# MDS Foundation Meeting 2019

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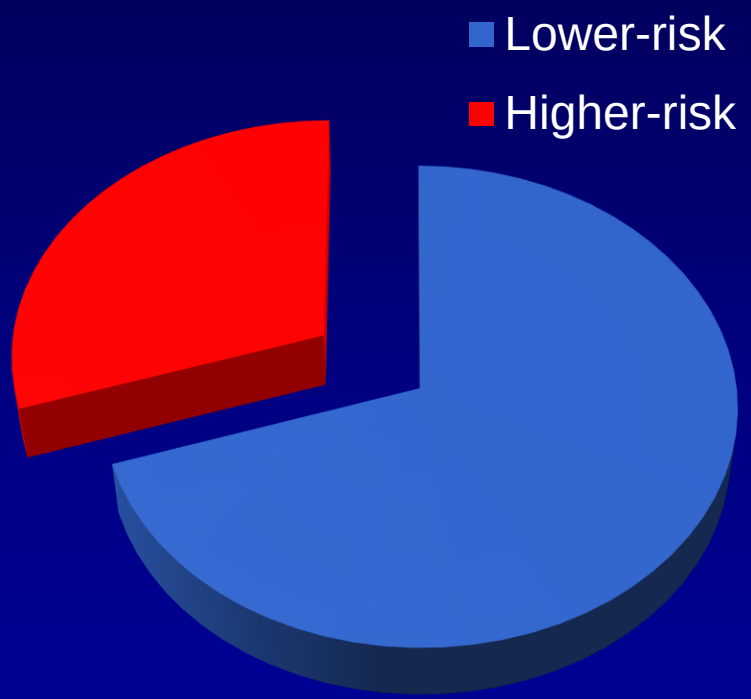
# Lower-risk MDS

- Accounts for approximately 70% of all MDS patients[1]
- Has relatively better rate of survival, lower transformation to AML compared with higher-risk MDS[1]
- Anemia the main clinical challenge[2]

**Relative Incidence of Myelodysplastic Syndromes by IPSS Risk**




1. Greenberg et al. Blood 1997;89:2079-88
2. Santini V. Semin Hematol. 2015;52:348-56.

# International Prognostic Scoring System Critical Prognostic Features

| Prognostic factor | Category score (sum all 3 for overall IPSS score) | | | | |
|---|---|---|---|---|---|
| | 0 (best) | 0.5 | 1 | 1.5 | 2 (worst) |
| Marrow blasts (%) | < 5 | 5–10 | – | 11–20 | 21–30 |
| Karyotype | Good | Intermediate | Poor | – | – |
| Peripheral blood cytopenias | 0 or 1 | 2 or 3 | – | – | – |



1. Greenberg et al. Blood 1997;89:2079-88

# International Prognostic Scoring System Defining Risk

Scores are then combined to determine a patient's prognostic risk category

| Risk category | Total score (sum of category scores) | Median survival (years) | Time to 25% AML progression (years) |
|---|---|---|---|
| Low-risk | 0 | 5.7 | 9.4 |
| Intermediate-1-risk | 0.5 or 1.0 | 3.5 | 3.3 |
| Intermediate-2-risk | 1.5 or 2.0 | 1.2 | 1.1 |
| High-risk | ≥ 2.5 | 0.4 | 0.2 |



1. Greenberg et al. Blood 1997;89:2079-88

# “Lower-risk” Includes IPSS Low-risk and Intermediate-1-risk Disease

| | IPSS risk category | | | |
|---|---|---|---|---|
| | Low | Intermediate-1 | Intermediate-2 | High |
| Median survival (years) | 5.7 | 3.5 | 1.2 | 0.4 |
| Time to 25% AML progression (years) | 9.4 | 3.3 | 1.1 | 0.2 |

“Lower-risk” MDS



1. Greenberg et al. Blood 1997;89:2079-88

# IPSS-R Prognostic Features

| Prognostic factor | Category score (sum overall IPSS-R score) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 |
| Cytogenetics | Very good | – | Good | – | Intermediate | Poor | Very poor |
| BM blasts, % | ≤ 2 | – | > 2 to < 5 | – | 5 to 10 | > 10 | – |
| Hb (g/dL) | ≥ 10 | – | 8 to < 10 | < 8 | – | – | – |
| Platelets ($x 10^9$/L) | ≥ 100 | 50 to < 100 | < 50 | – | – | – | – |
| ANC ($x 10^9$/L) | ≥ 0.8 | < 0.8 | – | – | – | – | – |



1. Greenberg et al. Blood 2012;120:2454-65

# IPSS-R Risk Categories

| Risk category | Risk score | Median survival, years (95% CI) |
|---|---|---|
| Very low | ≤ 1.5 | 8.8 (7.8–9.9) |
| Low | > 1.5–3 | 5.3 (5.1–5.7) |
| Intermediate | > 3–4.5 | 3.0 (2.7–3.3) |
| High | > 4.5–6 | 1.6 (1.5–1.7) |
| Very high | > 6 | 0.8 (0.7–0.8) |



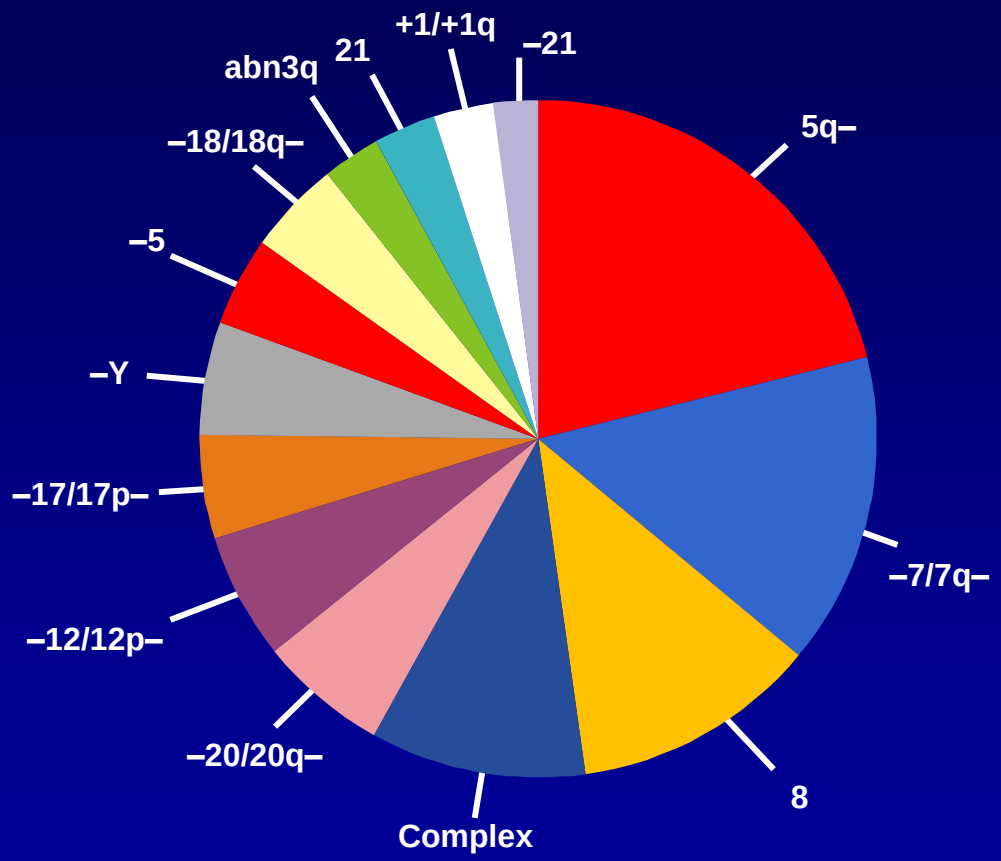
1. Greenberg et al. Blood 2012;120:2454-65

# Iron Metabolism in MDS

- Anemia in MDS caused by ineffective erythropoiesis
- Defective erythroid cell maturation associated with increased iron absorption and abnormal iron accumulation
- RBC transfusions also causes secondary iron overload

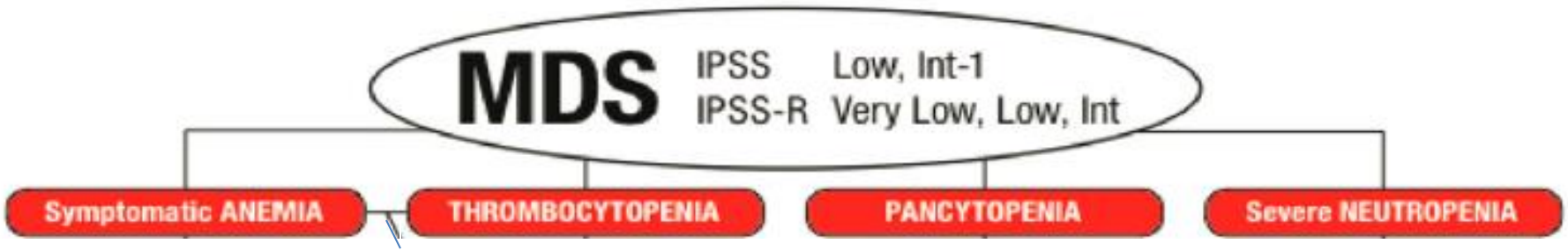
# Most Common Cytogenetic Abnormalities

del(5q) - most frequently occurring abnormality

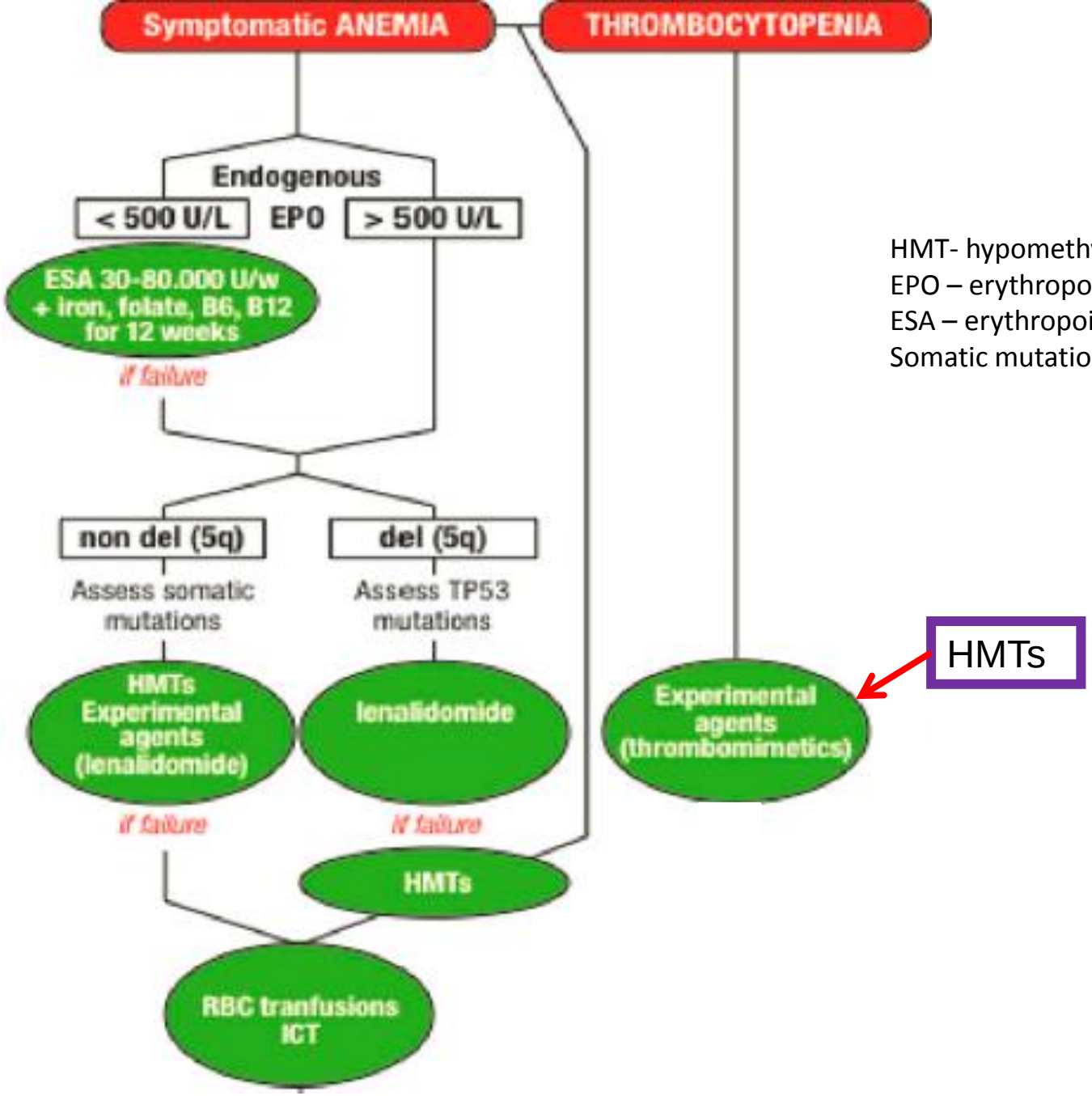





1. Giagounidis. Haematologica reports.2006;2:5-10



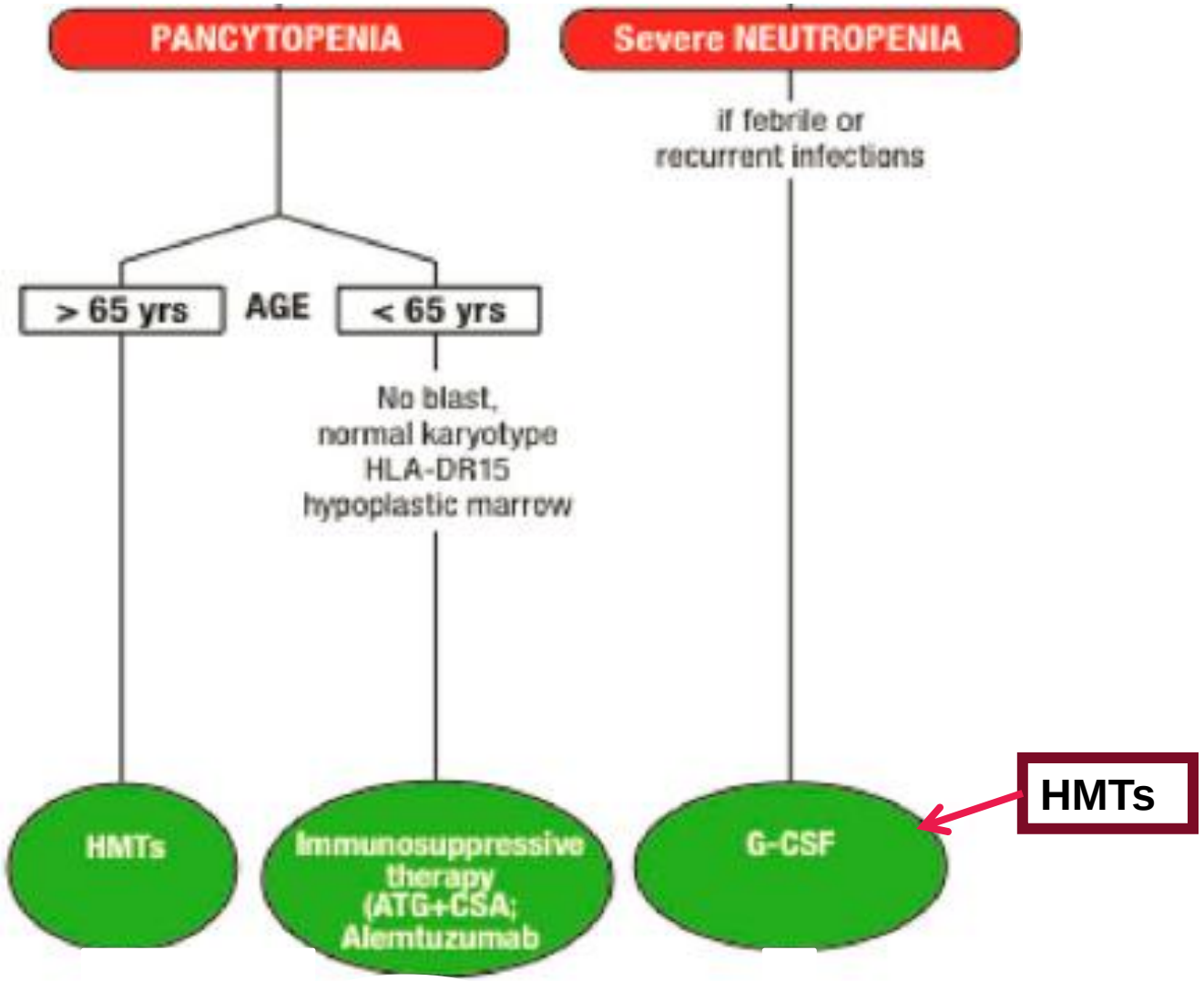

Santini V, ASH 2016



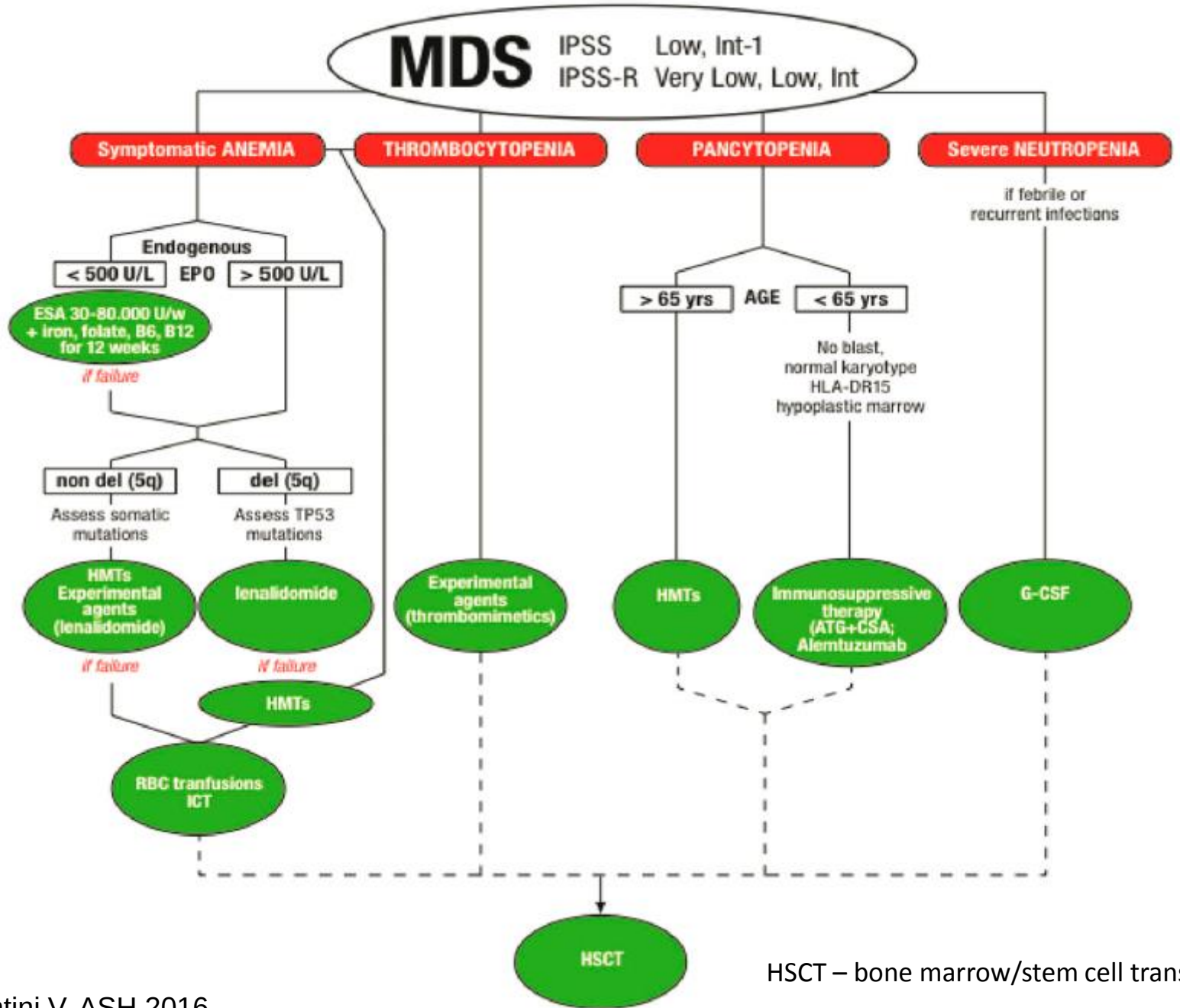

HMT- hypomethylator therapy
EPO – erythropoietin blood level
ESA – erythropoietin therapy
Somatic mutation – gene mutation

HMTs

Santini V, ASH 2016



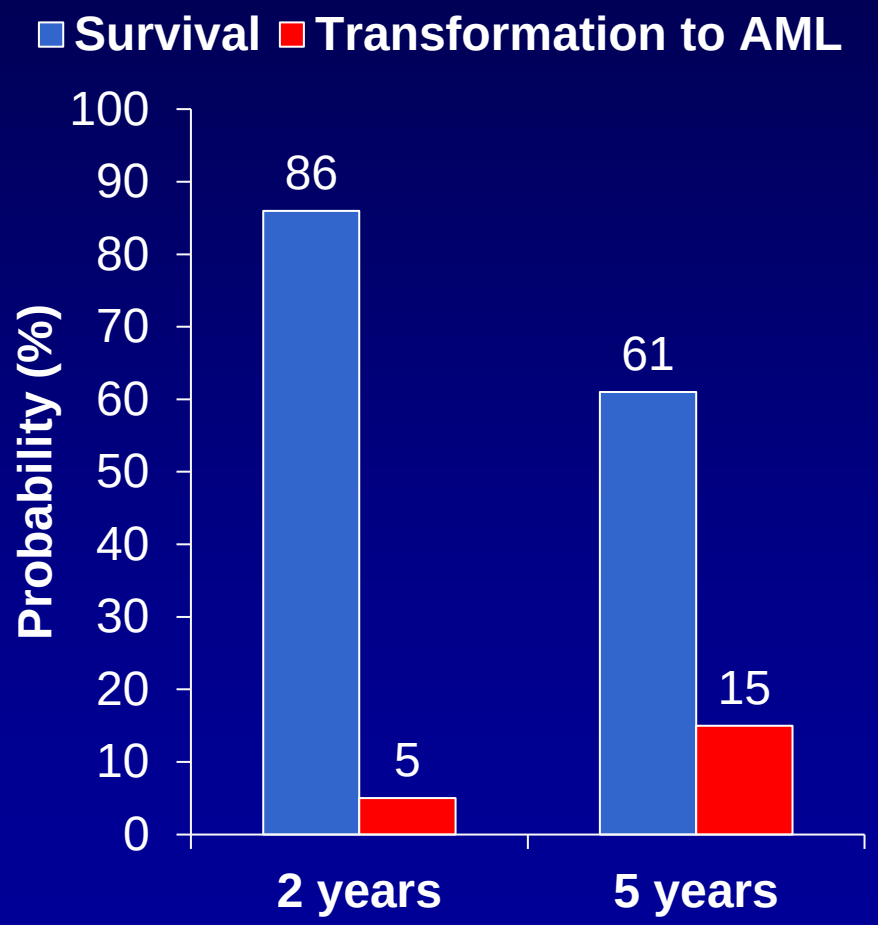

Santini V, ASH 2016




HSCT – bone marrow/stem cell transplant

Santini V, ASH 2016

# Outcomes in 381 Untreated Patients With Lower-risk MDS and del(5q)



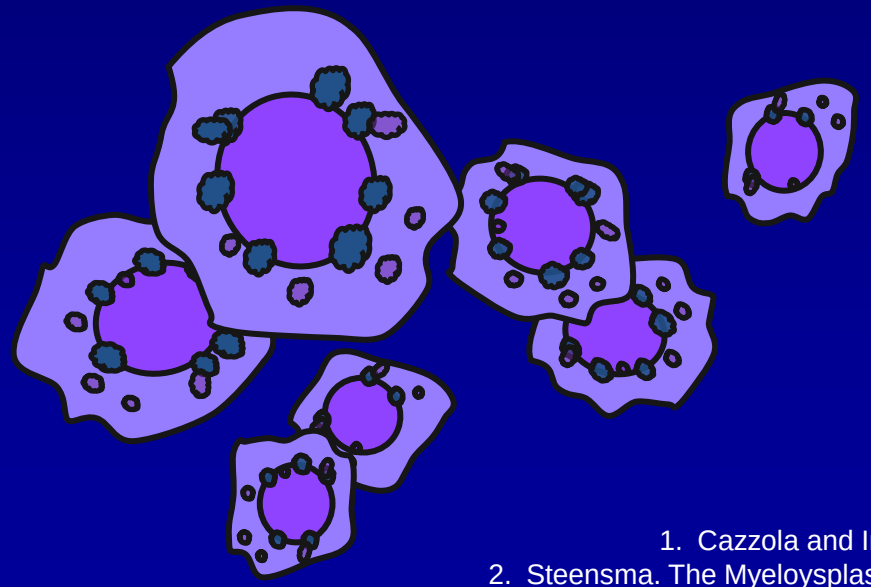

- Have relatively good prognosis, but still have risk of transformation to AML
- Need for RBC transfusions associated with worse prognosis and higher risk of AML transformation



Germing U, et al. Leukemia. 2012;26:1286-92.

# Ring Sideroblasts in MDS

- In MDS, erythroblasts in the bone marrow may have a ring-like structure of iron-rich mitochondria surrounding the nucleus[1]
- These atypical erythroblasts are known as ring sideroblasts (RS);[1] one-third of MDS patients have ≥ 15% RS and 5–10% have RARS (refractory anemia with RS)[2,3]




1. Cazzola and Invernizzi, Haematologica 2011;96:789-92
2. Steensma. The Myeloysplastic Syndromes: Pathobiology and Clinical Management. 2009. 2nd Ed. New York, NY: Informa Healthcare
3. Avgerinou et al. Ann Hematol. 2013;92:877-87

# Common Treatment Options for Patients With Lower-risk MDS and del(5q)

| Treatment | Comment |
|---|---|
| RBC transfusion | Improve anemia, but chronic transfusions may negatively affect patient quality of life and lead to iron overload[1,2] |
| ESAs | Lower response rates (39%) and shorter response duration (13 months) [1,3] |
| Lenalidomide | A treatment option for transfusion-dependent patients with lower-risk MDS and del(5q); 56% of patients achieved RBC transfusion independence[4] |
| Other supportive care measures | Platelet transfusions, growth factors[1] |


1. Fenaux P, Ades L. Blood. 2013;121:4280-6.
2. Santini V. Semin Hematol. 2015;52:348-56.
3. Kelaidi C, et al. Leuk Res. 2008;32:1049-53.
4. Fenaux P, et al. Blood. 2011;118:3765-76.

# Treating Higher-risk MDS

# Higher-risk MDS patients have a poor prognosis

| | IPSS risk category | | | |
|---|---|---|---|---|
| | Low | Intermediate-1 | Intermediate-2 | High |
| Median survival (years) | 5.7 | 3.5 | 1.2 | 0.4 |
| Time to 25% AML progression (years) | 9.4 | 3.3 | 1.1 | 0.2 |

“Higher-risk” MDS

About 30% of all MDS patients have higher-risk disease



1. Greenberg et al. Blood 1997;89:2079-88

# Treating Higher-risk MDS

- Prognosis for patients with higher-risk MDS generally poor. Treatment should start as soon as possible[1]
- Standard treatments include hypomethylating agents azacitidine and decitabine[1-3]
- Once these drugs fail, further treatment options are very limited and survival is guarded[1]
- Clinical trials ongoing involving a number of drugs for treatment of higher-risk MDS – should be considered


1. Sekeres and Cutler. Blood 2014;123:829-36.
2. Vidaza package insert; Celgene Corporation
3. Dacogen package insert; Otsuka America Pharmaceutical

# Treatment Options for Patients With Higher-risk MDS

## Proceed to stem cell transplant as soon as feasible

| Treatment | Comment |
|---|---|
| Azacitidine | In a phase 3 study, azacitidine led to OS of 24 mnths, delayed AML occurrence, reduced RBC transfusions |
| Decitabine | In a phase 3 study, complete and partial response rate was 23%[2] |
| Lenalidomide | Day 1-28 of 42-d cycles) not well tolerated |
| Stem Cell Transplant | Associated with improvements to quality-adjusted life expectancy; however, less than 10% of patients over 65 years of age undergo HSCT[4] |


1. Ades L et al. Blood 2015;126:abstract 2869
2. Lübbert et al. J Clin Oncol 2011;29:1987-96
3. Zeidan A et al. Blood 2015;126:abstract 2901
4. Atallah E et al. Curr Hematol Malig Rep 2014;9:57–65

# Recommended HMT Dosing

## Azacitidine (5AC)

- 75 mg/m$^2$ SC or IV x 7 days every 28 days
- Alternate doses examined (HI similar)
  - 75 mg/m$^2$/d for 5d, off 2d and on 2d (5-2-2)
  - 50 mg/m$^2$/d for 5d, off 2d and on 5d (5-2-5)
  - 75 mg/m$^2$/d for 5d

## Decitabine (DAC)

- 15 mg/m$^2$ IV Q8 hours x 3 days every 28 days
- 20 mg/m$^2$ IV x 5d every 28 days

## Administer at least 4-6 cycles