Studien der deutschen MDS-Studiengruppe

Stand März 2019

Uwe Platzbecker

Medizinische Klinik und Poliklinik I
Hämatologie und Zelltherapie
Universitätsklinikum Leipzig

Potentielle Interessenskonflikte

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1. Arbeitgeber und Position:
2. Berater oder Expertenrolle für:
3. Aktienbesitz:
4. Patent, Copyright, Lizensierung:
5. Honorar: Celgene, Amgen, JAZZ, Novartis
6. Finanzierung von Forschungsprojekten:
   Celgene, Amgen, JAZZ, Novartis
7. weitere finanzielle Beziehungen zu:

Das Deutsche MDS Register

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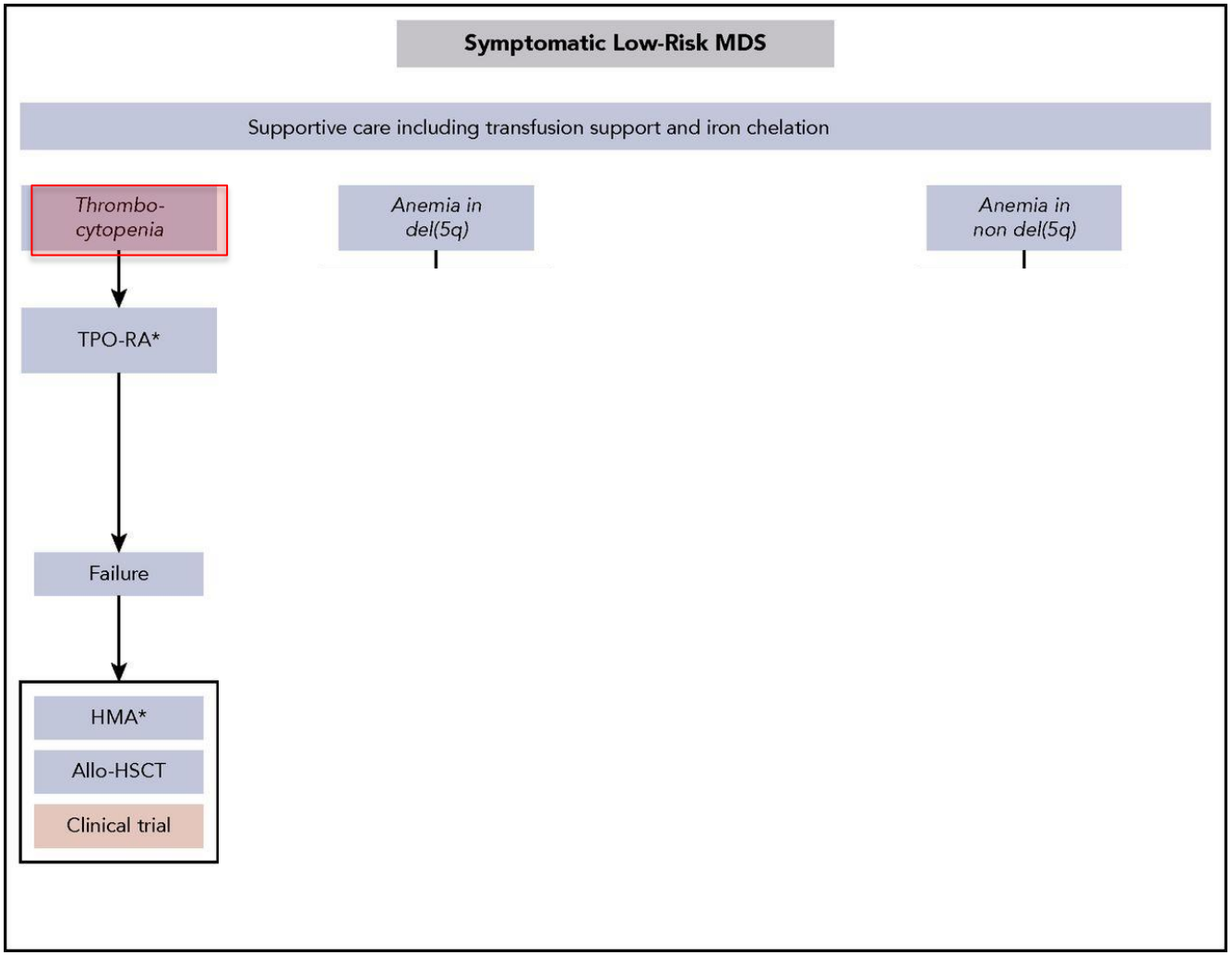
Therapeutic algorithm in LR-MDS patients



EMSCO MYELODYSPLASTIC SYNDROMES

D·MDS

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EUROPE

PROSPECTIVE VALIDATION OF A PREDICTIVE MODEL OF RESPONSE TO ROMIPLOSTIM IN PATIENTS WITH IPSS LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROME (MDS) AND THROMBOCYTOPENIA - THE EUROPE-TRIAL

EUROPE – rationale

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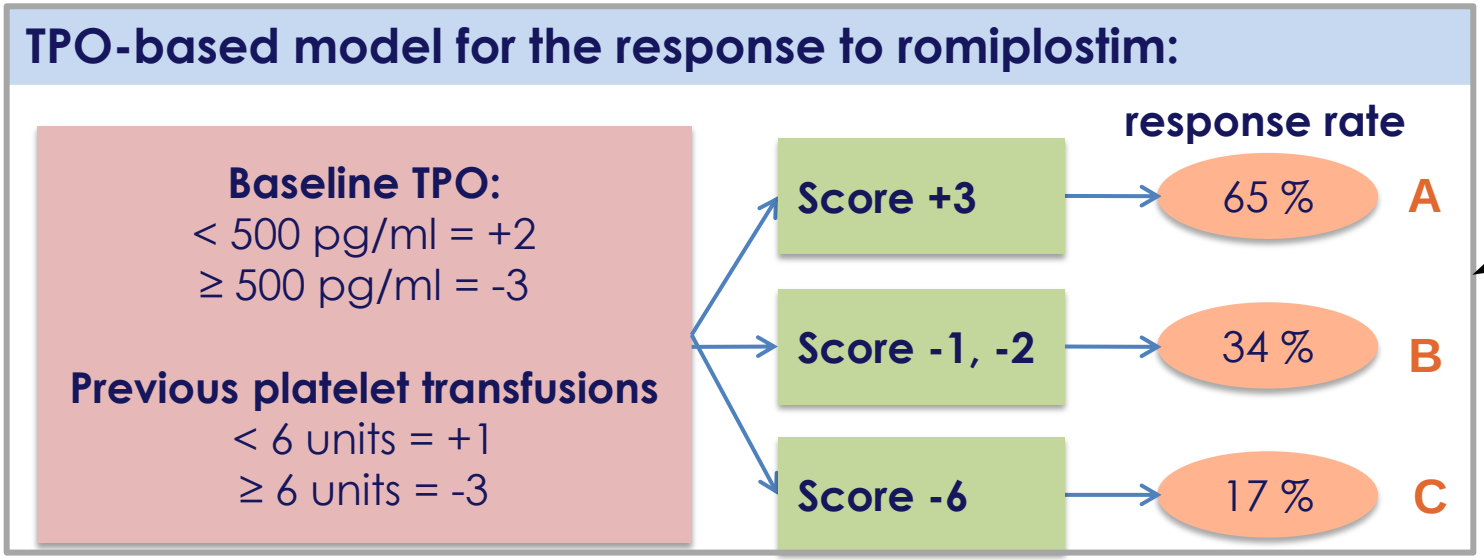
2 clinical trials in low-risk MDS have shown that:

1. low TPO baseline levels (< 500 pg/mL)
2. few platelet transfusions (< 6 units in the previous year)

lead to better response to romiplostim.



Sekeres/Platzbecker et al. Brit. J. of Haem. 2014

EUROPE – recruitment

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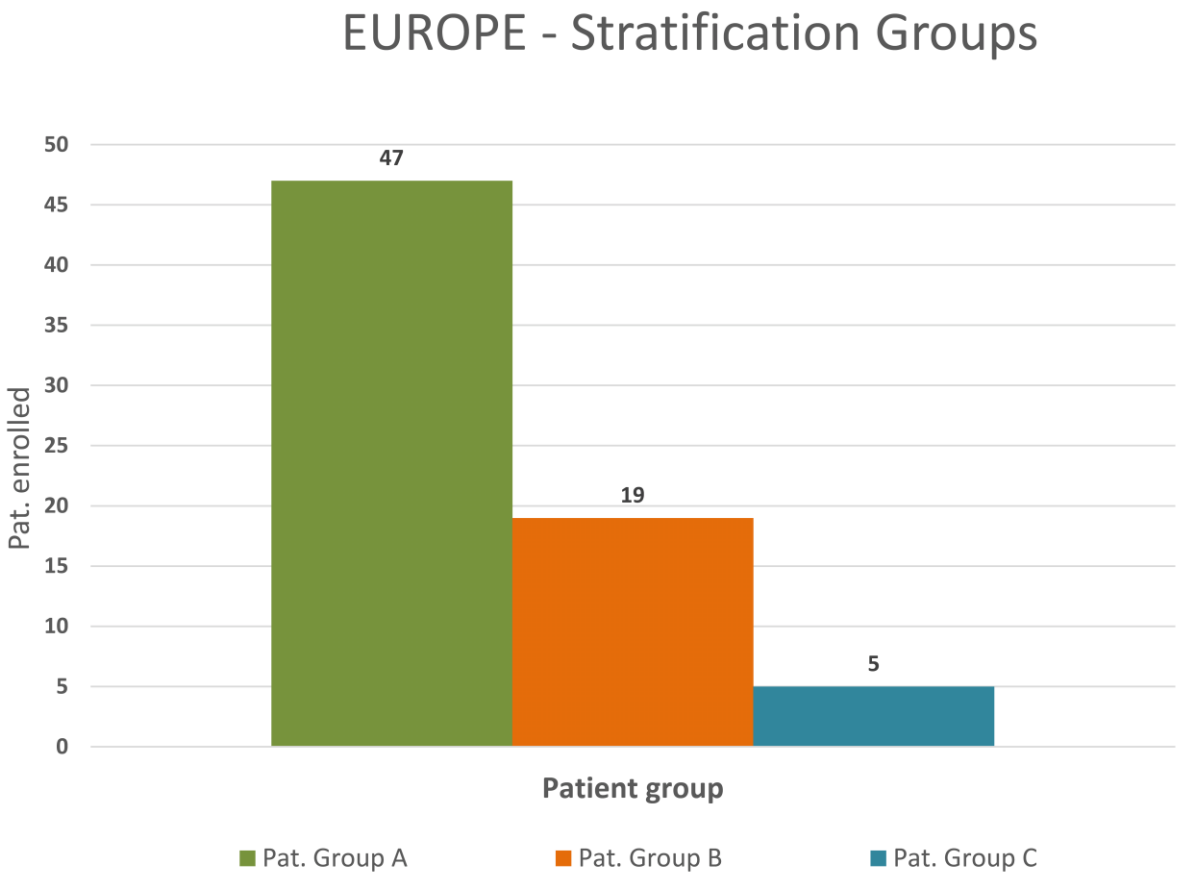
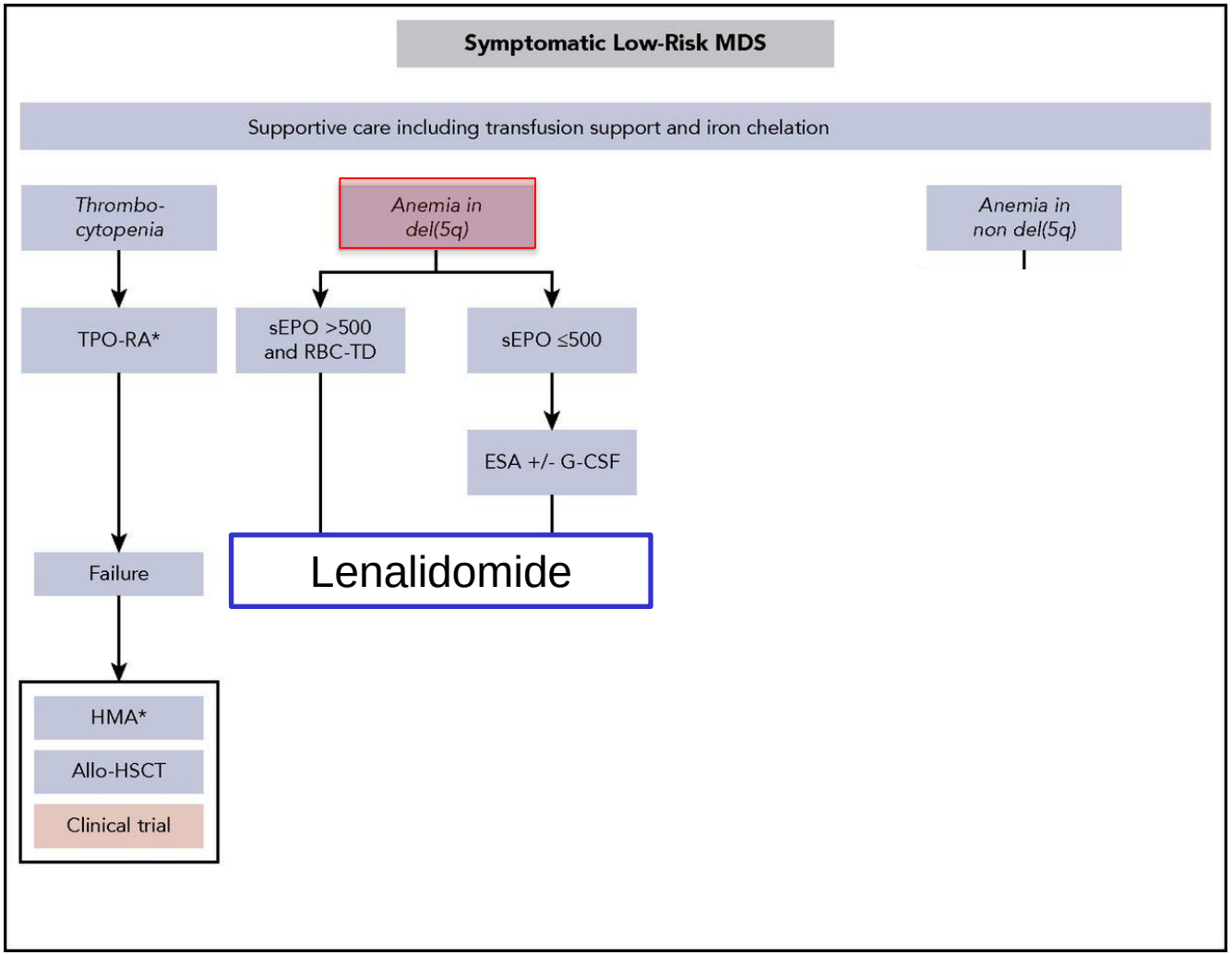


Therapeutic algorithm in LR-MDS patients



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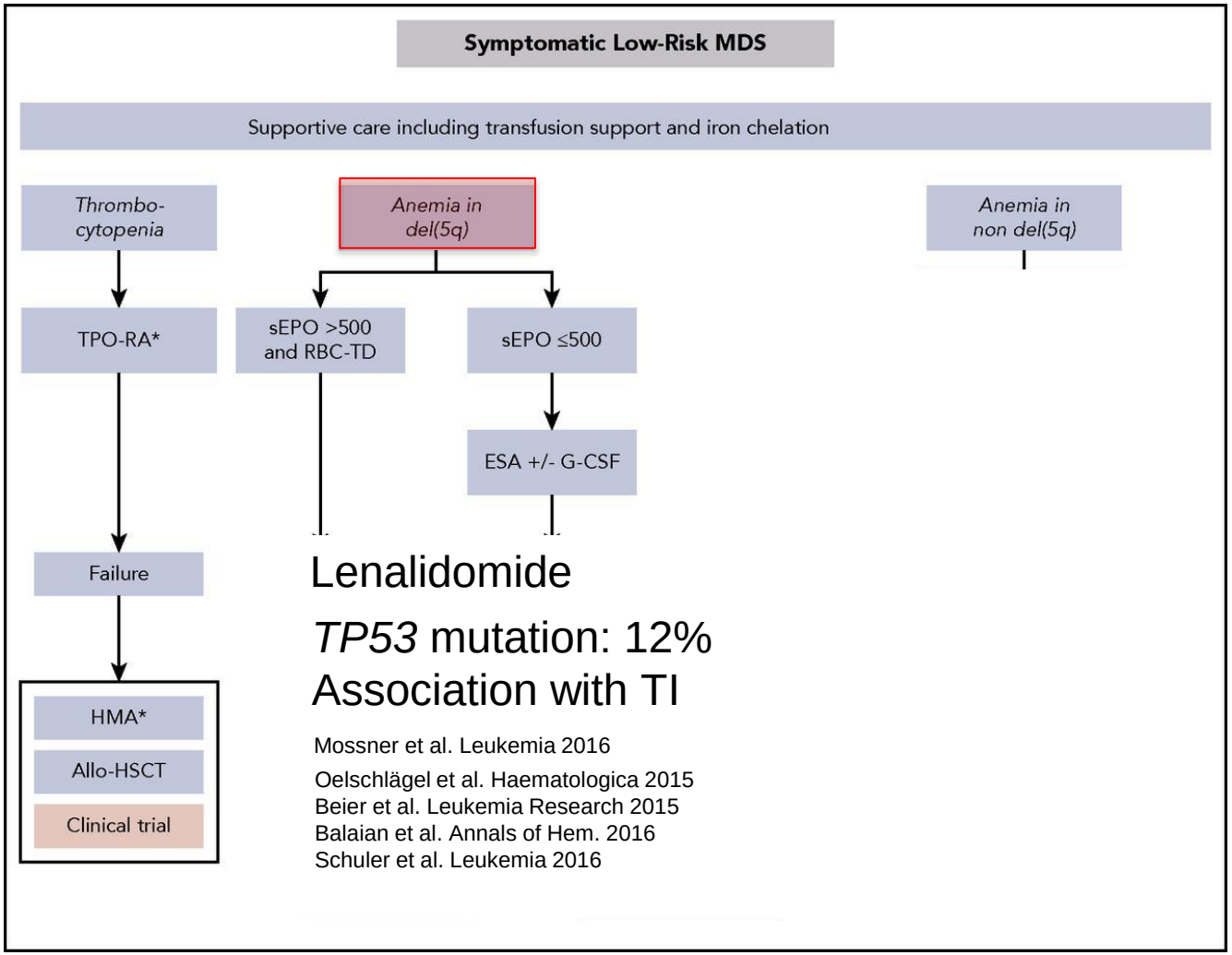
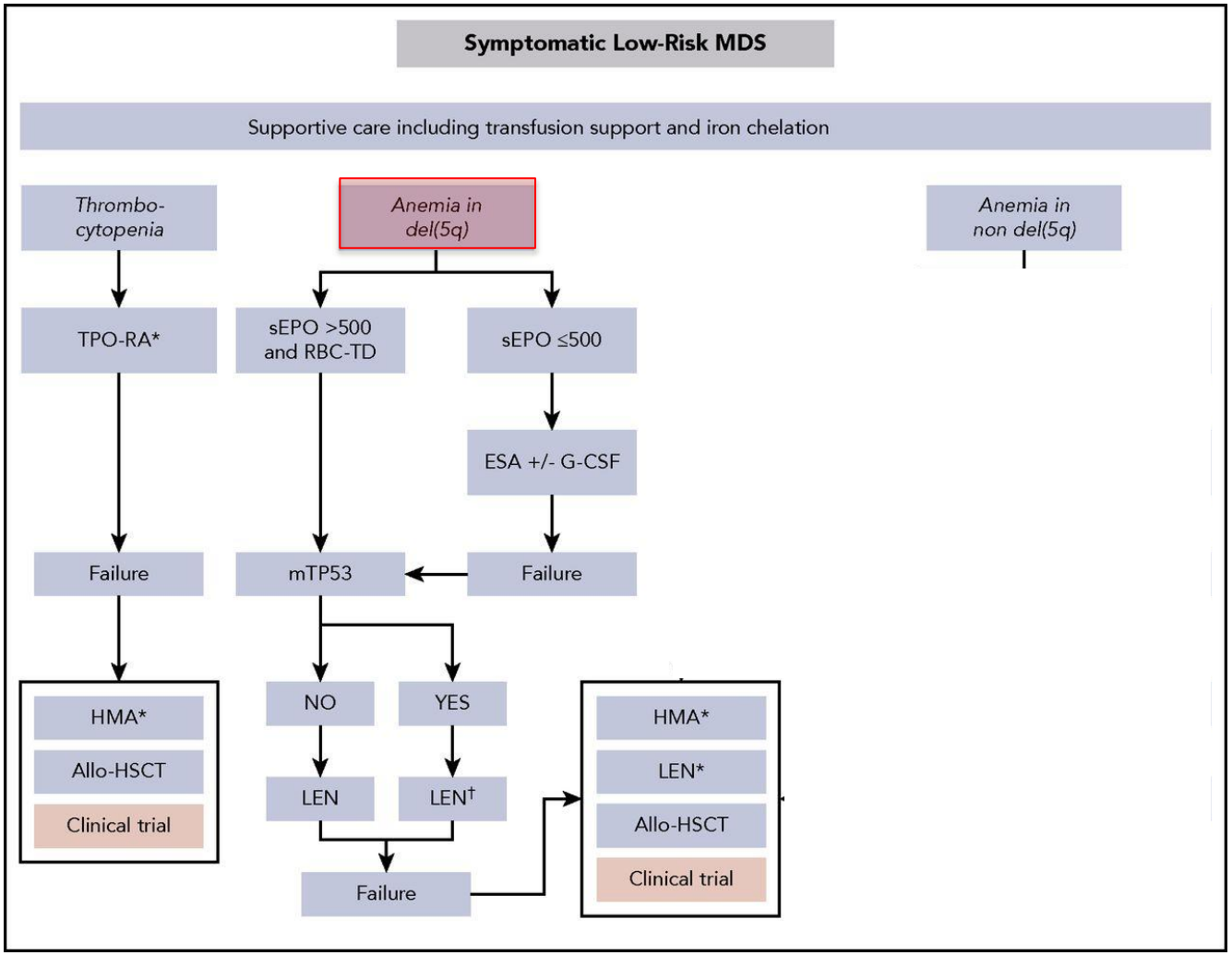
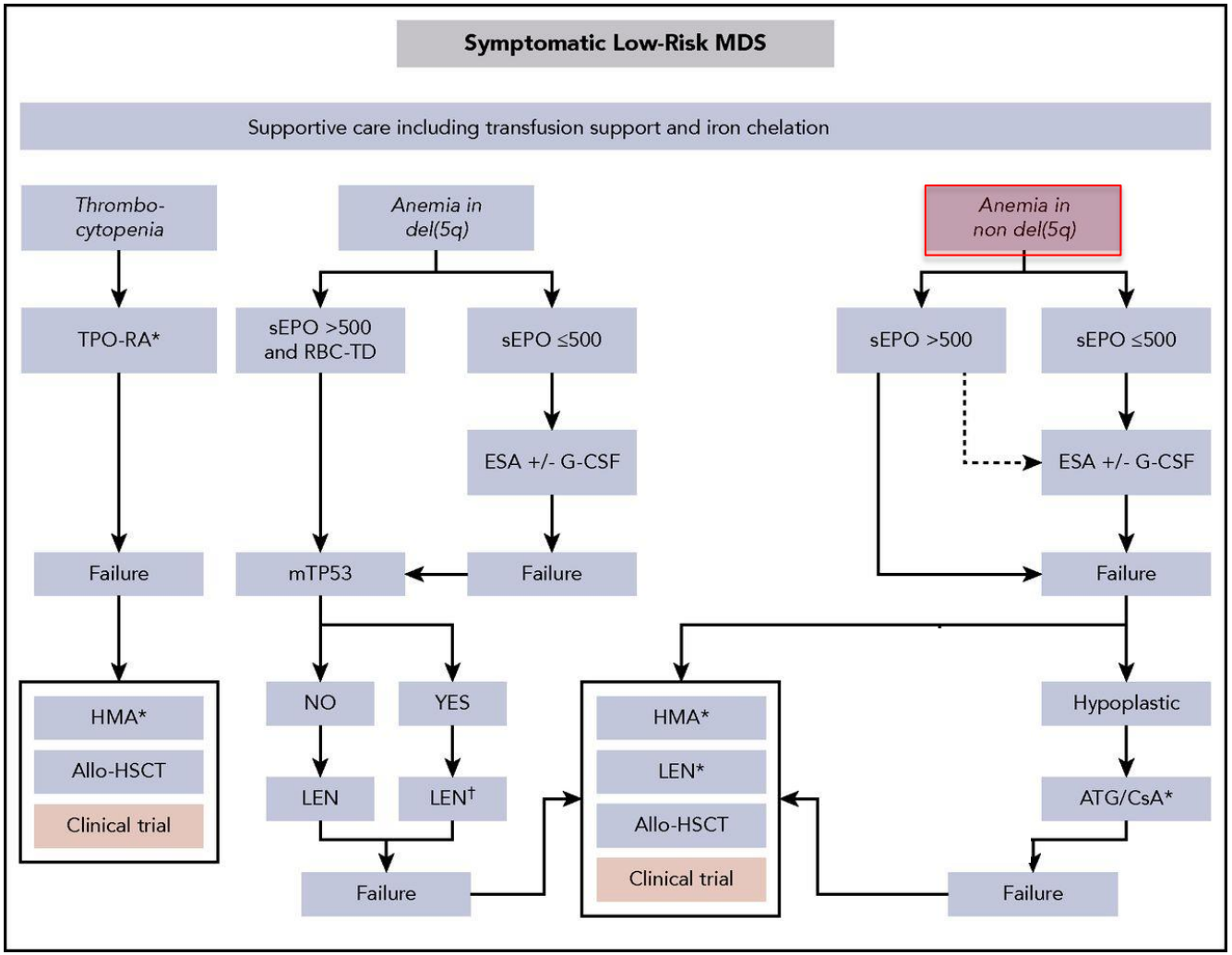


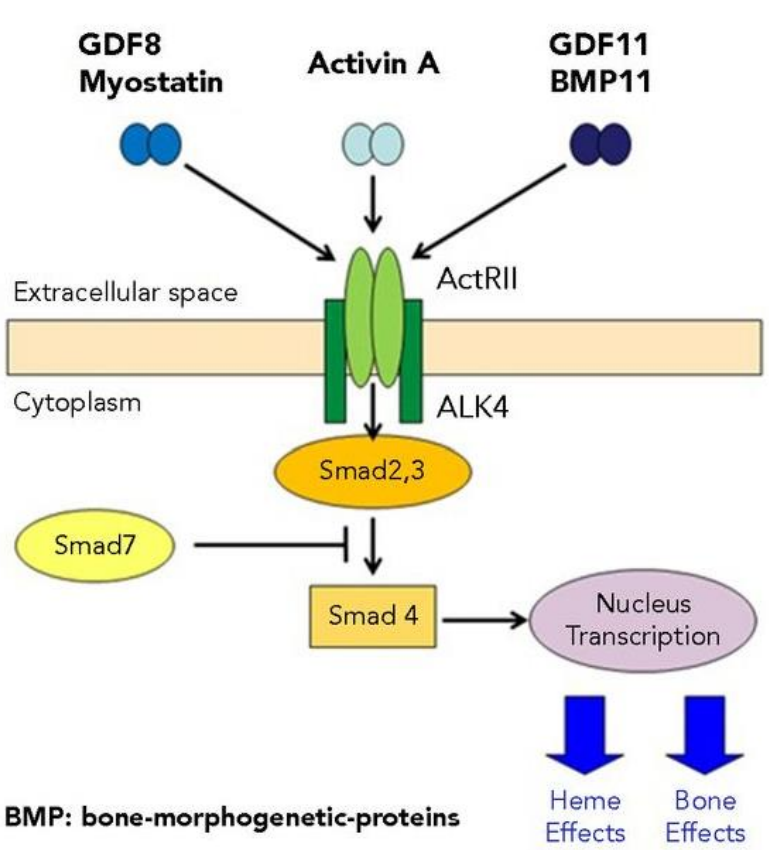
Therapeutic algorithm in LR-MDS patients

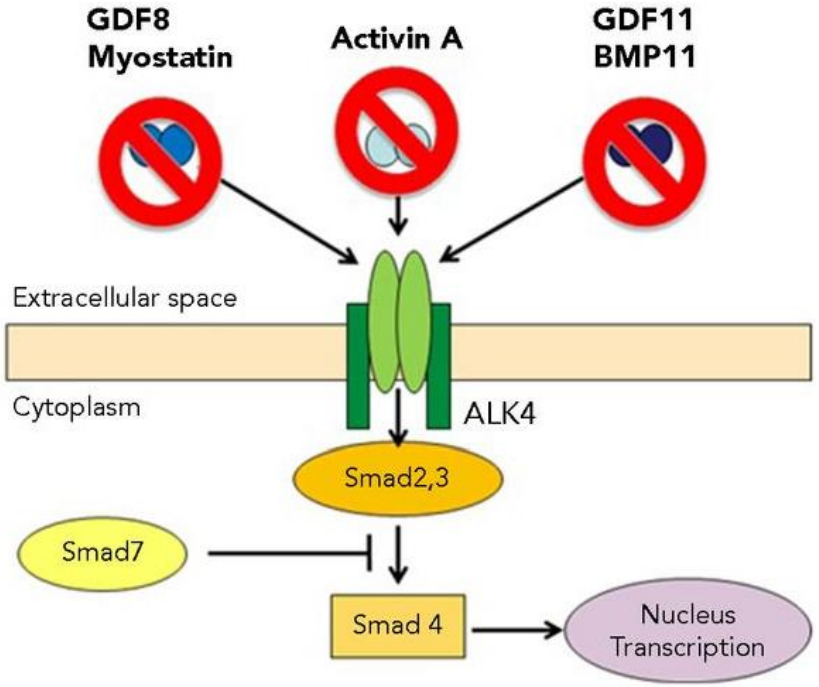


Therapeutic algorithm in LR-MDS patients

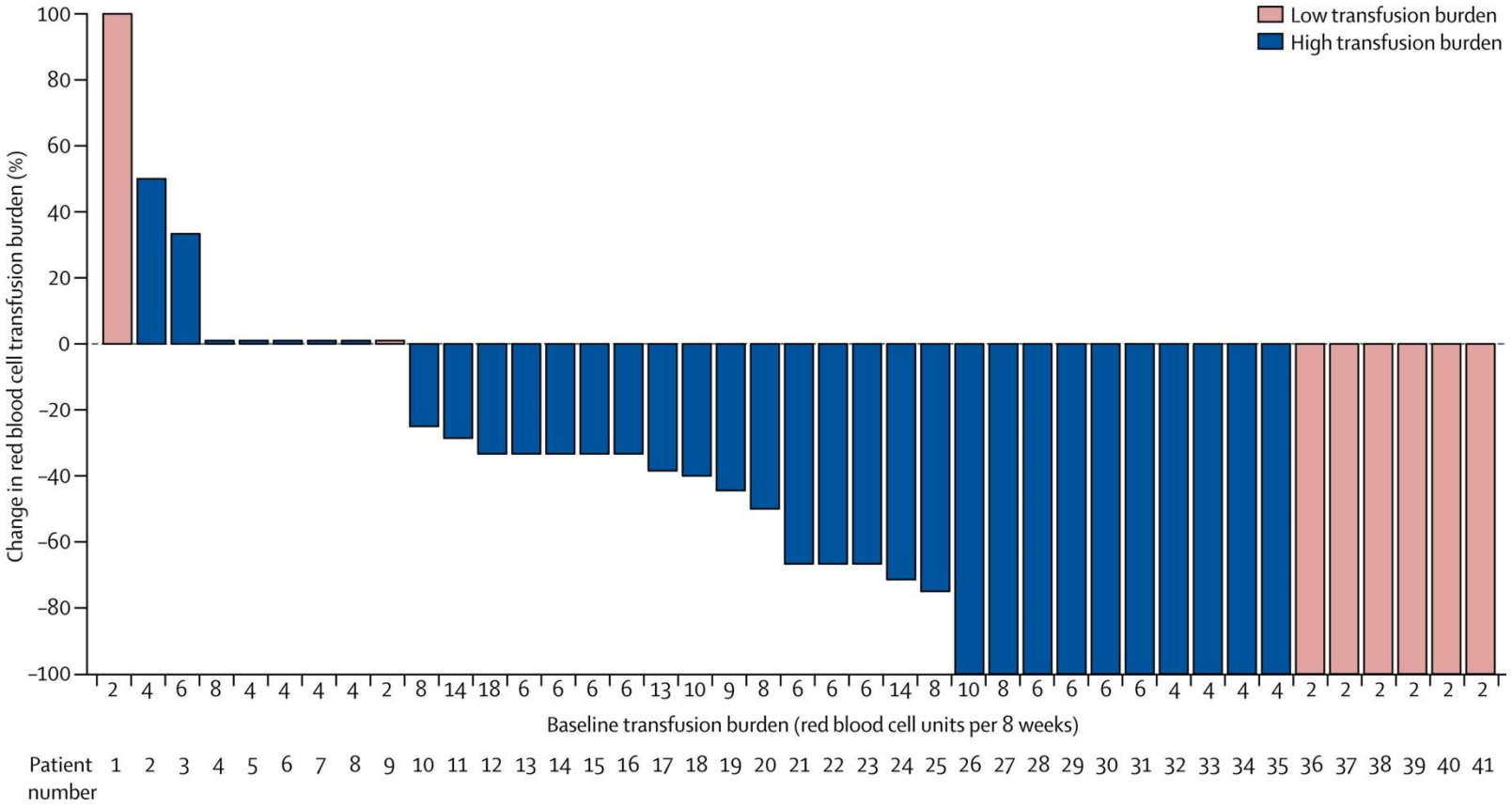


Luspatercept
a ligand trap





Luspatercept
Transfusions



Platzbecker et al. Lancet Oncology 2017

Erythroid Response with Luspatercept by Mutation

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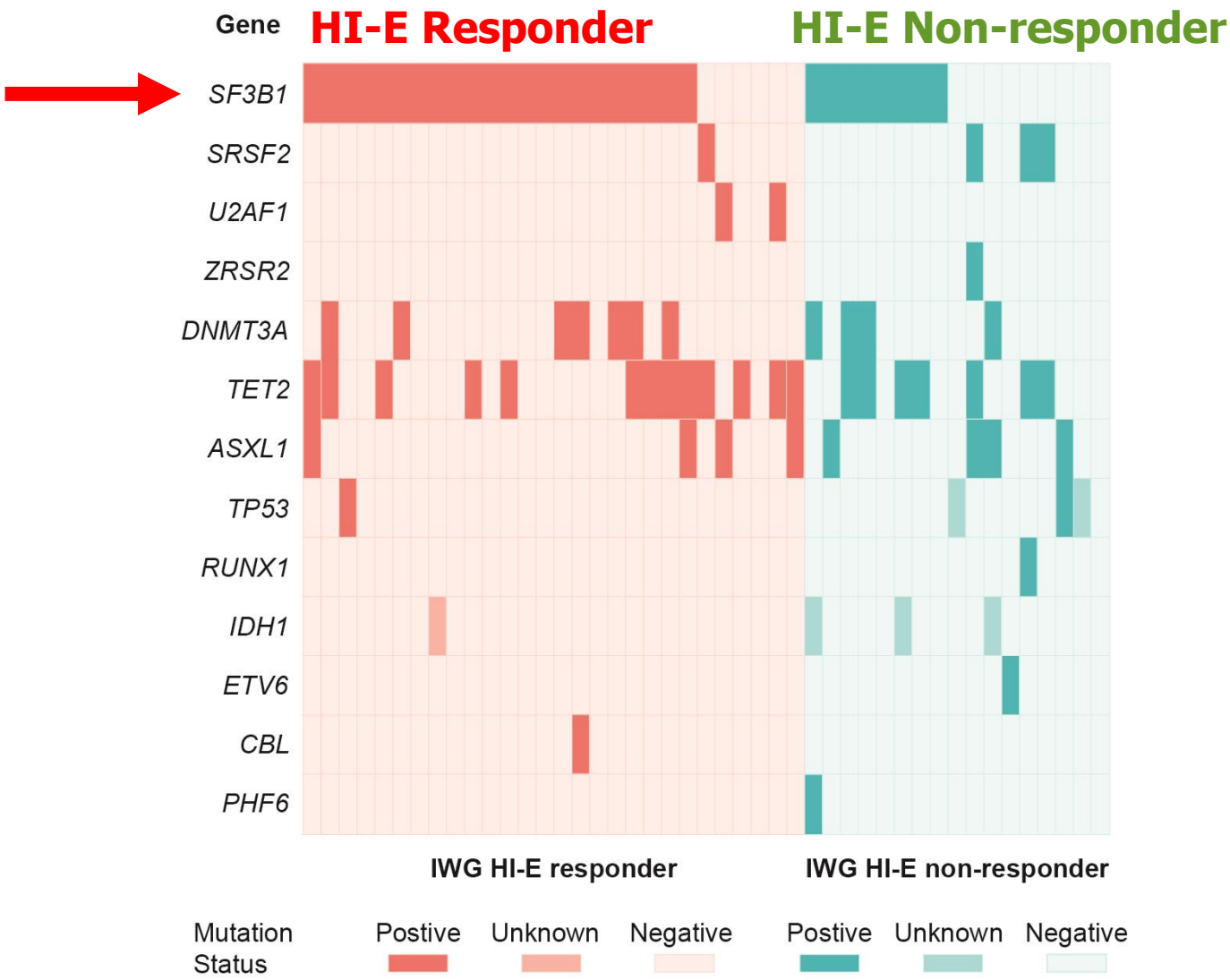

Response rate extended MDS cohort

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Response Rates	IWG-HI-E, n/N (%) (N=99)	RBC-TI, n/N (%) (N=67)
All patients	52/99 (52.5)	29/67 (43.3)
ESA-naïve	28/53 (52.8)	17/31 (54.8)
ESA-exposed	24/46 (52.2)	12/36 (33.3)
RS Status		
RS+	40/60 (66.7)	20/40 (50.0)
Non-RS	10/31 (32.3)	7/22 (31.8)
Unknown	2/8 (25.0)	2/5 (40.0)

MEDALIST Trial
Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

Patient Population

- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)

Randomize 2:1

Luspatercept 1.0 mg/kg (s.c.) every 21 days
n = 153

Dose titrated up to a maximum of 1.75 mg/kg

Placebo (s.c.) every 21 days
n = 76

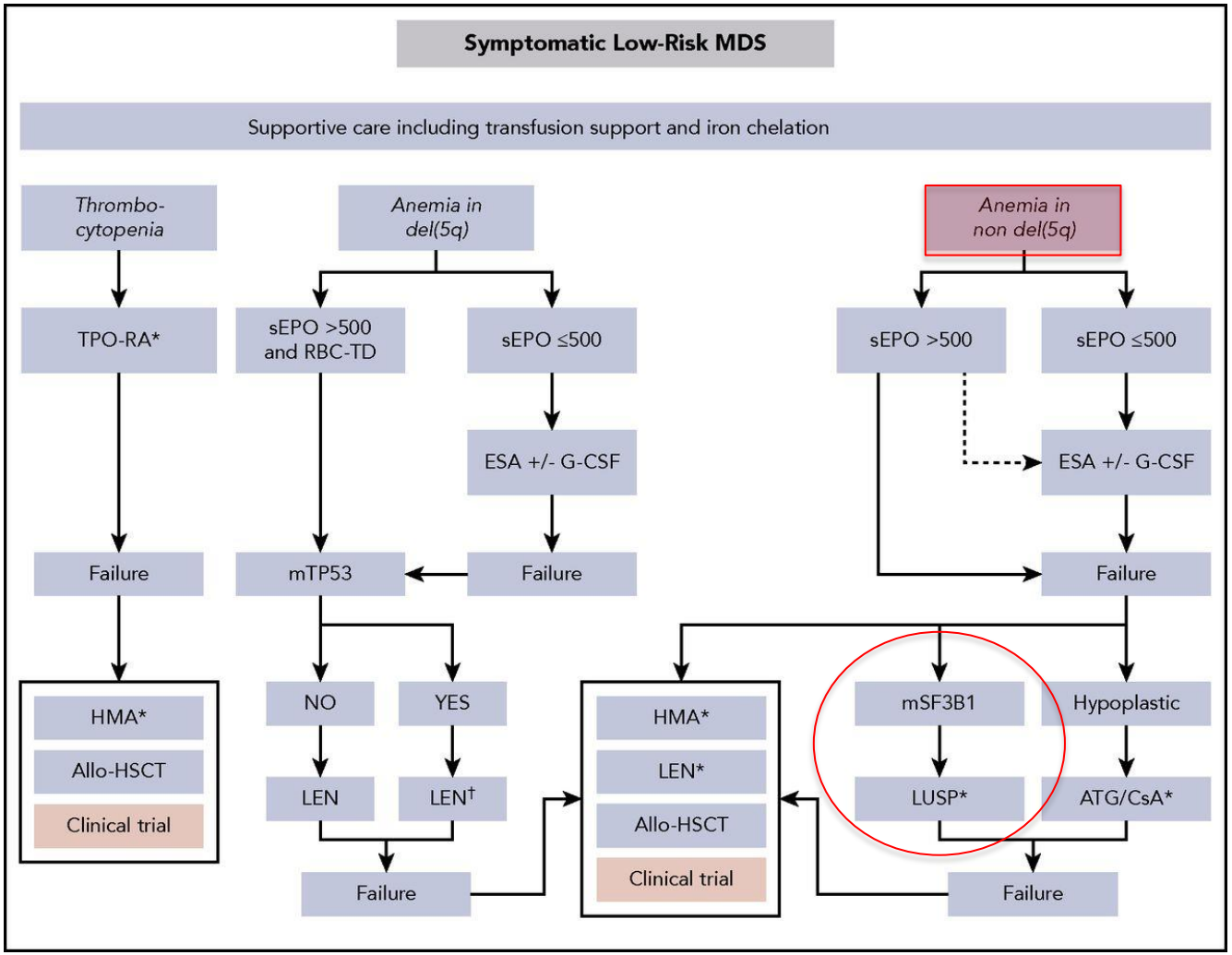
Data cutoff: May 8, 2018 Includes last subject randomized + 48 weeks.
EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

MEDALIST Trial
Primary Endpoint: Red Blood Cell Transfusion Independence ≥ 8 Weeks

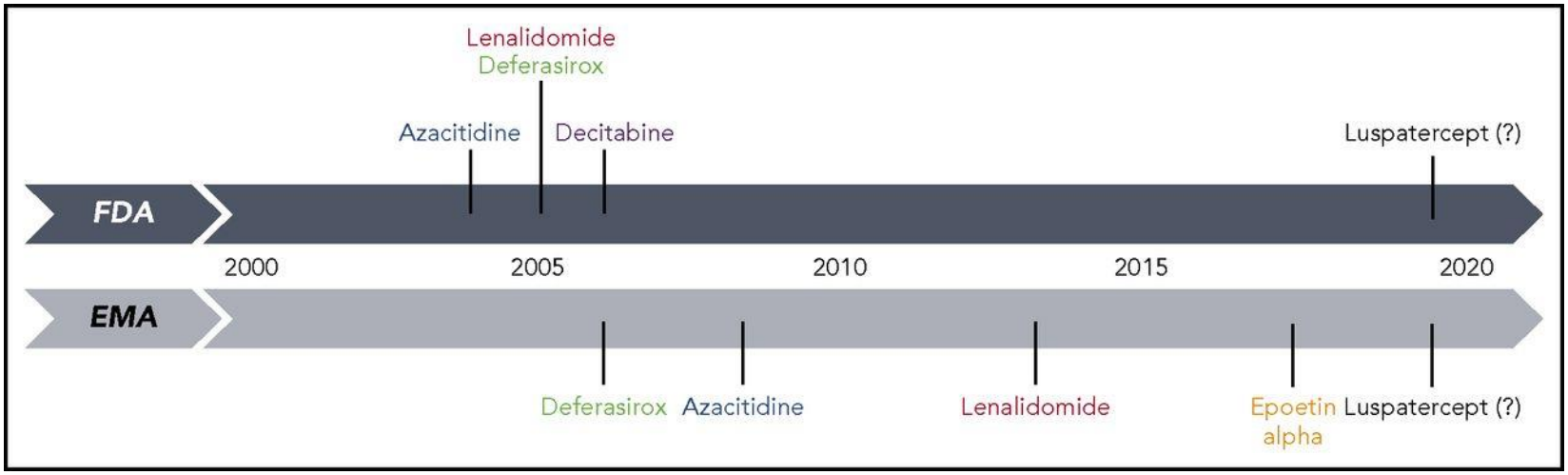
RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P value[a]	< 0.0001	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval.

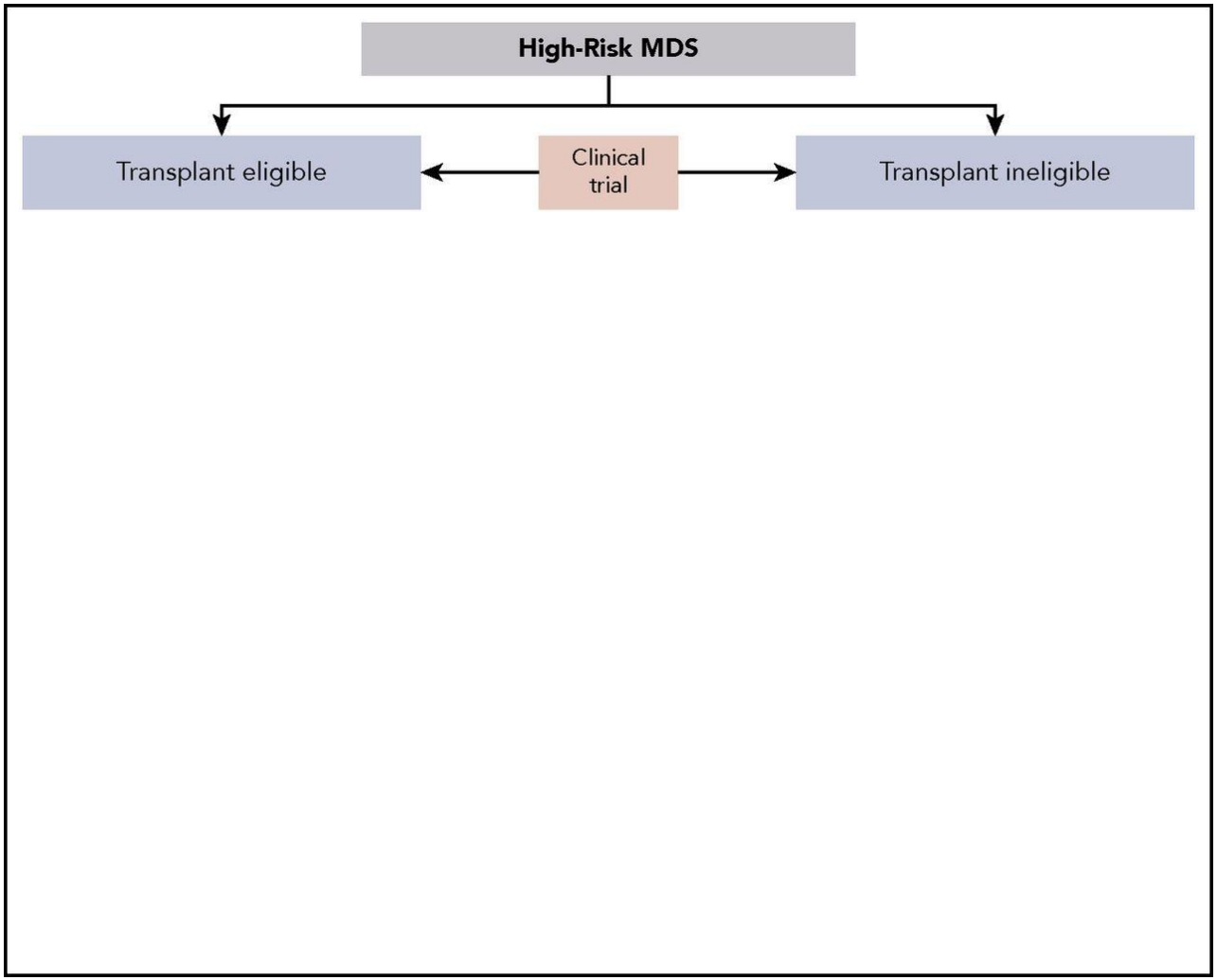
Therapeutic algorithm in LR-MDS patients.



America first – EU second?

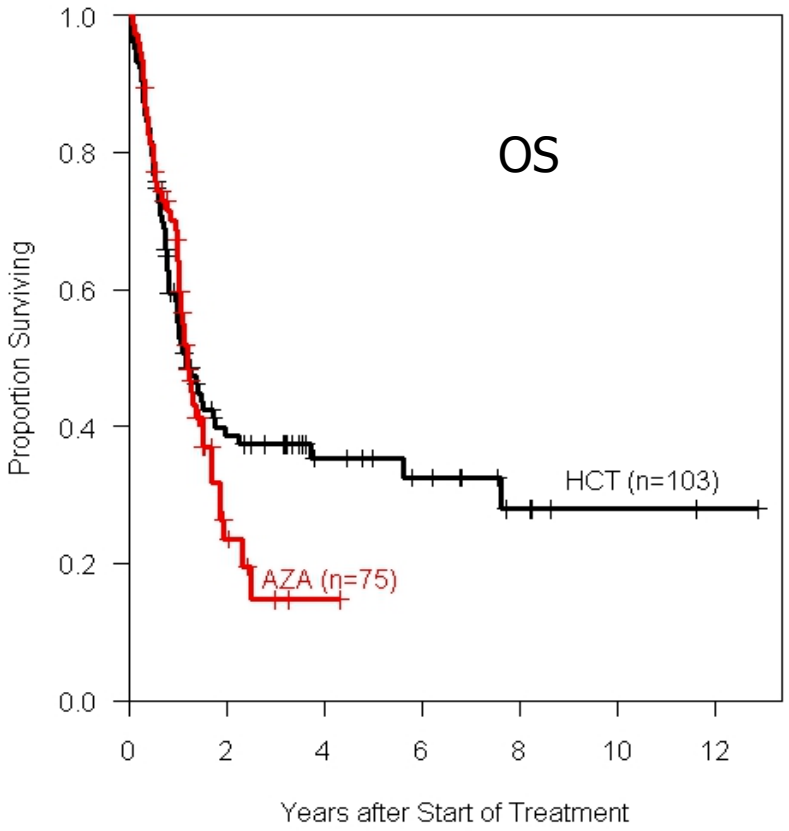


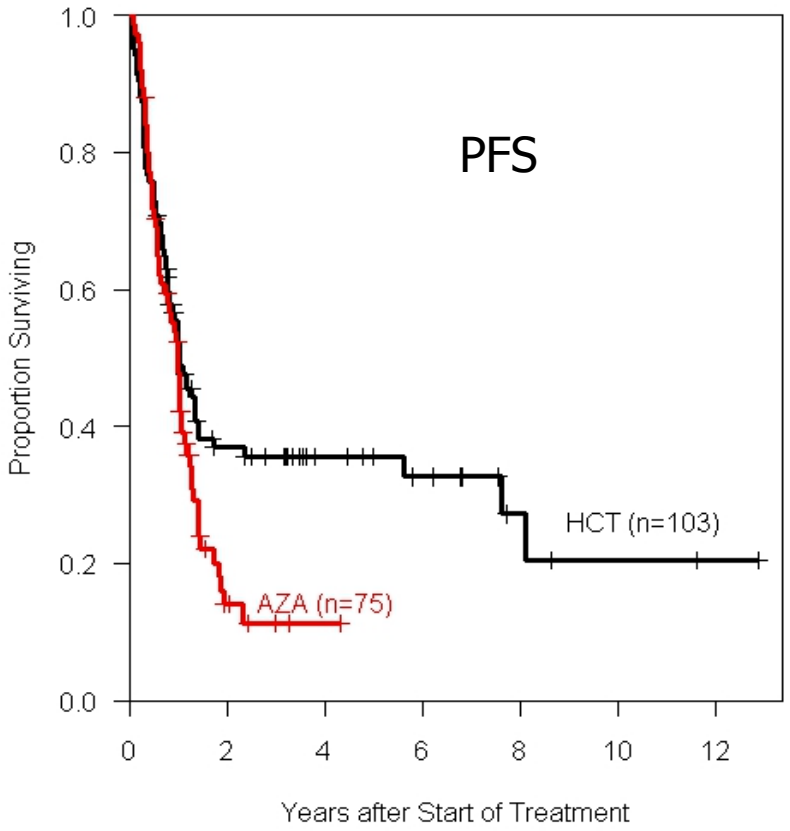
Therapeutic algorithm in HR-MDS patients



Allogeneic SCT vs. AZA in HR-MDS

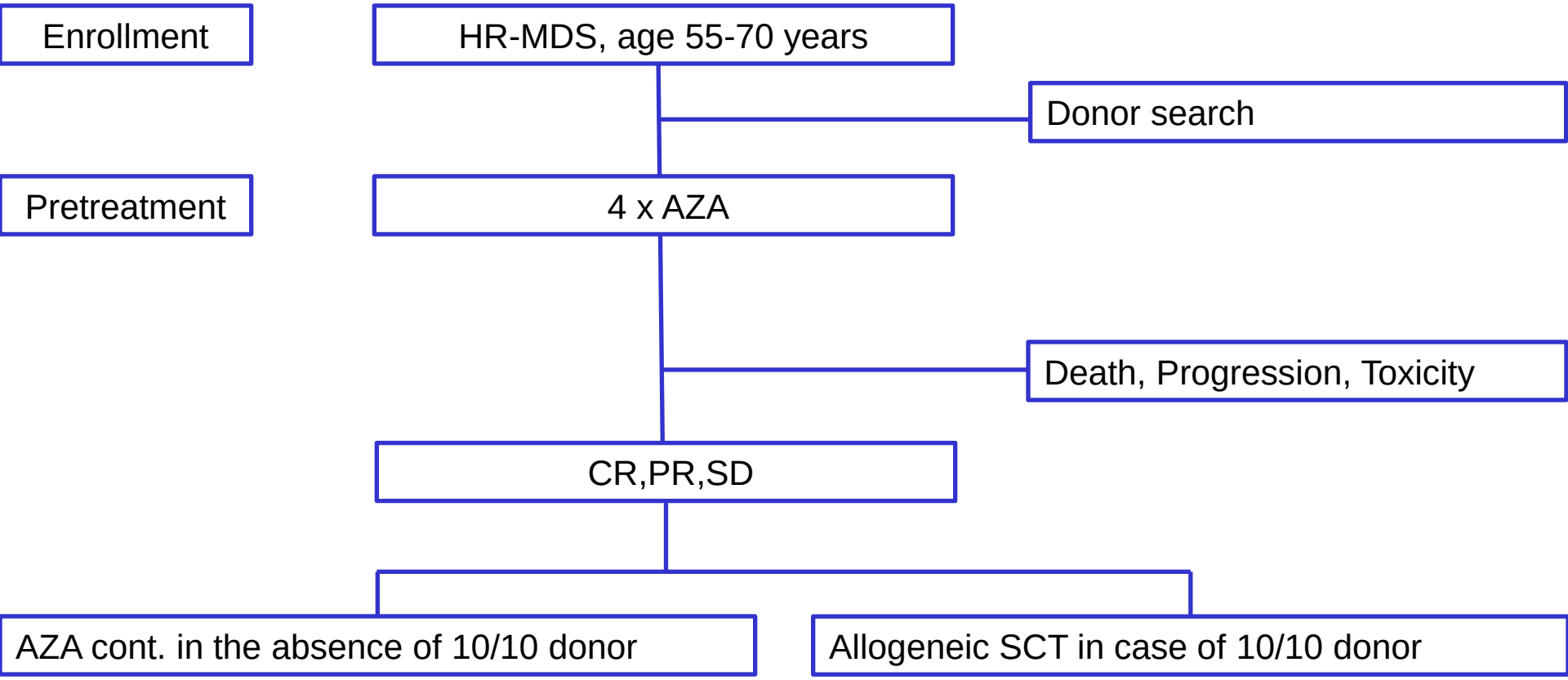
retrospective analysis age 60-70 years





Study Design

VIDAZALLO Trial



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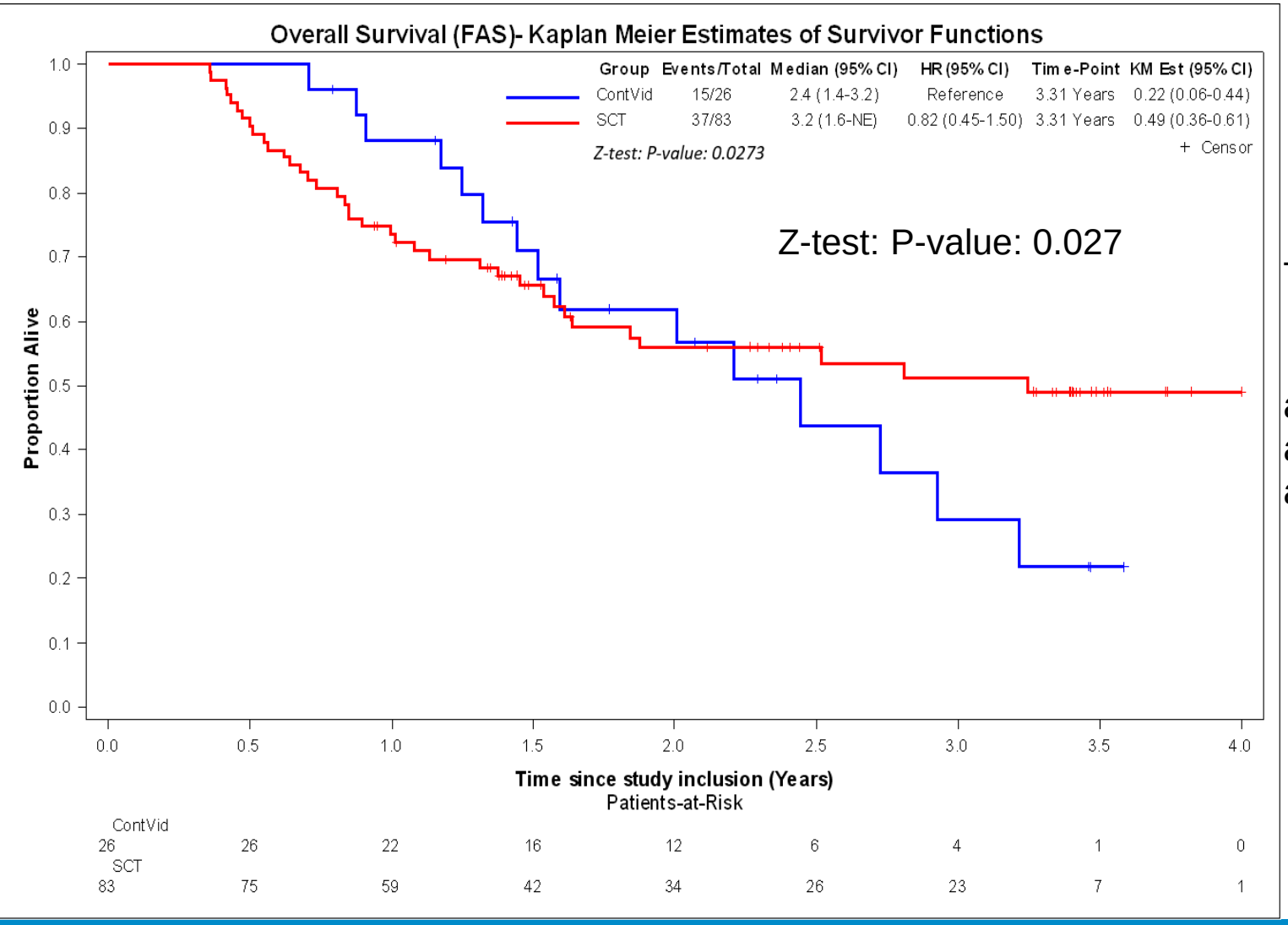
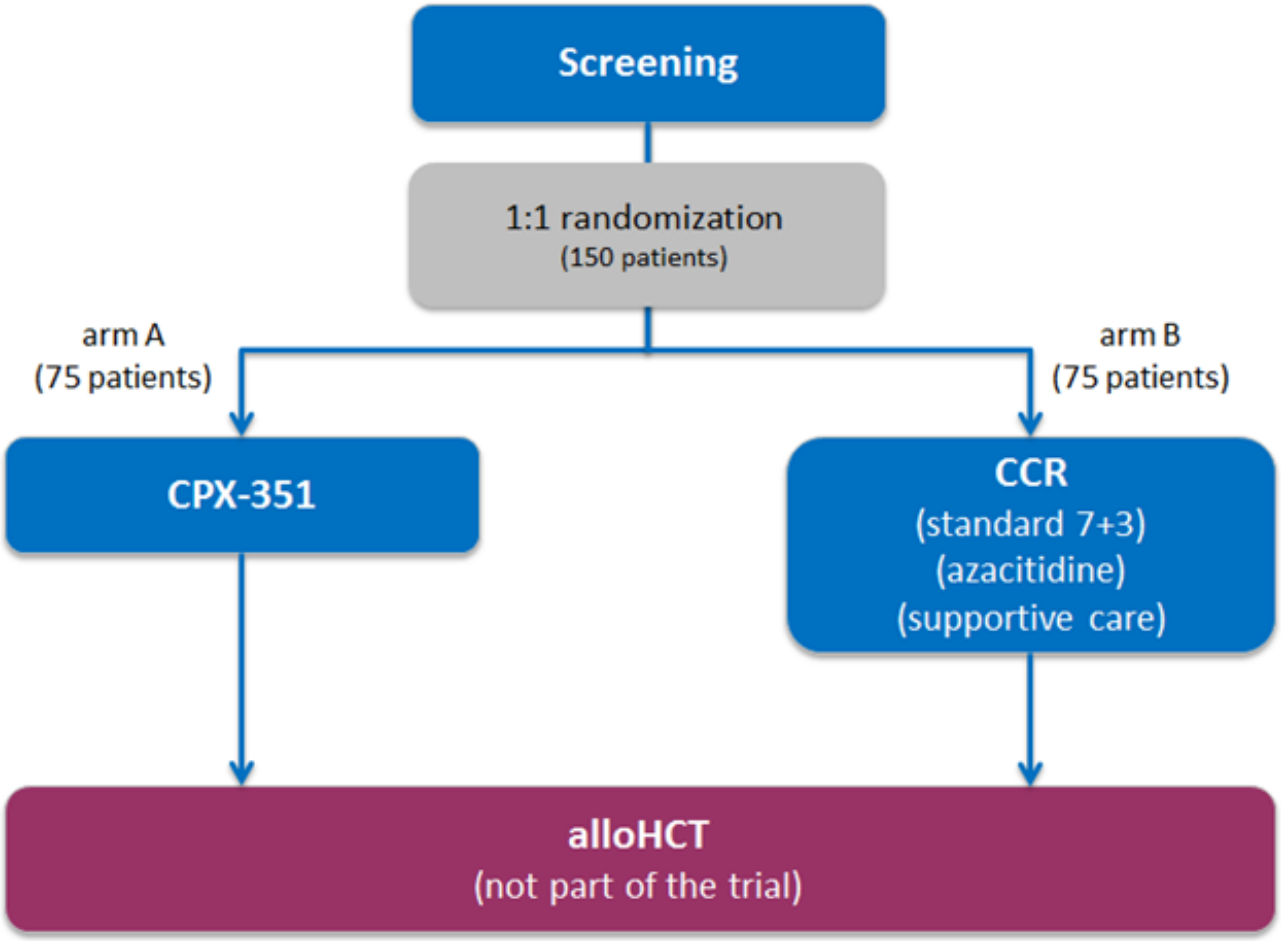
VidazaAllo Study: Overall Survival



The time dependent HR ratio for AHSCT decreased over time
at 1 year HR 1.4
at 2 years HR 0.35
at 3 years HR 0.09 .

PALOMA – trial design



PALOMA – sites

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Main IN:

- High risk MDS including oligoblastic non-proliferative (WBC <13 Gpt/l) AML
- BM blasts ≥ 5%
- IPSS score intermediate or high
- alloHCT intended within the next 6 months

Main OUT:

- AML with t(15;17), PML-RARA; AML with t(8;21), RUNX1-RUNX1T1, AML with inv(16)/t(16;16), CBFβ-MYH11; AML with biallelic CEBPA mutation; AML with mutated FLT3 or NPM1
- Prior treatment with either CPX-351, HMAs, cytarabine or IC for

Diese illustrative Abbildung wurde urheberrechtlichen Gründen entfernt.

TELESTO – study objectives

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Primary

To evaluate event-free survival (composite endpoint)

- Defined as the time from randomization to first documented non-fatal event (worsening cardiac function, hospitalization for congestive heart failure, liver function impairment, liver cirrhosis, transformation to AML), based on review and confirmation by an **independent adjudication committee**, or death, whichever occurred first

Primary endpoint EFS: Stratified log-rank test and Cox regression model

All patients*	Log-rank test			Cox model
	Event/N (%)	Median time to event (95% CI), days†	P value‡	HR (95% CI)§
Deferasirox	**62/149 (41.6)**	1440 (1167, 1559)	0.015	0.636 (0.42, 0.96)
Placebo	**37/76 (48.7)**	1091 (820, 1348)		

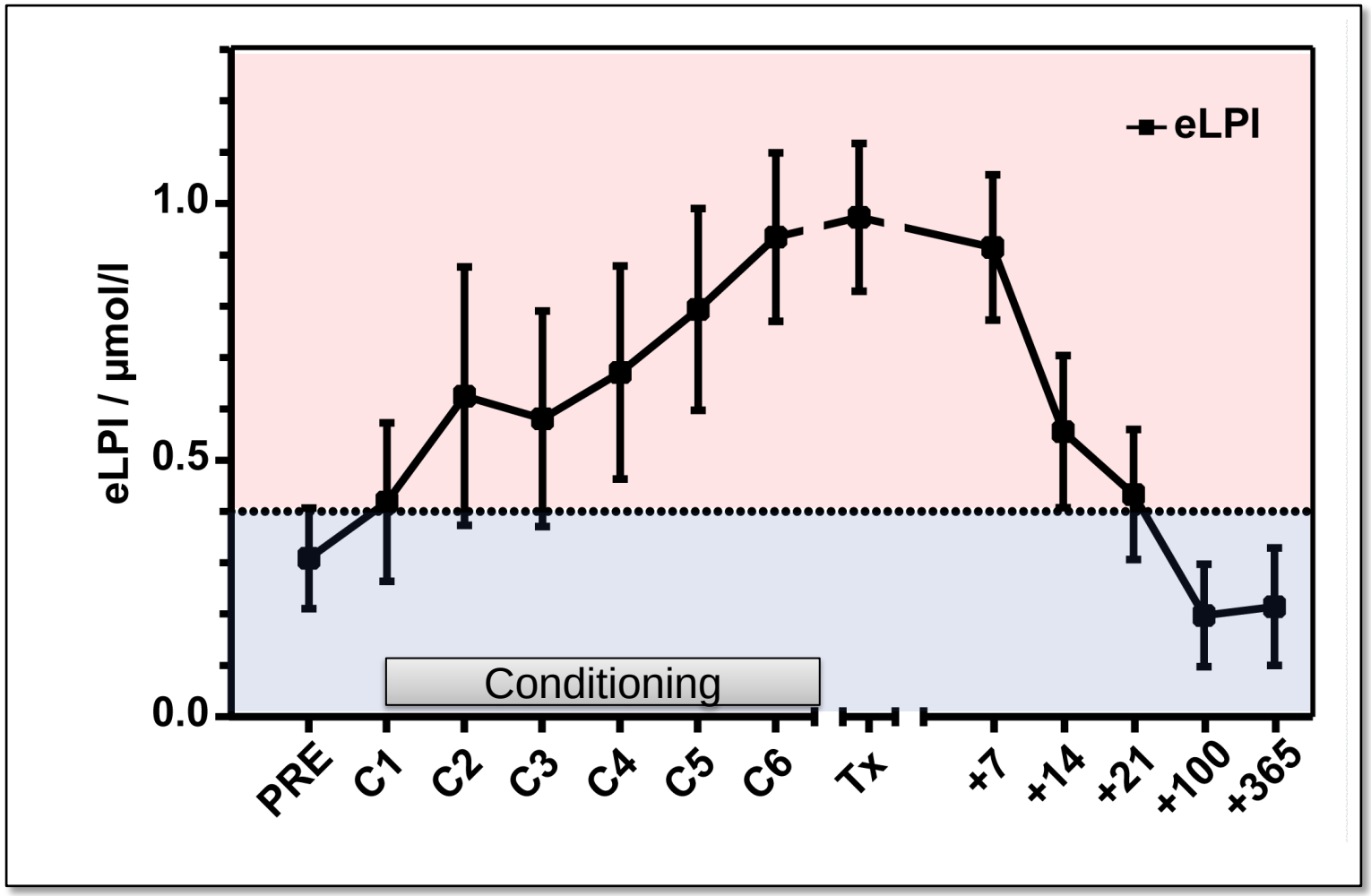
*Both the log-rank test and Cox proportional hazards model were stratified by stratification factors; †Median time to event and 95% CI generated by Kaplan–Meier estimation; ‡Exploratory *P* value is one tailed and based on the stratified log-rank test; §Based on a Wald test from the Cox model

A **36.4%** risk reduction in EFS was observed in the deferasirox arm compared with the placebo arm
(HR: 0.636; 95% CI: 0.42, 0.96; nominal *P*=0.015)

CI, confidence interval; HR, hazard ratio

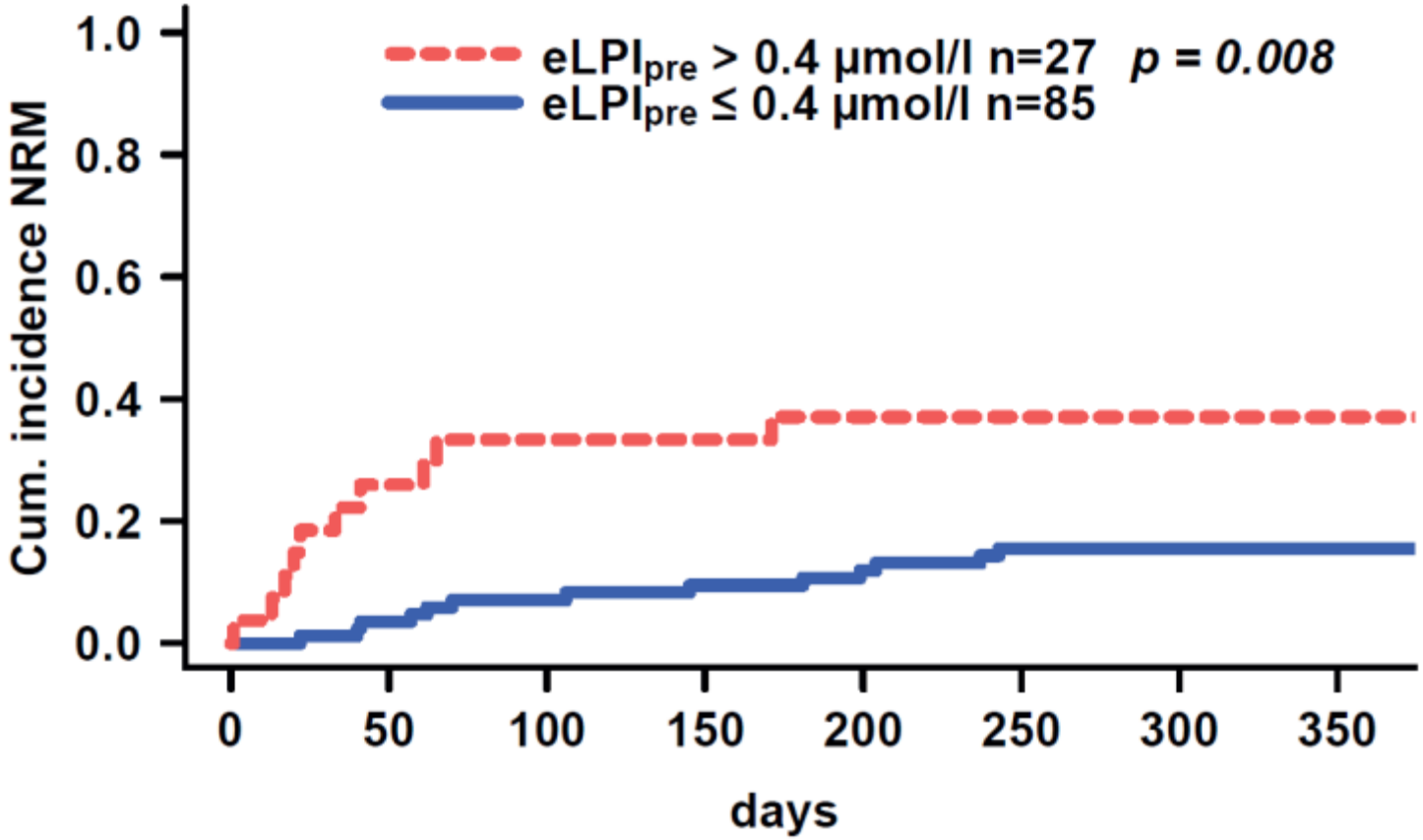
Iron (LPI) during conditioning

in MDS/AML

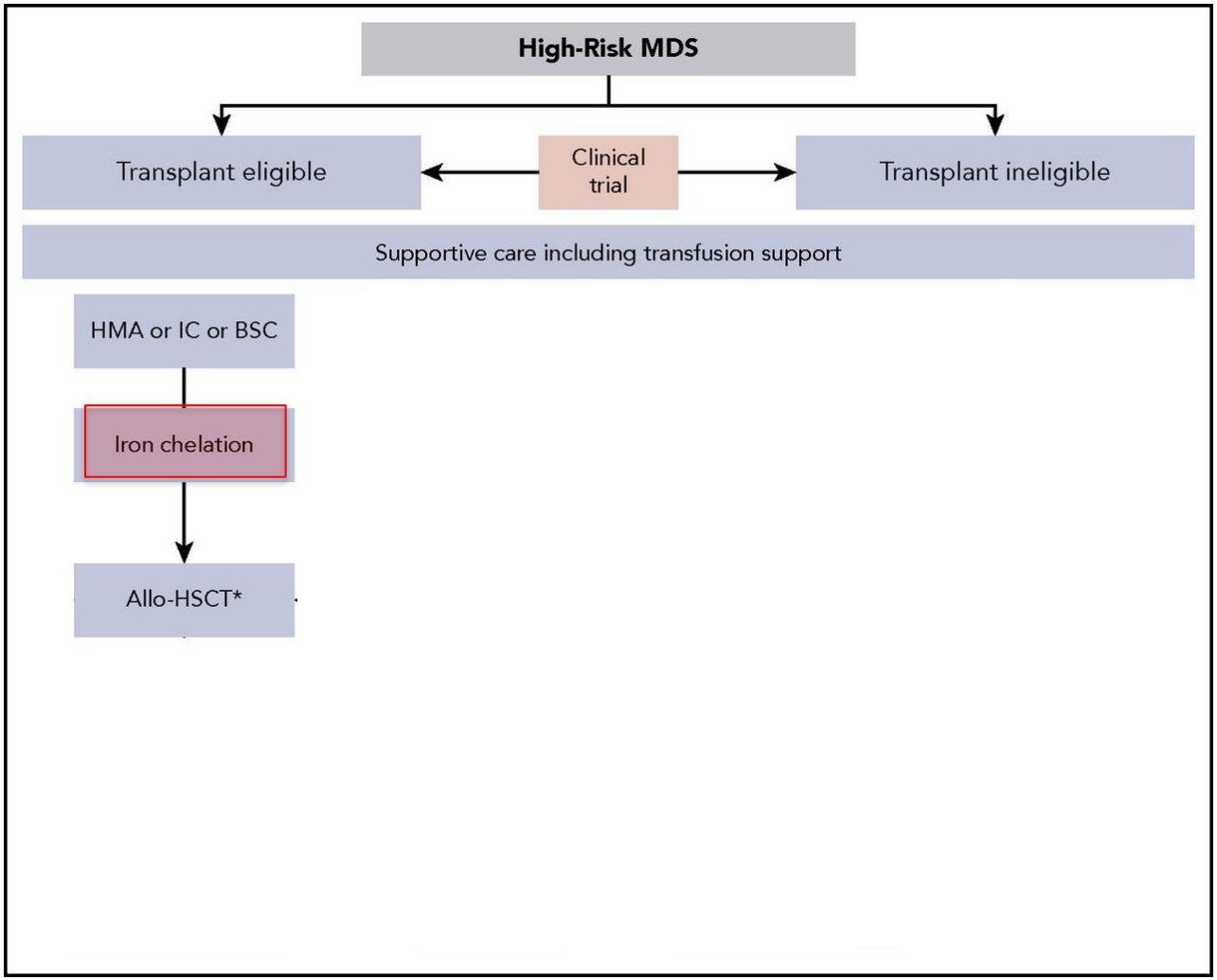


Wermke et al. Lancet Haematology 2018

Iron (LPI) and mortality after Tx

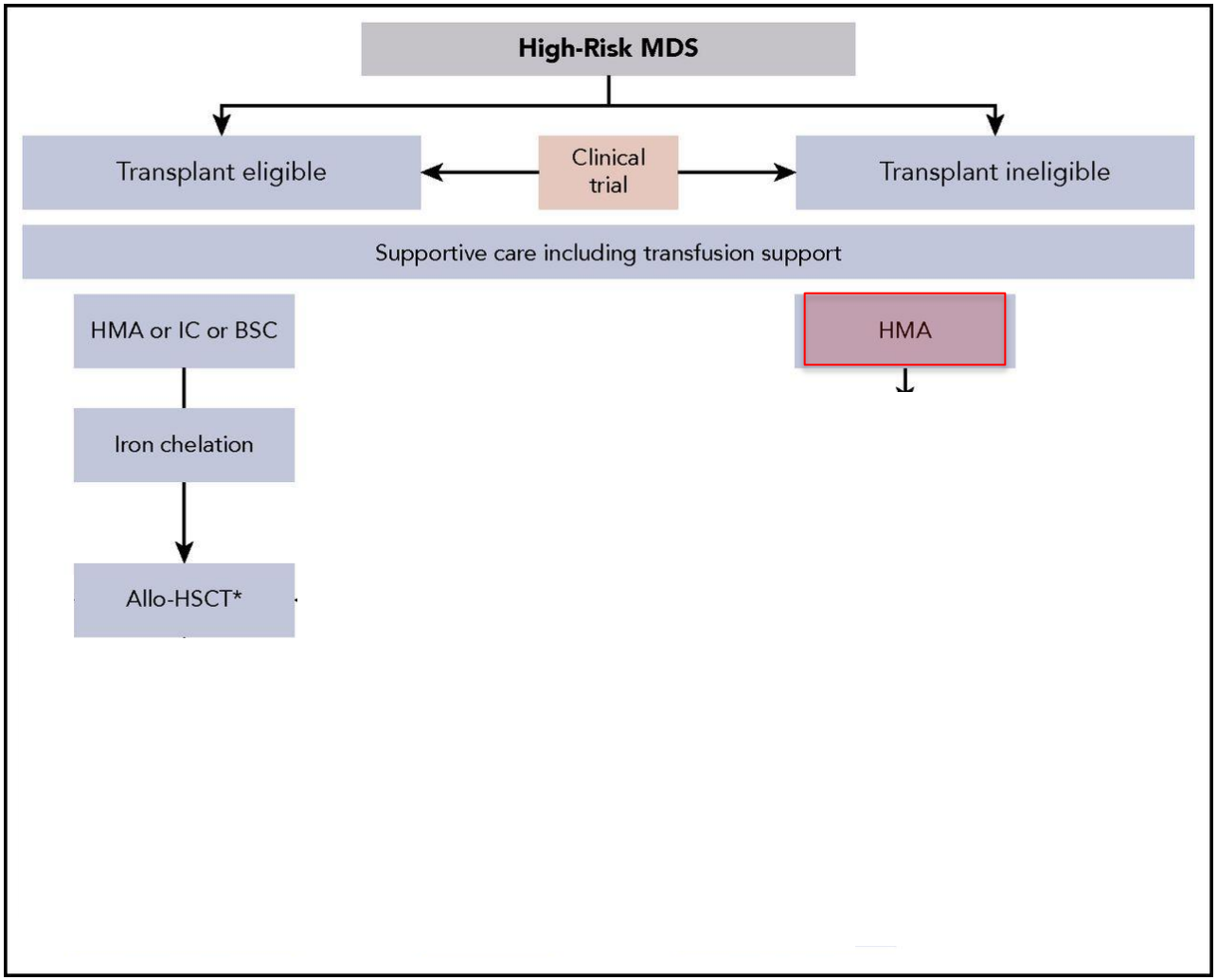


Therapeutic algorithm in HR-MDS patients



Blood 2019;133:1096-1107

Therapeutic algorithm in HR-MDS patients



HMA + VENETOCLAX > HMA

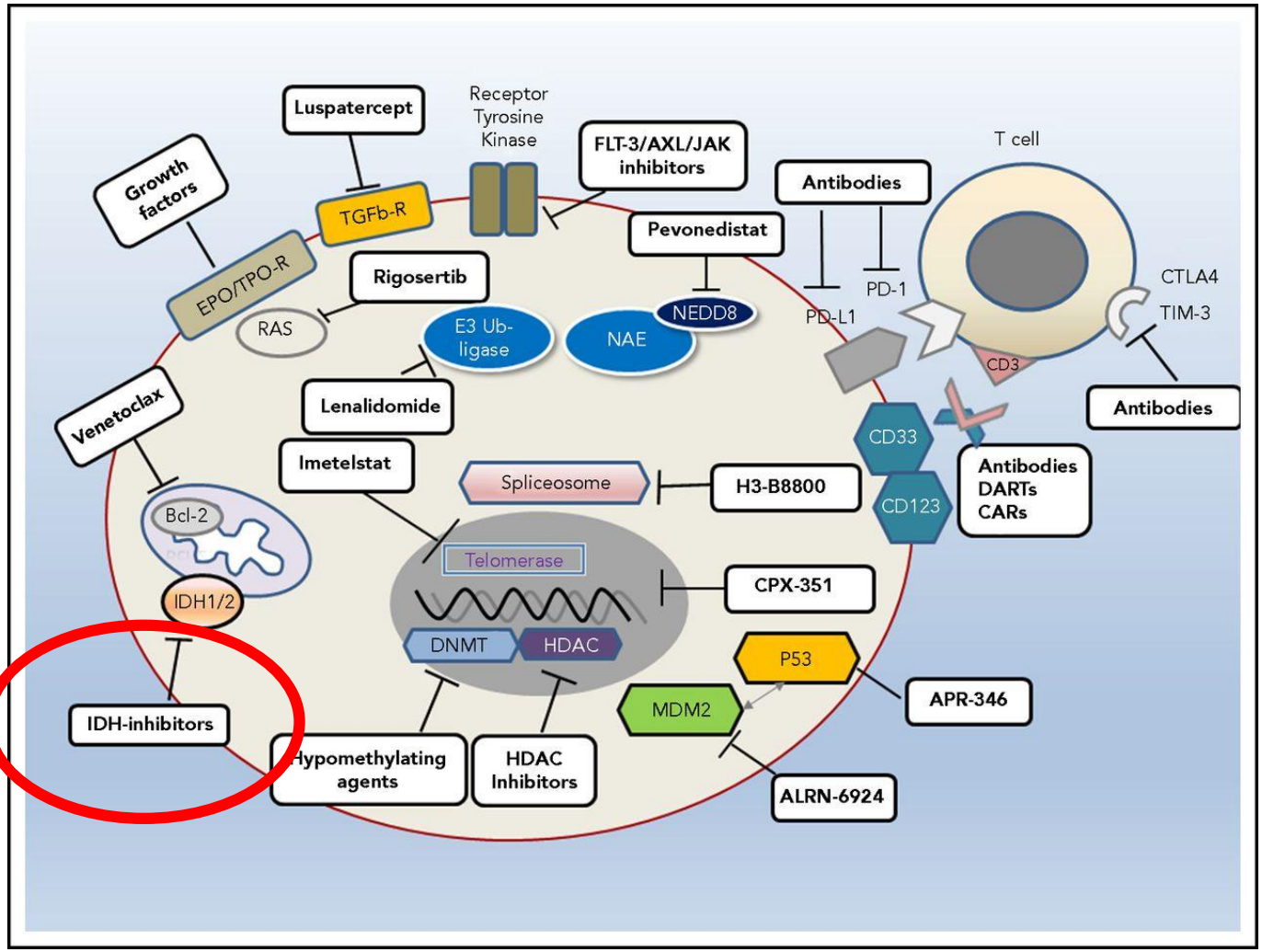
1st line elderly AML

DAC AZA

	Group A (n=23)	Group B (n=22)
Complete remission	8 (35%)	6 (27%)
CRi	6 (26%)	7 (32%)
Partial remission	1 (4%)	0
MLFS*	2 (9%)	5 (23%)
Resistant disease	3 (13%)	2 (9%)
Non-evaluable†	3 (13%)	2 (9%)
Complete remission and CRi	14 (61%)	13 (59%)
Overall response‡	15 (65%)	13 (59%)
Overall outcome§	17 (74%)	18 (82%)

DiNardo et al. Lancet Oncology 2018

Different therapeutic avenues in current clinical practice or ongoing clinical trials



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IDEAL

A single-arm Phase II Multicenter Study of IDH2 (AG 221) Inhibitor in Patients with IDH2 Mutated Myelodysplastic Syndrome

IDEAL – trial design

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Screening

Cohort A

HR MDS relapsed / refractory after at least 6 cycles of AZA

n = 29

Cohort B

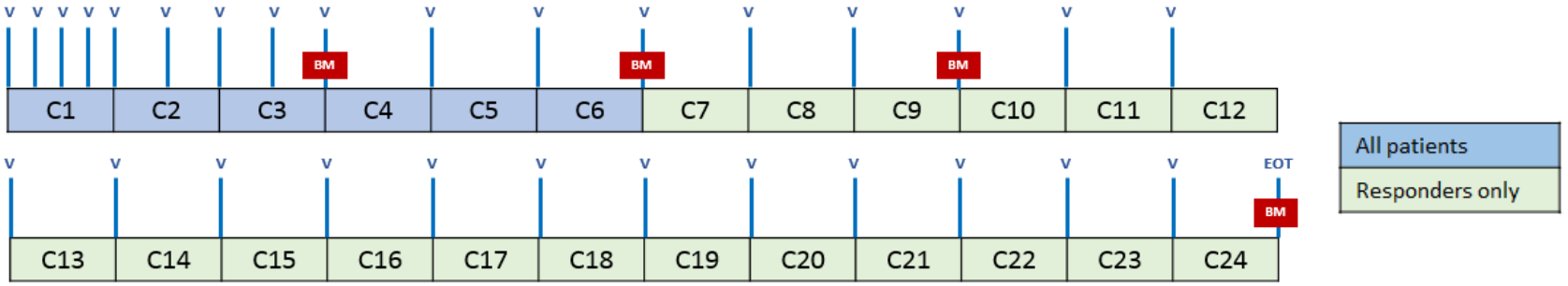
Untreated HR MDS without life threatening cytopenias

n = 29

Cohort C

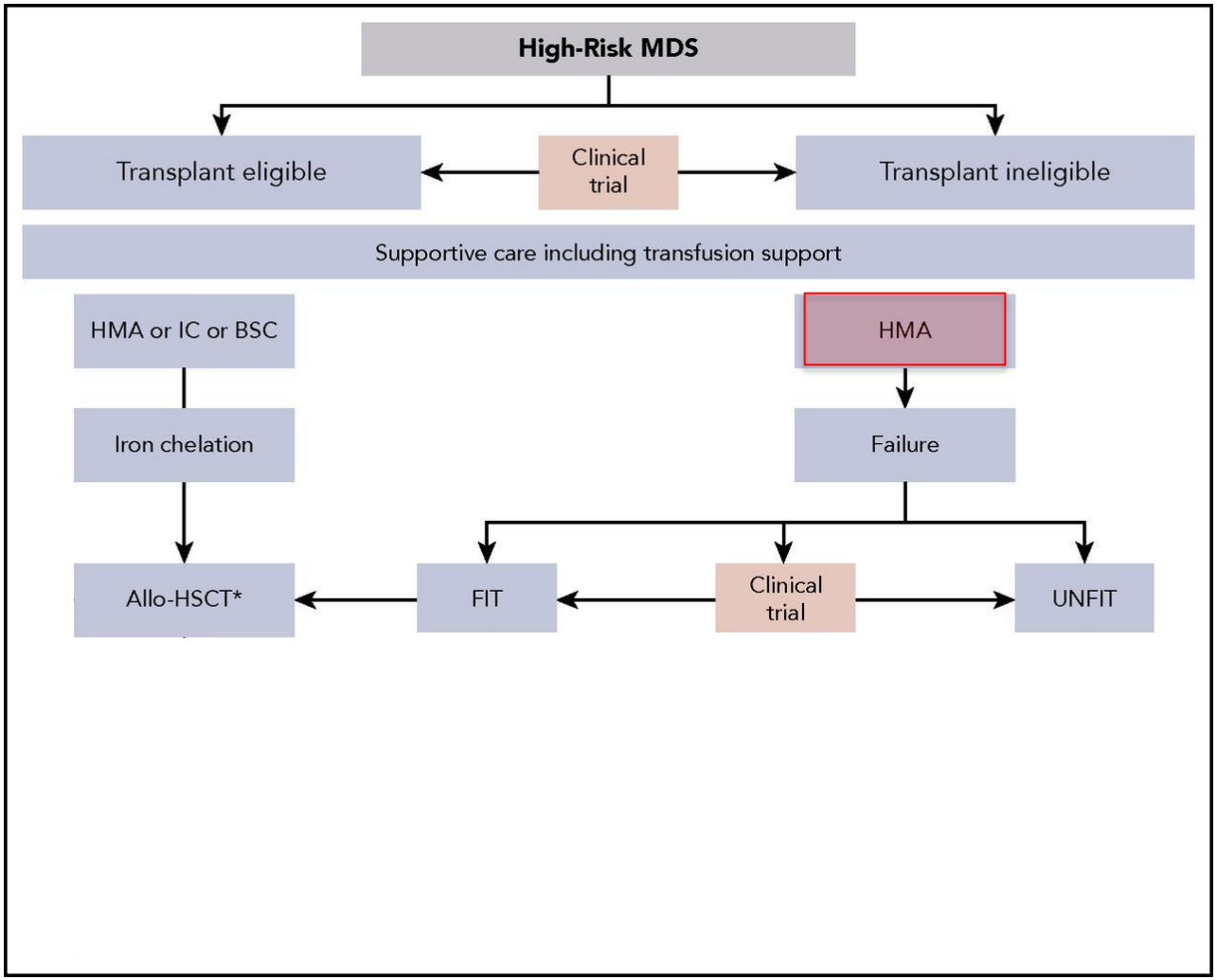
LR MDS with anemia resistant to ESAs

n = 10

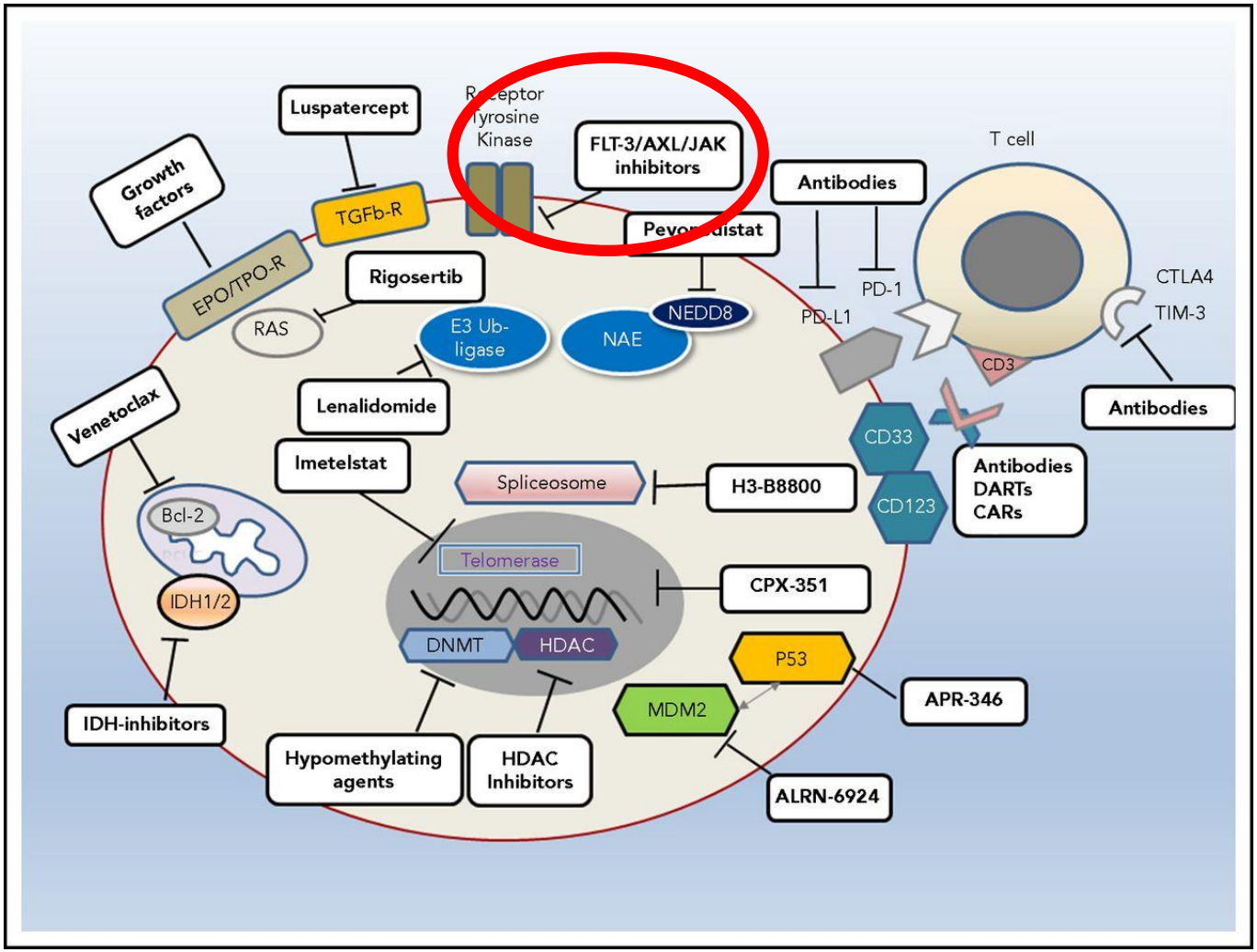


Primary EP: **Overall hematological response at 3 and 6 months** (including CR, PR, stable disease with HI according to IWG 2006) for **cohort A and B**. **Safety** for **cohort C**.

Therapeutic algorithm in HR-MDS patients



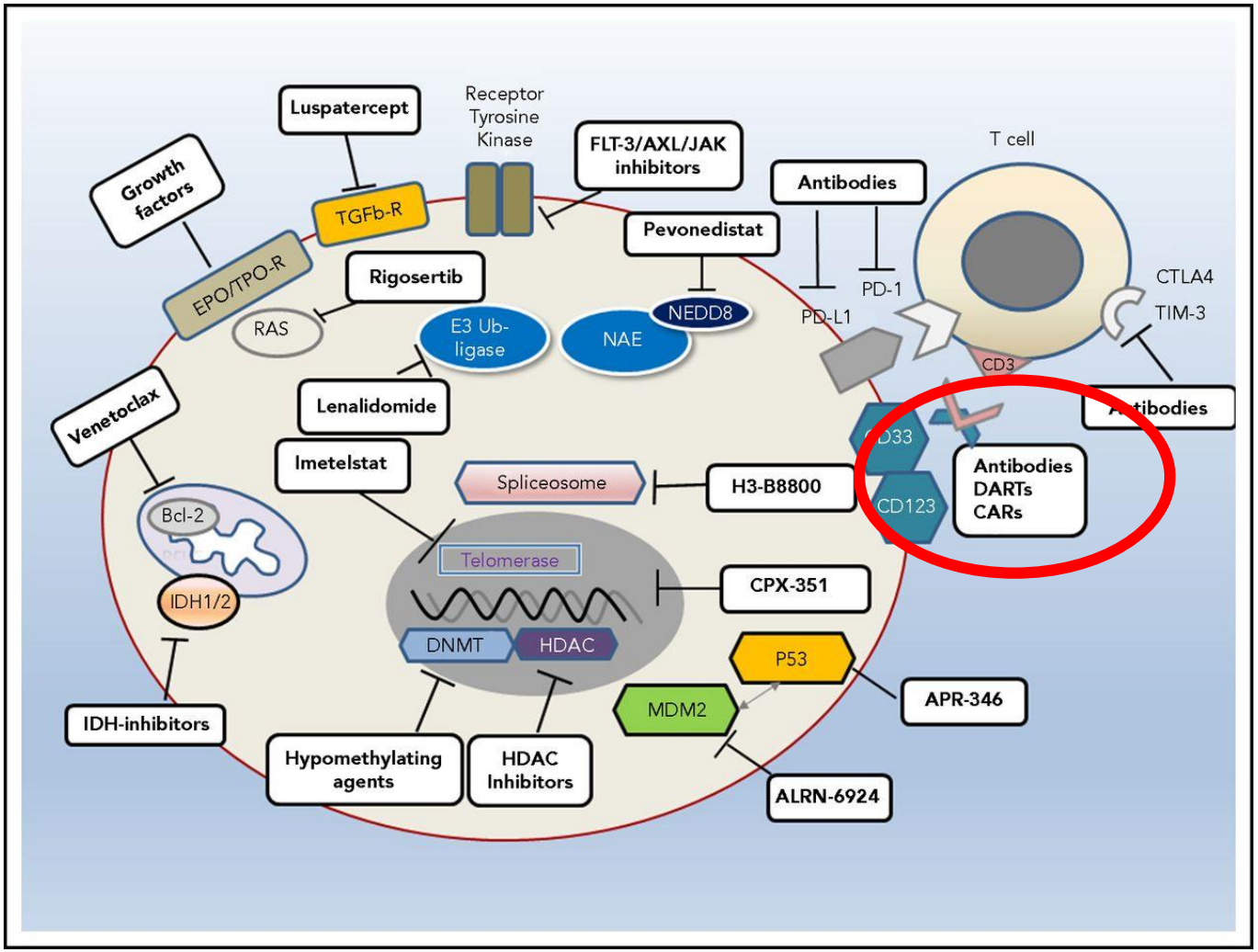
Different therapeutic avenues in current clinical practice or ongoing clinical trials



BERGAMO

A Phase II Study Evaluating the Efficacy and Safety of Bemcentinib in Patients With Myelodysplastic Syndromes Failing Standard of Care Therapy

Different therapeutic avenues in current clinical practice or ongoing clinical trials



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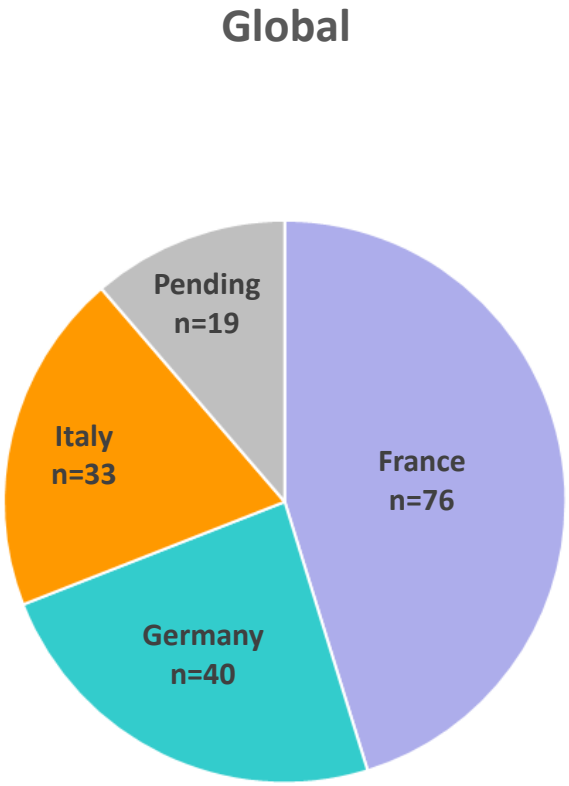
SAMBA

SINGLE AGENT TALACOTUZUMAB (JNJ-56022473) IN MDS AND AML PATIENTS FAILING HYPOMETHYLATING AGENT BASED THERAPY

DACOTA

A Randomized Phase III Study of Decitabine (DAC) With or Without Hydroxyurea (HY) Versus HY in Patients With Advanced Proliferative Chronic Myelomonocytic Leukemia (CMML)

DACOTA – recruitment



Response Criteria in MDS

blood®
Special Report
EMSCO MYELODYSPLASTIC SYNDROMES

Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials

U. Platzbecker,[1-3,*] P. Fenaux,[3-5,*] L. Adès,[3-5] A. Giagounidis,[3,6] V. Santini,[3,7] A. A. van de Loosdrecht,[3,8] D. Bowen,[9] T. de Witte,[10] G. Garcia-Manero,[11] E. Hellström-Lindberg,[12] U. Germing,[3,13] R. Stauder,[14] L. Malcovati,[15] M. Sekeres,[16] D. P. Steensma,[17] and S. Gloaguen[3]

[1]Medical Clinic and [2]Policlinic 1, Hematology and Cellular Therapy, Leipzig University Hospital, Leipzig, Germany; [3]European Myelodysplastic Syndromes Cooperative Group (EMSCO Group; www.emsco.eu); [4]Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Paris, France; [5]Université Paris 7, Paris, France; [6]Klinik für Onkologie, Hämatologie und Palliativmedizin, Marien Hospital, Düsseldorf, Germany; [7]Azienda Ospedaliero Universitaria (AOU) Careggi, University of Florence, Florence, Italy; [8]Department of Haematology, Cancer Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands; [9]St. James's Institute of Oncology, Leeds Teaching Hospitals, Leeds, United Kingdom; [10]Department of Tumor Immunology, Nijmegen Center for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands; [11]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; [12]Division of Haematology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [13]Department of Haematology, Oncology and Clinical Immunology, Universitätsklinik Düsseldorf, Düsseldorf, Germany; [14]Department of Internal Medicine V (Hematology and Oncology), Medical University Innsbruck, Innsbruck, Austria; [15]Department of Haematology Oncology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, University of Pavia, Pavia, Italy; [16]Leukemia Program, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; and [17]Dana-Farber Cancer Institute, Boston, MA

Danke

K. Götze (München)

N. Kröger (Hamburg)

A. Giagounidis/N. Gattermann/
A. Kündgen/U. Germing (Düsseldorf)

W.K. Hofmann, F. Nolte (Mannheim)

D. Haase, J. Schanz (Göttingen)

M. Sekeres (Cleveland)

K. Sockel/E. Balaian (Dresden)

G. Mufti (London)

L. Ades/P. Fenaux (Paris)

Leipzig MDS team

German MDS Study Group (D-MDS)
teilnehmende Studienzentren

Groupe Francophone Des Myelodysplasies (GFM)

German Cooperative Transplant Group (GCTSG)

Study Alliance Leukemia (SAL)

European MDS study coordinating office (EMSCO)

European Leukemia Net (ELN)

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D-MDS / EMSCO Studientreffen

8.-9.11. 2019 in Leipzig

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MYELODYSPLASTIC SYNDROMES

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Deutsche MDS-Studiengruppe