



How to integrate molecular findings and clinical data for therapeutic decisions in MDS?

Chantana Polprasert MD.

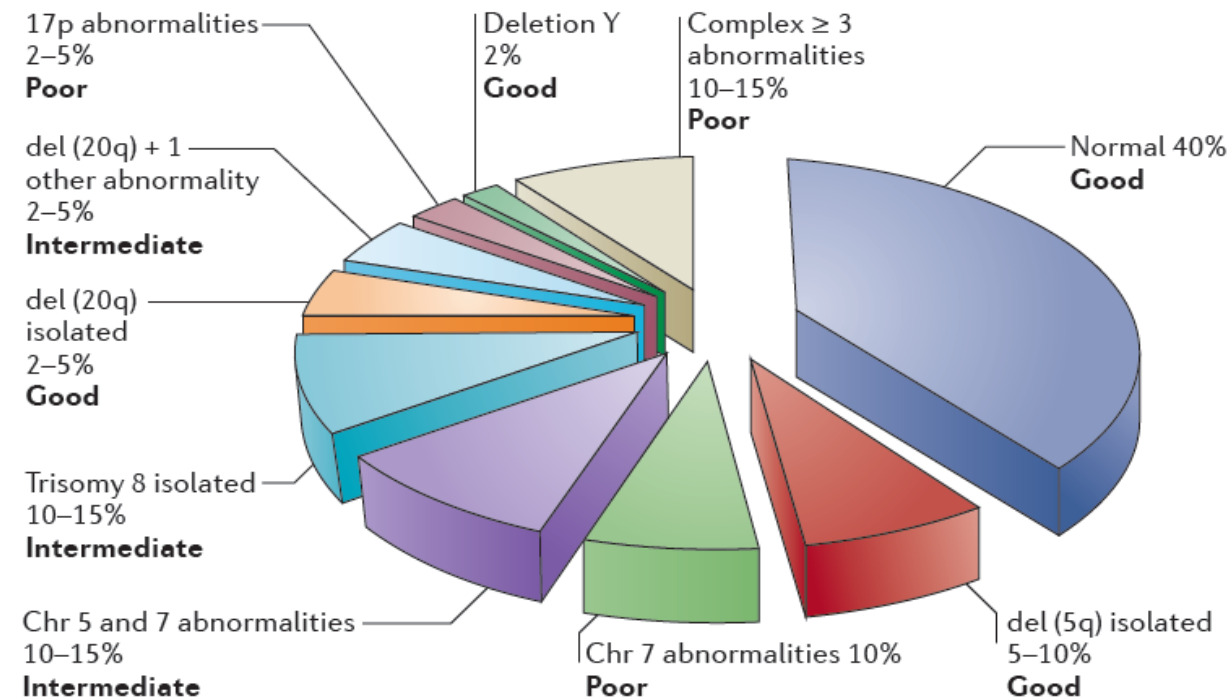
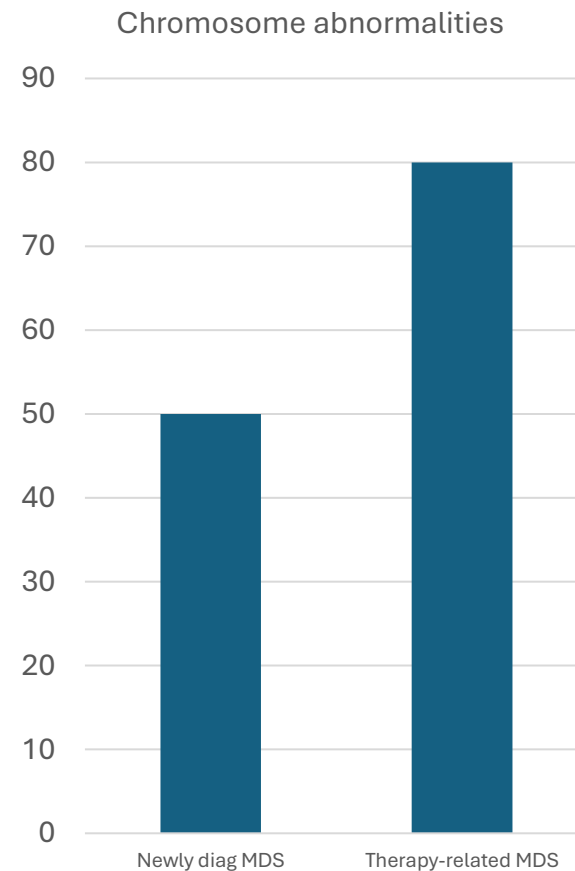
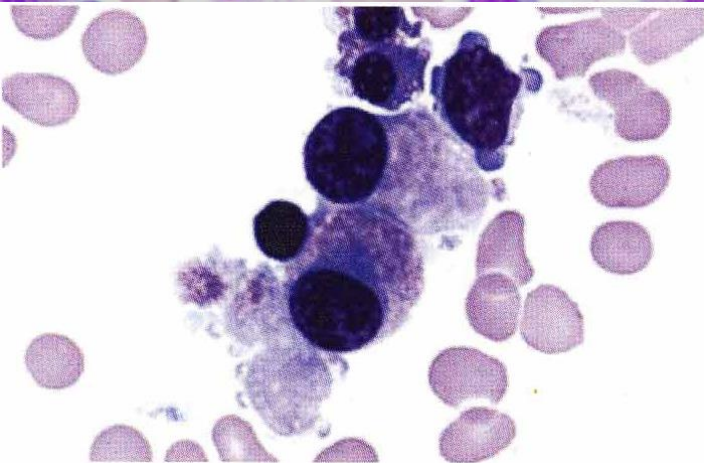
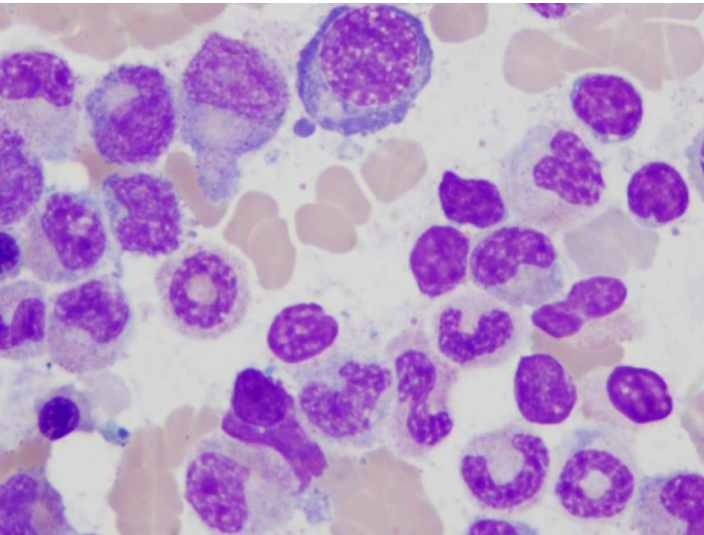
Overview



- Prognostication and risk stratification
- Classification and personalized treatment
- Germline predisposition
- Non-invasive approach at diagnosis

Prognostication and risk stratification

Chromosomal abnormalities in MDS

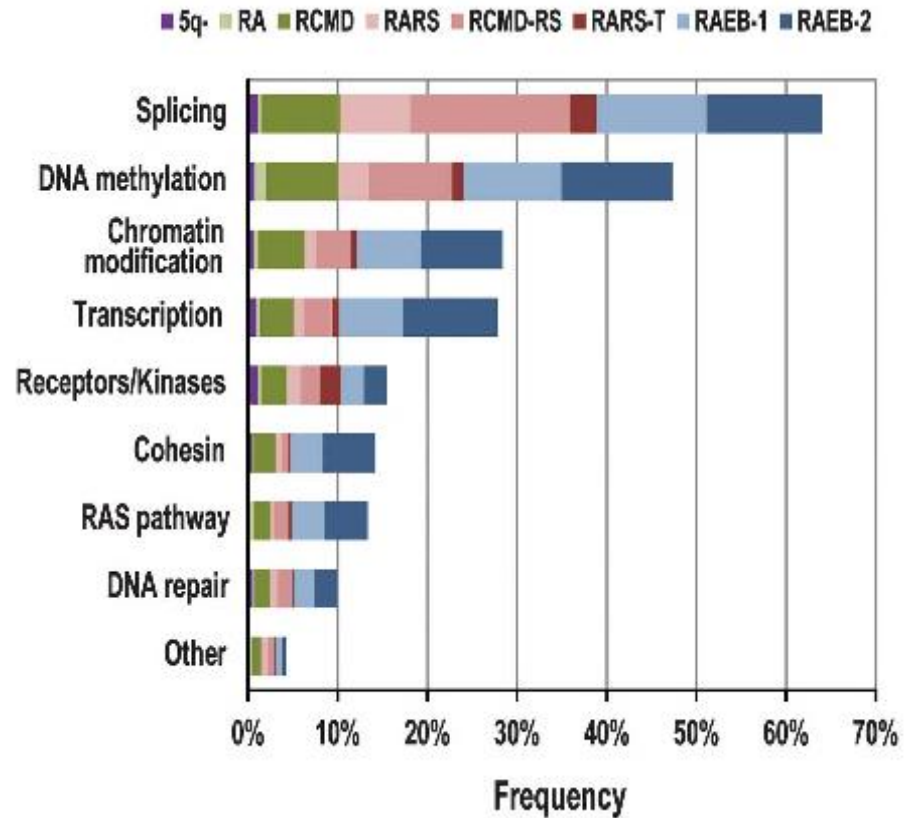


IPSS and IPSS-R prognostic scoring systems for MDS

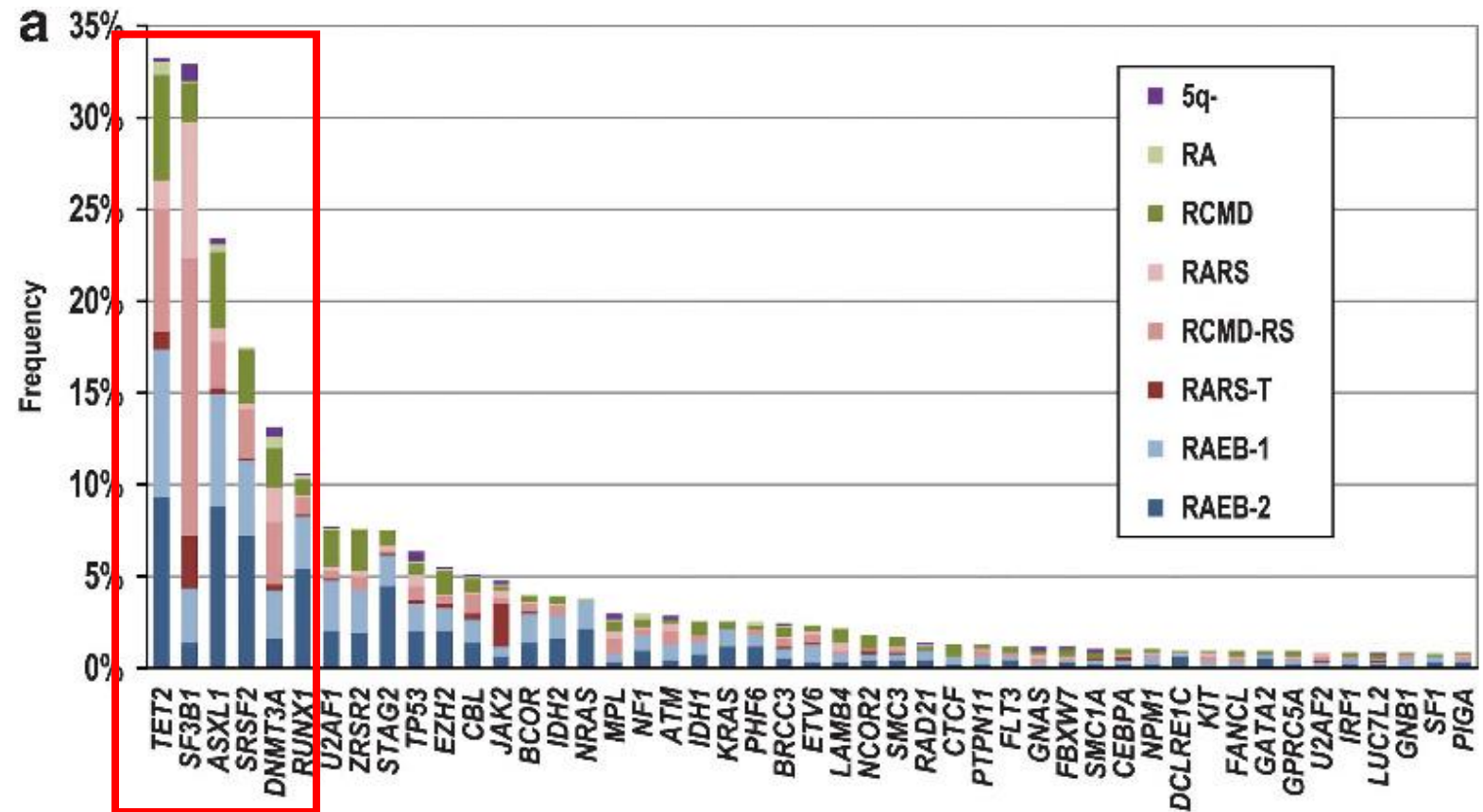
Risk classification system	Prognostic variables	Karyotype/cytogenetic classification criteria	Prognostic risk group	Proportion of MDS patients, %	Median OS, years	Median time to 25% AML transformation, years
IPSS (Greenberg et al.) [64]	1. Cytopenias	•Good: normal, $-Y$, $\text{del}(5q)$, $\text{del}(20q)$ •Poor: complex (≥ 3 abnormalities), chromosome 7 anomaly •Int: other abnormalities	Low	lower risk	5.7	9.4
	2. Karyotype		Int-1		3.5	3.3
	3. BM blast percentage		Int-2	higher risk	1.2	1.1
			High		0.4	0.2
IPSS-R (Greenberg et al.) [65]	1. Cytogenetics	•Very good: $-Y$, $\text{del}(11q)$ •Good: normal, $\text{del}(5q)$, $\text{del}(12p)$, $\text{del}(20q)$, double incl. $\text{del}(5q)$ •Int: $\text{del}(7q)$, $+8$, $+19$, $i(17q)$, other single or double independent clone •Poor: -7, $\text{inv}(3)/t(3q)/\text{del}(3q)$, double incl. $-7/\text{del}(7q)$, complex (3 abnormalities) •Very poor: complex (>3 abnormalities)	Very low	19	8.8	NR
	2. BM blast percentage		Low	lower risk R-IPSS ≤ 3.5	5.3	10.8
	3. Hemoglobin		Int		3.0	3.2
	4. Platelets		High	higher risk R-IPSS > 3.5	6	1.4
	5. ANC		Very high		0.8	0.7

AML acute myeloid leukemia, *ANC* absolute neutrophil count, *BM* bone marrow, *Int* intermediate, *IPSS(-R)* (revised) International Prognostic Scoring System, *MDS* myelodysplastic syndromes, *NR* not reached, *OS* overall survival.

Somatic mutations in MDS



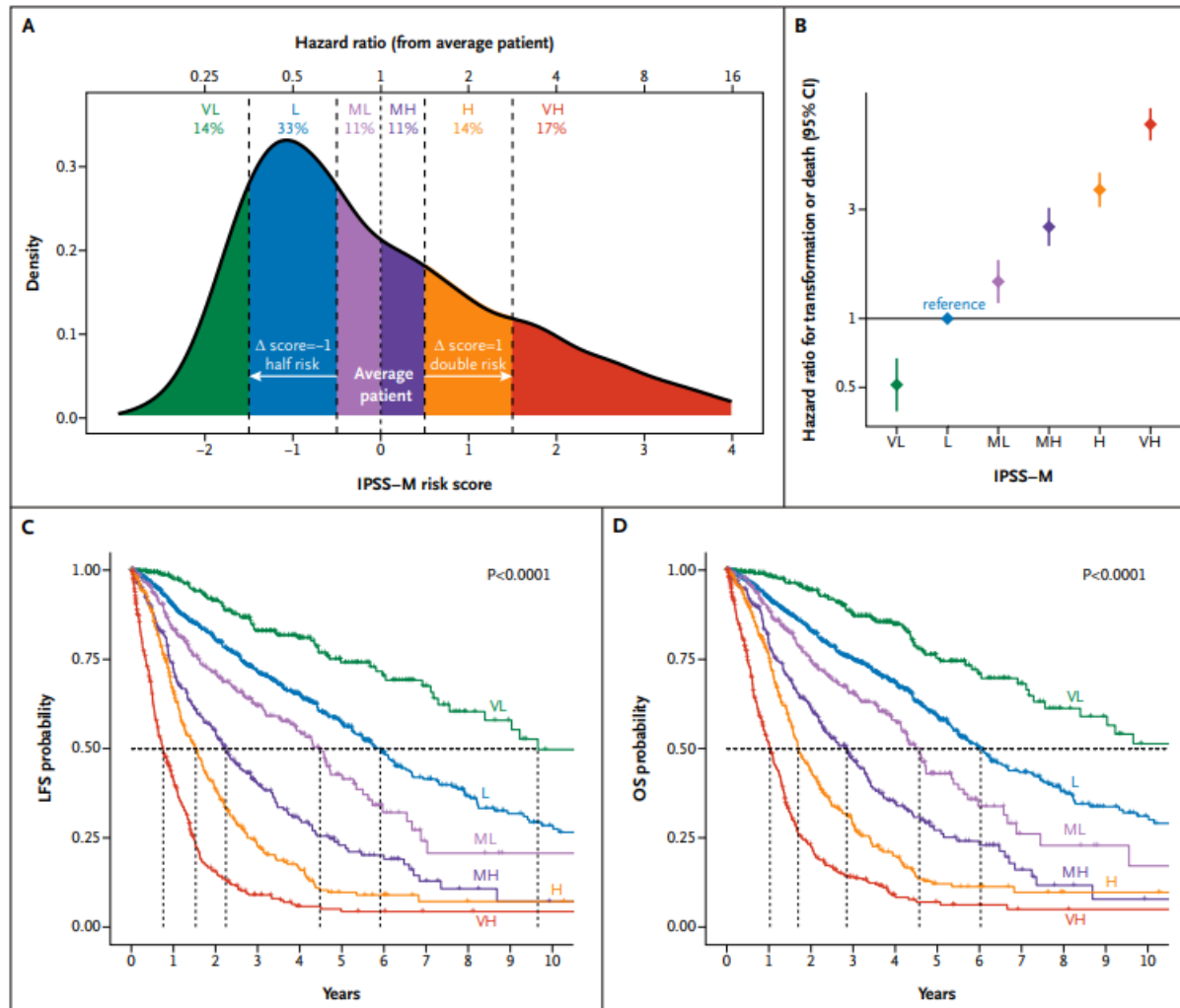
- Somatic mutation found in >90% of MDS
- *TET2*, *SF3B1*, *ASXL1*, *SRSF2*, *DNMT3A*, and *RUNX1* mutated in >10%



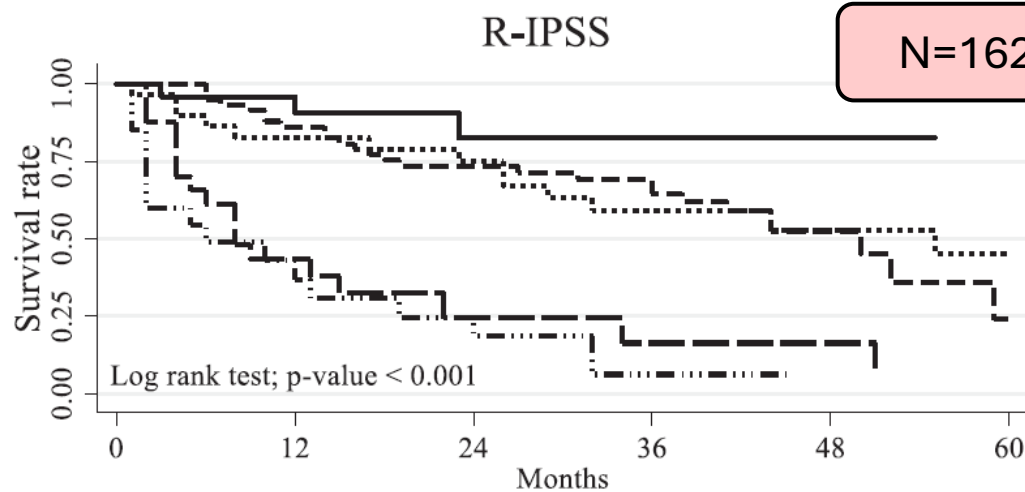
IPSS-M (R-IPSS+mutation)

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

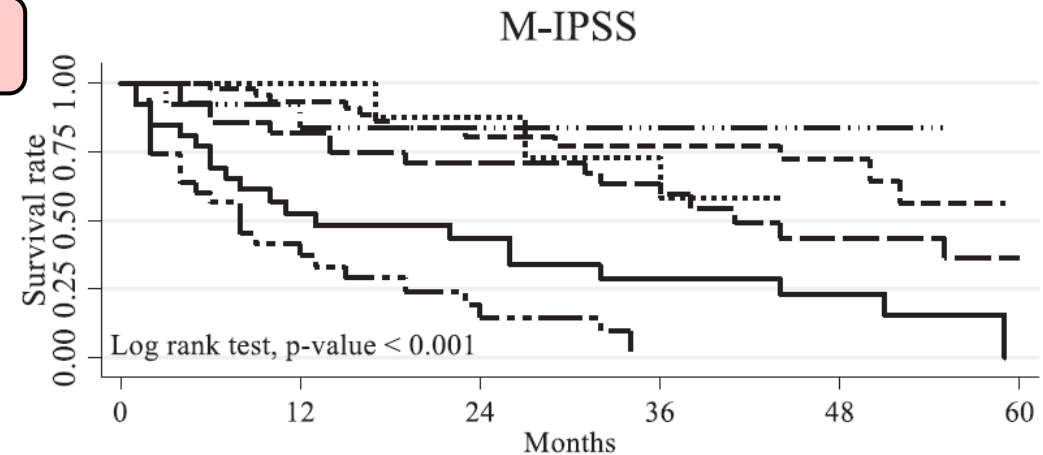
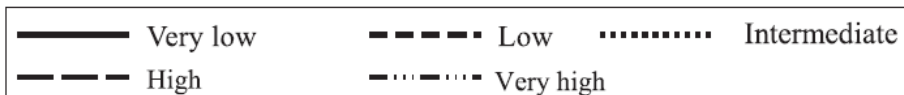
Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — $\times 10^9/l$	0.998 (0.997–0.999)	–0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	–0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
<i>TP53</i> ^{mut/hi}	3.27 (2.38–4.48)	1.18
<i>MLL</i> ^{PTD}	2.22 (1.49–3.32)	0.798
<i>FLT3</i> ^{ITD+TKD}	2.22 (1.11–4.45)	0.798
<i>SF3B1</i> ^{Sq}	1.66 (1.03–2.66)	0.504
<i>NPM1</i>	1.54 (0.78–3.02)	0.430
<i>RUNX1</i>	1.53 (1.23–1.89)	0.423
<i>NRAS</i>	1.52 (1.05–2.20)	0.417
<i>ETV6</i>	1.48 (0.98–2.23)	0.391
<i>IDH2</i>	1.46 (1.05–2.02)	0.379
<i>CBL</i>	1.34 (0.99–1.82)	0.295
<i>EZH2</i>	1.31 (0.98–1.75)	0.270
<i>U2AF1</i>	1.28 (1.01–1.61)	0.247
<i>SRSF2</i>	1.27 (1.03–1.56)	0.239
<i>DNMT3A</i>	1.25 (1.02–1.53)	0.221
<i>ASXL1</i>	1.24 (1.02–1.51)	0.213
<i>KRAS</i>	1.22 (0.84–1.77)	0.202
<i>SF3B1</i> ^T	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



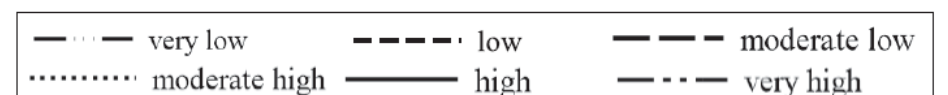
Comparison of R-IPSS and M-IPSS



Number at risk						
Very low	25	19	10	9	7	5
Low	63	48	37	30	11	2
Intermediate	30	22	19	13	8	4
High	24	8	3	2	2	1
Very high	20	7	4	1	0	0



Number at risk						
Very low	26	12	9	6	3	0
Low	54	41	26	21	12	4
Moderate low	8	8	6	5	2	2
Moderate high	30	22	19	16	8	5
High	31	10	4	0	0	0
Very high	13	11	9	7	3	1



- Concordance Index (C-index) of R-IPSS = 0.71 (95% Confidence interval [CI] 0.64–0.78) and M-IPSS = 0.75 (95% CI 0.69–0.80), (p=0.22).
- Comparing the two, 13 of 162 (8%) cases were re-staged Four cases were downstaged from high-risk (R-IPSS) to low-risk MDS (M-IPSS), while 9 cases were upstaged from low-risk (R-IPSS) to high-risk MDS (M-IPSS).

Treatment goal in LR and HR MDS

Lower risk

IPSS (low, int-1)

R-IPSS ≤ 3.5

M-IPSS (very low, low, mod low)

- Decrease transfusion need
- Decrease transformation to higher risk
- Improve survival
- Treatment: growth factors

Higher risk

IPSS (int-2, high)

R-IPSS > 3.5

M-IPSS (mod high, high, very high)

- Prolong survival
- Treatment: HMA±bone marrow transplantation

Classification and personalized treatment

WHO classification 2022 of MDS

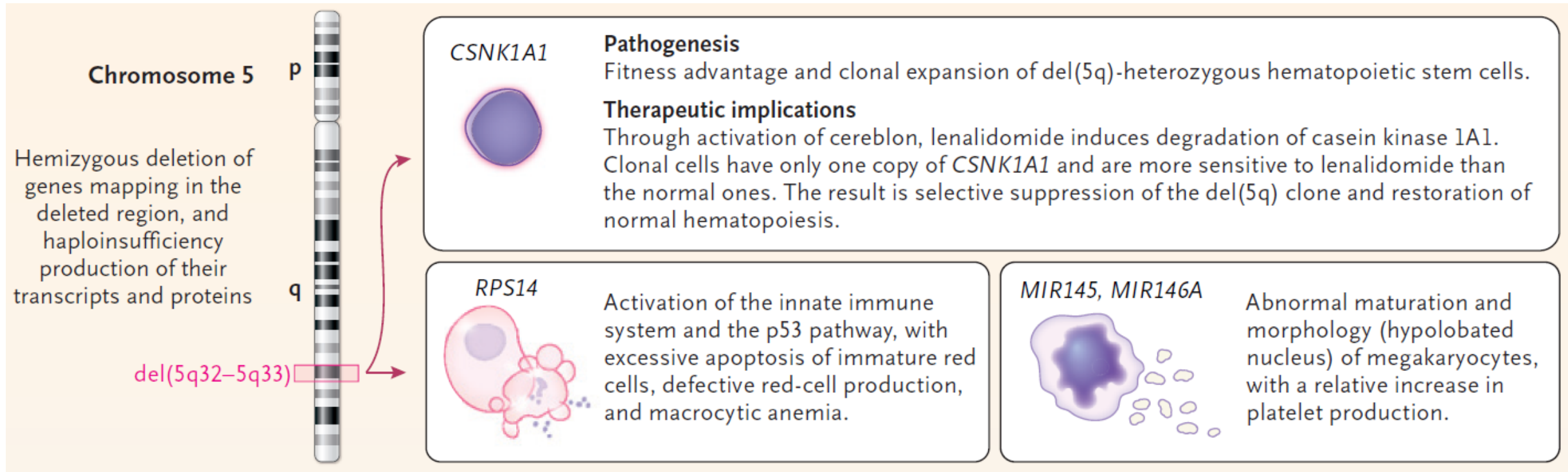
	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and <i>SF3B1</i> mutation ^a (MDS- <i>SF3B1</i>)		Absence of 5q deletion, monosomy 7, or complex karyotype	<i>SF3B1</i>
MDS with biallelic <i>TP53</i> inactivation (MDS-bi <i>TP53</i>)	<20% BM and PB	Usually complex	Two or more <i>TP53</i> mutations, or 1 mutation with evidence of <i>TP53</i> 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		

^aDetection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.

^bBy definition, ≤25% bone marrow cellularity, age adjusted.

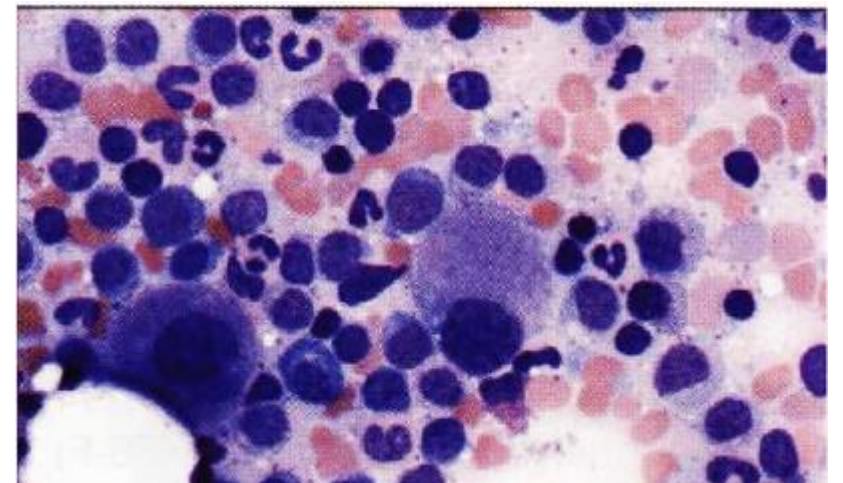
BM bone marrow, PB peripheral blood, cnLOH copy neutral loss of heterozygosity.

MDS with isolated del5q: genotype and phenotype association



Cazzola M. NEJM 2020; 383: 1358-74.

- Distinct phenotype: macrocytic anemia, a normal or high platelet count, and hypolobulated megakaryocytes in the bone marrow
- Female preponderance and a good prognosis with approximately 10% of patients transforming to AML
- Transfusion dependent



Lenalidomide in MDS with del(5q)

	MDS-003* (LEN 10 mg/d 21 day)	MDS-004** (LEN 10 mg)
RBC-TI $\geq$ 8 weeks	67%	61%
Cytogenetic response	73%	50%
Median peak Hb increase (g/dL)	5.4 (1.1-11.4)	6.3 (1.8-10)
Median OS in RBC-TI (years)	4.3 vs. 2 (p<0.0001)	p=0.0028

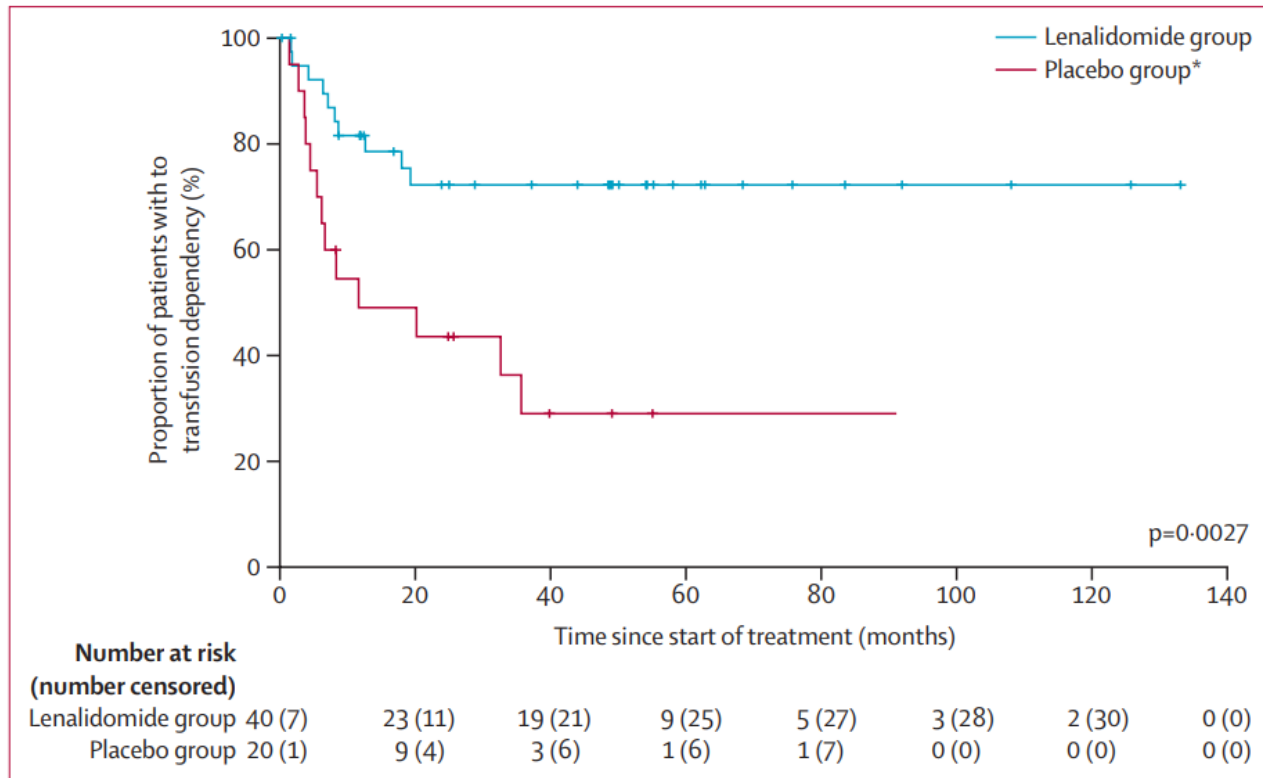
- Response was fast: median time 4.6 weeks
- *TP53* mutation can be detected in 12-17% of MDS5q-
- Lenalidomide exposure has been associated with a selective expansion of *TP53*-mutated clones (Sperling AS, et al. Blood 2022;140:1753-1763).

*List AF, et al. NEJM 2006; 355: 1456-65.
** Fenaux P, et al. Blood 2011; 118: 3765-76.

Early lenalidomide treatment in anaemic non-TD MDS-del(5q)

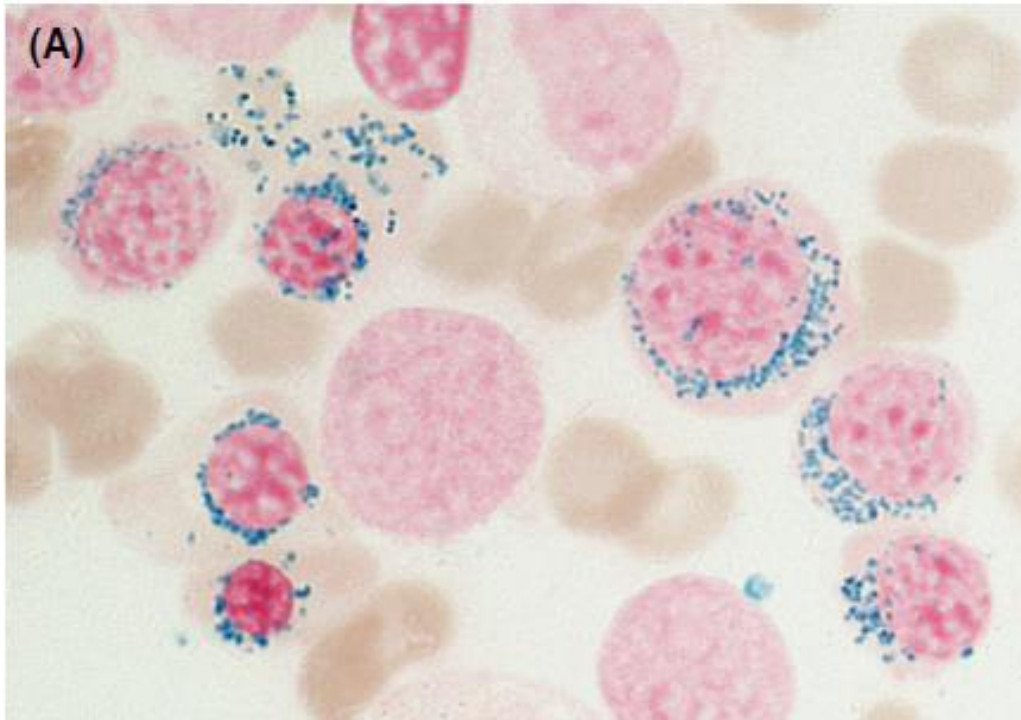
SintraRev Phase 3 trial

: Lenalidomide 5 mg daily in 28-day cycles versus placebo for 2 years.



- Lenalidomide significantly reduced the risk of transfusion dependency by 69.8% (hazard ratio 0.302, 95% CI 0.132–0.692; p=0.0046).
- An early approach with low doses of lenalidomide across two years delays the time to transfusion dependency and improves the rate and quality of the responses

MDS with *SF3B1* mutation

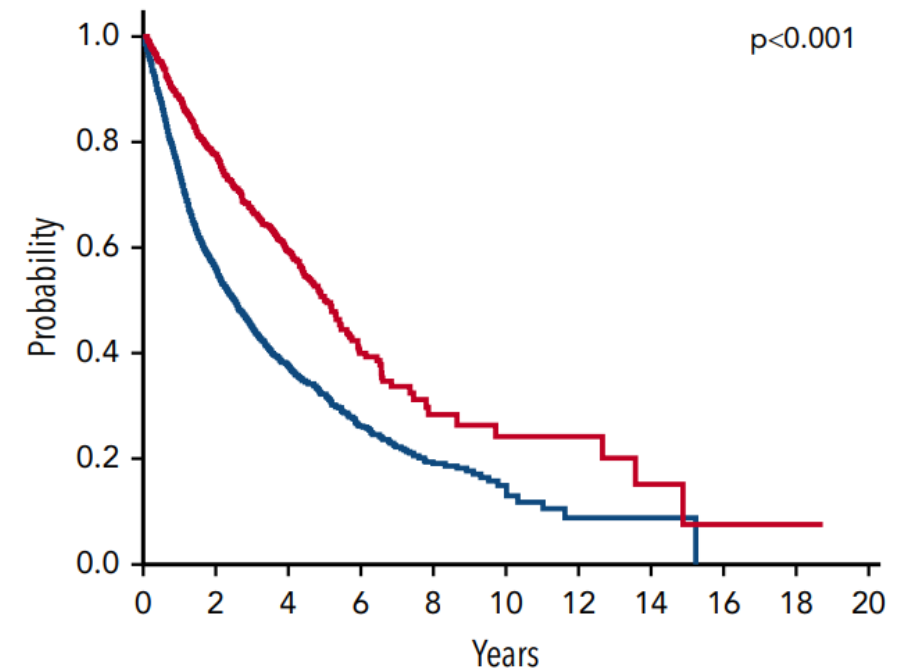


Malcovati et al. Blood 2015; 126: 233-41.

	No <i>SF3B1</i> mutation (N = 151)	<i>SF3B1</i> mutation (N = 16)	P-value
Haemoglobin (g/dL)	8.4 (7.1–10.1)	7.9 (6.8–8.9)	0.02
Platelet ($\times 10^9/L$)	93 (56–184)	286 (160.5–449.5)	<0.001

Polprasert et al. Hematology 2022; 27:1, 765-771

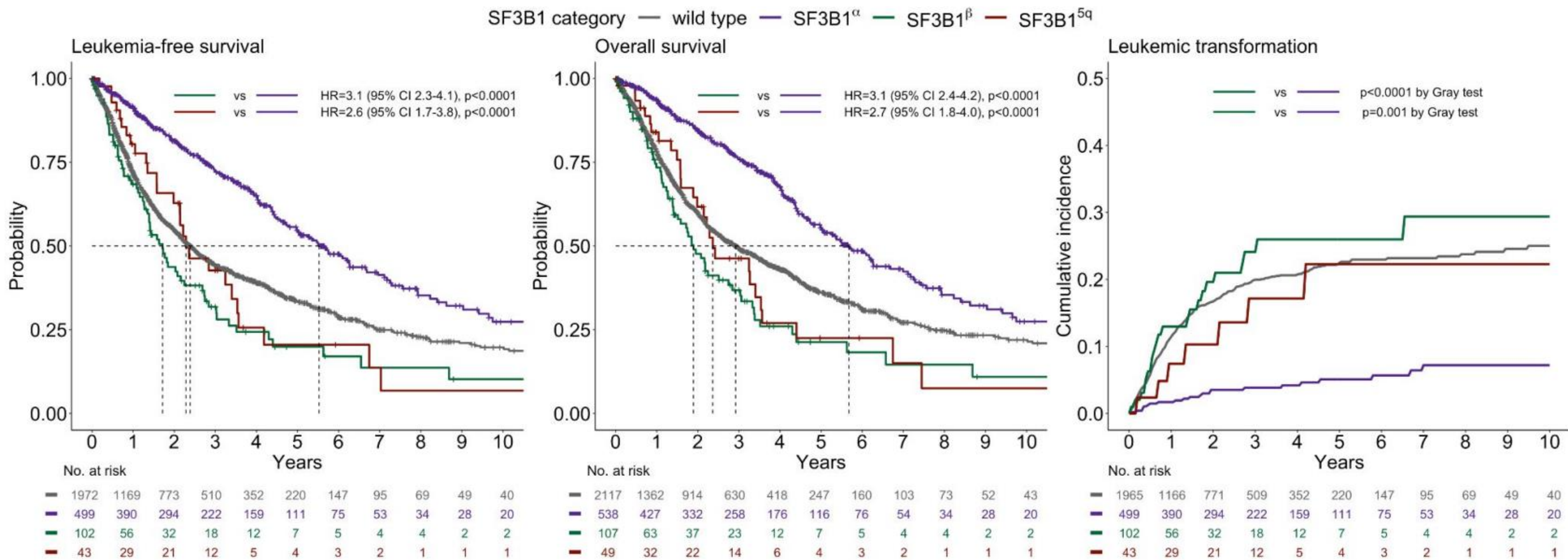
- *SF3B1* mutation is strongly associated with ring sideroblast
- Associated with longer survival, lower AML transformation rate, normal karyotypes and harbored less accompanying mutations



- Although not a targeted drug, luspaterecept showed good response in MDS with *SF3B1* mutation

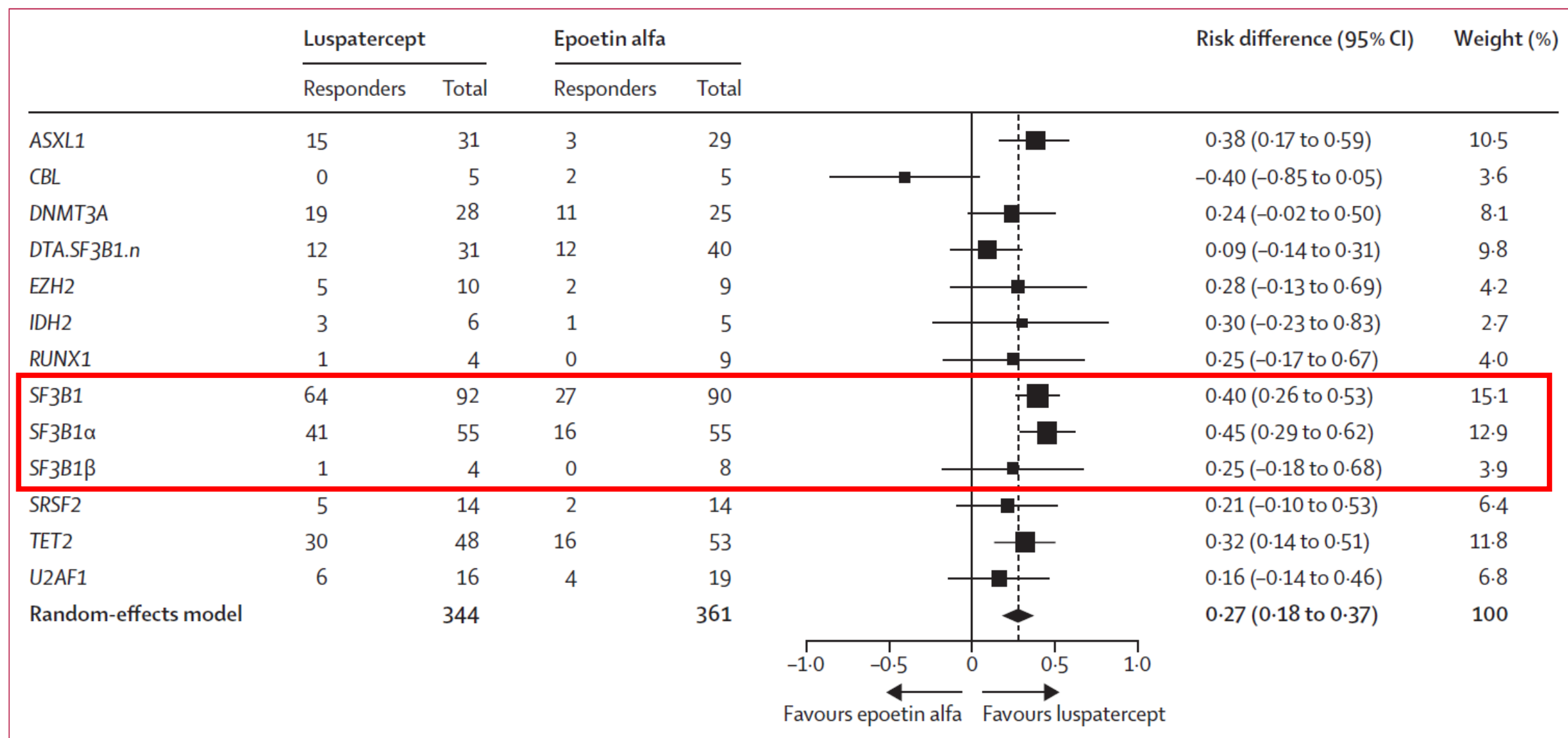
Malcovati et al. Blood. 2020;136(2):157-170

Outcomes by *SF3B1* categories



SF3B1^α corresponds to mutated *SF3B1* with concomitant mutations in *DNMT3A* or *ASXL1* and/or *TET2*;
SF3B1^β is mutated *SF3B1* with concomitant mutations in any of *BCOR*, *BCORL1*, *NRAS*, *RUNX1*, *SRSF2*, or *STAG2*

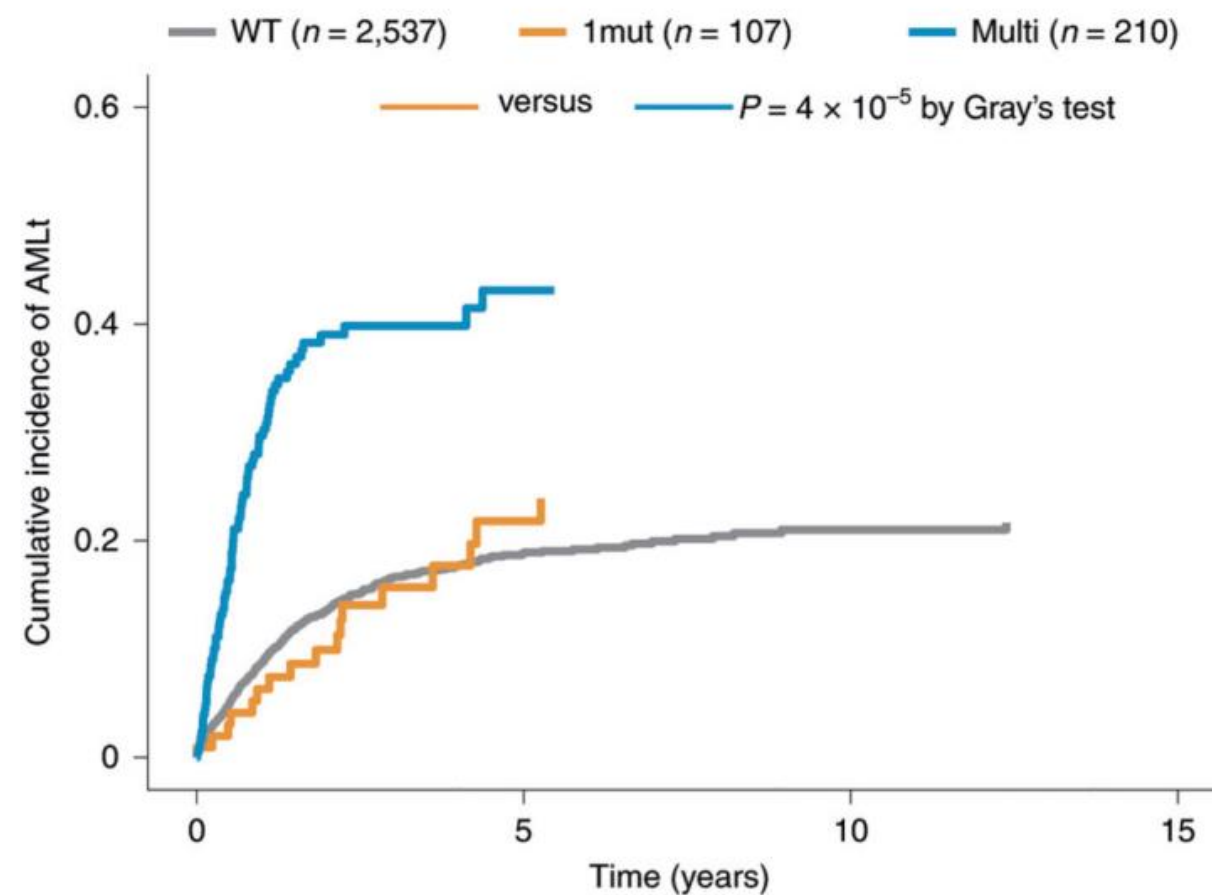
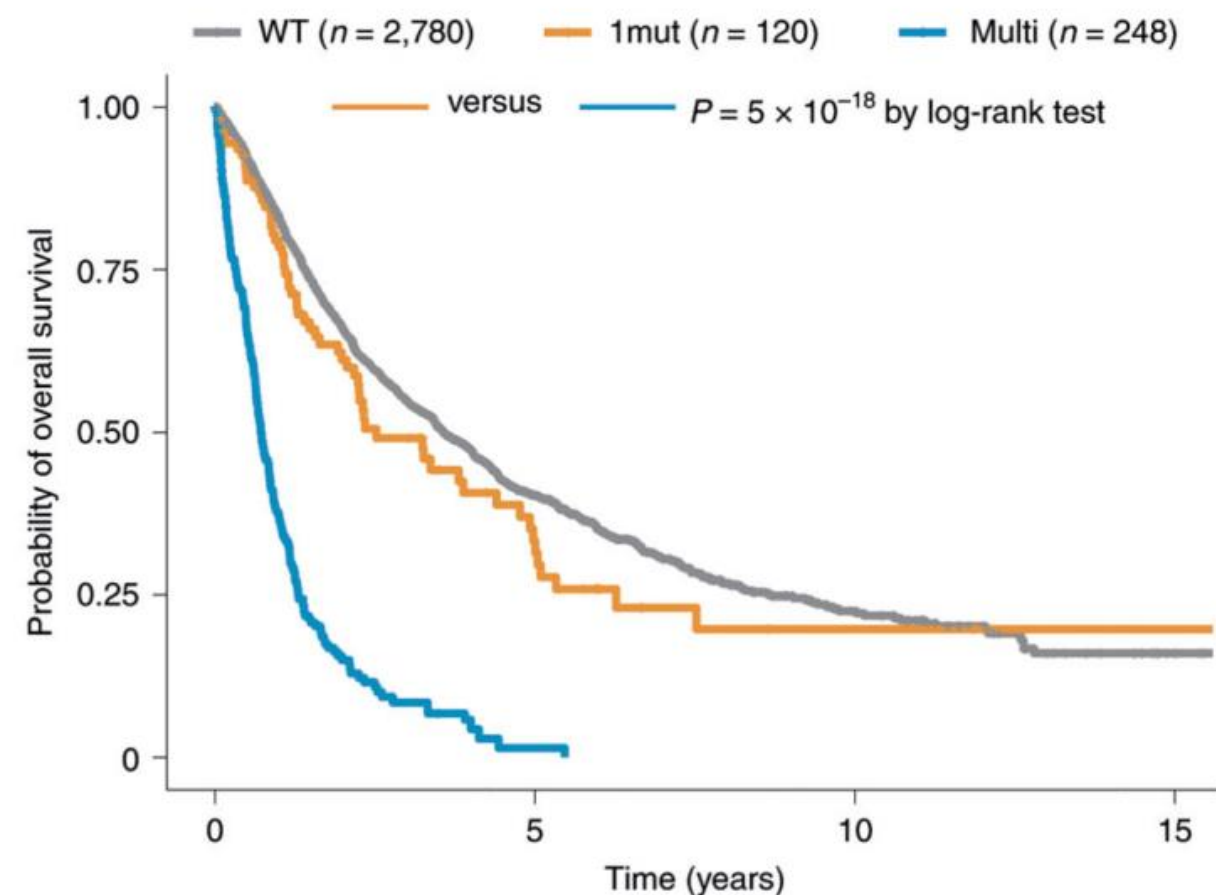
COMMANDS study: Responder status in patients with common genetic mutations



SF3B1 α corresponds to mutated SF3B1 with concomitant mutations in DNMT3A or ASXL1 and/or TET2;
 SF3B1 β is mutated SF3B1 with concomitant mutations in any of BCOR, BCORL1, NRAS, RUNX1, SRSF2, or STAG2

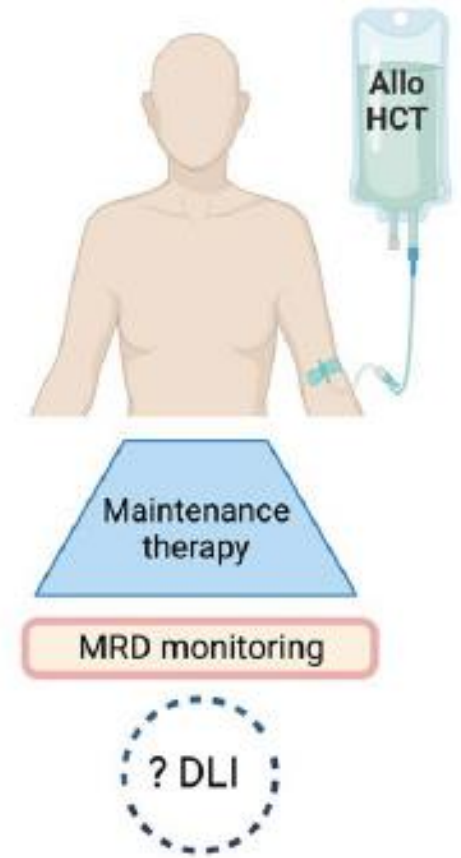
MDS with biallelic *TP53* inactivation

- TP53* multi-hit associated with **complex chromosome**, high-risk presentation and poor outcome



Treatment in MDS with biallelic *TP53* inactivation

- *TP53* mutations result in negative functional impact and intrinsic chemotherapy resistance.
- Hypomethylating agents (azacitidine, decitabine) ± venetoclax are the most commonly use in frontline treatment
- Allo-HSCT remains the only potentially curative approach
- OS is improved in patients with *TP53* VAF<5% pre-transplant
- Ongoing study of novel treatment: APR-246, magrolimab, cellular therapy



Germline predisposition

Germline predisposition in myeloid neoplasms

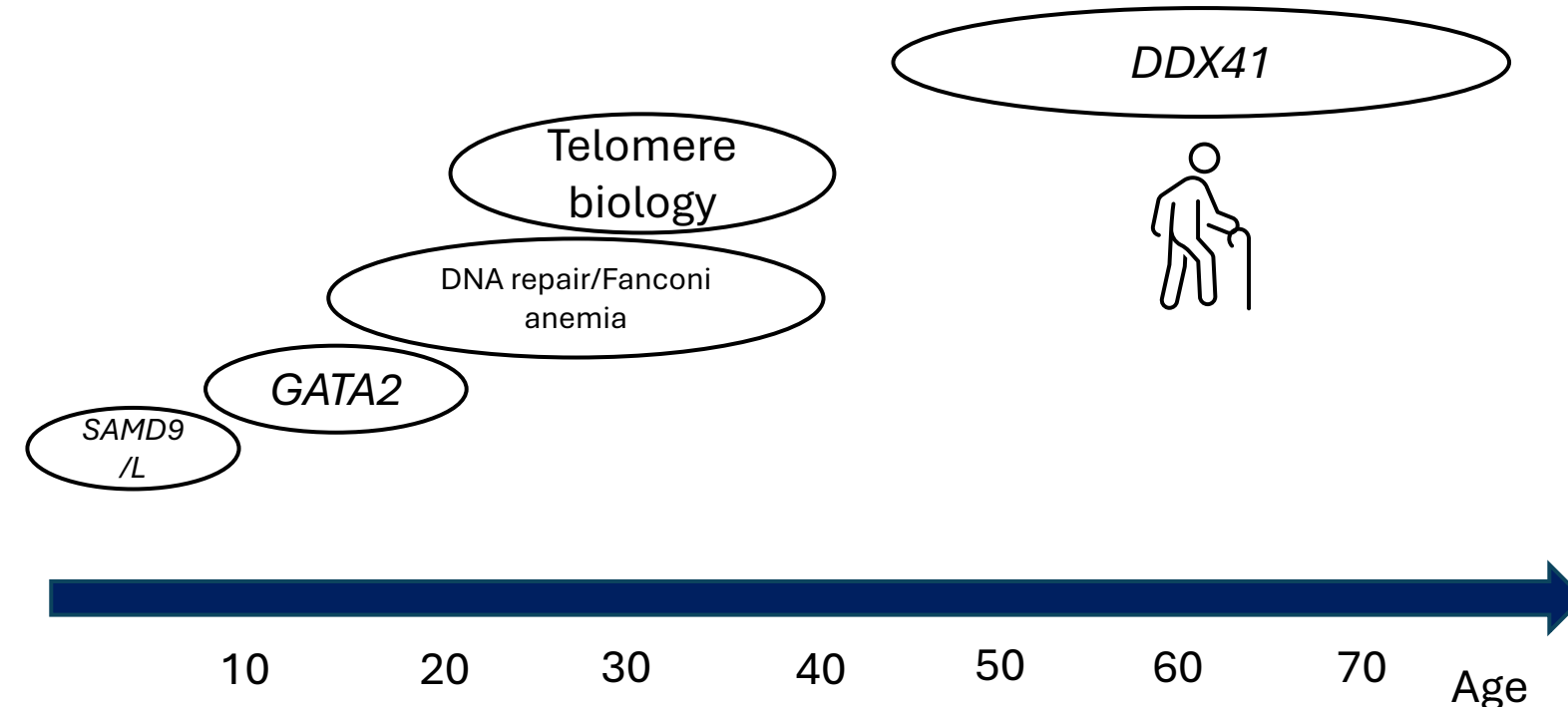
- Germline predisposition risk should be considered for all patients diagnosed with MN regardless of age.

Consider GL mutation in:

- Presence of pathogenic germline variants: *GATA2*, *DDX41*, *RUNX1*, *TP53*, *CEBPA*, occurring at VAF >30%
- Mutations persist at remission state

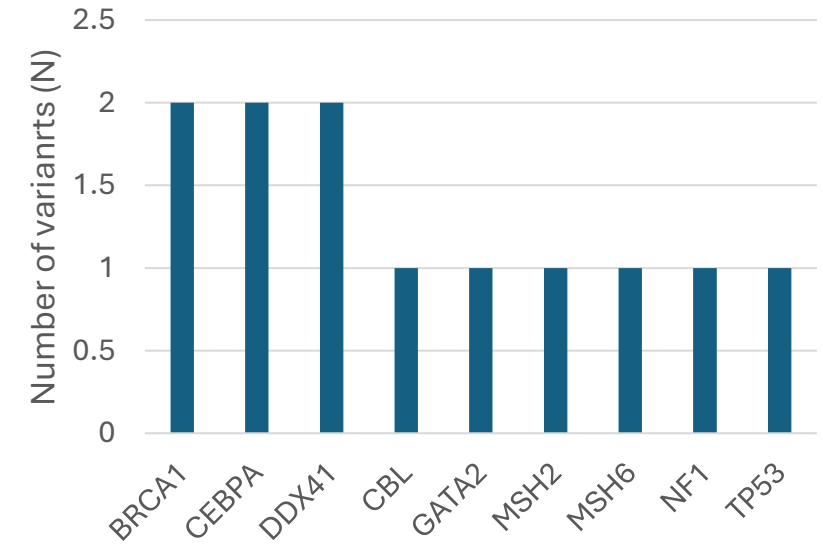
Clinical implication

- Donor for HSCT (MSD or MUD)
- Conditioning regimens



Germline predisposition in Thai MDS/AML

- The total of 127 unselected adult (> 15 years old) patients from 3 medical centers comprising MDS (66%), MDS/MPN (14%) secondary AML (sAML, 20%) were enrolled.
- 14 pathogenic and likely pathogenic germline variants were identified in 15 patients (15/127; 12%).



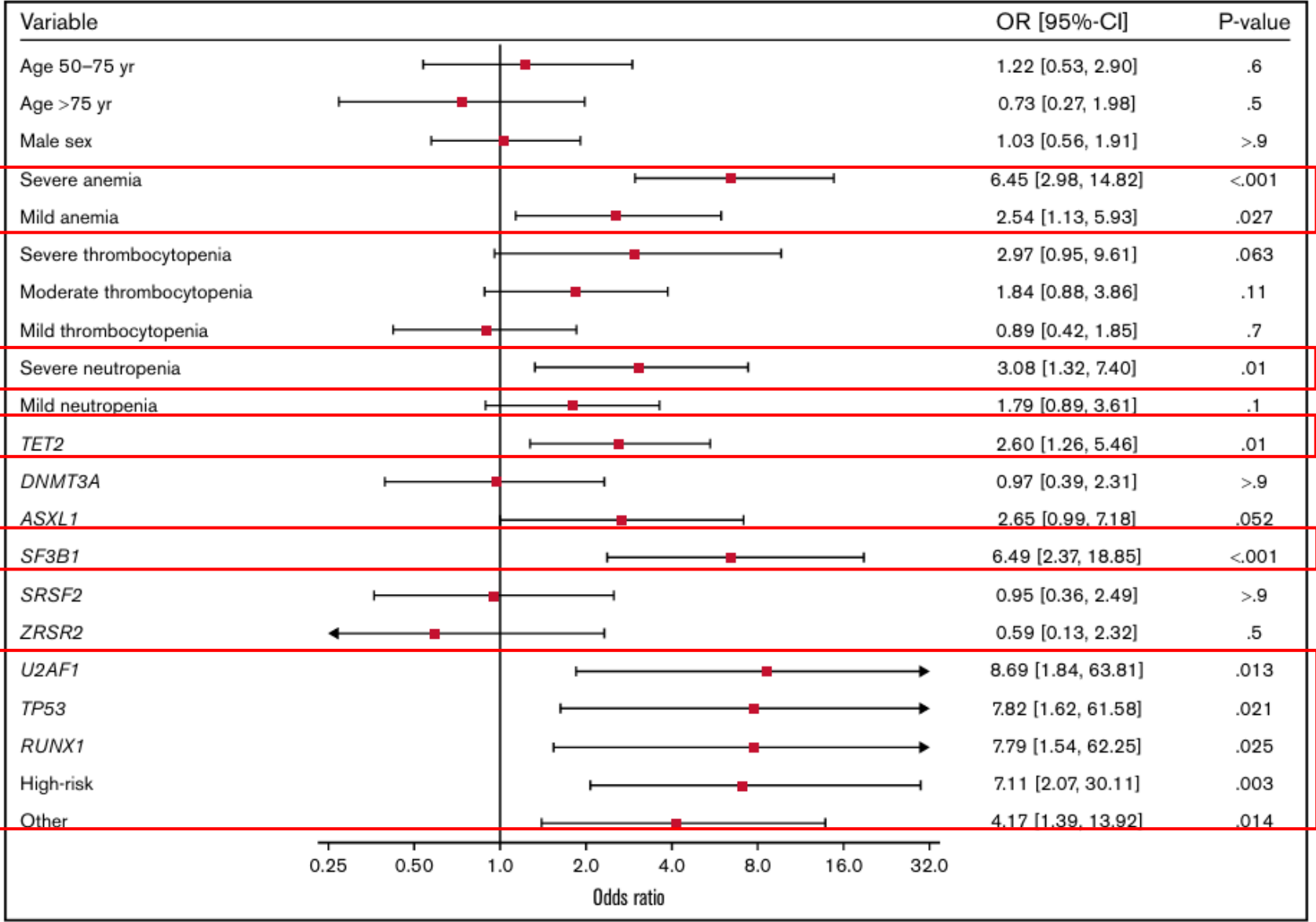
Kongkiatkamon S., et al. JCO 2024; jcp-2023-209264

Target sequencing 27 genes: *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, *GATA2*, *SRP72*, *SAMD9*, *SAMD19*, *TP53*, *TERC*, *TERT*, *BRCA1*, *BRCA2*, *RPS19*, *ELANE*, *MPL*, *FANCA*, *FANCB*, *FANCC*, *FANCG*, *CSF3R*, *DNMT3A*, *CEBPA*, *FANCD2*, *MSH2*, *MSH6*, *ATM*

Non-invasive approach at diagnosis

Factors associated with abnormal BM morphology

- 508 unexplained cytopenia
- Abnormal BM: MDS, CMML, AML
- a model combining mutational status and clinical data identified **low-risk**: 34 patients (20%) without abnormal bone marrow morphology with a sensitivity of 100% (95% confidence interval: 93%-100%).
- Disease in the bone marrow is rarely observed in patients with isolated neutropenia.



Thai (bone marrow) biopsy-free score

- 285 unexplained cytopenia
- MDS group 210:
 - MDS 68%
 - MDS/MPN 15%
 - AML-MR 16%
- non-MDS 75
- Univariate analysis revealed 13 factors associated with MDS
- High-risk mutations: *NRAS*, *NPM1*, *IDH2*, *SETBP1*, *CEBPA*, *JAK2*, *IDH1*, *FLT3*, *KRAS*.
- Other-risk mutations: *BCOR*, *U2AF1*, *STAG2*, *ZRSR2*, *PTPN11*.

Predictors	Odds Ratio (OR)	P-value	95% CI
Anemia (Hb<10 g/dL)	1.166	0.698	(0.537, 2.528)
Thrombocytopenia (<100x10 ⁹ /L)	1.574	0.186	(0.804, 3.084)
Neutropenia (ANC<1x10 ⁹ /L)	2.320	0.064	(0.952, 5.652)
RDW≥15%	2.143	0.050	(1.000, 4.590)
≥2 mutations	2.191	0.412	(0.337, 14.262)
<i>TET2</i>	5.604	0.037	(1.108, 28.337)
<i>ASXL1</i>	1.956	0.399	(0.412, 9.298)
<i>SRSF2</i>	4.036	0.215	(0.445, 36.590)
<i>SF3B1</i>	5.875	0.051	(0.994, 34.731)
<i>RUNX1</i>	2.657	0.434	(0.230, 30.744)
<i>TP53</i>	9.647	0.035	(1.172, 79.404)
High Risk mutations	13.352	0.020	(1.492, 119.499)
Other Risk mutations	4.160	0.107	(0.734, 23.568)

http://tsh.or.th/mds/calculator

← → ↻ 🔍 tsh.or.th/mds/calculator/ ⌨️ ☆ 📁 | 👤 New Chrome available



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The Thai Society of Hematology

registry mission knowledge biopsy-free score contact 👤

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Biopsy-Free Score

Platelet count

☒ <100,000
☐ >= 100,000

ANC

☒ <1,000
☐ >=1,000

Hb

☒ <10
☐ >=10

Mutation count

☒ >=2
☐ -

For patients with a probability score of $\geq 45\%$, sensitivity was 90.47%, specificity was 42.67%, PPV was 81.5%, and LR+ was 1.58 for diagnosing MDS and related diseases.

Support & Enquiries

Case demonstration



- Female 19 years old, previously healthy
- Present with anemia with abnormal bleeding
- 2 years PTA: Present with epistaxis , no other abnormal bleeding, go to private hospital

Work up : plt 13k , mild anemia=>IDA (ferritin 2.53)

ANA positive 1:160 homogenous speckle, antidsDNA neg, antiSm neg

- BMBx : normocellular (80-85% of total marrow volume) with normal trilineage maturation
 - mild increase in mature megakaryocytes with **occasional immature non-lobulated and single nuclei**
- start treatment as ITP : start pred 1x3, Eltrombopag (25) 1-2 tab/day => platelet 20-30K for 1 year
- 6 mn PTA develop anemia with anemic symptoms received pulse dexamethasone then

prednisolone 0.5 MKD=> not response

Case demonstration

- PE : HEENT : mild pale conjunctiva,

anicteric sclera, subconjunctival hemorrhage

Skin : generalized ecchymosis 1-2 cm, no petechiae, no rash, no abnormal skin pigmentation, normal nail

LN : no peripheral lymphadenopathy

Heart and lung : within normal limit

Abd : soft, not tender, no hepatosplenomegaly

- **Lab** : Hb 11 g/dL Plt 6,000/mm³ WBC 3,720/mm³ N51% (ANC 1898) L39% M9.4%

Reticulocyte 0.3% (10,000/mm³)

antiHIV-, antiHCV-, HBsAg-, antiBs + , antiHBc-, Ferritin 792 ng/mL

ANA profile: neg all



Case demonstration



- BMA: Specimen : Satisfactory specimen
- BM Cellularity : marked hypocellularity M:E ratio 2:1 Iron : trace Ringed Sideroblasts : negative
Megakaryopoiesis: markedly decreased, normal morphology normal
- Conclusion : Aplastic marrow with some myeloblasts seen but <5%
- BMBx : severely hypocellular marrow with markedly decreased megakaryocytes, granulocytes and erythroblasts, Relatively increased small round cells of undetermined nature, No histologic evidence of dysplasia
- IHC : CD34 + (15%)
- chromosome : 46, XX[3]

Case demonstration



KING CHULALONGKORN
MEMORIAL HOSPITAL



FACULTY OF MEDICINE
CHULALONGKORN UNIVERSITY



CETH
Center of Excellence in
Translational Hematology

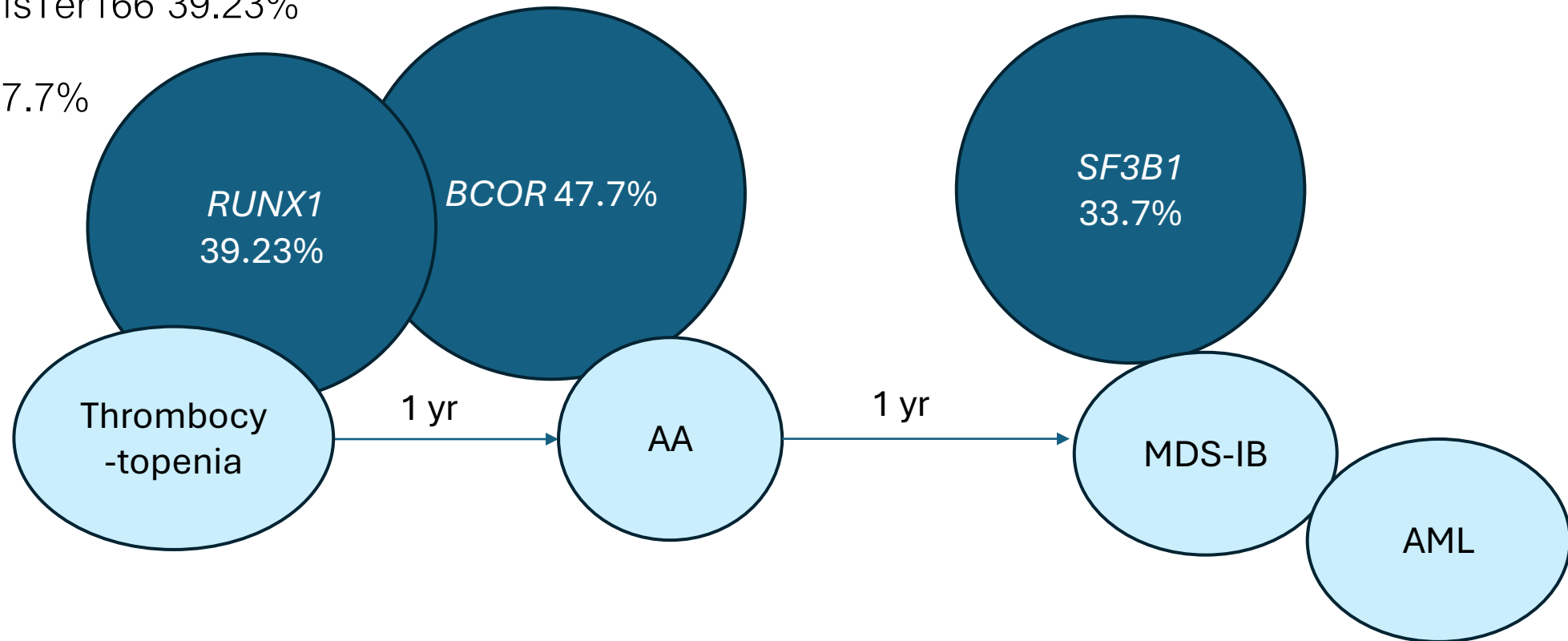
- Flow for PNH : no PNH clone

- NGS for myeloid panel :

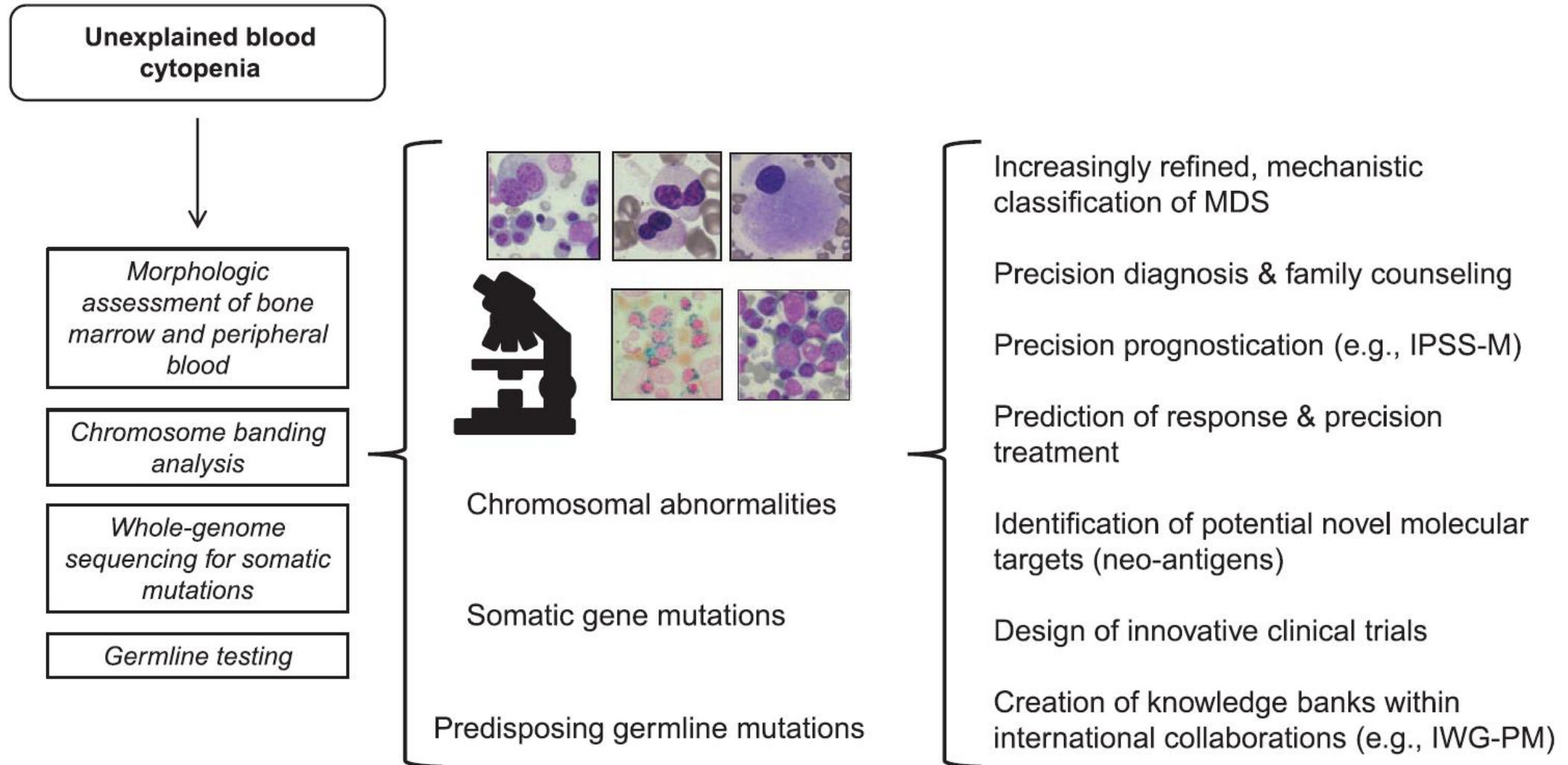
SF3B1 p.Arg625Cys 33.7%

RUNX1 p.ASn434GlnfsTer166 39.23%

BCOR p.Glu983Ter 47.7%



Approach to the diagnosis and risk stratification of MDS that will enable precision treatments



Conclusion



- Genomic profile assessment provide more concise patient risk stratification.
- Genetic studies help identify specific subtypes with distinct clinical features and outcomes
- Comprehensive approach integrating morphology, cytogenetics and NGS are necessary to effectively diagnose and guide management in MDS patients

INTERNATIONAL SCIENTIFIC SYMPOSIUM

“Scientific Forum on Myeloid and Lymphoid Malignancies :
Advancing Knowledge and Innovation ”

Registration: 8.00-8.20 | Opening Remark: 8.20-8.30

••• Session I BONE MARROW FAILURE SYNDROMES

Moderator	Asso. Prof. Suporn Chuncharunee	
8.30 - 8.55	Deciphering the Genetic Landscape of Myelodysplastic Syndromes in the Modern Era	Prof. Seishi Ogawa (Japan) 
8.55 - 9.20	Unraveling the Impact of <i>DDX41</i> Mutations in Myeloid Malignancies: Genetic Insights and Clinical Relevance	Prof. Hideki Makishima (Japan) 
9.20 - 9.45	The Role of HLA in Aplastic Anemia: Uncovering Pathogenic Mechanisms	Assist. Prof. Sunisa Kongkiatkamon (Thailand) 

••• Session II MYELOPROLIFERATIVE DISORDERS

Moderator	Asso. Prof. Noppacharn Uaprasert	
9.45 - 10.10	Investigating MPN in the iPSC model: Insights into the pathogenesis and screening for novel therapy	Prof. Ponlapat Rojnuckarin (Thailand) 
10.10 - 10.35	Chronic Myelomonocytic Leukemia (CMML): Bridging the Gap from Bench to Bedside	Prof. Mrinal S. Patnaik (USA) 

Break 10.35 - 10.50

••• Session III ACUTE MYELOID LEUKEMIA

Moderator	Asso. Prof. Pimjai Niparuck	
10.50 - 11.15	<i>FLT3</i> Inhibition in AML: Targeting Pathways for Therapeutic Advancement	Assist. Prof. Naoko Hosono (Japan) 
11.15 - 11.40	Prognostic significance and therapeutic implication of TIM-3 in AML	Assist. Prof. Chantiya Chanswangphuwana (Thailand) 

LUNCH | Symposium I 11.40 - 12.20 | Break 12.20 - 13.10 | Symposium II 13.10 - 13.50



Professor
Seishi
Ogawa

Professor
Mrinal
S. Patnaik



Professor
Ponlapat
Rojnuckarin

Asso. Prof.
Chantana
Polprasert

Asso. Prof.
Kitsada
Wudhikarn

••• Session IV LYMPHOID MALIGNANCIES

Moderator	Prof. Tanin Intragumtornchai	
13.50 - 14.15	The Genomic Landscape of CLL: Unveiling Clinical Implications in Asian Population	Asso. Prof. Ja min Byun (South Korea) 
14.15 - 14.50	Personalized Medicine in DLBCL: Advancing from Traditional to Innovative Diagnostic Strategies	Dr. Narittee Suksawai (Thailand) 
14.50 - 15.15	Germline <i>HAVCR2</i> Mutation in SPTCL and HLH: Implications for Pathogenesis and Clinical Outcomes	Asso. Prof. Chantana Polprasert (Thailand) 

Break 15.15 - 15.30

••• Session V CELLULAR THERAPY

Moderator	Prof. Nattiya Hirankarn	
15.30 - 15.55	Integrating CAR T-Cell Therapy into the Evolving Landscape of R/R DLBCL Treatment	Asso. Prof. Kitsada Wudhikarn (Thailand) 
15.55 - 16.20	Harnessing CAR T-Cell Therapy in AML: A New Era in Therapeutic Innovation	Assist. Prof. Shoji Saito (Japan) 
16.20 - 16.45	Navigating the Management of Complications in CAR T-Cell Therapy	Asso. Prof. Jakrawadee Julamanee (Thailand) 

SATURDAY **20.09.25**

Venue : Bhumisirimangalanusorn Building, Room 1210,
King Chulalongkorn Memorial Hospital (370 seats)

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