POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

9° SESSIONE - SINDROMI MIELODISPLASTICHE

Stato dell'arte

Fabrizio Pane

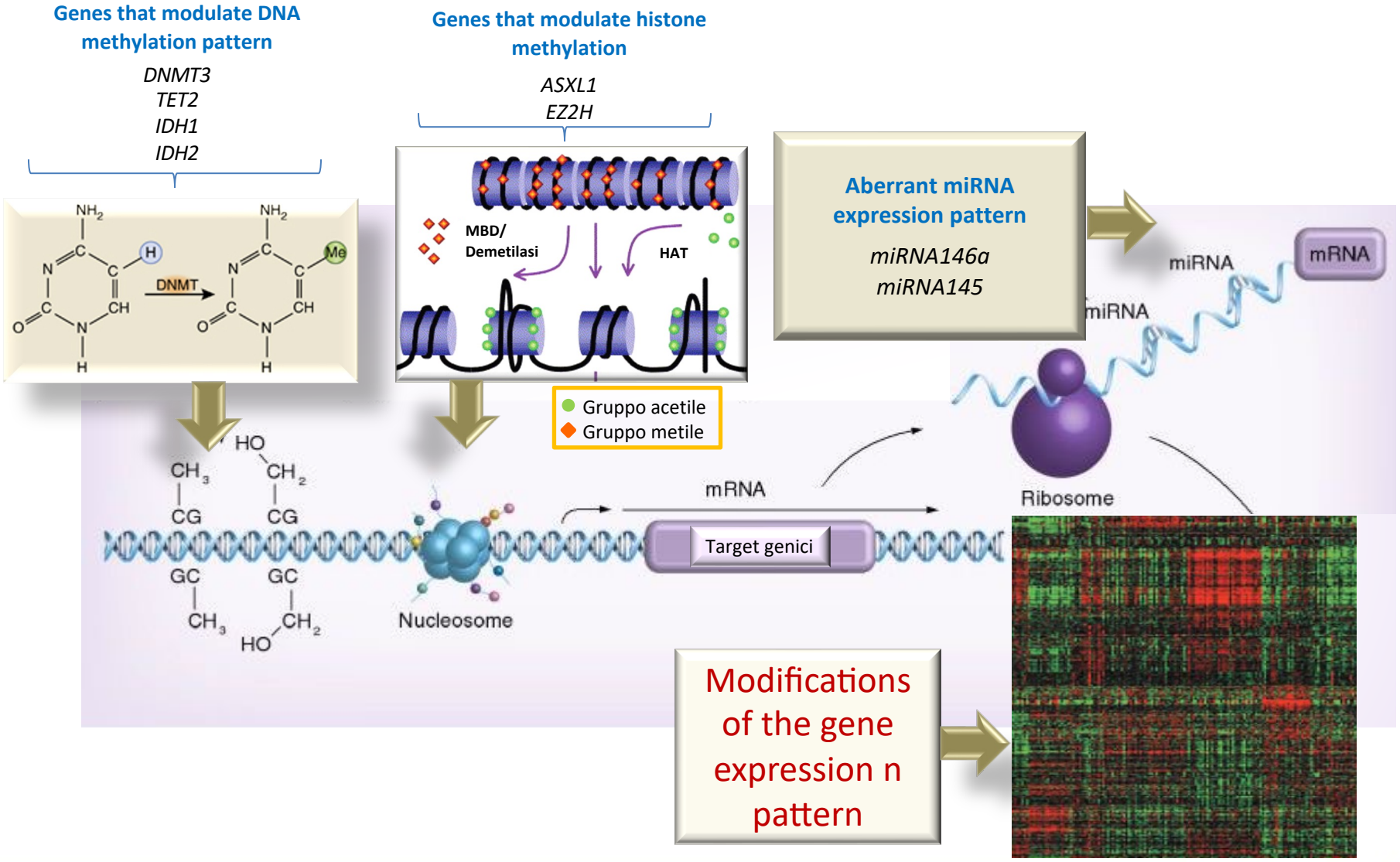
DICHIARAZIONE

Fabrizio Pane

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario (***NIENTE DA DICHIARARE***)
- Consulenza ad aziende con interessi commerciali in campo sanitario (***Incyte***)
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (***Novartis***)
- Partecipazione ad Advisory Board (***Incyte, Novartis, Janssen, BMS, GSK, Sandoz***)
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario (***NIENTE DA DICHIARARE***)
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (***NIENTE DA DICHIARARE***)
- Altro

Central Theme in MDS Pathogenesis: Somatic Mutation-Driven Methylator Phenotypes



Genetic Abnormalities in MDS

Translocations/ Rearrangements	Uniparental Disomy/ Microdeletions	Copy Number Change	Point Mutations
Rare in MDS	Rare; often at sites of point mutations	~50% of cases	Most common
t(6;9) i(17q) t(1;7) t(3;?) t(11;?) inv(3) idic(X)(q13)	4q - TET2 7q - EZH2 11q - CBL 17p - TP53	del(5q) -7/del(7q) del(20q) del(17p) del(11q) +8 -Y	Likely in all cases ~80% of cases have mutations in a known gene
Karyotype	**Array CGH SNP Array**	**Karyotype/FISH**	**Genotyping Sequencing**

Observed Frequency in MDS

Comparison Between ICC and WHO Classification

ICC

MDS with mutated *SF3B1* (MDSSF3B1)	**<5% BM and <2% PB**
MDS with del(5q) [MDS del(5q)]	
MDS, NOS - without dysplasia	
MDS, NOS - with single lineage dysplasia	
MDS, NOS - with multilineage dysplasia	
MDS with excess blasts (MDS-EB)	**10%-19% BM or 5%-19% PB; Auer rods (WHO)**
MDS/AML	
MDS with mutated *TP53*	
MDS/AML with mutated *TP53*	

WHO

MDS with defining genetic abnormalities

- MDS with low blasts and *SF3B1*
- MDS with low blasts and isolated 5q deletion (MDS-5q)
- MDS with biallelic *TP53* inactivation

MDS, morphologically defined

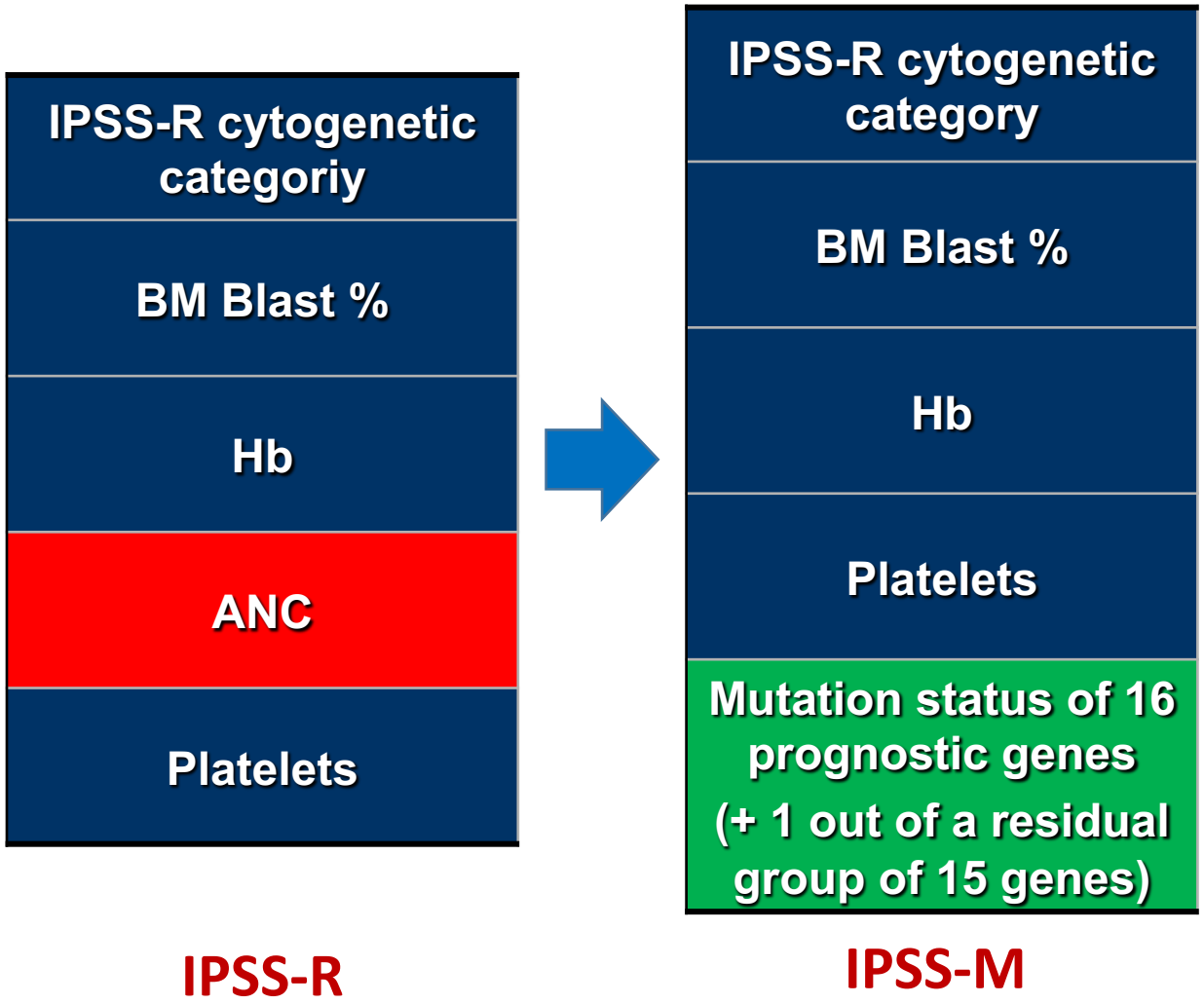
- MDS with low blasts (MDS-LB)
- MDS, hypoplastic (MDS-h)
- MDS with increased blasts (MDS-IB)
  - MDS-IB1
  - MDS-IB2
- MDS with fibrosis (MDS-f)

1. Arber. Blood. 2022;140:1200. 2. Khoury. Leukemia. 2022;36:1703.

Major Changes in the 5th Edition WHO Guidelines

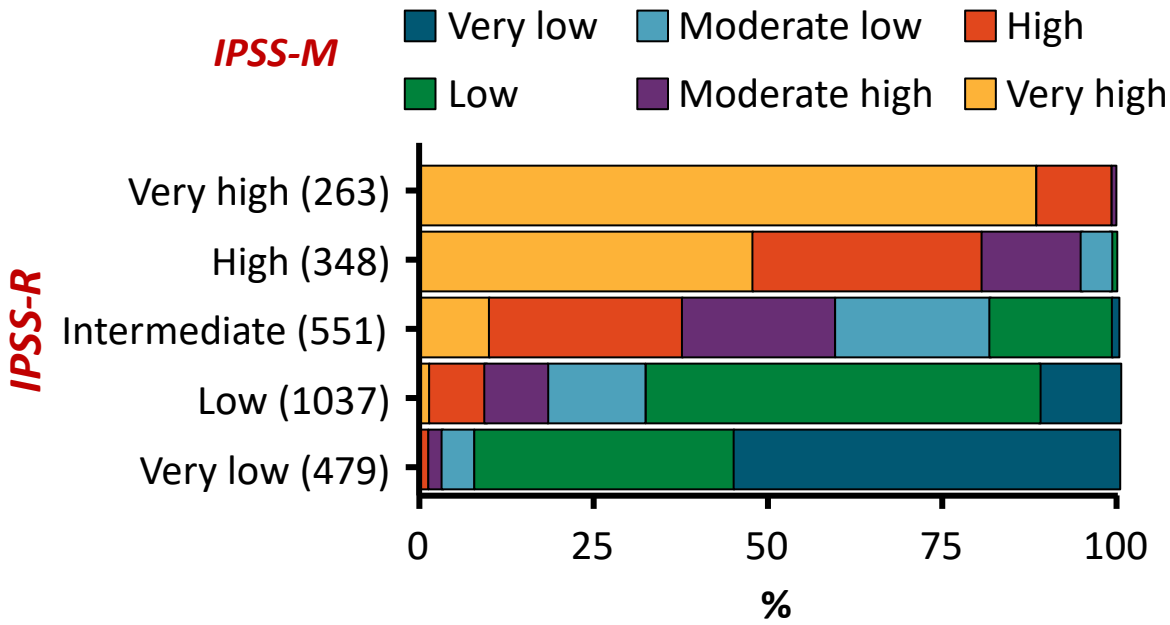
- Inclusion of CH, CHIP, CCUS definition
- Unified cytopenia definition for CHIP, CCUS, and MDS
  - *Hb <13 g/dL (male) <12 g/dL (female), ANC <1.8 x 10^9/L, plt <150 x 10^9/L*
- MDS: myelodysplastic **neoplasms**
- 2 groups of MDS: *genetically defined*, *morphologically defined*
- Biallelic *TP53* mutations supersedes del5q and *SF3B1*
- Hypocellular MDS recognized as a distinct subtype
- Childhood MDS separated into own section

From Revised-IPSS to Molecular-IPSS

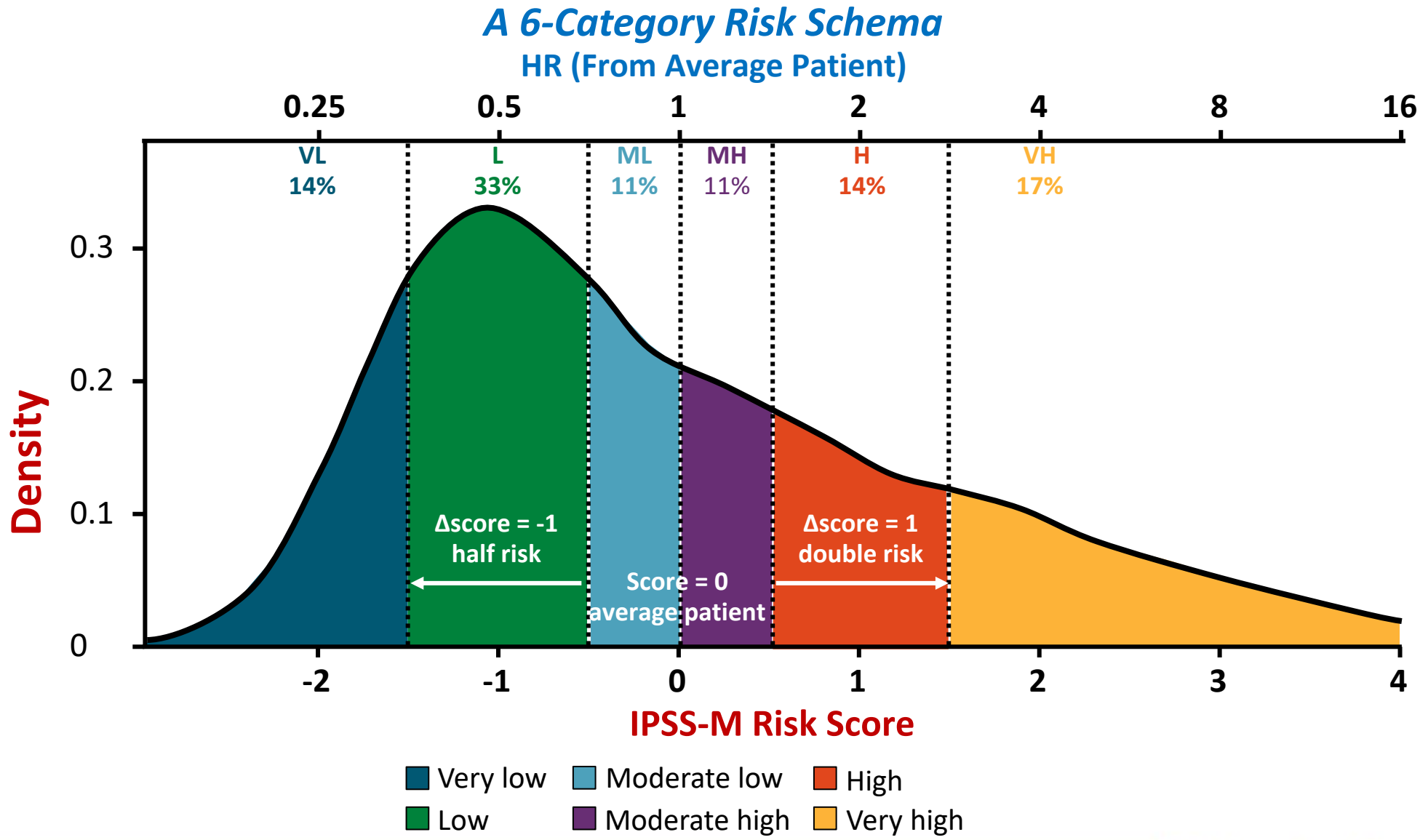


Restratification of patients from 5 IPSS-R to 6 IPSS-M categories

- 46% (n = 1223) of patients were restratified
- 7% (n = 196) of patients were restratified by more than 1 strata



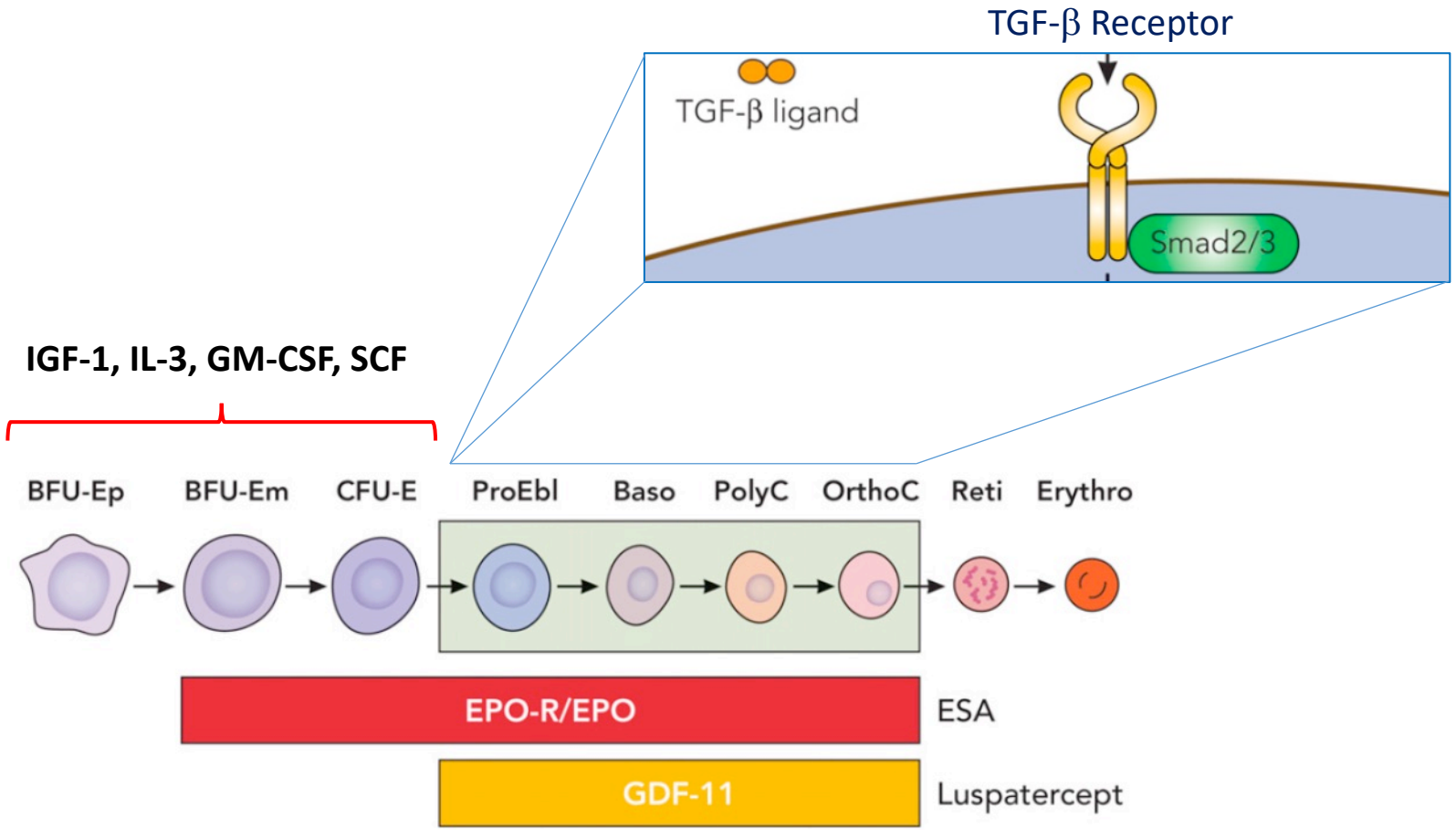
IPSS-M Risk Categories



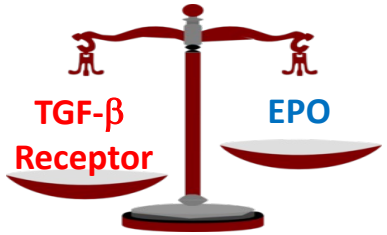
MDS Treatment Goals

- *Lower-risk MDS*
  - **Maximize quality of life**
  - Minimize transfusions
  - Minimize cytopenias and their consequences (eg, fatigue, functional impairment, cognitive impairment, infection risk, bleeding risk)
  - *Attempt* to reduce risk of progression and improve survival
- *Higher-risk MDS*
  - Quality-of-life measures
  - Delay progression to AML

Ineffective erythropoiesis in MDS through marrow inflammatory background

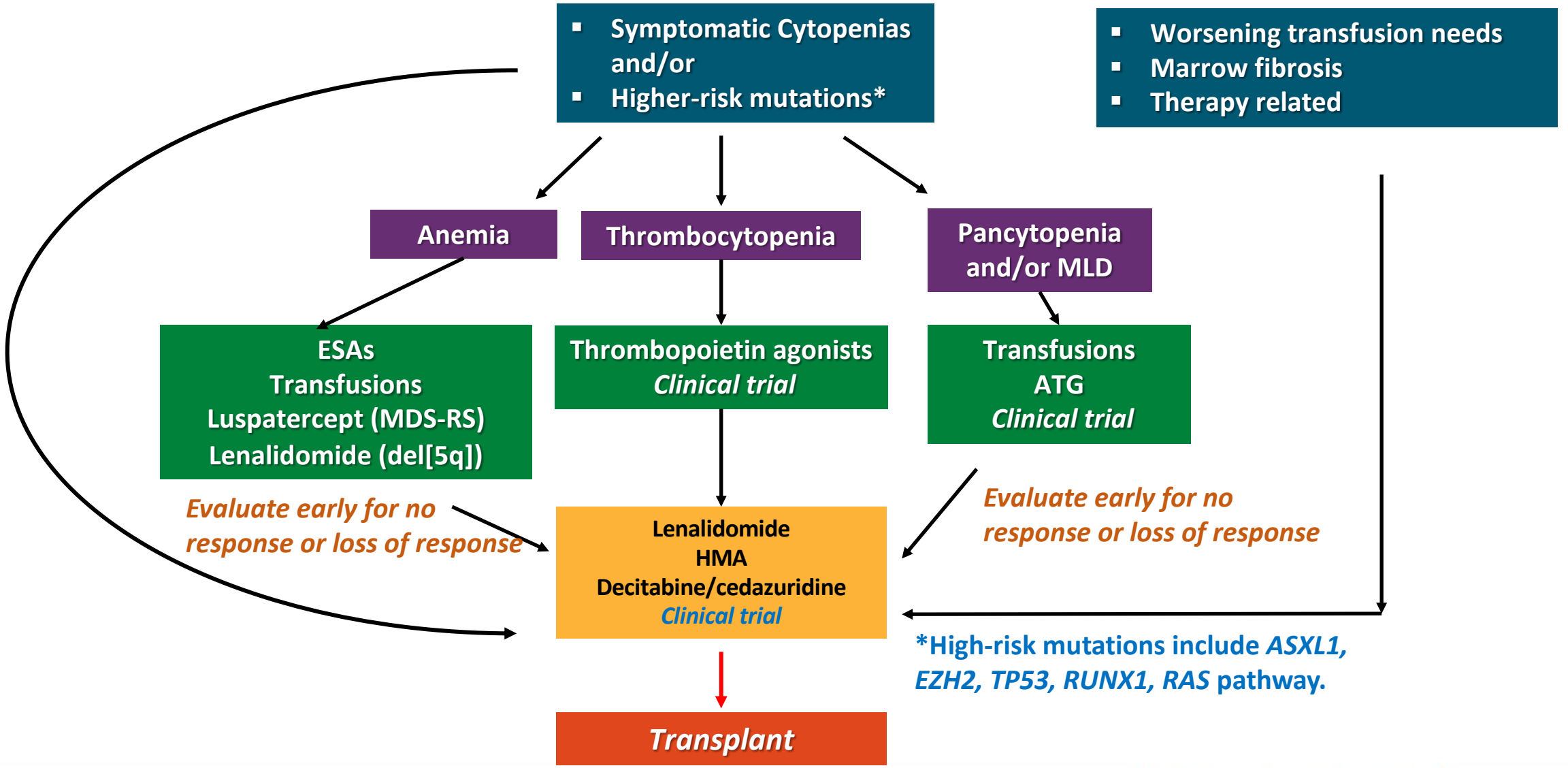


Inbalance of pro-apoptotic to anti-apoptotic signals at pro-erythroblast level



Ineffective erythropoiesis with expansion of progenitors and early precursors compartments

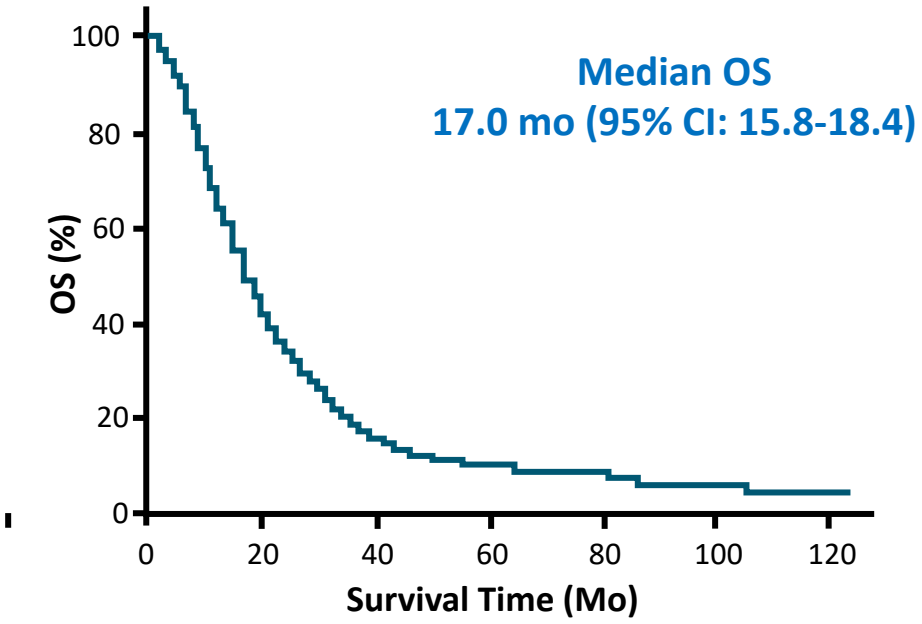
Lower-Risk MDS Treatment Paradigm Considerations



Jain. Biol Blood Marrow Transplant. 2020;26:e263.

The Dawn of the Precision Medicine Era for MDS

Median OS after 5 Cycles HMA



Median OS
17.0 mo (95% CI: 15.8-18.4)

636 HR-MDS of all ages in the MDS Clinical Research Consortium who received HMA (median 5 cycles), 72% received ≥4 cycles.
68% received AZA.

Novel therapies for HMA-resistant/refractory MDS

Molecularly targeted agents:
- IDH1/2 inhibitors (eg, ivosidenib, enasidenib, FT-2102)
- Eprenetapopt
- H3B-8800
- FLT3 inhibitors (eg, gilteritinib)

Genetically agnostic small molecule inhibitors:
- Pevonedistat
- Venetoclax
- Glasdegib
- Rigosertib

Immunotherapies:
- Anti-PD1/PD-L1 antibodies
- Anti-CTLA4
- Anti-TIM3 (eg, sabatolimab)
- Anti-CD47 antibodies (eg, magrolimab)

Chemotherapy/epigenetic agents:
- CPX-351
- Novel HMA (eg, ASTX727, CC486, guadecitabine)
- HDAC inhibitors

9° SESSIONE

SINDROMI MIELODISPLASTICHE — F. PANE

09.10	Stato dell'arte	F. PANE
09.20	Biologia e prognosi	M.T. VOSO
09.40	Terapia delle sindromi mielodisplastiche a basso rischio	P. MUSTO
10.00	Terapia delle sindromi mielodisplastiche ad alto rischio	V. SANTINI
10.20	Discussione	