FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Convegno della Fondazione Italiana Sindromi Mielodisplastiche

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Trattamento della piastrinopenia nei pazienti a basso rischio: algoritmo terapeutico

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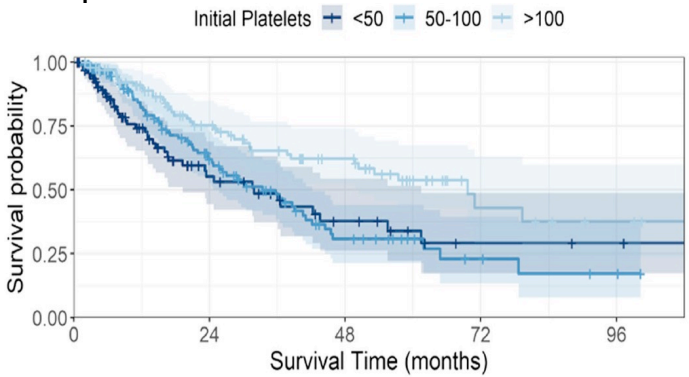
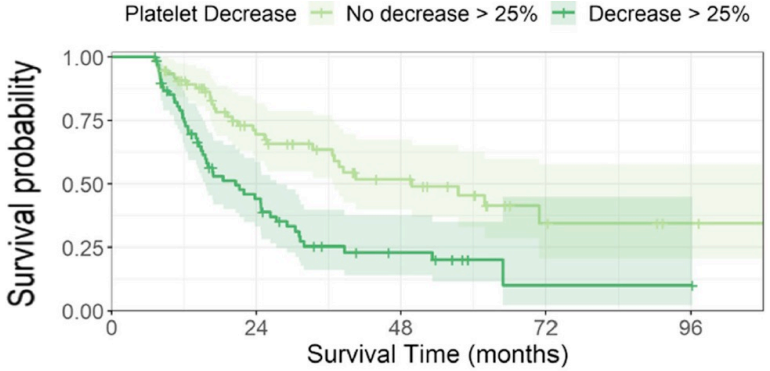
Varese

Disclosures of Andrea Castelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Servier							x
Novartis					x		x
Incyte					x		x
Celgene-BMS					x		x

- Circa il 35-65% di tutti i pazienti con MDS si presentano con piastrinopenia all'esordio
- I pazienti con LR-MDS che si presentano con piastrinopenia isolata sono meno del 10%
- La conta piastrinica all'esordio costituisce un'importante fattore prognostico
- La dipendenza trasfusionale piastrinica alla diagnosi e la flessione precoce (entro i primi 6 mesi) della conta piastrinica (≥25% rispetto al baseline) durante il decorso della malattia sono fattori predittivi di ridotta sopravvivenza





Steensma DP et al. Mayo Clin Proc 2006
Kantarjian H et al. Cancer 2007
Itzykson R et al. Blood Adv 2018
Strapatsas J et al. Ann Hematol 2021

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO

AGENDA:

- Supporto trasfusionale piastrinico
- Terapia steroidea/immunosoppressiva (ATG ± CyA)
- Danazolo
- TPO-RA
- HMA low-dose
- Nuovi farmaci

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OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
Terapia immunosoppressiva

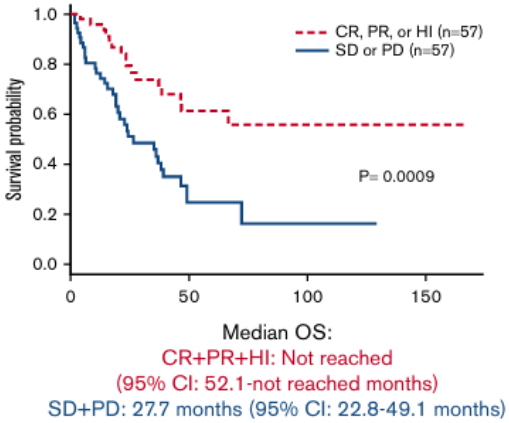
- Terapia steroidea: dosi simili a quelle usate per ITP, ma efficacia limitata e presenza di effetti collaterali steroide-relati

- ATG ± CyA:

Table 2. Response to IST

Response	Percentage	95% CI
CR	11.2	6.5-18.4
PR	5.6	2.5-11.6
HI	32.0	24.1-41.0
SD	39.2	30.7-48.4
PD	12.0	7.1-19.3
ORR (CR+PR+HI)	48.8	39.8-57.9
TI	30	22.3-39.5

PLT response 35-40%



Median OS:
CR+PR+HI: Not reached
(95% CI: 52.1-not reached months)
SD+PD: 27.7 months (95% CI: 22.8-49.1 months)

Fattori predittivi di risposta:
- BM ipoplastico (cellularità<20%)
- HLA DR15
- Età<60 aa
- Trisomia 8
- Low transfusion burden
- Horse ATG

Stahl M et al. Blood Adv. 2018
Parikh, A.R et al. Semin. Hematol. 2012

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO

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OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
Danazolo

- Androgeno sintetico con proprietà progestiniche e glucocorticoidi→inibizione di TNFα e IL-1
- Danazolo inibisce gli enzimi steroidogenici e il rilascio di FSH ed LH dall'ipofisi attraverso il blocco della funzione ovarica/testicolare (approvato per il trattamento di endometriosi, mastopatia fibrocistica ed angioedema ereditario)
- Possibile azione di stabilizzazione dei telomeri→risposta ematologica quando utilizzato nelle telomeropatie
- In ambito ematologico, efficacia ben documentata nel trattamento delle citopenie autoimmuni (ITP ed AA)

Sangam S et al. Oncology 2023
Riva M et al. Hemasphere 2023

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO

Danazolo

Efficacy Results of the Included Studies

Study number	Lead author, study year	Efficacy measure(s)	Outcomes
1	Jaime-Pérez et al, 2017[17]	1. MR	Sixty percent of patients experienced any response. MR for patients with anemia was 23.8%. MR for ANC was 36.8% and for platelet count was 60%. Median increase in hemoglobin level was 1.1 g/dL (95% CI, 0.7-1.5), in ANC was 0.6 × 10^9/L (95% CI, 0.3-1.1 × 10^9/L), and in platelet count was 42 × 10^9/L (95% CI, 16-83 × 10^9/L).
		2. Time to initial response	Time to initial response was 2 months; time to best response was 3 months. Median DOR was 6 months. Responders were significantly older than nonresponders (median age 70 vs 52 years, respectively) and had a higher baseline hemoglobin level (9.7 g/dL vs 7.7 g/dL) (P = .025 and P = .009).
		3. Transfusion independence	Thirteen of 23 patients dependent on transfusion support (57%) became platelet transfusion independent, and 8 of 23 patients dependent on PRBC transfusion support (35%) became independent.
2	Letendre et al, 1995[18]	MR	One patient improved after danazol treatment, 1 patient had a partial response, and 9 patients had no response (1 nonresponder with an initial neutrophil count of .7 × 10^9/L did experience a 1-month increase in ANC to 1.5 × 10^9/L; another had an increased hemoglobin level of 1 g/dL). Crossover to high dose showed no improvement.
3	Chan et al, 2002[11]	Increase in platelet count	The mean platelet count of participants after 6 weeks of therapy rose to 60 × 10^9/L (9-223 × 10^9/L; P < .015); 76% of participants had an increase in platelet count (1-181 × 10^9/L), with 36% of them experiencing a platelet count increase of more than 50%.
4	Catalano et al, 1993[25]	Increase in platelet count	A response was evident in 6 patients who had platelet count increase > 40 × 10^9/L (in 1 case with an increased WBC count and in 2 cases with discontinuation of the transfusion requirement).
5	Viniou et al, 2002[2]	Increase in platelet count	Platelet antibodies were detected in 70.6% of patients with MDS. Seven patients (41.2%) responded to treatment and achieved a significant increase in platelet count (median value increased from 40 × 10^9/L to 122 × 10^9/L).
6	Stadtmauer et al, 1991[25]	Increase in platelet count	Eleven of 22 evaluable patients taking danazol showed improvement of peripheral counts.
7	Wattel et al, 1994[24]	Increase in platelet count	Eight of 13 evaluable patients taking danazol showed improvement of peripheral counts.
8	Doll et al, 1987[19]	Increase in platelet count	No patient had a response to therapy as determined by an increase in either the hemoglobin level or platelet count, and none of the patients had a prolongation of their transfusion interval.
9	Buzaid et al, 1987[23]	Increase in platelet count	Three patients (15%) responded to the treatment; all responders had an increase in platelet count only.

ANC, absolute neutrophil count; DOR, duration of response; MDS, myelodysplastic syndromes; MR, major response; PRBC, packed red blood cells; WBC, white blood cell.

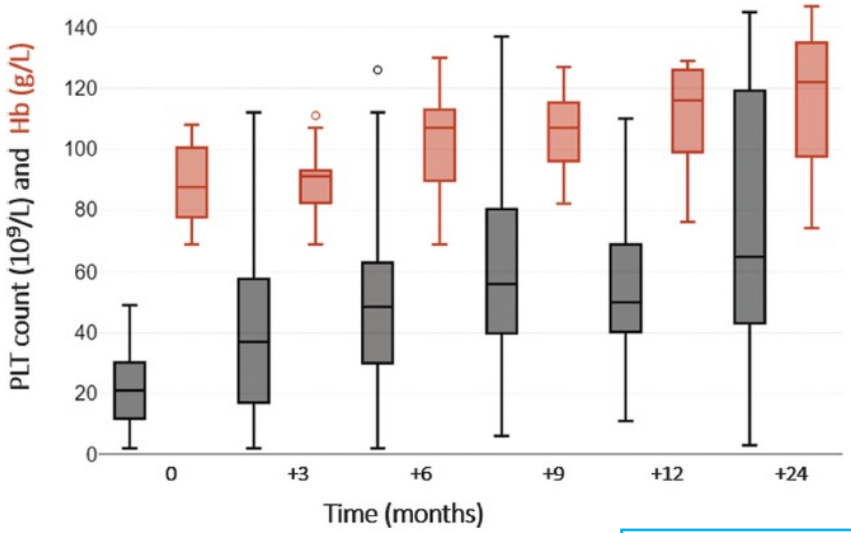
- Nell'ambito delle MDS, meccanismo d'azione ancora non noto
- Dati di efficacia estrapolati da studi retrospettivi

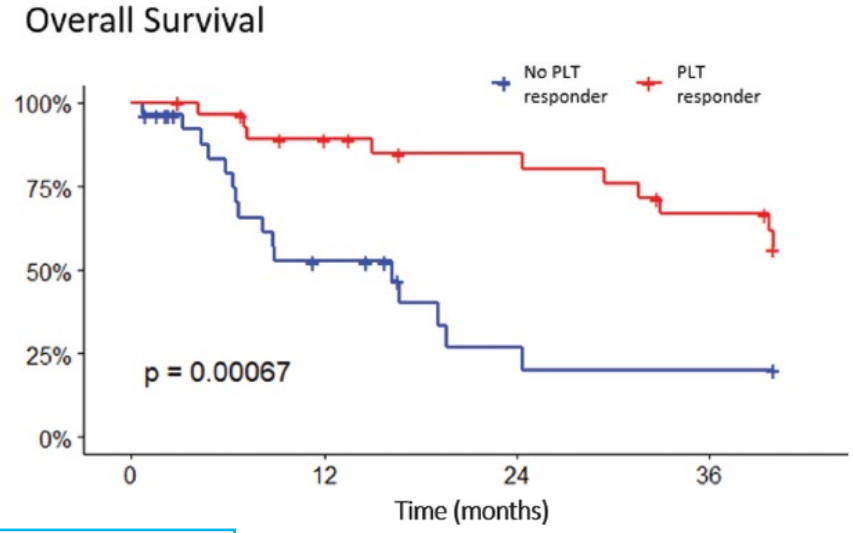
Risposte piastriniche (maggiori o minori) tra 40-60% nella maggior parte degli studi

Sangam S et al. Oncology 2023

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
Danazolo

Multicenter retrospective study
N= 57 pz; IPSS low (33%)/int-1 (67%), PLT<50.000. Danazole median dose= 500 mg/die for 12 months





PLT response 51%
Median time to response 3.3 months
Erythroid HI 42%
Neutrophil HI 44%

Riva M et al. Hemasphere 2023

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO

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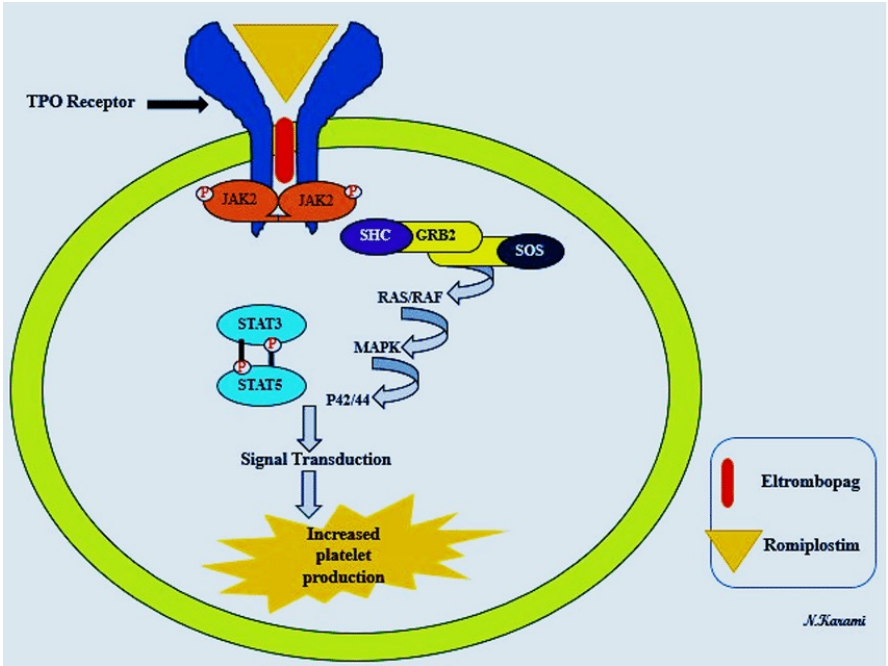
OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
TPO-RA



Courtesy of Karami N, 2018

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
TPO-RA: Romiplostim

Phase II, placebo-controlled trial, LR-MDS reciving romiplostim (750 ug/wk) or placebo
N=250, PLT<20.000/uL or <50.000/uL with bleading

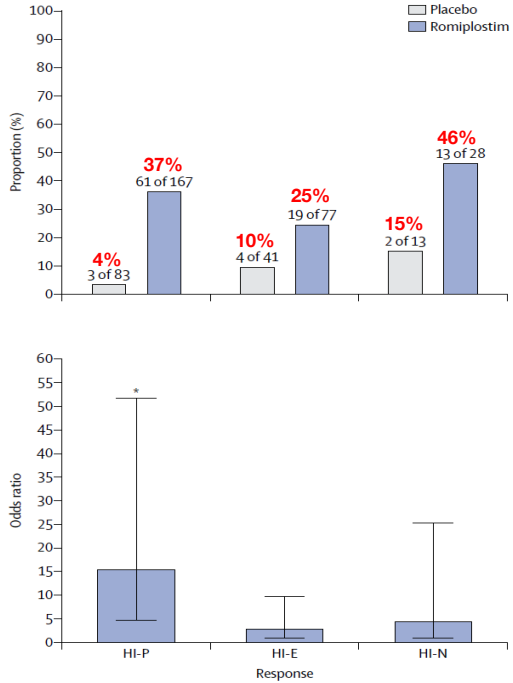
	Romiplostim (n=167)	Placebo (n=83)
Sex		
Male	95 (57%)	53 (64%)
Female	72 (43%)	30 (36%)
Age, years	71 (62–77)	69 (61–76)
WHO classification		
Refractory anaemia	6 (4%)	5 (6%)
Refractory anaemia with ringed sideroblasts	2 (1%)	0
Refractory anaemia with excess blasts-1	24 (14%)	9 (11%)
Refractory anaemia with excess blasts-2	1 (1%)	0
Refractory cytopenia with multilineage dysplasia	114 (68%)	55 (66%)
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts	4 (2%)	2 (2%)
Unclassified myelodysplastic syndromes	16 (10%)	12 (14%)
Chromosome 5q deletion	0	0
International Prognostic Scoring System		
Low risk	46 (28%)	23 (28%)
Intermediate-1 risk	121 (72%)	60 (72%)
Baseline platelet count		
$<20\times10^9$ per L	87 (52%)	43 (52%)
$\geq20\times10^9$ per L	80 (48%)	40 (48%)

Data are n (%) or median (IQR).

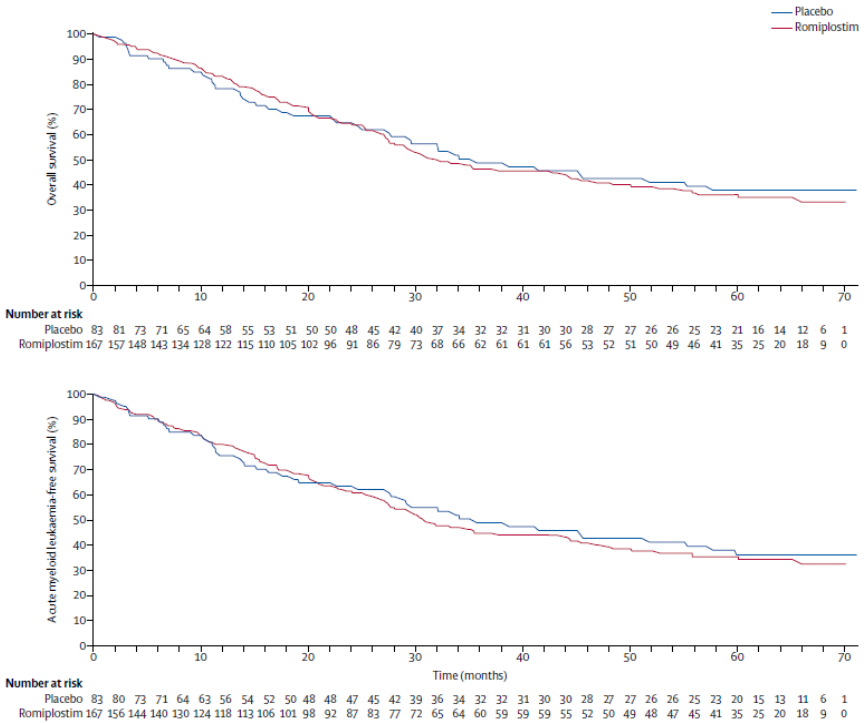
Kantarjian H et al. Lancet Hematol 2018

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
TPO-RA: Romiplostim

Phase II, placebo controlled trial, LR-MDS reciving romiplostim (750 ug/wk) or placebo
N=250. PLT<20.000/uL or <50.000/uL with bleading



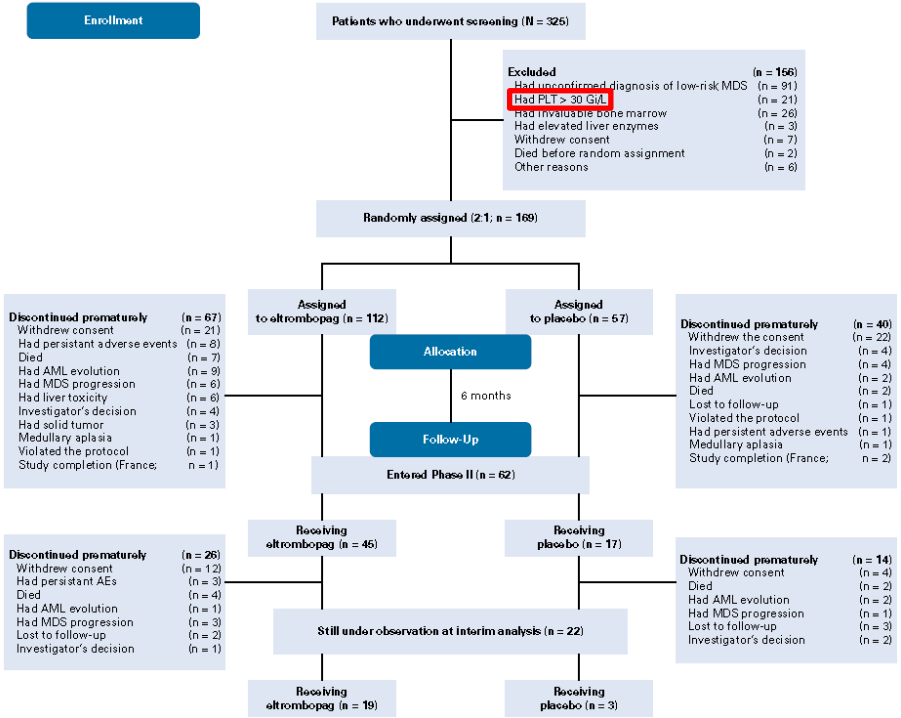
Significant HI-P and PLT transfusion reduction with romiplostim, but no bleeding events improvement



Kantarjian H et al. Lancet Hematol 2018

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
TPO-RA: Eltrombopag (EQOL-MDS TRIAL)

Single-blind, randomized, placebo-controlled, phase-II trial (EQoL-MDS), LR or INT-1 MDS reciving eltrombopag or placebo



Eltrombopag dose 50 mg→300 mg

Oliva EN et al. JCO 2023

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
TPO-RA: Eltrombopag (EQOL-MDS TRIAL)

TABLE 1. Main Demographic and Clinical Characteristics of Patients

Characteristic	Total (N = 169)	Eltrombopag Group (n = 112)	Placebo Group (n = 57)	P
Age, years (IQR)	72 (65-79)	72 (65-79)	71 (65-79)	.807
Sex, No. (%)				
Male	104 (61.5)	72 (64.3)	32 (56.1)	.312
Female	65 (38.5)	40 (35.7)	25 (43.9)	.312
Duration of MDS, months (IQR)	14 (4-40)	15 (4-42)	10 (4-39)	.286
WHO (2016) classification, No. (%)				.311
MDS-SLD	61 (36.1)	44 (39.3)	17 (29.8)	
MDS-MLD	49 (29.0)	29 (25.9)	20 (35.1)	
MDS RS-MLD	1 (0.6)	–	1 (1.8)	
MDS with del (5q)	1 (0.6)	1 (0.9)	–	
MDS EB-1	21 (12.4)	16 (14.3)	5 (8.8)	
MDS unclassified	36 (21.3)	22 (19.6)	14 (24.5)	
IPSS risk, No. (%)				.685
Low	50 (29.6)	32 (28.6)	18 (31.6)	
Int-1	119 (70.4)	80 (71.4)	39 (68.4)	
IPSS-R, No. (%)				.294
Very low	4 (2.4)	1 (0.9)	3 (5.3)	
Low	100 (59.2)	65 (58.0)	35 (61.4)	
Intermediate	51 (30.2)	36 (32.2)	15 (26.3)	
High	14 (8.2)	10 (8.9)	4 (7.0)	
Cytogenetics by IPSS-R, No. (%)				
Very good and good				
Normal	118 (69.8)	84 (75.0)	34 (59.6)	
Del(5q)	3 (1.8)	1 (0.9)	2 (3.5)	
Y	7 (4.1)	2 (1.8)	5 (8.8)	
Del(11q)	3 (1.8)	2 (1.8)	1 (1.8)	
Del(20q)	16 (9.5)	9 (8.0)	7 (12.3)	
Del (12p)	1 (0.6)	1 (0.9)	–	
Intermediate				
+8	8 (4.7)	5 (4.5)	3 (5.3)	
+15	1 (0.6)	–	1 (1.8)	
Del (1)	1 (0.6)	1 (0.9)	–	
Del (9)	2 (1.2)	1 (0.9)	1 (1.8)	
Trisomy 6	1 (0.6)	1 (0.9)	–	
Del (13)	1 (0.6)	1 (0.9)	–	
Der (14) + del (20q)	1 (0.6)	1 (0.9)	–	
Der (20) + del (20q)	1 (0.6)	1 (0.9)	–	
Trisomy 14	1 (0.6)	1 (0.9)	–	
Der (11)	1 (0.6)	–	1 (1.8)	
Del (11q) + del (20q)	1 (0.6)	–	1 (1.8)	
Der (11) + del (11q)	1 (0.6)	–	1 (1.8)	
Poor				
Complex (3 abnormalities)	1 (0.6)	1 (0.9)	–	

Characteristic	Total (N = 169)	Eltrombopag Group (n = 112)	Placebo Group (n = 57)	P
WHO bleeding score ≥ 2, No. (%)	14 (8.3)	9 (8.0)	5 (8.528)	.774
PLT transfusion, No. (%)				.934
Dependent	52 (30.8)	35 (31.3)	17 (29.8)	
Independent	117 (69.2)	77 (68.8)	40 (70.2)	
Hypoplasia, No. (%)	34 (20.1)	27 (24.1)	7 (12.3)	.165
WHO fibrosis, grade, No. (%)				.120
0	77 (45.6)	57 (50.9)	20 (35.1)	
1	25 (14.8)	14 (12.5)	11 (19.3)	
2	3 (1.8)	3 (2.7)	–	
Not done	64 (37.8)	38 (33.9)	26 (45.6)	
RBC transfusion, No. (%)				.726
Dependent	46 (27.2)	30 (28.8)	16 (25.8)	
Independent	123 (72.8)	82 (71.2)	41 (74.2)	
Hemoglobin, g/dL	10.7 ± 2.2	10.7 ± 2.3	10. 8 ± 2.1	.545
PLT count, $\times 10^3/mm^3$	16.8 ± 8.2	16.9 ± 8.4	16. 3 ± 7.7	.940
WBC, $\times 10^3$	3.9 (IQR, 2.6-6.3)	3.8 (IQR, 2.6-5.8)	4.3 (IQR, 2.6-6.9)	.342
Concomitant treatment, No. (%)				
GCSF	1 (0.6)	1 (0.9)	0 (0.0)	1.000
ESA	27 (16.0)	18 (16.1)	9 (15.8)	.940
Deferasirox	10 (5.9)	8 (7.1)	2 (3.5)	.500
Steroids	27 (16.0)	20 (17.9)	7 (12.3)	.410

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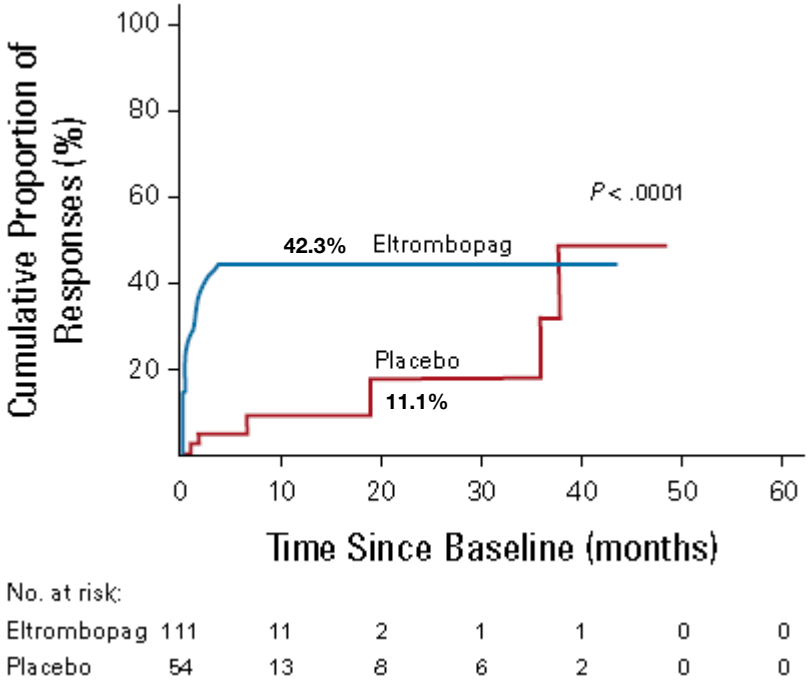
OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
TPO-RA: Eltrombopag (EQOL-MDS TRIAL)

PLT RESPONSE



WHO Bleed Scale	Total (N – 165)	Eltrombopag Group (n – 111)	Placebo Group (n – 54)
Grade 0 no bleeding, No.	65	48	17
Grade I petechiae, No.	61	41	20
Grade II mild blood loss, No.	33	19	14
Grade III gross blood loss, No.	6	3	3

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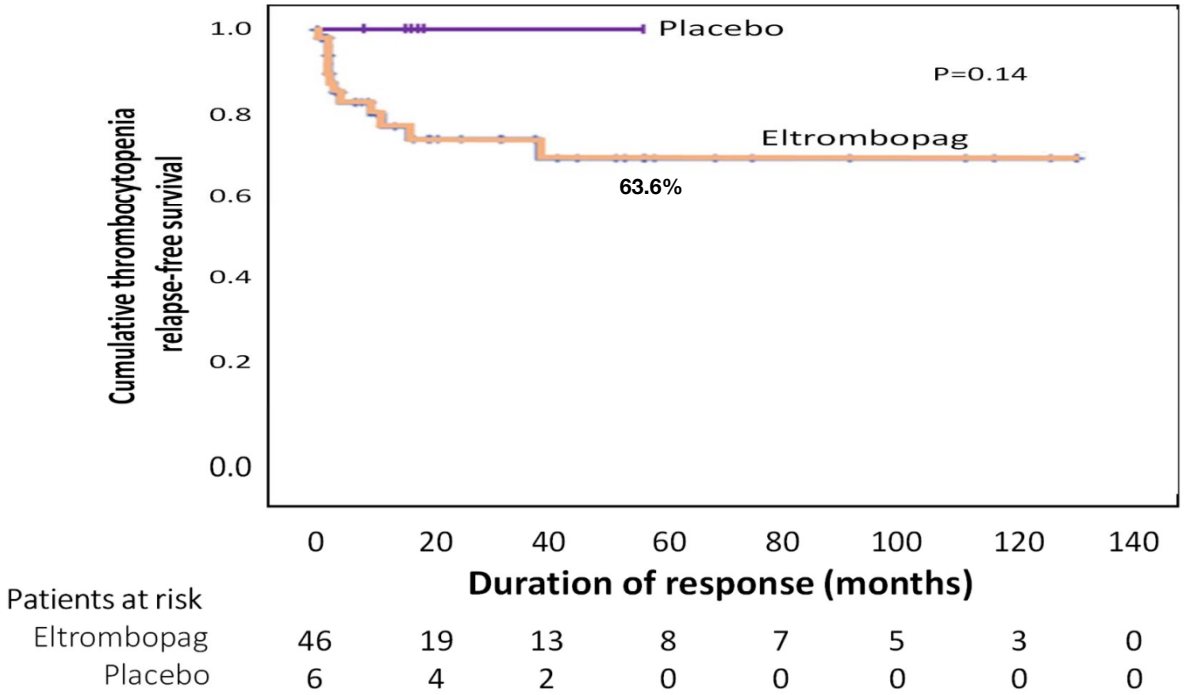

PLT-R loose (Eltrombopag)= 25.5%

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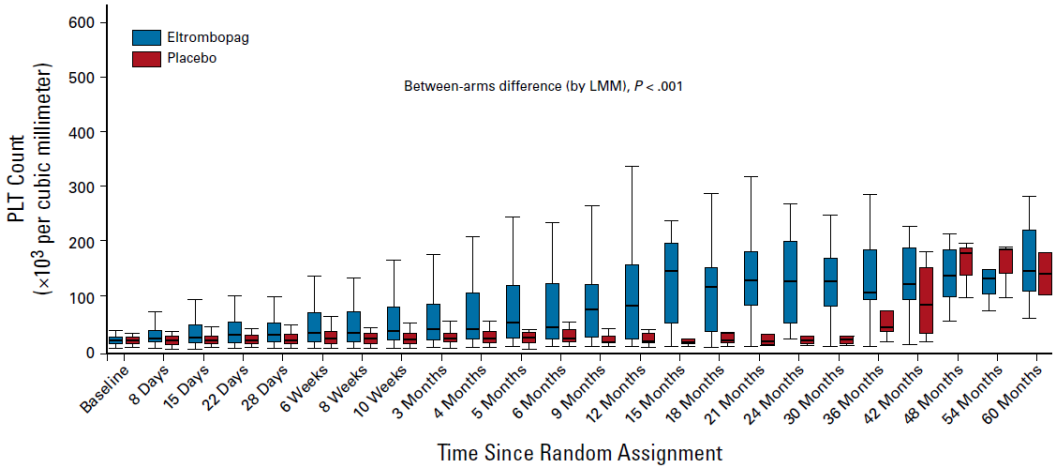
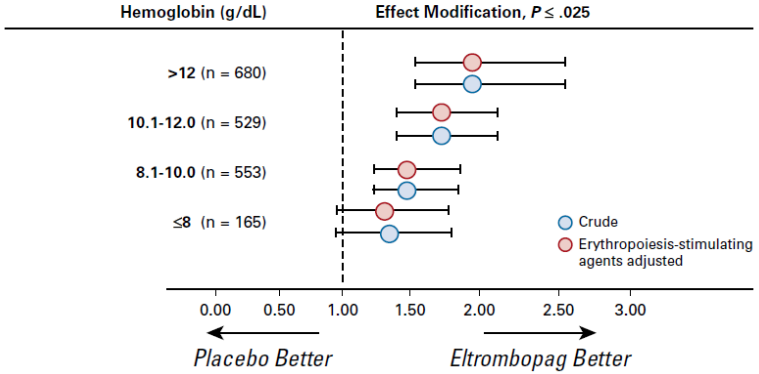
TPO-RA: Eltrombopag (EQOL-MDS TRIAL)





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OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO

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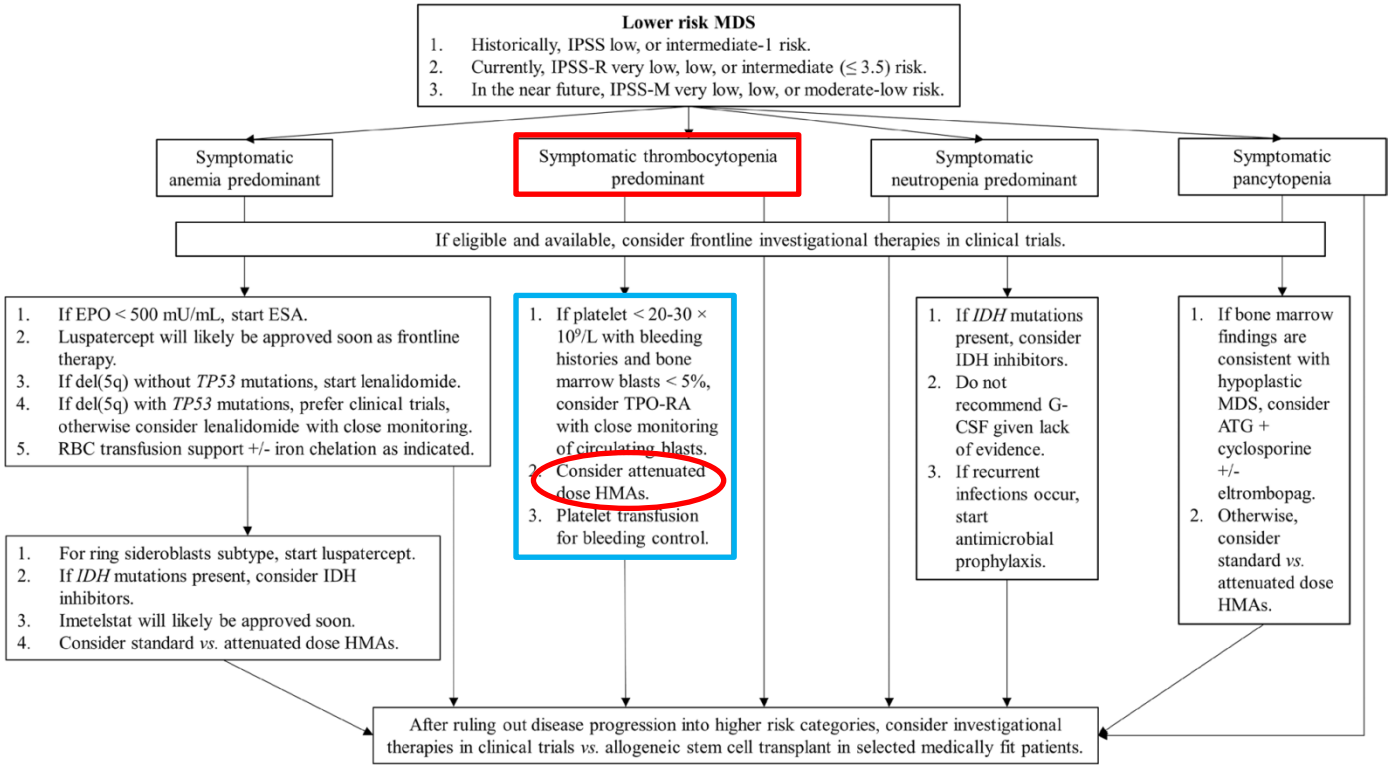


Wang C & Sallman DA., Curr. Treat. Options in Oncol 2023

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
Low-dose HMA

Randomized phase-2 study, low-dose HMA (decitabine 20 mg/m^2 for 3 days vs azacytidine 75 mg/m^2 for 3 days)

Table 1. Patient characteristics

Parameter n (%)/median [range]	Overall (n = 113)	Decitabine (N = 73)	Azacitidine (N = 40)
Age, years	70 [44-88]	70 [44-88]	70 [53-84]
WHO diagnosis			
RCUD	15 (13)	10 (14)	5 (13)
RCMD	40 (35)	29 (40)	11 (28)
MDS with ringed sideroblasts	3 (3)	2 (3)	1 (3)
MDS-EB	25 (22)	14 (19)	11 (28)
5q-	2 (2)	0	2 (5)
MDS-U	6 (5)	6 (8)	0
MDS/MPN-U	6 (5)	2 (3)	4 (10)
CMML	16 (14)	10 (14)	6 (15)
Therapy-related MDS	20 (18)	13 (18)	7 (18)
≥2 cytopenias	68 (50)	34 (47)	22 (55)
Transfusion dependence	59 (52)	39 (53)	20 (50)
BM blasts percentage	3 [0-10]	2 [0-10]	3 [0-10]
Blasts ≥5%	32 (28)	21 (29)	11 (27)
Cytogenetic risk (IPSS)			
Good	69 (61)	43 (63)	26 (65)
Intermediate	30 (27)	17 (23)	13 (33)
Poor	11 (10)	10 (14)	1 (3)
IPSS risk group			
Low	22 (19)	16 (22)	6 (15)
Intermediate-1	91 (81)	57 (78)	34 (85)
IPSS-R risk group			
Very low	14 (12)	10 (14)	4 (10)
Low	41 (36)	25 (34)	16 (40)
Intermediate	34 (30)	21 (29)	13 (33)
High	23 (20)	16 (22)	7 (18)
Very high	1 (1)	1 (1)	0
MDACC LR-MDS score			
Low	13 (11)	10 (14)	3 (8)
Intermediate	52 (46)	35 (48)	14 (43)
High	48 (42)	28 (38)	20 (40)
Prior therapy			
Growth factors	22 (19)	12 (16)	10 (25)
Others	9 (8)	5 (7)	4 (10)
Time from diagnosis, weeks	5 [1-271]	6 [1-216]	4 [1-271]

Jabbour E et al., Blood 2017

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
Low-dose HMA

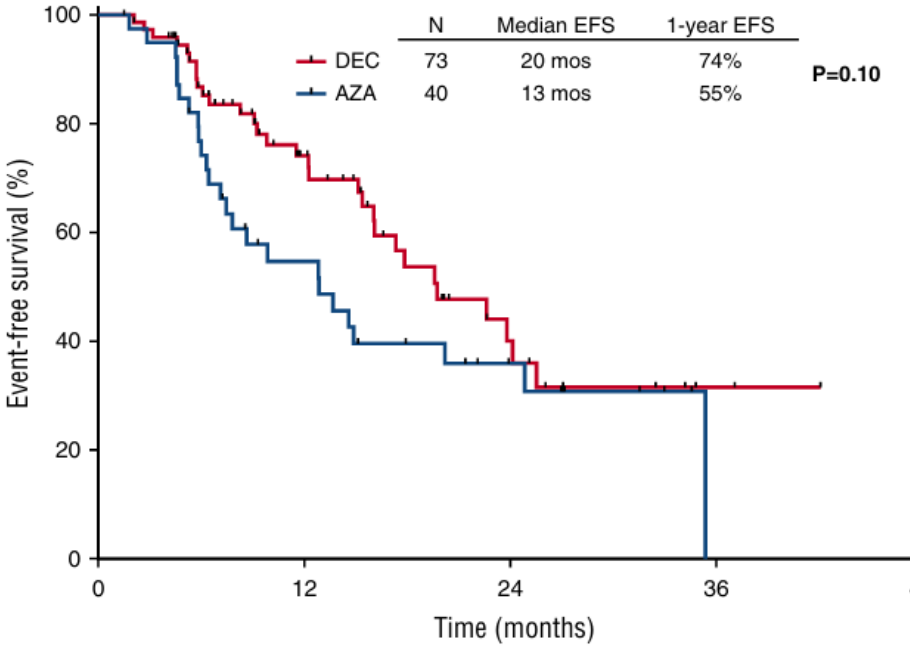
Randomized phase-2 study, low-dose HMA (decitabine 20 mg/m^2 for 3 days vs azacytidine 75 mg/m^2 for 3 days)

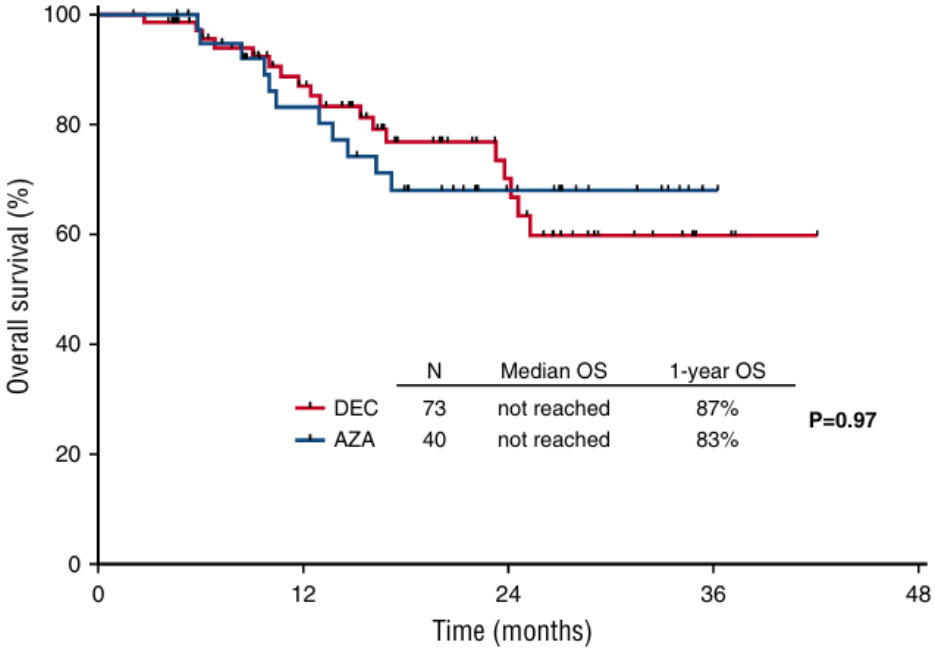
N=113 (73 pz DAC, 40 pz AZA)

Parameter	Overall, n (%)	Decitabine, n (%)	Azacitidine, n (%)	*P*
Morphologic response, N	109	70	39	
CR	40 (37)	26 (37)	14 (36)	
mCR	8 (7)	6 (9)	2 (5)	
HI	20 (18)	17 (24)	3 (8)	
Overall	68 (62)	49 (70)	19 (49)	.03
Transfusion response, N	57	38	19	
RBC	11/46 (24)	8/29 (28)	3/17 (18)	
Platelets	3/5 (60)	3/4 (75)	0/1	
RBC + Platelets	1/6 (17)	1/5 (20)	0/1	
Overall	15 (26)	12 (32)	3 (16)	.2
Cytogenetic response, N	44	28	16	
Complete	8 (18)	7 (25)	1 (6)	
Partial	13 (30)	10 (36)	3 (19)	
Overall	21 (48)	17 (61)	4 (25)	.02
Morphologic response (BM blasts ≥5%), N	32	21	11	
CR	14 (44)	12 (57)	2 (18)	
mCR	8 (25)	6 (29)	2 (18)	
HI	3 (9)	3 (14)	0	
Overall	25 (78)	21 (100)	4 (36)	<.001
Hematologic response (BM blasts <5%), N	72	45	27	
≥1 lineage	29 (40)	16 (36)	13 (48)	
All lineages	17 (24)	10 (22)	7 (26)	

Jabbour E et al., Blood 2017

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO
Low-dose HMA





AE di tipo infettivo= 7% con DAC, 5% con AZA

Jabbour E et al., Blood 2017

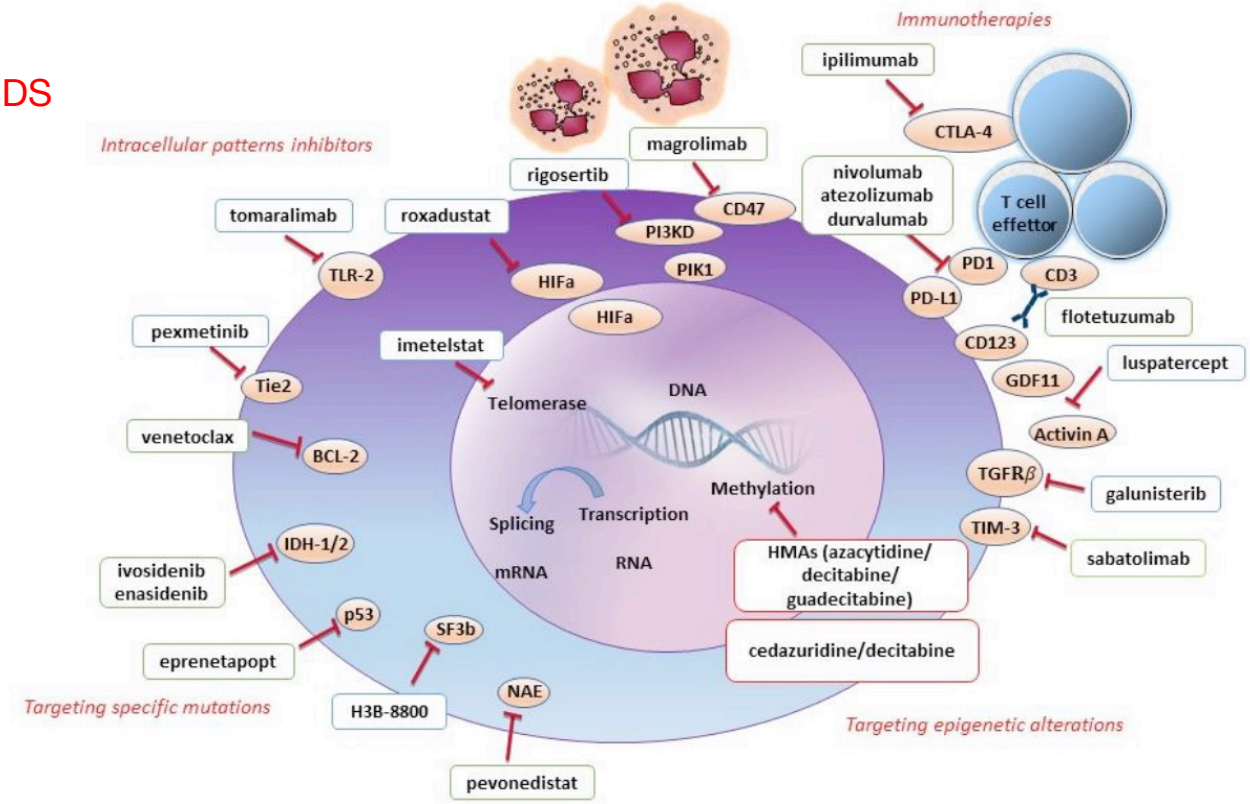
OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO

AGENDA:

- Supporto trasfusionale piastrinico
- Terapia steroidea/immunosoppressiva (ATG + CyA)
- Danazolo
- TPO-RA
- HMA low-dose
- Nuovi farmaci

OPZIONI TERAPEUTICHE PAZIENTE CON LR-MDS PIASTRINOPENICO
Nuovi farmaci

- LR-MDS
- LR/HR-MDS
- HR-MDS



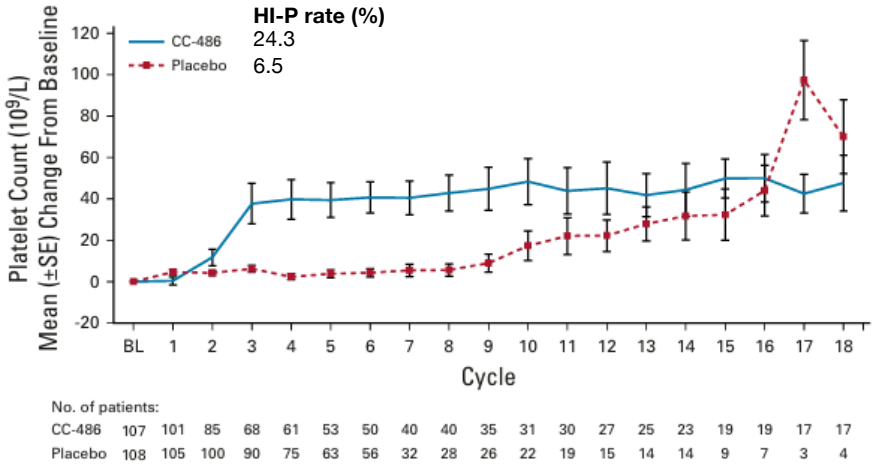
Cassanello G et al., Cancers 2022

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO

Nuovi farmaci: azacitidina orale

Phase 3 randomized trial, CC-486 300 mg/die d1-21/28 (n=107) vs Placebo (n=109)

Characteristic	CC-486 (n = 107)	Placebo (n = 109)	Total (N = 216)
Age, years, median (range)	74.0 (30-89)	73.0 (44-88)	74.0 (30-89)
Age ≥ 65 years, n (%)	91 (85.0)	95 (87.2)	186 (86.1)
Sex, n (%)			
Male	79 (73.8)	79 (72.5)	158 (73.1)
Female	28 (26.2)	30 (27.5)	58 (26.9)
WHO 2008 MDS classification, n (%)			
RCMD	80 (74.8)	73 (67.0)	153 (70.8)
RAEB-1	17 (15.9)	29 (26.6)	46 (21.3)
RA	4 (3.7)	3 (2.8)	7 (3.2)
RARS	3 (2.8)	2 (1.8)	5 (2.3)
MDS-U	2 (1.9)	2 (1.8)	4 (1.9)
RT	1 (0.9)[a]	0 (0.0)	1 (0.5)
IPSS risk, n (%)			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate-1	106 (99.1)	109 (100)	215 (99.5)
Intermediate-2	1 (0.9)	0 (0.0)	1 (0.5)
High	0 (0.0)	0 (0.0)	0 (0.0)
IPSS-R risk, n (%)			
Very low (≤ 1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Low (> 1.5-3)	24 (22.4)	21 (19.3)	45 (20.8)
Intermediate (> 3-4.5)	51 (47.7)	48 (44.0)	99 (45.8)
High (> 4.5-6)	27 (25.2)	33 (30.3)	60 (27.8)
Very high (> 6)	1 (0.9)	0 (0.0)	1 (0.5)
Missing	4 (3.7)	7 (6.4)	11 (5.1)
Months since MDS diagnosis, median (range)	18.9 (0.9-153)	16.1 (0.4-381)	17.5 (0.4-381)
Platelet transfusion–dependent,[d] n (%)	30 (28.0)	35 (32.1)	65 (30.1)
RBC transfusion requirement per 28 days,[e] units, median (range)	3.3 (1.3-10.0)	3.3 (1.3-9.5)	3.3 (1.3-10.0)
> 4 units, n (%)	36 (33.6)	34 (31.2)	70 (32.4)
ECOG-PS score, n (%)			
0-1	91 (85.0)	94 (86.2)	185 (85.6)
2	16 (15.0)	15 (13.8)	31 (14.4)
Hemoglobin, g/dL, median (range)	8.3 (5.4-10.9)	8.1 (5.7-10.1)	8.1 (5.4-10.9)
Platelets, 10^9/L, median (range)	24 (566)	25 (573)	25 (573)
Platelet count < 20 × 10^9/L, n (%)	44 (41.1)	48 (44.0)	92 (42.6)
ANC, 10^9/L, median (range)	1.36 (0.07-25.2)	1.28 (0.06-20.5)	1.31 (0.06-25.2)
Absolute lymphocyte count, n (%)			
< 0.5 ×10^9/L	20 (18.7)	11 (10.1)	31 (14.4)
≥ 0.5 ×10^9/L	87 (81.3)	97 (89.0)	184 (85.2)



Preferred Term	CC-486 (n = 107) n (%)	Placebo (n = 109) n (%)
≥ 1 Grade 3-4 TEAE	96 (89.7)	80 (73.4)
Neutropenia	50 (46.7)	13 (11.9)
Thrombocytopenia	31 (29.0)	17 (15.6)
Febrile neutropenia	30 (28.0)	11 (10.1)
Anemia	20 (18.7)	18 (16.5)
Pneumonia	13 (12.1)	10 (9.2)

Garcia-Manero G. et al., JCO 2021

OPZIONI TERAPEUTICHE NEL PAZIENTE CON LR-MDS PIASTRINOPENICO

New drugs: Pexmetinib

Phase 1 trial, LR/int-1 MDS
Pexmetinib: p38 MAPK/Tie2 dual inhibitor. Dose: 400, 600, 900 or 1200 mg QD; 200 or 300 mg BID

Patient demographics and baseline disease characteristics (ITT Population)

Demographics/Characteristics (N=45)	Value
Median age, years (range)	72 (47 – 84)
Sex, n (%)	
Male	39 (87)
Female	6 (13)
ECOG performance status, n (%)	
0	11 (24)
1	28 (62)
2	6 (13)
Median time since first diagnosis, years (range)	3.3 (0.2 – 16.3)
IPSS risk score at screening, n (%)	
Low	12 (27)
Intermediate-1	33 (73)
WHO classification at screening, n (%)	
RA/RARS	11 (24)
RCMD/RCMD-RS	18 (40)
RAEB-1	7 (16)
RAEB-2	2 (4)
MDS-U	6 (13)
MDS with isolated del(5q)	1 (2)
% Blasts (bone marrow aspirate), n (%)	
< 5	40 (89)
≥ 5	4 (9)
>10	0 (0)
No data	1 (2)
Number of cytopenias, n (%)	
0	1 (2)
1	19 (42)
2	12 (27)
3	13 (29)
Hemoglobin < 11 g/dL[1], n (%)	41 (91)
ANC[2], n (%)	
0.5 – < 1.0 × 10⁹/L	7 (16)
< 0.5 × 10⁹/L	9 (20)
Platelets[3]	
50 – < 100 × 10⁹/L	22)
< 50 × 10⁹/L	15 (33)
Karyotype[4], n (%)	
Good	
Normal	29 (64.4)
-Y	4 (8.9)
del (20q)	2 (4.4)
del (5q)	1 (2.2)
Intermediate	8 (17.8)
Complex	1 (2.2)
Transfusions within 8 weeks prior to first day of dosing in Cycle 1, n (%)	
Any RBC transfusion	38 (84)
RBC transfusion dependent[5]	25 (56)
Any platelet transfusion	7 (16)
Median number of prior therapies, n (range)	2 (0 – 9)
≥ 1 prior hypomethylating agent (HMA)[5], n (%)	36 (80)
Prior lenalidomide, n (%)	19 (42)
Prior erythropoiesis-stimulating agent[6], n (%)	26 (58)

Response rates for hematologic improvement and transfusion independence

	All Patients				1200 mg QD Patients			
Response[1]	Responders N	Evaluable Patients N	%	Median Duration of Response[2] (Range) Weeks	Responders N	Evaluable Patients, N	%	Median Duration of Response[2] (Range) Weeks
Hematologic Improvement								
HI-Any	14	44	32	21 (8 – 178+)	6	16	38	21 (8 – 178+)
HI-E	8	41	20	19 (9 – 178+)	2	15	13	19 (9 – 178+)
HI-N	5	16	31	21 (13 – 26)	4	8	50	21 (15 – 26)
HI-P	6	25	24	21 (8 – 158+)	4	11	36	12 (8 – 158+)
Transfusion Independence								
Red blood cell	3	25	12	20 (10 – 178+)	1	11	9	NC (178+)
Platelet	5	7	71	20 (12 – 66)	1	2	50	NC (31)

Treatment-related AEs (safety population)

AE N (%)	400 mg QD (n=7)	400 mg QD FED (n=5)	200 mg BID (n=3)	600 mg QD (n=4)	300 mg BID (n=7)	900 mg QD (n=3)	1200 mg QD (n=16)	Total (n=45)
Treatment-related AEs of all grades reported in ≥5% of patients								
Rash	3 (43)	0 (0)	0 (0)	0 (0)	4 (57)	1 (33)	6 (38)	14 (31)
Diarrhea	3 (43)	1 (20)	1 (33)	0 (0)	1 (14)	1 (33)	5 (31)	12 (27)
Dry Skin	1 (14)	0 (0)	0 (0)	2 (50)	0 (0)	1 (33)	2 (12)	6 (13)
Fatigue	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	4 (25)	5 (11)
Anorexia	1 (14)	1 (20)	0 (0)	0 (0)	2 (29)	1 (33)	0 (0)	5 (11)
Pruritus	0 (0)	0 (0)	0 (0)	1 (25)	1 (14)	1 (33)	1 (6)	4 (9)
Increased ALT	0 (0)	0 (0)	0 (0)	0 (0)	1 (14)	0 (0)	2 (12)	3 (7)
Prolonged ECG QT	0 (0)	1 (20)	2 (67)	0 (0)	0 (0)	0 (0)	0 (0)	3 (7)
Most common treatment-related Grade 3 AEs[2]								
Rash[#]	0 (0)	0 (0)	0 (0)	0 (0)	2 (29)	1 (33)	2 (12)	5 (11)
Diarrhea	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (19)	4 (9)
Asthenia	0 (0)	1 (20)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)	2 (4)
Prolonged ECG QT	0 (0)	1 (20)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)

Garcia-Manero G. et al., Clin Canc Res 2015

CONCLUSIONI

- Il trattamento della piastrinopenia severa nel paziente mielodisplastico a basso rischio costituisce ancora un «unmet need»
- Le opzioni terapeutiche che si sono dimostrate più efficaci (danazolo, TPO-RA) e ad oggi disponibili, sono comunque terapie *off label* (in Italia)
- I dati preliminari su nuove schedule o formulazioni di farmaci (low-dose HMA, AZA orale) hanno dimostrato efficacia in circa 1/3 dei pazienti, con un profilo di safety accettabile
- Nuovi farmaci (es. pexmetinib), in fase di studio, sembrano dare risultati promettenti per il prossimo futuro, ma i dati andranno confermati su casistiche più ampie ed in studi randomizzati

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GRAZIE PER L'ATTENZIONE