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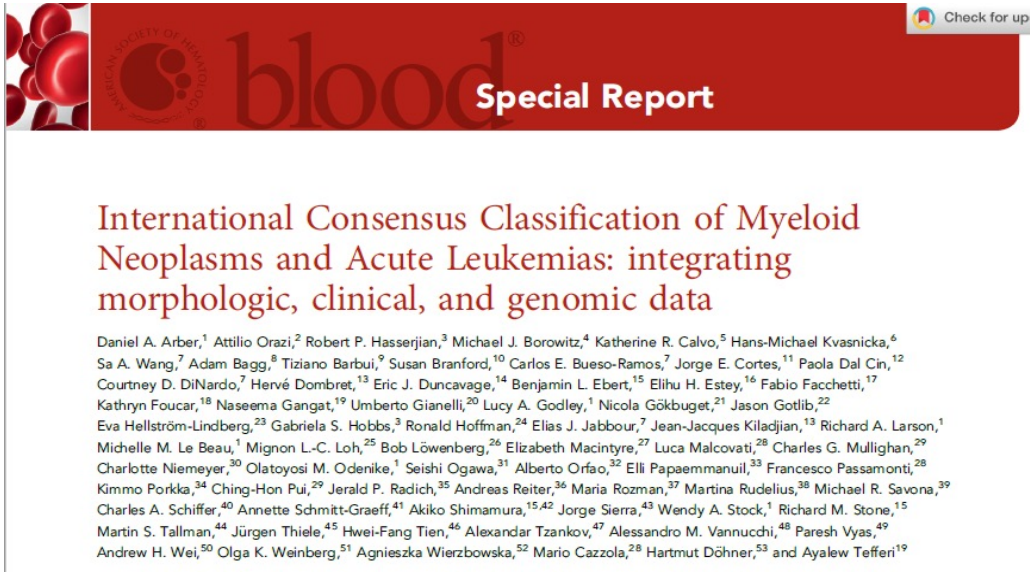
Mielodisplasia: novità nelle MDS a basso rischio e ad alto rischio

What's new in MDS – 1. Classifications



blood® Special Report

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International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Daniel A. Arber,[1] Attilio Orazi,[2] Robert P. Hasserjian,[3] Michael J. Borowitz,[4] Katherine R. Calvo,[5] Hans-Michael Kvasnicka,[6] Sa A. Wang,[7] Adam Bagg,[8] Tiziano Barbui,[9] Susan Branford,[10] Carlos E. Bueso-Ramos,[7] Jorge E. Cortes,[11] Paola Dal Cin,[12] Courtney D. DiNardo,[7] Hervé Dombret,[13] Eric J. Duncavage,[14] Benjamin L. Ebert,[15] Elihu H. Estey,[16] Fabio Facchetti,[17] Kathryn Foucar,[18] Naseema Gangat,[19] Umberto Gianelli,[20] Lucy A. Godley,[1] Nicola Gökbuget,[21] Jason Gotlib,[22] Eva Hellström-Lindberg,[23] Gabriela S. Hobbs,[3] Ronald Hoffman,[24] Elias J. Jabbour,[7] Jean-Jacques Kiladjian,[13] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.-C. Loh,[25] Bob Löwenberg,[26] Elizabeth Macintyre,[27] Luca Malcovati,[28] Charles G. Mullighan,[29] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Elli Papaemmanuil,[33] Francesco Passamonti,[28] Kimmo Porkka,[34] Ching-Hon Pui,[29] Jerald P. Radich,[35] Andreas Reiter,[36] Maria Rozman,[37] Martina Rudelius,[38] Michael R. Savona,[39] Charles A. Schiffer,[40] Annette Schmitt-Graeff,[41] Akiko Shimamura,[15,42] Jorge Sierra,[43] Wendy A. Stock,[1] Richard M. Stone,[15] Martin S. Tallman,[44] Jürgen Thiele,[45] Hwei-Fang Tien,[46] Alexandar Tzankov,[47] Alessandro M. Vannucchi,[48] Paresh Vyas,[49] Andrew H. Wei,[50] Olga K. Weinberg,[51] Agnieszka Wierzbowska,[52] Mario Cazzola,[28] Hartmut Döhner,[53] and Ayalew Tefferi[19]

Leukemia

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REVIEW ARTICLE OPEN

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The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury[1✉], Eric Solary[2✉], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52✉]

The new **International Consensus Classification of Myeloid Neoplasms and Acute Leukemias** represents a major revision of the prior classifications and includes many authors of the prior WHO editions but is no longer affiliated with the WHO.

The main objective of the **consensus process** is: the definition of real disease entities, including the introduction of new entities and refined criteria for existing diagnostic categories, based on accumulated data.

It is aimed at **facilitating diagnosis and prognostication** of these neoplasms, improving treatment of patients, and allowing the design of innovative clinical trials.

Arber DA, et al. The International Consensus Classification of Myeloid Neoplasms and Acute Leukemias. Blood. 2022

Khoury, J.D., Solary, E., Abla, O. *et al.* The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia* **36**, 1703–1719 (2022).

Myelodysplastic syndromes (MDS) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics†	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1‡	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex	*SF3B1* (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1‡	≥1	Thrombocytosis allowed	<5% BM <2% PB§	del(5q), with up to 1 additional, except −7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS without dysplasia	0	≥1	0	<5% BM <2% PB§	−7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥ 10% VAF)
MDS, NOS with single lineage dysplasia	1	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1‡	≥1	0	5-9% BM, 2-9% PB§	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1‡	≥1	0	10-19% BM or PB‖	Any, except AML-defining¶	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

Arber D, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood. 2022; 140*(11), 1200–1228.

Myeloid neoplasms with mutated TP53

- This disease category encompasses separate diagnoses of MDS, MDS/AML, and AML with mutated TP53 (including pure erythroid leukemia), according to the blast percentage.

- These diseases are grouped together because of their overall similar aggressive behavior irrespective of the blast percentage, warranting a more unified treatment strategy across the blast spectrum.

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF > 10%)

- The presence of multihit TP53 mutations in cytopenic myeloid neoplasms corresponds to a highly aggressive disease with short survival.

Multihit TP53 can be confirmed by:

- The presence of **2 or more distinct TP53 mutations** (VAF ≥ 10%) **or** a **single** TP53 mutation associated **with**:

    I. a cytogenetic deletion involving the TP53 locus at 17p13.1;
    II. a VAF of ≥ 50%;
    III. copy-neutral loss of heterozygosity (LOH) at the 17p TP53 locus.

- In the absence of LOH information, **the presence of a single TP53 mutation in the context of any complex karyotype** is considered equivalent to a multihit TP53.

What's new in MDS – 2. IPSS-Mol, a new prognostic model integrating molecular data

NEJM Evidence

Published June 12, 2022

DOI: 10.1056/EVIDoa2200008

ORIGINAL ARTICLE

Molecular International Prognostic Scoring System for Myelodysplastic Syndromes

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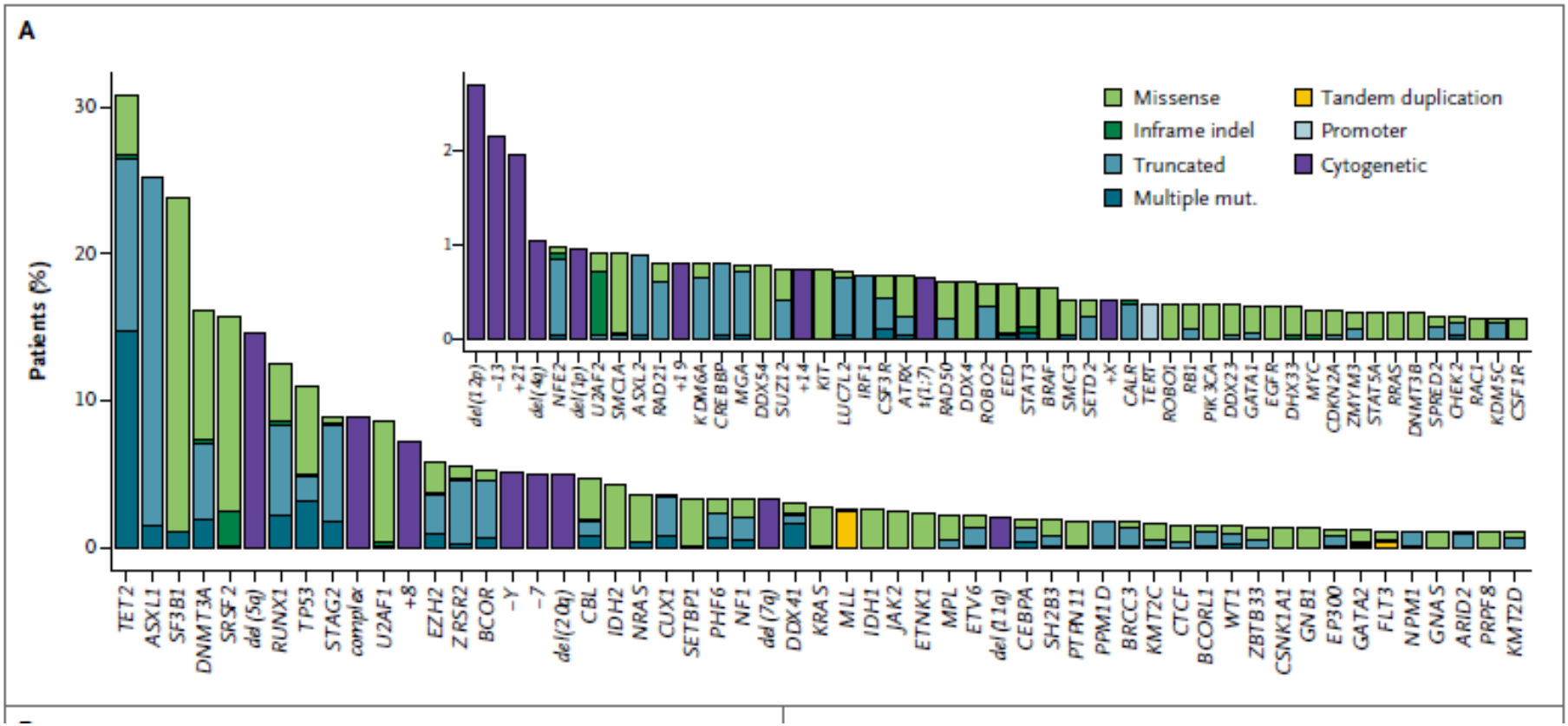
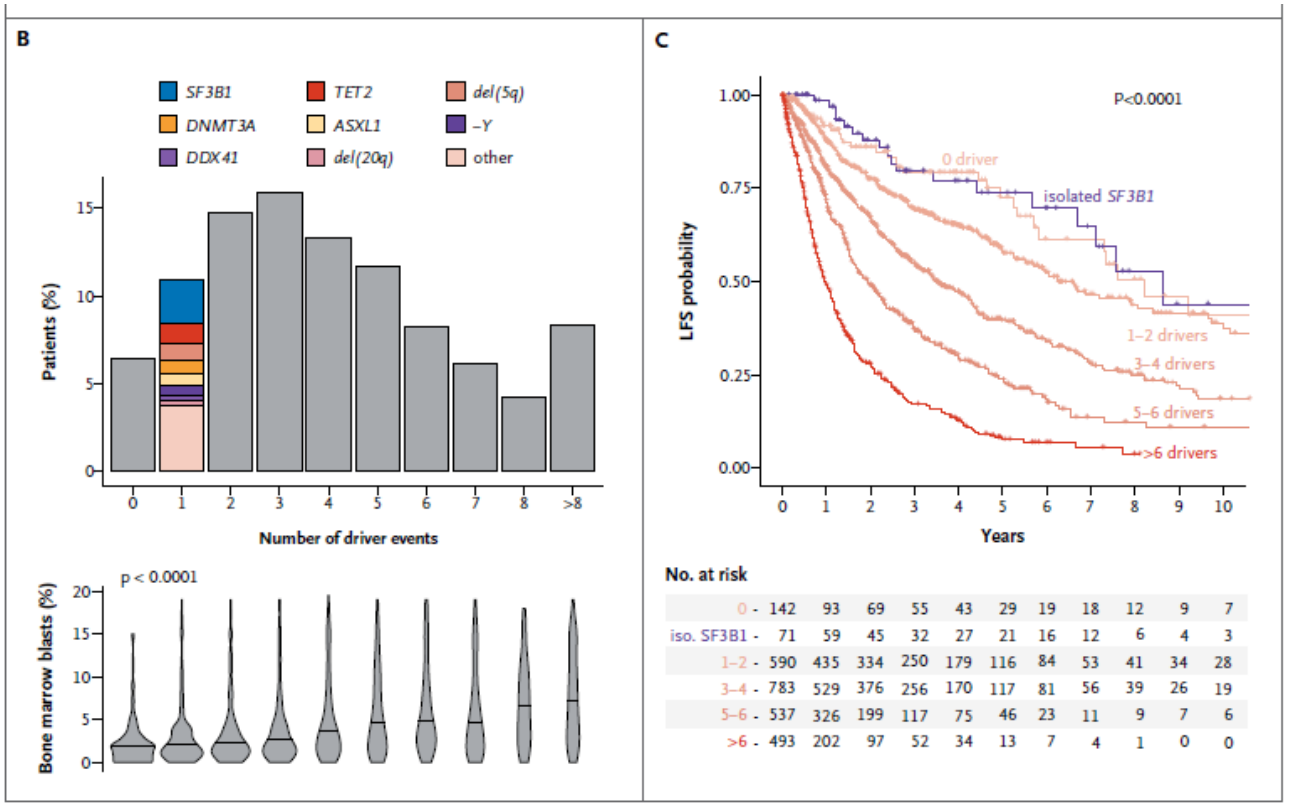
- To develop a clinical-molecular prognostic model (IPSS-Molecular [IPSS-M]), pretreatment diagnostic samples from **2957** patients with MDS were **profiled for mutations in 152 genes**.

- Clinical and molecular variables were evaluated for associations with leukemia-free survival, leukemic transformation, and overall survival.



- A total of 94% of patients had at least one molecular abnormality (**median 4**), with 53% of patients having gene mutations only, 4% having cytogenetic alterations only, and 37% having both.

- **The molecular landscape was consistent with prior studies**



- Mutations in SF3B1 and TET2, as well as del(5q), were enriched in patients with only one driver event (Fig. B)
- As expected, the number of abnormalities correlated with disease severity (Fig. C)

- **TP53multihit** (but not monoallelic TP53 mutations), **mutations in FLT3** (tyrosine kinase domain and internal tandem duplication) and KMT2A (**MLL**) partial tandem duplication (**PTD**) ranked as **top predictors of adverse outcomes,** with the latter two exhibiting the strongest hazard ratios for AML transformation.

- Mutations in **ASXL1**, **BCOR**, **EZH2**, **NRAS**, **RUNX1**, **STAG2**, and **U2AF1** were significantly associated with adverse risk for the three end points.

- **SF3B1 mutations** were associated with favorable outcomes consistently across clinical end points, however, this association was strongly modulated by **patterns of comutation**.

- SF3B1-mutated cases segregates into three independent groups:

  I. **SF3B1-5q** (7% of SF3B1-mutant) for concomitant presence with isolated del(5q);
  II. **SF3B1β** (15%) as the comutation between SF3B1 and any gene from BCOR, BCORL1, NRAS, RUNX1,SRSF2, or STAG2
  III. **SF3B1α** (78%) as any other mutant SF3B1

- **The favorable outcomes associated with SF3B1 mutations were confined to the SF3B1a group**, and not observed for SF3B1-5q or SF3B1β

The IPSS-M improves the risk stratification of patients with MDS and represents a valuable tool for clinical decision-making

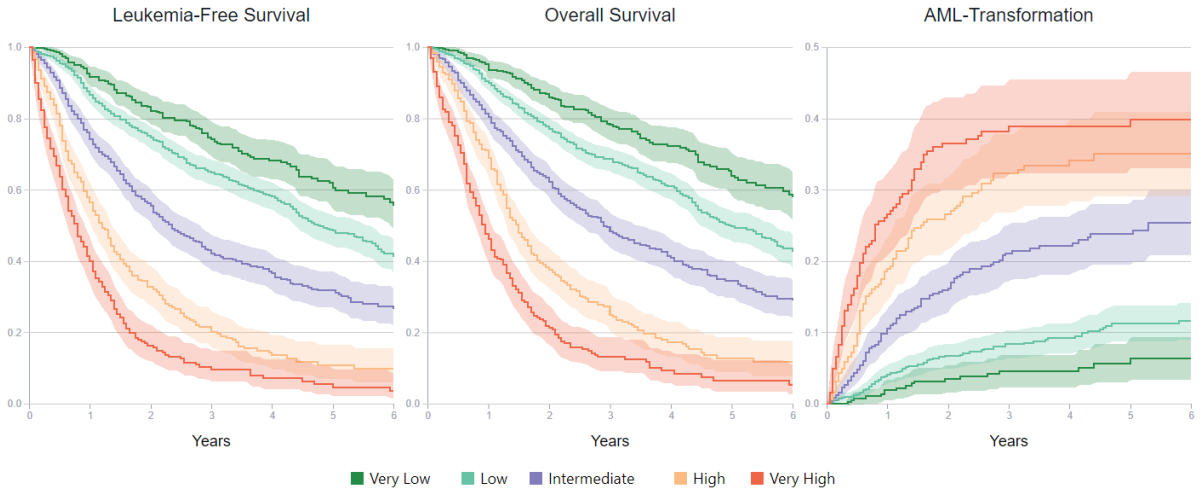
IPSS-M parameters					
Cinical variables	BM blasts	Hb	ANC	PLT	Age
Cytogenetics	Very good	Good	Intermediate	Poor	Very Poor
Molecular Data	TP53 mut (number of)	P53 LOH	MLL (PTD) FLT3 (ITD or TKD)	Other genes* (individual weight and number of mutations)	

** **Individual weight**: ASXL1, CBL, DNMT3A, ETV6, EZH2, IDH2, KRAS, NPM1, NRAS, RUNX1, SF3B1, SRSF2, U2AF1, **number of residual mutations**: BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1.*

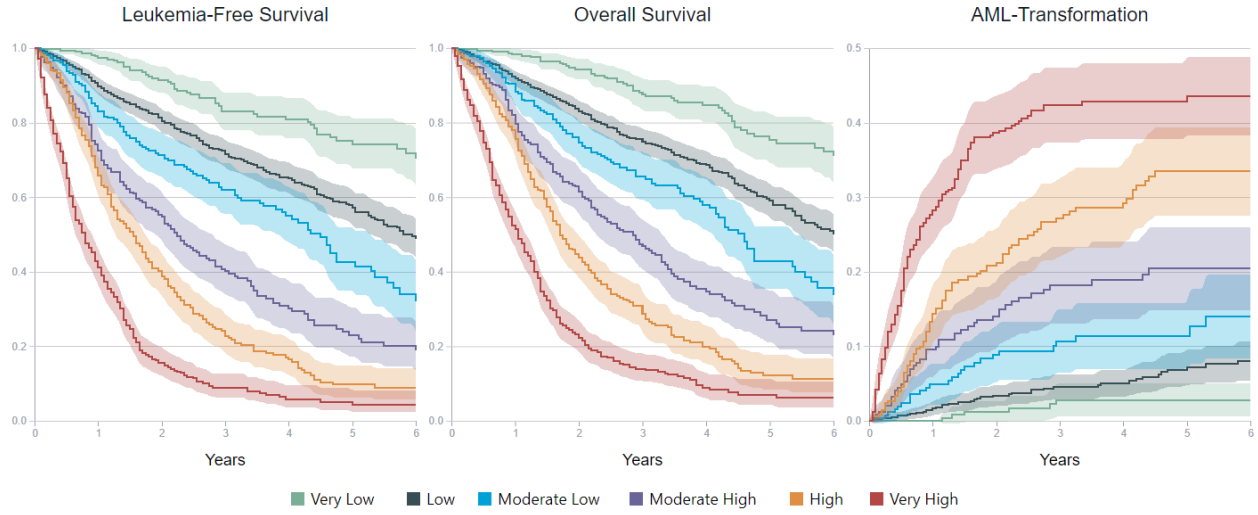
https://mds-risk-model.com/

Very Good	-Y, del(11q).
Good	Normal, del(5q), del(12p), del(20q), double including del(5q).
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones.
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities.
Very Poor	Complex: > 3 abnormalities.

IPSS-R



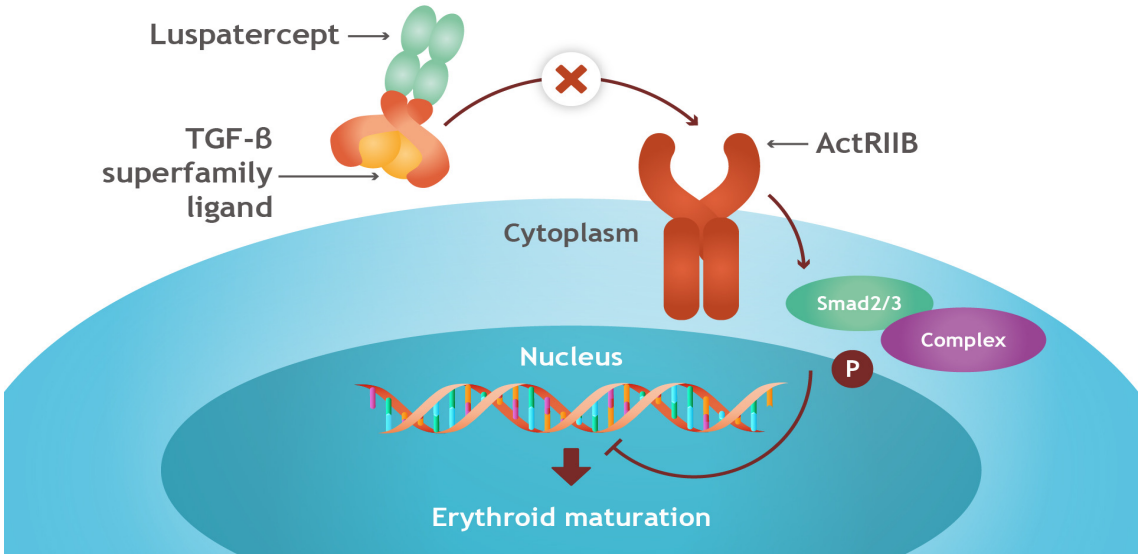
IPSS-Mol



Novel options for low-risk AML - LUSPATERCEPT

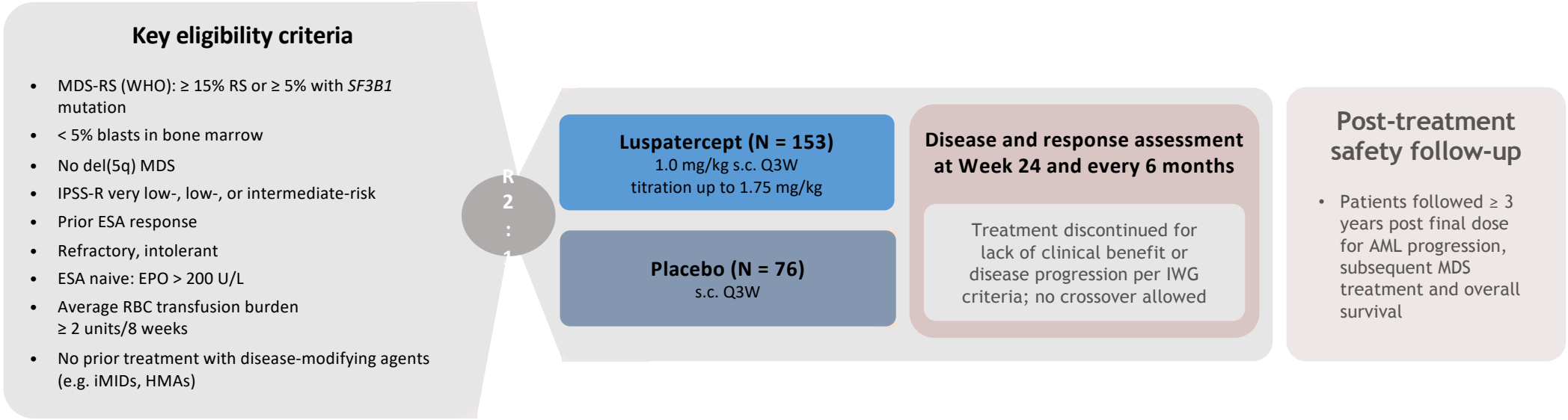
- Luspatercept is a TGFβsuperfamily trap-ligand
- Modified Activin Receptor IIb
- It acts as a ligand trap for **GDF11** and other **TGFβ family ligands** to suppress Smad2/3 signalling
- Smad2/3 phopsphorylation inhibits erythroid maturation

In patients with MDS with ring sideroblasts (reclassified as MDS-SF3B1 in 2022), luspatercept received regulatory approval as it achieved RBC transfusion independence for ≥8 weeks in 38% of patients post ESA therapy or those ineligible to receive ESA therapy due to baseline EPO of >500 IU/L (MEDALIST TRIAL)



MEDALIST trial - Study design

MEDALIST (NCT02631070), Phase 3, double-blind, placebo-controlled study evaluating the efficacy and safety of luspatercept for patients with LR-MDS and RS who had been receiving regular RBC transfusions and had disease that was refractory to or was unlikely to respond to ESAs.



Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med. 2020 Jan 9;382(2):140–151.

MEDALIST trial – Study endpoints

Primary endpoint:
- RBC-TI ≥ 8 weeks (Weeks 1–24)

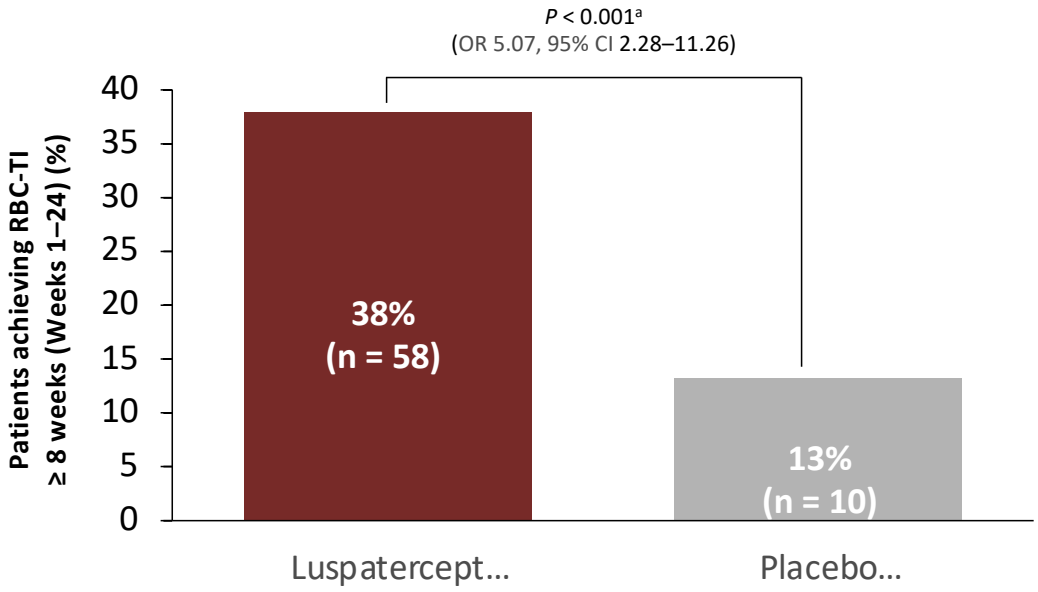
Key secondary endpoint:
- RBC-TI ≥ 12 weeks (Weeks 1–24 and Weeks 1–48)

Additional secondary endpoints:
- RBC-TI ≥ 8 weeks (Weeks 1–48)
- Duration of the longest single period of the primary response
- HI-E
- Mean Hb increase ≥ 1.0 g/dL
- Serum ferritin mean change
- Progression to AML
- Safety

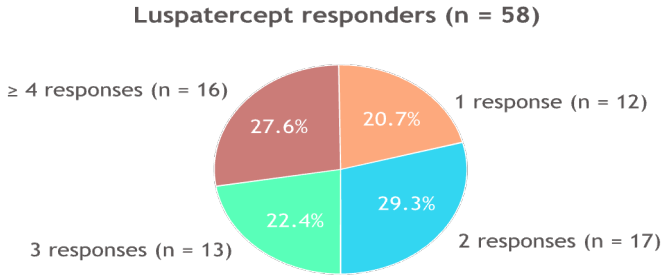
Exploratory endpoints:
- Subgroup analyses

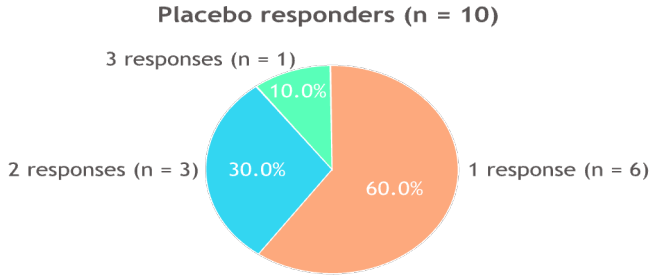
Other analyses:
- RBC-TI ≥ 16 weeks (Weeks 1–24 and Weeks 1–48)

Efficacy: Primary endpoint



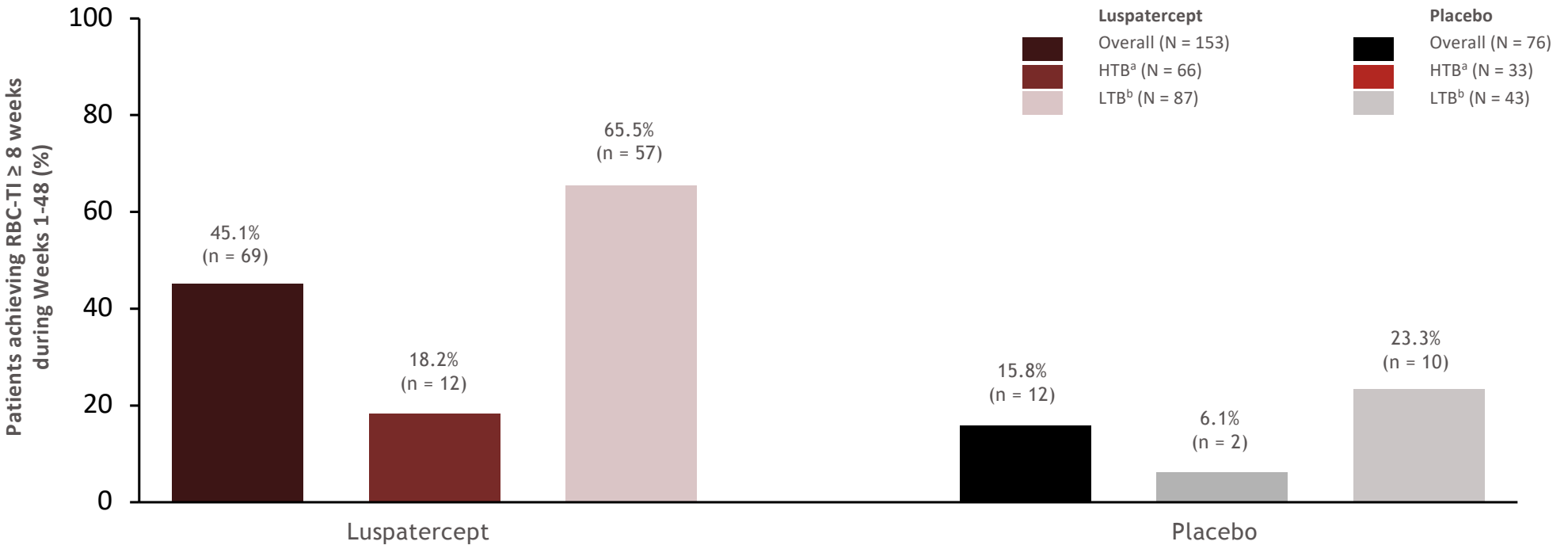
- **Response rates** were similar regardless of *SF3B1* allelic burden and total number of baseline somatic mutations
- The **median duration** of the longest single period of RBC-TI (by primary endpoint) was 30.6 weeks in the luspatercept arm compared with 13.6 weeks in the placebo arm
- In addition, a **subpopulation analysis for patients with low neutrophil and low platelet counts** demonstrated hematologic improvements in neutrophil/platelet counts, indicating that luspatercept may have other poorly understood effects that may be beneficial to patients with MDS





Number of responses refers to the number of separate response events (RBC-TI ≥ 8 weeks) occurring during the entire treatment period among patients who initially achieved a response (RBC-TI ≥ 8 weeks) during weeks 1–24. Patients that achieved 1 response event did so during weeks 1-24.

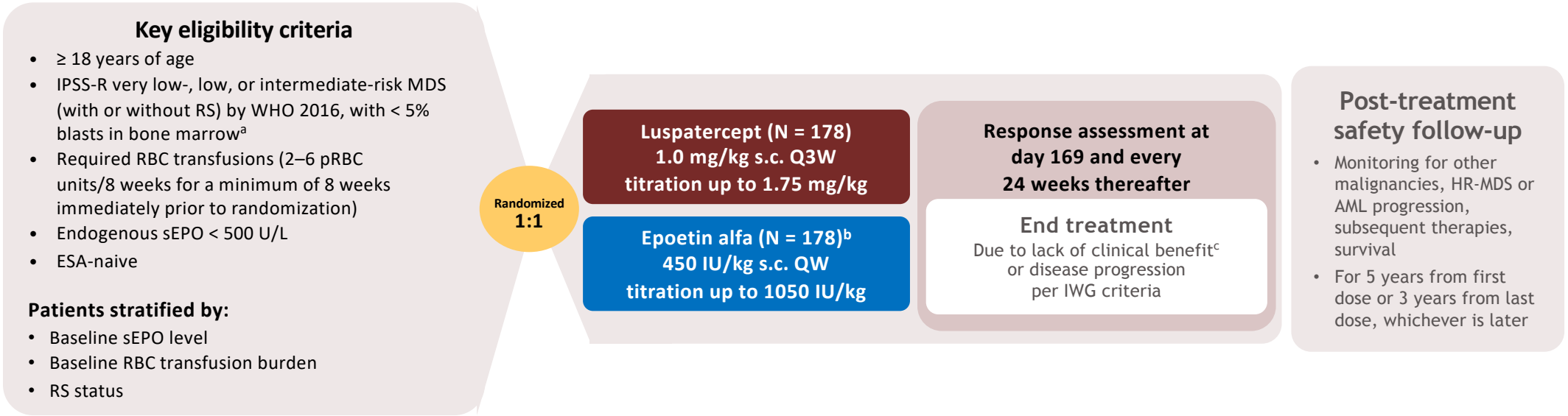
Patients achieving RBC-TI ≥ 8 weeks during Weeks 1–48



HTB, high transfusion burden; LTB, low transfusion burden
[a]HTB defined as patients receiving transfusion of ≥ 6 RBC units within 8 weeks prior to study.
[b]LTB defined as patients receiving < 6 RBC units within 8 weeks prior to study.Data cut-off July 1, 2019.

COMMANDS trial - Study design

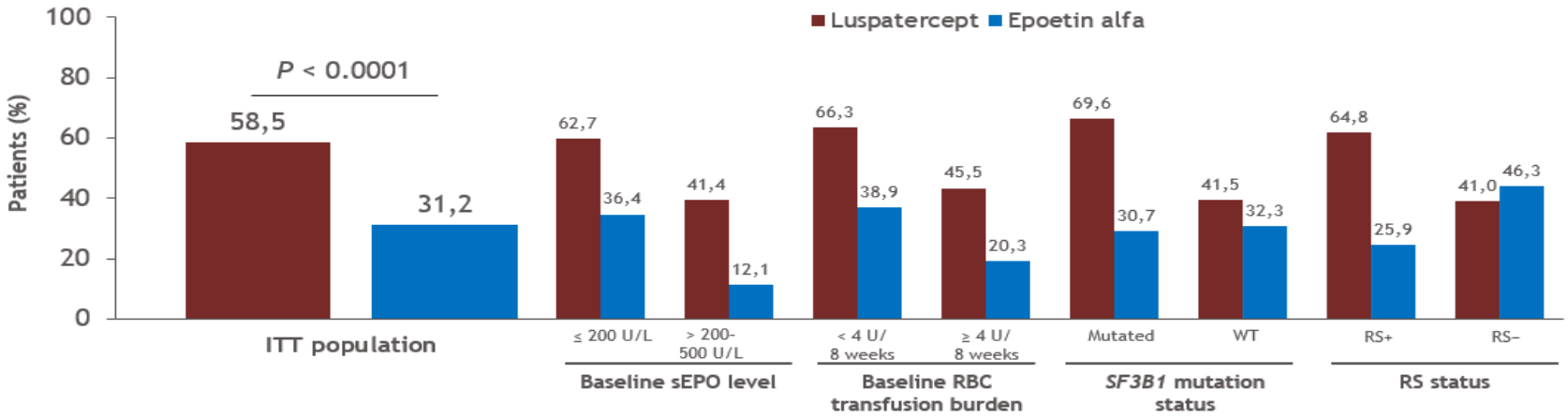
The COMMANDS study (NCT03682536) is a phase 3, global, open-label, randomized trial comparing the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to IPSS-R LR-MDS in ESA-naive patients who require RBC transfusions



The purpose of this study is to determine the effectiveness of luspatercept (ACE-536) compared to epoetin alfa on red blood cell (RBC) **transfusion independence (for at least 12 weeks)** with a **concurrent hemoglobin increase of at least 1.5 g/dL** in participants with anemia due to revised international prognostic scoring system (IPSS-R) very low, low, or intermediate risk myelodysplastic syndromes (MDS) who require RBC transfusions and have never been exposed to erythropoiesis stimulating agent (ESA).

COMMANDS trial - results of the pre-planned interim analysis

- Of 301 pts included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) epoetin alfa achieved the primary endpoint
- Achievement of the primary endpoint favored luspatercept or was similar to epoetin alfa for all subgroups analyzed



Della Porta MG, et al. EHA 2023

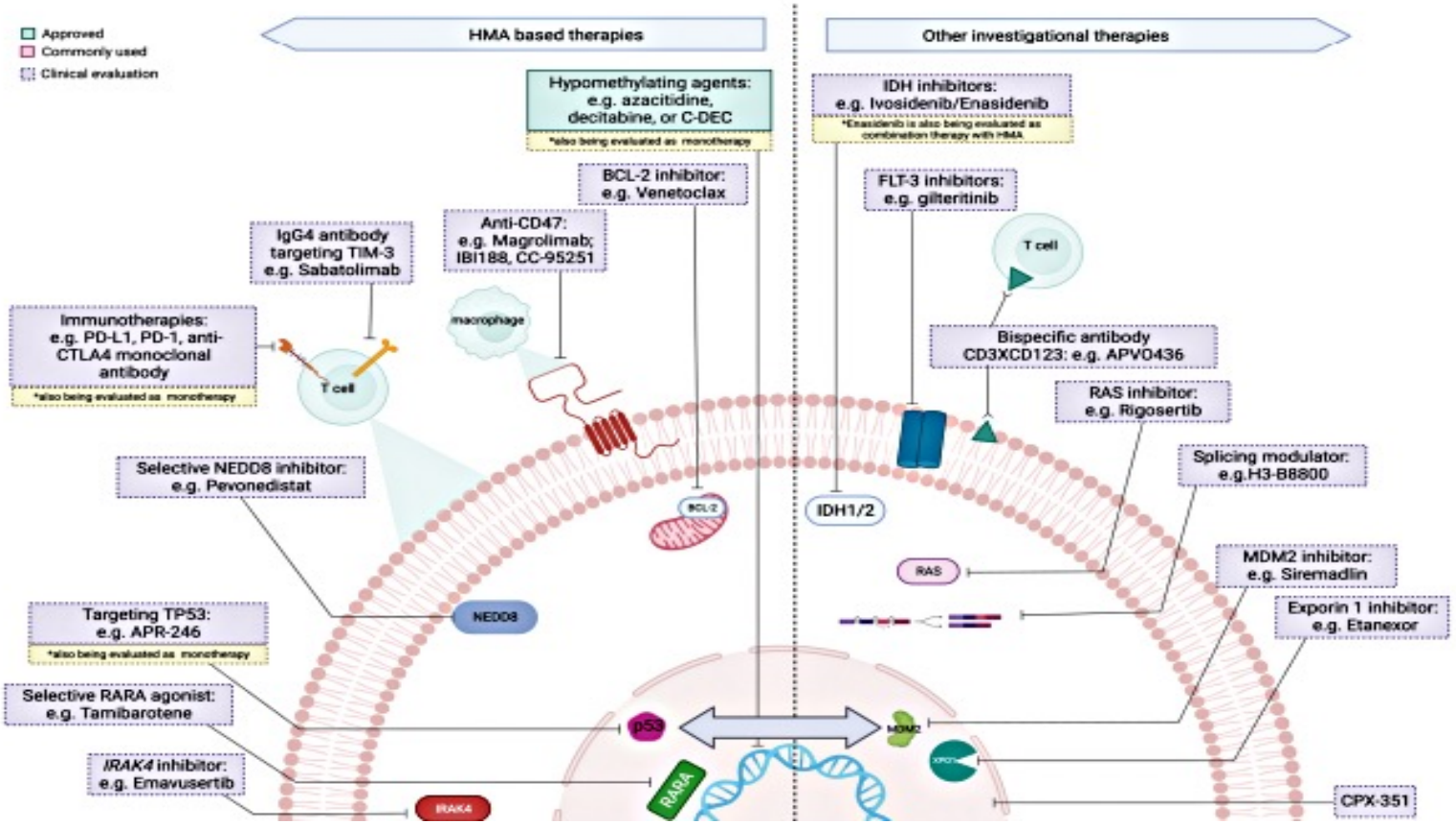
CORRESPONDENCE

Real-world efficacy and safety of luspatercept and predictive factors of response in patients with lower risk myelodysplastic syndromes with ring sideroblasts

- Real life data confirm results from MEDALIST trial
- Older patients, real life cohort is enriched in concomitant comorbidities
- At least one increase from the baseline recommended dose of 1 mg/kg occurred in >90% pts
- Significant association between baseline transfusion burden and the individual probability to achieve transfusion independence.
- SAEs in 17.4% pts. Most frequently observed: **hypertension**, acute heart failure, atrial fibrillations, acute kidney injury, infections, COVID-19 pneumonia, falls leading to bone fractures

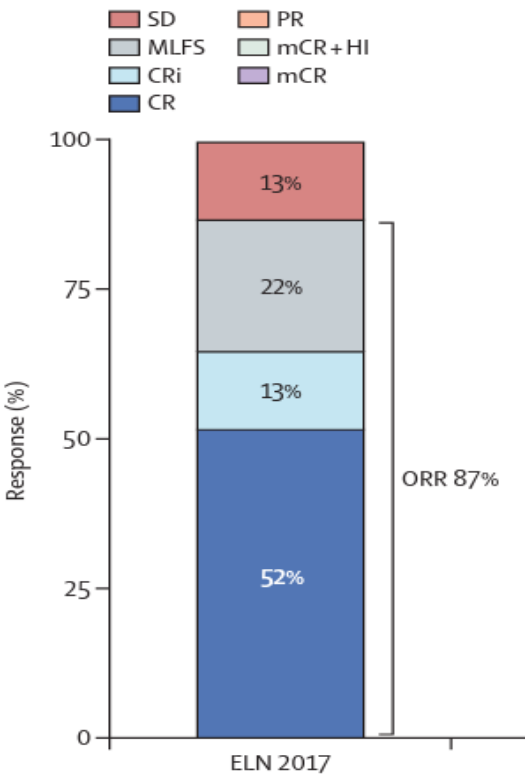
Lanino L, et al. Real-world efficacy and safety of luspatercept and predictive factors of response in patients with lower risk myelodysplastic syndromes with ring sideroblasts. Am J Hematol, 98: E204-E208.

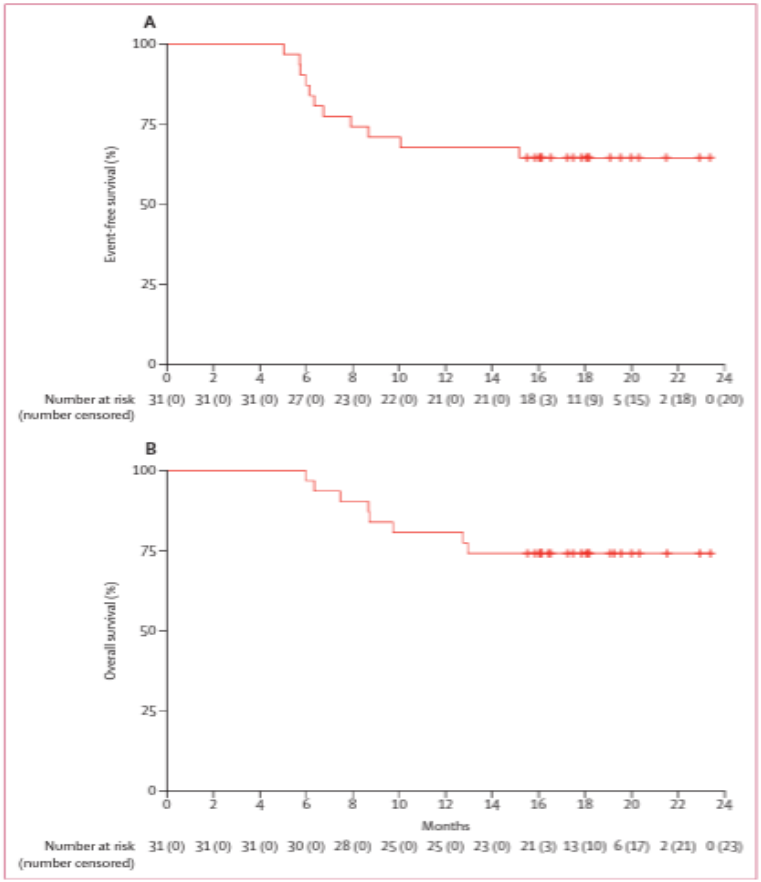
Novel options for high-risk AML



Yazan F, et al. Advances in myelodysplastic syndromes: promising novel agents and combination strategies. Exp Rev Haematol. 2023

CPX-351

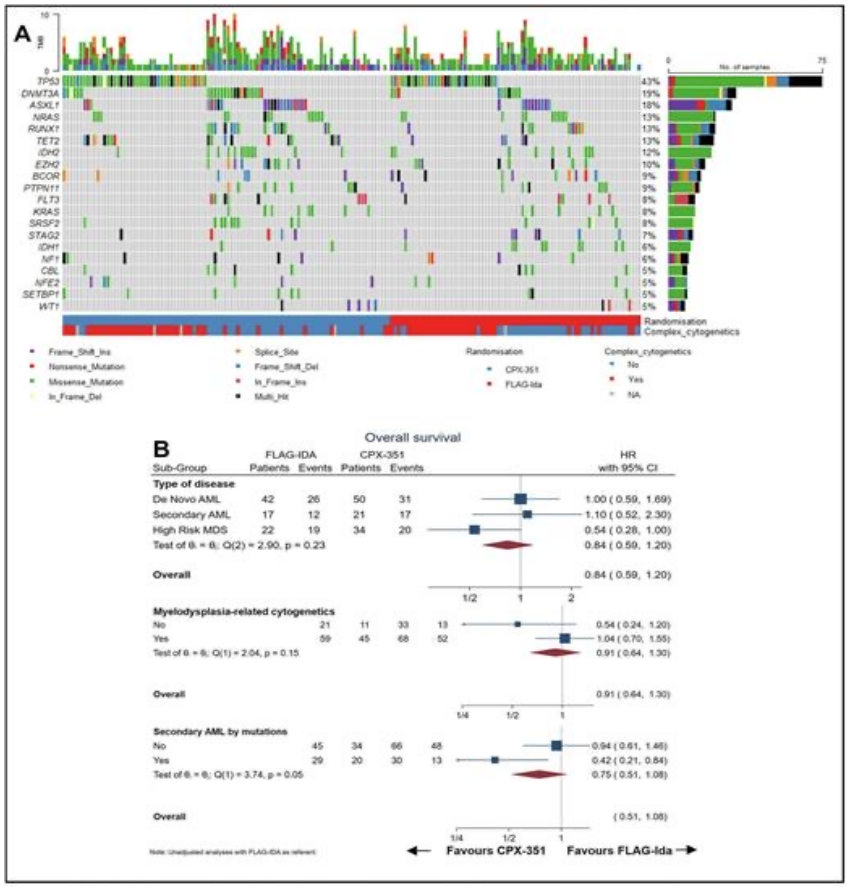




- 31 patients were enrolled.
- 27 (87%) of 31 patients responded (95% CI 70–96)
- 16 (52%) of the 31 patients received at least one consolidation cycle.
- 30 (97%) of the 31 patients included were initially considered eligible for allogeneic HSCT and 29 (94%) of the 31 patients had the procedure.
- Median follow-up was 16·1 months (IQR 8·3–18·1).
- The most common grade 3–4 adverse events were pulmonary (eight [26%] of 31 patients) and cardiovascular (six [19%] of 31 patients).
- There were 14 serious adverse events (mainly hospitalization for infection [n=5] and no treatment-related death.

Peterlin P, et al. CPX-351 in higher risk myelodysplastic syndrome and chronic myelomonocytic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Haematol. 2023 Jul;10(7):e521-e529.

CPX vs FLAG-Ida in younger patients: UK MRC-AML 19 trial



A. Oncoplot showing variants in the top 20 most mutated genes
B. Overall survival subgroup analyses based on clinical categorisation; the presence or absence of myelodysplasia-related cytogenetic abnormalities; and the presence of absence of secondary AML mutations (*ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*, without *TP53* mutation)

CPX-351 vs FLAG-Ida in younger adults with newly-diagnosed adverse cytogenetic AML or high-risk myelodysplastic syndromes (MDS).

189 patients were randomized (median age 56y).
The overall response rate (CR + CRi) after course two was 64% and 76% for CPX-351 and FLAG-Ida (OR:0.54, 95%CI 0.28-1.04, p=0.06).

There was **no difference** in OS (13.3 months vs 11.4 months, HR:0.78, 95%CI 0.55-1.12, p=0.17) or event-free survival (HR:0.90, 95%CI 0.64-1.27, p=0.55) in multivariable analyses.

However, relapse-free survival was significantly longer with CPX-351 (median 22.1 vs 8.35 months, HR:0.58, 95% CI 0.36-0.95, p=0.03).

OS in younger patients with adverse risk AML/MDS was not significantly different between CPX-351 and FLAG-Ida.

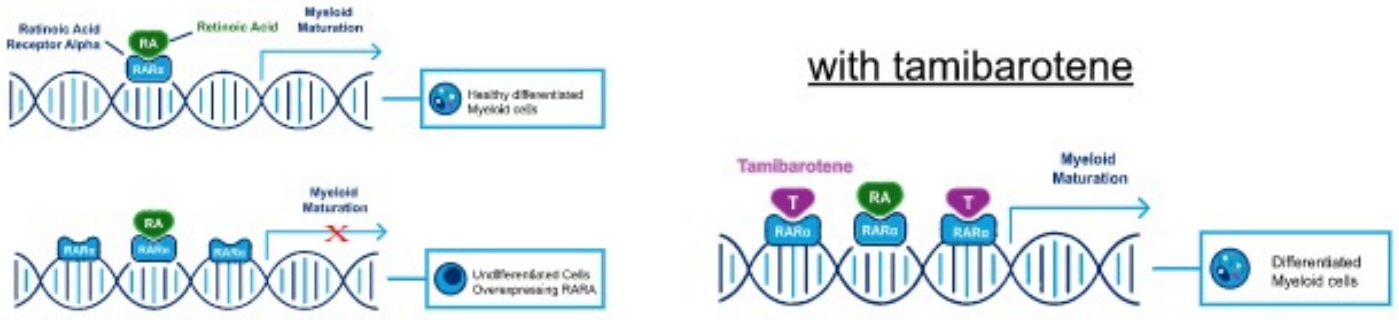
Othman J, et al. Presented at ASH 2022
Othman J et al. Blood Advances 2023 (ahead of print)

TAMIBAROTENE in RARa-positive HR MDS

- Tamibarotene (formerly SY-1425) is an oral selective retinoic acid receptor alpha (RARα) agonist developed for genomically defined subsets of patients whose disease is characterized by the overexpression of the *RARA* gene.

- Tamibarotene is approved for the treatment of LAP R/R in Japan

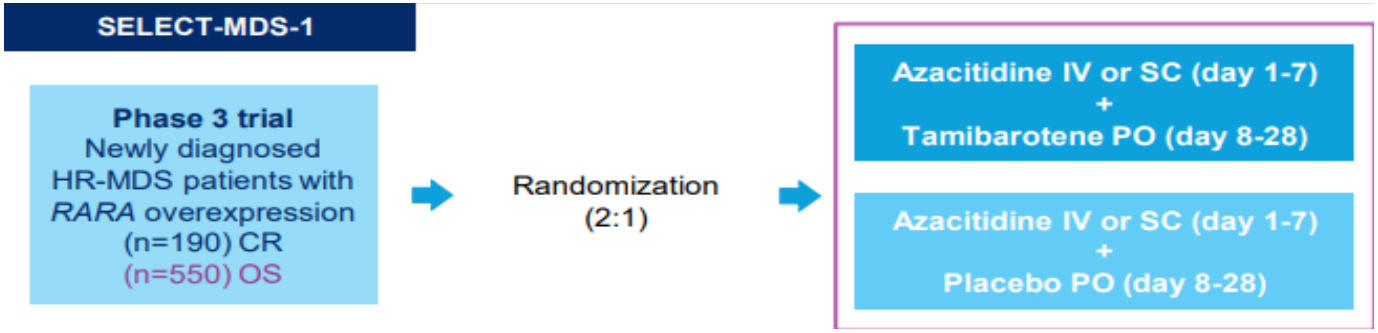
- Approximately 50% of MDS patients and 30% of AML patients have *RARA* overexpression leading to impaired myeloid precursors differentiation.



- Initial clinical data in RARA+ R/R HR-MDS patients treated with tamibarotene showed myeloid differentiation, improved blood counts, and reduced bone marrow blasts

- Promising results of Tamibarotene/AZA association in elderly unfit HR MDS and AML patients (de Botton 2020 ASH Meeting)

ONGOING STUDIES - U.O. EMATOLOGIA E TERAPIE CELLULARI IRCCS OSPEDALE POLICLINICO SAN MARTINO



A Phase 3 randomized, double-blind, placebo-controlled trial of

SY-1425 plus Azacitidine versus Placebo plus Azacitidine in newly diagnosed, RARA-positive adult patients with HR-MDS

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

Grazie per l'attenzione

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DI GENOVA

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