Myelodysplastic Syndromes Diagnosis and Treatment Overview

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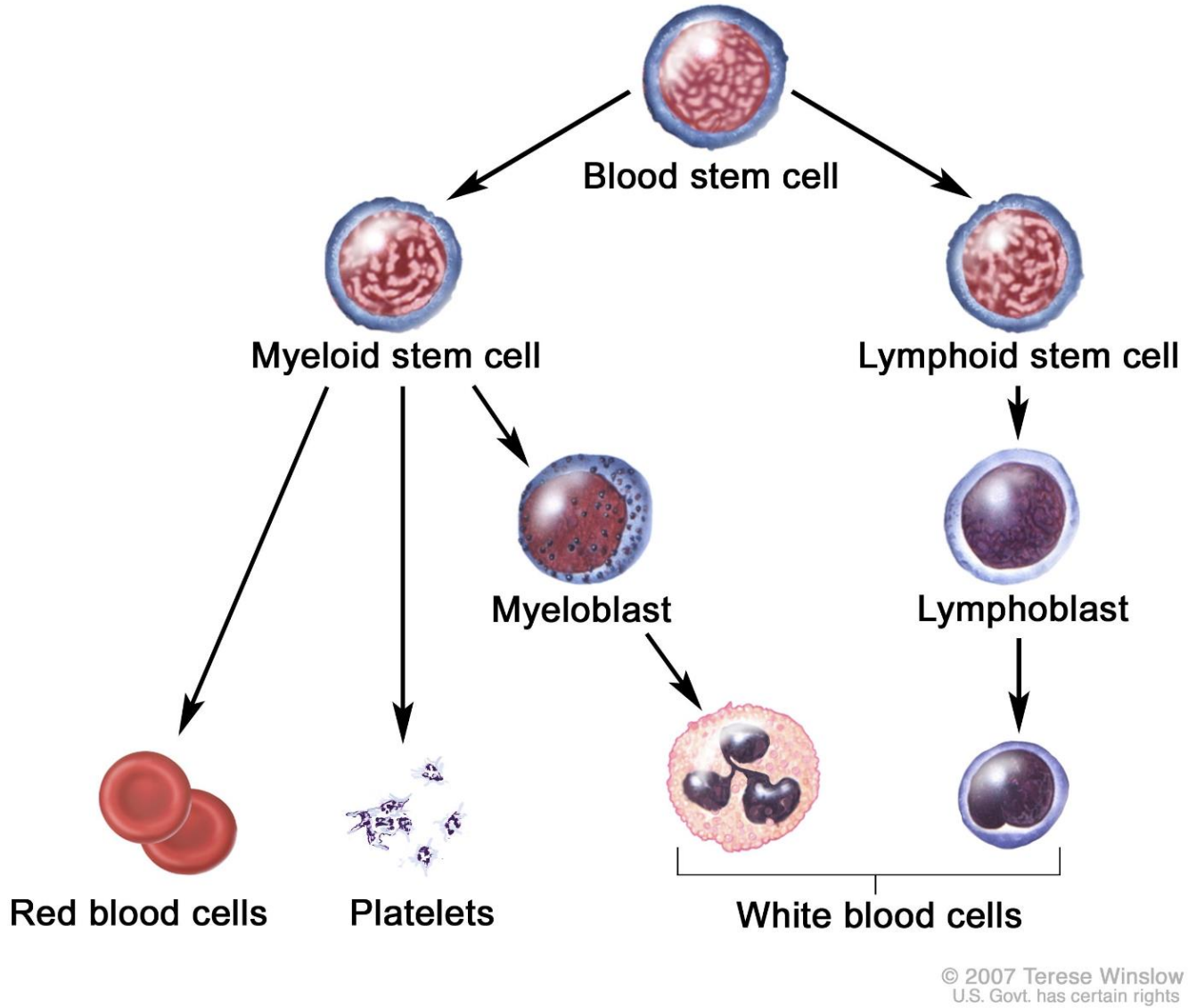
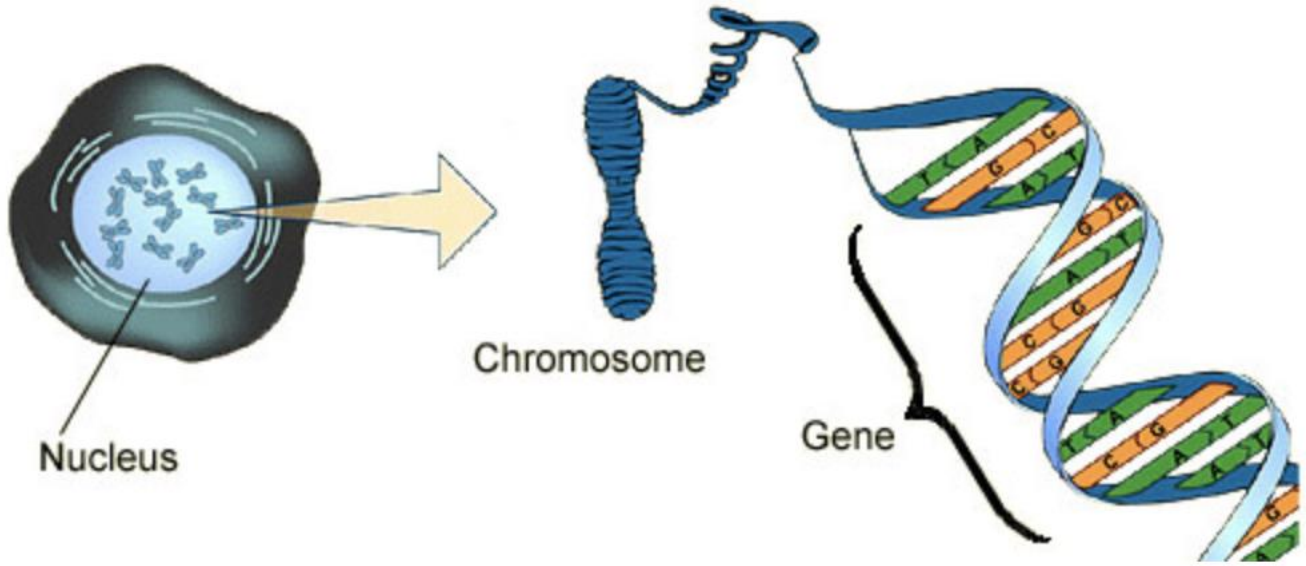


https://nci-media.cancer.gov/pdq/media/images/765030.jpg

Diagnosis of MDS

- Morphology
- Flow Cytometry
- Cytogenetics: karyotype and FISH
- Molecular diagnostics: Next generation Sequencing Panels



WHO Classification of Haematolymphoid Tumours 5th Edition

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.

[b]By definition, ≤25% bone marrow cellularity, age adjusted.

BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Khoury et al, leukemia 2022

International Prognostication Scoring System, Revised (IPSS-R)

Parameter	Categories and Associated Scores (Scores in italics)				
Cytogenetic risk group[a]	Very good	Good	Intermediate	Poor	Very Poor
	0	*1*	*2*	*3*	*4*
Marrow blast proportion	≤2.0%	>2.0–<5.0%	5.0–<10.0%	≥10.0%	
	0	*1*	*2*	*3*	
Hemoglobin	≥10 g/dL	8–<10 g/dL	<8 g/dL		
	0	*1*	*1.5*		
Absolute neutrophil count	$\geq 0.8 \times 10^9$/L	$<0.8 \times 10^9$/L			
	0	*0.5*			
Platelet count	$\geq 100 \times 10^9$/L	$50–100 \times 10^9$/L	$<50 \times 10^9$/L		
	0	*0.5*	*1*		

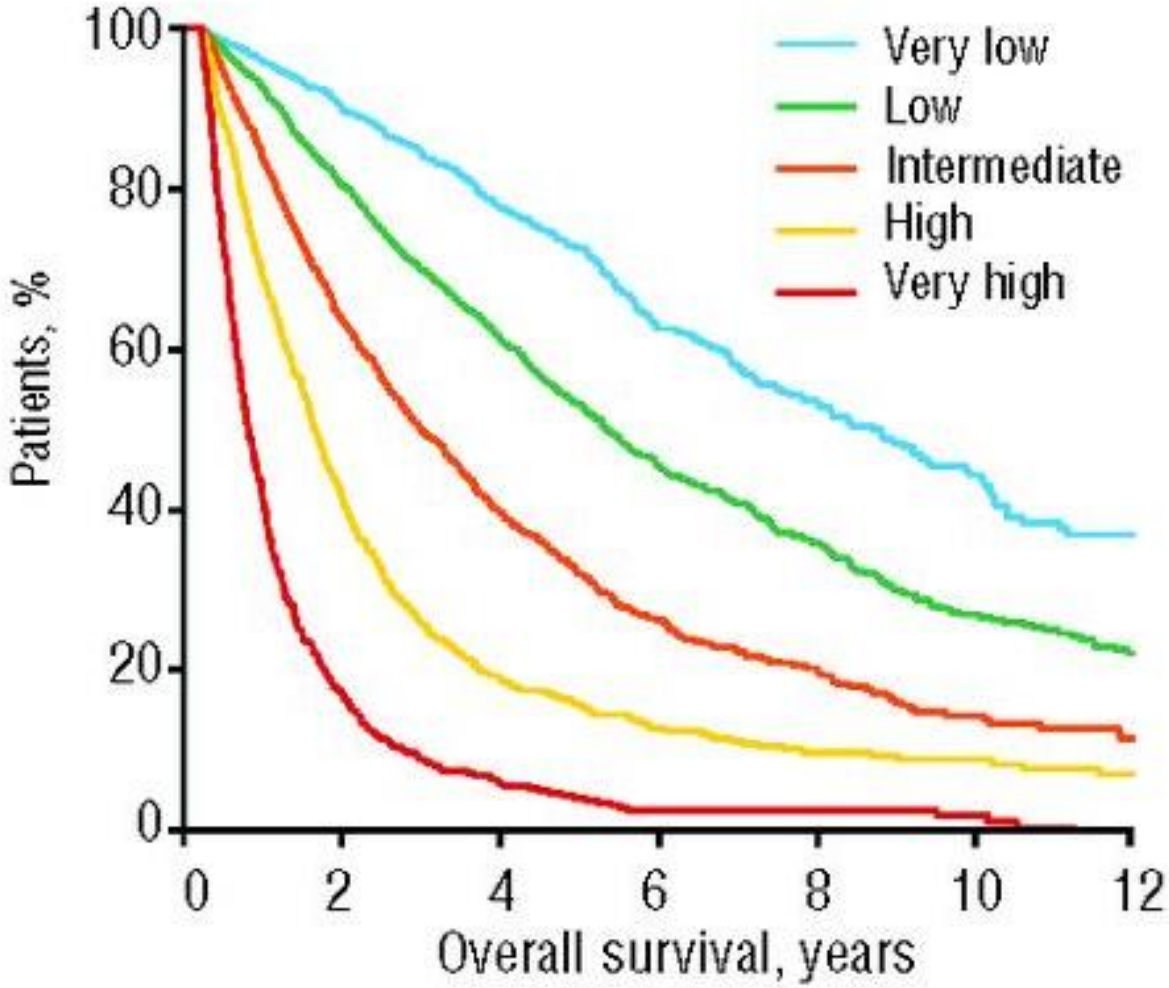
Risk group	Total score[b]	Proportion of patients in category (%)	Median survival (survival data based on $n = 7012$) (years)	Time until AML progression (AML data available based on $n = 6485$) (years)
Very low	0–1.0	19	8.8	Not reached
Low	1.5–3.0	38	5.3	10.8
Intermediate	3.5–4.5	20	3.0	3.2
High	5.0–6.0	13	1.5	1.4
Very high	>6.0	10	0.8	0.7

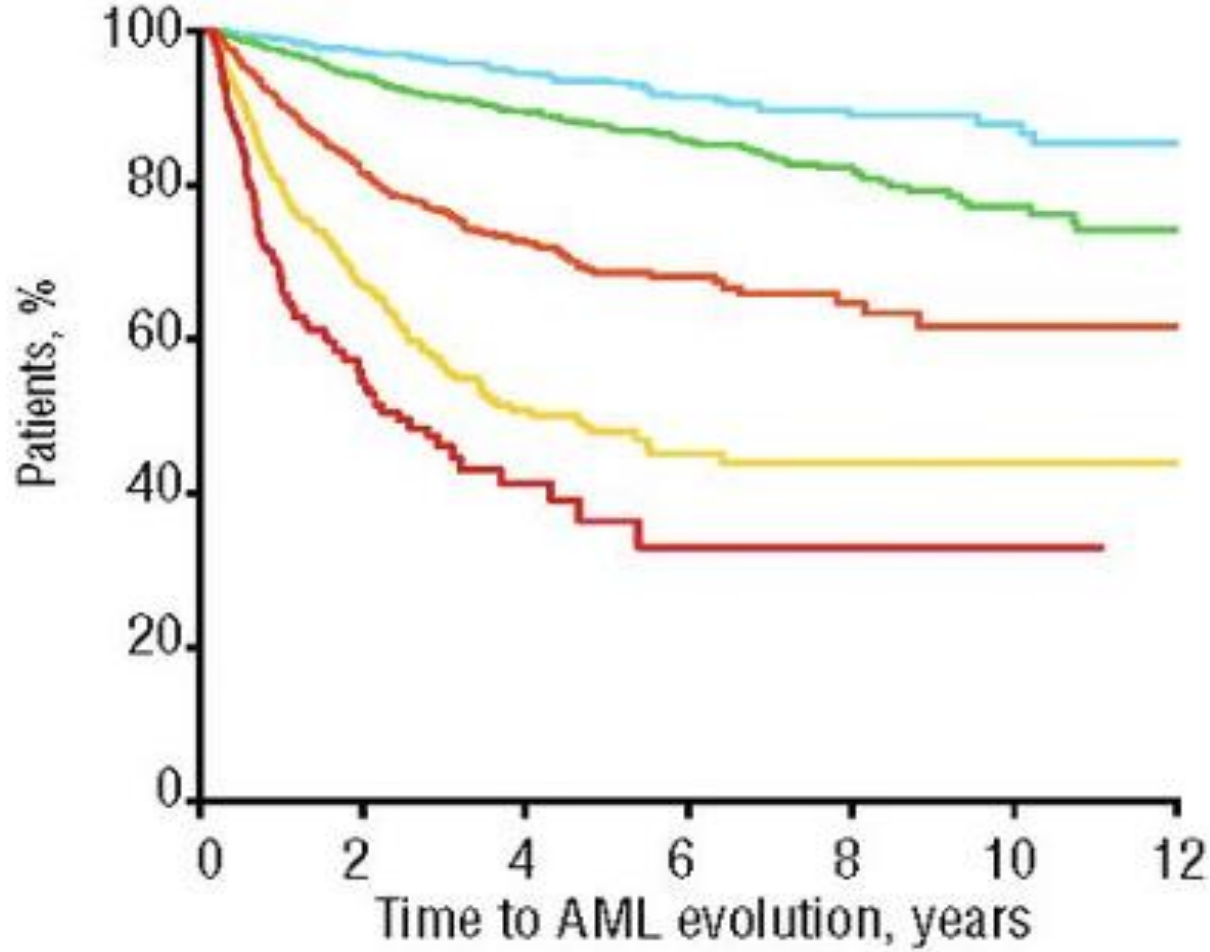
[a] Cytogenetic risk group, very good: -Y, del(11q); good: normal; del(5q) ± 1 other abnormality del(20q), or del(12p); intermediate: + 8, i(17q), del(7q), + 19, any other abnormality not listed including the preceding with 1 other abnormality; poor: −7 ± del(7q), inv(3)/t(3q)/del(3q), any 3 separate abnormalities; very poor: more than 3 abnormalities, especially if 17p is deleted or rearranged

[b] Sum scores on a 0–10 point scale

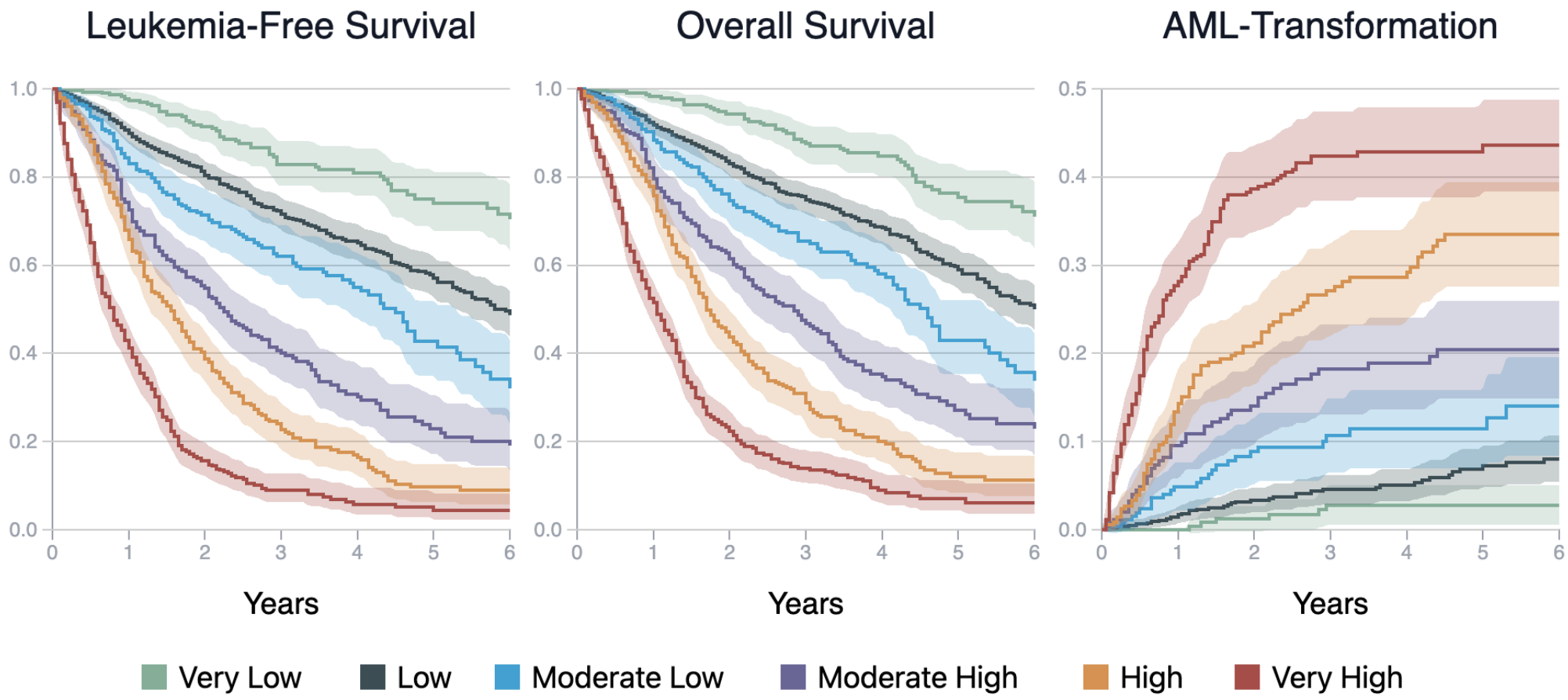
Source: adapted from Greenberg P et al, *Blood* 120(12):2454–65

IPSS-R


Very low
Low
Intermediate
High
Very high
Patients, %
100
80
60
40
20
0
0
2
4
6
8
10
12
Overall survival, years


Patients, %
100
80
60
40
20
0
0
2
4
6
8
10
12
Time to AML evolution, years

IPSS-Molecular

- 

https://mds-risk-model.com/

Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — $x10^9$/l	0.998 (0.997–0.999)	–0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	–0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{5q}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	–0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

* CI denotes confidence interval; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, International Prognostic Scoring System–Revised; ITD, internal tandem duplication; min, minimum; PTD, partial tandem duplication; and TKD tyrosine kinase domain.

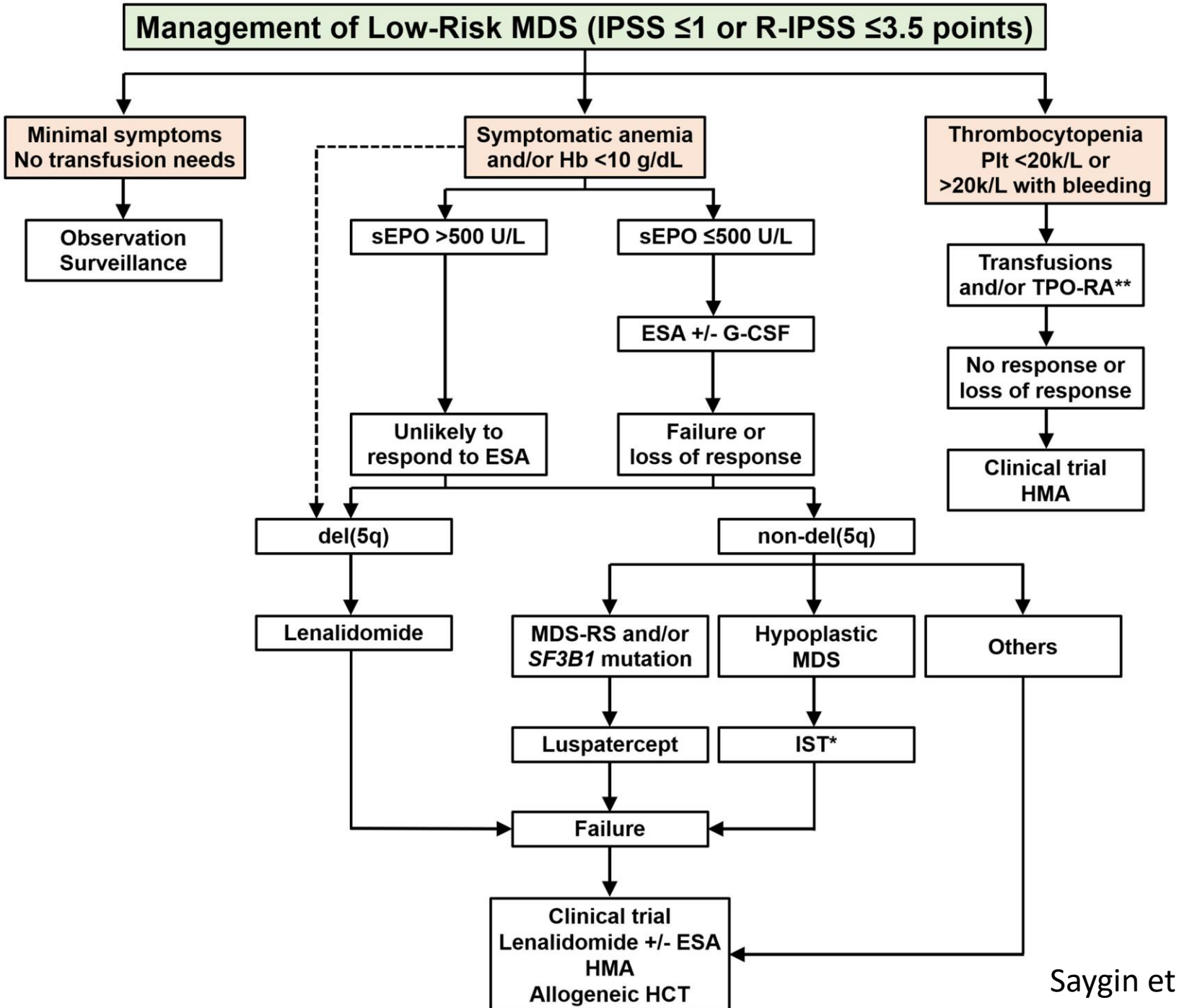
† Hazard ratio is for the risk of leukemic transformation or death, adjusted for age, sex, and secondary/therapy-related versus primary myelodysplastic syndrome. Cox regression was performed for 2428 patients with available covariables and leukemia-free survival data.

‡ Model weights were derived from the logarithm of the raw hazard ratios up to three significant digits. The following formula applies: IPSS-M score = $1.15467 + (\sum_{\text{variables } j} w_j x_j)/\log(2)$, where w_j denotes the weight of variable j, and x_j the value of the variable j observed in a given patient.

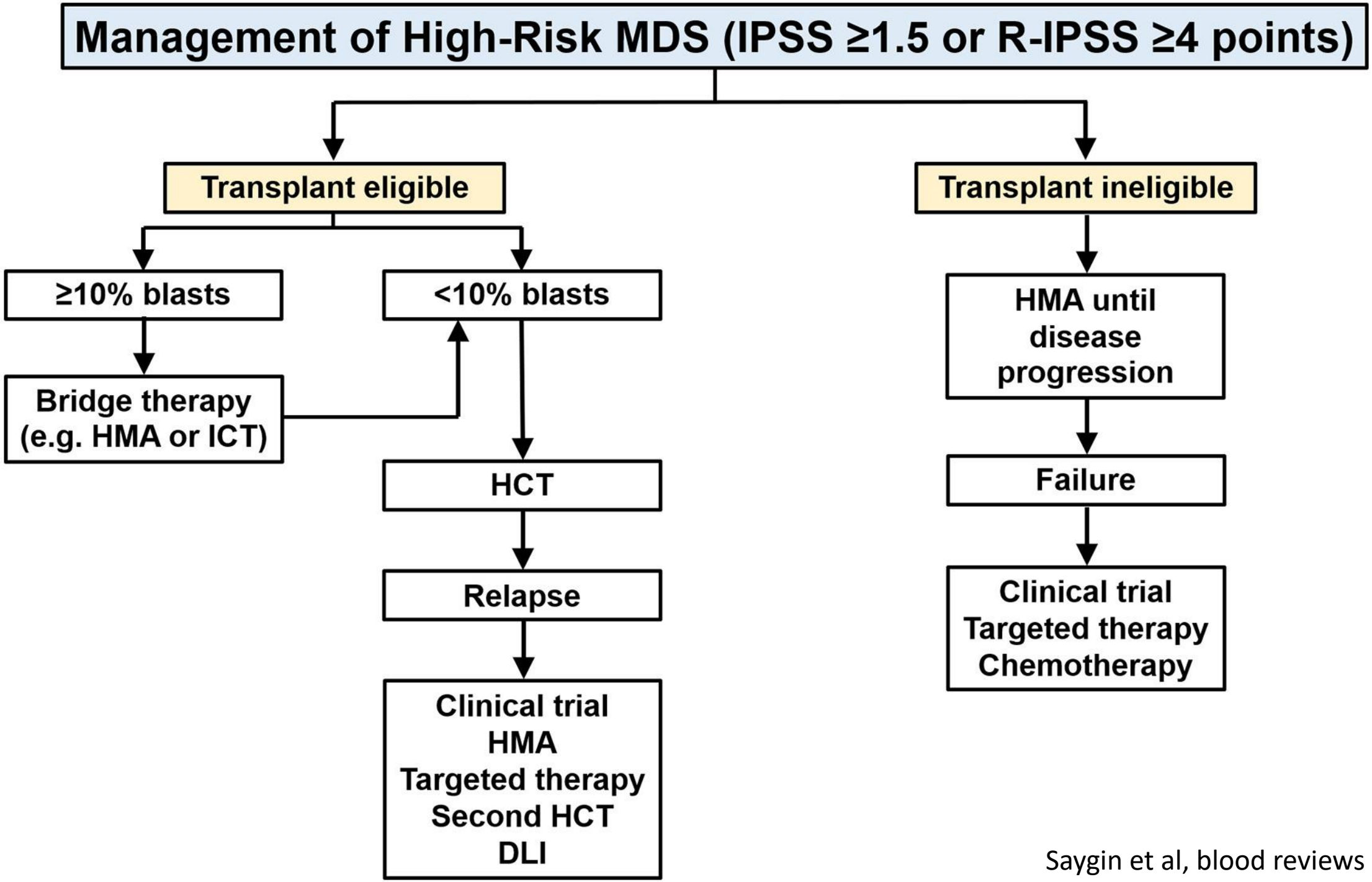
§ IPSS-R cytogenetic categories were as follows: 0 denotes very good, 1 good, 2 intermediate, 3 poor, and 4 very poor.

¶ *SF3B1*^{5q} is the *SF3B1* mutation in the presence of isolated del(5q) —that is, del(5q) only or with one additional aberration excluding -7/del(7q). *SF3B1*$^{\alpha}$ is the *SF3B1* mutation without comutations in *BCOR*, *BCORL1*, *RUNX1*, *NRAS*, *STAG2*, *SRSF2*, and del(5q).

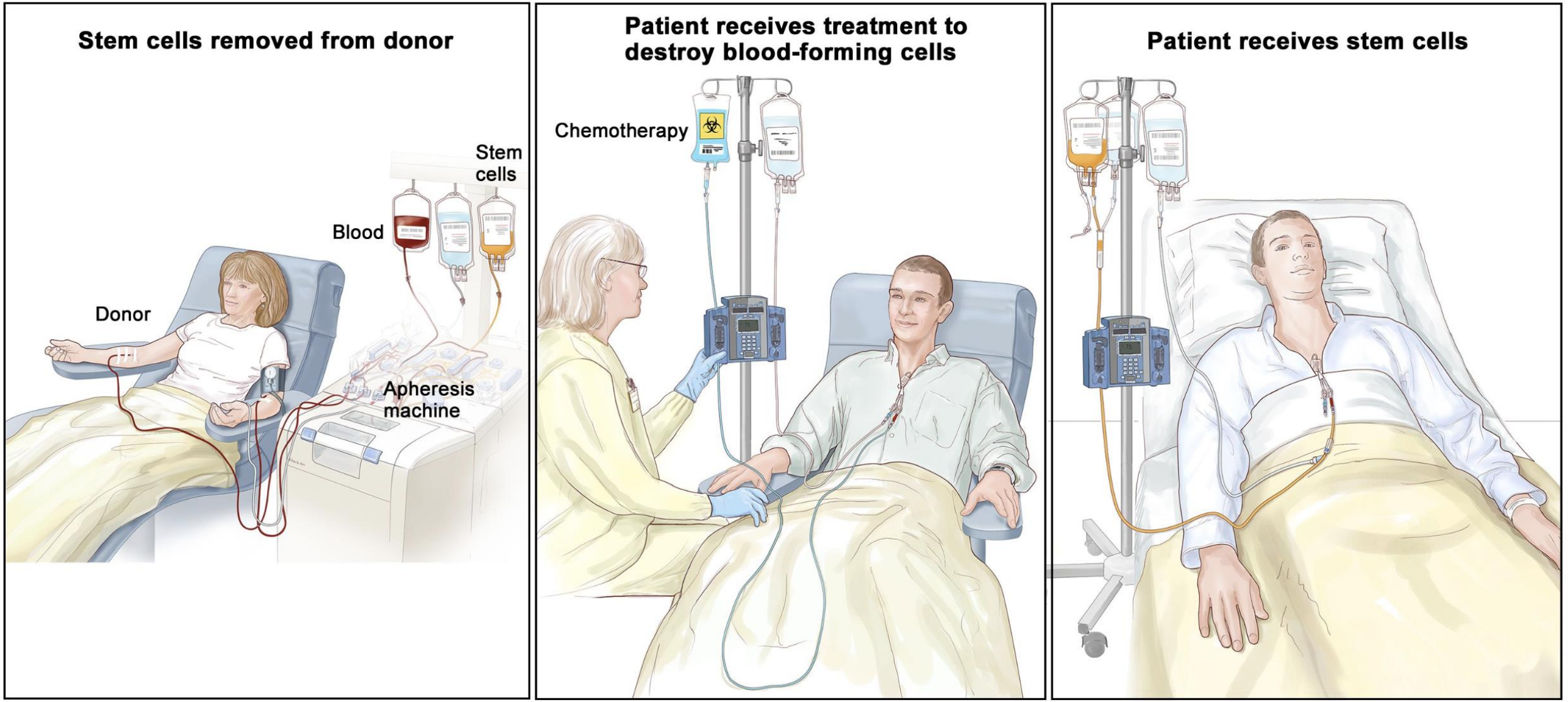
‖ Nres is defined as the number of mutated genes within the following list: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, and *WT1*. The variable min(Nres,2) can therefore take the value 0, 1, or 2.



Saygin et al, blood reviews 2021



Saygin et al, blood reviews 2021



https://nci-media.cancer.gov/pdq/media/images/765030.jpg

New Therapies Currently Being Tested for MDS

- Eltanexor
- Tamibarotene
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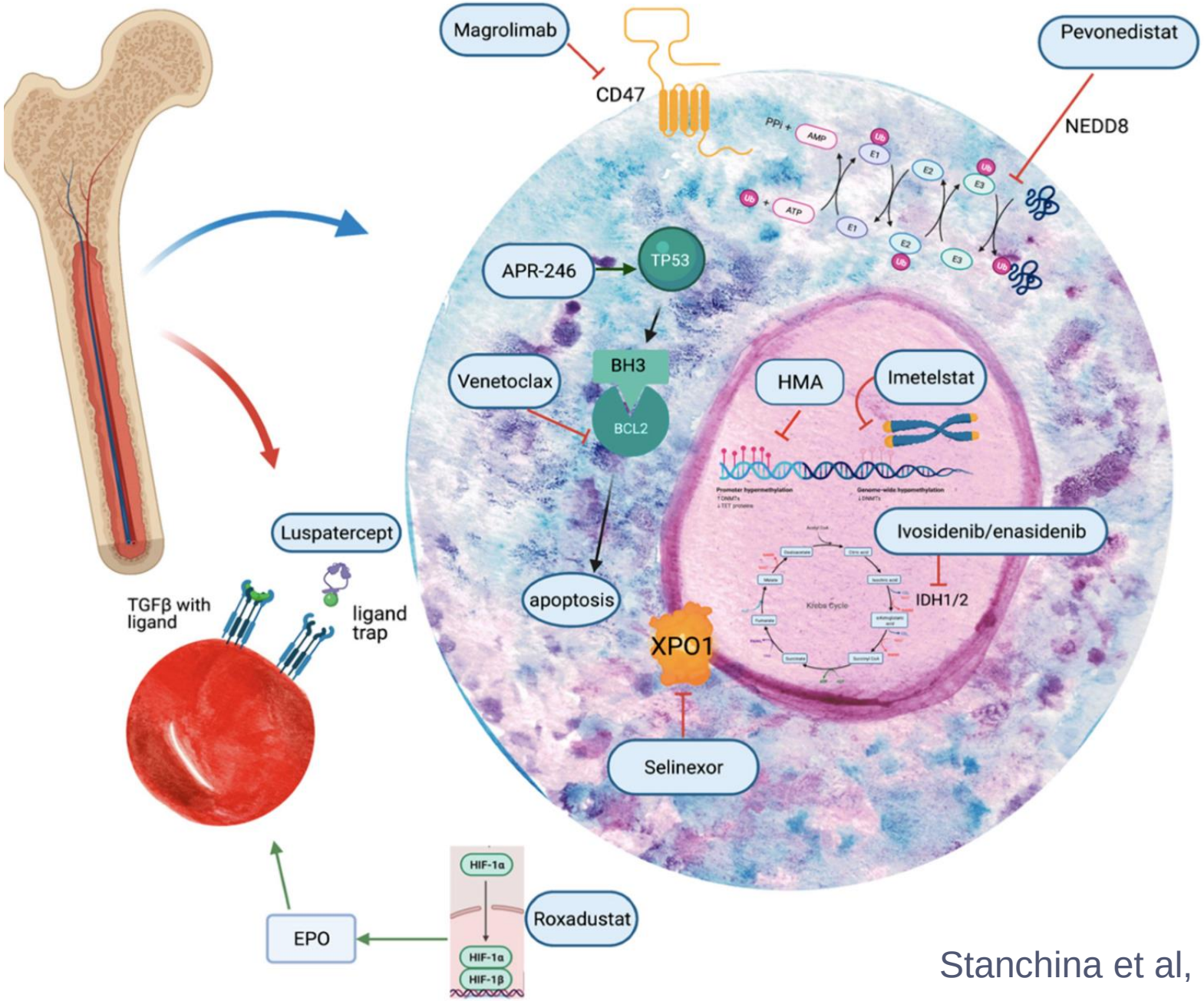

Stanchina et al, *Hemato* 2021