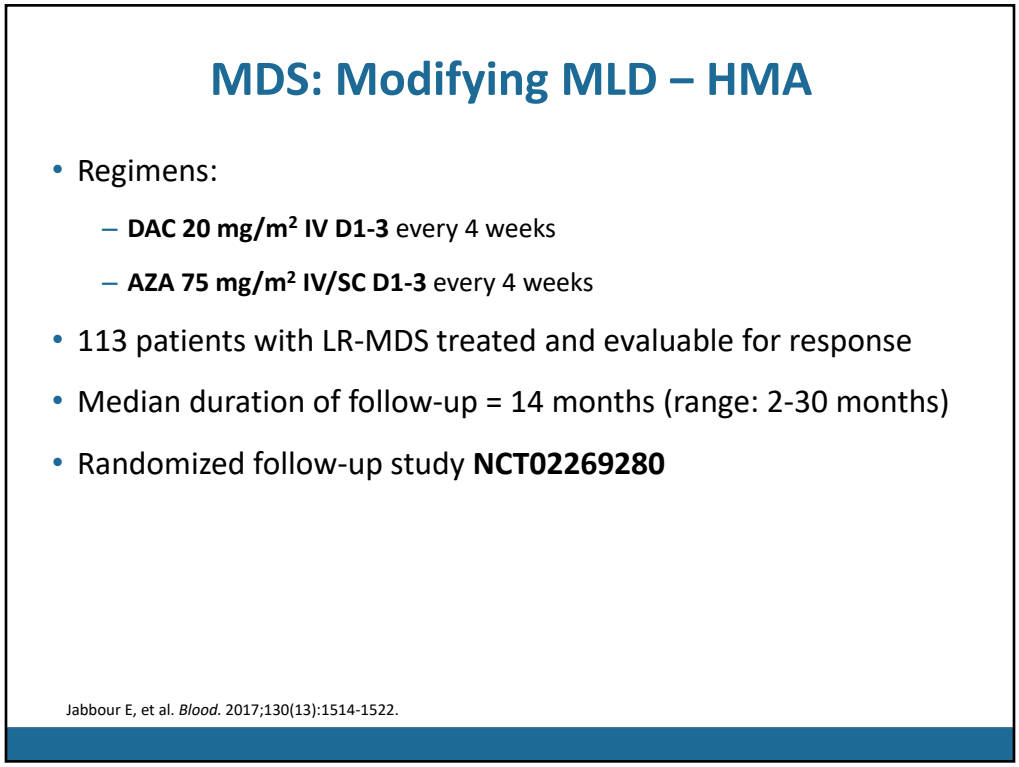
Giagounides A, et al. *Cancer.* 2014;120(21):1838-1846.;
Fenaux P, et al. *Br J Haematol.* 2017;178(6):906.

There was a problem with this study, though. If you're an MDS nerd like I am, you may recognize that patients can be technically classified as having lower-risk MDS even when they have up to 9% blasts, and TPO mimetics can stimulate blasts to grow. Blasts have TPO receptors on them and, unfortunately, about 13% of patients who were enrolled on this study had excess blasts to start with. So when a Data and Safety Monitoring Board was reviewing the data from this study, they actually halted the study because there was a 2.5-fold higher rate of AML transformation in those patients who got romiplostim versus those who got placebo. Now you may not be surprised to learn that three-quarters of those patients who transformed to AML started this study with excess blasts, so the study was halted and never actually reached completion. Now with five years of follow up, the rates of AML transformation actually equalized between the romiplostim arm and the placebo arm, but the damage had already been done. So this is an off-label use of romiplostim or of eltrombopag in patients who have lower-risk MDS with thrombocytopenia and these drugs should never ever, ever be given to somebody who has excess blasts to start with.



Sekeres MA, Patel BJ. *Hematology Am Soc Hematol Educ Program.* 2019;2019(1):267-372.

Finally, we can discuss drugs that may have effects on multiple cell lines at the same time.



Hypomethylating agents are approved for the treatment of MDS, both lower-risk and higher-risk. In a lower-risk setting, I become increasingly a fan of shortening the length of the schedule of receiving one of the hypomethylating agents, either azacitidine or decitabine. Decitabine is most commonly given over a five-day period in the United States, in this study, we gave it for three days, every 28 days, and azacitidine is approved for seven-day dosing, every 28 days. In this study, we also gave it over three days; 113 patients with lower-risk MDS were enrolled onto this study, and they were followed for a median of 14 months.

MDS: Modifying MLD – HMA

Response	N (%)
CR	33 (36)
mCR	8 (9)
HI	13 (14)
ORR	54 (59)
SD	31 (34)
PD	6 (7)

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)

Jabbour E, et al. *Blood.* 2017;130(13):1514-1522.

On this study, the overall response rate to hypomethylating agents was 50%. Now you'll notice on this slide, overall response rate is listed as 59% but I'm discounting marrow CR as a study that we completed within the MDS Clinical Research Consortium showed that marrow CRs are no different than stable disease. Still, even discounting that a response rate of 50% to hypomethylating agents is about 15% higher than what we've seen in single institution studies, and that's for giving even less of the hypomethylating agents than had been given in those studies, the response duration was about 15 months.

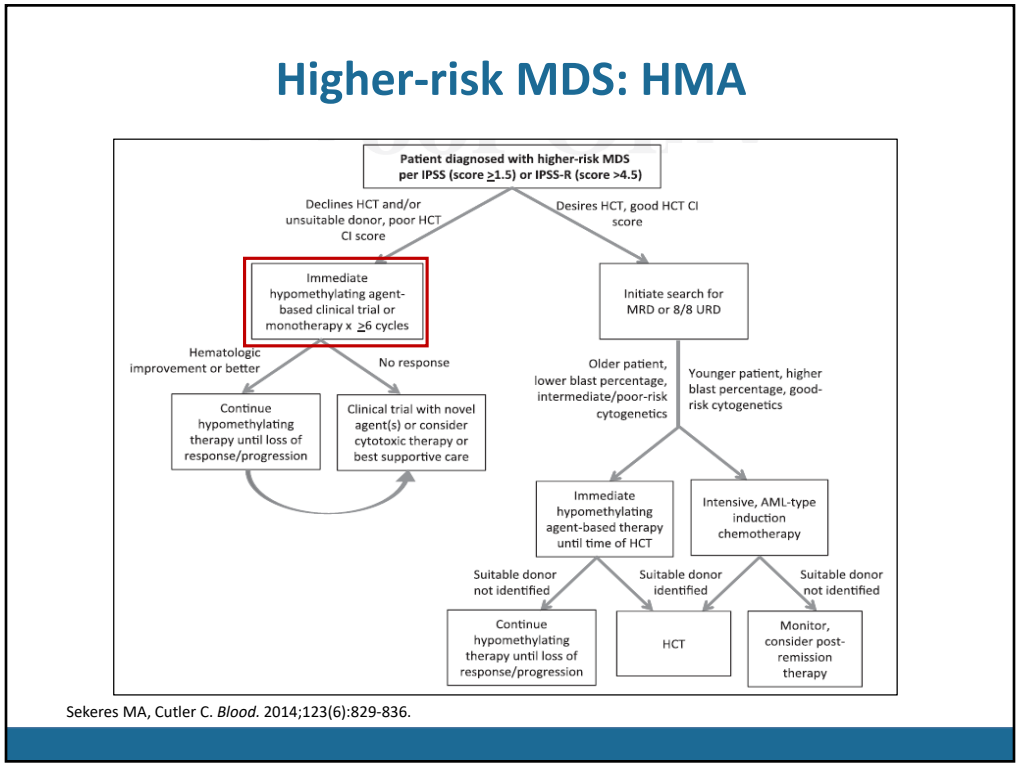
MDS: Modifying MLD – ATG

	N. (total)	% (95%CI)
All responses - intent to treat	9 (27)	33.3 (17-54)
HI-E[†]	7 (18)	38.9
HI-E, major	6	
HI-E, minor	1	
HI-N, major%	3 (10)	30.0
HI-P, major[§]	3 (13)	23.0
No response - intent to treat	18 (27)	66.7 (46-83)

Measure	Treatment Arm		*P*
	ATG+CSA (n = 45)	BSC (n = 43)	
No treatment, No. of patients*	5	—	
Crossed over to ATG+CSA, No. of patients	—	14	
Hematologic response (CR+PR) by 3 months			
No. of patients	9	4	
%	20	9	
Hematologic response (CR+PR) by 6 months†			.016
No. of patients	13	4	
%	29	9	
Hematologic response (CR+PR+HI) by 6 months (IWG criteria)†‡			.009
No. of patients	14	4	
%	31	9	

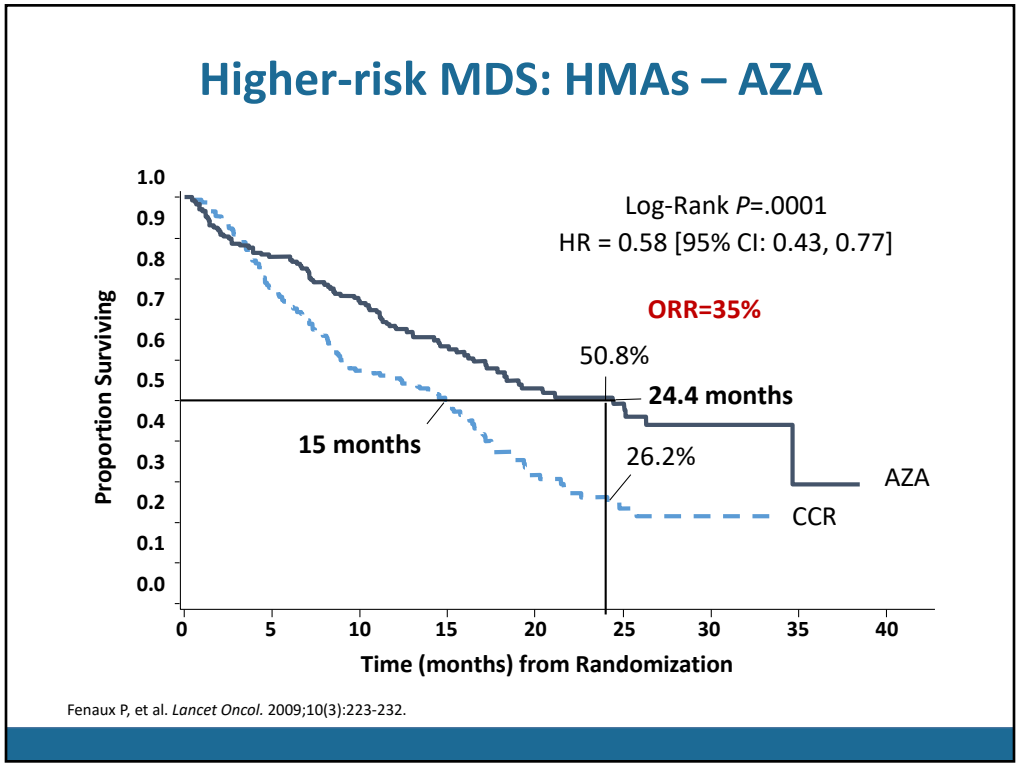
Komrokji RS, et al. *Haematologica.* 2014;99(7):1176-1183.; Passweg JR, et al. *J Clin Oncol.* 2011;29(3):303-309.

Another approach to treating patients who have multilineage dysplasia is to give antithymocyte globulin. In a phase 2 study conducted in the US, the response rate to ATG was 33%, and in a randomized study conducted in Europe, the response rate was 31%, and those responses could be durable at a median that approached a year and a half, particularly in the European study. So these are options for patients with multiple cytopenias who have lower-risk MDS, particularly if those patients may have other stigmata of having autoimmune conditions that are affecting their MDS such as a hypoplastic marrow or other autoimmune conditions at the same time.

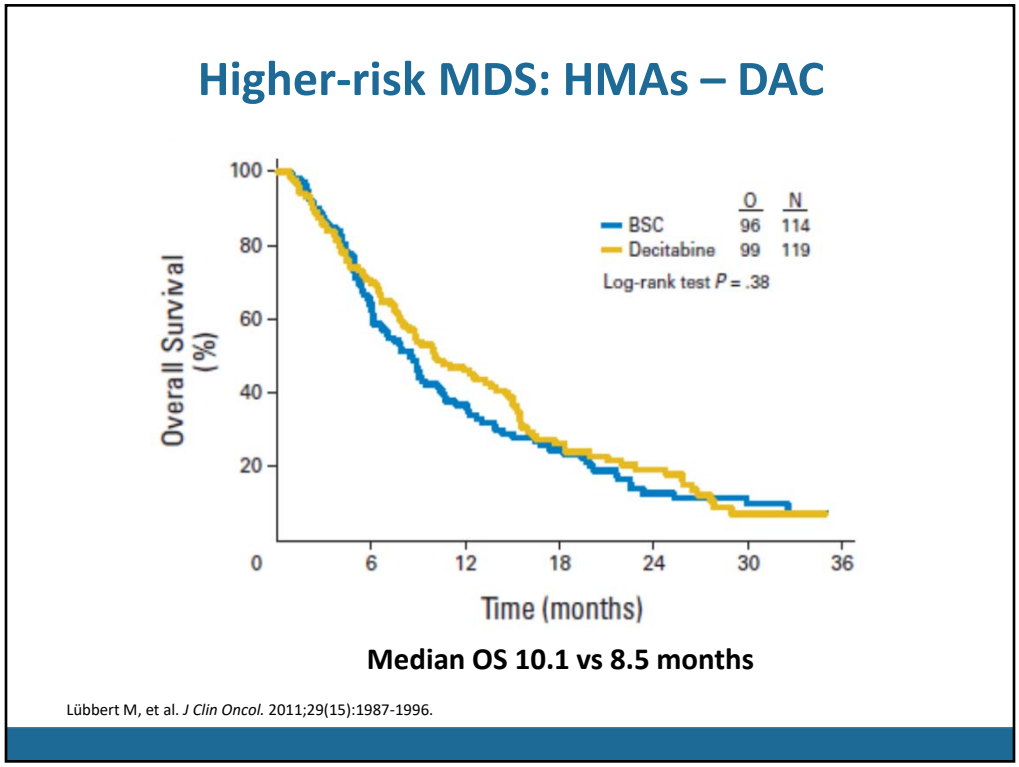


Sekeres MA, Cutler C. *Blood.* 2014;123(6):829-836.

For higher-risk MDS, the upfront treatment is often hypomethylating agents and these can include azacitidine or decitabine or a new drug that I'll discuss.



The only prospective randomized trial that we have showing a survival advantage for any treatment approach in MDS is this one. Patients with higher-risk MDS were enrolled onto this study in randomized receiving azacitidine or conventional care regimens. Those conventional care regimens could include best supportive care, low-dose cytarabine, or AML-type treatment with 7+3 of cytarabine and anthracycline. About 60% of patients enrolled on the conventional care arm actually received best supportive care, and the median survival for patients receiving azacitidine was about two years compared to 15 months for those receiving conventional care regimens, and that difference was significant. Now, multiple trials that are large, randomized, and have an azacitidine backbone have failed to replicate this median of 24 months overall survival that was seen in this study, so what I quote to my patients is a median survival that's closer to about 20 months as opposed to 24 months.



A similarly designed study looking at decitabine that was conducted in Europe randomized higher-risk patients to receive decitabine or best supportive care. But in this study, decitabine did not lead to a significant improved overall survival compared to the best supportive care. Now decitabine is a very similar drug to azacitidine, why did this study fail where the previous one was a success? I think the reason is that these were entirely different patient populations who were enrolled. In this study, the control arm had a median survival of eight and a half months. Compare that to the previous study with azacitidine where the control arm had a median survival of 15 months. Even when you adjust for those patients who received treatment on the control arm of the azacitidine study, there shouldn't be this big a difference in control arm. So I think these were different patients populations enrolled, the level one evidence in the US is for azacitidine upfront treatment for higher-risk MDS, but I think decitabine is an acceptable alternative.

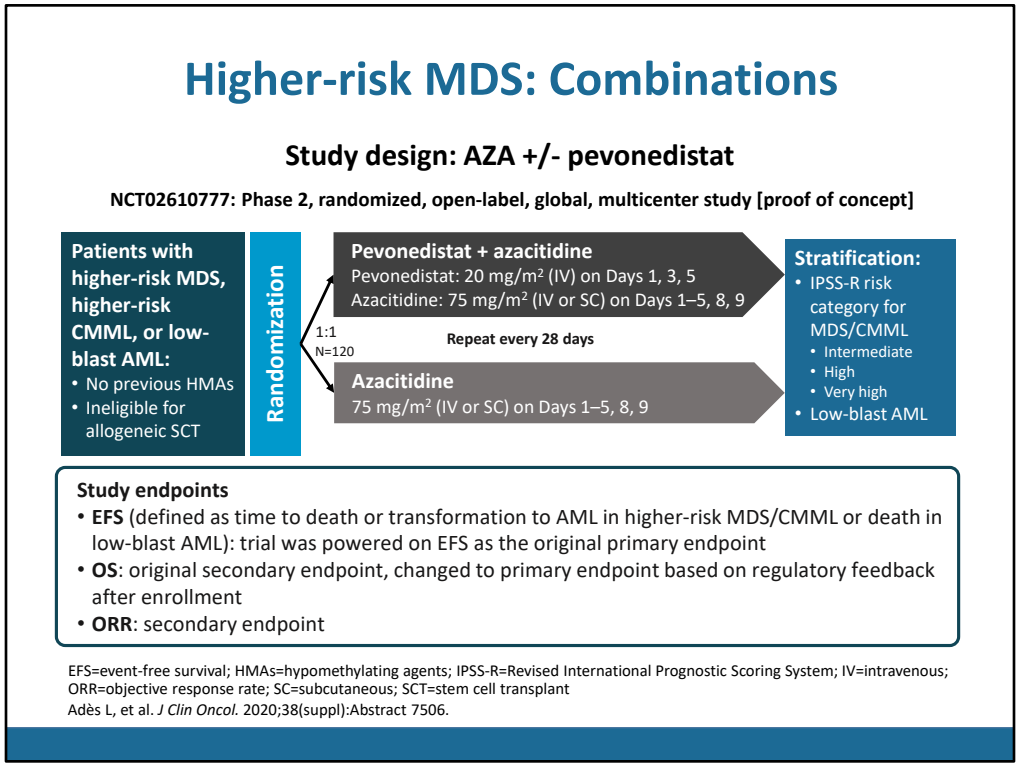
Higher-risk MDS: HMAs – DAC/CED

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

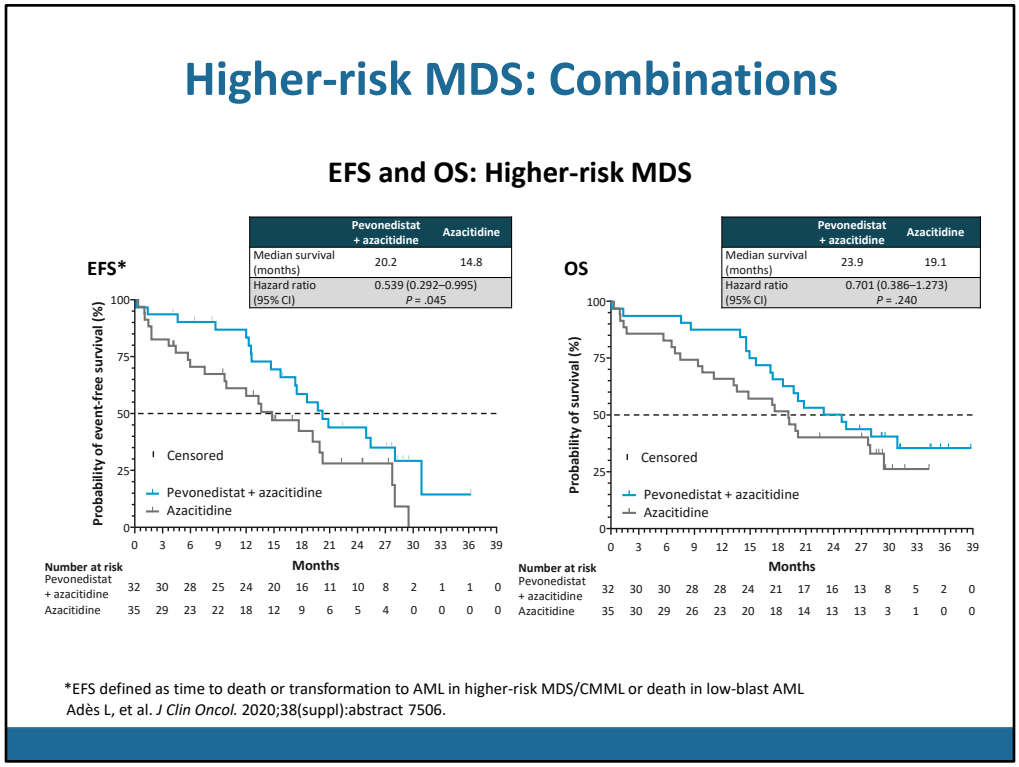
Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13, 32
PR	0	
mCR	18 (22)	14, 33
mCR with HI	6 (7)	3, 16
HI	13 (16)	9, 26
HI-E	8 (10)	4, 19
HI-N	2 (2)	0, 9
HI-P	11 (14)	7, 23
Overall response (CR + PR + mCR + HI)	48 (60)	48, 71
No response	32 (40)	29, 52

Garcia-Manero G, et al. *Blood.* 2020;136(6):674-683.

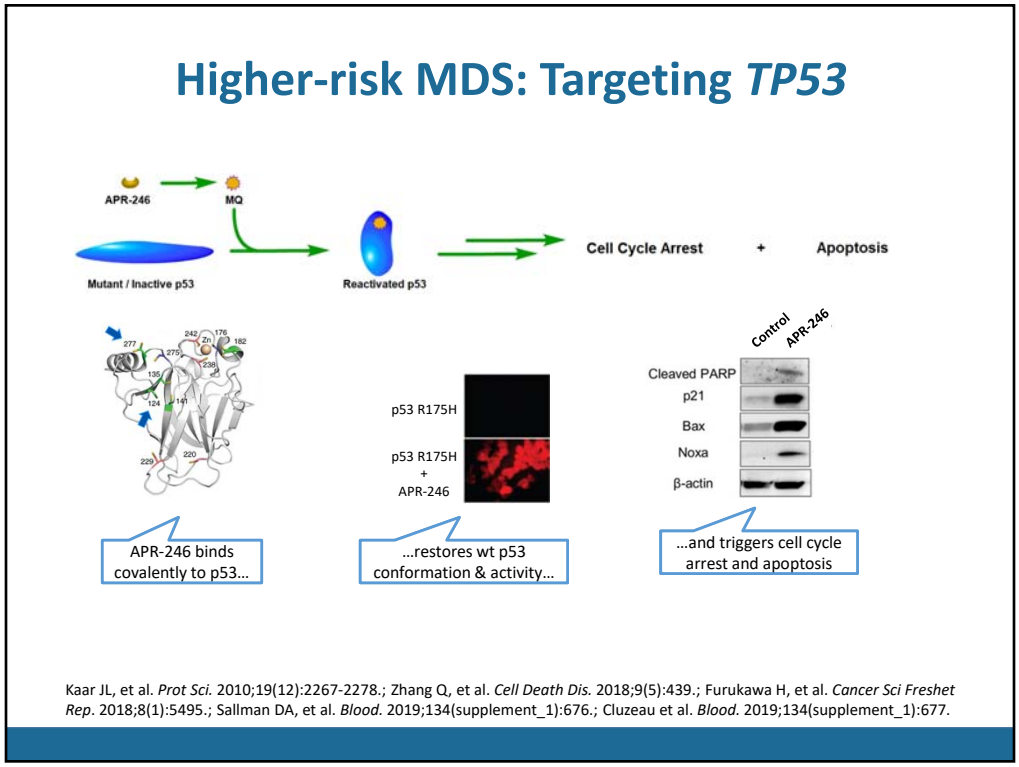
Now more recently, an oral decitabine combination was approved by the FDA and this is the study that led to its approval. Keep in mind there were some patients who had lower-risk MDS who were enrolled onto this study, and the study had an unusual design in which patients received oral decitabine or IV decitabine for their first cycle and then could switch over, so the study was really designed to look at distribution of the drug within the body to get across approval on the already approved IV decitabine. We don't have any survival data with the oral decitabine regimen. It looks like the response rates are pretty similar to what we would see with IV decitabine, but I still don't think we're quite there yet with level-one evidence for using this upfront for patients who have higher-risk MDS. There are other considerations, though that may lead to this. Certainly, there's convenience in taking a pill versus receiving the drug IV, and as patients are fearful of contracting infections, such as COVID-19 in medical centers, they may prefer less contact with healthcare facilities and opt for an oral regimen.



There are some combinations that have been explored in higher-risk MDS that capitalize on this azacitidine backbone. This trial randomized patients to receive azacitidine monotherapy or azacitidine plus pevonedistat which is a neddylation inhibitor, and all of these patients had higher-risk MDS.

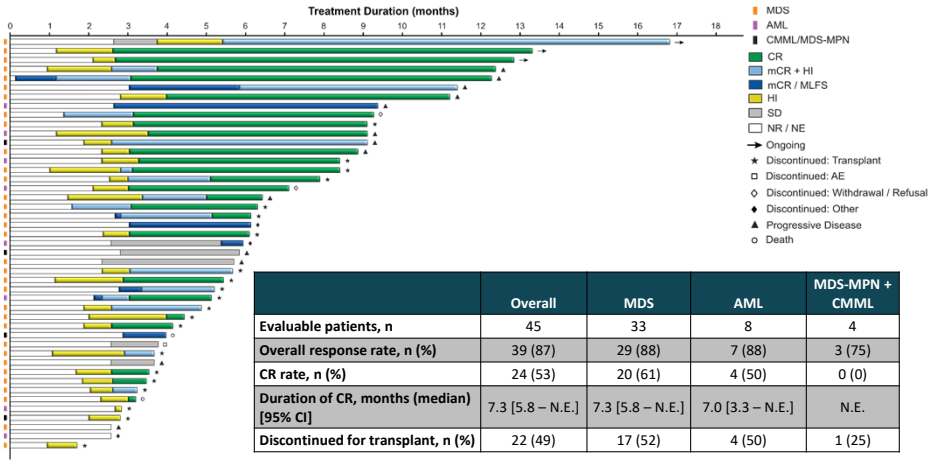


The primary endpoint of this study was event-free survival and there was a significantly prolonged event-free survival for those who got the combination of azacitidine and pevonedistat versus azacitidine alone at 20 months versus 15 months. Overall survival, the study was not powered to show a difference, however, numerically, there was a prolonged overall survival for those who got the combination at 24 months versus 19 months for azacitidine monotherapy.



Now we talked before about actionable mutations and targeting those mutations with drugs. This is a study of the drug APR-246. This drug binds covalently to p53 and restores p53 conformation and activity in cells.

Higher-risk MDS: Targeting *TP53*



	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
Overall response rate, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, months (median) [95% CI]	7.3 [5.8 – N.E.]	7.3 [5.8 – N.E.]	7.0 [3.3 – N.E.]	N.E.
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)

Median duration of follow-up = 10.8 months

Sallman DA, et al. *Blood.* 2019;134(supplement_1):676.; Cluzeau T, et al. *Blood.* 2019;134(supplement_1):677.

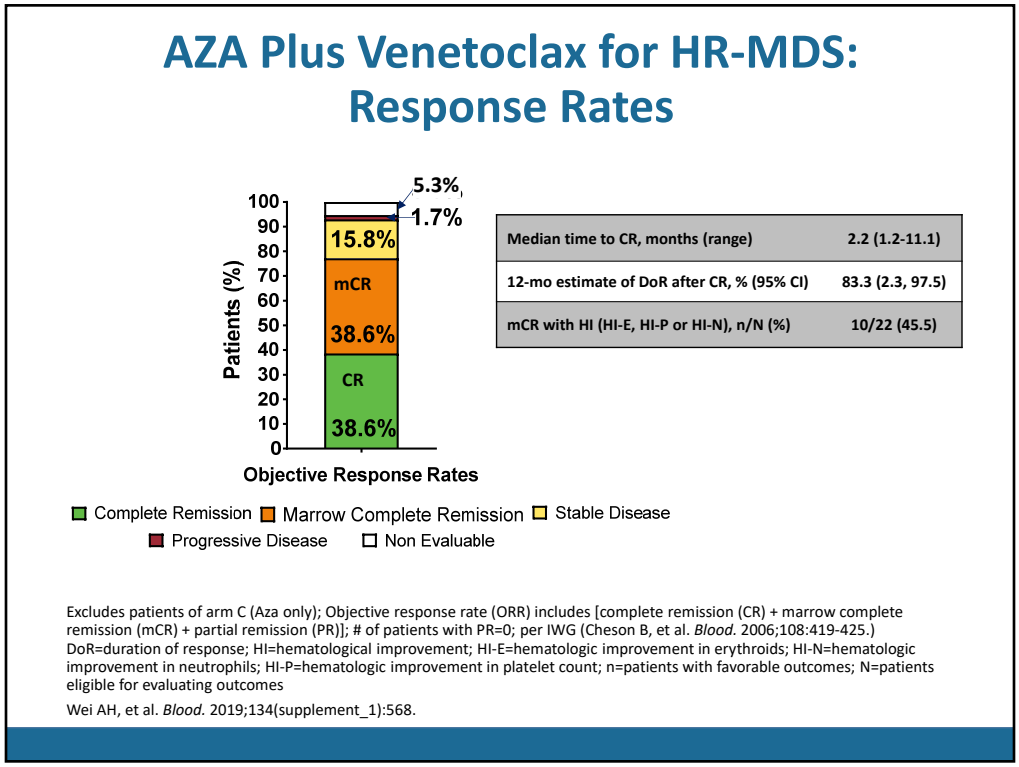
In a single-arm study in which APR-246 was added to azacitidine, the overall response rate was 87% for patients who had MDS or AML, and the response duration was about seven months. Now, that response duration is short because a lot of these patients went on to receive a hematopoietic cell transplantation and were censored at that time point. So we're eagerly awaiting results from a randomized study in which patients received APR-246 plus azacitidine versus azacitidine alone when those patients all had a p53 abnormality.

AZA Plus Venetoclax for HR-MDS

- Phase 1b study
- Untreated *de novo* MDS, IPSS Int-2 or high risk, not planning intensive chemo or transplant
- Ven days 1-14 (400 mg/day, no ramp up)
  - Prophylactic antimicrobials required
- 57 patients
  - Med age 71 (26-85);
  - IPSS-R very high risk: 60%

Wei AH, et al. *Blood.* 2019;134(supplement_1):568.

You've already heard about the combination of azacitidine and venetoclax. This has been explored in higher-risk MDS in a study that was led by Andrew Wei from Australia. Fifty-seven patients were enrolled on this study.



The response rate is actually hard to determine from the slides that have been presented. It settles out to be slightly over 50% for hematologic improvement or a CR. The response duration hasn't yet been reported. Now, one of the concerns with adding venetoclax to azacitidine is that that doesn't truly represent less intensive therapy, and that patients with MDS may not be able to tolerate the combination, particularly given how myelosuppressive venetoclax is. So more to come on this combination, we still do not recommend it for the treatment of higher-risk MDS.

MDS: Conclusions

- **Biology** >> what we can do about it
- For lower-risk MDS, focus on what bugs patient most:
  - **Anemia**
  - **Thrombocytopenia**
  - **Lots o' penia**
- Same for higher-risk, and focus on response duration, overall survival
- Goals of therapy should reflect goals of patient

What can we conclude about treatments for MDS? Well, unfortunately our knowledge of biology in MDS is much greater than what we can do about it, but we're getting there. For lower-risk MDS, we focus on what bugs a patient most, it may be anemia, it may be thrombocytopenia or it may be what I call 'lots of penias,' multiple cytopenias, that we need to try to fix. It's the same for higher-risk MDS but we also focus on response duration and overall survival. And we always have to ensure that the goals of therapy that we're recommending are actually reflecting the goals of our patients.

Treatment Advances in Acute Myeloid Leukemia and Myelodysplastic Syndromes

I want to thank you for listening to this portion of the presentation, along with all of the folks who comprise our Leukemia and MDS Program at Cleveland Clinic and, of course, our patients.

Vijaya Bhatt: Thank you, Dr. Sekeres.

Now, we are going to discuss a few illustrative cases to discuss management of newly diagnosed AML, relapsed/refractory AML, and MDS.

Case #1: Newly Diagnosed AML

- 72-year-old woman, independent and fully functional
- Presented with fatigue and pancytopenia
- Marrow: 80% cellularity with 25% blast with significant multilineage dysplasia
- Karyotype: 46,XX,del(7)(q22q36)[10]/47,XX,+8[10]
- FISH: Deletion 7q31 , trisomy 8
- **Acute myeloid leukemia with myelodysplasia related changes**
- Underwent a geriatric assessment

Let's start with the case scenario of a newly diagnosed AML. A 72-year-old woman presents with fatigue and pancytopenia. A bone marrow biopsy demonstrates acute myeloid leukemia with significant multilineage dysplasia. Karyotyping and FISH analysis demonstrate deletion 7q. Based on the presence of multilineage dysplasia and deletion 7q31, the patient is diagnosed with acute myeloid leukemia with myelodysplasia-related changes. She undergoes a geriatric assessment.

Case #1: Newly Diagnosed AML

- **Geriatric assessment:** KPS 80%, excellent self-report of physical function confirmed on objective assessment (short physical performance battery), normal cognition on MOCA test, comorbidities included osteoporosis

Geriatric assessment, which is an emerging tool to evaluate functional status of an older patient, demonstrates excellent physical function, normal cognition, and relatively few comorbidities such as osteoporosis.

We know that acute myeloid leukemia with MRC is a common diagnosis in older adults. There are several treatment options. As I discussed previously, CPX-351 is approved based on randomized phase 3 trial data that demonstrated superior overall survival over 7+3. There are also low-intensity chemotherapy options such as azacitidine and venetoclax combination as well as others that we have discussed. These low-intensity chemotherapy options are used for patients who are unfit for intensive chemotherapy. So when I think about how to select a treatment option, I think about patient's fitness for tolerating intensive chemotherapy, looking at their physical functional status, comorbidities, as well as it's quite important to engage the patient in decision-making and find out what their preferences are. Dr. Sekeres, do you have any comment about this?

Mikkael Sekeres: Yes, I love, in particular, two aspects of what you just presented and that is your focus on patient preferences, so patient goals, and an assessment of patient's true fitness and performance status. We just published guidelines from ASH on the treatment of older adults with AML in *Blood Advances*, and we constructed these guidelines around patient decision-making, patient goals, and patient's ability to tolerate therapy. In those guidelines, we recommend some therapy over no therapy, which may seem like a funny recommendation until you recognize that in SEER-Medicare databases, only about 50% of patients who are older are offered any therapy at all.

We then do recommend more intensive therapy compared to less intensive therapy in patients for whom that's their goal. And then we get into the discussion about azacitidine versus azacitidine and venetoclax. There are survival data, of course, that have just been published favoring azacitidine and venetoclax over azacitidine, but one tricky aspect of that is that all of those patients were actually hospitalized to receive their azacitidine and venetoclax, and that doesn't necessarily align with patient goals. And so a lot of us in the leukemia community are starting to think about azacitidine and venetoclax as not necessarily less intensive chemotherapy, but somewhere in between less intensive, such azacitidine, and traditional 7+3. And that was alluded to in an editorial that accompanied that primary article in the *New England Journal of M*edicine. I think for this patient who appears to be fit by your assessment, if it aligns with her goals, I would favor a more intensive chemotherapy in the inpatient setting. And I would also start to think about whether azacitidine and venetoclax should be considered more intensive as it was given an inpatient setting in that randomized trial.

Vijaya Bhatt: Thank you, Dr. Sekeres for that comment. I agree azacitidine and venetoclax combination does have significant risk of myelosuppression and infection. There are several considerations while using azacitidine and venetoclax, including how to adjust dose and duration based on myelosuppression. As I briefly discussed, there is significant drug-drug interaction between venetoclax and several antifungal agents which requires dose adjustment. There is also emerging practice pattern to perform bone marrow biopsy earlier after azacitidine-venetoclax given that many patients achieve remission within a month of treatment or so, and it's important to differentiate whether cytopenias are related to leukemia versus whether cytopenias are related to residual leukemia. And an early bone marrow biopsy can differentiate that, allowing to hold drug if it is because of drug-induced myelosuppression. On the other hand, if it's because of leukemia, we may not hold venetoclax sooner during the treatment course.

Case #1: Newly Diagnosed AML

- Willing to get admitted for intensive chemotherapy
- Treated with **CPX 351 induction**
- Subsequent mutation panel results: IDH2 34% and RUNX1 37%
- Complications: neutropenic fever, bacteremia
- Maintained functional status
- Achieved complete remission including negative flow and FISH
- One cycle of CPX 351 consolidation and then allogeneic stem cell transplant

For this patient, she was willing to get admitted for intensive chemotherapy, so she was treated with CPX-351. She had neutropenic fever and bacteremia, but she maintained her functional status and achieved complete remission including a negative flow and FISH test. Following another cycle of CPX-351 consolidation, she subsequently underwent allogeneic stem cell transplantation.

Case #2: Relapsed/Refractory AML

- 69-year-old man
- Presented with fatigue, dyspnea on exertion and pancytopenia
- Marrow: 80% cellularity with 40% blast with significant dysplasia
- Karyotype: **complex karyotype**
- **Treatment-related acute myeloid leukemia** (prior radiation)
- Underwent a geriatric assessment

Let's discuss another case where we'll discuss relapsed/refractory AML. A 69-year-old man presented with fatigue, dyspnea, and pancytopenia. A bone marrow biopsy demonstrated 40% blast with significant dysplasia. Karyotyping demonstrated complex karyotype. However, given prior radiation history, the patient was diagnosed with treatment-related acute myeloid leukemia. The patient again underwent a geriatric assessment.

Case #2: Relapsed/Refractory AML

- **Geriatric assessment:** KPS 70%, good physical function confirmed on objective assessment (short physical performance battery), normal cognition on MOCA test, **multiple comorbidities** including prior testicular and prostate cancer, COPD, diabetes, high BMI

The geriatric assessment demonstrated that physical function and cognition was good. However, the patient did have multiple comorbidities including prior testicular and prostate cancer requiring surgery and radiation, history of COPD, diabetes, and high BMI.

Case #2: Relapsed/Refractory AML

- Treated with **azacitidine and venetoclax**
- Blast count reduction to 6% but then progressed to 25%
- No FLT3, IDH1, or IDH2 mutations
- Treated with **FLAG** salvage – tolerated well and achieved complete remission
- Underwent **allogeneic stem cell transplant**

Again, therapy-related AML is another common diagnosis in older adults. The treatment options are similar to what we discussed for AML with myelodysplasia-related changes. CPX-351 is again approved for this indication. There are other options including azacitidine, venetoclax, and other treatment options we have discussed.

For this patient, because of comorbid conditions, we decided to treat this patient with azacitidine and venetoclax. Initially, blast count produced about 6% but then progressed to 25%. The molecular analysis during this time did not demonstrate FLT3, IDH1 or IDH2 mutations, hence targeted treatment options were not available for this patient. He underwent cytotoxic salvage chemotherapy with FLAG and underwent allogeneic stem cell transplantation.

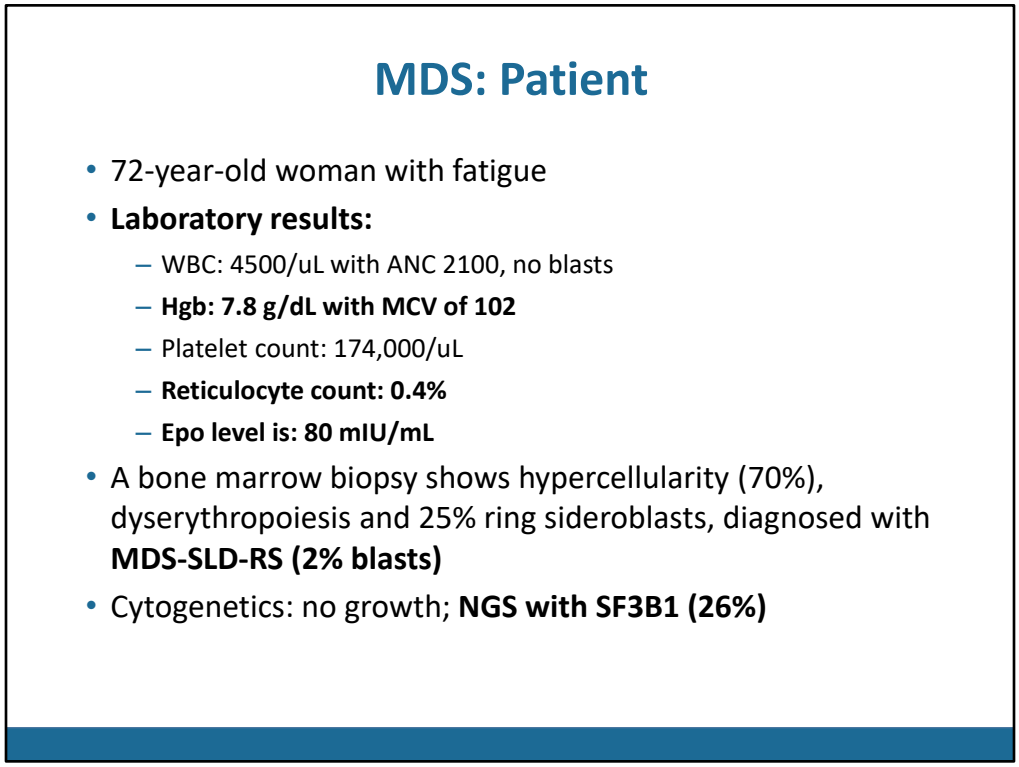
Now, we have discussed several novel treatment options during this discussion today. However, it's important to realize that even these novel treatment options may not achieve long-term cure. For example, azacitidine and venetoclax certainly improves overall survival over azacitidine; however, most patients still relapse. For fit patients who are able to undergo allogeneic stem cell transplantation, it's quite important to consider allo transplant if the patient is eligible, has a suitable donor, and wants to undergo allo transplantation. Dr. Sekeres, do you have any comment about this case?

Mikkael Sekeres: Yes, this is another complicated one. For patients who are higher risk like

this, so either poor karyotypic abnormalities, a poor molecular profile at baseline, or what we think is causality between a previous treatment for cancer either radiation therapy and chemotherapy, and subsequent myeloid malignancies, so true therapy-related AML, we need to consider more aggressive approaches in the post remission setting, and I would have considered this patient for hematopoietic cell transplantation as well. One of the areas that I've gotten a little bit stuck on is that although this patient would have certainly met the label for CPX-351, the cost is really so much more than classic 7+3. I think there are a lot of medical centers in the country that have been resistant to giving the new drug. The cost of CPX-351 for a couple of cycles, and most of these patients do require a couple of cycles, approaches $60,000.

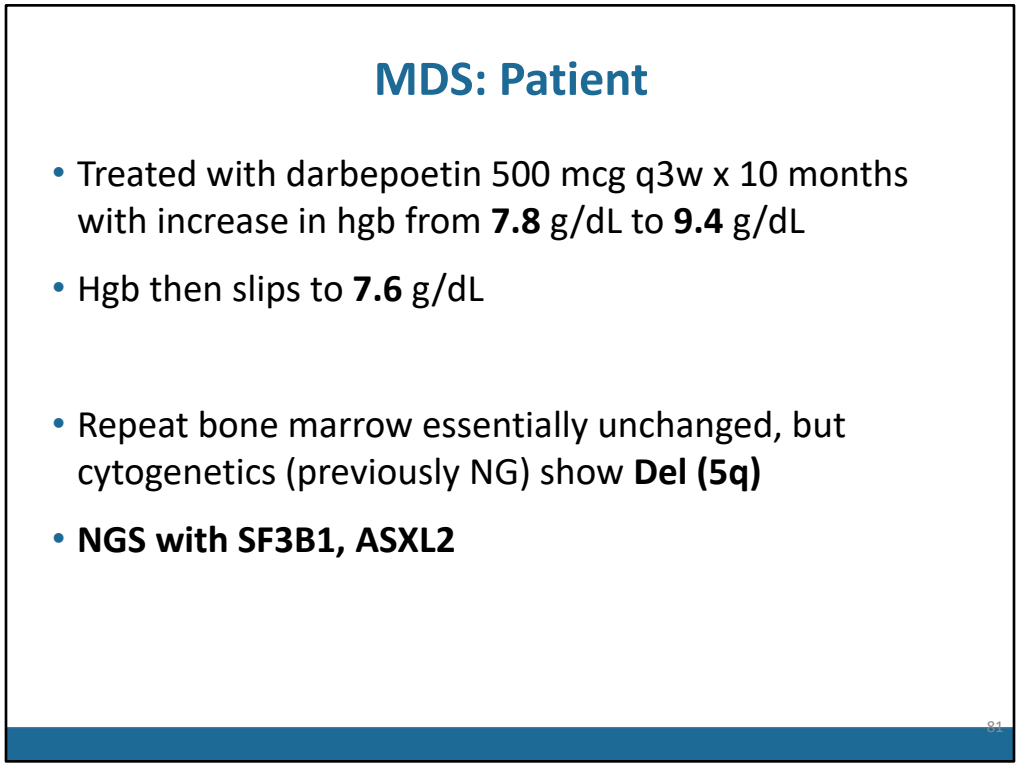
Actually in our institution, we don't have CPX-351 on formulary. We also have some concerns about the conduct of the confirmatory trial where patients in the control arm probably didn't do quite as well as they did in the CPX arm, and patients in the CPX arm seemed to have gotten more chemotherapy than those in the control arm since they were more likely to receive a couple of doses of the CPX-351. So in this patient, just as you indicated, depending on his goals and, as you mentioned, his performance status as measured by the assessments you reviewed, we would have considered either intensive therapy or somewhat less intensive therapy, whether that's azacitidine monotherapy or combined with venetoclax.

Vijaya Bhatt: Thank you, Dr. Sekeres for the comment. Now, Dr. Sekeres is going to discuss a patient with MDS.

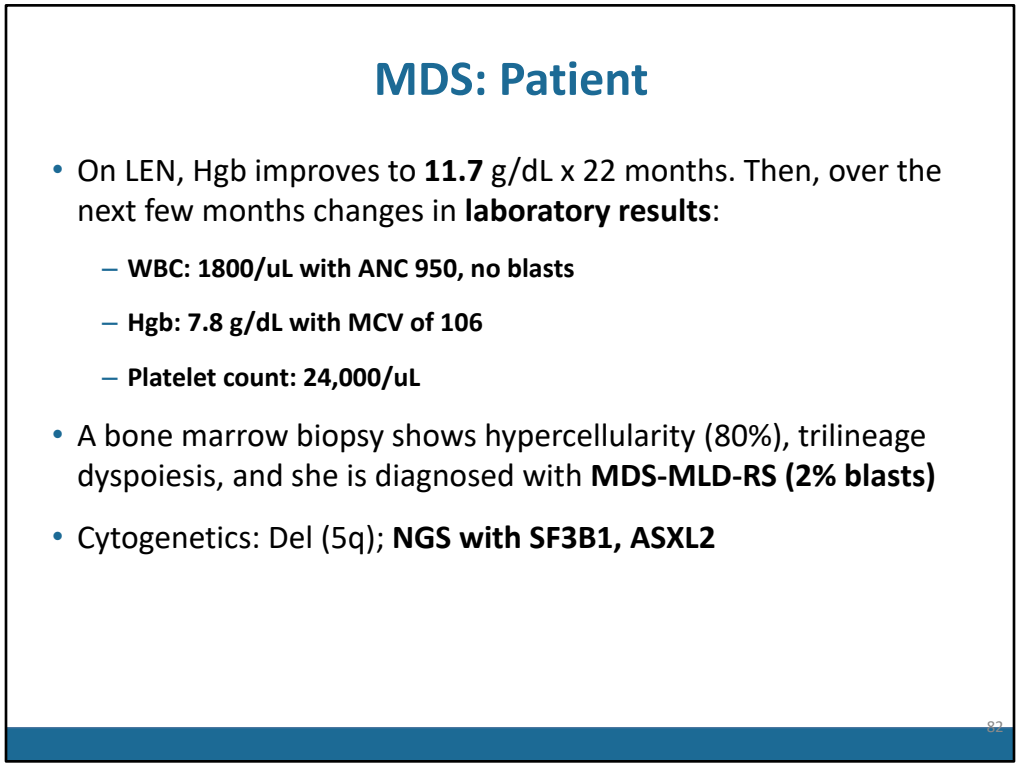


Mikkael Sekeres: So a 72-year-old woman presents to your clinic with fatigue and she has the following lab results. Her white count is relatively well preserved at 4500 with a neutrophil count of 2100. Her hemoglobin though is low at 7.8 with an MCV that's elevated at 102. Her platelet count is preserved. Her reticulocyte count is inappropriately low for the degree of anemia she has at 0.4%, and her EPO level is high by lab standards where the upper limit of normal is 25 but low by MDS standards at 80, at less 100. She undergoes a bone marrow biopsy. This shows a hypercellular bone marrow for her age at 70%, dyserythropoiesis, and 25% ring sideroblasts, and she is diagnosed with MDS with single lineage dysplasia with ring sideroblasts, she has 2% blasts. Her cytogenetics, unfortunately, are no growth and this does occur fairly often with patients with MDS, but her next-generation sequencing panel reveals an SF3B1 mutation.

So this is a patient who has a couple of options. She has an isolated anemia. We don't need to fix anything with her white count and her platelet count, and I would say that once a hemoglobin goes less than 8, we need to start thinking about interventions because that's the point at which we would also consider red blood cell transfusions. She does have ring sideroblasts and she has the associated SF3B1 abnormality, so I think we've got a couple of options here. And when we're considering treatment options for someone who has lower-risk MDS, recall that our focus is on improving their quality of life and minimizing their transfusion needs. No drug has ever been shown prospectively in lower-risk MDS to improve overall survival, so ultimately our focus is going to be on quality of life and transfusion needs. We need to think about what drugs could potentially improve her anemia and hopefully prevent her from receiving any transfusions. She does have fatigue, so we know we've got something to work on with her quality of life.

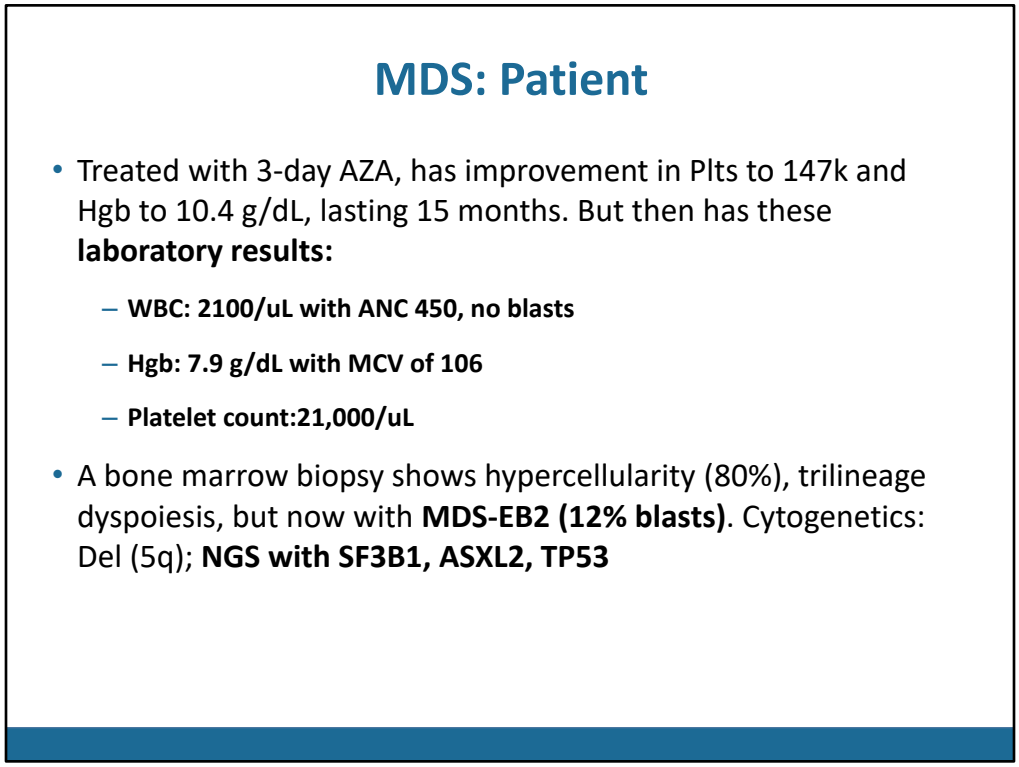


She is actually treated with an ESA, darbepoetin. Now, the study that was looked at in the US actually used darbepoetin at a dose of 500 mcg every three weeks and then if a patient didn't respond, that frequency was shortened to every two weeks. One of the things I've noticed in how darbepoetin is given is it's often given in a variety of different ways, but this is actually the way it should be given, 500 mcg every three weeks to start with. And this does result in an increase in her hemoglobin from 7.8 to 9.4 and her hemoglobin slips down to 7.6. She undergoes a bone marrow biopsy, which we always do when we're considering next rounds of therapy and when someone's blood counts are slipping, and recall her karyotype which previously was no growth and now shows a deletion 5q abnormality. Her next-generation sequencing continues to show the SF3B1 along with an ASXL2 mutation. I think she's got a couple of potential treatment options here. Because of the spliceosome mutation and the ring sideroblasts, we could consider luspatercept or because of the deletion 5q abnormality, we could consider lenalidomide.



Now in this case, she's treated with lenalidomide and her hemoglobin does improve for 22 months, but then she again starts to have her blood count slip with an anemia, a low white blood cell count with an ANC that's starting to get low, and thrombocytopenia. A repeat bone marrow biopsy shows she has multilineage dysplasia, still with ring sideroblasts, and her cytogenetics continued to show a deletion 5q, while her next-generation sequencing panel continues to show the same abnormalities.

This is where we would reflect. What do we need to fix with her? What's her predominating problem? If it was isolated thrombocytopenia, we could consider one of the TPO mimetics that we discussed earlier, romiplostim or eltrombopag. Isolated anemia, we still have luspatercept we haven't used. If she has an isolated neutropenia, it's a little bit tricky with patients with MDS. No study has really shown efficacy in giving a granulocyte colony-stimulating factor to somebody with MDS. If somebody isn't having recurrent infections, we basically leave them alone with their neutrophil count.



In this case, we used a hypomethylating agent. She has a couple of things that are worrisome, it's the low platelet count and the continued anemia, and she does respond to this with an improvement in her platelet count and an improvement in her hemoglobin that lasts 15 months. But then her counts start to drop again, always prompting another bone marrow biopsy. And this time, if you add all the time periods up, she has had MDS for a few years, and she evolves to a higher-risk MDS with excess blasts in the range of 12%. She also develops a p53 abnormality and this is common in patients who have deletion 5q, have been exposed to lenalidomide, and then become refractory to that lenalidomide. At this point, we would start to consider more aggressive therapies and either whether she should head towards a transplant. So I wonder Dr. Bhatt, this is kind of a typical referral for me, someone who's been exposed to a lot of the drugs that are on the market for MDS and now has an even more advanced MDS. What treatment would you consider for somebody with a higher-risk MDS who's already been on a hypomethylating agent?

Vijaya Bhatt: I would agree with you, Dr. Sekeres. This patient also had ASXL2 mutation. It's not clear whether 5q deletion was present at the time of diagnosis or not. Any patient who has cytogenetic evolution over time would be concerned about risk of developing AML and poor outcome. In patients with MDS, as you pointed out, azacitidine certainly improves overall survival. However, long-term survival is still low, especially in young fit patients or even older adults who are fit and willing to undergo allogeneic stem cell transplantation, at least discussing up risk and benefit of allogeneic stem cell transplantation makes a lot of sense.

Mikkael Sekeres: And would you recommend she go to a transplantation with 12% blasts in her bone marrow or would you try to reduce that somehow?

Vijaya Bhatt: That's an excellent question. There are several studies which have discussed how much pre-transplant chemotherapy is valuable. The current practice is to try to cytoreduce to the extent possible. There is a CIBMTR database study that demonstrates lower blast percentage at the time of transplantation correlates with better outcome. In general, the tendency of a transplant doctor would be to try to cytoreduce a patient before transplant if at all possible.

Mikkael Sekeres: Yes, and I completely agree and this is someone in whom we really don't have a lot of treatment options available. Rigosertib is a polo-like kinase inhibitor that is tried now twice to conduct randomized studies in this type of population and unfortunately has failed both times to show an improved overall survival compared to giving things like low-dose cytarabine. In this sort of patient, if it aligns with her goals, I would probably recommend cytotoxic therapy that is cytarabine-based to try to lower that blast percentage even further, and then try to get her to a bone marrow transplantation.

Vijaya Bhatt: The other important aspect that you highlight is patients with MDS, especially patients who have failed hypomethylating agent do not have great options. Certainly, we need more clinical trials in that setting.

Mikkael Sekeres: Absolutely. And I will say one practice I've seen that really does not work is switching from one hypomethylating agent to another, so I would not introduce now decitabine or the oral decitabine in this setting. It just simply has such an incredibly low likelihood of working, and this is someone where we might just have to reflect back to classic cytotoxic chemotherapy. Ideally, this is someone where we would enroll on a clinical trial.

Key Takeaway Points

- Genetic and molecular analyses have several diagnostic and prognostic for AML and MDS
- The diagnosis of AML MRC is based on the presence of cytogenetic changes
- Targeted agents are available for patients with IDH1, IDH2, or FLT3 mutated AML
- Availability of several novel drugs, discussed today, provide more treatment options for our patients, and can improve patients' survival and quality of life when used appropriately

Vijaya Bhatt: Well, we are reaching towards the end of this discussion. In conclusion, some of the take-home messages for the community oncologists in my mind include the fact that genetic and molecular analysis have several diagnostic and prognostic implications for AML and MDS as we discussed throughout this presentation. The diagnosis of AML with myelodysplasia-related changes is based on the presence of cytogenetic changes in addition to what pathological report indicates. Targeted agents are available for patients with IDH1, IDH2 or FLT3-mutated AML. We discussed several novel treatment options today, which can provide more treatment options for our patients, and can improve patient survival and quality of life when we use it appropriately. Before we conclude, Dr. Sekeres, do you have any other concluding remarks?

Mikkael Sekeres: What I really appreciate about your presentation, Dr. Bhatt, is the focus on patient decision making and patient goals. And I think this has to be upfront in our minds, particularly when we're treating older adults who have either MDS or acute myeloid leukemia. I always remind myself that I haven't lived the same life that my patients have, so I don't know that I would make the same choices about treatment that they would. And it's just worth it investing time and exploring that at the very beginning of a treatment course to make sure that we're ultimately doing right by our patients.

Vijaya Bhatt: I could not agree more with you, Dr. Sekeres. Thank you so much, Dr. Sekeres, for joining me today for this discussion, and thank you so much to our audience for joining us today. We hope that our presentation will be useful for your clinical practice. Thank you so much.

Mikkael Sekeres: Great, thank you.