# MDS: How and When to Choose

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# Disclosures

Syndax Pharmaceuticals-served on advisory board panel on menin inhibition in leukemia

# Objectives

- Describe the clinical presentation and diagnostic evaluation of MDS
- Discuss classification of MDS and tools to assess disease risk
- Summarize treatment options for patients with MDS, based on risk

# Case 1

**69-year-old man, saw his PCP for yearly check-up, reported mild fatigue**

| PMH | SocHx | FHx | Meds | Exam |
|---|---|---|---|---|
| HTN | 40 pk-yr tobacco | GF-prostate CA | B-blocker | ECOG= 1 |
| Hyperlipidemia | Occ. alcohol | | Baby ASA | Otherwise NL |

- WBC 4.2, ANC 2.2k, HGB 9, MCV 109, PLT 140k
- Normal: B12/folate/TSH/Copper/HIV/Hepatitis

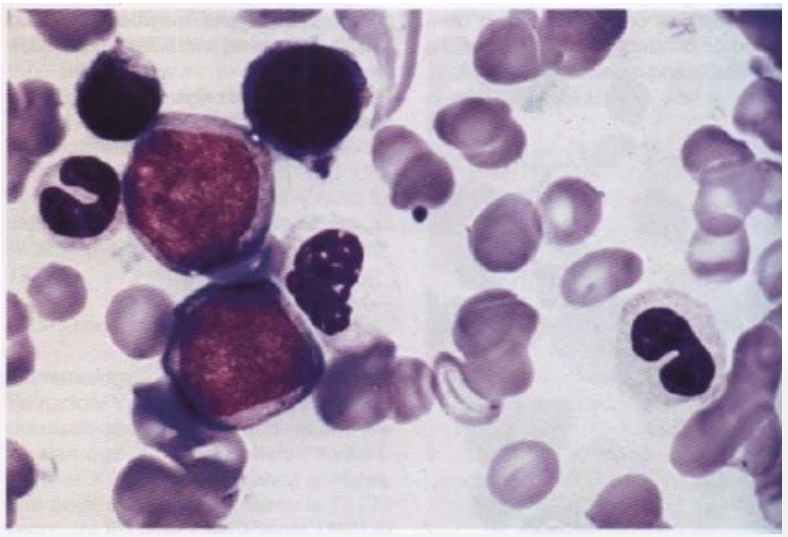
# Case 1

- Marrow was 80% cellular.
- Dysplasia in > 20% of megakaryocytic and erythroid lineage.
- Blasts 3% on aspirate smear, 5% by flow cytometry.
- Karyotype: 46, XY [21].
- NGS myeloid panel not sent.

# Myelodysplastic Syndromes (MDS)

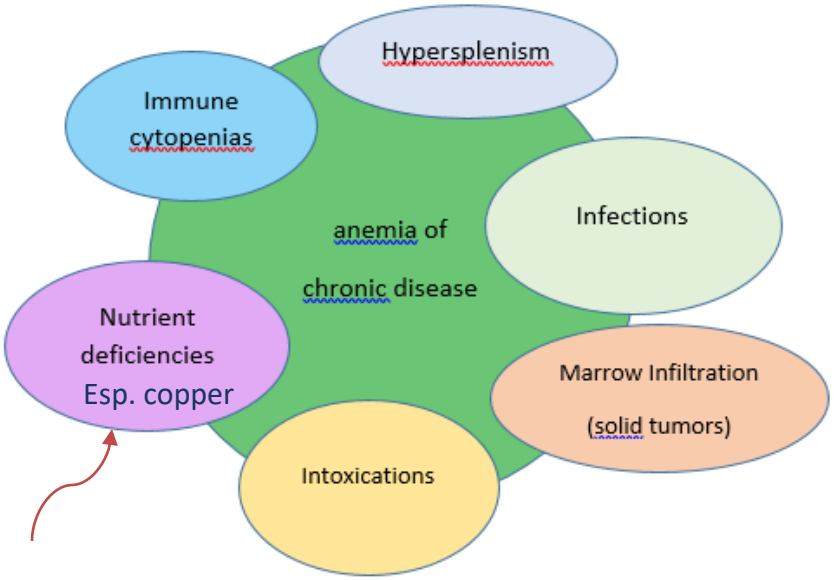
- Incidence in the US approx. **4:100,000**
  (approx. 75:100,000 among persons ≥ 65 y/o)

- **Risk factors:**
  - **Age (median age 71-76)**
  - Genetics (esp. in younger pts.)
  - Environmental exposures
  - Prior chemo, XRT (t-MDS)

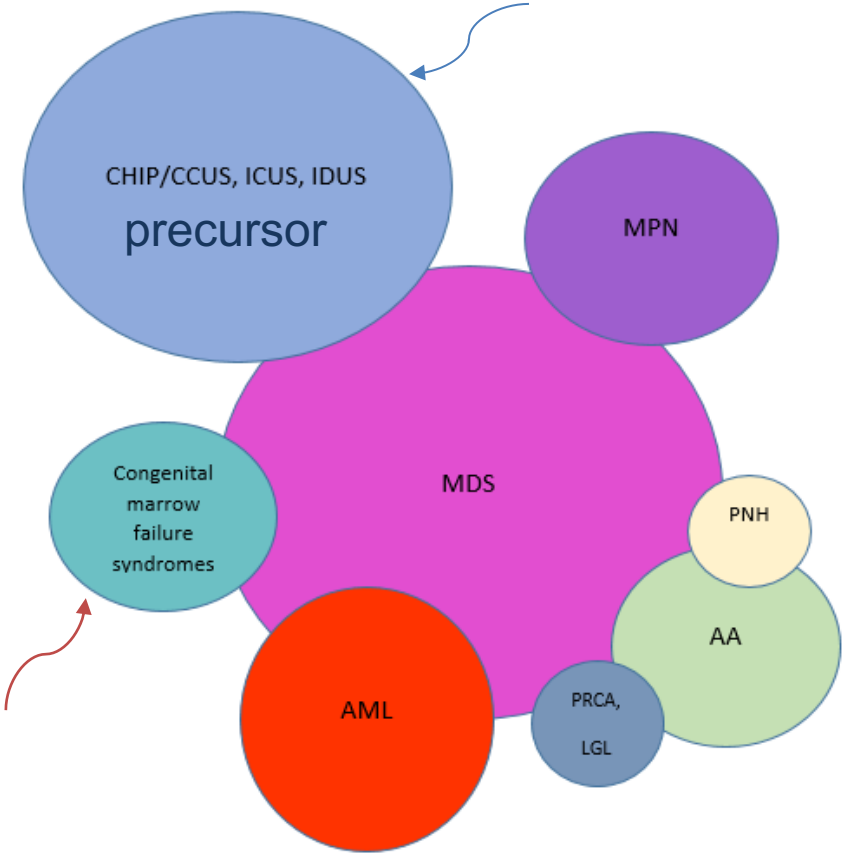


# Differential dx. of Suspected MDS

## Issues External to Marrow




## Issues Internal to Marrow




Arellano & Dyer 2021. Fast Facts MDS (Publisher- S. Karger)

# Minimum Work-up and Diagnostic Criteria for MDS

- Bone marrow biopsy and aspirate
- Karyotype (at least 20 metaphases)*
- Myeloid mutation panel

- Dysplasia in ≥ 10% of cells in ≥ 1 myeloid lineage or persistent cytopenia (s) with a defining MDS-related genetic abnormality.

- Blasts % from aspirate differential (not flow cytometry).

* Flourescence in situ hybridization (FISH) only useful if karyotype fails.
* Microarray may be useful in certain cases.



Jaffe ES, Harris NL, Stein H, et al. WHO classification of tumours: Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Annals of Oncology. 2002;13(3):490-491. DOI: 10.1093

# WHO Classification of MDS- 2022

| MDS with defining genetic abnormalities | Blasts | Cytogenetics | Mutations |
|---|---|---|---|
| MDS-5q | < 5% BM and < 2% PB | del(5q) only or with 1 other abnormality except -7 or -7q | |
| MDS-*SF3B1*<br>(> 15% RS may substitute) | < 5% BM and < 2% PB | No del(5q), -7, or complex karyotype | *SF3B1* |
| MDS-bi*TP53* | < 20% BM and < 2% PB | Usually complex | ≥ 2 *TP53* mutations or 1 mutation and *TP53* copy # loss or cnLOH |
| **MDS, morphologically defined** | | | |
| MDS-LB (low blasts) | < 5% BM and < 2% PB | | |
| MDS-h (hypoplastic) | | ≤ 25% marrow cellularity, age adjusted. Can benefit from Immunotherapy | |
| MDS-IB1 | 5-9% BM or 2-4% PB | | |
| MDS-IB2 | 10-19% BM, 5-19% PB, Auer rods | | |
| MDS-f | 5-19% BM, 2-19% PB | | |

- MDS-IB2 may be regarded as AML-equivalent for therapeutic considerations
- BM= bone marrow, PB= peripheral blood, IB= increased blasts, cnLOH= copy neutral loss of heterozygosity

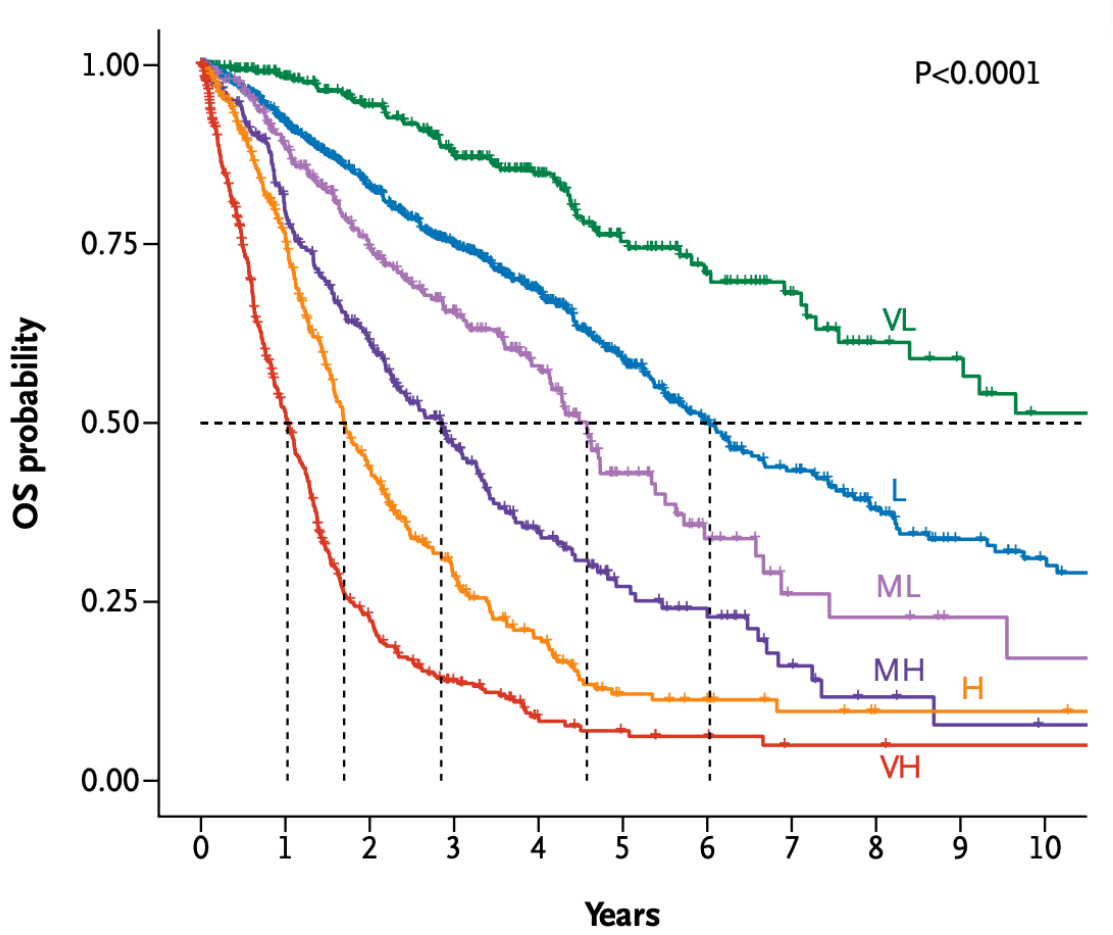


Khoury JD, Solary E, Abla O, et al. Leukemia (2022) 36:1703–1719; https://doi.org/10.1038/s41375-022-01613-1

# Defining Risk in MDS

| Patient-related Factors | Disease-related Factors |
|---|---|
| Symptomatology<br>-Symptomatic anemia<br>-Bleeding<br>-Infection | Disease classification<br>-Ring sideroblasts<br>-Hypocellular<br>-Blast % |
| Age<br>Fitness | Disease risk score<br>-IPSS-R<br>-IPSS-M |
| Co-morbid conditions | Transfusion requirements |
| Social determinants | Inherited syndrome (s) |

# Driver Mutations in MDS, IPSS-M




- 46% of pts. re-stratified into 6 categories.

VL, very low, N= 344; L, low, N=852; ML, moderate low, N= 296;
MH, moderate high, N= 278; H, high, N= 367; VH, very high, 460

https://mds-risk-model.com



E. Bernard, H. Tuechler, P. L. Greenberg, M, et al. NEJM Evid 2022; 1(7)DOI:https://doi.org/10.1056/EVIDoa2200008

# Case 1 cont. IPSS-R

- ANC 2,200, hemoglobin 9, platelets 140,000
- Bone marrow: 80% cellular, 3% blasts
- Karyotype: 46, XY [21].

| Variable | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|
| CTG | Very good | - | Good | - | Interm. | Poor | Very poor |
| %BM blasts | ≤ 2% | - | > 2 - < 5% | - | 5 - 10% | > 10% | - |
| Hgb. | ≥ 10 | - | 8 - < 10 | < 8 | - | - | - |
| Platelets | ≥ 100 | 50 - 99 | < 50 | - | - | - | - |
| ANC | ≥ 0.8 | < 0.8 | - | - | - | - | - |

**Cytogenetic (CTG) groupings:**

**-Very good**: -Y, del(11q)

**-Good**: NL, del(5q), del(12p), del(20q), double incl. del (5q)

**-Intermediate**: del(7q), +8, +19, i(17q), any other single or double clone

**-Poor**: -7, inv(3)/t(3q)/del(3q), double incl. -7/del(7q)

**-Very poor**: complex (> 3 abn)

| Risk Category | Risk Score |
|---|---|
| Very Low | ≤ 1.5 |
| Low | 2- 3 |
| Intermediate | 3.5 - 4.5 |
| High | 5- 6 |
| Very High | > 6 |

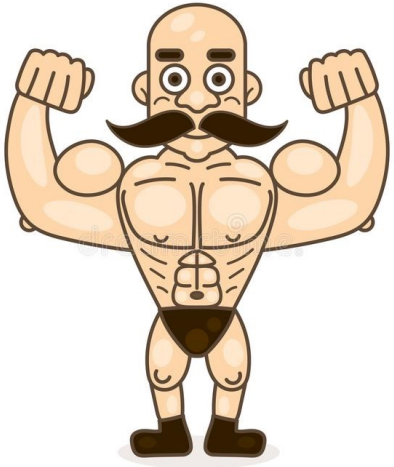


Greenberg, et al. Blood 2012. 120: 2454-2465

# MDS Treatment - The 1st Question

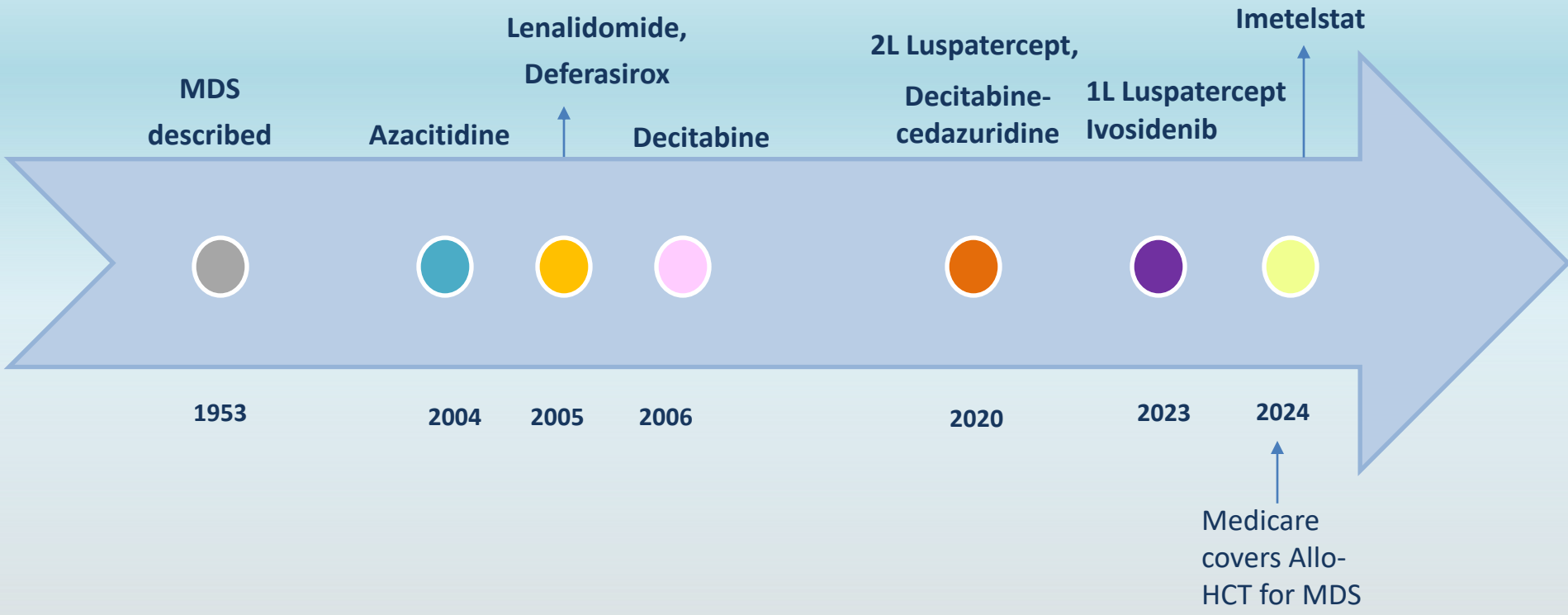
- Is the patient a candidate for Allogeneic Stem Cell Transplantation?
  - Age up to 70-75
  - Fit patient (comorbidity score)
  - Intermediate to high-risk disease

    (IPSS-R > 3.5, IPSS-M > 0)



- BMT CTN 1102:
  - OS at 3 years 47.9% in donor arm vs. 26.6% in no-donor arm.
  - LFS at 3 years 35.8% (donor) vs. 20.6% (no donor).

# Approved Treatments for MDS



# Options for Lower Risk MDS

| Agent | Responses | Comments |
|---|---|---|
| rHEPO | 25-40% (less in RS) | •Nordic score still useful to predict response. +/- G-CSF |
| ATG+/- CSP | CR 24-48% | •Younger age, low risk **MDS-h**, ?HLA-DR15, ?PNH clone |
| TPO mimetics | Evolving field | •Useful under certain conditions |
| Lenalidomide | 43-76% TI | •Best in 5q-, younger age, shorter MDS duration, lower transfusion needs. Cytopenias can be an issue. |
| Luspatercept | **2nd line**: RBC TI ≥ 8 wks. 38% vs. 13%. -RBC TI ≥ 12 wks. 28% vs. 8%. | **1st line:** TI for ≥ 12 wks in the first 24 weeks + rise in HGB ≥ 1.5 g/dL in **60.4% with Lus vs. 34.8% with epo**. •TI in **RS+ 65% Lus/29% epo**. TI in **RS- 46% Lus/50% (epo).** •81% vs. 51% ANC increase, 71% vs. 42% PLT increase. |
| Imetelstat vs. placebo | -RBC-TI ≥ 8 wks 40% vs. 15% | •Benefit in pts. with high transfusion burden. •Thrombocytopenia/neutropenia an issue (74-75%). |

TPO = Thrombopoietin, ESA = Erythropioesis stimulating agent, TI = transfusion independence

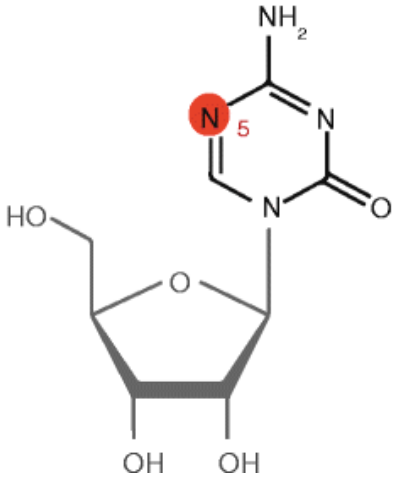
Zeidan AM, et al. ASCO Annual Meeting. 2023 (abstr 7004), MG DellaPorta, G Garcia-Manero, V Santinin, et al. Lancet Haematology 2024. https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(24)00203-5/abstract , Sloand et al. JCO 2008 Passweg et al. JCO 2011

P Fenaux, U Platzbecker,GJ Mufti et al. blood-2018-99-110805, EN Olivia, et al. *JCO* **41**, 4486-4496(2023).DOI: 10.1200/JCO.22.0269

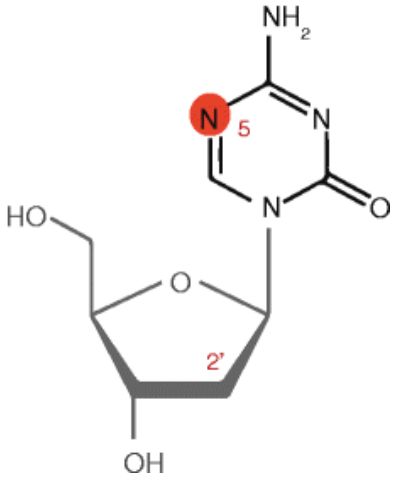
Balleari et al. Ann Hematol 2005 Sekeres Leukemia 2012 List et al. NEJM 2006, G. Garcia-Manero J Clin Oncol 41, 2023 (suppl 16; abstr 7003)

# Hypomethylating agents

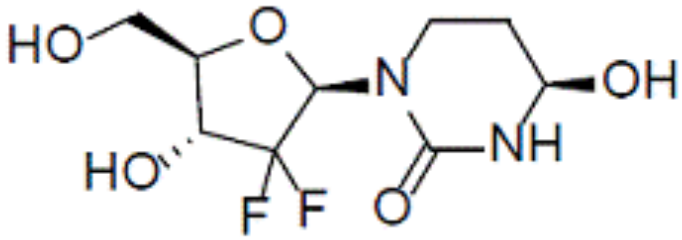
Azacidine




Decitabine




**Cedazuridine**




- Cytidine analogues (pyrimidine nucleoside):
  - Cytotoxic at high doses, induce DNA damage response.
  - At low doses, inhibit DNA methyltransferases.
- Cedazuridine inhibits cytidine deaminase in gut and liver, prevents degradation of decitabine (orally bioavailable).



Diesch, J., Zwick, A., Garz, A. *et al. Clin Epigenet* **8,** 71 (2016)

# Ivosidenib for MDS with *IDH1mut*

| Efficacy outcomes | MDS efficacy set N = 18 | 95% CI |
|---|---|---|
| CR+PR | 7 (38.9%) | (17.3, 64.2) |
| Time to CR/PR | 1.87 mos. (1-5.6 mos.) | (58.6, 96.4) |
| Duration of CR/PR | NR (1.9, NR) | |
| **Best response** | | |
| **ORR** | **15 (83.3)** | (58.6, 96.4) |
| CR | 7 (38.9) | ( 17.3, 64.3) |
| mCR | 8 (44.4) | (21.5, 96.2) |
| HI in non-CR/PR pts | 4 (36.4) | |

- 79% pts. enrolled had HMA failure.
- AEs of interest: differentiation syndrome in 2 (10.5%)
- Median OS 86.9% at 1-year, 46.3% at 7 years.

HI = Hematologic improvement

DiNardo CD, Roboz GJ, Watts JM, et al. Blood Adv. 2024. doi: 10.1182/bloodadvances.2023012302.

# Back to case 1.

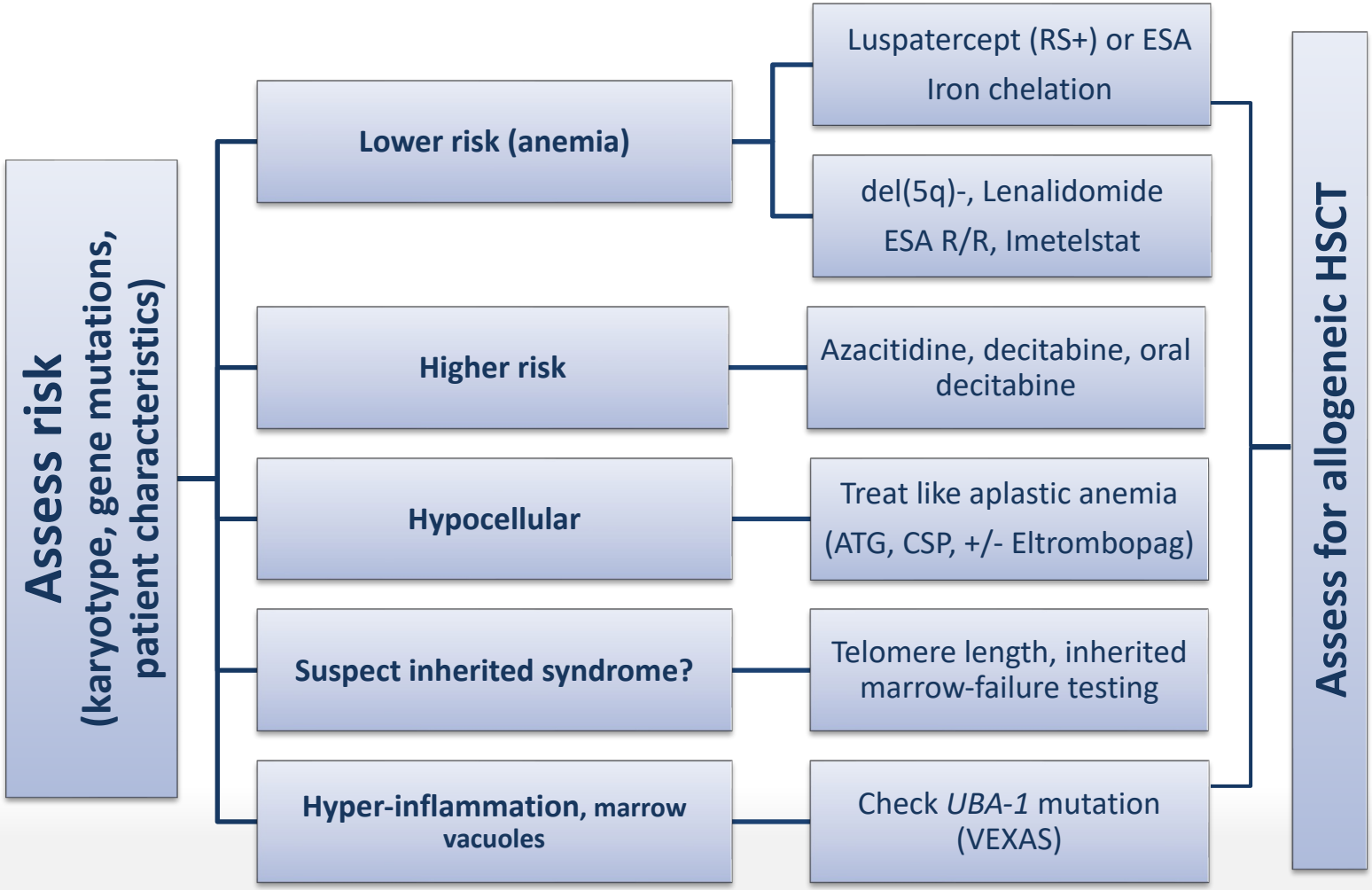
## 69 y/o man with good performance status and low risk MDS

- Receives epo followed by azacitidine after 4 months.
- Became pancytopenic.
- BM bx was 30% cellular, 15% blasts
- Karyotype: 47, XY, +8 [12]/46, XY [8]
- NGS: *IDH1*-R132

-Clinical trial of ivosidenib for R/R MDS with *IDH1* mutation.
-Achieved CR and proceeded to allo-HCT.

- ❖ Early assessment of transplant eligibility is important (esp. in higher risk MDS).
- ❖ NGS can provide prognostic and therapeutic information.

# How I Assess and Treat MDS




**Consider clinical trial for all patients**

# QUESTIONS?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