Myelodysplastic Syndromes

Lymphoma Tumor Board
Friday, September 16, 2016

Background

- Myelodysplastic syndrome (MDS): heterogeneous collection of bone marrow disorders characterized by:
    - dysplasia in bone marrow and blood cells
    - ineffective hematopoiesis
    - cytopenias
    - a tendency to develop acute myeloid leukemia

- Mean age at onset: 68 years

- Associated in some cases with environmental exposures such as to ionizing radiation or hydrocarbons such as benzene

- "Secondary" or therapy-related MDS can occur as a late sequela to previous treatment with genotoxic agents

- Aplastic anemia and Fanconi anemia can evolve into MDS

- Etiology: mutation[s] in multipotential bone marrow stem cells

- Classification system recently updated by the WHO in 2016: "*WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*"

Revised 2016 WHO Classification System

- Intended to incorporate new knowledge of these disorders

- Revisions were influenced by the following:

- *"The discovery of recently identified molecular features has yielded new perspectives regarding diagnostic and prognostic markers that provide novel insights for the understanding of the pathobiology of these disorders."*

- *"Improved characterization and standardization of morphological features aiding in the differentiation of disease groups, particularly of the BCR-ABL1⁻ myeloproliferative neoplasms (MPNs), has increased the reliability and reproducibility of diagnoses."*

- *"A number of clinical-pathological studies have now validated the WHO postulate of an integrated approach that includes hematologic, morphologic, cytogenetic, and molecular genetic findings."*

Revised 2016 WHO Classification System for MDS

- Terminology has changed to remove terms such as "refractory anemia" and "refractory cytopenia"

- New modifiers are: single vs. multilineage dysplasia, ring sideroblasts, excess blasts, or the del(5q) cytogenetic abnormality

- No changes to childhood MDS

- Biggest challenge is separating MDS from reactive causes of cytopenia and dysplasia

- Threshold to define dysplasia remains as 10% dysplastic cells in any hematopoietic lineage

- Myeloblast percentage determined by BM aspirate smears or touch preps remains critical in WHO MDS categories

Revised 2016 WHO Classification of MDS
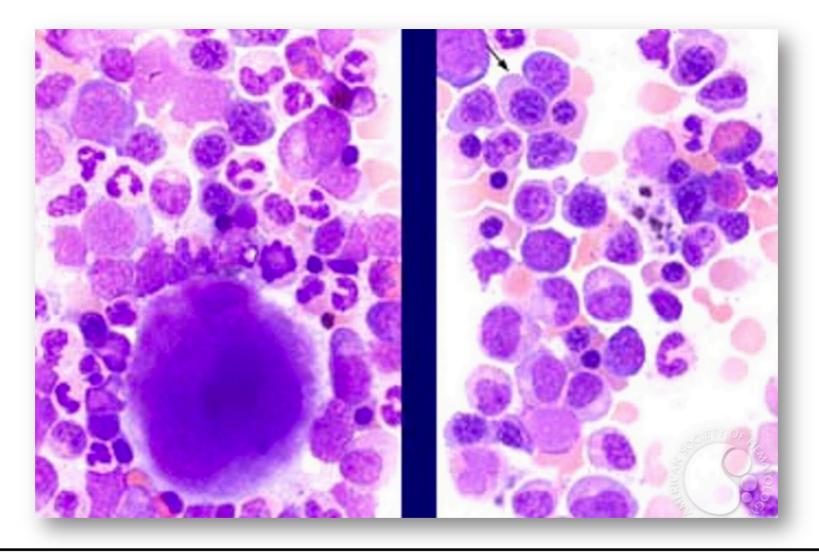
Table 15. PB and BM findings and cytogenetics of MDS

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

*Cytopenias defined as: hemoglobin, <10 g/dL; platelet count, <100 × 10⁹/L; and absolute neutrophil count, <1.8 × 10⁹/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 × 10⁹/L

†If *SF3B1* mutation is present.

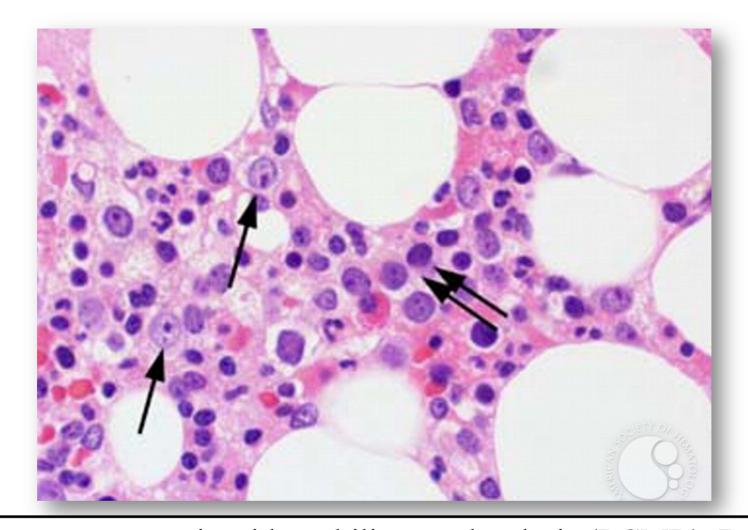‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Daniel A. Arber et al. _Blood_ 2016;127:2391-2405

"Refractory anemia with ringed sideroblasts (RARS). Bone marrow aspirate smear (Wright-Giemsa stain). The two panels in this slide illustrate that the megakaryocytes and the granulocytes show normal morphology. The erythroid precursors in this slide do show some mild nuclear/cytoplasmic dyssynchrony (arrow)."
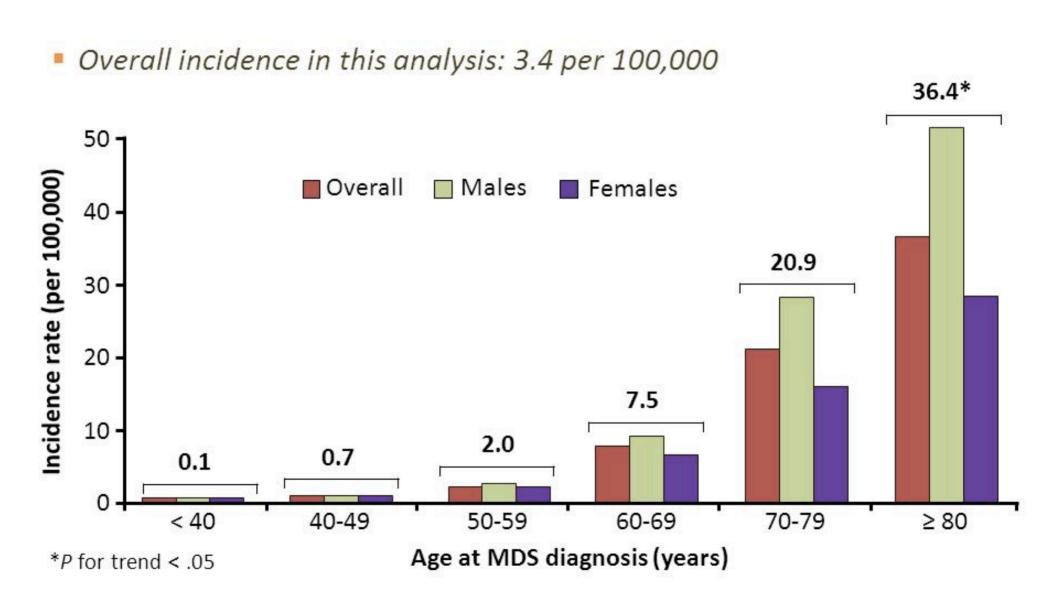
5

del(5)(q11q33)

7

del(7)(q11q36)

"Refractory cytopenia with multilineage dysplasia (RCMD). Cytogenetic preparation. The karyotype performed from bone marrow cells was: 46, XY [80%] 46, XY, del (5q)(q11q33), del (7q) (q11q36) [20%]."

"Refractory cytopenia with multilineage dysplasia (RCMD). Bone marrow biopsy (H & E stain). The biopsy demonstrates erythroid hyperplasia. Immature erythroid precursors (arrows) have round to oval vesicular nuclei, a prominent, comma-shaped nucleolus that often is close to the nuclear membrane, and a rim of amphophilic cytoplasm. Erythroid precursors that are more mature (double arrows) have homogenous, darkly-stained nuclei."

Age and Sex in MDS

- *Overall incidence in this analysis: 3.4 per 100,000*

*P for trend < .05

Rollison DE et al Blood 2008;112:45-52.

MDS cytogenetic scoring system

Prognostic subgroups, % of patients	Cytogenetic abnormalities	Median survival,[*] y	Median AML evolution, 25%,[*] y	Hazard ratios OS/AML[*]	Hazard ratios OS/AML[†]
Very good (4%[*]/3%[†])	−Y, del(11q)	5.4	NR	0.7/0.4	0.5/0.5
Good (72%[*]/66%[†])	Normal, del(5q), del(12p), del(20q), double including del(5q)	4.8	9.4	1/1	1/1
Intermediate (13%[*]/19%[†])	del(7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5	1.5/1.8	1.6/2.2
Poor (4%[*]/5%[†])	−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities	1.5	1.7	2.3/2.3	2.6/3.4
Very poor (7%[*]/7%[†])	Complex: > 3 abnormalities	0.7	0.7	3.8/3.6	4.2/4.9

OS indicates overall survival; and NR, not reached.

↵* Data from patients in this IWG–PM database, multivariate analysis (n = 7012).

↵† Data from Schanz et al[8] (n = 2754).

Peter L. Greenberg et al. Blood 2012;120:2454-2465
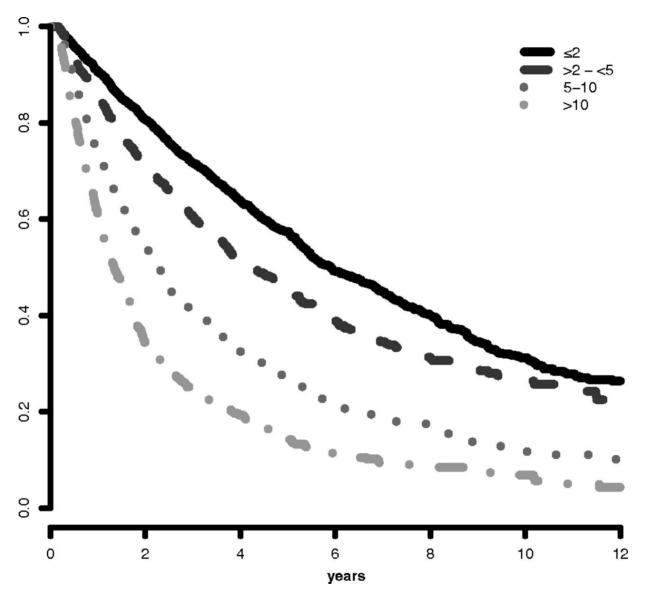
IPSS-R prognostic score values

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	—	—	—	—	—

— indicates not applicable.
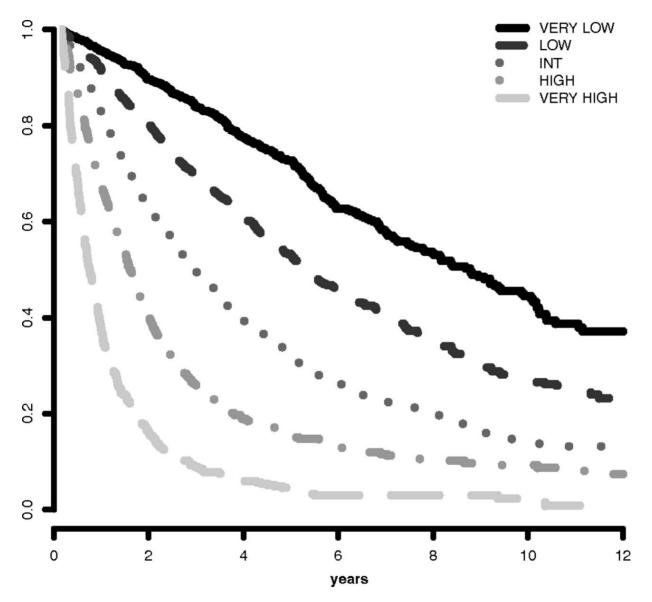
Survival stratified by marrow blast subgroup

Legend:
- ≤2
- >2 – <5
- 5–10
- >10

Peter L. Greenberg et al. Blood 2012;120:2454-2465

blood
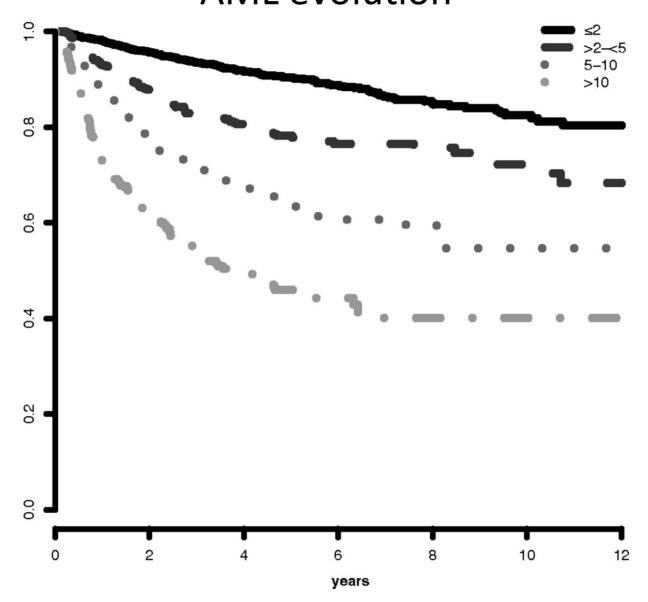
Survival based on IPSS-R prognostic risk-based category

Peter L. Greenberg et al. Blood 2012;120:2454-2465
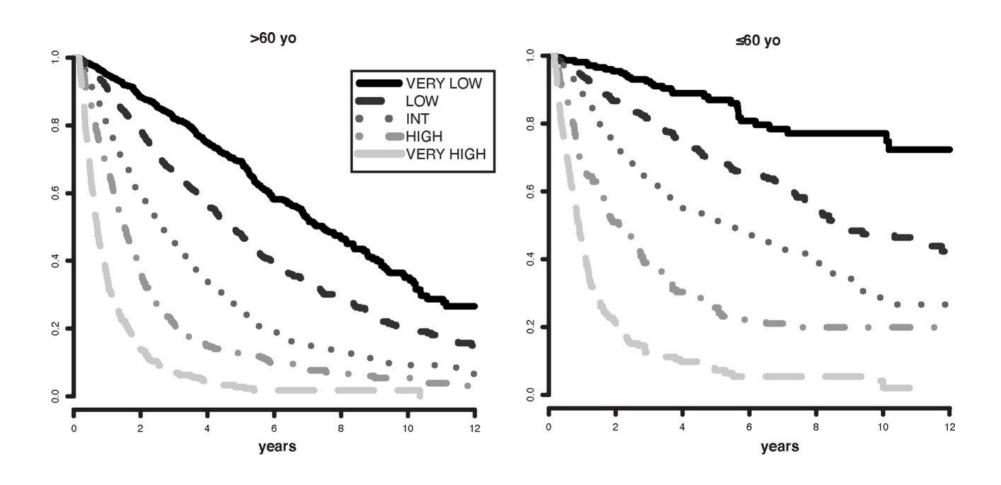
IWG-PM patients marrow blast subgroups: Impact on AML evolution

Peter L. Greenberg et al. Blood 2012;120:2454-2465

blood
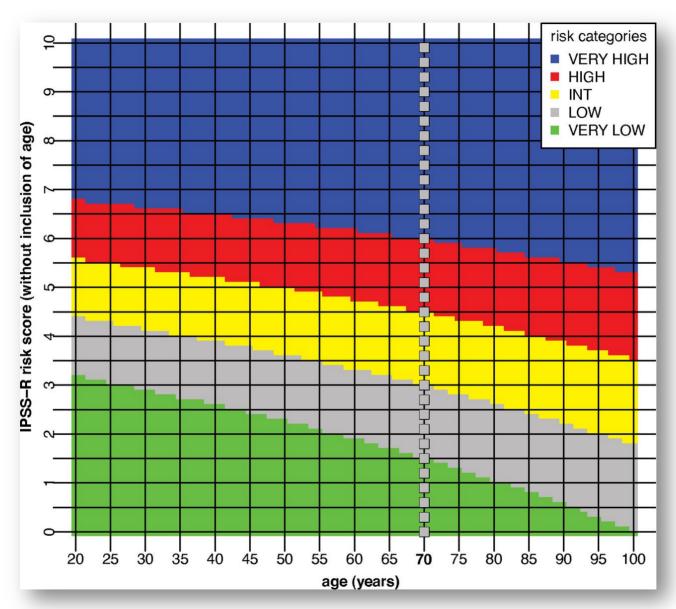
Survival stratified by patient age (> 60 years vs. ≤ 60 years) and IPSS-R prognostic category
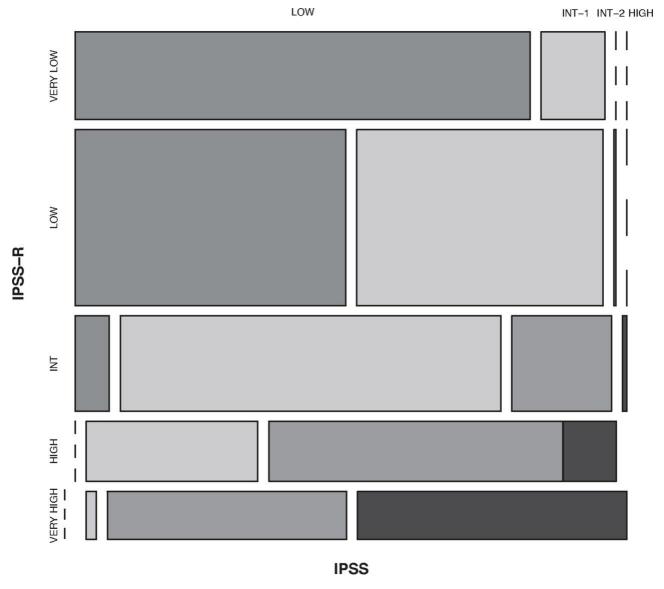
Age-adjusted IPSS-R risk categories

Peter L. Greenberg et al. Blood 2012;120:2454-2465
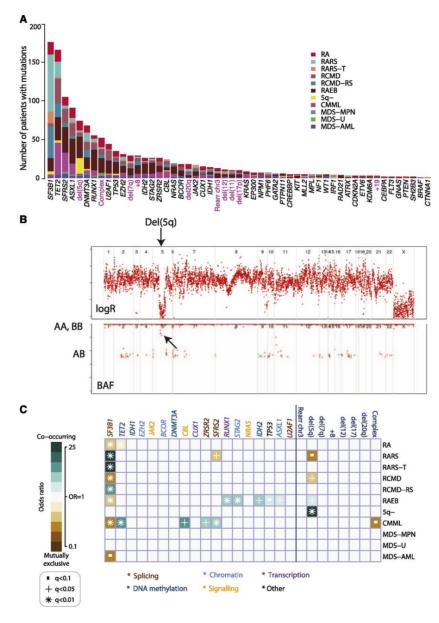
Comparison of IPSS-R and IPSS subgroups within the IWG-PM database patient cohort
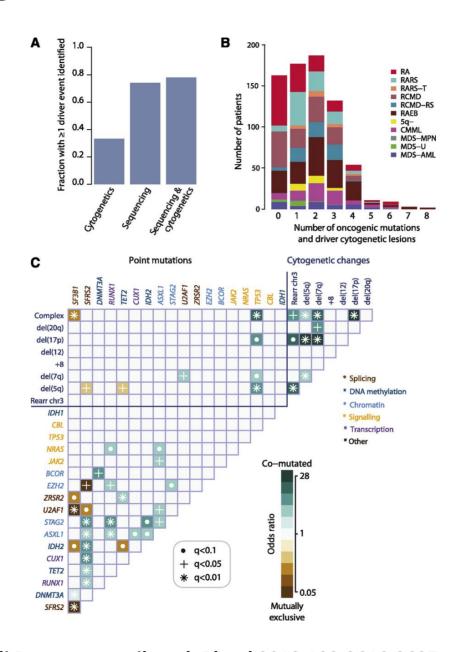

Peter L. Greenberg et al. Blood 2012;120:2454-2465

Genomic architecture of MDS

Frequency of driver mutations identified in the sequencing screen or by cytogenetics in a cohort of 738 patients, broken down by MDS subtype
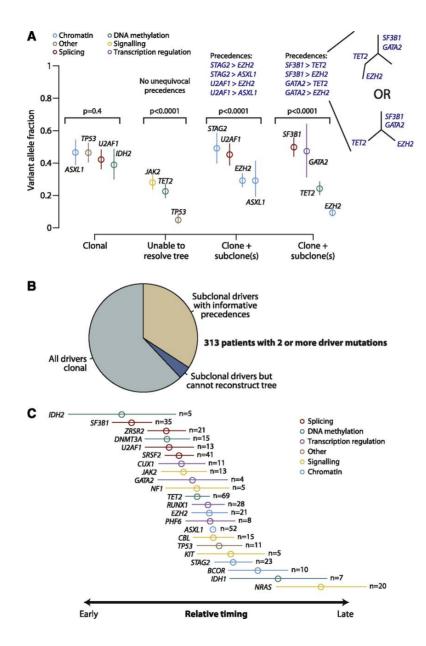
Elli Papaemmanuil et al. Blood 2013;122:3616-3627

blood

Oncogenic mutations identified in MDS
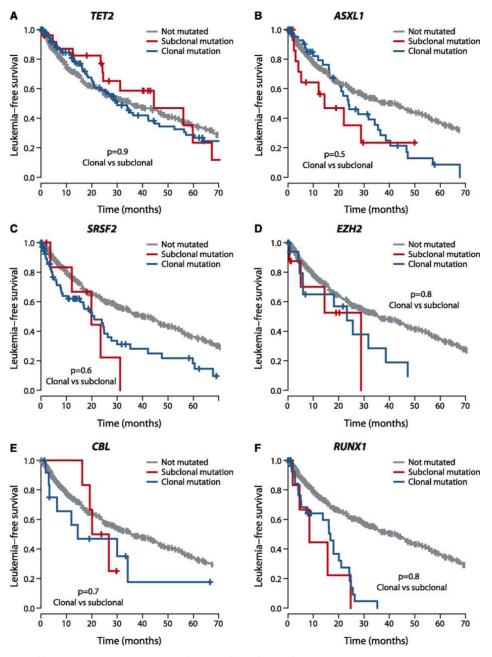

Elli Papaemmanuil et al. Blood 2013;122:3616-3627

Clonal and subclonal driver mutations in MDS
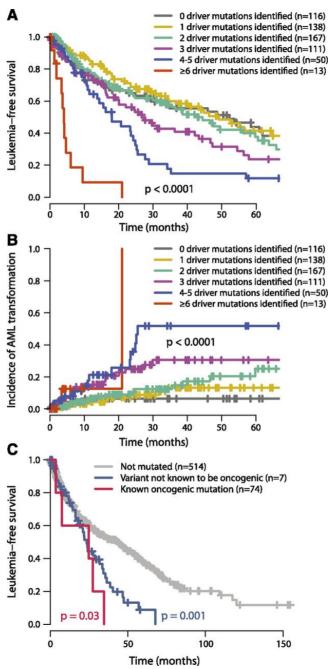

Elli Papaemmanuil et al. Blood 2013;122:3616-3627

Outcome by clonal or subclonal driver mutations
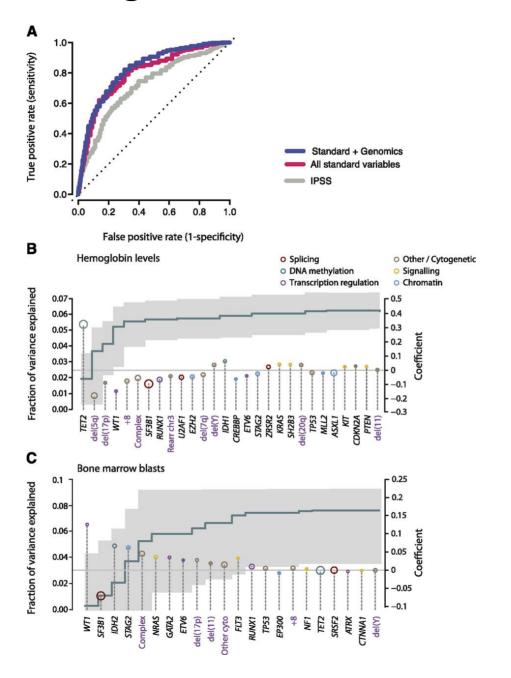

Elli Papaemmanuil et al. Blood 2013;122:3616-3627

blood

Relationship between # of oncogenic mutations & outcome

Elli Papaemmanuil et al. Blood 2013;122:3616-3627

blood

Predicting leukemia-free survival
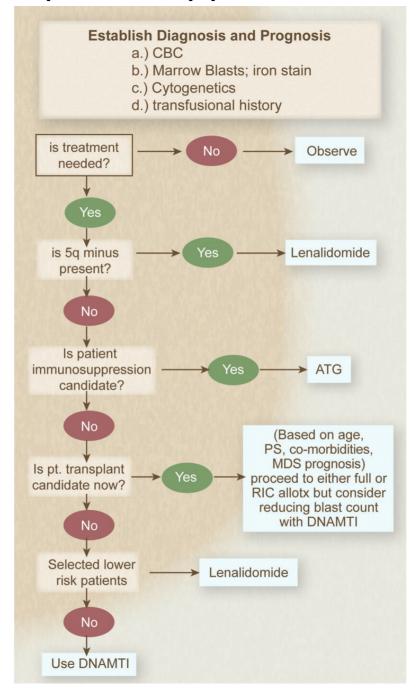
Therapeutic Approach to MDS

- The IPSS scoring system can help guide patients for more aggressive treatment and can help determine the best timing of this therapy

- Supportive care with blood product support and hematopoeitic growth factors (e.g. erythropoietin) is the main type of therapy.

- *Three* agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDS:

  - 5-azacytidine: 21-month median survival

  - Decitabine: Complete response rate reported as high as 43%

  - Lenalidomide: Effective in reducing red blood cell transfusion requirement in patients with the chromosome 5q ("5q-") deletion subtype of MDS
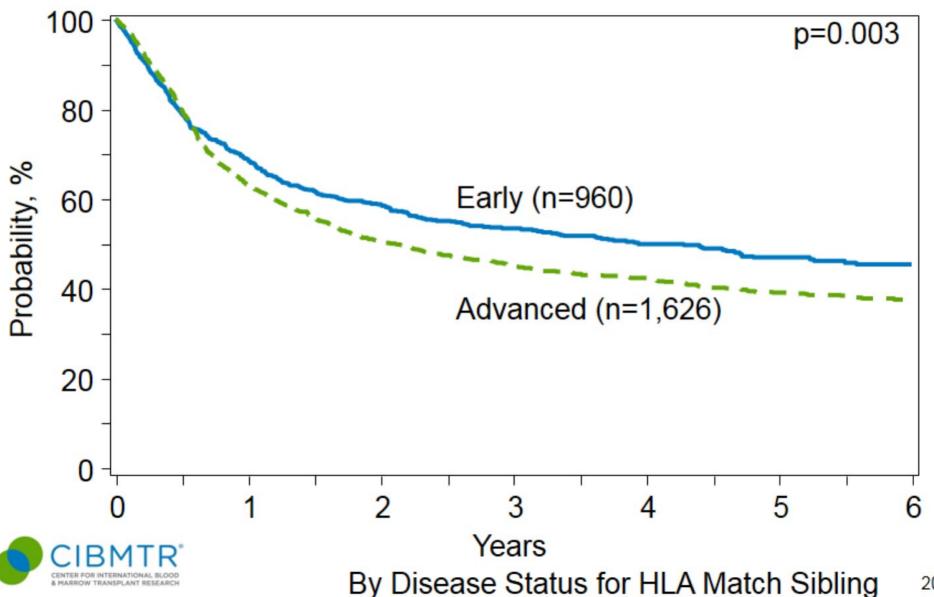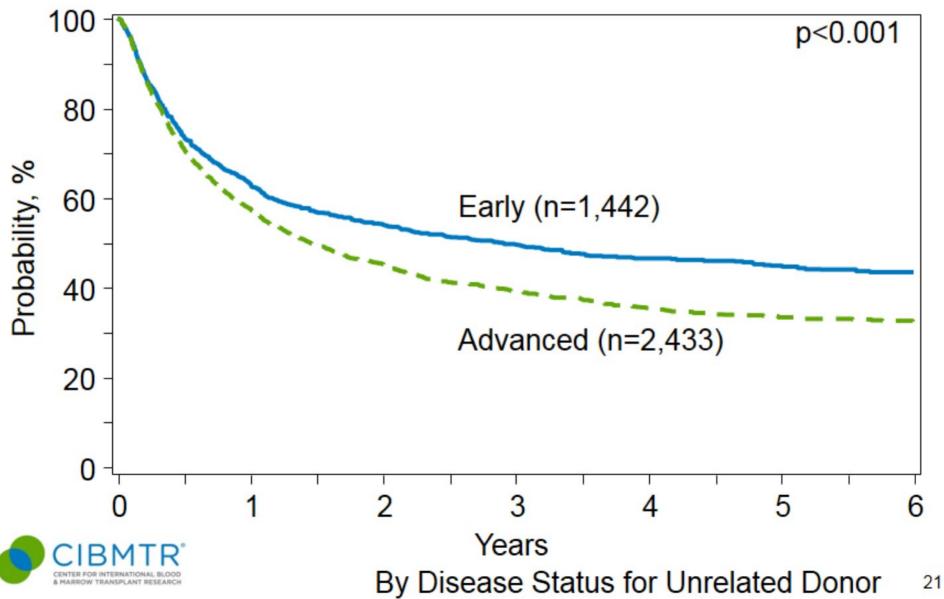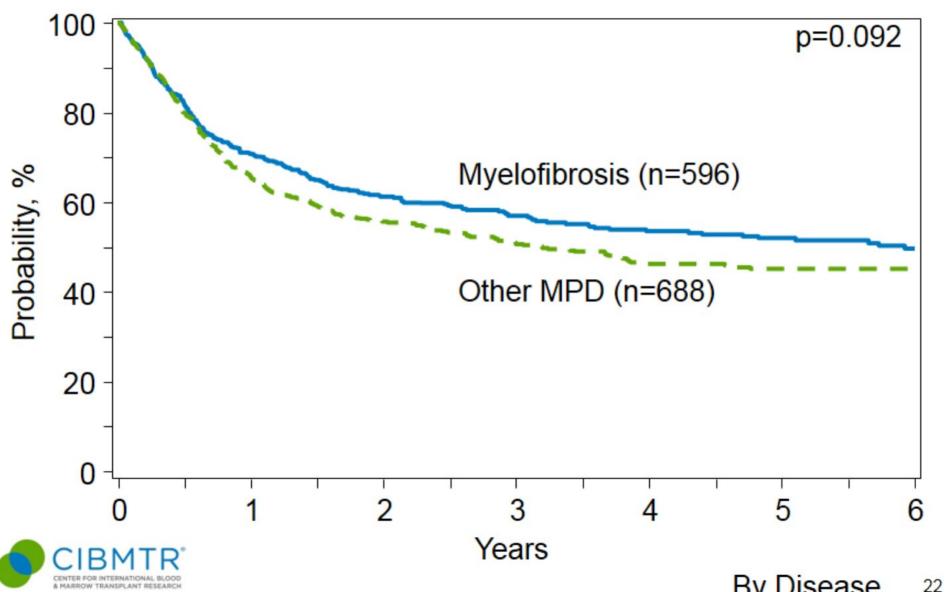
Therapeutic Approach to MDS

blood

Survival after Allogeneic Transplants for Myelodysplastic Syndrome (MDS), 2003-2013

By Disease Status for HLA Match Sibling

Survival after Allogeneic Transplants for Myelodysplastic Syndrome (MDS), 2003-2013

p<0.001

Early (n=1,442)

Advanced (n=2,433)

Probability, %

Years

By Disease Status for Unrelated Donor

21

Survival after HLA Match Sibling Donor Transplants for Myeloproliferative Diseases, 2003-2013

By Disease

22

References

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