FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Clinica e Terapia delle Sindromi Mielodisplastiche

28 maggio 2022

•Trombocitopenie in MDS

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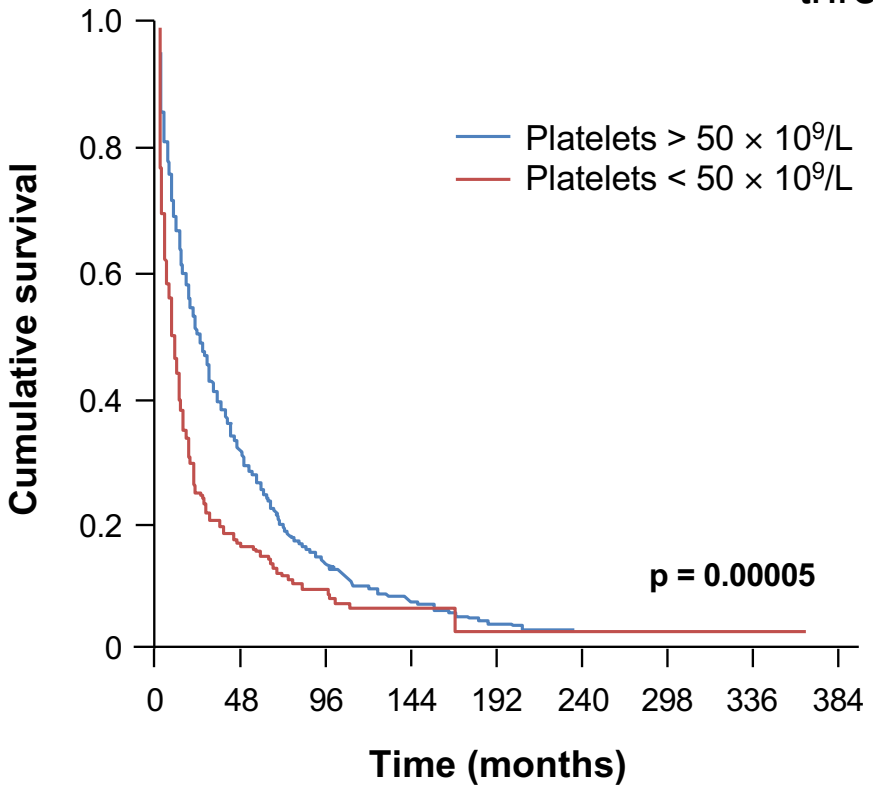
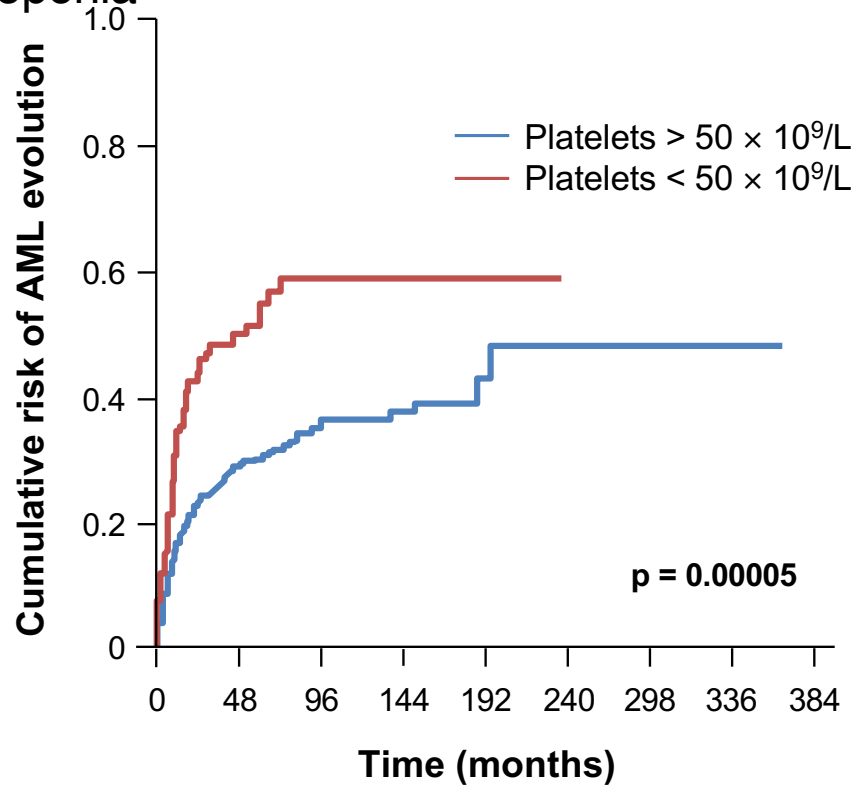
Thrombocytopenia is associated with poor outcomes in MDS

Reduced survival and increased risk of progression to AML in MDS patients with thrombocytopenia





Neukirchen J, et al. Eur J Haematol. 2009;83:477-82.

Thrombocytopenia is associated with poor outcomes in MDS

IPSS-R prognostic score

Prognostic factor	Points						
	0	0.5	1	1.5	2	3	4
Blasts, %	≤ 2	–	> 2 and < 5	–	5–10	> 10	
Hemoglobin, g/dL	≥ 10		8–< 10	< 8			
ANC, g/L	≥ 0.8	< 0.8					
Platelets, g/L	≥ 100	≥ 50 and < 100	< 50				
Cytogenetics	**Very good** -Y del(11q)		**Good** Normal der(1;7) del(5q) del(20q) del(12p) Double, incl del(5q)		**Intermediate** -7/7q +8 Iso(17q) +19 +21 Other double inclusions	**Poor** der3q(21) der3q(26) Complex Double inclusion 7q/7	**Very poor** Complex > 3

Greenberg PL, et al. Blood 2012;120:2454–65.

Treatment for lower risk MDS: approved drugs in Europe

» **Lower risk MDS**

- Iron chelation
  - Deferasirox: an oral medication taken once daily
  - Deferoxamine: a subcutaneous infusion administered 5–7 days/week
- Lenalidomide
  - In Europe it is indicated for MDS with isolated del(5q)
- Erythropoietin alfa
- Luspatercept
  - adult patients with transfusion-dependent anaemia due to very low, low and intermediate-risk IPSS-R MDS-RS, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy.
- Allogeneic stem cell transplantation
  - Severe cytopenias and/or bone marrow blasts ≥ 5% in younger and fit patients with an available donor….

» **Higher risk MDS**

- Azacitidine
- Allogeneic stem cell transplantation

Treatment of thrombocytopenia in MDS

In higher risk MDS patients with thrombocytopenia, treatment with azacitidine may improve thrombocytopenia in a proportion of responsive patients

In lower-risk MDS, about 10% of patients experience severe thrombocytopenia [1,2]

- No approved drugs in Europe (azacitidine approved by FDA)
- Treatment consists of platelet transfusions mainly in the presence of bleeding, occurring in about 25% of patients
  - Short therapeutic effect and development of refractoriness to platelet transfusions

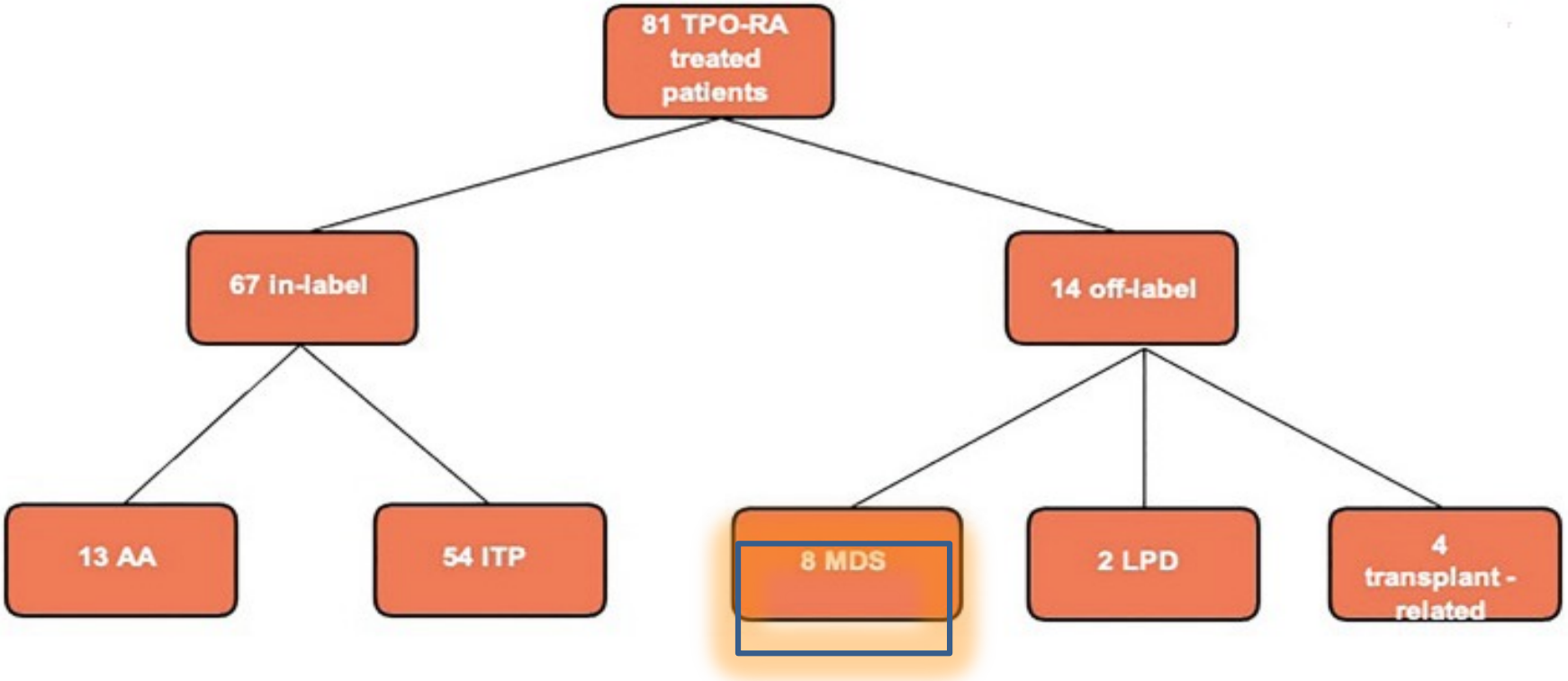
The clinical management remains challenging

- Approved therapeutic agents for MDS, such as lenalidomide and azacitidine, can also lead to a transient worsening of thrombocytopenia

1. Kantarjan H, et al. Cancer. 2007;109:1705-14. 2. Neukircken J, et al. Eur J Haematol. 2009;83:477-82.

Off-label use of TPO-R agonists

A single-center experience of TPO-RA use from 2010 to 2020
17% patients received a TPO-RA off-label



TPO-R, Thrombopoetin receptor

Capecchi M, et al. Front. Oncol., 28 September 2021

TPO-R agonists in MDS: review of the literature

» This meta-analysis included eight studies comprising 1047 patients.

Study	Year	Clinical trial ID	Number	Median age	Male (%)	IPSS<=1(%)	disease	Caucasian	Funding
Kantarjian et al. (31)	2018	NCT00614523	250	70	148 (59%)	250 (100%)	MDS	235(94%)	Amgen Inc
Greenberg et al. (28)	2013	NCT00321711	29	68	19 (66%)	14 (48%)	MDS	20 (69%)	Amgen Inc
Kantarjian et al. (30)	2010	NCT00321711	40	71	24 (60%)	26 (65%)	MDS	37 (93%)	Amgen Inc
Dickinson (23)	2018	NCT02158936	356	70	234 (66%)	125 (35%)	MDS	294 (83%)	Novartis Pharma AG
Oliva et al. (26)	2017	EudraCT201002289033	90	69	52 (58%)	90 (100%)	MDS	NA	Associazione QOL-ONE
Wang et al. (29)	2012	NCT00418665	38	74	24 (62%)	35 (90%)	MDS	36 (92%)	Amgen Inc
Mittelman (17)	2018	NCT01440374	145	72	97 (67%)	0 (0)	MDS+AML	126 (87%)	Novartis Pharma AG
Platzbecker et al. (27)	2015	NCT00903422	98	NA	59 (60%)	NA	MDS+AML	68 (70%)	GlaxoSmithKline

NA, not available; MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; IPSS, international prognostic scoring system.

Studies of TPO-R agonists for the treatment of thrombocytopenia in patients with higher risk MDS

Eltrombopag in high-risk MDS (ASPIRE trial)

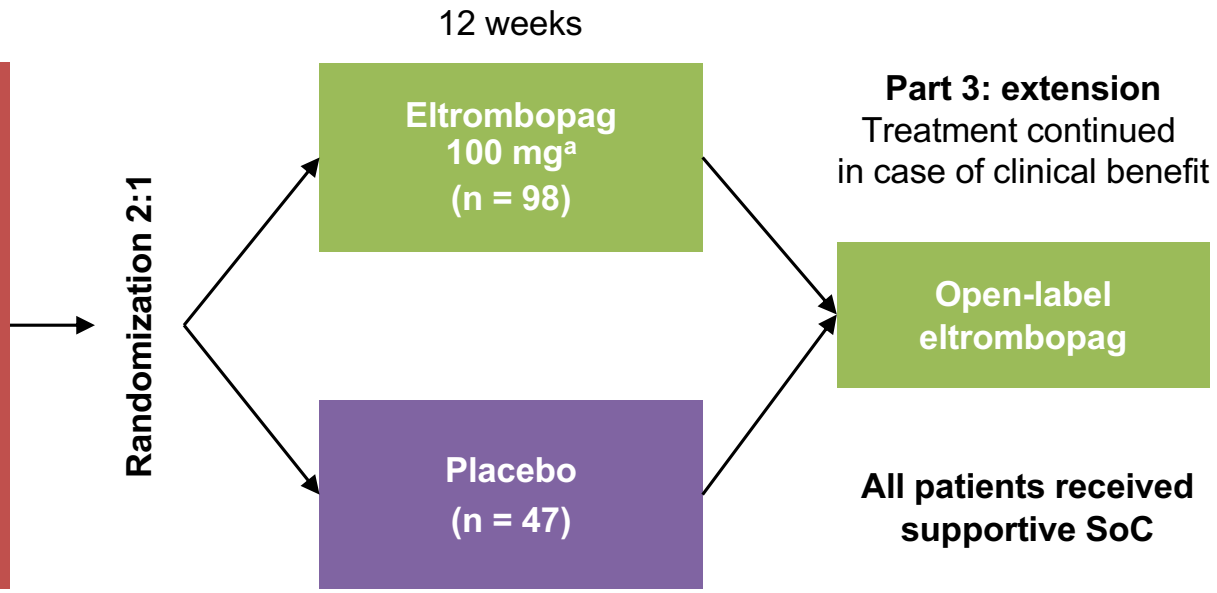
» Phase 2, randomized, placebo-controlled

Inclusion criteria

- Adult patients with IPSS int-2- or high-risk MDS or AML and BM blasts ≤ 50%

and

- PLT count < 10 × 10^9/L or < 25 × 10^9/L with PLT transfusion
- Bleeding or transfusion or PLT count < 10 × 10^9/L within the 4-week screening period



Stratification

- PLT count < 10 × 10^9/L vs > 10 × 10^9/L
- Int-2-/high-risk MDS vs AML

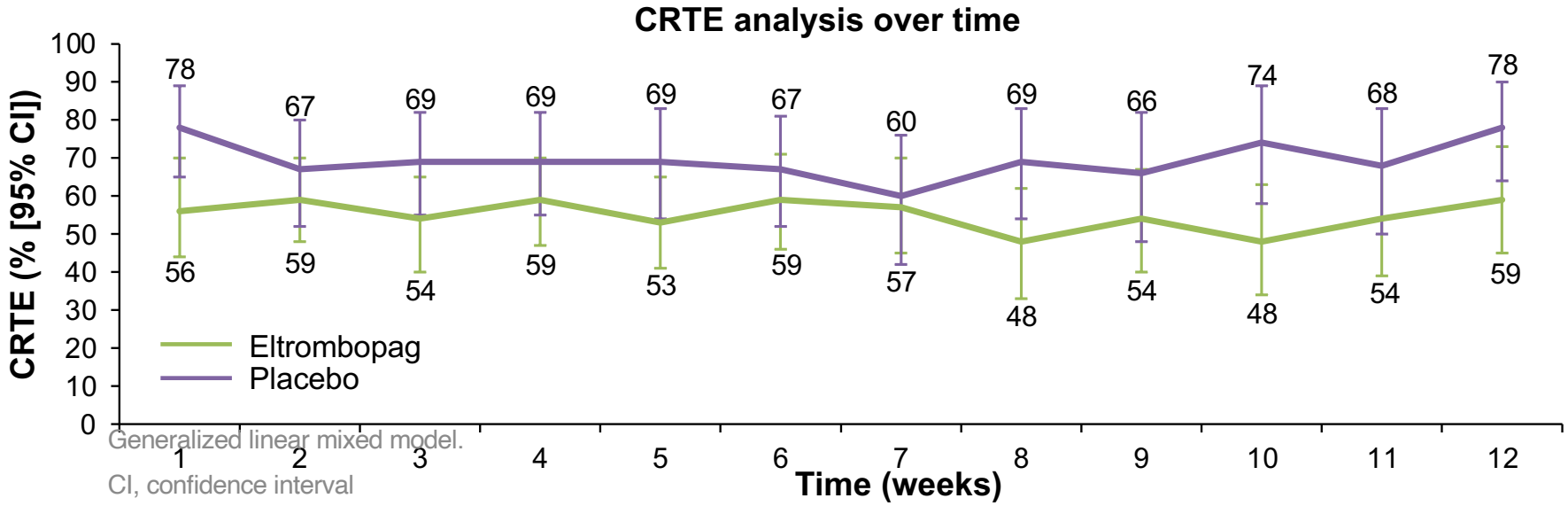
[a] The dose could be escalated to a maximum of 300 mg daily.
BM, bone marrow; SoC, standard of care.

Mittelman M, et al. Lancet Haematol. 2018;5:e34-43.

ASPIRE: clinically relevant thrombocytopenic events (CRTEs)

CRTEs during Weeks 5–12

	Eltrombopag (n = 98)	Placebo (n = 47)	Odds ratio (95% CI)	p value[a]
Mean CRTEs, % (95% CI)	54 (43–64)	69 (57–80)	0.20 (0.05–0.87)	0.032



Generalized linear mixed model.
CI, confidence interval

Mittelman M, et al. Lancet Haematol. 2018;5:e34-43.

ASPIRE results

- Few patients had PLT response in both groups
- Progressive disease was somewhat lower with eltrombopag

Disease response and progression

	Placebo (n = 47)	Eltrombopag (n = 98)	Odds ratio (95% CI), p value[a]
Responder, n (%)	1 (2)	1 (1)	0.47 (0.03–7.75), 0.59
Stable disease, n (%)	10 (21)	18 (18)	–
Progressive disease, n (%)	36 (77)	61 (62)	–

Not evaluable for stable disease: 18 placebo patients and 36 eltrombopag patients.
Not evaluable for progressive disease: 5 placebo patients and 23 eltrombopag patients.

AML transformation

Placebo	Eltrombopag
16/22	31/50
73%	62%

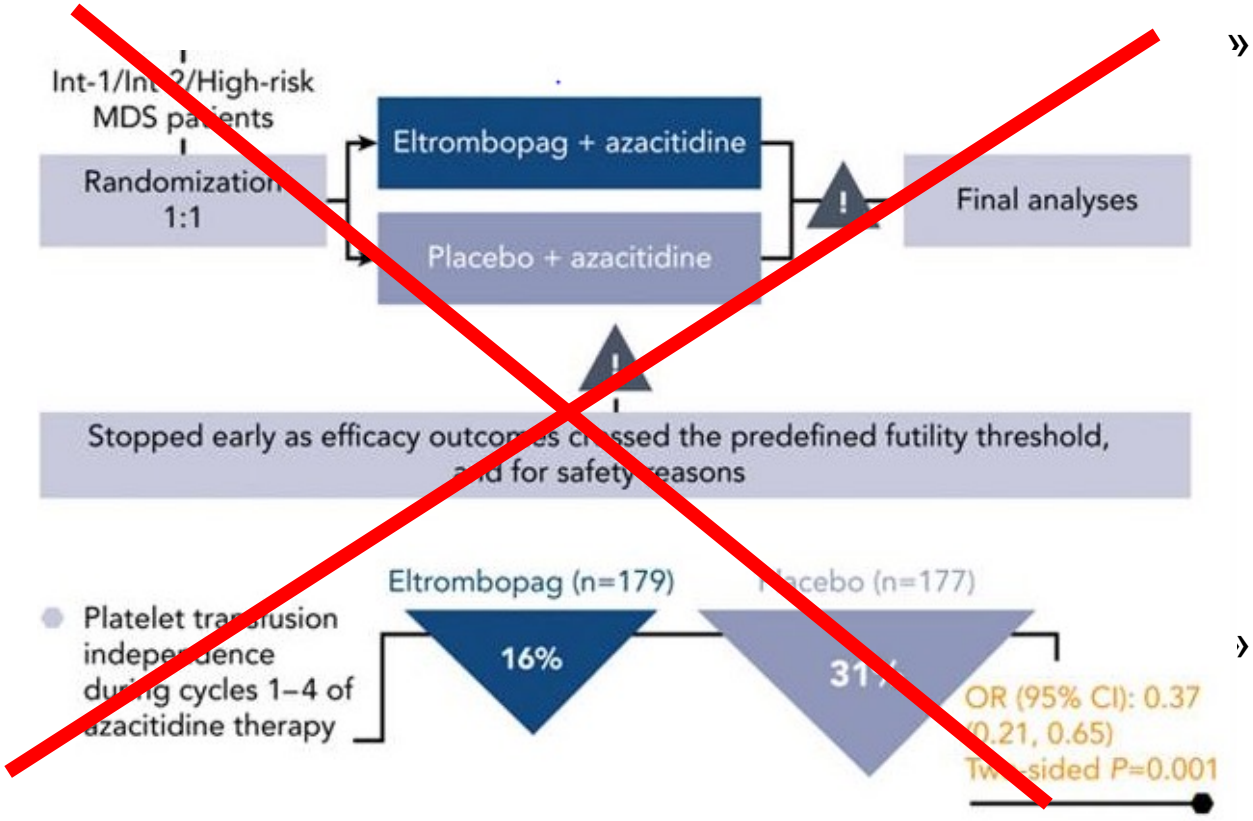
Median overall survival

Placebo	Eltrombopag
4.6 months	4.3 months
(IQR 1.5–12.0)	(IQR 2.4–8.5)

IQR, interquartile range.

Mittelman M, et al. Lancet Haematol. 2018;5:e34-43.

Azacitidine +/- eltrombopag



» Eltrombopag/azacitidine was inferior to placebo/azacitidine in higher-risk MDS patients with respect to PLT-related and survival end points.

– Compared with azacitidine alone, eltrombopag + azacitidine worsened PLT recovery, with lower response rates **and a trend toward increased progression to acute myeloid leukemia.**

› Findings from this study do not indicate a role for combining eltrombopag with azacitidine in patients with intermediate/high-risk MDS.

Dickinson M, et al. Blood. 2018 Dec 20; 132(25): 2629–2638

Conclusions:
Eltrombopag in high-risk MDS patients

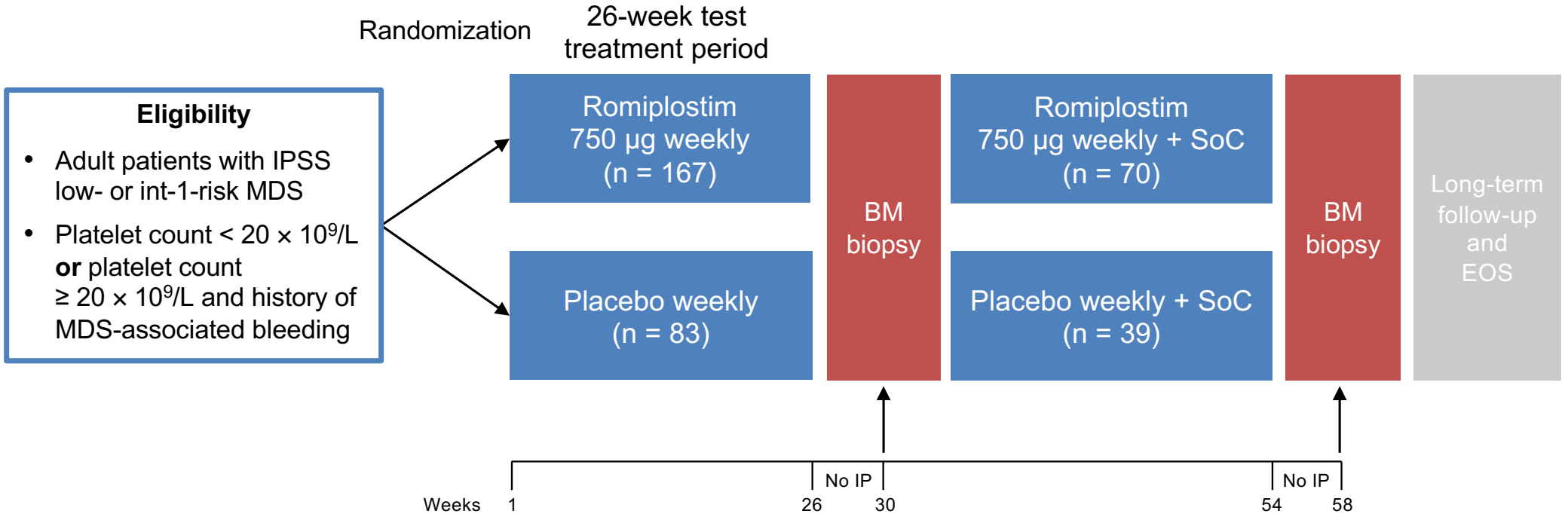
- Treatment with eltrombopag and best supportive care resulted in fewer clinically relevant thrombocytopenic events compared with placebo
- Combination of eltrombopag with azacitidine is contraindicated

Mittelman M, et al. Lancet Haematol. 2018;5:e34-43.

Studies of TPO-R agonists for the treatment of thrombocytopenia in patients with lower risk MDS

Romiplostim in low- and int-1-risk MDS

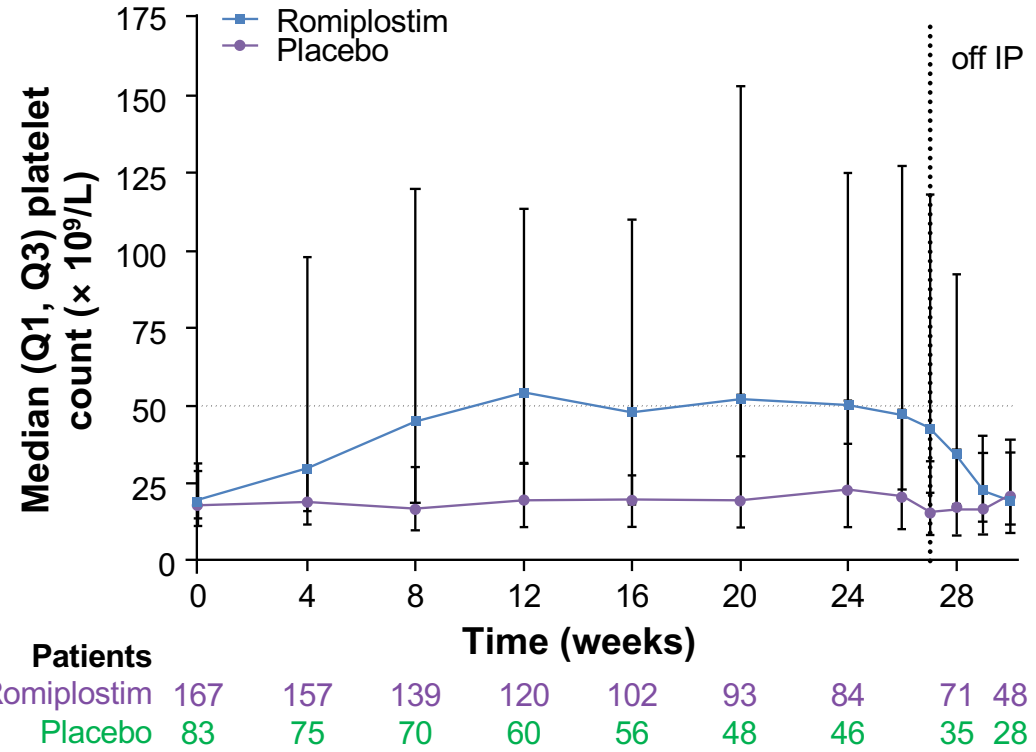
» Phase 2, randomized, double-blind, placebo-controlled study

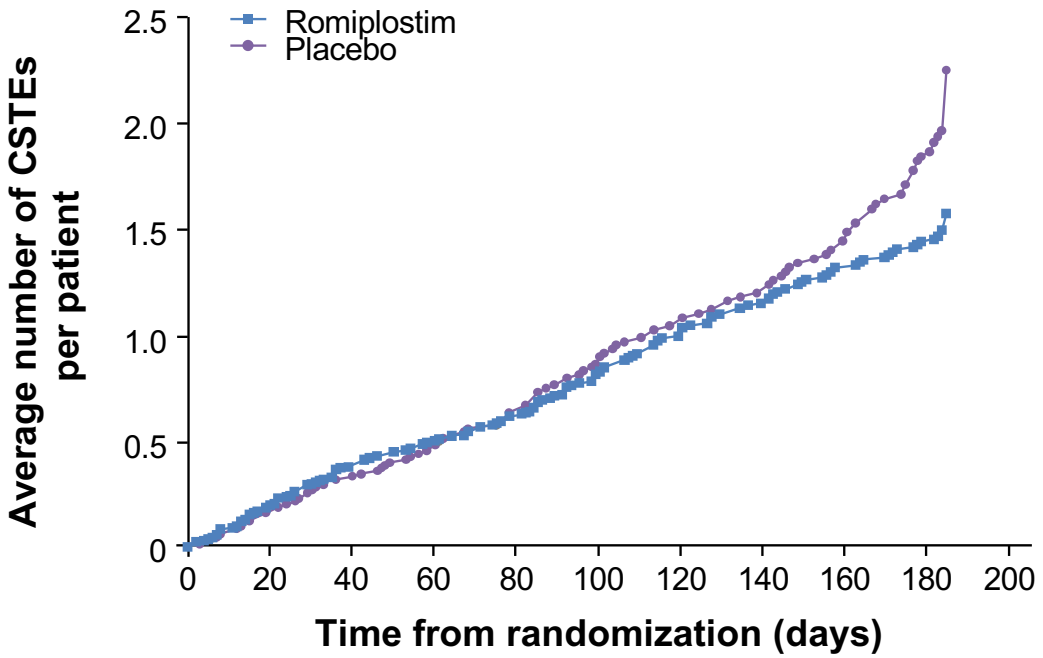


EOS, end of study; IP, investigational product.

Giagounidis A, et al. Cancer. 2014;120:1838-46.

Romiplostim in low- and int-1-risk MDS: efficacy





Giagounidis A, et al. Cancer. 2014;120:1838-46.

Romiplostim in low- and int-1-risk MDS: safety

» Study was discontinued due to an increase in disease worsening/progression in the romiplostim arm

Interim analysis at Week 30

	Placebo (n = 83)	Romiplostim (n = 167)
Peripheral blast count increased by > 10%, n (%)	3 (3.7)	25 (14.9)

	Placebo (n = 82)	Romiplostim (n = 168)
Progression to AML, n (%)	2 (2.4)	10 (6.0)

Giagounidis A, et al. Cancer. 2014;120:1838-46.

Eltrombopag in lower risk MDS: EQoL-MDS study

» Phase 2, randomized, placebo-controlled, international, multicentre trial in IPSS low and intermediate risk MDS with severe thrombocytopenia

Phase 1

To determine the efficacy and safety of eltrombopag in the first 6 months

Phase 2

To assess the long-term response and safety

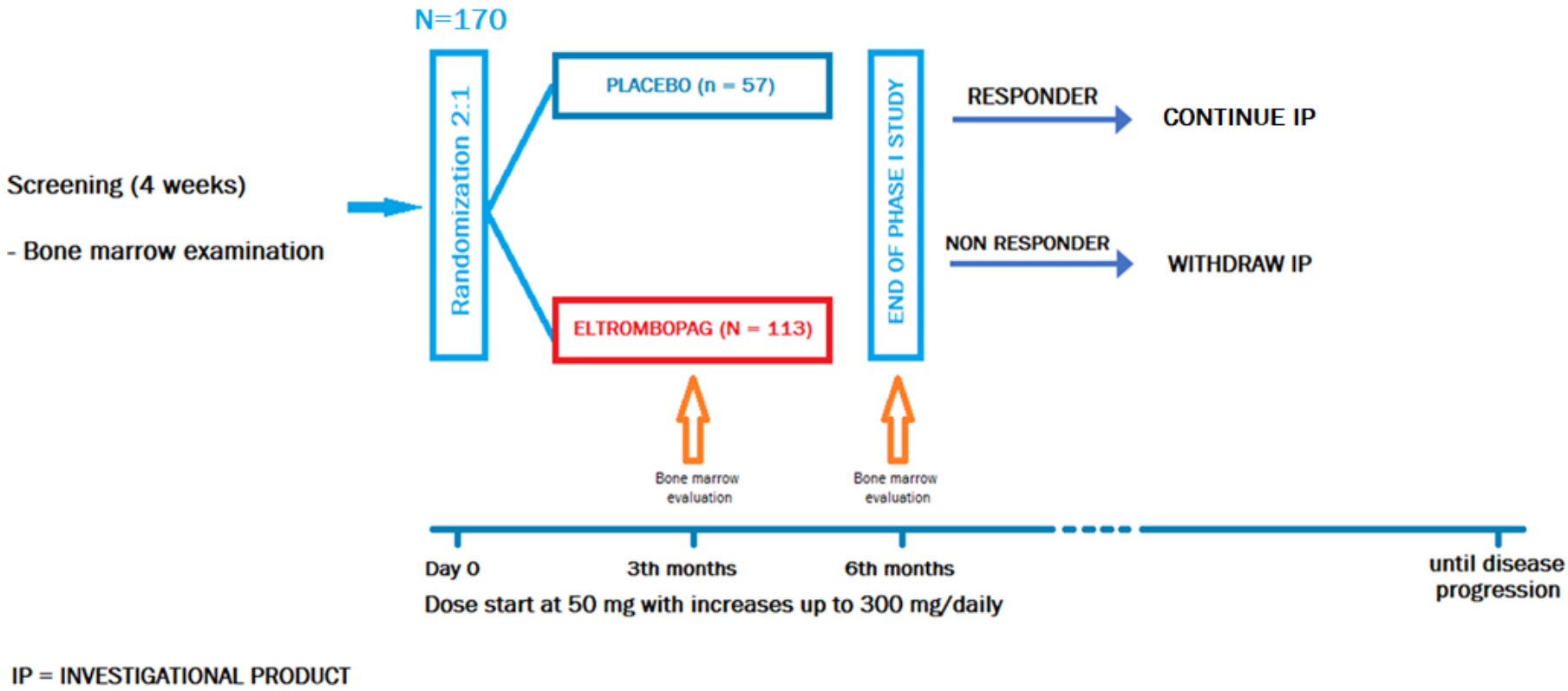
Inclusion criteria

- Adult patients with IPSS low- or int-1-risk MDS
- Platelet count < 30 × 10^9/L
- Ineligible or relapsed or refractory to other treatments
- ESAs or G-CSF allowed during the study as per accepted standards
- ECOG performance status 0–3
- Adequate baseline organ function

ECOG, Eastern Cooperative Oncology Group; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte-colony stimulating factor.

Oliva EN, et al. Lancet Haematol. 2017;4:e127-36.

EQoL-MDS: Study design



IP = INVESTIGATIONAL PRODUCT

Oliva EN, et al. American Society of Hematology Annual Congress, 2021, #1516

EQoL-MDS: Study endpoints

The endpoints of the first phase of the EQoL-MDS trial - response rate and safety in the first 24 weeks - have been reached and published (Oliva et al. Lancet Haematol. 2017).

Primary endpoints of 2nd phase

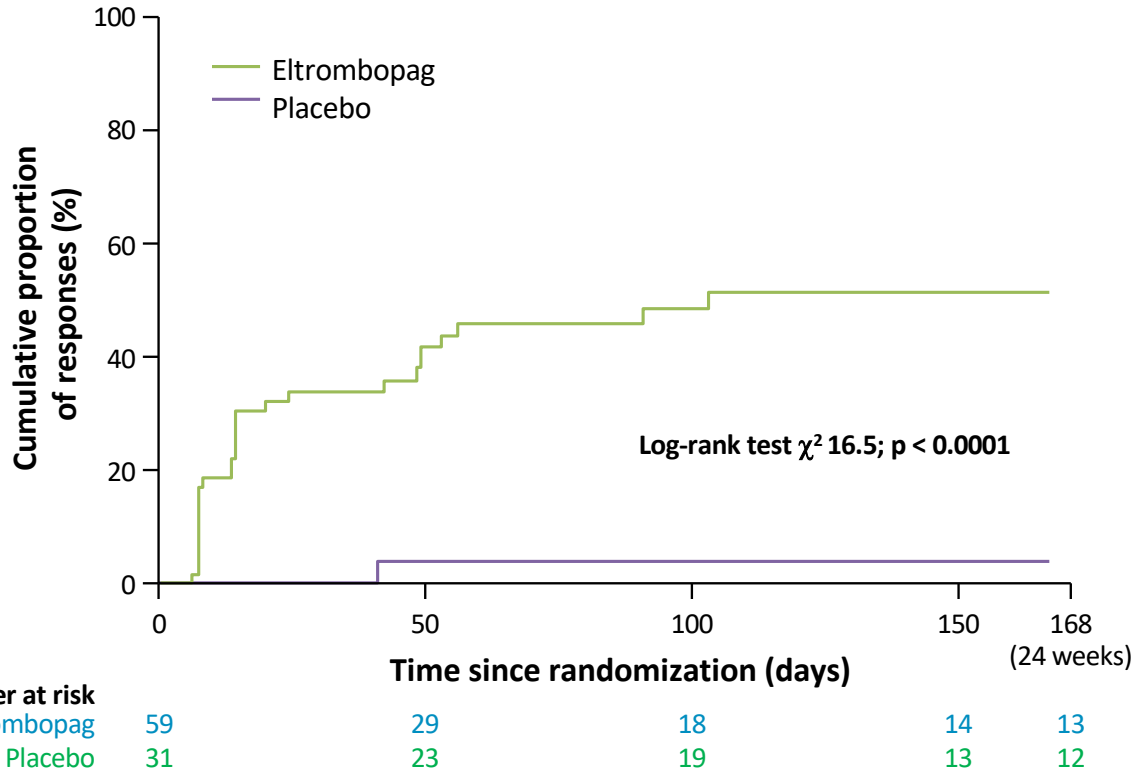
- duration of platelet (PLT) response
- long-term safety and tolerability

Secondary endpoints

» quality of life (QoL) scores
» number of monthly PLT transfusions
» duration of PLT transfusion independence
» time to response
» incidence and severity of bleeding
» overall survival (OS) at 2 and at 5 years
» leukemia-free survival (LFS) at 2 and at 5 years
» pharmacokinetics.

Oliva EN, et al. Lancet Haematol. 2017;4:e127-36.

EQoL-MDS: Platelet response



Platelet response

Placebo		Eltrombopag
1/31	P<0.0001	28/59
3%		47%

OR 7.1 (95% CI 3.5–211.9; p=0-002)

Median platelet count change

124 × 10^9/L (IQR 50–217 × 10^9/L)

Platelet transfusion independance

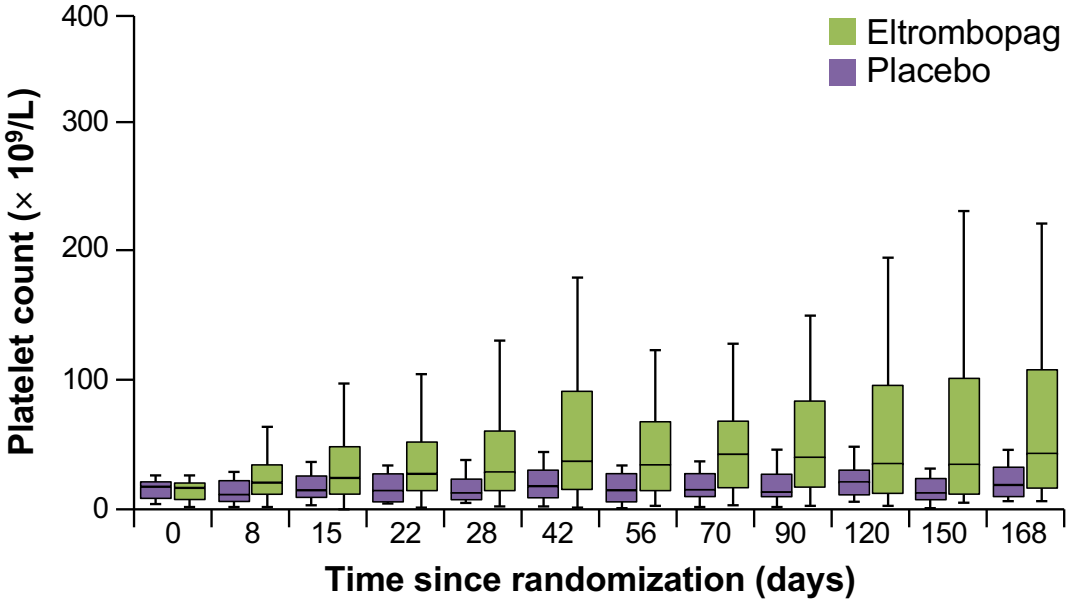
Placebo	Eltrombopag
0/8	7/13
0%	54%

Oliva EN, et al. Lancet Haematol. 2017;4:e127-36.

EQoL-MDS: Platelet response

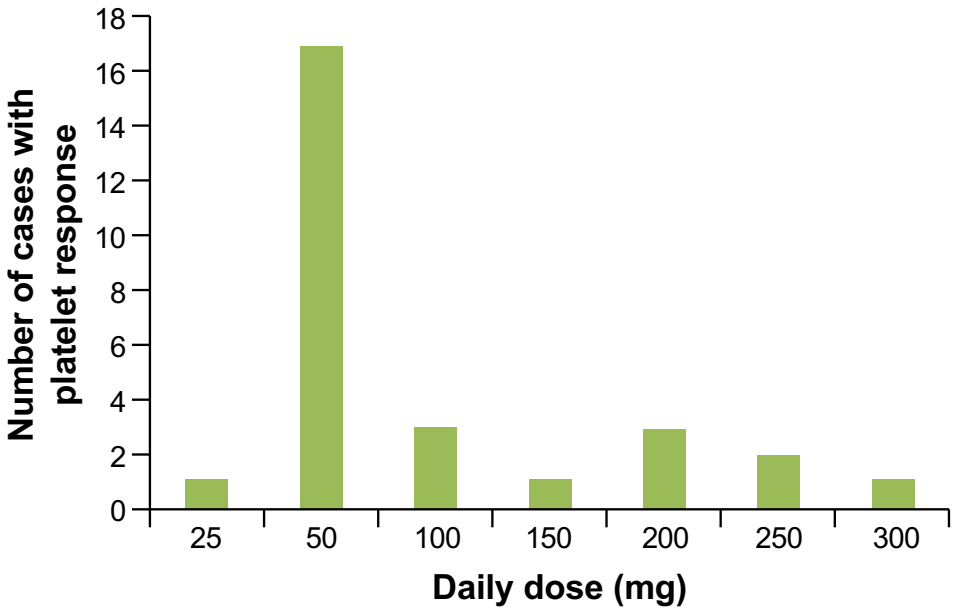
Median time to response

2 weeks (range 1–15)



Median daily dose at response

50 mg



Box plot shows median and 75th and 25th percentiles.
The whiskers above and below the box plot mark the 97.5th and 2.5th percentiles, respectively.

Oliva EN, et al. Lancet Haematol. 2017;4:e127-36.

EQoL-MDS: Updated results on efficacy

- **Platelet responses**
- Median time to response 14 days (95% CI 7-40 days). The median dose of study drug at response was 50 mg.

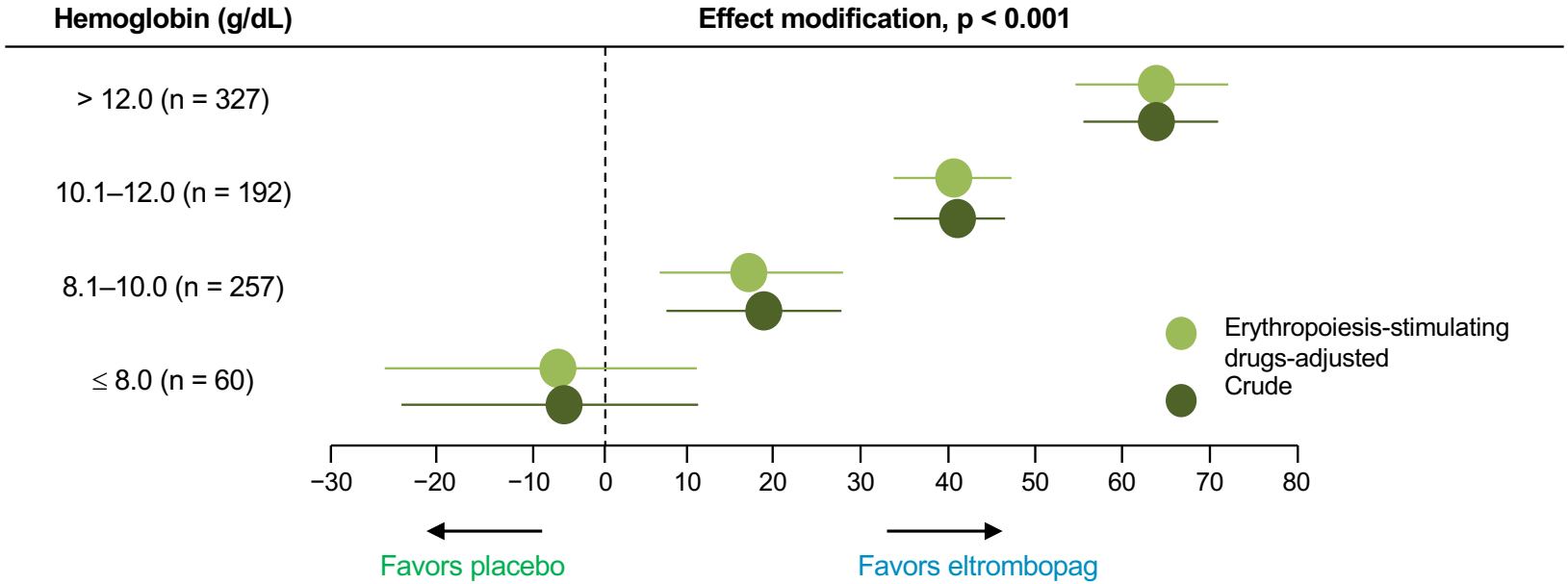
- **Bleeding**
- WHO bleeding score ≥2 occurred in 19 patients, with a significantly higher incidence in the placebo (11 cases [35.3%]) than in the eltrombopag arm (8 cases [13.6%]; p=0.015).

Oliva EN, et al. ASH 2019

EQoL-MDS: Factors associated with response

Factors **not** associated with response: Gender, MDS duration, WHO classification, IPSS, IPSS-R, cytogenetics, bleeding, PLT transfusions, hypoplasia, and fibrosis

» The effect of eltrombopag on platelet levels was observed at hemoglobin > 8.1 g/dL and increased linearly with hemoglobin level



The horizontal axis shows platelet count difference (eltrombopag vs placebo × 10^9 platelets) with 95% CIs across the study period

Oliva EN, et al. Lancet Haematol. 2017;4:e127-36.

EQoL-MDS: Impact of MDS with severe thrombocytopenia on patient's quality of life

QoL-E index	Baseline, median (IQR)			Difference between arms (eltrombopag vs placebo) (95% CI), p value
	All patients (N = 90)	Placebo (n = 31)	Active (n = 59)	
Physical	50 (25–75)	62 (25–75)	50 (25–62)	−5.7 (−13.3–2.0), p = 0.15
Function	56 (22–100)	56 (22–89)	33 (22–100)	−6.5 (−16.2–3.3), p = 0.19
Social	50 (12–75)	50 (22–75)	37 (12–75)	−1.0 (−9.7–7.7), p = 0.82
Sexual	67 (42–100)	71 (42–100)	67 (42–100)	−3.4 (−12.7–5.9), p = 0.47
Fatigue	71 (56–86)	71 (57–86)	74 (52–85)	−0.3 (−5.0–4.3), p = 0.89
MDS-specific	62 (42–81)	55 (42–72)	67 (41–81)	4.5 (−2.4–11.4), p = 0.20
General	57 (43–74)	61 (48–76)	55 (41–74)	−2.4 (−9.5–4.7), p = 0.51
Treatment outcome index	55 (36–74)	56 (40–74)	52 (34–75)	−0.6 (−8.2–7.0), p = 0.88
All	58 (43–74)	58 (49–74)	58 (41–75)	−0.1 (−7.2–7.0), p = 0.97

Oliva EN, et al. Lancet Haematol. 2017;4:e127-36.

EQoL-MDS:
Impact of PLT change on patient's quality of life

- Subjects on placebo experienced a significant worsening in QOL-E sexual domain (P=0.025)
- Subjects in the eltrombopag arm had a significant improvement in QOL-E MDS specific (P<0.001) and total scales (P=0.047) and a trend of improvement in QOL-E physical and social scores (both P=0.054).
  - Between-arm comparison revealed that longitudinal changes in QOL-E MDS specific domain significantly differed between the two study arms in favour of eltrombopag (P=0.005).
- Finally, QOL-E functional (P=0.026), social (P<0.001), fatigue (P=0.01), MDS specific (P<0.001), general (P=0.001), treatment outcome index (P<0.001) and total scale (P<0.001) significantly improved with increasing PLT counts.

Oliva EN, et al. ASH 2019

EQoL-MDS interim analysis Adverse events

Number (and %) of adverse events				
	1-2 grade (>10%)		3-4 grade	
Type of adverse event	Eltrombopag (n=59)	Placebo (n=31)	Eltrombopag (n=59)	Placebo (n=31)
Nausea/vomiting	8 (13.6)	2 (6.5)	8 (13.6)	0 (0)
Lower respiratory tract infection			6 (10.2)	2 (6.5)
Heart failure			3 (5.1)	1 (3.2)
Hypertransaminasaemia			3 (5.1)	1 (3.2)
Sepsis			3 (5.1)	0 (0)
Ascites			2 (3.4)	0 (0)
Bone marrow fibrosis			2 (3.4)	0 (0)
Mylgia			2 (3.4)	0 (0)

Oliva EN *et al. Lancet Hematol.* 2017;4(3):e127-e136.

EQoL-MDS survival

- At the time of the present analysis, 5/59 subjects died in the eltrombopag arm for cardiorespiratory failure (n=2), infection, hemorrhage and heart failure and 2/31 subjects died in the placebo arm for infection and heart failure.
- MDS progression and acute myeloid leukemia (AML) evolution occurred in 9/59 eltrombopag cases and in 5/31 placebo cases.

Oliva EN, et al. ASH 2019

EQoL-MDS survival

Fig.1A Leukemia Free Survival

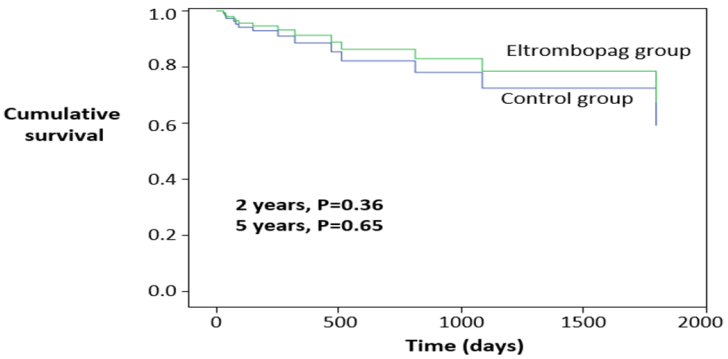


Fig.1B Combined outcome AML, disease progression, and death

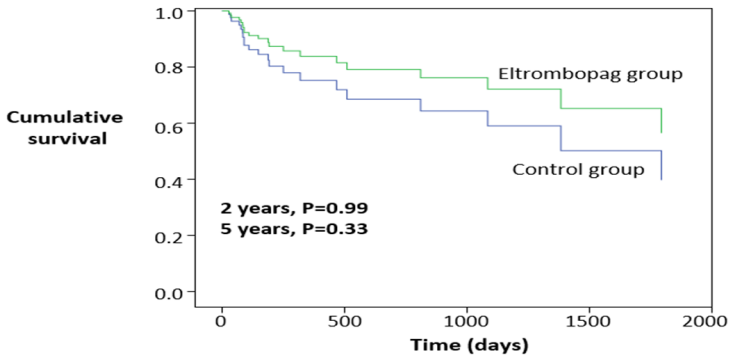
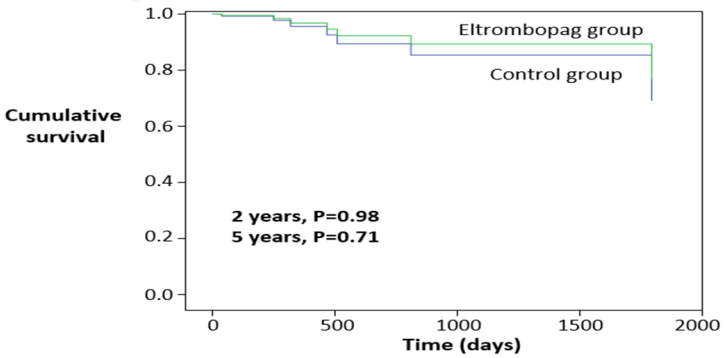


Fig.1C Overall survival



•Median LFS, combined outcome (AML, disease progression and death) and OS were not reached in the whole group.

- adjusted for baseline bone marrow blasts since the proportion of subjects with >2% blasts tended to be higher (P=0.06) in the eltrombopag arm (59.3%) than in the placebo arm (38.7%) and resulted to be a strong predictor of study outcomes at both 2 and 5 years (P<0.002).

Oliva EN, et al. ASH 2019

EQoL-MDS other hematological improvements

- Erythroid response
  - 13/23 patients (57%) in the eltrombopag arm
- Hemoglobin response (IWG 2006 criteria)
  - 4 platelet responders
  - 2 platelet non-responders
- Neutrophil response in neutropenic patients
  - 5/16 patients (31%)
    - 1 platelet responder
    - 4 platelet non-responders
- Transfusion independence
  - Reached in 9 red blood cell transfusion-dependent patients; of the patients who became transfusion-free, 2 also had a significant hemoglobin response, whereas only 3 had a concomitant platelet response
- 1 of the platelet non-responders had a bi-lineage (erythroid/neutrophil) response

Oliva EN, et al. Lancet Haematol. 2017;4:e127-36.

NGS Evaluation of the Eqol-MDS Trial: Preliminary Analysis

Rationale

- Though results are favourable, there are concerns of regulatory agencies regarding the use of TPO-RA in MDS due to previous reports signalling disease progression in clinical trials with the use of romiplostim and of eltrombopag, the latter in high risk MDS and AML.
- Therefore, further translational research is required to assess the safety in terms of MDS progression during treatment with eltrombopag

Oliva EN, et al. American Society of Hematology Annual Congress, 2021, #1516

AIM

» **long-term safety** by conducting a comprehensive analysis of mutations in a panel of major driver or candidate driver genes in all evaluable cases

METHODS

» Serial sequencing was performed using the SureSelect custom kit (Agilent Technologies) for which 350 genes were selected from known oncogenes or tumour suppressor genes in hematological malignancies.
  – Relevant somatic mutation data with (i) VAF > 0.05; (ii) depth > 100; (iii) P value for EBCall < 0.0001, were filtered by exclusion based on (i) synonymous SNVs; (ii) variants present only in unidirectional reads; (iii) variants occurring in repetitive genomic regions; (iv) missense SNVs with VAF of 0.4–0.6 or <0.04; and (v) known variants listed in SNP databases.
» This preliminary analysis has been conducted at baseline, at 12 and 24 weeks and will be performed on all evaluable patients in the trial.

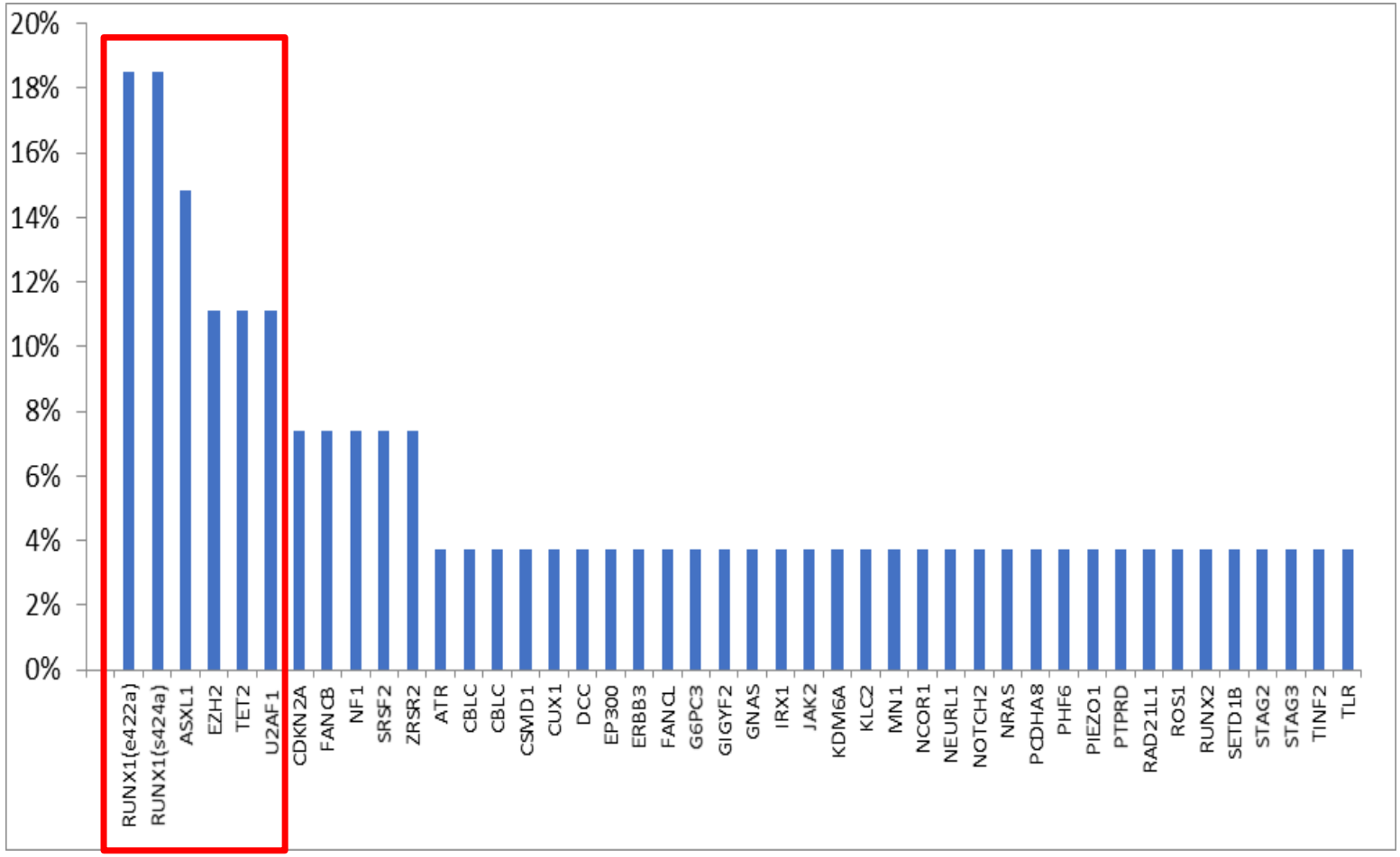
Oliva EN, et al. American Society of Hematology Annual Congress, 2021, #1516

Baseline characteristics of patients

	Total (N. 27)	Eltrombopag (N. 18)	Placebo (N. 9)	p-value
Age, mean (± SD)	65 (± 14)	67 (± 14)	62 (± 16)	*0.67
Male, N. (%)	16 (59%)	10 (56%)	6 (67%)	#0.58
WHO 2016 Classification, N. (%)				#0.92
- MDS-SLD	13 (48%)	9 (50%)	4 (45%)	
- MDS-MLD	8 (30%)	5 (28%)	3 (33%)	
- MDS-U	4 (15%)	3 (17%)	1 (11%)	
- MDS-EB-1	2 (7%)	1 (5%)	1 (11%)	
IPSS N. (%)				#0.39
- Low	11 (41%)	6 (33%)	5 (56%)	
- Int-1	16 (59%)	12 (67%)	4 (44%)	
IPSS-R N. (%)				#0.14
- Low	19 (70%)	11 (61%)	8 (89%)	
- Intermediate	8 (30%)	7 (39%)	1 (11%)	
Karyotype, N. (%)				#0.09
- Normal	20 (74%)	15 (82%)	5 (56%)	
- Del (20q)	5 (18%)	1 (6%)	4 (44%)	
- +14	1 (4%)	1 (6%)	-	
- +8	1 (4%)	1 (6%)	-	
Hemoglobin g/dL , mean (± SD)	11.7 (± 2.3)	11.4 (± 2.6)	12.3(± 1.8)	*0.43
Platelet count x10^9/L	16.1 (± 7.0)	14.7 (± 6.9)	18.7(± 6.8)	*0.21
White Blood Cells x10^9/L	6.3 (± 3.0)	6.0 (± 3.4)	6.9 (± 2.0)	*0.32
Absolute neutrophil count x10^9/L	3.7 (± 2.4)	3.4 (± 2.7)	4.3 (± 1.6)	*0.19

Oliva EN, et al. American Society of Hematology Annual Congress, 2021, #1516

Baseline gene mutations



Changes in mutations from baseline: eltrombopag

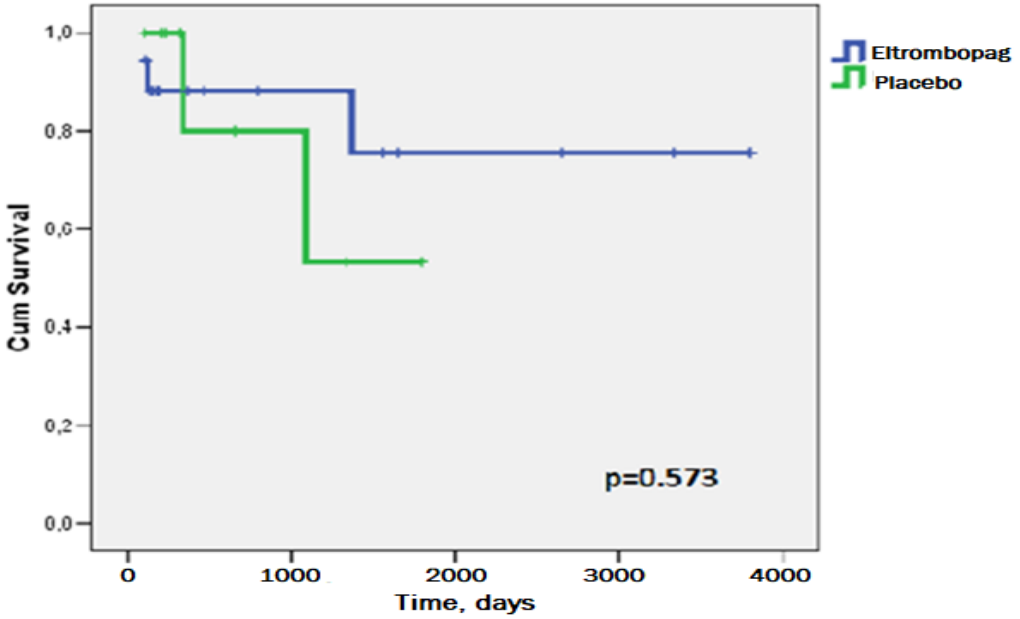
Patient ID	IPSS-R	Karyotype	Baseline mutations (VAF)	PLT responder	+3 mo.s mutations	+6 mo.s mutations	Progression/ Evolution	Trilinear response	Follow-up, days	Status
ID-1	Low	Normal	FANCB (52), FANCL (33) IRX1 (50); MN1 (25) RAD21L1 (51) RUNX1 (S424A) (20) RUNX1 (E422A) (19) STAG3 (53); TLR2 (48)	Yes	-	-	No	No	3801	Ongoing
ID-2	Low	Normal	ATR (50); FANCB 45) GIGYF2 (31); ROS1 (49) RUNX1 (S424A) 14) RUNX1 (E422A) (24) RUNX2 (19); TSC2 (50)	Yes	-	-	No	No	3801	Ongoing
ID-3	Low	Normal	-	Yes	ND	-	No	No	3331	Ongoing
ID-4	Low	Normal	-	Yes	-	-	No	No	2652	Ongoing
ID-5	Low	Normal	ASXL1 (51)	Yes	-	-	No	No	1650	Ongoing
ID-6	Low	Normal	EZH2 (27)	Yes	ND	- EZH2	No	No	1559	Ongoing
ID-7	Intermediate	+14	CUX1 (11); KLC2 (50);	Yes	-	+ GNAQ - MYH11 + SRSF2	Yes	No	1385	Death to disease progression
ID-8	Low	Normal	CDKN2A (14)	Yes	- CDKN2A	ND	No	No	793	Alive in transfusion therapy
ID-9	Low	Normal	NF1 (24);	Yes	-	- NF1 + TERT	No	No	463	Lost to F-UP
ID-10	Low	+8	Phf6 (64)	No	-	ND	No	No	364	Withdrew informed consent
ID-11	Low	Normal	U2AF1 (27); CDKN2A (11) EP300 (46)	No	- CDKN2A	ND	No	No	195	Withdrew informed consent
ID-12	Intermediate	Normal	-	No	-	-	No	No	172	Withdrew informed consent
ID-13	Intermediate	del(20q)	U2AF1 (30); ERBB3 (26)	No	-	ND	No	No	150	Withdrew informed consent
ID-14	Low	Normal	-	No	-	ND	No	No	136	Withdrew informed consent
ID-15	Intermediate	Normal	-	Yes	-	ND	Yes	No	118	Death to disease progression
ID-16	Intermediate	Normal	U2AF1 (16)	No	-	ND	No	No	111	Withdraw informed consent
ID-17	Intermediate	Normal	-	Yes	-	ND	No	Yes	103	Lost to F-UP
ID-18	Intermediate	Normal	TET2 (31), STAG2 (46), RUNX1 32), NRAS (26), EZH2 (97), ASXL1 (48)	No	+ ZRSR2	ND	Yes	No	86	Lost to F-UP

Changes in mutations from baseline: placebo

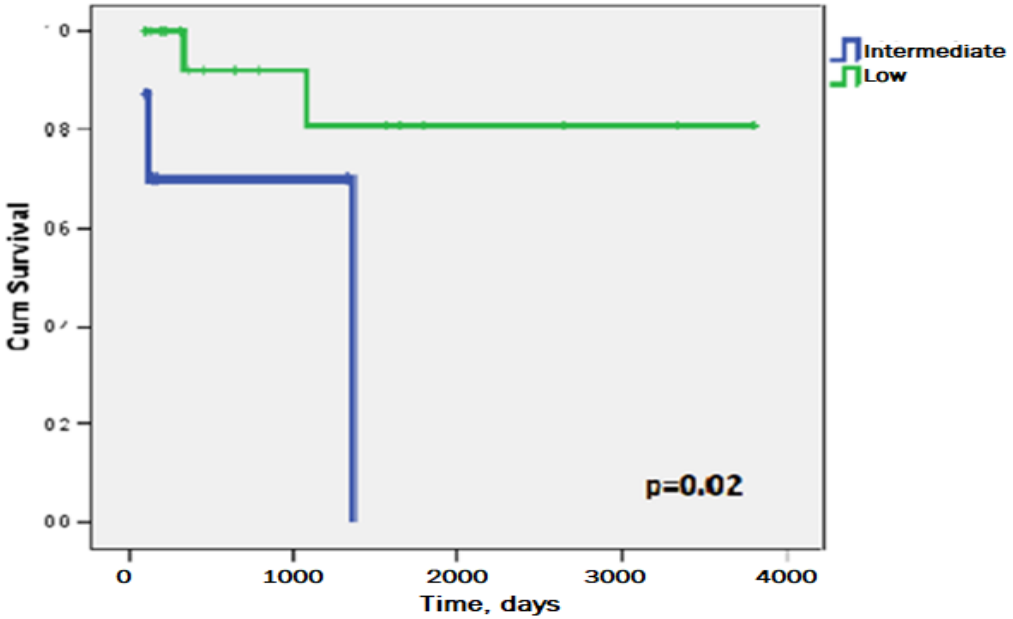
Patient ID	IPSS-R	Karyotype	Baseline mutations (VAF)	PLT responder	+3 mo.s mutations	+6 mo.s mutations	Progression/ Evolution	Trilinear response	Follow-UP, days	Status
ID-19	Low	Normal	CBLB (47); DCC (50); G6PC3 (48); GNAS (44); NEURL1 (49); PCDHA8 (17); PIEZO1 (50); PTPRD (47); RUNX1 (S424A) (18) RUNX1 (E422A) (18); ZRSR2 (59)	No	+MED12	-	No	No	1795	Death due to heart failure
ID-20	Intermediate	del(20q)	JAK2 (22); TINF2 (49) NOTCH2 (46)	No	+CREBBP	+CDKN2A	No	No	1335	Death due to heart failure
ID-21	Low	Normal	TET2 (41), ASXL1 (13), RUNX1 (15), SRSF2 (42)	No	-	-	Yes	No	1085	AML Evolution
ID-22	Low	del(20q)	CBL (15), SETD1B (10)	No	- SETD1B	- CBL + NF1	No	No	654	Withdrew informed consent
ID-23	Low	Normal	EZH2 (87), ZRSR2 (85), ASXL1 (41), TET2 (43), CSMD1 (11)	Yes	ND	+ STAG2	Yes	No	334	Death to disease progression
ID-24	Low	Normal	-	Yes	+TET2	-	No	No	314	Lost to F-UP
ID-25	Low	Normal	-	No	-	+CDKN2A	No	No	228	Withdrew informed consent
ID-26	Low	del(20q)	NF1 (11)	No	- NF1	ND	No	No	207	Lost to F-up
ID-27	Low	del(20q)	KDM6A (10)	No	- KDM6A	ND	No	No	101	Withdrew informed consent

Progression free survival by treatment arm and IPSS-R

Eltrombopag versus placebo



IPSS-R low versus intermediate



Risk of progression by mutations

The hazard ratio (HR) of disease progression in the presence of mutations occurring in ≥ 10% of the subjects was evaluated by univariable analysis (Cox regression).

» *EZH2* (*HR 5.37 [95% CI, 0.89 to 32.33], P=0.07*) mutation did not reach statistical significance for risk of progression.

» Interestingly, mutations in *RUNX1* (*HR 1.76 [95% CI, 0.28 to 11.06], P=0.55*) genes was not associated with the probability of progression.

– In fact, in subjects ID-1 and ID-2 harboring *RUNX1*, progression did not occur during a 10-year follow-up while still responding to eltrombopag.

» *ASXL1* (HR 8.04 [95% CI, 1.33 to 48.73], P=0.02) and *TET-2* (HR 25.31 [95% CI, 2.62 to 244.88*], P=0.005*) mutations were associated with an increased probability of disease progression.

» *TET-2* mutations appeared in the context of other poor-risk mutations.

Conclusions

- There is no evident advantage of TPO-RAs in higher risk MDS
  - combination with azacitidine is unfavourable
- Romiplostim has been associated with an increased risk of progression
- First randomized, placebo-controlled clinical trial assessing eltrombopag for the treatment of thrombocytopenia in patients with IPSS low- and int-1-risk MDS seems promising:
  - Eltrombopag induced platelet responses and other hematologic improvements (erythroid and neutrophil) may be observed, independent of platelet response
  - Eltrombopag improved patient-reported outcomes (QoL)
  - Treatment-related adverse events, particularly nausea and vomiting, were problematic in a few patients and led to some premature discontinuations in the eltrombopag group; however, overall the treatment was well tolerated
  - No biological nor clinical safety signals

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Thank you for your attention.

Invitation to contribute:

Special Issue "Myelodysplastic Syndrome: Recent Advances and Future Directions"