Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

Explorando las últimas estrategias en el manejo de los Síndromes Mielodisplásicos

Ana Alfonso-Piérola

Clínica Universidad de Navarra, Pamplona

Disclaimers

- **Honoraria from lectures**: BMS, Novartis, Abbvie, Jazz Pharma, Janssen, Astellas
- **Participation in Ad Board meetings**: BMS, Syros, Jazz Pharma, Otsuka, Ascentage Pharma, Janssen.
- **Consultant**: Astellas, Jazz Pharma; Janssen
- **Research Founding**: Astra Zeneca

Prognosis

Prognosis

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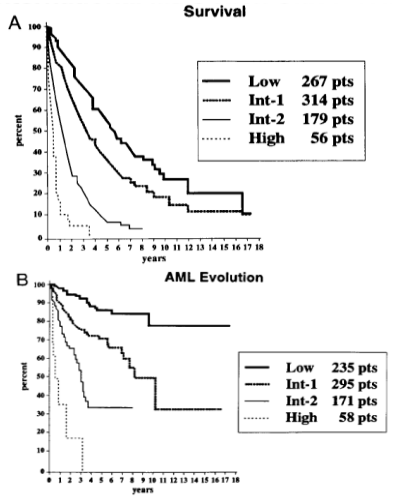
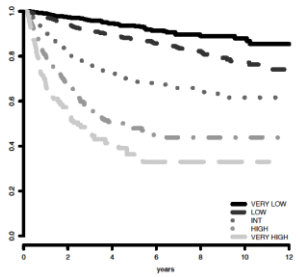
IPSS

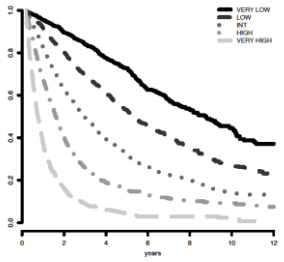
	0	0.5	1	1.5	2
BM blasts	< 5%	5-10 %		11-20 %	21-30 %
Karyotype*	Good	Intermediate	Poor		
Cytopenia(s)	0-1	2-3			
*** Karyotype**					
Good	Normal, -Y, isolated del(5q), del(20q).				
Poor	Complex (≥ 3 abnormalities) o chromosome 7 aberration				
Intermediate	Other				



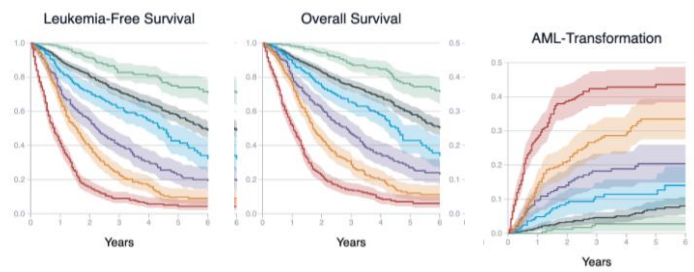
IPSS-R

	0	0.5	1	1.5	2	3	4
Karyotype*	Muy bueno		Bueno		Inter	Pobre	Muy pobre
BM blasts	0-2 %		3-4.9 %		5-10%	> 10%	
Hgb (g/dL)	≥ 10		8-9.9	< 8			
Plt (x10⁹/L)	≥ 100	50-99	< 50				
ANC (x10⁹/L)	≥ 0.8	< 0.8					
*** Karyotype**							
Very Good	-Y, del(11q)						
Good	Normal, del(20q), isolated del(5q) or +1 additional abndormality, del(12p)						
Intermediate	+8, del(7q), i(17q), +19, any other single or double independent clones						
Poor	3q abnormalities, -7, -7/del(7q), complex with 3 abnormalities						
Very Poor	Complex ≥ 3 abnormalities						





IPSS-M



Greenberg P et al. Blood 1997; 89(6): 2079-88; Schanz J et al. J Clin Oncol 2012; 30 (8): 820-9; Greenber PL et al. Blood. 2012 Sep 20;120(12):2454-65. Bernard et al. NEJM Evidence 2022.https://mds-risk-model.com/

Prognosis I **IPSS-R vs IPSS-M**

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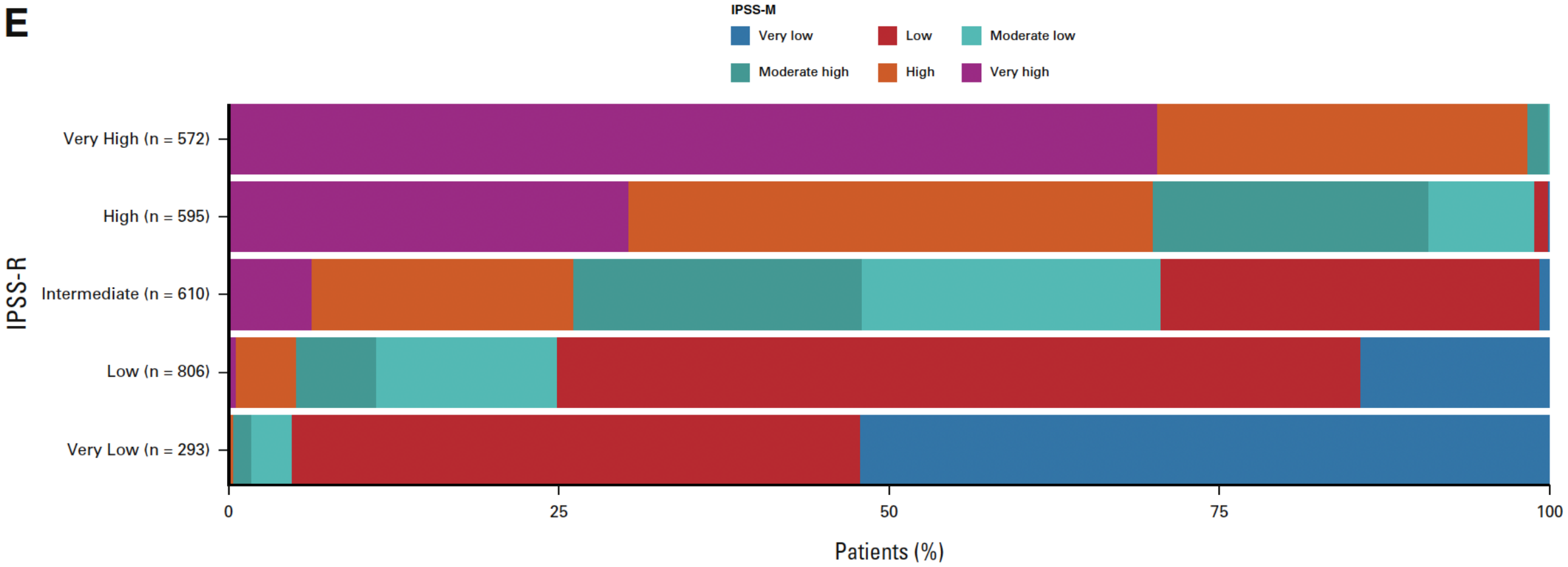
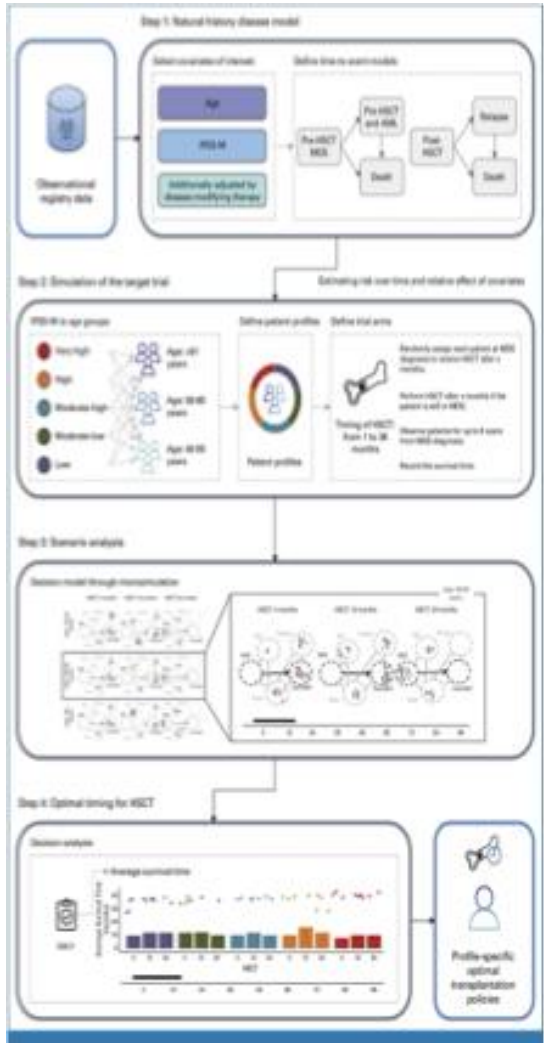
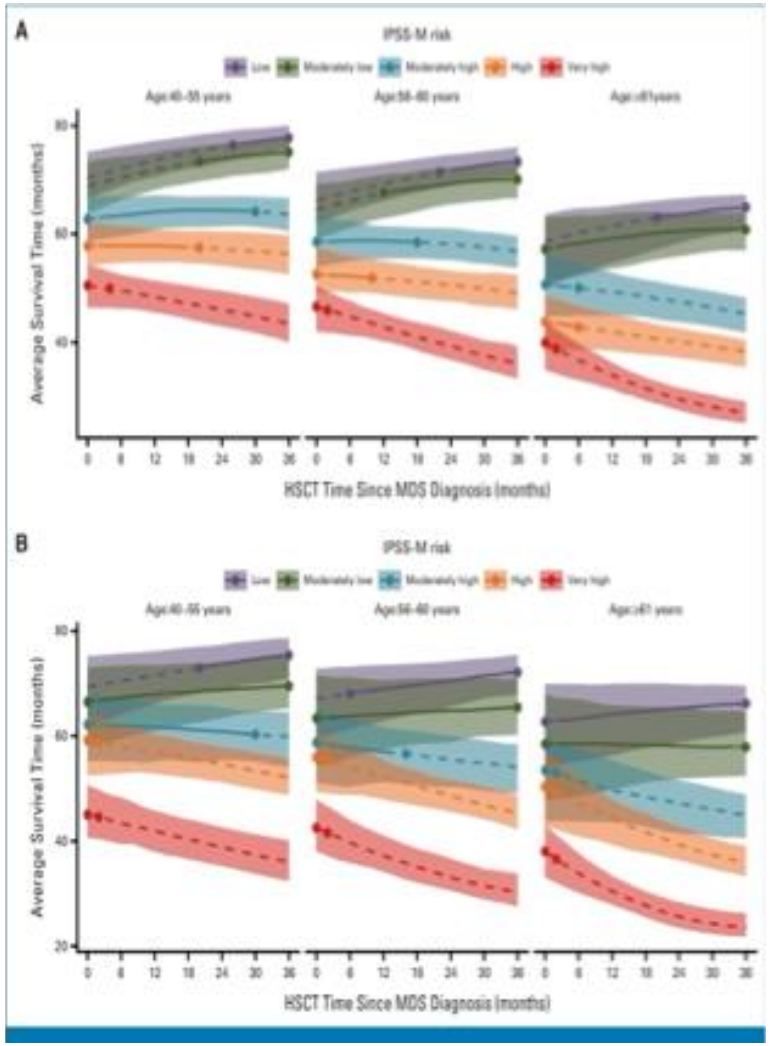
E

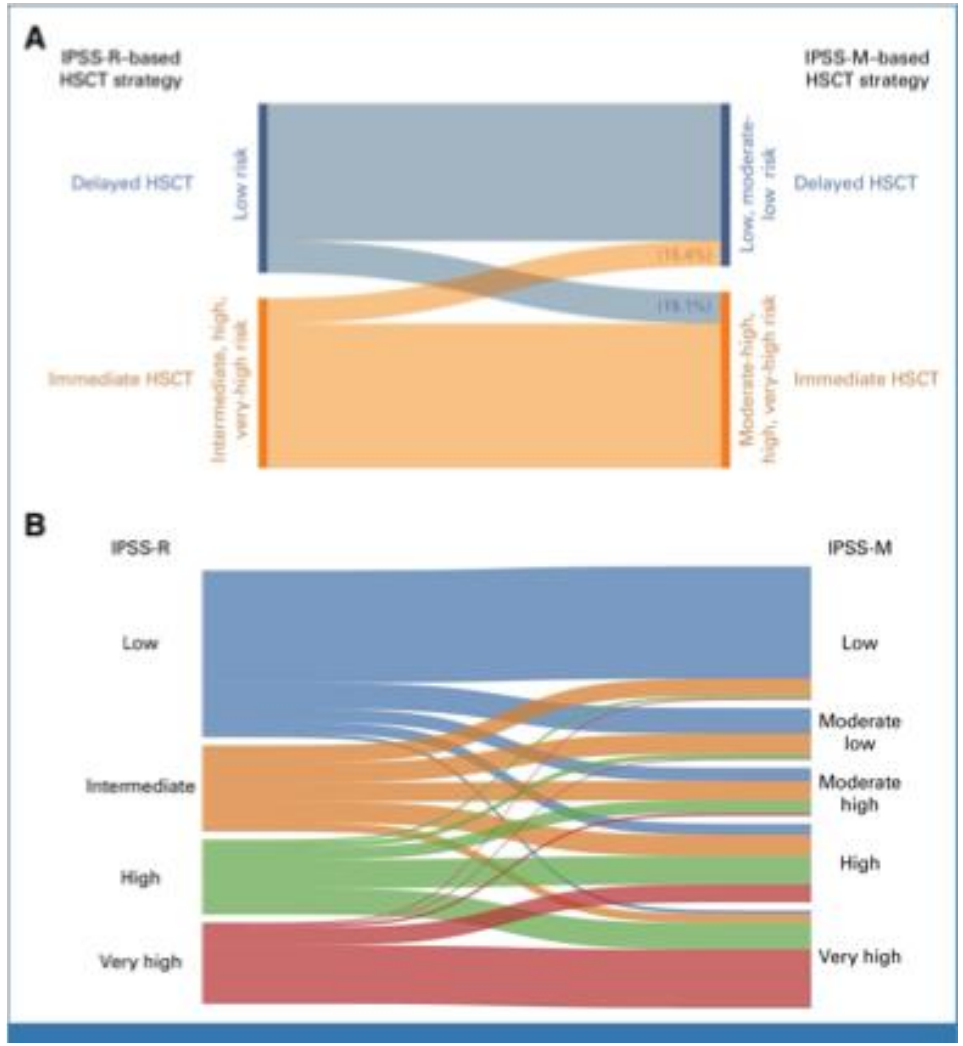


Sauta E. JCO 41, 2827-2842(2023).DOI:10.1200/JCO.22.01784

Prognosis I **IPSS-R vs IPSS-M: timing of Allo-SCT**







Prognosis I **IPSS-del5q**

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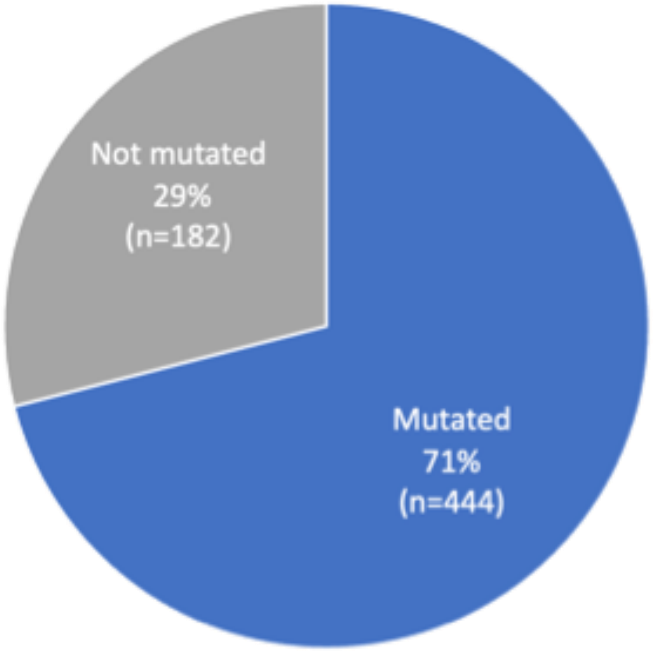
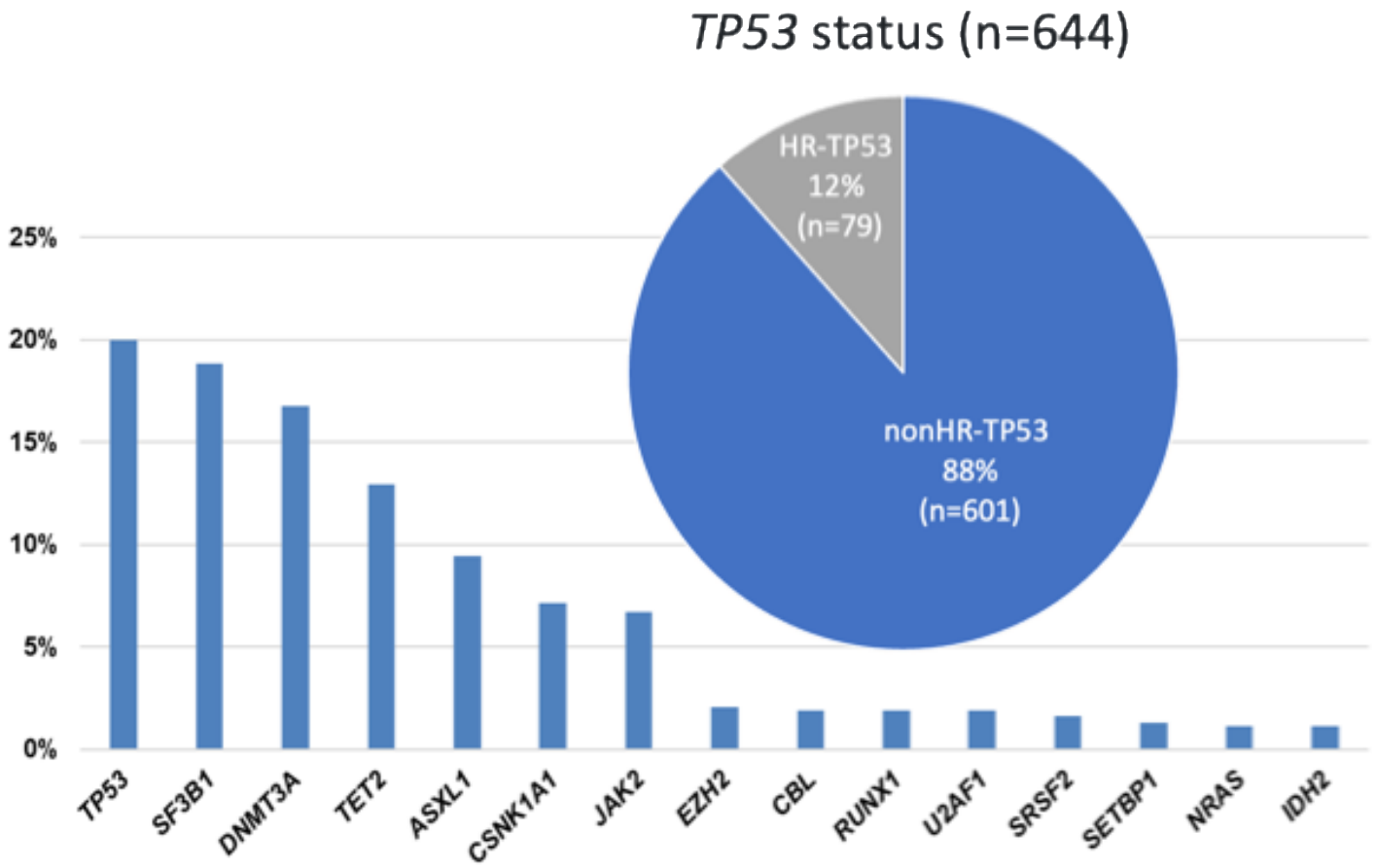
PATIENTS (n=682)		
• *de novo* MDS-del(5q) according to WHO 2017 with mutational analysis		
CLINICAL DATA		
• Demographics, blood counts, BM blasts %		
• **Risk stratification**	IPSS-R:	Lower-risk: ≤3.5 points Higher-risk: >3.5 points
	IPSS-M:	Lower-risk: very-low + low + moderate-low Higher-risk: moderate-high + high + very high
BIOLOGICAL DATA		
• **G-banding for del(5q) breakpoints**		Type 1: q13q31, q13q33, q22q33, q12q33, q14q34 Type 2: other
• **NGS:** *ASXL1, CALR, CBL, CEBPA, CSF3R, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, WT1, ZRSR2*		

Montoro J. ASH 2024. Blood (2024) 144 (Supplement 1): 666.

Prognosis I **IPSS-del5q**



% of cases with mutations (n=626)

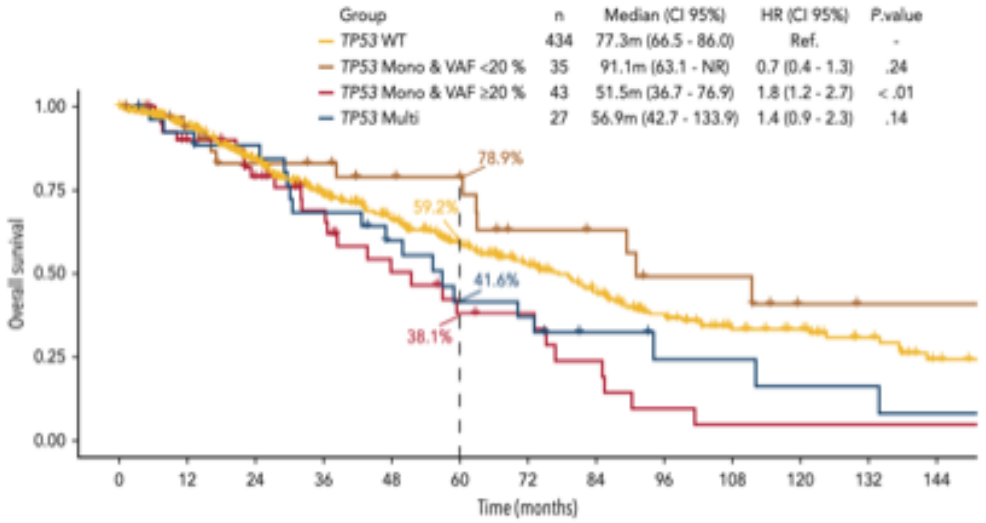


Molecular profile (n=626)

Montoro J. ASH 2024. Blood (2024) 144 (Supplement 1): 666.

Prognosis I **IPSS-del5q**

- ***TP53* status**
  - *Non-High Risk TP53 (nonHR-TP53)*
    TP53-wt or
    TP53-monoallelic with VAF <20%
  - *High Risk TP53 (HR-TP53)*
    TP53-multihit or
    TP53-monoallelic with VAF ≥20%



Montoro MJ *et al. Blood*, 2024

RISK SCORE

1) LASSO minimum lambda test with Leukemia-free Survival as an event of interest
2) Multivariate Cox proportional hazard model → Rounding hazard ratios for scoring

Montoro J. ASH 2024. Blood (2024) 144 (Supplement 1): 666.

Prognosis I **IPSS-del5q**

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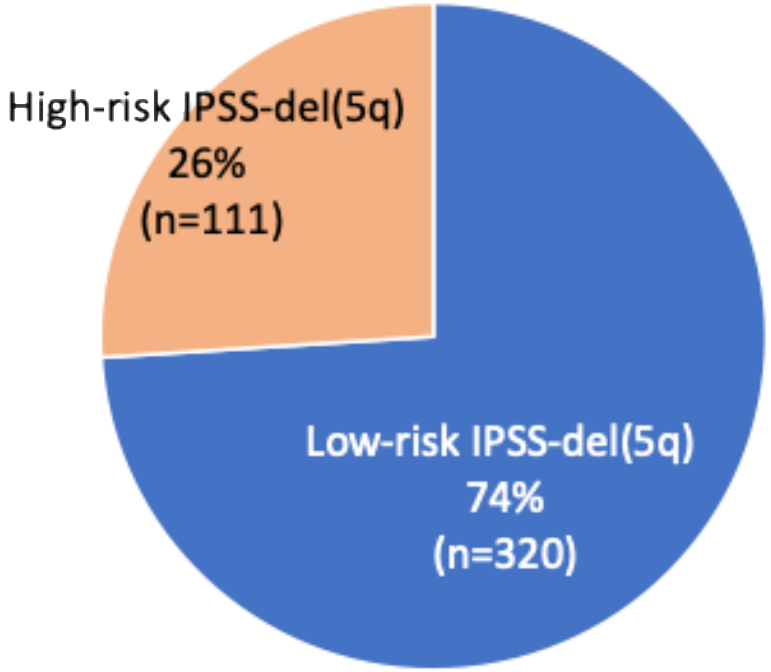
LASSO-Cox analysis

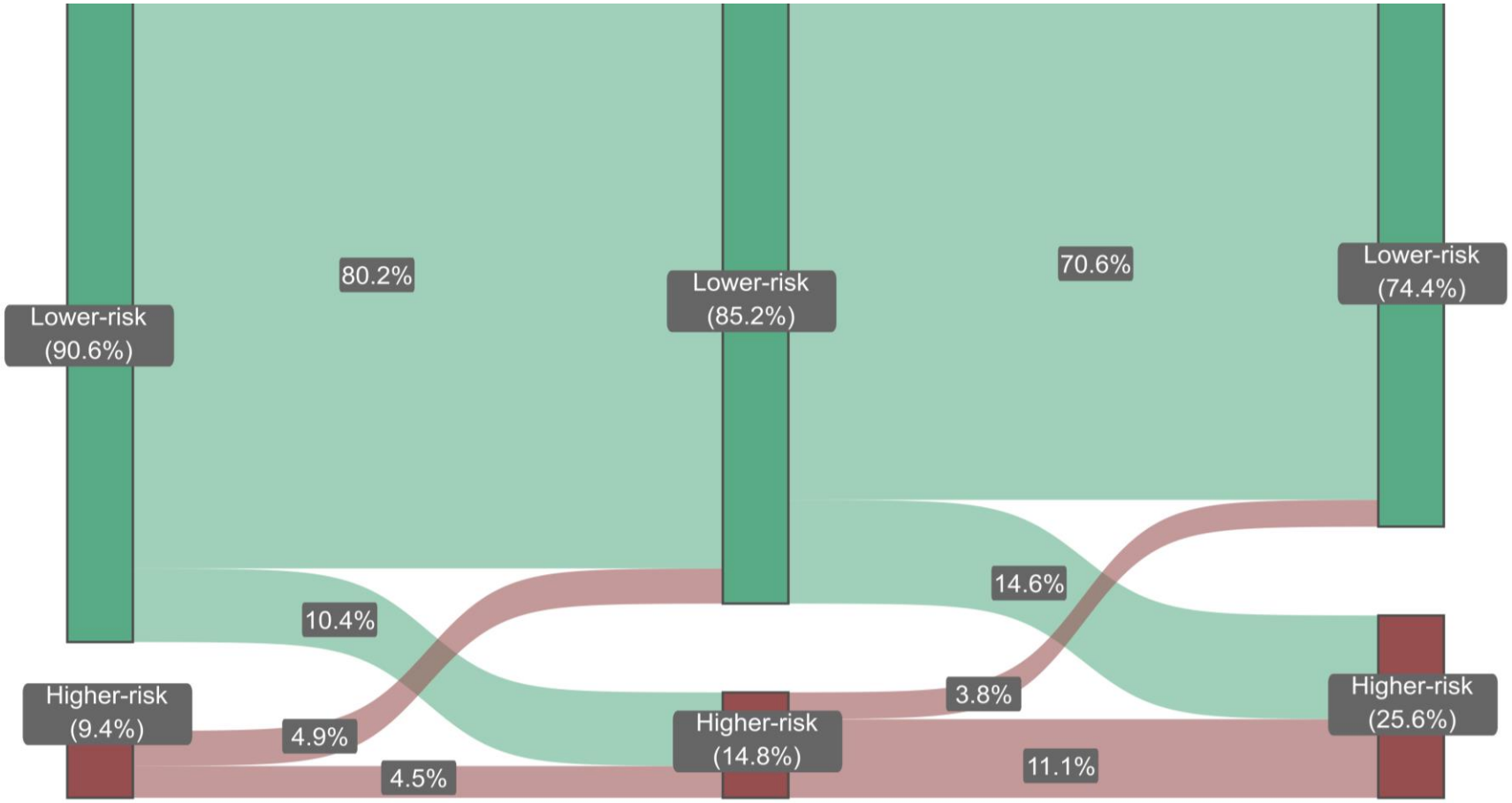
Variable	Points
Sex, male	1
Hemoglobin ≤ 10 g/dL	2
Platelet ≤ 100 x10^9/L	2
≥ 2 additional mutations	2
SF3B1 mutations	1
HR-*TP53 status*	1



0-3 points	Standard-risk
>3 points	High-risk

Montoro J. ASH 2024. Blood (2024) 144 (Supplement 1): 666.

Prognosis I **IPSS-del5q**



Montoro J. ASH 2024. Blood (2024) 144 (Supplement 1): 666.

Prognosis I **Clonal Hematopoiesis Risk Score (CHRS)**

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Goal: Determine predictors of myeloid neoplasm (MN) risk in individuals with clonal hematopoiesis (CH) or clonal cytopenia of undetermined significance (CCUS)

Methods:

1. Exome sequencing analysis of healthy participants (N = 193,743)
2. Analyze genetic mutations, laboratory values, and myeloid neoplasm outcomes and use combined statistical weights to define CHRS
3. Validate in clonal hematopoiesis CH/CCUS patient cohort

Results

~5.9% of participants met criteria for having CH or CCUS

Among the individuals with CH/CCUS, there were **2.4% incident MN events**

Mutations in splicing factors *(SRSF2, SF3B1, ZRSR2)*, AML-like genes *(IDH1, IDH2, FLT3, RUNX1)*, *JAK2*, and *TP53*-related mutations were classified **as high-risk MN predictors**

Clonal Hematopoiesis Risk Score Values

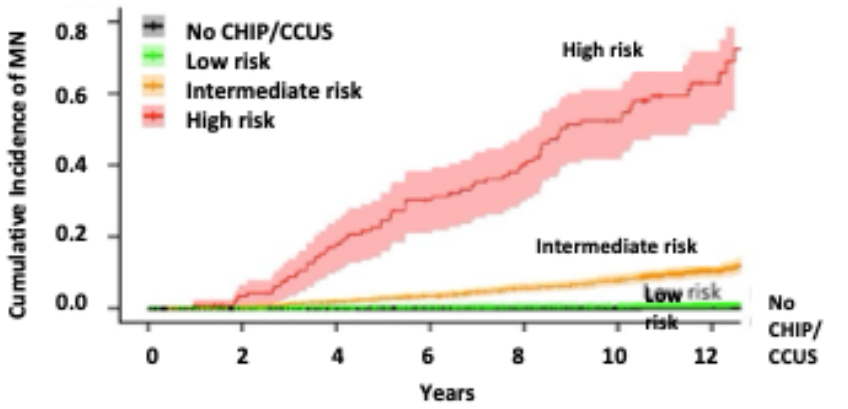
Prognostic Variable	0.5	1	1.5	2	2.5
Single DNMT3a	Present	Absent			
High-risk mutation		Absent			Present
Mutation #		1		≥2	
VAF		<0.2		≥0.2	
RDW		<15			≥15
MCV		<100			≥100
Cytopenia		CHIP	CCUS		
Age (yr)		<65	≥65		

VAF = Variant Allele Frequency; RDW = Red Cell Distribution Width; MCV = Mean Corpuscular Volume

Weeks LD, et al. *NEJM Evid.* 2023;2(5) DOI:10.1056/EVIDoa2200310

Tools Available

http://www.chrsapp.com/



Time (yr)	0	2	4	6	8	10	12
High risk	123	109	90	72	60	43	15
Int. risk	1,196	1,174	1,125	1,080	1,016	961	336
Low risk	10,018	9,958	9,821	9,699	9,540	9,348	3,772
No CH/CCUS	182,406	181,674	180,407	178,734	176,174	174,455	72,254

Weeks LD, et al. NEJM Evid. 2023;2(5) DOI:10.1056/EVIDoa2200310

Prognosis I **Clonal cytopenia risk score (CCRS)**

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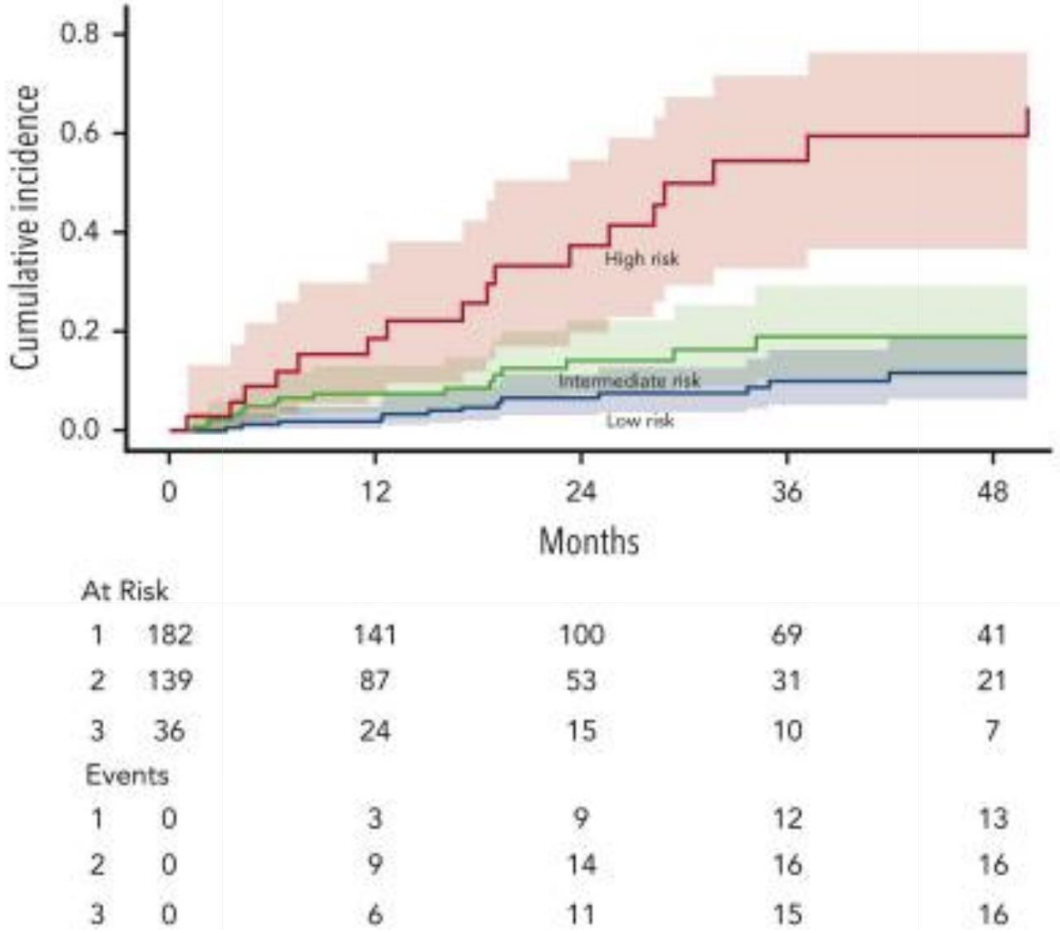
A

Adverse factor	HR (95% CI)	*P* value	Assigned score
Splicing mutations	2.13 (1.10-4.10)	.02	2
PLT<100×10^9/L	2.49 (1.38-4.50)	.003	2.5
Mutation number≥2	2.57 (1.28-5.15)	.008	3

C

Assigned score	Total (%)	Cumulative events	2-year Cumulative incidence (%, 95% CI)
High risk (≥5)	36 (10.1)	18	37.2% (19.8-54.7)
Intermediate risk (2.5≤5)	139 (38.9)	16	14.1% (7.9-22.2)
Low risk (<2.5)	182 (51)	13	6.4% (3-11.4)

B

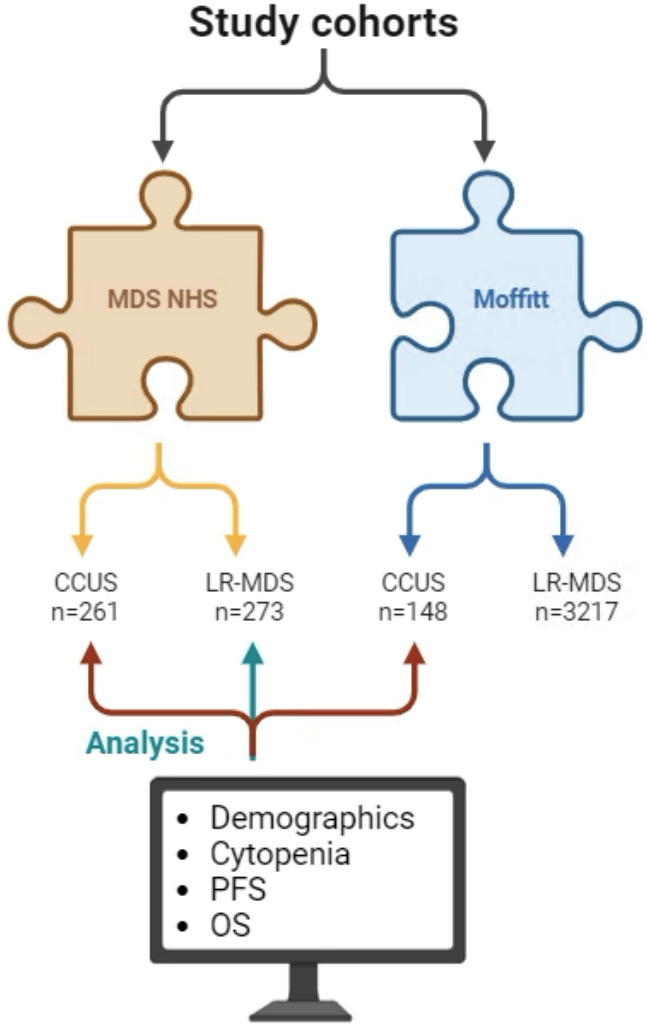


Xie Z. Blood. 2024 Jul 20;144(19):2033–2044. doi: 10.1182/blood.2024024756

Prognosis I **HR-CCUS = MDS?**

1. **The primary analysis** combined patients from MDS NHS cohort and Moffitt cohort pathologically confirmed CCUS (n=409) vs. LR-MDS (n=273)

2. CCUS and LR-MDS were compared in terms of
   - **Demographics**
   - **Cytopenia**
   - **Progression-free survival** (PFS): time to disease progression or death
   - **Overall survival** (OS): time to death



Weeks LD, et al. NEJM Evid. 2023;2(5) DOI:10.1056/EVIDoa2200310

Prognosis I **HR-CCUS = MDS?**

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LR-MDS vs CCUS, by CHRS and CCRS risk category

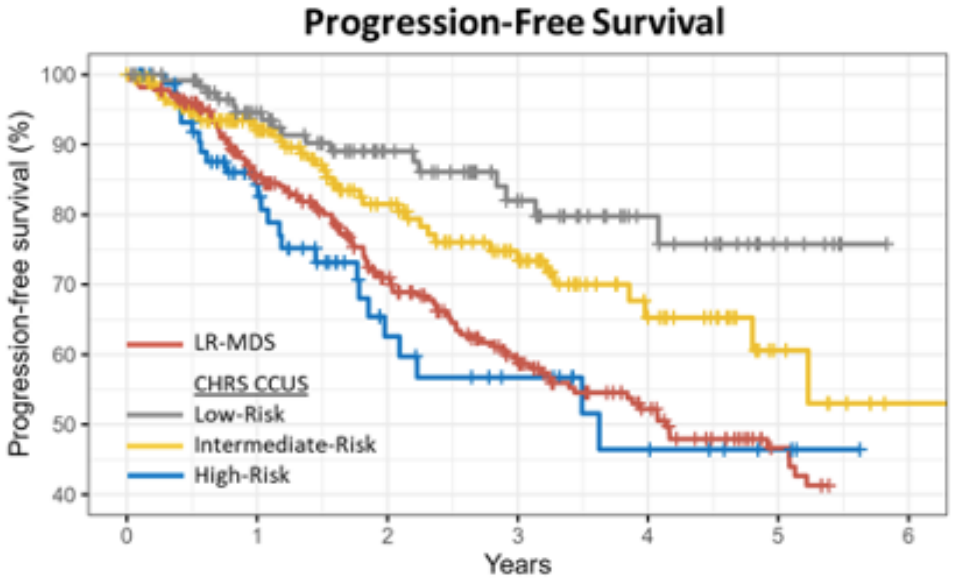
- High-Risk CCUS were more similar to LR-MDS in terms of median (IQR) hemoglobin, platelets and absolute neutrophil count (ANC)

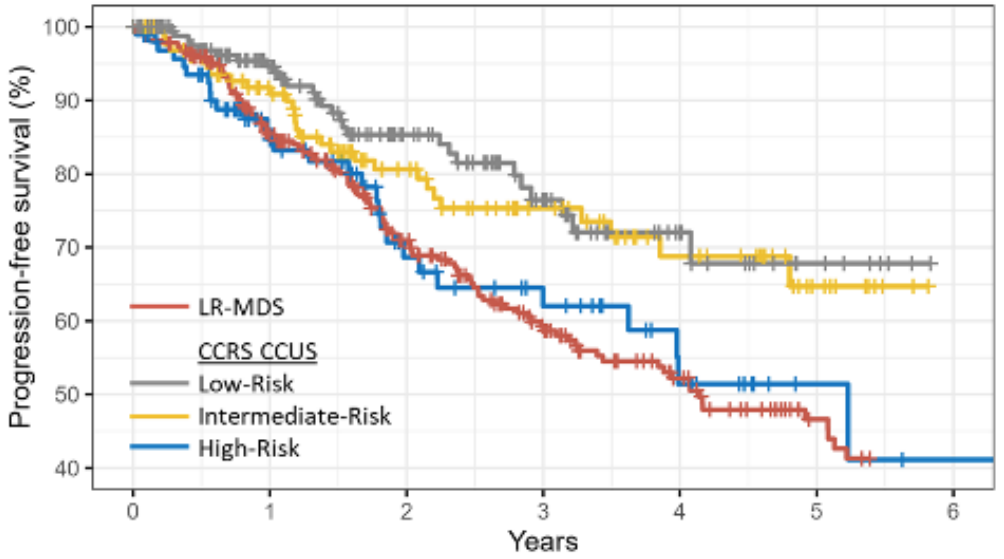
		CCUS, CHRS Risk Category			CCUS, CCRS Risk Category		
	LR-MDS	**Low**	**Inter-mediate**	**High**	**Low**	**Inter-mediate**	**High**
Hemoglobin g/dL	10.5 (9.0-11.6)	12.3 (10.9-13.4)	11.6 (9.6-13.2)	10.4 (9.5-12.5)	11.8 (9.8-13.1)	11.5 (10.0-13.0)	11.9* (9.9-13.3)
Platelets x 10^9	138 (96-232)	145 (105-207)	132 (97-184)	138 (89-203)	167 (131-231)	116 (67-159)	99* (68-154)
ANC x 10^9	2.0 (1.2-3.0)	2.6 (1.8-4.1)	2.6 (1.6-3.9)	2.2 (1.4-3.8)	3.1 (1.7-4.2)	2.4 (1.7-3.8)	2.0 (1.1-3.6)

Weeks LD, et al. NEJM Evid. 2023;2(5) DOI:10.1056/EVIDoa2200310

Prognosis I **HR-CCUS = MDS?**

- PFS: LR-MDS vs CCUS by CHRS and CCRS risk category





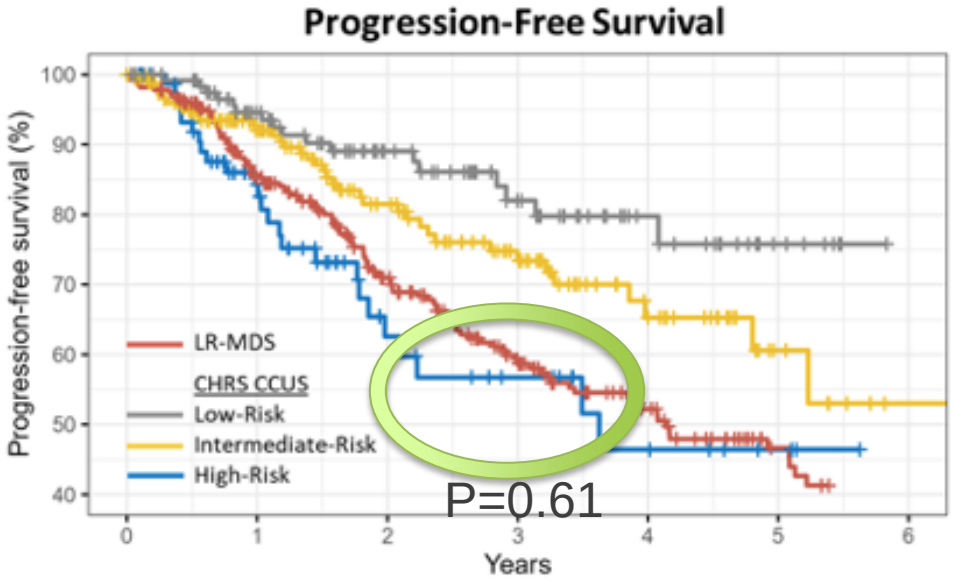
	CHRS CCUS vs LR-MDS	
CCUS Risk Category	**HR**	**P-value**
Low-Risk	0.36 (0.21-0.61)	< 0.001
Intermediate-Risk	0.62 (0.44-0.89)	0.01
High-Risk	1.12 (0.72-1.73)	0.611

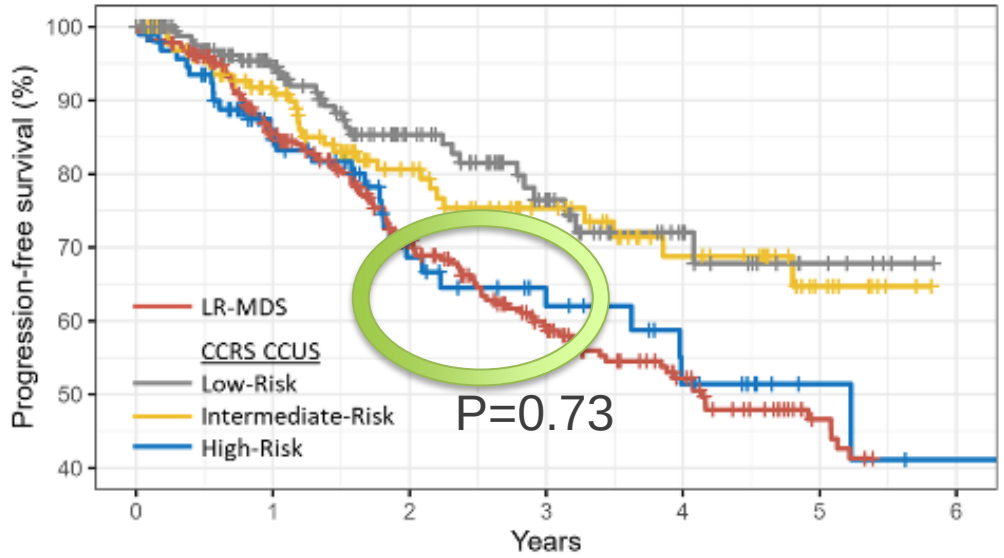
	CCRS CCUS vs LR-MDS	
CCUS Risk Category	**HR**	**P-value**
Low-Risk	0.49 (0.32-0.75)	< 0.001
Intermediate-Risk	0.58 (0.39-0.88)	0.009
High-Risk	0.93 (0.62-1.40)	0.726

Weeks LD, et al. NEJM Evid. 2023;2(5) DOI:10.1056/EVIDoa2200310

Prognosis I **HR-CCUS = MDS?**

- PFS: LR-MDS vs CCUS by CHRS and CCRS risk category





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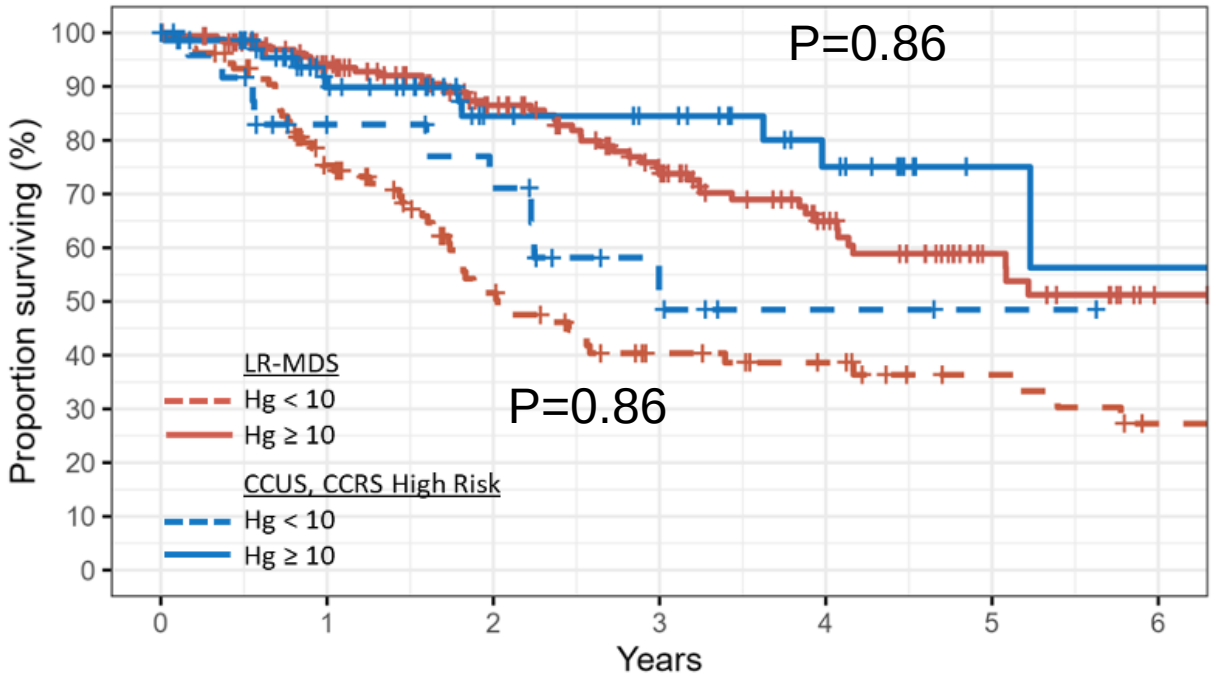
Prognosis I **HR-CCUS = MDS?**

- OS: Stratified OS by hemoglobin level

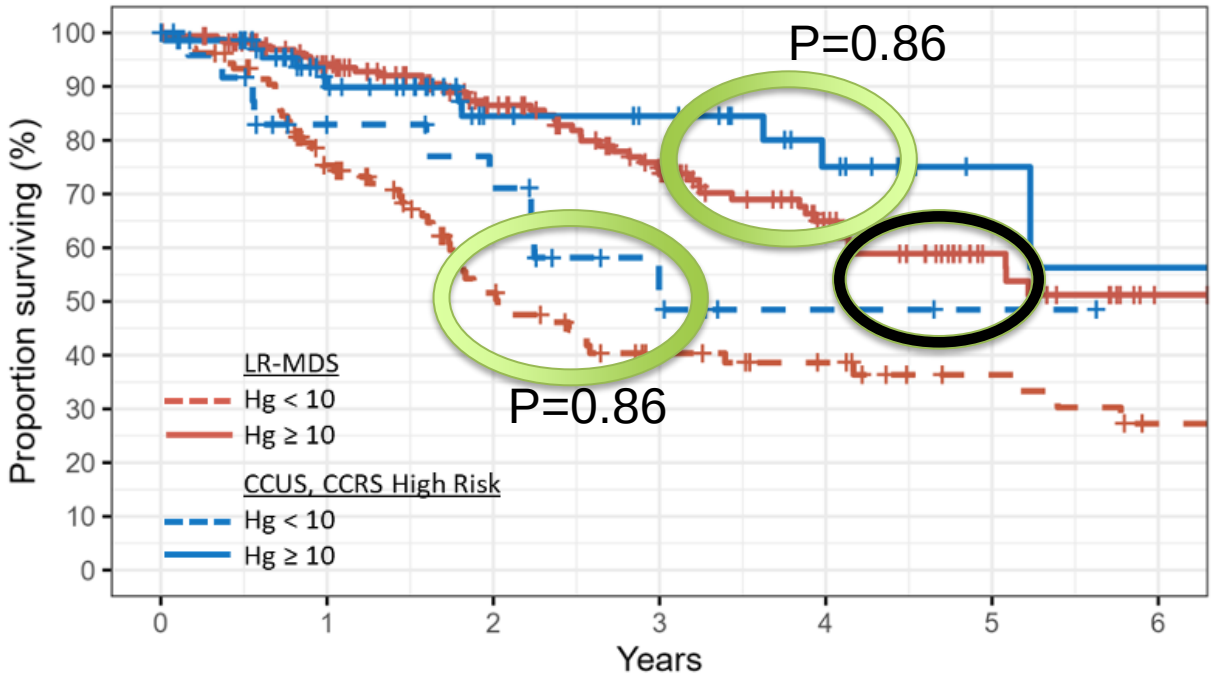


Characteristic	HR	P-value
CCUS Risk category		
Low vs LR-MDS	0.47 (0.28-0.77)	0.003
Intermediate vs LR-MDS	0.60 (0.39-0.93)	0.024
High vs LR-MDS	0.74 (0.46-1.21)	0.237

Weeks LD, et al. NEJM Evid. 2023;2(5) DOI:10.1056/EVIDoa2200310

Prognosis I **HR-CCUS = MDS?**

- OS: Stratified OS by hemoglobin level



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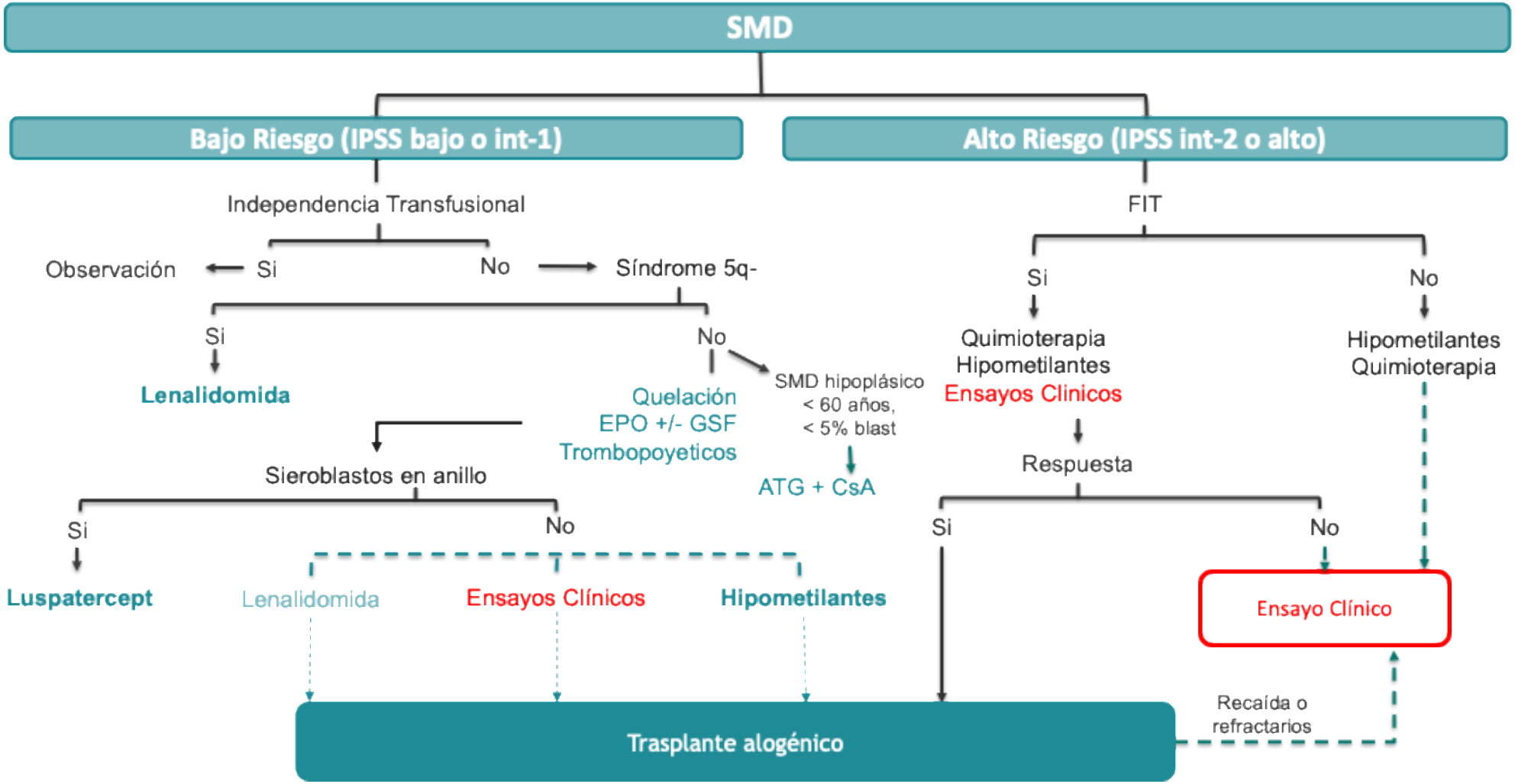
Treatment

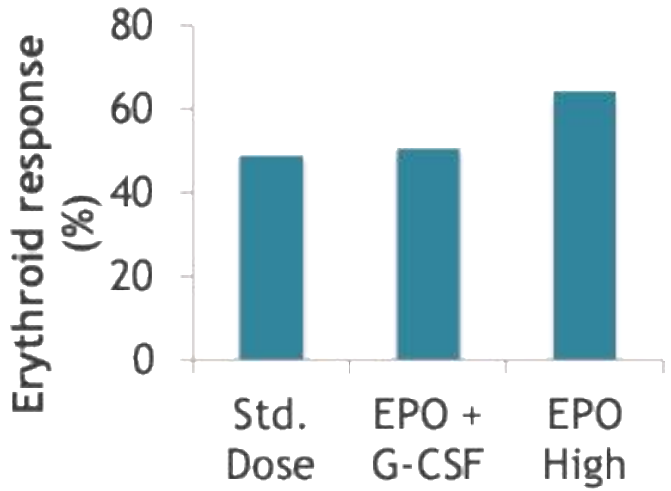
Treatment

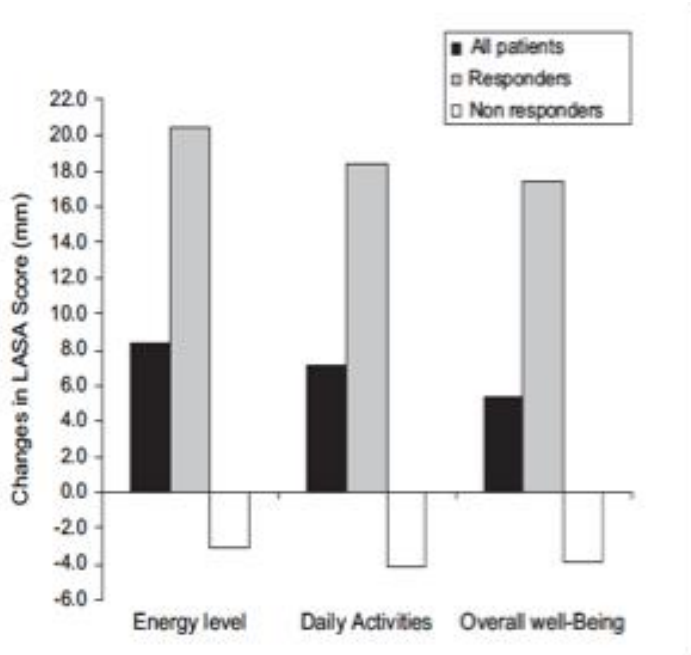


Dr. Alfonso's personal opinión

Treatment I **Low-Risk MDS - ESA**

- > 100 clinical trials. 5 randomized.
- Responses 30-60%





High doses of epoetin alfa (weekly dose 60-80ku) and darbopoetin alfa (weekly dose between 150-300 µg) → higher number of responses

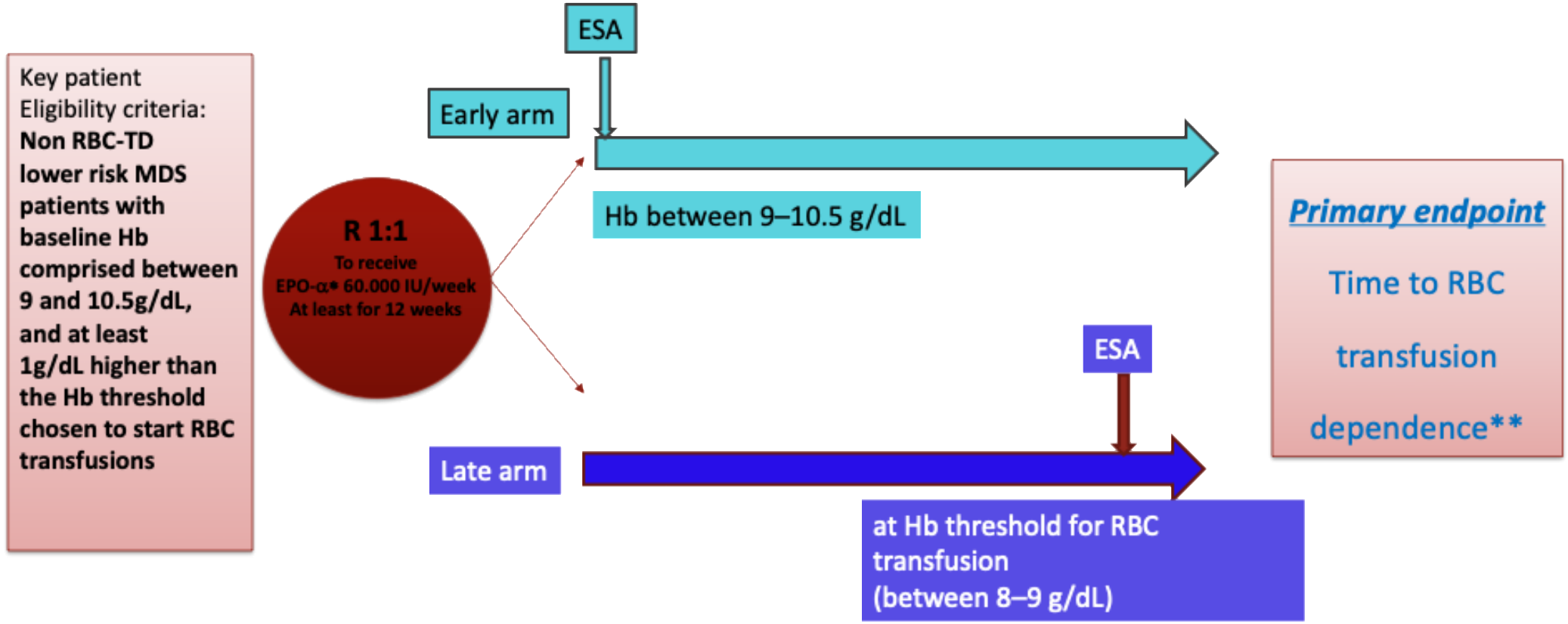
Italian group of SMD.Br J Haematol 1998;103(4):1070-4.
Casadevall N et al. Blood 2004;104(2):321-7.
Greenberg PL et al. Blood 2009; 114 (12): 2393-400.

Balleari E et al. Ann Hematol 2006;85(3):174-80.
Mundle S et al. Cancer 2009;115(4):706-15.
Moyo V et al. Ann Hematol 2008; 87 (7): 527-36.

Hellström-Lindberg et al. BJH 2003;120(6):1037-46.
Stasi et al. Ann Oncol 2005;16:1921–1927
Ross et al, Oncologist 2007; 12:1264

Treatment I **Low-Risk MDS - ESA**

GFM-EPO-PRETAR Phase III



- EudraCT: 2016-000327-10
- ClinicalTrials.gov nb: NCT03223961

*France marketing approval for low-risk MDS with Hb< 10g/dl

**RBC transfusion dependence is defined by requirement of at least 2 RBC transfusions within an interval of less than 8 weeks, given for Hb <9g/dL

Sophie Park, ASH 2024, abs 349

Treatment I **Low-Risk MDS - ESA**

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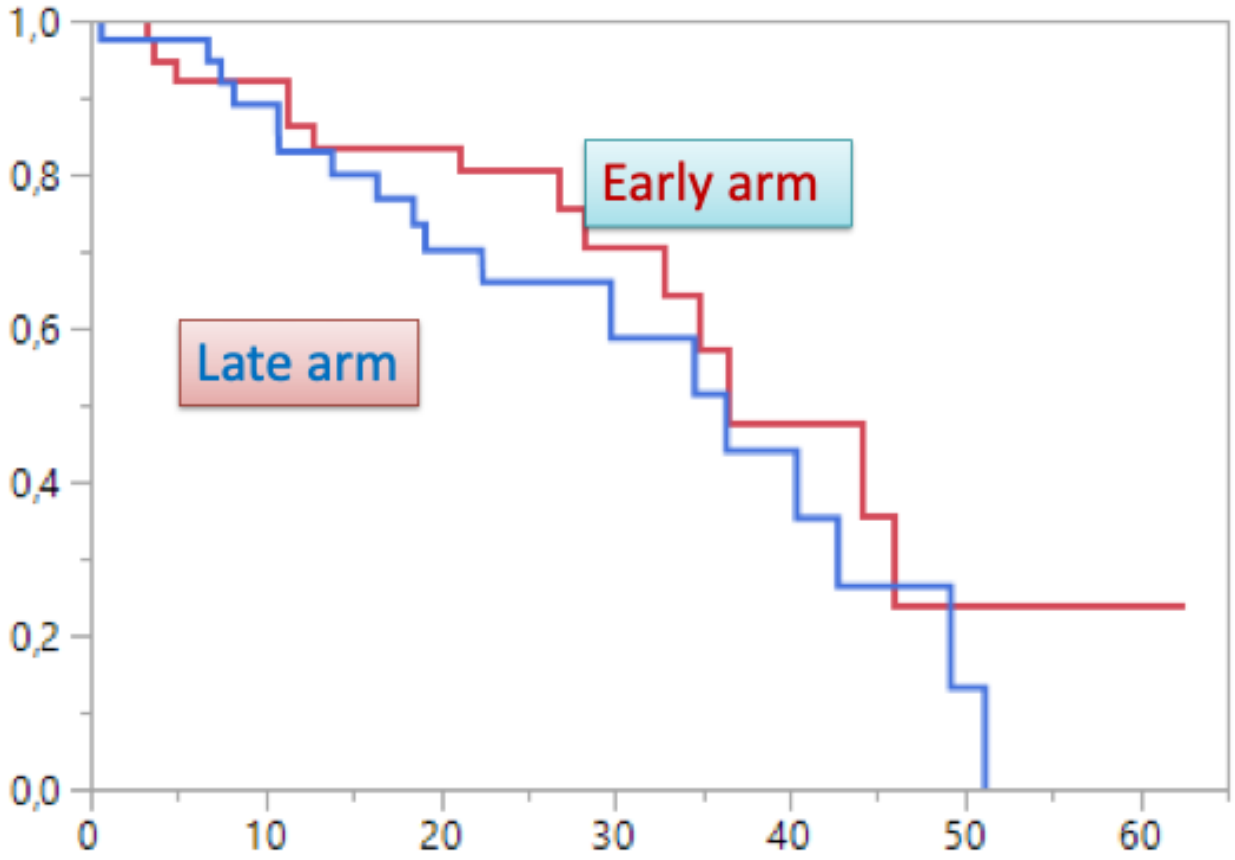
GFM-EPO-PRETAR Phase III



P=0.3

Sophie Park, ASH 2024, abs 349

Treatment I **Low-Risk MDS - ESA**

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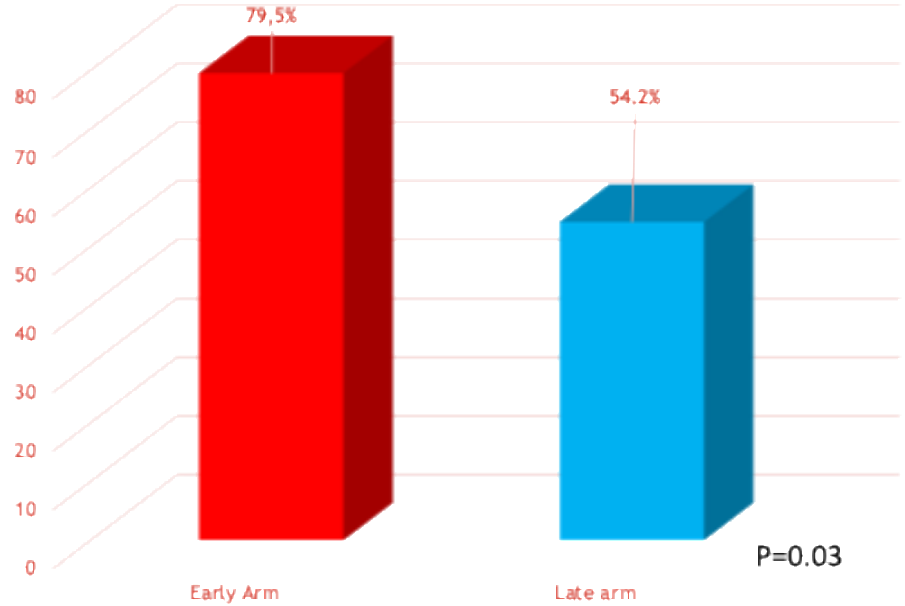
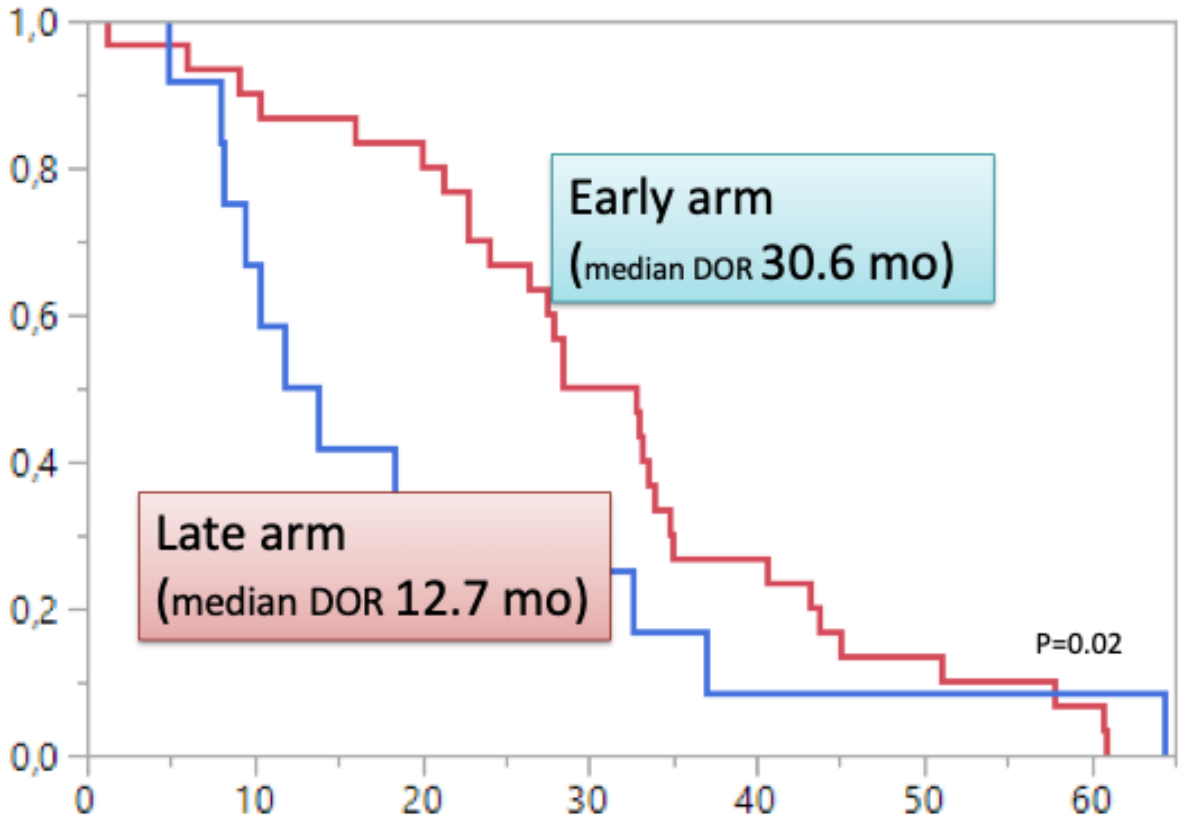
GFM-EPO-PRETAR Phase III



ORR (IWG 2018)



Duration of response to ESA (months)

Sophie Park, ASH 2024, abs 349

Treatment I **Low-Risk MDS**

Clínica Universidad de Navarra

NOT REIMBURSED

COMMANDS: Phase III, Luspa vs EPO in untreated MDS – 1st line

Key eligibility criteria

- ≥ 18 years of age
- IPSS-R very low-, low, or intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow[a]
- Required RBC transfusions (2-6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

Patients stratified by:

- Baseline sEPO level
- Baseline RBC transfusion burden
- RS status

Randomized 1:1

Luspatercept (N = 178)
1.0 mg/kg s.c. Q3W
titration up to 1.75 mg/kg

Epoetin alfa (N = 178)[b]
450 IU/kg s.c. QW
titration up to 1050 IU/kg

Response assessment at day 169 and every 24 weeks thereafter

End treatment
Due to lack of clinical benefit[c] or disease progression per IWG criteria

Post-treatment safety follow-up

- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

*Not reimbursed

Della Porta et al. EHA 2023, Presentation S102

Treatment I **Low-Risk MDS**

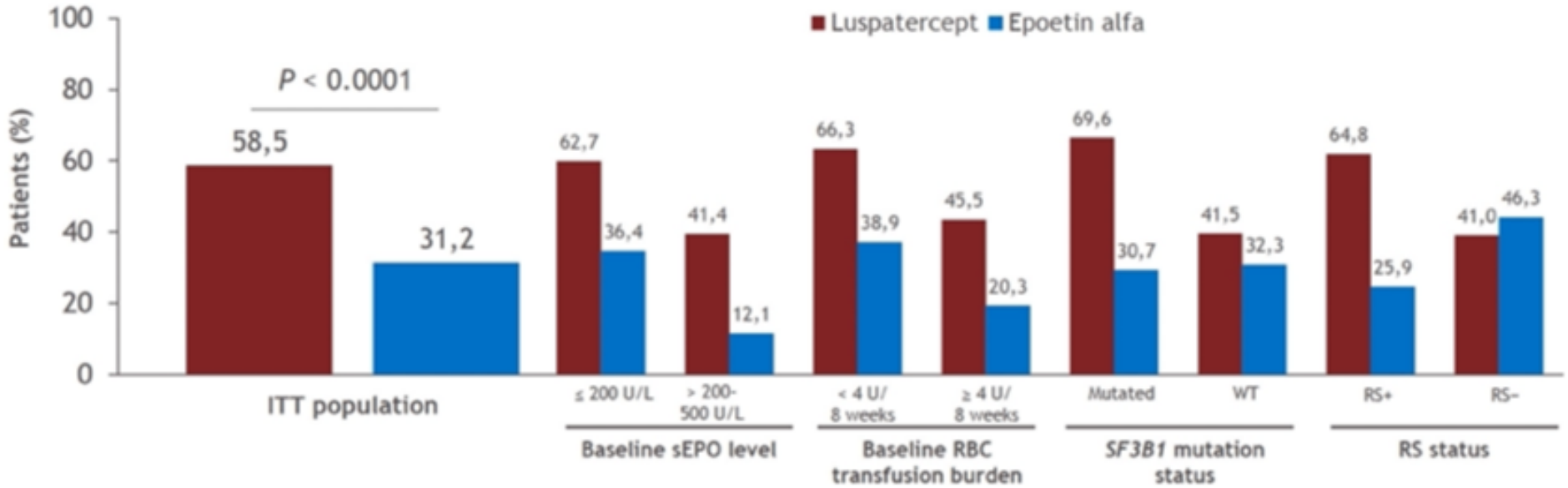
Clínica Universidad de Navarra

COMMANDS: Phase III, Luspa vs EPO in untreated MDS – 1st line

Composite primary endpoint (weeks 1-24)

- RBC-TI for ≥ 12 weeks WITH CONCURRENT mean hemoglobin increase ≥ 1.5 g/dL

- 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 primaryendpoint favored luspatercept or was similar to epoetinalfa for



*Not reimbursed

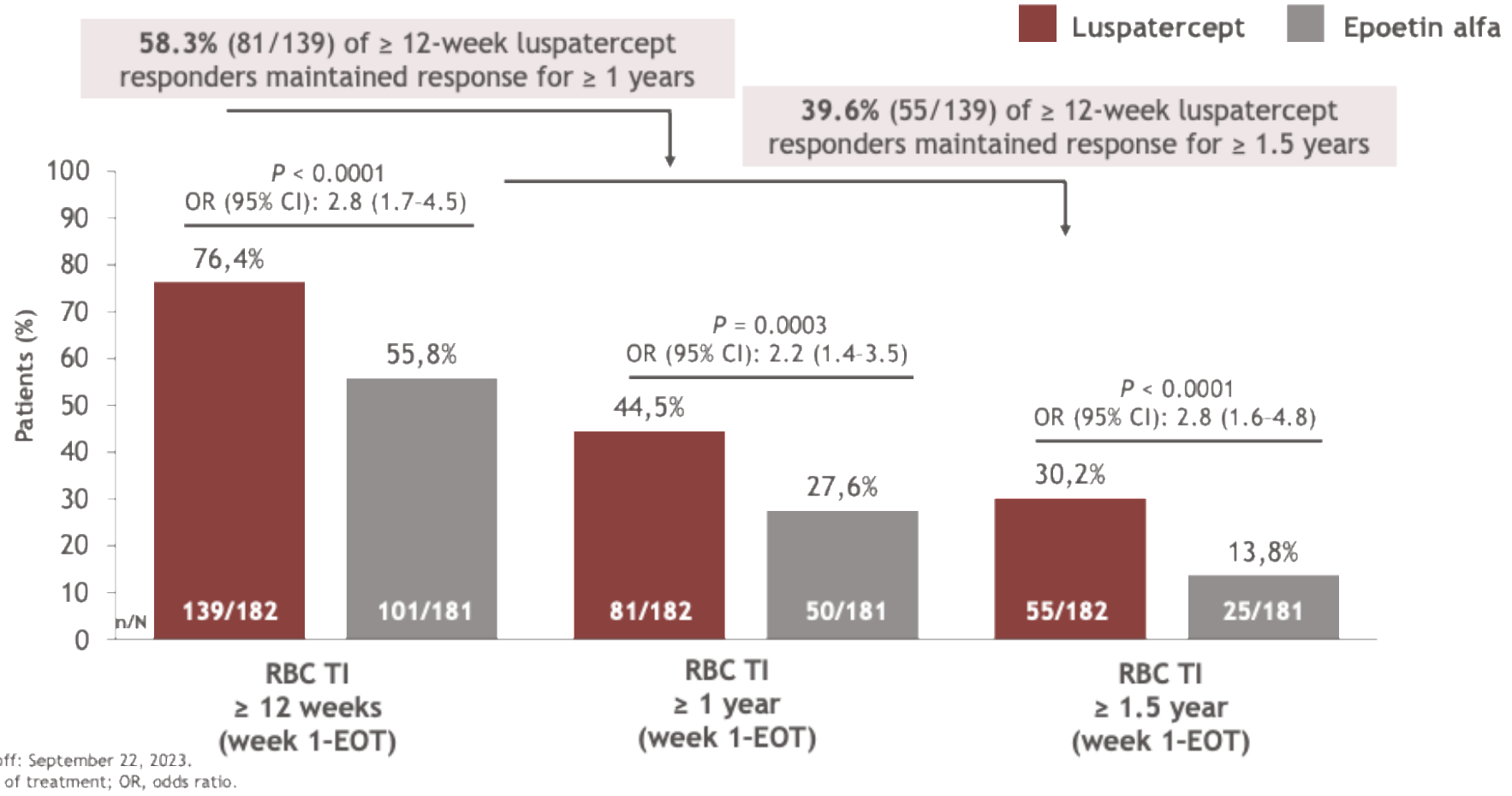
Della Porta et al. EHA 2023, Presentation S102

Treatment I **Low-Risk MDS**

Clínica Universidad de Navarra

NOT REIMBURSED

COMMANDS: Phase III, Luspa vs EPO in untreated MDS – 1st line



Data cutoff: September 22, 2023.
EOT, end of treatment; OR, odds ratio.

*Not reimbursed

García Manero G, ASH 2024

Treatment I **Low-Risk MDS: del5q**

Clínica Universidad de Navarra | Cancer Center

SMD-001 (PI-II; 2005)

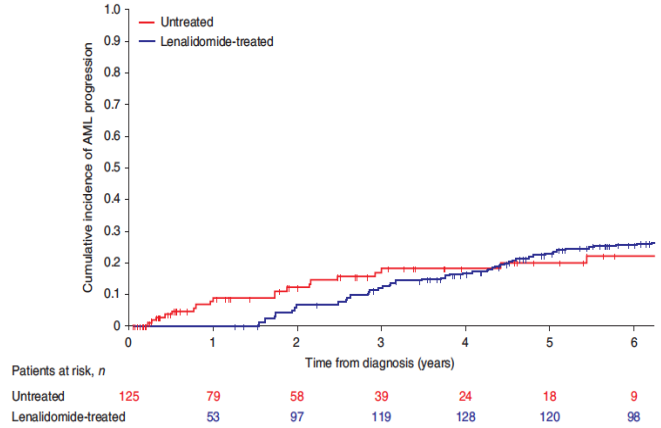
- Includes all FAB subtypes (n=43)
- Erythroid responses in del (5q)= **83%**

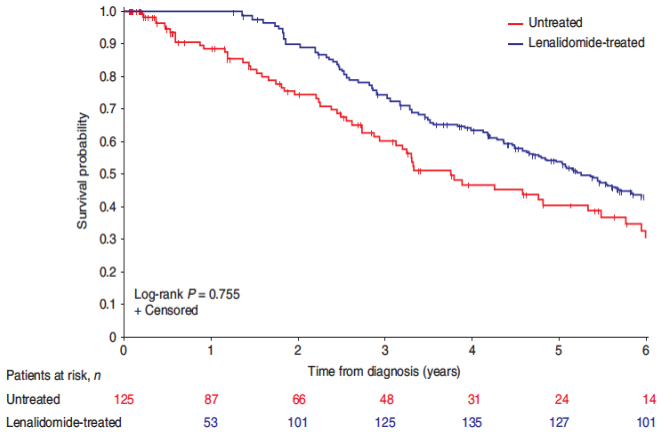
SMD-003 (PII; 2006)

- Low-risk + transf-dependent (n=148)
- Erythroid responses = **76%**

SMD-004 (PIII; 2011)

- Low-risk + transf-dependent (n=205)
- Placebo controlled. RBC-TI ≥ 26 weeks = **42-56%** (5mg-10mg)





Lenalidomide: doesn't increase the risk of AML, but increases OS

List A, et al. N Engl J Med 2005;352:549–57;List A, et al. N Engl J Med 2006;355:1456–65;Fenaux P, et al. Blood 2011 6;118(14):3765-76].

Treatment I **Low-Risk MDS: del5q – SINTRA-REV**

Clínica Universidad de Navarra

Patient Population

- MDS diagnosis (WHO 2008)
- IPSS-Low or Intermediate-1
- No RBC transfusion requirements
- Anemia (Hb<12 g/dL)
- del(5q) MDS solely and/or + other abnormality

RANDOMIZATION (2:1)

Lenalidomide 5 mg/day on days 1 to 28 of every 28-day cycle
n = 40

Placebo 5 mg/day on days 1 to 28 of every 28-day cycle
n = 20

End of treatment

Follow up

Treatment Phase
108 weeks

Follow up
108 weeks

1st patient: Feb 2010

62nd patient: Feb 2018

120 months

MDS Disease Assessment after 12 weeks and every 6 months thereafter
Discontinue treatment if no clinical benefit and/or disease progression (TD) and/or unacceptable toxicity
No crossover allowed

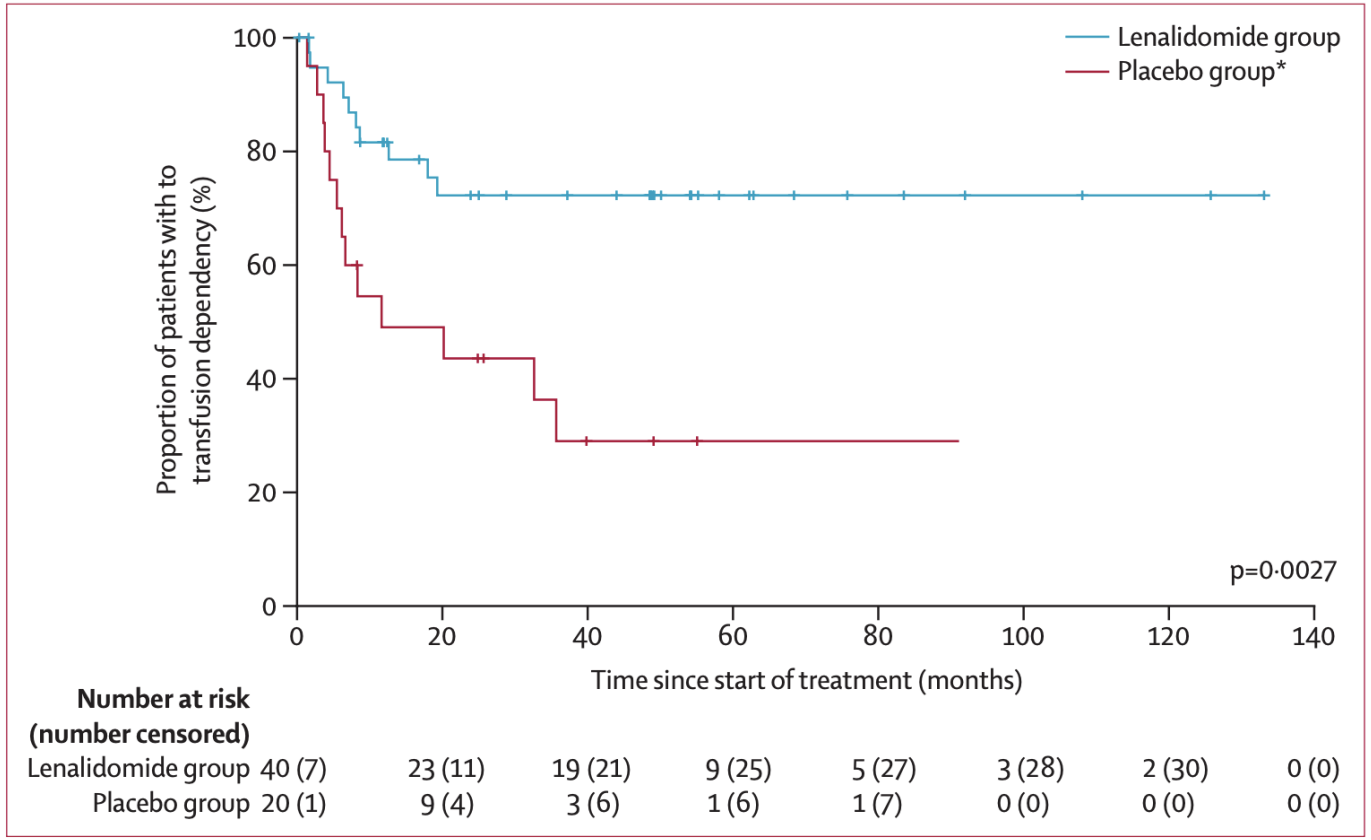
Diez-Campelo M. Lancet Haematol. 2024 Sep;11(9):e659-e670.

Treatment I **Low-Risk MDS: del5q – SINTRA-REV**

Efficacy (ITT, N=61)

Low doses of Len delayed and decreased transfusion dependency

- TD in 23 patients (38.3%): 10 in Len (25%) vs 13 in placebo (65%)
- Len decreased in 69.8% the risk of TD: HR 0.302 (0.132-0.692), p=0.005



Number at risk (number censored)								
Lenalidomide group	40 (7)	23 (11)	19 (21)	9 (25)	5 (27)	3 (28)	2 (30)	0 (0)
Placebo group	20 (1)	9 (4)	3 (6)	1 (6)	1 (7)	0 (0)	0 (0)	0 (0)

Diez-Campelo M. Lancet Haematol. 2024 Sep;11(9):e659-e670.

Treatment I **Low-Risk MDS: del5q – SINTRA-REV**

Clínica Universidad de Navarra

Secondary Objectives: Outcome

Similar median overall survival (no deaths related)

- Len 15 pts (37.5%)
- Placebo 8 pts (38.1%)

OVERALL SURVIVAL

AML in 11 patients (p=ns)

- Len 6 pts (15%)
  - me 52 mo
  - 2/6 (33.3%) *TP53* mut
- Placebo 5 pts (23.8%)
  - me 55 mo
  - 1/5 (20%) *TP53* mut

LEN me OS 8.4y

PLACEBO me OS 7.4y

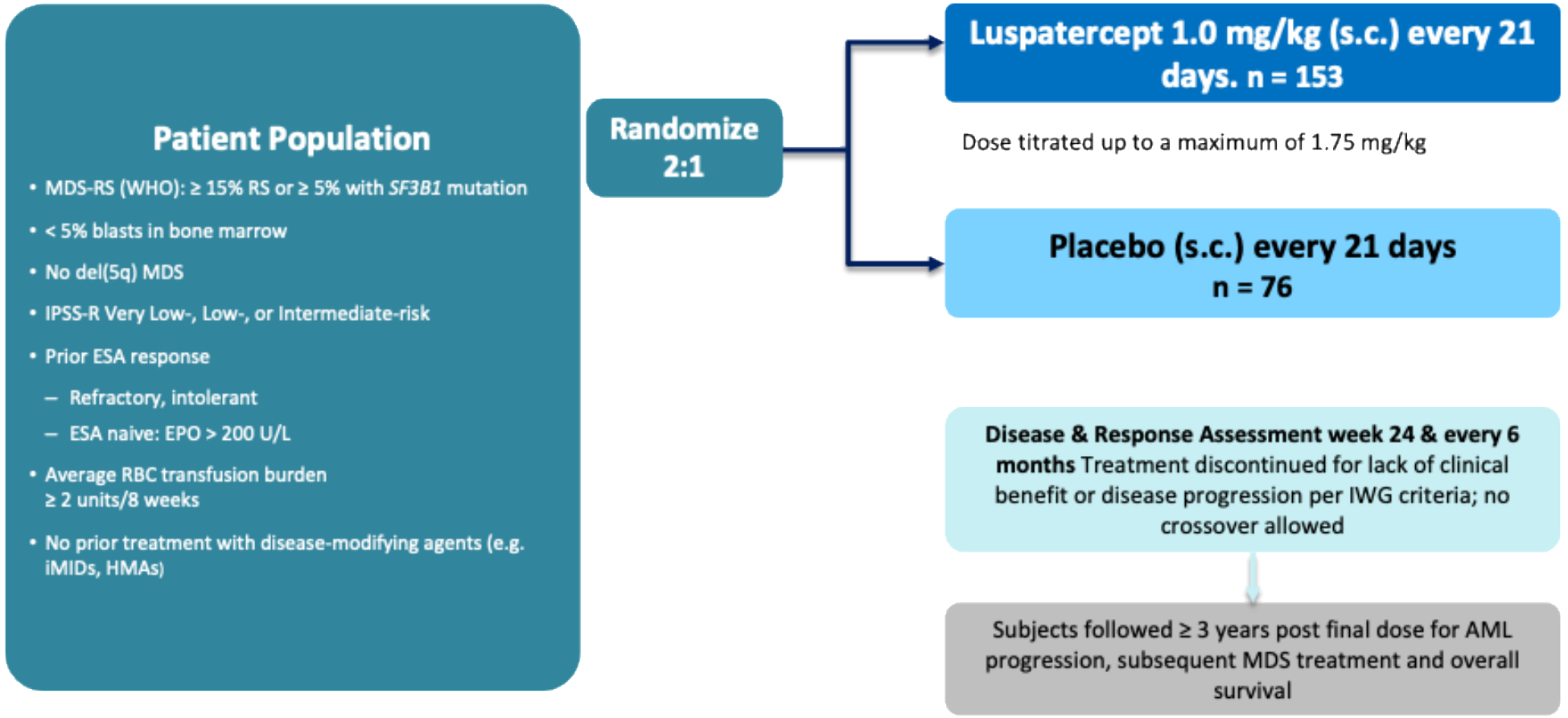
Median follow up 5.05y (0.3-11): 5.2 vs 4.85, p=ns

Diez-Campelo M. Lancet Haematol. 2024 Sep;11(9):e659-e670.

Treatment I **Low-Risk MDS – EPO R/R**

Clínica Universidad de Navarra | Cancer Center

Medalist: Phase III, Luspa vs Pbo in ESA refractory or intolerant in RS-MDS

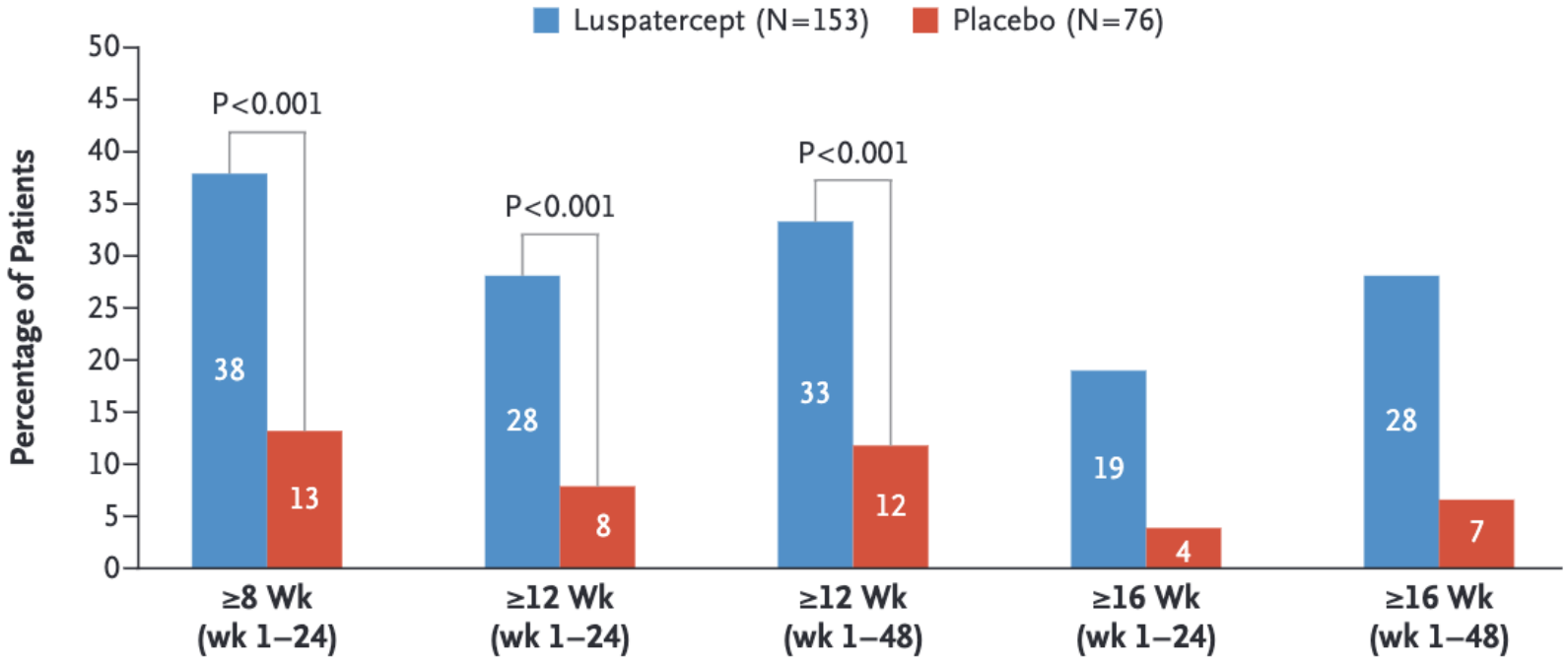


Data cutoff: May 8, 2018 Includes last subject randomized + 48 weeks.
EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; *SF3B1*, splicing factor 3b subunit 1; WHO, World Health Organization.

Fenaux, Pierre, et al. New England Journal of Medicine, vol. 382, no. 2, 2020, pp. 140–51

Treatment I **Low-Risk MDS – EPO R/R**

Medalist: Phase III, Luspa vs Pbo in ESA refractory or intolerant in RS-MDS



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])

Fenaux, Pierre, et al. New England Journal of Medicine, vol. 382, no. 2, 2020, pp. 140–51

Treatment I **Low-Risk MDS – EPO R/R**

Clínica Universidad de Navarra

IMERGE: Phase III, Imetelstat vs EPO in untreated MDS, refractory or intolerant to EPO

Phase 3
Double blind, randomized
118 clinical sites in 17 countries

Patient Population (ITT n=178):
- IPSS Low- or Intermediate 1- Risk MDS
- Relapsed/Refractory* to ESA or EPO >500 mU/ml
- Transfusion dependent: ≥4 units RBCs every 8 weeks over 16-week pre-study
- Non-deletion 5q
- No prior treatment with lenalidomide or HMAs

RANDOMIZE 2:1

Imetelstat
7.5mg/kg every 4 weeks
(n=118)

Stratification:
- Transfusion burden (4 - 6 vs. >6 units)
- IPSS risk category (Low vs. Intermediate-1)

Supportive care, including RBC and platelet transfusions, myeloid growth factors (e.g., G-CSF), and iron chelation therapy administered as needed on study per investigator discretion

Placebo
(n=60)

Primary Endpoint:
8-week RBC Transfusion Independence (TI)**

Key Secondary Endpoints:
- 24-week RBC TI**
- Duration of TI
- Hematologic Improvement-Erythroid (HI-E)

* Received at least 8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U or darbepoetin alfa 150 mcg or equivalent per week) without Hgb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥ 4 units/8 weeks ***or*** transfusion dependence or reduction in Hgb by ≥1.5 g/dL after hematologic improvement from ≥ 8 weeks of ESA treatment.

Safety population (treated) n=177
Imetelstat n=118
Placebo n=59

** Proportion of patients without any RBC transfusion for at least eight consecutive weeks since entry to the trial (8-week TI); proportion of patients without any RBC transfusion for at least 24 consecutive weeks since entry to the trial (24-week TI)

geron

EPO = erythropoietin; ESA = erythropoietin stimulating agents; G-CSF = granulocyte colony stimulating factor; Hgb = hemoglobin; IPSS = International Prognostic Scoring System; ITT = intent to treat; RBC = red blood cell; HI-E = hematologic improvement-erythroid; HMAs = hypomethylating agents; MDS = myelodysplastic syndromes

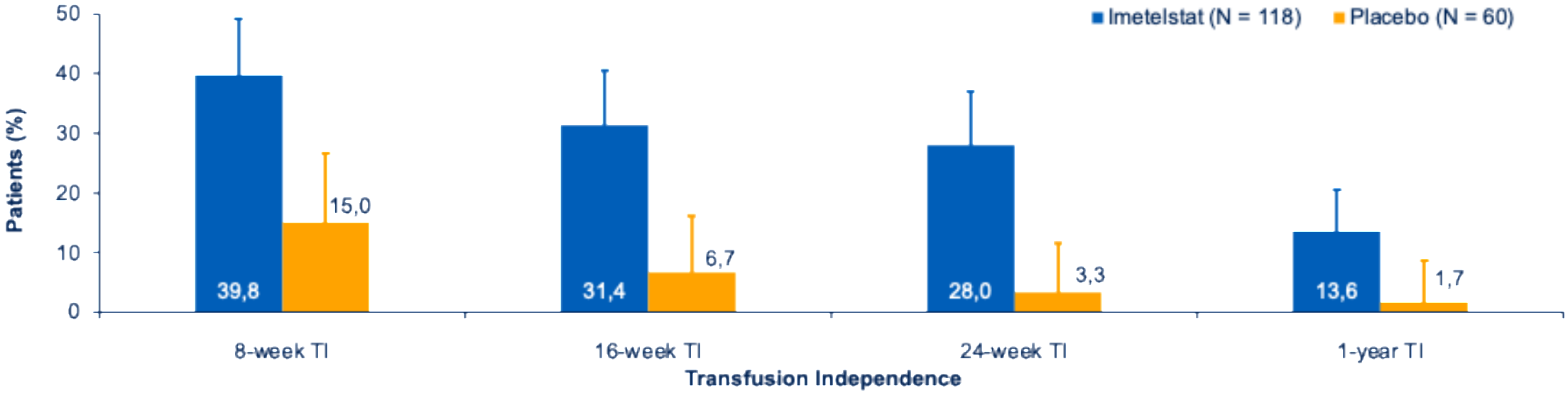
Platzbecker U. Lancet. 2024 Jan 20;403(10423):249-260.

Treatment I **Low-Risk MDS – EPO R/R**

Clínica Universidad de Navarra

NOT REIMBURSED

IMERGE: Phase III, Imetelstat vs EPO in untreated MDS, refractory or intolerant to EPO



Patients With Response, n (% [95% CI])				
Imetelstat	47 (39.8 [30.9–49.3])	37 (31.4 [23.1–40.5])	33 (28.0 [20.1–37.0])	16 (13.6 [8.0–21.1])
Placebo	9 (15.0 [7.1–26.6])	4 (6.7 [1.9–16.2])	2 (3.3 [0.4–11.5])	1 (1.7 [0.0–8.9])

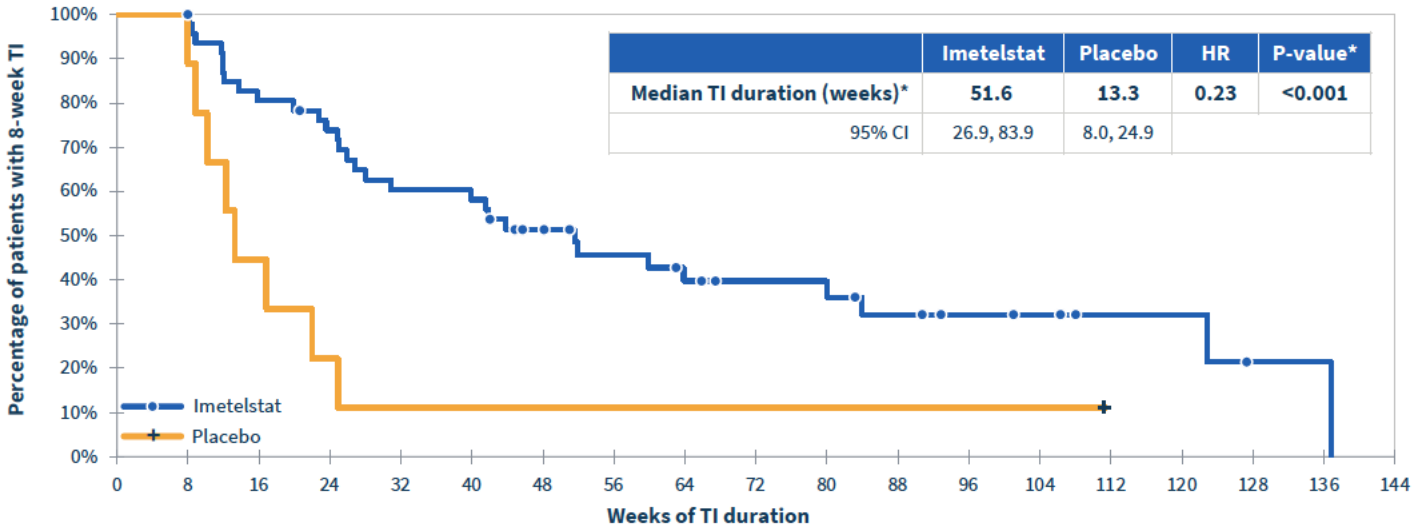
Platzbecker U. Lancet. 2024 Jan 20;403(10423):249-260.

Treatment I **Low-Risk MDS – EPO R/R**

Clínica Universidad de Navarra

IMERGE: Phase III, Imetelstat vs EPO in untreated MDS, refractory or intolerant to EPO

	Imetelstat (n=118)	Placebo (n=60)	P-value*
8-week TI, n (%)	**47 (39.8)**	**9 (15.0)**	**<0.001**
95% CI	(30.9, 49.3)	(7.1, 26.6)	



	Imetelstat	Placebo	HR	P-value*
Median TI duration (weeks)*	**51.6**	**13.3**	**0.23**	**<0.001**
95% CI	26.9, 83.9	8.0, 24.9		

Number of patients

Imetelstat	47	47	37	33	27	26	20	16	13	11	11	8	6	5	3	3	1	1	0
Placebo	9	9	4	2	1	1	1	1	1	1	1	1	1	1	0				

VAF reduction was significantly greater in pats treated with Imetelstat than placebo

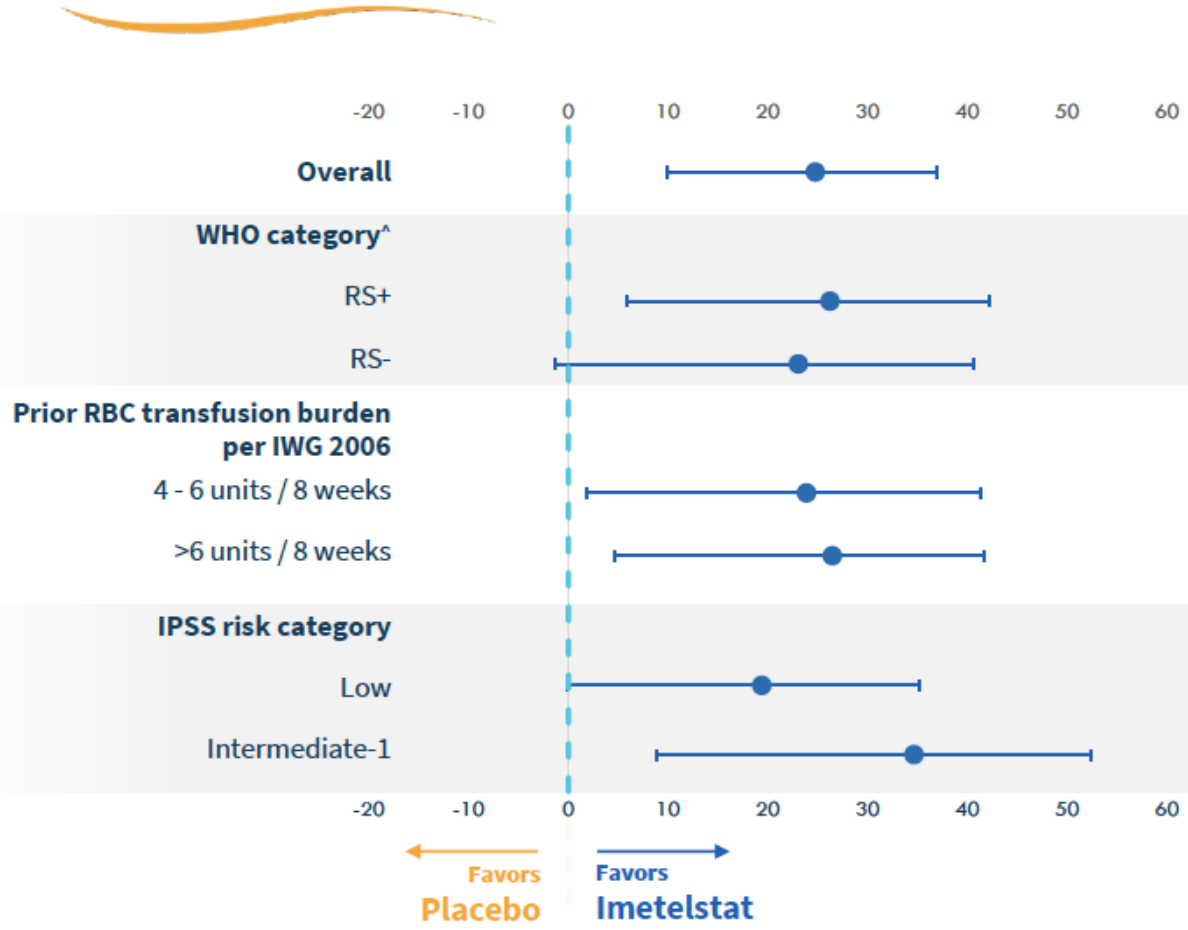
- *SF3B1* p<0.001 (related with TI dur)
- *TET2* p=0.032
- *DNMT3A* p=0.019
- *ASXL1* p=ns

Platzbecker U. Lancet. 2024 Jan 20;403(10423):249-260.

Treatment I **Low-Risk MDS – EPO R/R**

Clínica Universidad de Navarra

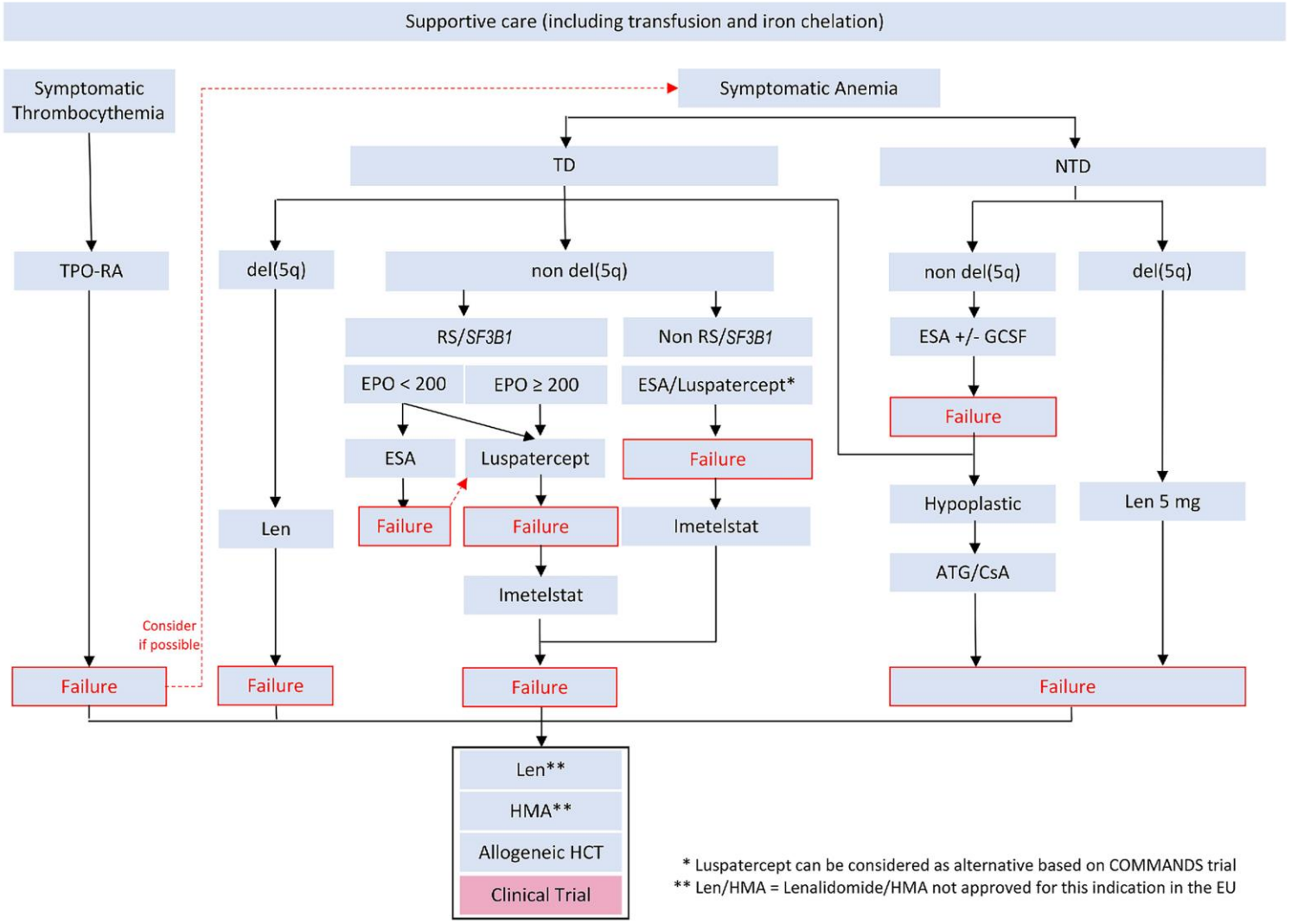
IMERGE: Phase III, Imetelstat vs EPO in untreated MDS, refractory or intolerant to EPO



	Imetelstat, n (%)	Placebo, n (%)	% Difference (95% CI)	P-value*
Overall	47/118 (39.8)	9/60 (15.0)	24.8 (9.9, 36.9)	**<0.001**
WHO category^				
RS+	33/73 (45.2)	7/37 (18.9)	26.3 (5.9, 42.2)	**0.016**
RS-	14/44 (31.8)	2/23 (8.7)	23.1 (-1.3, 40.6)	**0.038**
Prior RBC transfusion burden per IWG 2006				
4 - 6 units / 8 weeks	28/62 (45.2)	7/33 (21.2)	23.9 (1.9, 41.4)	**0.027**
>6 units / 8 weeks	19/56 (33.9)	2/27 (7.4)	26.5 (4.7, 41.8)	**0.023**
IPSS risk category				
Low	32/80 (40.0)	8/39 (20.5)	19.5 (-0.1, 35.2)	**0.034**
Intermediate-1	15/38 (39.5)	1/21 (4.8)	34.7 (8.8, 52.4)	**0.004**

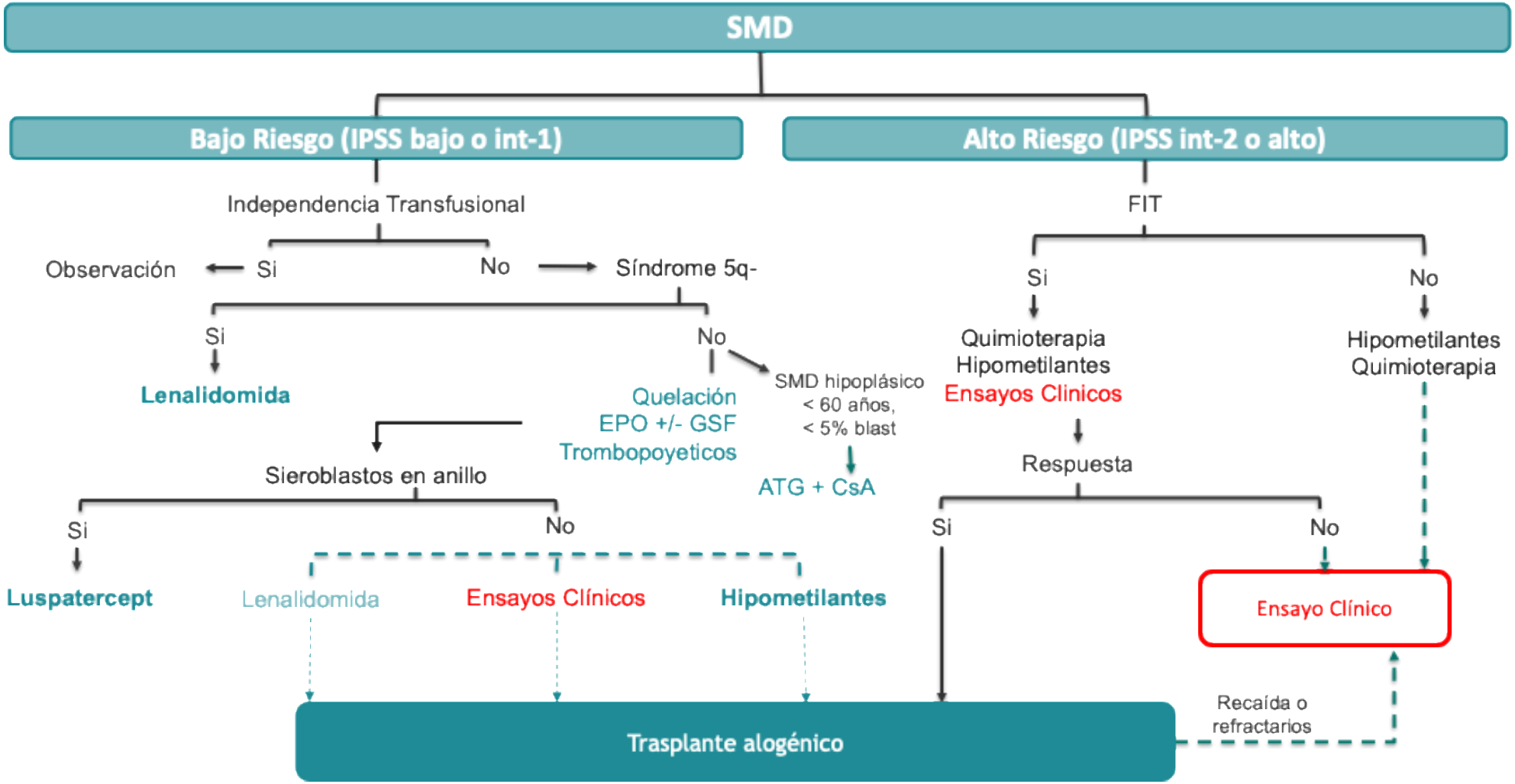
Platzbecker U. Lancet. 2024 Jan 20;403(10423):249-260.

Treatment I **Low-Risk MDS**



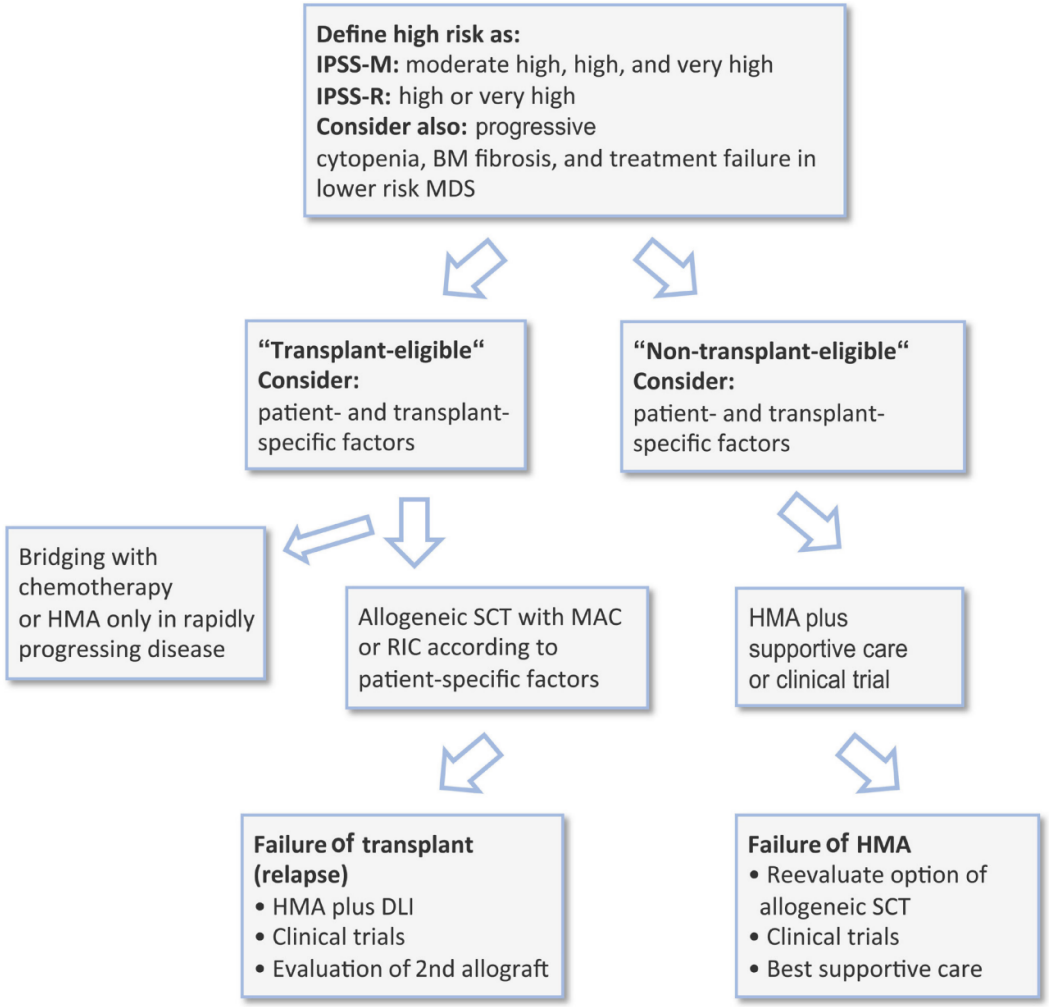
Merz. Haematologica 2025;110(2):330-338

Treatment



Dr. Alfonso's personal opinión

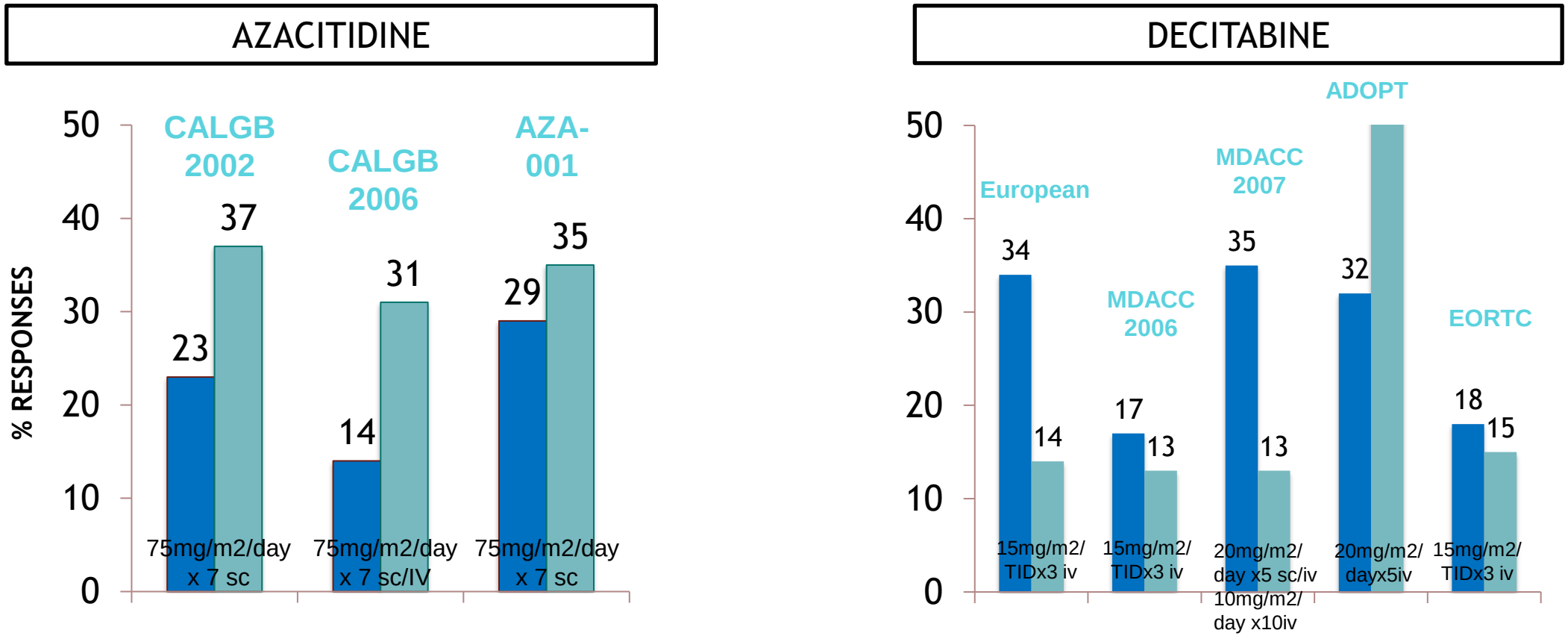
Treatment I **High Risk – MDS**



Kroger. Haematologica. 2025 Feb 1;110(2):339-349. doi: 10.3324/haematol.2023.284946.

Treatment I **High-Risk MDS – HMA**

ORR



Silverman LR. J Clin Oncol. 2002;20(10):2429-40
Silverman LR. J Clin Oncol. 2006 ;24(24):3895-903.
Fenaux P et al. Lancet Oncol. 2009 Mar;10(3):223-32
Wjiermans Ann Hematol 2005;84:9-17

Kantarjian H et al. Cancer 2006;106:1794-803
Kantarjian H et al. Blood 2007;109:52-7
Steensma DP et al. JCO 2009;24:3842-8
Lubberrt M et al. JCO. 2011;29(15):1987-96.

Treatment I **High-Risk MDS – Chemo**

Vyxeos

COHORTE A

Pacientes en primera linea de tratamiento

Criterios de inclusión

- Riesgo intermedio-2 o superior no tratado de síndrome mielodisplásico o leucemia mielomonocíticos crónicos. (incluidas las formas proliferativas con WBC ≥13×10⁹ células por L)
- 18 a 70 años, sin contraindicaciones para quimioterapia intensiva, menos del 20% de blastos en la médula y ECOG de 0 a 1

COHORTE B

Pacientes tratados previamente con HMA sin resultado

Criterios de exclusión

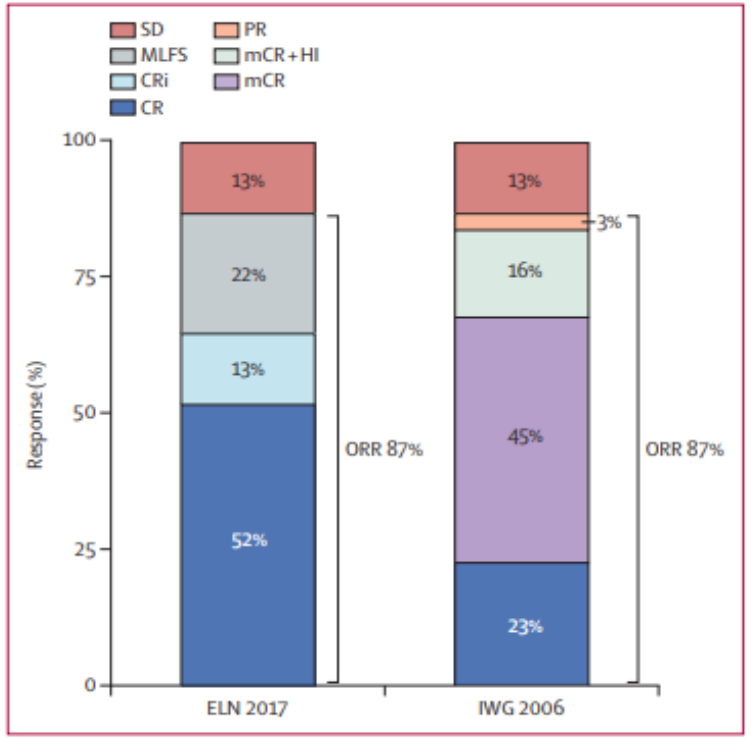
- Infección activa y no controlada, VIH, infección o cáncer relacionado con el VIH, clínicamente activo, infección por hepatitis B o C, alergia o hipersensibilidad a cualquier componente del CPX-351, secundario actualmente activo. malignidad (aparte del cáncer de piel no melanoma y carcinoma in situ del cuello uterino).
- Antecedentes de enfermedad de Wilson u otro trastorno relacionado con el cobre, tratamiento con factores de crecimiento en los 30 días previos a la inclusión, tratamiento con esteroides sistémicos que no habían sido estabilizados al equivalente de 10 mg/día o menos de prednisona durante 4 semanas antes del inicio de los fármacos del estudio, clínico.
- Evidencia de leucemia del SNC y embarazo o lactancia materna durante la duración del estudio.

Peterlin P. Lancet Haematol. 2023 Jul;10(7):e521-e529.

Treatment I **High-Risk MDS – Chemo**

Vyxeos

	Patients (N=31)
Age (years)	62 (56 to 66)
Gender	
Male	21 (68%)
Female	10 (32%)
At baseline	
Myelodysplastic syndrome subtype	
EB-2	26 (84%)
CMML-2	5 (16%)
Bone marrow blasts	13% (11 to 15)
Peripheral blasts	1% (0·00 to 2·25)
IPSS	
Intermediate 2	26 (84%)
High	5 (16%)
ECOG	
0	22 (71%)
1	9 (29%)
Comorbidities by patient*	2·0 (1·0 to 3·7)
Time between diagnosis and induction (days)	55 (28 to 154)
Previous treatment	
ESA	3 (10%)
Lenalidomide	1 (3%)
None	27 (87%)
Transfusion dependency in the 8 weeks before enrolment	12 (39%)
After induction treatment	
Recovery of CD13/CD16 neutrophil maturation pattern	15/19 (79%)
FCM progenitors decrease	−65·2 (−95·6 to −27·9)
nmVAF decrease†	−97·8 (−91·6 to −99·0)
VAF <2%‡	18/29 (62%)
VAF <0·1%§	8/29 (28%)

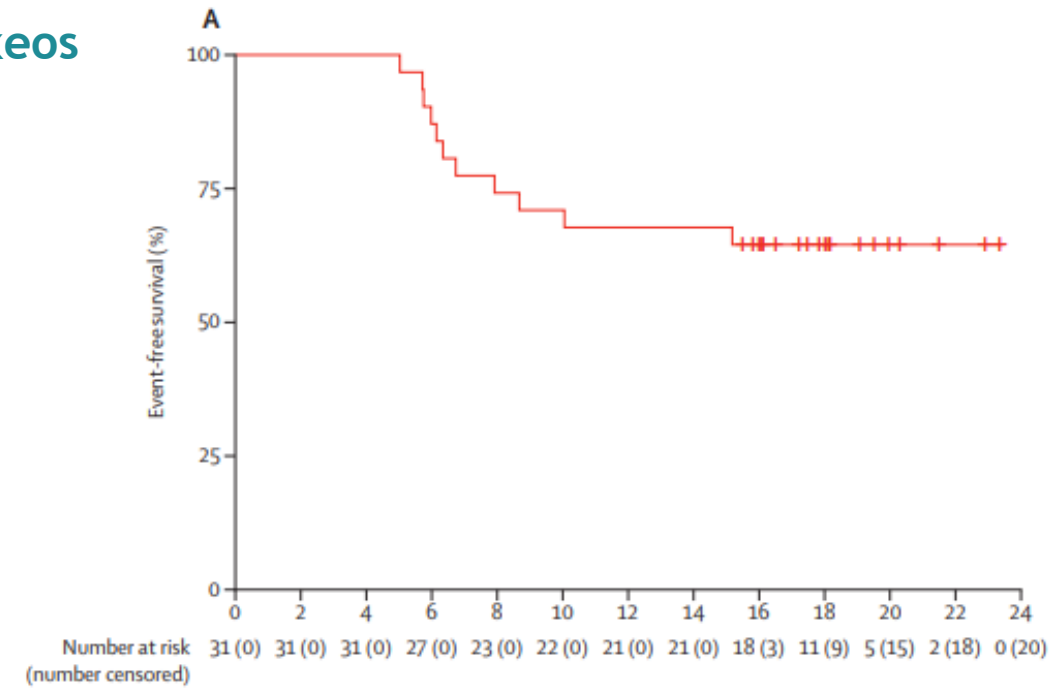


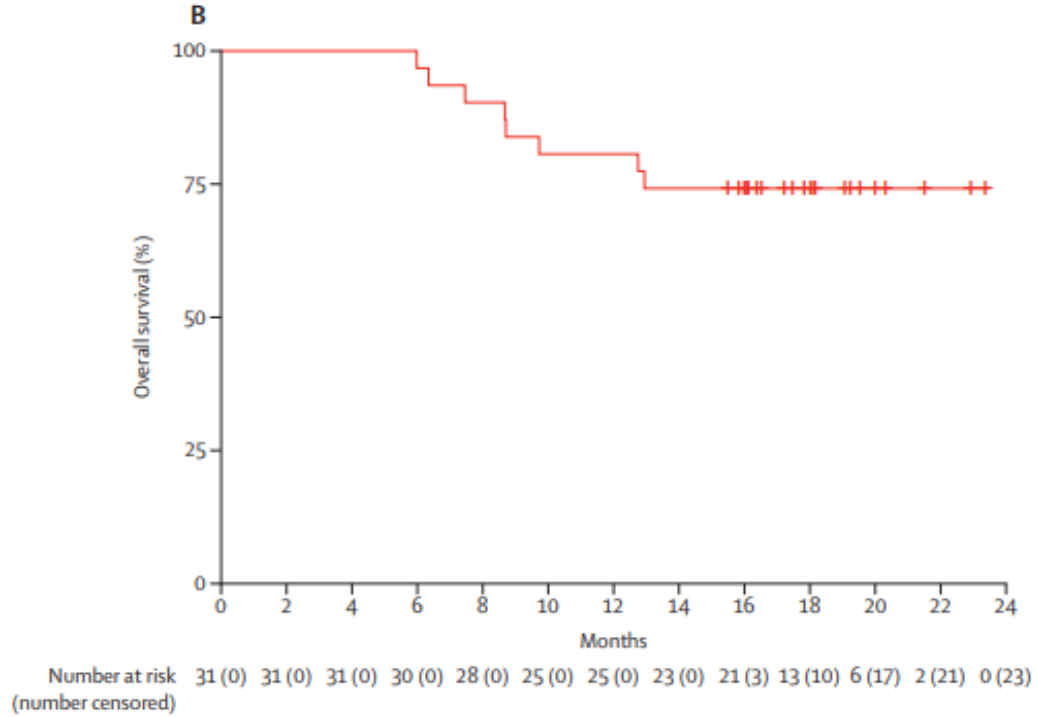
- Se observó **tasa de respuesta general** en el 87 % (IC 95 %: 70–96) de 31 pacientes.
- 16 (52%) de 31 pacientes tuvieron **RC**, 4 (13%) tuvieron **RCi,** 7 (22%) **MLFS** y 4 (13%) permanecieron en enfermedad estable.
- 30 de 31 pacientes (97%) incluidos se consideraron inicialmente elegibles para un **TCMH alogénico** y 29 (94%) se sometieron al procedimiento.

Peterlin P. Lancet Haematol. 2023 Jul;10(7):e521-e529.

Treatment I **High-Risk MDS – Chemo**

Vyxeos





- La mediana de seguimiento fue de 16,1 meses (RIQ 8,3–18,1)
- No se alcanzó la mediana de EFS, con una EFS estimada a 12 meses de 67,7 % (IC 95 %: 53,1–86,4)
- Tampoco se alcanzó la mediana de SG, que fue del 80,6 % (IC del 95 %: 67,9–95,8) a los 12 meses.

Peterlin P. Lancet Haematol. 2023 Jul;10(7):e521-e529.

Treatment I **High-Risk MDS – Chemo**

Clínica Universidad de Navarra | Cancer Center

Ven+ Azacitidine for Patients With Treatment-Naive, Higher-risk Myelodysplastic Syndromes

Characteristic	N=107
Median age, years (range)	68 (26–87)
Male, n (%)	74 (69.2)
ECOG performance score, n (%)[a]	
0	56 (52.8)
1	43 (40.6)
2	7 (6.6)
Baseline BM blast category, n (%)	
≤5%	11 (10.3)
>5≤10%	32 (29.9)
>10%	64 (59.8)
Baseline BM blast count, median (range), %	11.0 (1.0–19.5)
IPSS-R prognostic score, n (%)	
Low	1 (0.9)
Intermediate	14 (13.1)
High	40 (37.4)
Very high	52 (48.6)
IPSS-R cytogenetic risk, n(%)	
Very good/good[b]	*39 (36.4)*
Intermediate	*35 (32.7)*
Poor/very poor[c]	*33 (30.8)*
Most common mutations, n/N (%)[d]	
ASXL1	29/84 (34.5)
TP53	20/84 (23.8)
SRSF2	19/84 (22.6)
RUNX1	18/84 (21.4)

- Ven 100–400 mg doses in combination with Aza 75mg/m^2 x 7 days were evaluated in 124 patients
- Ven 400 mg dose for 14 days in each 28-day cycle was confirmed as RP2D
- 107 patients received the RP2D Ven 400 for 14 days + Aza
- 34 (31.8%) patients were deemed eligible for SCT by treating investigators at study entry

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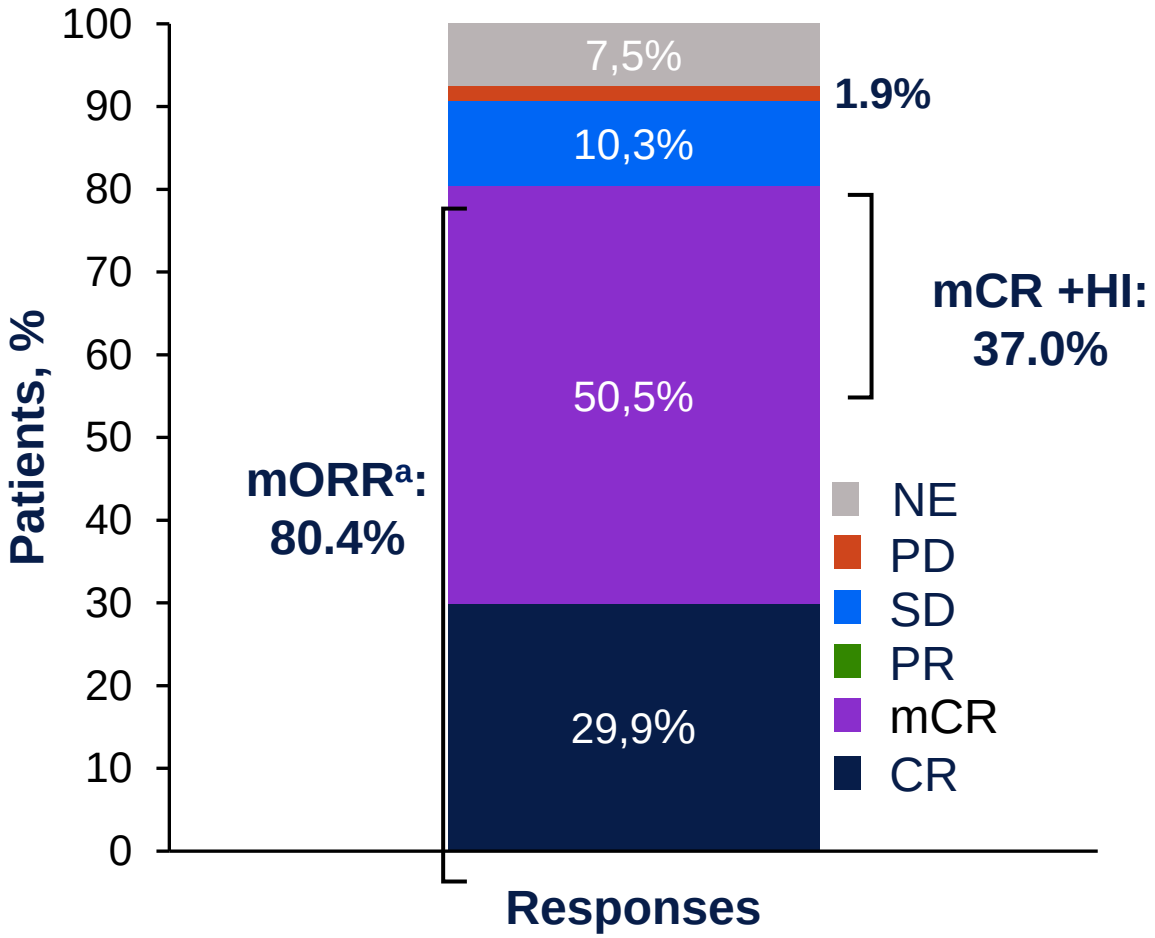
Treatment I **High-Risk MDS – Chemo**

Ven+ Azacitidine for Patients With Treatment-Naive, Higher-risk Myelodysplastic Syndromes

>80% of Patients Who Received Ven + Aza Responded



- Median number of treatment cycles with Ven 400 + Aza: 4.0 (range, 1–57)
- Median time to CR: 2.8 months (range, 1.0–16.1)
- Median duration of CR: 16.6 months (95% CI, 10.0–NR)
- MDS to AML transformation: in 13 (12.3%) patients (95% CI, 6.7–20.1)
  - Median time to AML transformation was 5.95 months (range, 0.72–29.31)

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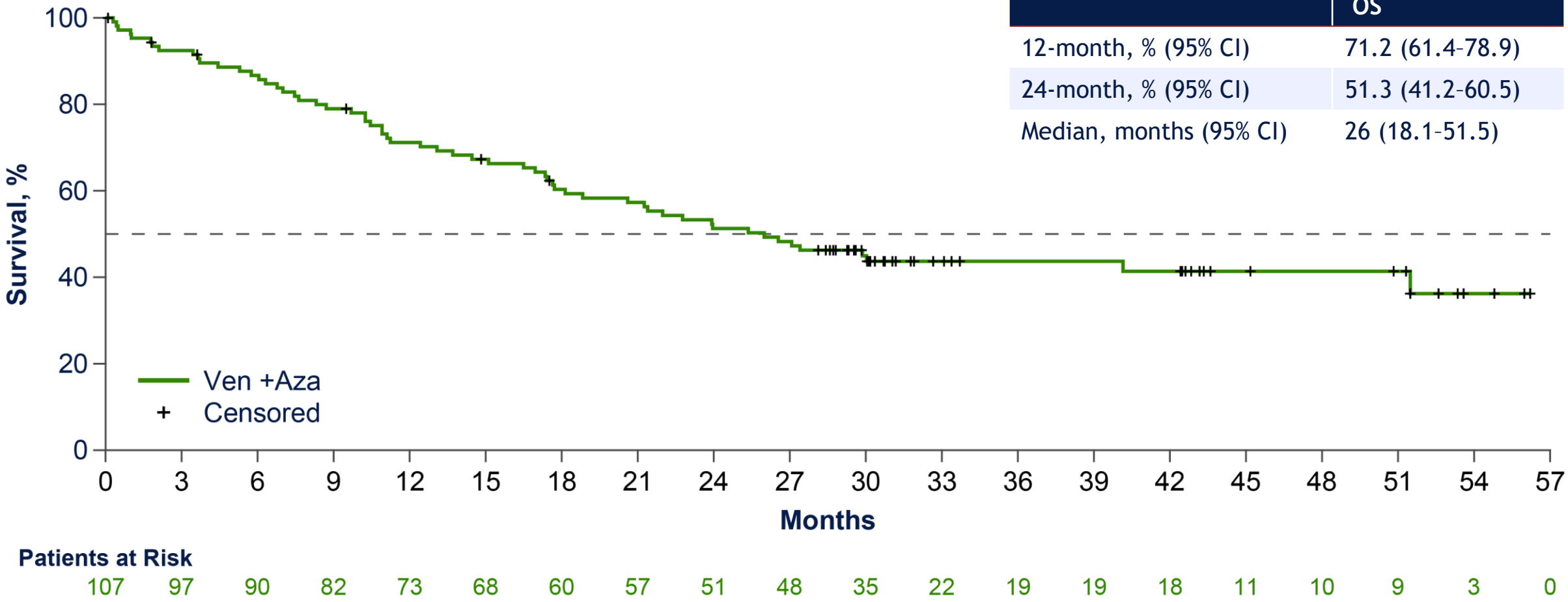
Treatment I **High-Risk MDS – Chemo**

Ven+ Azacitidine for Patients With Treatment-Naive, Higher-risk Myelodysplastic Syndromes

	OS
12-month, % (95% CI)	71.2 (61.4-78.9)
24-month, % (95% CI)	51.3 (41.2-60.5)
Median, months (95% CI)	26 (18.1-51.5)



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Organizado por:

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PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

ACTUALÍZATE 48 HORAS

Explorando las últimas estrategias en el manejo de los Síndromes Mielodisplásicos

Ana Alfonso-Piérola

Clínica Universidad de Navarra, Pamplona