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Therapeutic Advancements in Myelodysplastic Syndromes: Bridging the Gap Between Patient Safety and Quality Care Through the Latest Science and Evidence–Based Learning in Nursing Practice
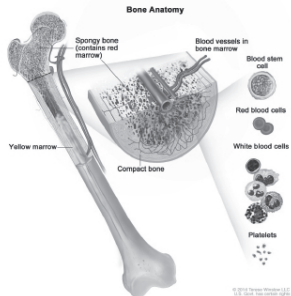
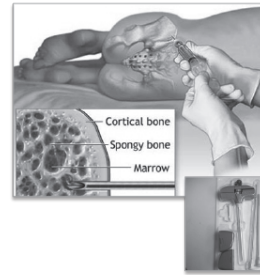## Myelodysplastic Syndromes (MDS)[1]

A group of heterogeneous clonal hematopoietic cell neoplasms
1. Cytopenia
2. Dysplasia and possible presence of blasts
3. Ineffective hematopoiesis
4. Recurrent cytogenetic or molecular abnormalities
5. Tendency towards AML

1. Bennett J et al. *Int J Hematol*. 2002;76(suppl 2):228-238.

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Bone Marrow Aspiration and Biopsy

Key Findings From a Bone Marrow Biopsy
Cellularity
- Ratio of hematopoietic cells to fat
- Naturally declines with age
- Subtract age from 100 = normocellular
- Most accurately taken from H&E sections of core biopsy

Hypercellular marrows
- Majority of cases of MDS
- Extramedullary cell destruction
- Leukemias
- Infection
- Hypoxia

Hypocellular marrows
- Aplastic anemia (immune mediated)
- Chemotherapy or other toxin such as radiation
- Infections
- Hypoxia

Image Credits: https://www.mountsinai.org/health-library/tests/bone-marrow-biopsy and courtesy of Sara M. Tinsley, PhD, APRN, AOCN.

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Ancillary Studies From Bone Marrow Biopsy
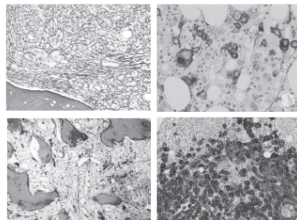
- Immunohistochemical studies
- Chromosomal analysis—cytogenetics
- Fluorescence in situ hybridization (FISH) for MDS if failed cytogenetics
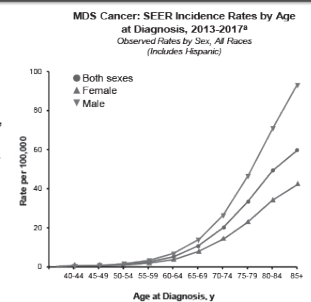- Molecular testing—NGS 54 gene myeloid panel
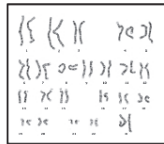
Images courtesy of Sara M. Tinsley, PhD, APRN, AOCN.

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Incidence of MDS[1,2]

- Overall incidence: ~5 per 100,000 = most common myeloid neoplasm

- Overall incidence may be artificially low, as MDS is under-represented in most cancer registries; some estimate 75 per 100,000 in the >60-y age group

- Approximately 10,000/y in the United States; median age >70 y

MDS Cancer: SEER Incidence Rates by Age at Diagnosis, 2013-2017[a]
Observed Rates by Sex, All Races (Includes Hispanic)

- Both sexes
- Female
- Male

[a] Estimates based on less than 16 cases are suppressed and not shown.
1. https://seer.cancer.gov/explorer/application.html. 2. Ma X. *Am J Med*. 2012;125(7 suppl):s2-s5.

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Epidemiology and Clinical Presentation[1,2]

- Median age of diagnosis is between 70—75 y
- Risk factors: approximately 90% of cases occur de novo with no identifiable cause
  - De novo
    - Cigarette smoking
    - Ionizing radiation
    - Organic chemicals (eg, benzene, toluene, xylene, chloramphenicol)
    - Heavy metals
    - Herbicides, pesticides, fertilizers
  - Secondary MDS
    - Chemotherapy with alkylating agents
- Presentation
  - Clinical symptoms of pancytopenia (eg, anemia, bleeding, easy bruising, fatigue)
  - Laboratory abnormalities: macrocytosis, neutropenia, thrombocytopenia, anemia, signs of hemolysis due to ineffective erythropoiesis

1. Du Y et al. *Leuk Res*. 2010;34:1-5. 2. Strom SS et al. *Leukemia*. 2005;19:1912-1918.

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Patient Evaluation and Diagnosis[1]

Cytopenia(s), suspect myelodysplasia →
- H&P
- CBC, platelets, differential, reticulocyte count
- Examination of peripheral blood smear
- Bone marrow aspiration with iron stain + biopsy + cytogenetics by standard karyotyping
- Consider testing bone marrow sample for fibrosis
- Serum erythropoietin (prior to RBC transfusion)
- RBC folate, serum B12
- Serum ferritin, iron, TIBC
- Documentation of transfusion history
- TSH
- LDH
- Genetic testing for somatic mutations (ie, acquired mutations) in genes associated with MDS is highly recommended
- Recommend additional molecular and genetic testing for hereditary hematologic malignancy predisposition in a subset of patients, particularly in younger patients
- HIV testing if clinically indicated
- Consider evaluation of copper deficiency in patients with GI malabsorption, severe malnutrition, gastric bypass surgery, or patients on zinc supplementation
- Consider distinction from CSA

1. NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf.

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Diagnosing MDS According to 2016 WHO Classification[1]

Observation	Sufficient to Diagnose MDS in a Patient With Cytopenia?
Dysplastic morphology (≥10%)	**Yes**, provided possible secondary causes of cytopenia and dysplasia are excluded clinically
Excess marrow blasts (≥5%)	**Yes**, provided marrow recovery and growth factor effect are excluded
Cytogenetic abnormality	**Yes**, provided it is on the WHO list of "approved" abnormalities (excluding +8, -Y, del[20q])
Flow cytometry abnormality	**No**, but can support an MDS diagnosis suspected by other observations
MDS-type mutation	**No**, as these can be found in normal individuals ("clonal hematopoiesis of indeterminate potential"); may support an MDS diagnosis suspected by other observations

1. Arber DA et al. *Blood*. 2016;127:2391-2405.

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Prognostic Impact of Mutations in MDS[1]

Somatic Mutations and Prognostic Significance in the IPSS-Rm[a]

Prognostic Impact	Mutation (Frequency in MDS Patients)
Improved OS	*SF3B1* (14%)
Intermediate/undefined impact on OS	*TET2* (17%), *DNMT3A* (11%), *GPR98* (8%), *ZRSR2* (7%), *BCOR* (6%), *APC* (5%), *SUZ12* (5%), *PRP58* (4%), *CUX1* (3%), *DDX54* (3%), *IDH1* (3%), *KDM6A* (3%), *PHF6* (3%), *SETBP1* (3%)
Inferior OS	*ASXL1* (15%), *STAG2* (11%), *RUNX1* (10%), *U2AF1* (9%), *TP53* (5%), *NF1* (5%), *EZH2* (5%), *CBL* (4%), *NRAS* (3%)

[a] Remaining independent prognostic factors in a Cox proportional hazard model including age and IPSS-R score.
1. Mufti GJ et al. *Leukemia*. 2018;32:1679-1696.

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[a] Remaining independent prognostic factors in a Cox proportional hazard model including age and IPSS-R score.
1. Mufti GJ et al. *Leukemia*. 2018;32:1679-1696.

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Revised International Prognostic Scoring System (IPSS-R)[1]

| Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	≤ 2		>2 to <5%		5-10%	>10%	
Hemoglobin	≥ 10		8 to <10	<8			
Platelets	≥ 100	50 to <100	<50				
ANC	≥ 0.8	<0.8					

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

1. Greenberg PL, et al. *Blood*. 2012;120:2454-2465.

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IPSS-R Risk Groups: Overall Survival and Progression to AML[1]

	Risk Group	Points	Median Survival, y	Time Until 25% of Patients Develop AML, y
Lower-Risk	Very low	≤1.5	8.8	NR
	Low	>1.5-3	5.3	10.8
	Intermediate	>3-4.5	3.0	3.2
Higher-Risk	High	>4.5-6	1.6	1.4
	Very high	>6	0.8	0.73
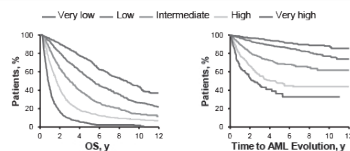
1. Greenberg PL et al. *Blood*. 2012;120:2454-2465.

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Treatment Goals in MDS[1-3]

| MDS Type (IPSS)	Treatment Goals
Lower-risk MDS IPSS-R: Score <3.5	• Achieving RBC-transfusion independence • Decreasing the symptom burden of iron overload • Hematologic improvement • Improving QOL
Higher-risk MDS IPSS-R: Score ≥3.5	• Overall survival and lowering the risk of transformation to AML • Altering disease's natural history • Reducing the symptom burden and improving QOL

1. Komrokji RS et al. *Curr Hematol Malig Rep*. 2011;6:145-153. 2. Fenaux P et al. *Blood*. 2013;121:4280-4286. 3. Beierdorf JP, Zeidan AM. *Cancers (Basel)*. 2021;13:1610.

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European Leukemia Net Study: HRQOL in Patients With LR-MDS Compared With Age- and Sex-Matched Reference Populations[1]
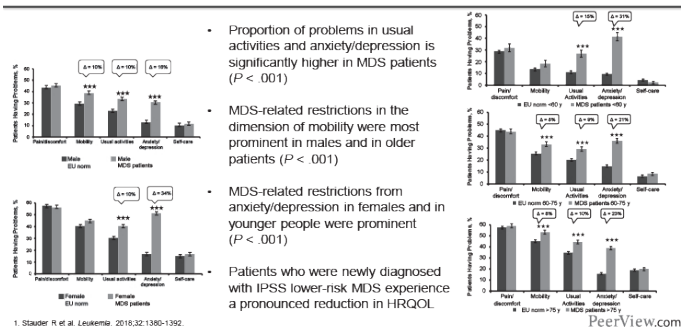
• Proportion of problems in usual activities and anxiety/depression is significantly higher in MDS patients ($P < .001$)

• MDS-related restrictions in the dimension of mobility were most prominent in males and in older patients ($P < .001$)

• MDS-related restrictions from anxiety/depression in females and in younger people were prominent ($P < .001$)

• Patients who were newly diagnosed with IPSS lower-risk MDS experience a pronounced reduction in HRQOL

1. Stauder R et al. *Leukemia*. 2018;32:1380-1392.

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Prospective International Validation of the QOL in Myelodysplasia Scale (QUALMS)[1,2]

Key: Both instruments; Fact-An-Only; Qualms only
1. Abel G et al. *Haematologica*. 2016;101:781-788. 2. Trudeau JJ et al. *J Patient Rep Outcomes*. 2020;4:69.

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Summary

• Diagnosing MDS remains challenging but is a crucial first step

• Point mutations in MDS are significant
  – Large body of information confirms significant impact of mutations on prognosis
  – Most data are still too immature to determine how to incorporate mutations into the existing, primarily morphologic classification

• Integration of new clinical risk models and somatic mutations will refine the risk stratification in MDS

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Clinical Case 1

Kathy is a 76-year-old woman diagnosed with MDS	• 1-year history of increasing fatigue and macrocytic anemia • Medical history: fatty liver • Past history – Left breast cancer (status: post left radical mastectomy, no chemo or radiotherapy) • Family history – No siblings, no children
Further testing shows…	• Bone marrow biopsy – Normocellular with ring sideroblasts (>5%), dyserythropoiesis, 3% blasts – Megakaryocytes: consistent with MDS – Cytogenetics: 46XX – Genetics: *SF3B1* mutation – Hb 8.1, WBC 4.2, platelets 240,000
Diagnosis and further management	• MDS with progressive anemia • Epoetin alpha 60,000 units/wk • No response

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Which of the Prognostic Subgroups Would Kathy Fall Into Based on the IPSS-R Staging System?

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
BM blast, %	≤2		>2 - <5		5 - 10	>10	
Hemoglobin	≥10		8 - <10	<8			
Platelets	≥100	50 - <100	<50				
ANC	≥0.8	<0.8					

Risk Category	Risk Score
Very low	≤1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very high	>6

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Nursing Implications for Managing Patients With MDS

Addressing patient concerns: Psychosocial factors influencing treatment
- Disease perception and coping with disease
- Goals of treatment, strategies for monitoring blood counts and transfusion burden
- Criteria for considering disease modifying treatment
- Patient support: family and caregivers
- Logistics of treatment, financial implications for patients

Setting expectations for symptom burden and QOL issues
- Physical: decreased strength, dyspnea, limited ability to adequately treat other conditions
- Emotional: anxiety, loneliness, despair
- Functional: fatigue, diminished stamina
- Social: altered role function, financial burden
- Spiritual: search for balance, renewed appreciation for life, hopelessness
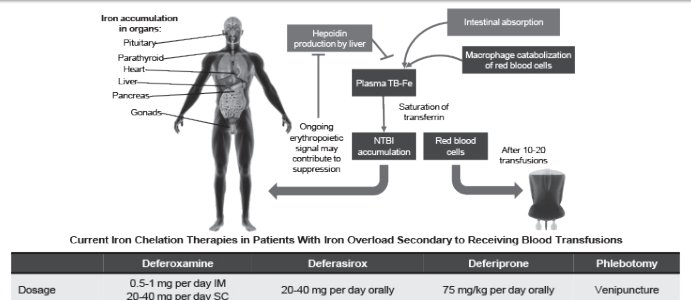
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The Burden of Transfusion Dependence in LR-MDS[1-5]

- Anemia is usually the most common cytopenia present in LR-MDS
- Transfusion dependence is inevitable for most patients with MDS over the course of their disease
- Transfusion dependence is associated with:
  - A higher incidence of dyspnea, hepatic disease, infections, and cardiac events within 3 years of follow-up
  - Increased risk of death (age adjusted) compared with other MDS patients
  - Inferior response to disease modifying treatments when transfusion frequency is increased
  - Higher health care related costs
  - Inferior health related QOL
  - Increased risk of iron overload

1. Goldberg SL et al. J Clin Oncol. 2010;28:2847-2852. 2. Fenaux P et al. Blood. 2013;121:4280-4286. 3. Harnan S et al. Acta Haematol. 2016;136:23-42. 4. Zeidan AM et al. Leukemia & Lymphoma. 2019;60:3181-3187. 5. Abel GA et al. Haematologica. 2016;101:781-788.

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Iron Overload: The Burden of Blood Transfusion[1]

Current Iron Chelation Therapies in Patients With Iron Overload Secondary to Receiving Blood Transfusions

	Deferoxamine	Deferasirox	Deferiprone	Phlebotomy
Dosage	0.5-1 mg per day IM 20-40 mg per day SC	20-40 mg per day orally	75 mg/kg per day orally	Venipuncture

1. Shah J et al. Clin J Oncol Nurs. 2012;16:37-46.

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Slow Progress in MDS Until Now…

ESAs often used but not FDA approved
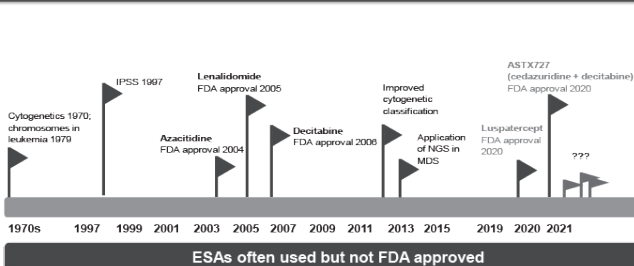
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Treatment Algorithm for LR-MDS: IPSS (Score <3.5)[1]
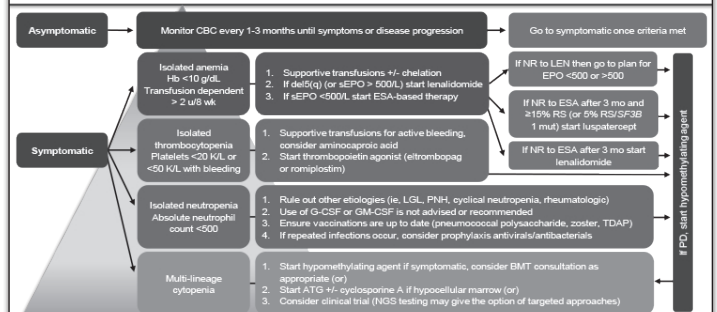
1. NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf.

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Luspatercept: Erythroid Maturation Agent[1-3]
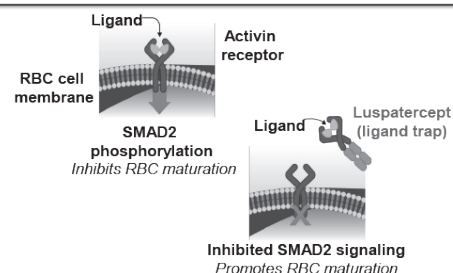
1. Piga A et al. 23rd Congress of European Hematology Association (EHA 2018). Abstract S844. 2. Attie K et al. Am J Hematol. 2014;89:766-770. 3. Suragani R et al. Nat Med. 2014;20:408-414.

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Phase 3 MEDALIST Study of Luspatercept in LR-MDS: Independence From RBC Transfusion[1,2]
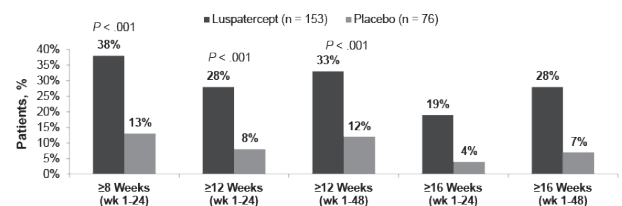
The most common AEs with luspatercept or placebo (of any grade and occurring in >10% patients) were fatigue, diarrhea, asthenia, nausea, dizziness, and back pain

1. Komrokji RS et al. EHA 2020. Abstract EP813. 2. Fenaux R et al. N Engl J Med. 2020;382:140-151.

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MEDALIST Study of Luspatercept in LR-MDS: Long-Term Transfusion Burden[1,2]

Mean Change From Baseline in RBC Units Transfused

+0.4 (-0.6 to +1.4)

3.0 (-3.9 to -2.1)

-4.9 (-5.9 to -3.9)

Placebo Weeks 9-24 (n = 68)
Luspatercept Weeks 9-24 (n = 128)
Luspatercept Weeks 33-48 (n = 78)

Mean Number of Transfusion Visits in Weeks 1-24

10.6
9.5
8.3

6.8
5.9
5.0

Luspatercept (n = 128)
Placebo (n = 68)

The FDA approved luspatercept on April 3, 2020, for treating anemia (failing an ESA and requiring ≥2 RBC units over 8 weeks) in adult patients with very low-risk to intermediate-risk MDS with ring sideroblasts or with MDS/MPN with ring sideroblasts and thrombocytosis

1. Komrokji RS et al. EHA 2020. Abstract EP813. 2. Fenaux R et al. N Engl J Med. 2020;382:140-151.

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DNA Methyltransferase Inhibitors (DNMTi) Are the Backbone of Disease-Modifying Therapy in MDS[1,2]

Median EFS
20 mo
14 mo

Azacitidine
Supportive care

Analyzed population = treatment-naive MDS patients

Decitabine (n = 69)
Supportive care (n = 65)

6 mo >

1. Silverman LR et al. J Clin Oncol. 2002;20:2429-2440. 2. Kantarjian H et al. Cancer. 2006;106:1794-1803.

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Improving Delivery of DNMT Inhibition

CC-486
Guadecitabine

CC-486: oral azacitidine
ASTX727: oral decitabine + CDA
ASTX030: oral azacitidine + CDA

Increase bioavailability

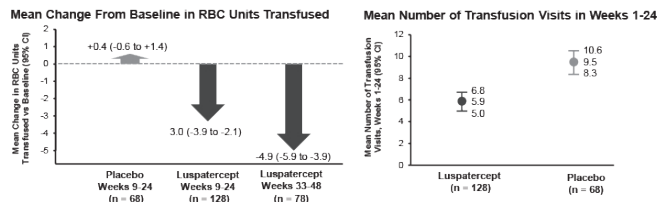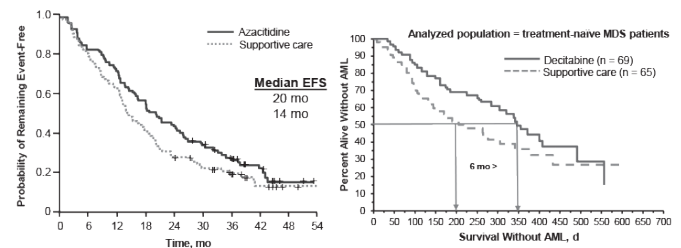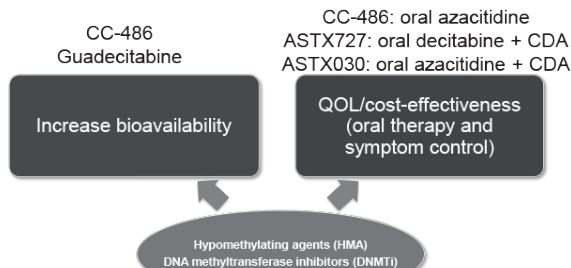QOL/cost-effectiveness (oral therapy and symptom control)

Hypomethylating agents (HMA)
DNA methyltransferase inhibitors (DNMTi)

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Oral Decitabine Plus Cedazuridine Combination (ASTX727)[1]

Decitabine

Cytidine deaminase (CDA) inhibitor

Inactive metabolite

- Cedazuridine is a novel, potent, and safe CDA inhibitor
- When given in combination with decitabine, cedazuridine enables efficient oral availability

1. Savona MR et al. Lancet Haematol. 2019;6:e194-e203.

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Phase 3 Study (ASCERTAIN) Trial: Preliminary Response of ASTX727 in MDS/CMML[1-3]

|	Evaluable Patients[a], n (%)
CR	12 (11.9)
PR	0 (0)
mCR	46 (45.5)
mCR with HI	14 (13.9)
HI	7 (5.3)
HI-erythroid	2 (2.0)
HI-neutrophils	1 (1.0)
HI-platelet	6 (5.9)
Overall response (CR + PR + HI)	33 (31.0)
SD	28 (27.7)
PD	8 (7.9)

ASTX727 responses are consistent with standard DNMTi use

The FDA approved ASTX727 on July 7, 2020 for adult patients with MDS with refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and CMML in intermediate 1-2 and high-risk IPSS groups

[a] Due to short median follow up (~5 mo) at data cutoff, 32 patients could not be evaluated for response by the Central IRC. Response was assessed by IWG 2006 criteria.
1. Garcia-Manero G et al. ASH 2019. Abstract 846. 2. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-oral-combination-decitabine-and-cedazuridine-myelodysplastic-syndromes. 3. Komrokji RS et al. EHA 2020. Abstract EP813.

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Phase 3 Trial of CC-486 (Oral Azacitidine) in RBC Transfusion-Dependent LR-MDS[1]

RBC-TI, ≥56 days

$P = .0002$

30.8%

11.1%
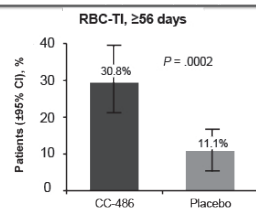
CC-486
Placebo

Median number of treatment cycles
- CC-486: 5 (range 1-70)
- Placebo: 6 (range 1-69)
Duration of response
- CC-486 vs placebo: 11.1 vs 5.0 months ($P = .42$)

- The most common AEs with CC-486 or placebo were low-grade GI events
- Other common grade 3-4 AEs were neutropenia, thrombocytopenia, febrile neutropenia, and anemia
- Patients with severe neutropenia are at higher risk of hematologic toxicity during early treatment cycles and may benefit by modifying the dose
- Management of AEs: regular monitoring, supportive care measures with dose modifications or interruptions if necessary

1. Garcia-Manero G et al. EHA 2020. Abstract S180.

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Improved Options With Currently Approved Therapies

Anemia is the dominant clinical problem in LR-MDS
- ESAs are standard of care
- Lenalidomide is effective, especially in del(5q) MDS
- Lenalidomide + ESA may resurrect anemia response
- Luspatercept provides a new option for patients who fail on ESAs

HMAs are the backbone of HR-MDS therapy
- HMAs improve OS, and expanded use of HMAs is vital for improving response
- Novel combinations with HMAs will continue to help individualize therapy and improve outcomes
- Maximizing delivery and pharmacokinetics with HMA enhances options
  – ASTX727 (oral decitabine + cedazuridine) is approved by the FDA and is equivalent to decitabine
  – Investigational agent CC-486 (oral azacitidine) has shown significant improvement in RBC-transfusion independence compared with placebo however CC-486 should NOT be considered equivalent to parenteral azacitidine

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Clinical Case 1: Back to Our Patient Kathy…

- Kathy, 76-year-old woman with LR-MDS
- Genetics: SF3B1 mutation
- BM: normocellular, 3% blasts, ring sideroblasts (>5%)
- ESA-resistant anemia
- Now requiring frequent transfusion

What Is the Most Appropriate Next Step for Kathy?
- Azacitidine
- Luspatercept
- Lenalidomide
- ASTX727 (cedazuridine + decitabine)
- Emerging therapies such as CC-486
- Immunosuppressive therapy
- Allogeneic stem cell transplant

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Nursing Implications for Managing Patients With LR-MDS

Patient education related to transfusion burden
- Risks associated with transfusion dependence and the goal to achieve transfusion independence
- Goals of treatment to achieve transfusion independence
- Strategies for monitoring blood counts and transfusion burden
- Criteria for considering disease modifying treatment

Setting expectations for patients initiating disease modifying treatment (DMT)
- A minimum of 4-6 months of treatment is required to evaluate initial response
- Best response may not be evident until 6-9 months of therapy
- Myelosuppression is the most common toxicity in DMT for MDS
  - Cytopenias may get worse before they get better
- Mild to moderate asymptomatic cytopenias may persist for months or years in patients responding to treatment

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Clinical Case 2: Matthew, a Newly Diagnosed Patient With MDS

|	
Matthew is a 65-year-old man with MDS	• Presents with fatigue and anemia
Further testing shows…	• Bone marrow biopsy – Hypercellular (66%) – Dyserythropoiesis – Myeloid: blasts 7% – Megakaryocytes: increased numbers, atypical – Cytogenetics: del(5q), del(7q), -17 – Genetics: TP53 mutation – Hb decline: 7.5 • RBC transfusions: 1-2 every 3-4 wk
Diagnosis and further management	• MDS • Categorized as high risk

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What Are the Treatment Options for Higher-Risk MDS?

| Initial Treatment	Next Options
If allo HCT is a good option and a donor is available: • Allo HCT • Azacitidine or decitabine, followed by allo HCT • High-intensity chemotherapy, followed by allo HCT	**Depending on prior treatment, options may include:** • Consider second HCT or DLI • Azacitidine or decitabine • Clinical trial • Supportive care only
If allo HCT is a good option but a donor is not available: • Azacitidine (preferred) or decitabine • Clinical trial	
If allo HCT is not a good option or a donor is not available: • Azacitidine (preferred) or decitabine • Clinical trial	

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Novel Targets Under Investigation in MDS[1]
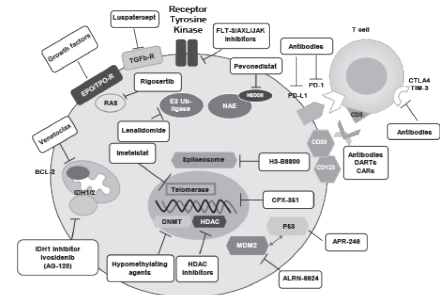
1. Platzbecker U. Blood. 2019;133:1096-1107.

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Magrolimab: Anti-CD47 Antibody[1]
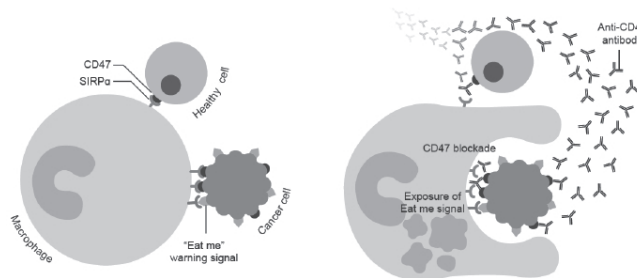
1. Chao MP et al. Front Oncol. 2019;9:1380.

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Phase 1b Study of Magrolimab + Azacitidine: Overall Response[1-3,a]

Best Overall Response	1L MDS (N = 33)
ORR	22/30 (73%)
CR	14 (42%)
PR	1 (3%)
HI	7 (21%)
SD	3 (9%)
PD	0
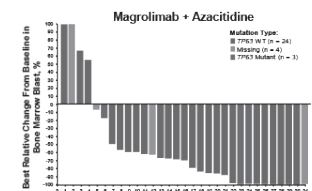
a Response assessments per 2006 IWG MDS criteria. Patients with at least 1 post-treatment response assessment are shown; all other patients are on therapy and are too early for first response assessment, except for 2 patients with MDS not evaluable (withdrawal of consent). Median OS was not reached in patients with MDS.
1. Sallman D et al. J Clin Oncol. 2020;38(suppl 15):7507. 2. Vidaza (azacitidine) Prescribing Information. https://packageinserts.bms.com/pi/pi_vidaza.pdf.

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Phase 1b Study: Magrolimab + Azacitidine in Patients with HR-MDS[1-3]

Outcome, n (%)	MDS (n = 33)
RBC transfusion independence	11/19 (58)
Complete cytogenetic response	9/26 (35)
MRD negativity in responders	6/30 (20)
Median DOR, mo	NR (0.03+ to 10.4+)
Median follow-up, mo (range)	5.8 (2.0 to 15.0)

- Maximum tolerated dose not reached with magrolimab + AZA
- Safety consistent with AZA monotherapy
- No evidence of significant cytopenias, infections, or immune-related AEs
- Majority of patients had significant hemoglobin improvement and decrease in transfusion frequency over time

1. Sallman D et al. J Clin Oncol. 2020;38(suppl 15):7507. 2. Vidaza (azacitidine) Prescribing Information. https://packageinserts.bms.com/pi/pi_vidaza.pdf.
3. Fenaux P et al. Lancet Oncol. 2009;10:223-232.

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Venetoclax: BCL-2 Inhibitor[1-3]

1. Jilg S et al. Exp Hematol Oncol. 2019;8:9. 2. Reidel V et al. Oncotarget. 2018;9:17270-17281. 3. Jilg S et al. Leukemia. 2016;30:112-123.

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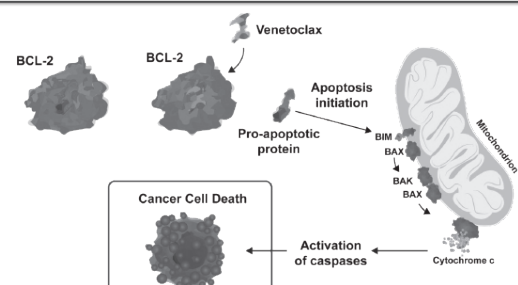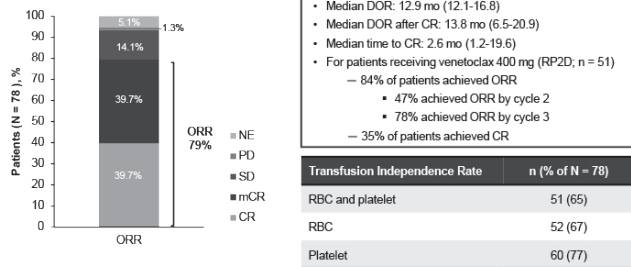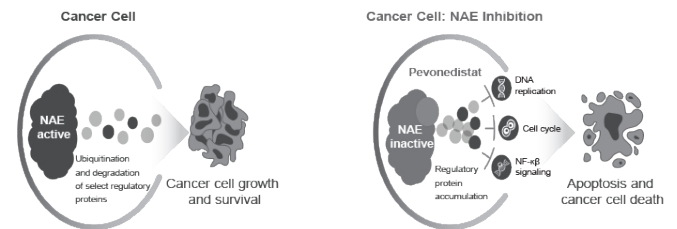Therapeutic Advancements in Myelodysplastic Syndromes: Bridging the Gap Between Patient Safety and Quality Care Through the Latest Science and Evidence–Based Learning in Nursing Practice

M15-531, Phase 1b Dose Escalation Study: Venetoclax + Azacitidine[1,a]

Patients (N = 78), %

ORR: 5.1%, 1.3%, 14.1%, 39.7%, 39.7%

ORR 79%

- NE
- PD
- SD
- mCR
- CR

- Median DOR: 12.9 mo (12.1-16.8)
- Median DOR after CR: 13.8 mo (6.5-20.9)
- Median time to CR: 2.6 mo (1.2-19.6)
- For patients receiving venetoclax 400 mg (RP2D; n = 51)
  — 84% of patients achieved ORR
    ▪ 47% achieved ORR by cycle 2
    ▪ 78% achieved ORR by cycle 3
  — 35% of patients achieved CR

Transfusion Independence Rate	n (% of N = 78)
RBC and platelet	51 (65)
RBC	52 (67)
Platelet	60 (77)

[a] Data cutoff: June 30, 2020.
1. Garcia JS et al. ASH 2020. Abstract 656.

Pevonedistat: NEDD8-Activating Enzyme Inhibitor[1-5]

Cancer Cell

NAE active — Ubiquitination and degradation of select regulatory proteins → Cancer cell growth and survival

Cancer Cell: NAE Inhibition

Pevonedistat — NAE inactive — Regulatory protein accumulation — DNA replication, Cell cycle, NF-κB signaling → Apoptosis and cancer cell death

1. Brownell JE et al. Mol Cell. 2010;37:102-111. 2. Soucy TA et al. Nature. 2009;458:732-736. 3. Soucy TA et al. Clin Cancer Res. 2009;15:3912-3916.
4. Smith PG et al. Blood. 2011;118:578. 5. Sekeres MA et al. Blood. 2020;136(suppl 1):653.

Phase 2 Study: Pevonedistat + Azacitidine in MDS, CMML, or Low-Blast AML[1,2]

EFS

	Pevonedistat + azacitidine	Azacitidine
Median EFS, mo	20.2	14.8
HR (95% CI)	0.539 (0.292-0.995)	
	P = .045	

20.2 mo
14.8 mo

OS

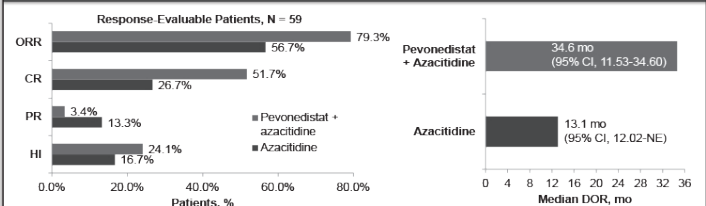|	Pevonedistat + azacitidine	Azacitidine
Median OS, mo	23.9	19.1
HR (95% CI)	0.701 (0.386-1.273)	
	P = .240	

— Pevonedistat + azacitidine — Azacitidine
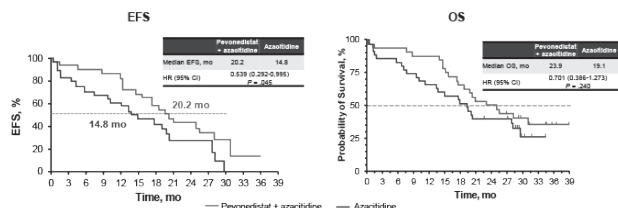
Rate of transfusion independence: 69.2% (pivonedistat + azacitidine) vs 50.0% (azacitidine)

1. Swords RT et al. Blood. 2018;131:1415-1424. 2. Ades L et al. Hemasphere. 2020;4(s1):s182.

Pevonedistat + Azacitidine: Responses in HR-MDS[1]

Response-Evaluable Patients, N = 59

	Pevonedistat + azacitidine	Azacitidine
ORR	79.3%	56.7%
CR	51.7%	26.7%
PR	3.4%	13.3%
HI	24.1%	16.7%

- Pevonedistat + azacitidine
- Azacitidine

Median DOR, mo

Pevonedistat + Azacitidine: 34.6 mo (95% CI, 11.53-34.60)
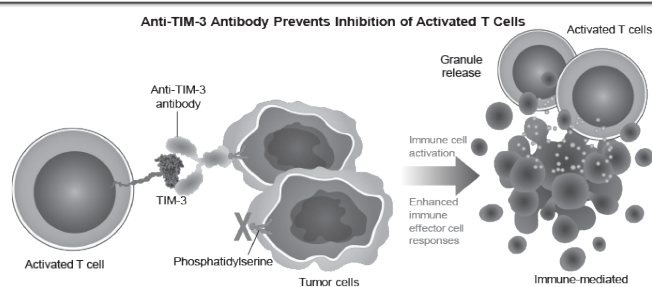
Azacitidine: 13.1 mo (95% CI, 12.02-NE)

The most common AEs with pevonedistat + azacitidine were nausea, constipation, diarrhea, and fatigue; other common grade 3-4 AEs were neutropenia, thrombocytopenia, febrile neutropenia, and leukopenia
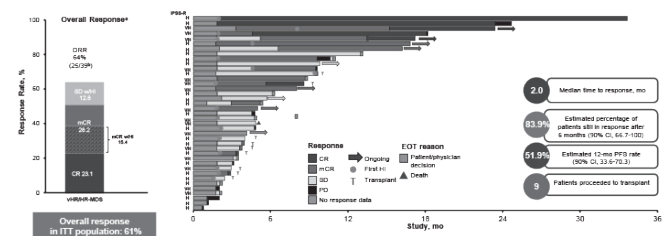
1. Ades L et al. Hemasphere. 2020;4(s1):s182.

Sabatolimab (MBG453): Anti-TIM-3 Antibody[1-6]

Anti-TIM-3 Antibody Prevents Inhibition of Activated T Cells

Anti-TIM-3 antibody — TIM-3 — Activated T cell — Phosphatidylserine — Tumor cells

Activated T cells — Granule release — Immune cell activation — Enhanced immune effector cell responses — Immune-mediated tumor killing

1. Acharya N et al. J Immunother Cancer. 2020;8:e000911. 2. Sabatos-Peyton C et al. The Society for Immunotherapy of Cancer Annual Meeting 2020 (SITC 2020). Abstract 439. 3. Borate U et al. HemaSphere. 2020;4(suppl 1):S185; 4. Borate U et al. EHA 2020. Oral presentation.
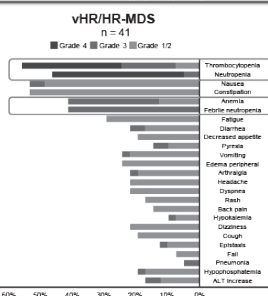5. Pardoll DM. Nat Rev Cancer. 2012;12:252-264. 6. Das M et al. Immunol Rev. 2017;276:97-111.

Phase 1b Study of Sabatolimab + DNMTi: Antileukemic Activity and Overall Response[1]

Overall Response

Response Rate, %

ORR 64% (25/39)

SD with HI 12.8
mCR 28.2
mCR with HI 15.4
CR 23.1

Response
- CR
- mCR
- SD
- PD
- No response data

EOT reason
- Patient/physician decision
- First HI
- Transplant
- Death

vHR/HR-MDS

Study, mo

Overall response in ITT population: 61%

2.0 — Median time to response, mo
83.9% — Estimated percentage of patients still in response after 6 months (90% CI, 66.7-100)
51.9% — Estimated 12-mo PFS rate (90% CI, 33.6-70.3)
9 — Patients proceeded to transplant

* Evaluable patients, including patients with a valid baseline and at least 1 postbaseline bone marrow assessment or if they had disease progression or disease-related death prior to the first marrow assessment; ᵇ ORR for patients with MDS or CMML was defined as CR + mCR + PR + SD with HI; ORR for patients with ND AML was defined as CR + CRi + PR.
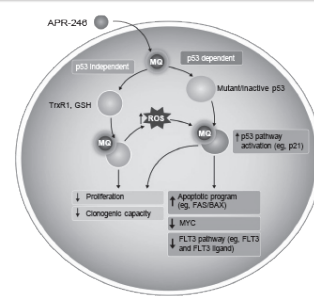1. Brunner AM et al. ASH 2020. Abstract 657.

Sabatolimab + DNMTi in MDS: Most Commonly Occurring TEAEs[1]

vHR/HR-MDS
n = 41

- Grade 4
- Grade 3
- Grade 1/2

Thrombocytopenia, Neutropenia, Nausea, Constipation, Anemia, Febrile neutropenia, Fatigue, Diarrhea, Decreased appetite, Pyrexia, Vomiting, Edema peripheral, Arthralgia, Headache, Dyspnea, Rash, Back pain, Hypokalemia, Dizziness, Cough, Epistaxis, Fall, Pneumonia, Hypophosphatemia, ALT increase

- Most common reported TEAEs were consistent with those for DNMTi alone
- Discontinuation due to AEs was infrequent: 0% for vHR/HR-MDS
- One patient with neutropenic colitis died of septic shock; the AE was suspected to be related to study treatment; no other treatment-related deaths were reported

1. Brunner AM et al. ASH 2020. Abstract 657.

APR-246: p53 Reactivator[1-5]

APR-246

p53 independent — MQ — p53 dependent
TrxR1, GSH — ROS — Mutant/inactive p53
↑ p53 pathway activation (eg, p21)
↓ Proliferation, ↓ Clonogenic capacity
Apoptotic program (eg, FAS/BAX)
↓ MYC
↓ FLT3 pathway (eg, FLT3 and FLT3 ligand)

1. Maslah N et al. Haematologica. 2020;105:1539-1551. 2. Zhang Q et al. Cell Death Dis. 2018;9:439. 3. Lambert JM et al. Cancer Cell. 2009;15:376-388.
4. Lehmann S et al. J Clin Oncol. 2012;30:3633-3639. 5. Sallman D. Haematologica. 2020;105:1470-1472.

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Therapeutic Advancements in Myelodysplastic Syndromes: Bridging the Gap Between Patient Safety and Quality Care Through the Latest Science and Evidence-Based Learning in Nursing Practice

Response to Treatment in Evaluable Patients (n = 45)[1]

Median OS: ITT = 10.8 mo and responding patients = 13.7 mo; median duration of follow-up = 10.8 mo

	Overall	MDS	AML	MDS-MPN + CMML
Evaluable patients, n	45	33	8	4
ORR, n (%)	39 (87)	29 (88)	7 (88)	3 (75)
CR rate, n (%)	24 (53)	20 (61)	4 (50)	0 (0)
Duration of CR, median mo (95% CI)	7.3 (5.8-NE)	7.3 (5.8-NE)	7.0 (3.3-NE)	NE
Discontinued for transplant, n (%)	22 (49)	17 (52)	4 (50)	1 (25)
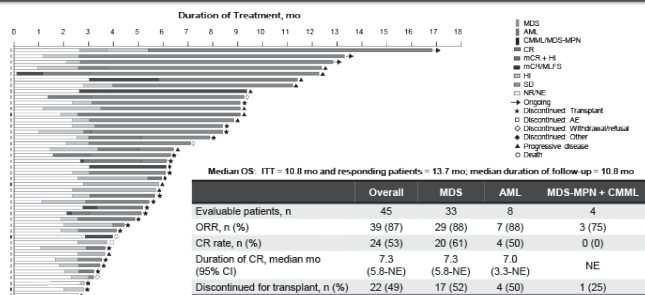
1. Sallman D et al. *J Clin Oncol.* 2021 Jan 15 [Epub ahead of print].

Clinical Take-Homes

- Novel DNMTi combinations are showing encouraging results and have a potential to change SOC in the future

- MDS with DNMTi failure remains a high-risk population without an established SOC with hope for some novel DNMTi combinations and targeted monotherapies for the future

- Results may help inform practice and future clinical investigation in this population

Back to Our Patient…

- Matthew, 65-year-old man with HR-MDS
- Cytogenetics: del(5q), del(7q), -17
- Genetics: *TP53* mutation
- BM: hypercellular (66%) with 7% blasts
- Progressive anemia requiring RBC transfusions: 1-2 every 3-4 wk

What are the emerging treatment options for patients with newly diagnosed HR-MDS?
- Clinical trial
- Intensive chemotherapy followed by HCT
- Combination therapy
- Targeted therapy
- Best supportive care

Newer Targeted Therapies or Combinations: An Option for Matthew

Targeted Therapies

Enrollment in Clinical Trials

- Clinical trials
  — Magrolimab + azacitidine
  — Sabatolimab + DNMTi
  — Pevonedistat + azacitidine
  — Venetoclax + azacitidine
  — APR-246/APR-548 + azacitidine

- Encourage and educate patients for trial enrollment

Nursing Implications for Managing Patients With HR-MDS

Nurse's responsibility in shared decision-making
- Maintaining a major influence in patient's education about the disease and treatment
- Identifying the most appropriate therapy options for patients based on: risk factors, efficacy, AEs associated with therapies, comorbidities, and psychosocial factors
- Educating patients and care givers about disease expectations
- Routine monitoring, assessment, and management of AEs associated with treatment
- Assessing patient benefit from newer therapies

Addressing patient's concerns about trial enrollment and novel therapies
- Counselling patient to address concerns regarding novel therapies
- Encouraging and educating patients about enrolling in clinical trials to explore newer treatment options
- Educating about current and newer treatment options to address therapy-related concerns, including financial implications