POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Terapia delle sindromi mielodisplastiche a basso rischio

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Disclosures of Maria Teresa Voso, MD

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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Servier			x		x	x	
BMS					x	x	
Jazz					x		
Daichy-Sankyo					x		
Abbvie					x		

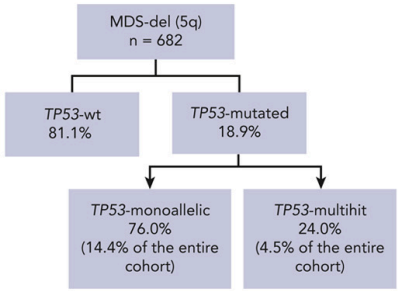
Outline

- del(5q) prognostic score
- «Early vs late» ESA
- Updates on:
  - ✓ Luspatercept
  - ✓ Imetelstat

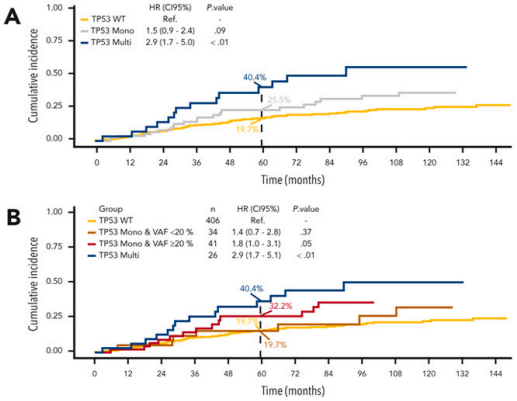
Influence of TP53 gene mutations and their allelic status in myelodysplastic syndromes with isolated 5q deletion

TP53 Gene Alterations in Myelodysplastic Syndromes With Isolated 5q Deletion (MDS-del (5q))

Classification of patients with MDS-del (5q) according to *TP53* gene alterations



Risk of AML evolution according to a) *TP53* allelic state and b) *TP53* VAF cutoff point of 20%



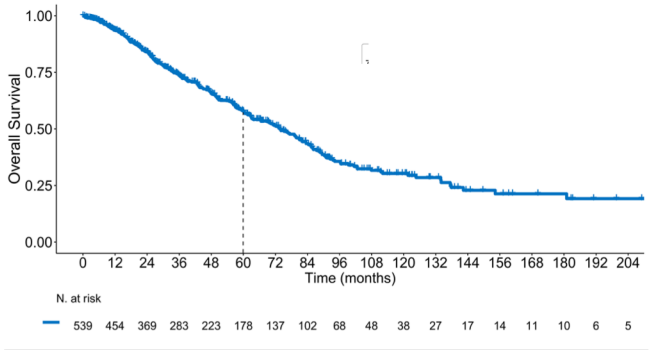
Conclusions: *TP53* mutations are prevalent in MDS-del (5q) (18.9%), but the presence of a multihit state is rare (4.5% of the entire cohort). *TP53*-multihit state and *TP53* VAF ≥20% are associated with poor outcomes.

*Montoro et al. DOI: 10.1182/**blood**.2024023840*

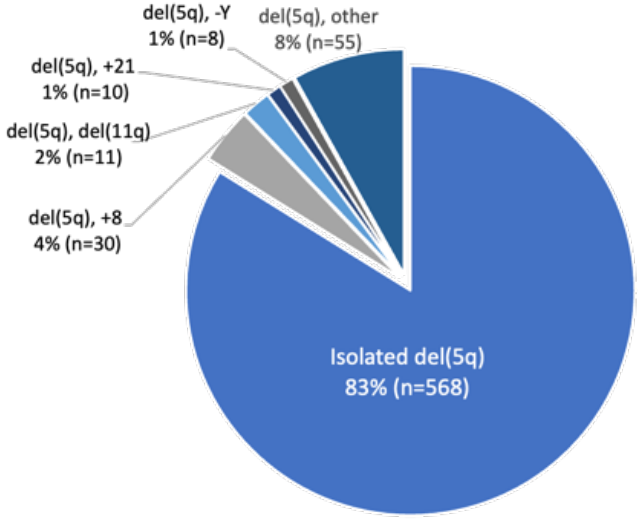
blood Visual Abstract

Newly Developed Prognostic Score for Myelodysplastic Syndrome (MDS) with Isolated 5q Deletion (IPSS-del(5q))

	Median (IQR)
N	682
Age, years	74 (66–80)
Sex, female (%)	73.3
Hemoglobin , g/dL	9.2 (8.1–10.3)
WBC, x10^9/L	4.1 (3–5.5)
Neutrophils, x10^9/L	2.0 (1.3–3.1)
Platelets, x10^9/L	249 (169–347)
Bone marrow blasts, %	2 (1–3.5)
Treatment (data available) %, n:	65 (439)
Lenalidomide	67 (294)
RBC transfusions	14 (63)
ESA alone	11 (48)
Other	8 (34)
HSCT	6 (25)



- Median follow-up: 69 months (CI95% 63–81)
- Median OS: 74 months (CI95% 63–83)
- AML evolution at 60 months: 23%
  - Median time to AML: 32m (CI95% 18–57)

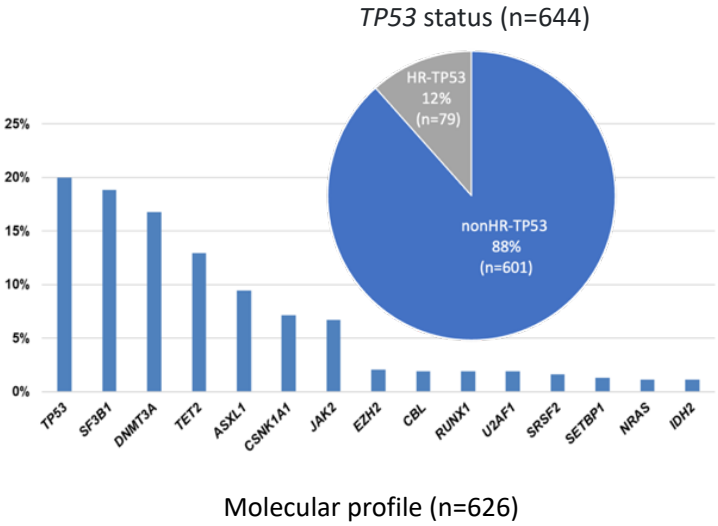


Cytogenetic abnormalities (n=682)

Courtesy of M.J. Montoro et al

IPSS-del(5q) Scoring System for LFS

- ❖ 71% of pts carriers of ≥1 mutation
- ❖ Tp53 status: HR: multi-hit or monoallelic with VAF ≥50%

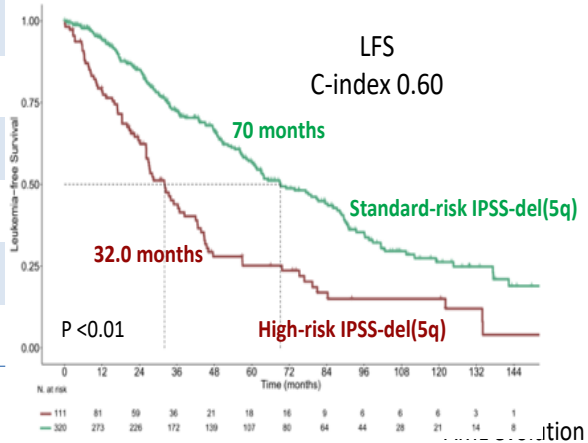


Molecular profile (n=626)

LASSO-Cox analysis

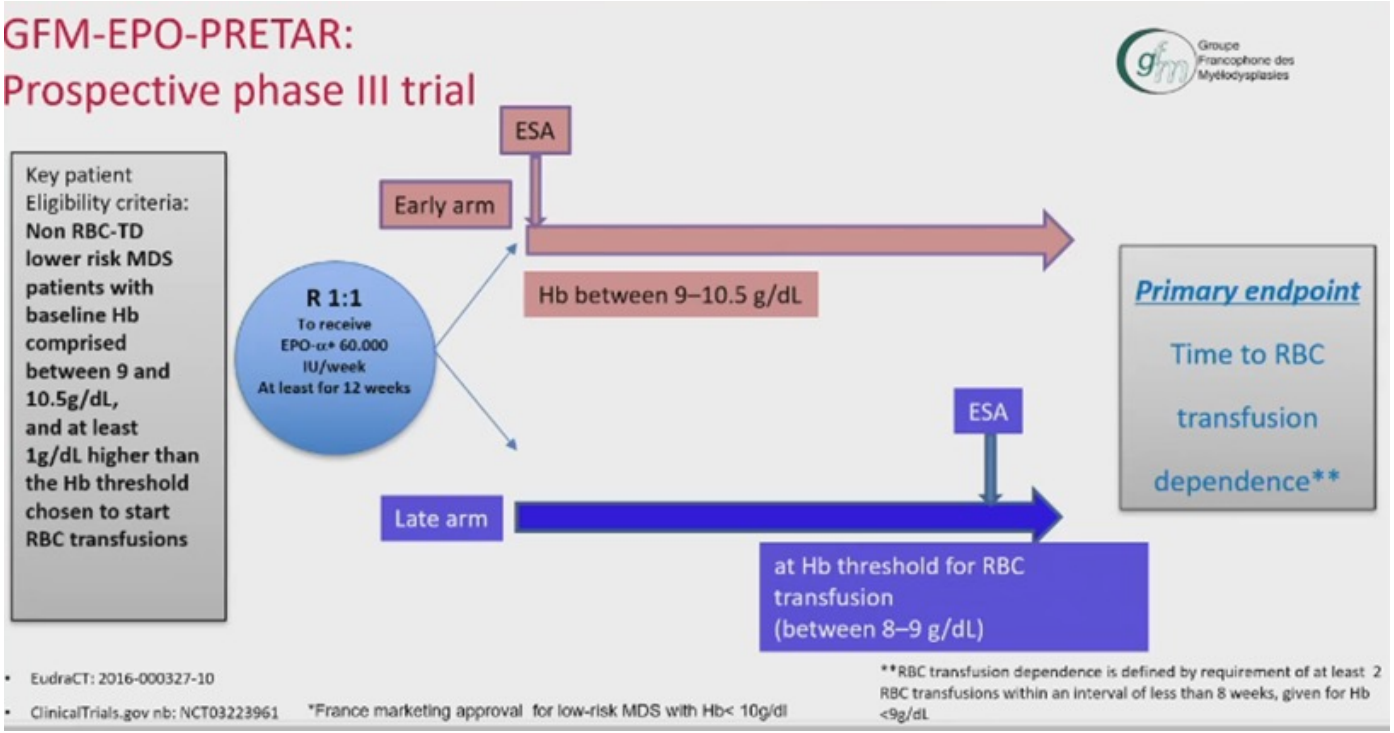
Variable	Points
Sex, male	1
Hemoglobin ≤ 10 g/dL	2
Platelet ≤ 100 x10^9/L	2
≥ 2 additional mutations	2
SF3B1 mutations	1
HR-*TP53 status*	1

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



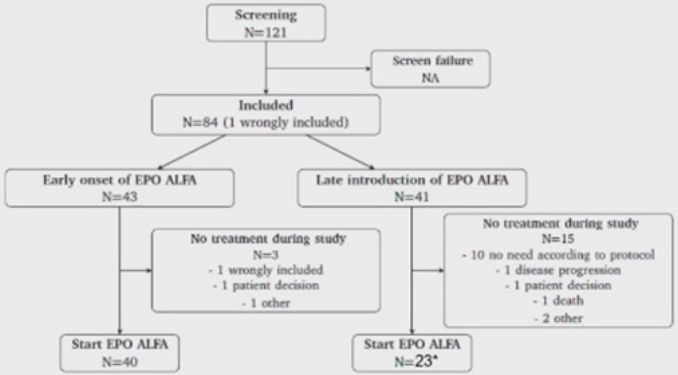
Courtesy of M.J. Montoro et al, ABS N.666

Early Versus Late Onset of ESA in Lower Risk Anemic MDS Patients: Results of the GFM Randomized Phase III EPO-Pretar Trial

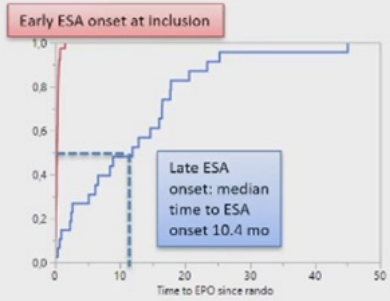


Park S. et al, ABS N. 349

Flow chart: inclusion from May 2018 to Dec 2022



*data cut-off: 10 Jul 2024



Baseline characteristics

Parameters	Early Arm (N = 43)	Late Arm (N = 41)	Global (N)	
Gender				
Male	53%	54%	54%	
Female	47%	46%	46%	
Age (years)	76.4	75.9	76.2	
Secondary MDS (yes)	7%	0%	4%	
Time from diagnosis to inclusion (median, months)	3.9 [2; 8.1]	4.4 [1.8; 14.9]	4.1 [2; 11]	
WHO classification				
RS-	43%	32%	38%	NS
RS+	38%	49%	43%	
MDS-EB1	14%	5%	10%	
Hemoglobin (g/dL) (IQR)	10.2 [9.6; 10.5]	10.3 [9.7; 10.8]	10.2 [9.7; 10.7]	
IPSS				
Low risk	76%	77%	76%	
Intermediate-1 risk	24%	23%	24%	
IPSS-R				
Very low	34%	51%	42%	NS
Low	46%	36%	46%	
Intermediate	15%	12%	10%	

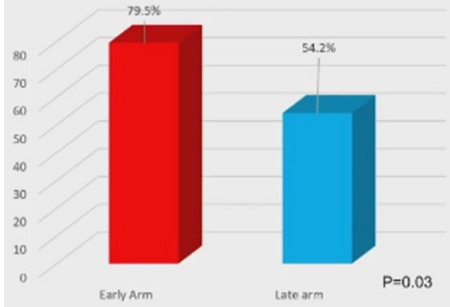
Comorbidities

Category	N (%) Early arm (43)	N (%) Late arm (41)
All	41 (95%)	40 (98%)
Cardio-Vascular	36 (84%)	27 (66%)
Endocrinology- Metabolic	26 (60%)	19 (46%)
Gastro-intestinal	15 (35%)	18 (44%)
Musculo-skeletal	14 (33%)	17 (41%)
Genito-Urinary	14 (33%)	17 (41%)
Other	13 (30%)	13 (32%)
Neurological	9 (21%)	10 (24%)
Psychiatric	6 (14%)	6 (15%)
Cutaneous	5 (12%)	5 (12%)
Pulmonary	4 (9%)	5 (12%)
Allergies	2 (5%)	3 (7%)
Hepatic	1 (2%)	0 (0%)

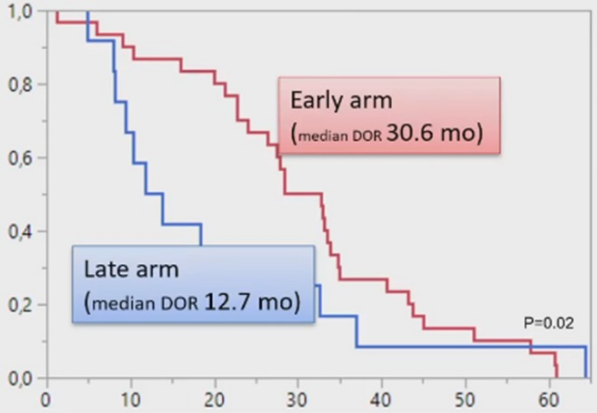
Groupe Francophone des Myélodysplasies

Park S. et al,
ABS N. 349

Higher response rate and longer erythroid response to ESA in the Early arm

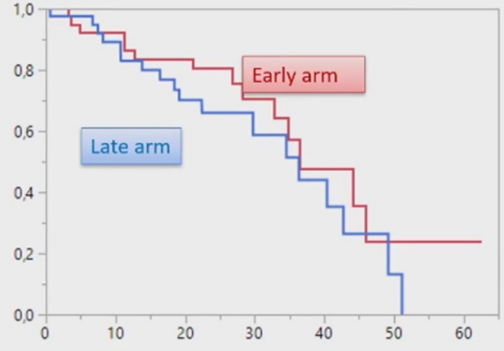


ORR (IWG 2018)

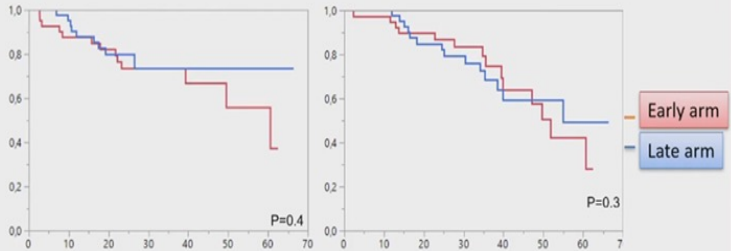


Duration of response to ESA (months)

No significant difference in time to RBC transfusion dependence from inclusion



No significant difference in PFS and OS



PFS from inclusion

OS from inclusion

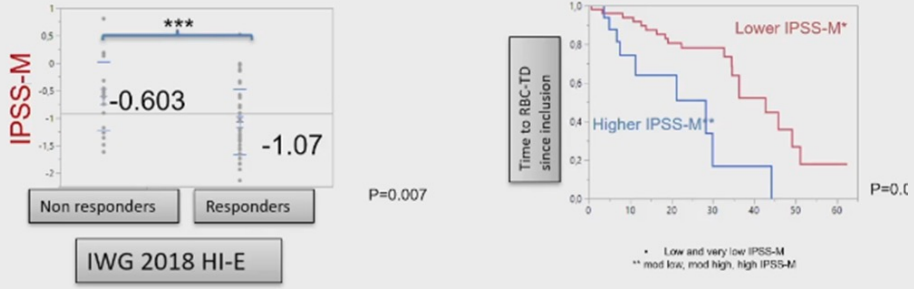
3 pts transformed in AML in each arm

PFS: progression to higher risk MDS or AML

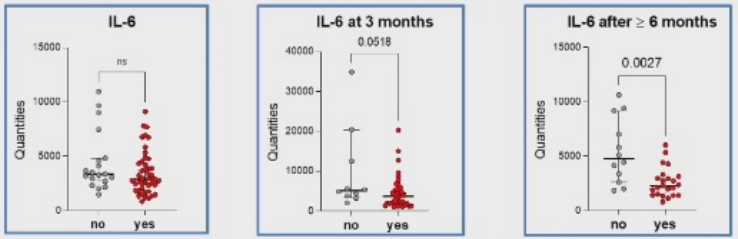
No differences in QoL

Park S. et al, ABS N. 349

Erythroid response and Time to RBC TD correlate with IPSS-M in the patients having received ESA (n=63)



IL-6 decreases over time in ESA-responsive patients



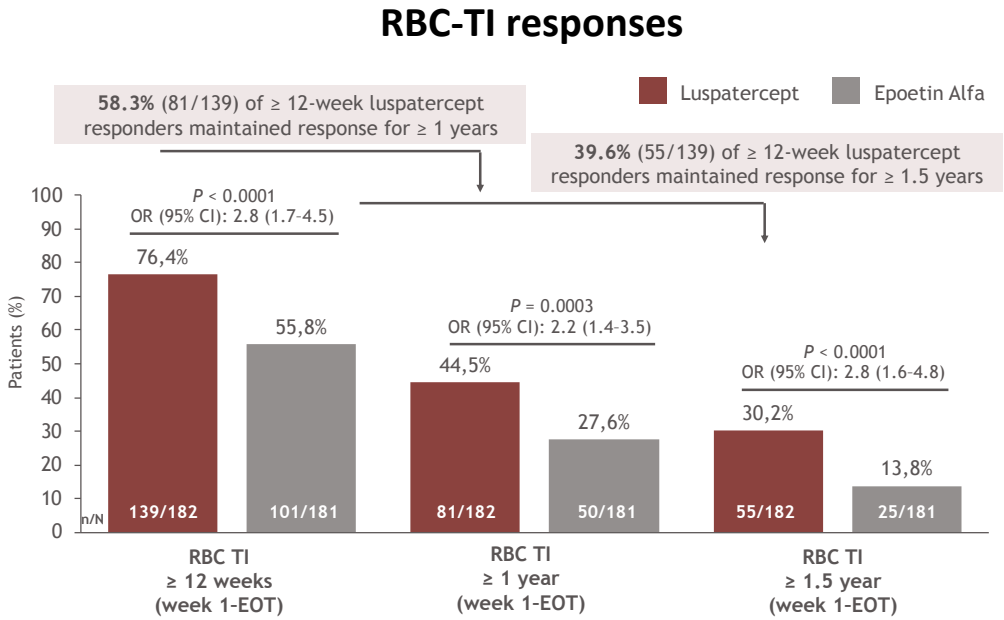
N=57

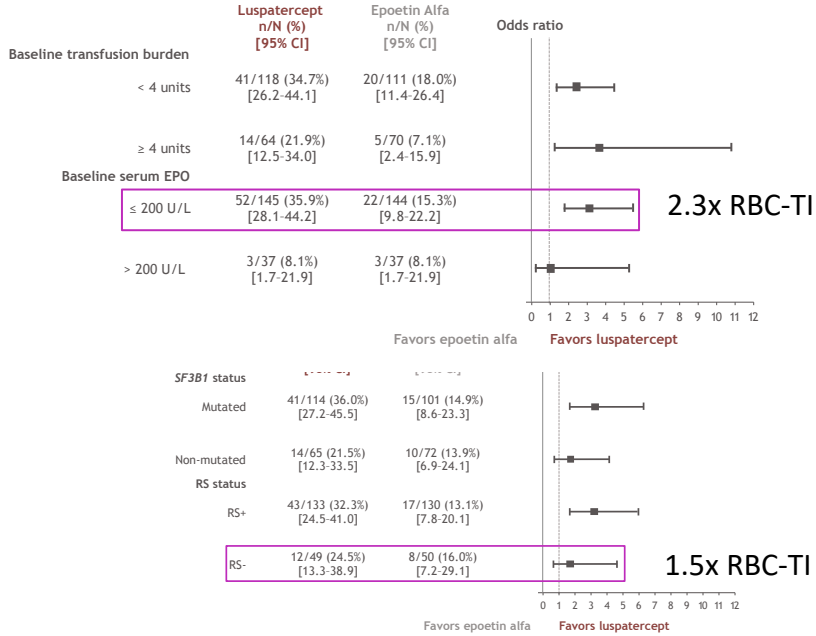
No modification of TGF-β, TNF-α, IL1-β and S100A8/A9

- An erythroid gene expression signature was prevalent in pts becoming TD
- Early introduction of ESA in LR-MDS with anemia:
  - ✓ Did not delay the time to RBC-TD from inclusion
  - ✓ Increased HI-E and duration of response

Park S. et al, ABS N. 349

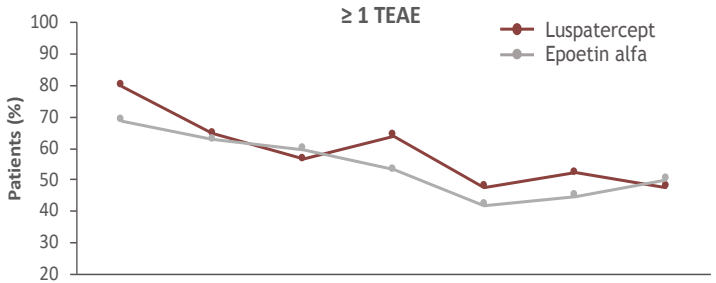
Long-term response analysis of transfusion independence in ESA–naive patients with very low-, low-, or intermediate-risk MDS treated with luspatercept versus epoetin alfa in the COMMANDS trial





G. Garcia-Manero et al, ABS N. 350

COMMANDS: TEAEs up to 1.5 years



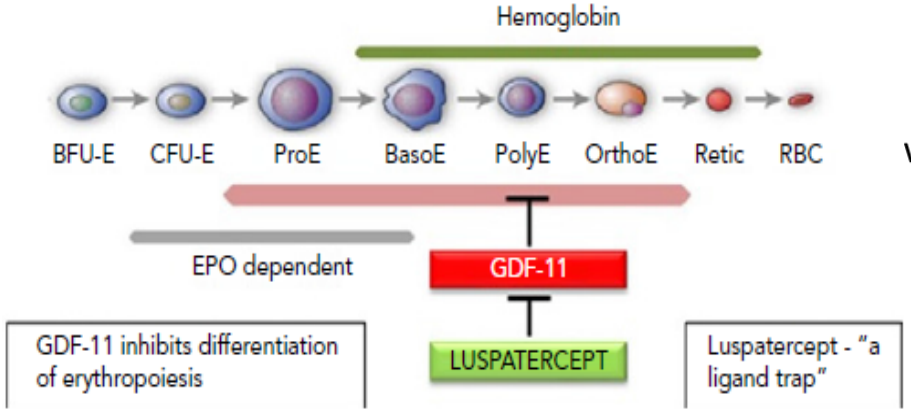
No. of patients							
Luspatercept	182	170	152	125	105	86	67
Epoetin alfa	179	156	124	90	69	49	40

Treatment-emergent EOI (any grade)	Luspatercept (n = 182)		Epoetin alfa (n = 179)	
	n (%)	EAIR/100 PY[a]	n (%)	EAIR/100 PY[a]
EOI	111 (61.0)	73.4	87 (48.6)	67.6
Asthenia (incl. fatigue, malaise, and lethargy)	59 (32.4)	28.9	46 (25.7)	29.6
Hypertension	31 (17.0)	13.7	17 (9.5)	9.4
Kidney toxicity	18 (9.9)	7.3	13 (7.3)	7.0
Malignancies	18 (9.9)	7.1	14 (7.8)	7.5
Premalignant disorders	12 (6.6)	4.6	14 (7.8)	7.2
Thromboembolic events	12 (6.6)	4.7	6 (3.4)	3.1
Immunogenicity hypersensitivity type reactions	7 (3.8)	2.7	3 (1.7)	1.5
Immunogenicity injection local type reactions	5 (2.7)	2.0	1 (0.6)	0.5
Liver toxicity	4 (2.2)	1.5	5 (2.8)	2.6

	Luspatercept (n = 182)	Epoetin alfa (n = 181)
Progression to high-risk MDS, n (%)	4 (2.2)	6 (3.4)[a]
High-risk MDS exposure-adjusted incidence rate per 100 person-years[b] (95% CI)	98.52 (36.98-262.49)	117.5 (52.79-261.56)
Median time to high-risk MDS progression from initial MDS diagnosis (95% CI)	NR (NR-NR)	NR (NR-NR)
Progression to AML, n (%)	7 (3.8)	8 (4.4)
AML incidence rate per 100 person-years (95% CI)[c]	2.02 (0.96-4.24)	2.48 (1.24-4.97)
Hazard ratio (95% CI)[d]	1.026 (0.36-2.925); *P* = 0.9612	
Median time to AML progression from initial MDS diagnosis (95% CI)	NR (132.1-NR)	NR (NR-NR)

G. Garcia-Manero et al, ABS N. 350

Combining ESA and Luspatercept in Non-RS MDS Patients Having Failed ESA – Results of the Phase 1-2 Part A of the GFM Combola Study



Patients with lower-risk MDS without del(5q) and without RS with primary or secondary ESA resistance (N = 24)

→ **Luspatercept** 1.75 mg/kg SC Q3W + **EPO** 60,000 UI SC Q1W (n = 15)

→ **Luspatercept** 1.75 mg/kg SC Q3W + **EPO** 30,000 UI SC Q1W (n = 3)

→ **Luspatercept** 1.33 mg/kg SC Q3W + **EPO** 30,000 UI SC Q1W (n = 3)

→ **Luspatercept** 0.8 mg/kg SC Q3W + **EPO** 30,000 UI SC Q1W (n = 3)

24 patients from 10 French centers included between 5/2022 and 11/2023.

Ades L. et al, Abs 351

Characteristic	All Patients (N = 24)
Median age, yr (Q1, Q3)	77.7 (71.4, 84.1)
Male sex, n	18
Median WBC, giga/L (Q1, Q3)	2.9 (1.9, 3.5)
Median hemoglobin, g/dL (Q1, Q3)	8.1 (7.4, 8.8)
Median platelets, giga/L (Q1, Q3)	94 (46.8, 141)
MDS subtype, n	
▪ MDS MLD	18
▪ MDS SLD	2
▪ MDS-EB1	4
MDS risk, n (%)	
▪ Low	2 (8.3)
▪ Intermediate-1	22 (91.7)
ESA resistance, n (%)	
▪ Primary	16 (67)
▪ Relapsed	8 (33)
Median RBC units/16 wk, n (Q1;Q3)	9.5 (5.8;15.2)
Transfusion burden, n (%)	
▪ Low	6 (25.0)
▪ High (≥4)	16 (66.7)
▪ Non-TD	2 (8.3)

- No unexpected toxicities
- No DLTs observed at Day 42

Outcome, n (%)	Low Transfusion Burden (n = 6)	High Transfusion Burden (n = 16)	Nontransfusion Dependent (n = 2)	Overall (N = 24)
Erythroid response* at Wk 25	2 (33)	4 (25)	1 (50)	7 (30)

*Per IWG 2018.

✓ Among 7 pts who achieved HE, 3 continue to respond
  ❖ Median DoR: 9.18 mo
✓ 2 pts achieved a platelet response, and 1 neutrophil response
✓ 2 pts experienced progression to AML,
✓ 5 died (n = 2 due to infection, n = 1 due to AML evolution; none deemed related to study drug)

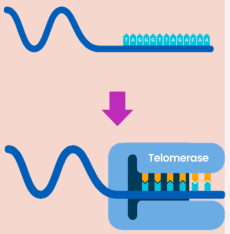
❖ Luspatercept 1.75 mg/kg SC Q21D + EPO 60,000 UI SC Q1W selected as RP2D in the randomized part B vs Luspatercept alone

Imetelstat overview

Background

Route of administration	7.1 mg/kg IV every 4 weeks (2-hour infusion)
Modality	Investigational first-in-class telomerase inhibitor
Key trials in MDS	IMerge (Phase 2/3) - NCT02598661
Target patient population	Patients with transfusion-dependent anemia due to LR-MDS, who are R/R to, or ineligible for ESAs

Mechanism of action



- Telomerase activity is elevated in the bone marrow of patients with MDS
- Imetelstat is an NPS oligonucleotide which is complementary to the RNA template of telomerase
- Imetelstat binds to telomerase with high affinity
- Once bound, imetelstat prevents telomerase binding to telomers
- This results in the apoptosis of malignant stem and progenitor cells in the bone marrow

Regulatory status

Approved in US for adults with LR-MDS with TD anemia requiring ≥ 4 or more RBC units over 8 weeks who have not responded to or have lost response to or are ineligible for ESAs

Phase 2 IMerge[1]
Single-arm, open-label

Patient population (all treated)
- IPSS low- or INT-1–risk MDS
- Relapsed or refractory to ESA or EPO >500 mU/mL
- Transfusion dependent: ≥4 RBC U/8 weeks over 16-week prestudy period
- Inclusion of del(5q) and allowance of prior LEN and HMA

Imetelstat
7.1 mg/kg active dose
(equivalent to 7.5 mg/kg imetelstat sodium)
IV every 4 weeks
(n=57)

Phase 3 IMerge[2]
Double-blind, randomized 2:1

Patient population (ITT)
- IPSS low- or INT-1–risk MDS
- Relapsed or refractory[a] to ESAs or EPO >500 mU/mL (ESA ineligible)
- Transfusion dependent: ≥4 RBC U/8 weeks over 16-week prestudy period
- Non-del(5q), no prior treatment with LEN or HMAs

Imetelstat
7.1 mg/kg active dose
(equivalent to 7.5 mg/kg imetelstat sodium)
IV every 4 weeks
(n=118)

Placebo

QTc Substudy of Phase 3 IMerge
Double-blind, randomized 2:1

Patient population differed from that of phase 3 IMerge as follows:
- ✓ Inclusion of patients with del(5q) MDS
- ✓ Allowance of prior LEN and HMA use
- ✓ Option to cross over from placebo to imetelstat after 2 cycles at the investigator's discretion

Imetelstat
7.1 mg/kg active dose
(equivalent to 7.5 mg/kg imetelstat sodium)
IV every 4 weeks
(n=35)

Crossover from placebo to imetelstat
(n=16)

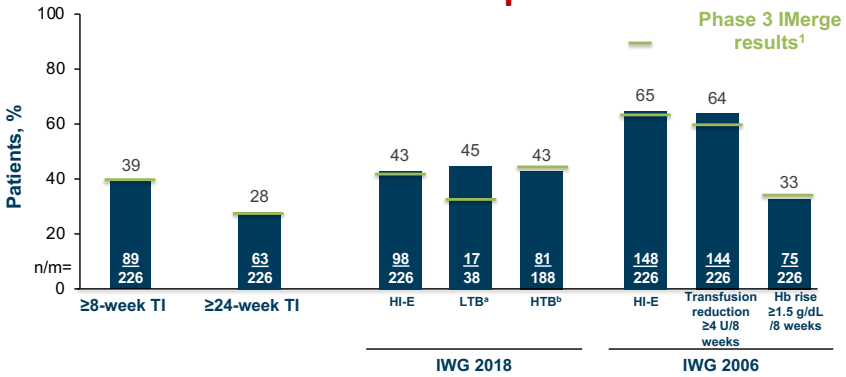
A total of 226 patients with LR-MDS treated with Imetelstat were included in this analysis

Courtesy of Platzbecker U et al, ASH, Abs 352

Baseline patient and disease characteristics	Imetelstat (N=226)
Age, median (range), y	71.0 (43-87)
≥65 y, n (%)	174 (77)
WHO classification, n (%)	
RS+	147 (65)
RS−	78 (35)
IPSS risk category, n (%)	
Low	151 (67)
Intermediate-1	75 (33)
Prior RBC transfusion burden, n (%)	
≤6 U/8 weeks	112 (50)
>6 U/8 weeks	114 (50)
Serum EPO level, n (%)	
≤500 mU/mL	155 (69)
>500 mU/mL	64 (28)
Missing	7 (3)
Transfusion burden per IWG 2018, n (%)	
LTB	38 (17)
HTB	188 (83)
Imetelstat duration, median (range), weeks	**33.6 (0.1-260.1)**
Number of imetelstat treatment cycles, n (%)	34 (15)
1-3 cycles	56 (25)
4-6 cycles	46 (20)
7-12 cycles	90 (40)
≥13 cycles	

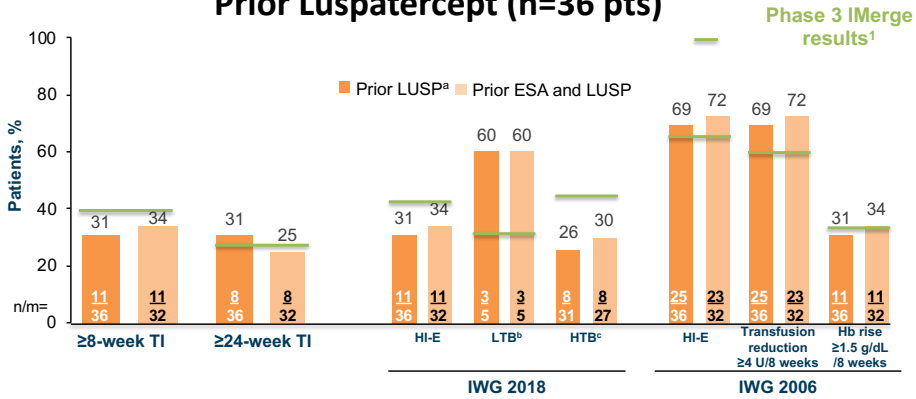
Courtesy of Platzbecker U et al, ASH, Abs 352

Overall Response



Activity was observed in pts with **prior ESA treatment**, ESA refractory or ineligible

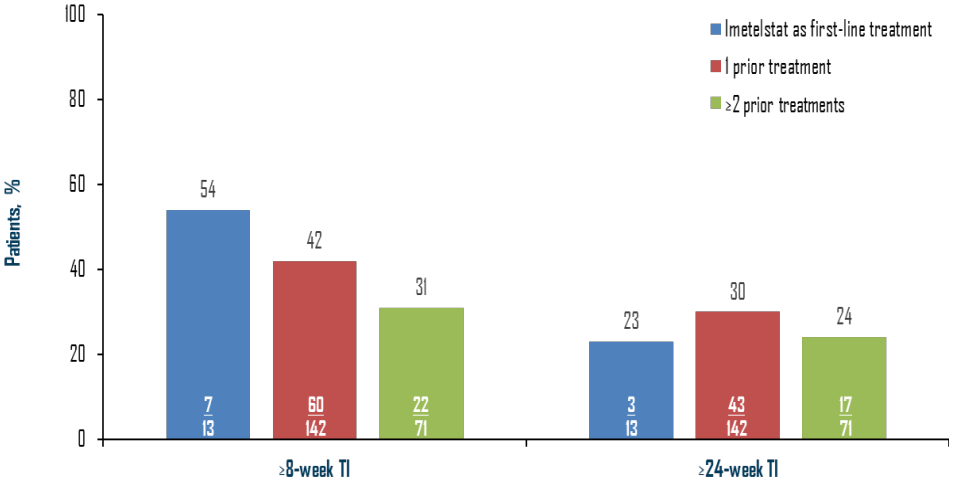
Prior Luspatercept (n=36 pts)



≥ 8w TI achieved by

- ✓ 6 of 26 pts (23%) with prior lenalidomide treatment
- ✓ Only 3 of 22 (14%) with prior HMA

Clinical Activity Regardless of Number of Prior Lines of Therapy (N=226)



TEAE

	Total (N=226)
TEAEs, n (%)	
Any grade	221 (97.8)
Serious	85 (37.6)
Grade ≥3	200 (88.5)
Most common TEAEs by preferred term in ≥15% of patients, n (%)	
Neutropenia	163 (72.1)
Thrombocytopenia	161 (71.2)
Anemia	48 (21.2)
Diarrhea	36 (15.9)
Alanine aminotransferase increased	35 (15.5)

Most cytopenia events occurred in earlier treatment cycles/months and were temporary and reversible, with most grade ≥3 neutropenia (82.6%) and thrombocytopenia (86.4%) events resolved to grade ≤2 in <4 weeks

Courtesy of Platzbecker U et al, ASH, Abs 352

Conclusions

- MDS-del(5q) tend to have shorter LFS in males, if Hb ≤10 g/dl, and/or PLTS ≤100.000/microl, in presence of ≥ 2 additional mutations, in particular SF3B1 and/or TP53
- «Early» ESA (Hb 9-10.5 g/dl) is associated with a higher probability and to longer duration of response, particularly in pts with lower IPSS-M
- At 1.5 yrs of f-up in the Commands trial, 30% of pts treated with Luspatercept remain RBC-TI (vs 14% with Epo), in particular in pts with endogenous Epo < 200
- The Luspatercept/EPO combination may induce ER in 30% of ESA resistant patients
- Imetelstat induces HI-E in 40% of pts resistant to ESA, independent of prior Luspatercept use, regardless of prior lines of therapy, with side effects prevalent during first treatment weeks