POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

TERAPIA DELLE SINDROMI MIELODISPLASTICHE A BASSO RISCHIO

Pellegrino Musto

Dipartimento di Medicina di Precisione e Rigenerativa e Area Ionica, Scuola di Medicina, Universita' degli Studi "Aldo Moro", Bari.

SC di Ematologia con Trapianto, AOU Consorziale Policlinico, Bari.

DICHIARAZIONE

Pellegrino Musto

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board/Onorari **(Abbvie, Alexion, Amgen, Astra-Zeneca, Astellas, Bei-Gene, Bristol-Myers Squibb/Celgene, Gilead, Glaxo-Smith-Kline, Grifols, Incyte, Janssen, Jazz, Novartis, Pfizer, Roche, Sanofi, Takeda).**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

AGENDA

- *Inflammation:*
  - ➢ *CANAKINUMAB and*
  - ➢ *LUSPATERCEPT Updates of MEDALIST and Italian Real-Life Study*
- *IMETELSTAT: update of IMERGE Study*
- *Oral DECITABINE-CEDAZURIDINE*
- *Low-dose LENALIDOMIDE*
- *Iron chelating therapy: Role of DEFERIPRONE*

NOVEL APPROACHES IN MDS

Targeting inflammation in lower-risk MDS

Jesus D. Gonzalez-Lugo and Amit Verma
Division of Hemato-Oncology, Department of Oncology, Montefiore-Einstein Cancer Center, Blood Cancer Institute, Bronx, NY

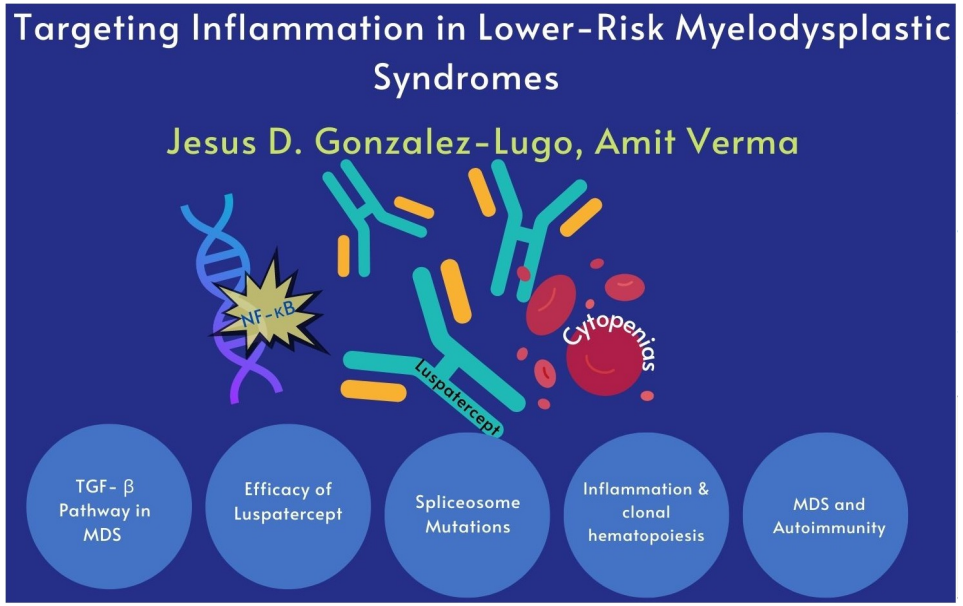


Table 1. Selected trials targeting inflammation in MDS and CH

Class	Agent	Trial name	Phase	Population	Status	Identifier
TGF-β pathway	Luspatercept	PACE-MDS (24)	2	LR-MDS	Completed	NCT01749514
TGF-β pathway	Luspatercept vs placebo	MEDALIST (25)	3	LR-MDS-RS	Completed	NCT02631070
TGF-β pathway	Luspatercept vs epoetin alfa	COMMANDS	3	LR-MDS	Recruiting	NCT03682536
TGF-β pathway	Luspatercept + lenalidomide	—	1/2	LR-MDS	Recruiting	NCT04539236
TGF-β pathway	Galunisertib	—	2	LR-MDS	Completed	NCT02008318
TGF-β pathway	Vactosertib	—	1/2	LR-MDS	Completed	NCT03074006
TIM-3 pathway TGF-β pathway IL-1β inhibitor	Sabatolimab NIS793 Canakinumab	—	1b	LR-MDS	Recruiting	NCT04810611
IL-1β inhibitor	Canakinumab	—	2	LR-MDS or MDS/MPN	Recruiting	NCT05237713
IL-8 inhibitor	BMS-986253±PO decitabine and cedazuridine	—	1/2	HR-MDS with prior HMA therapy or LR-MDS with cytopenias	Not yet Recruiting	NCT05148234
CXCR1 and *CXCR2* inhibitor	SX-682	—	1	MDS with disease progression or prior therapy intolerance	Recruiting	NCT04245397
TLR2 inhibitor	Tomaralimab	—	1/2	LR-MDS with prior HMA	Completed	NCT02363491
IRAK4 inhibitor	Emavusertib (CA-4948)	CURIS	1	HR-MDS and AML	Active	NCT04278768
IRAK4 inhibitor	Emavusertib (CA-4948)	LUCAS	2	LR-MDS	Recruiting	NCT05178342

AML, acute myelogenous leukemia; HMA, hypomethylating agent; MPN, myeloproliferative neoplasms; TBD, to be determined; TLR2, Toll-like receptor 2.

Clinical and Biological Effects of Canakinumab* in Lower-Risk Myelodysplastic Syndromes (MDS): Results from a Phase I/II Clinical Trial

Guillermo Garcia-Manero, Vera Adema, Samuel Urrutia, Feiyang Ma, Hui Yang, Irene Gañán-Gomez, Guatam Borthakur, Koichi Takahashi, Nicholas Short, Ghayas Issa, Kelly S. Chien, Guillermo Montalban-Bravo, Joby Joseph, and Simona Colla

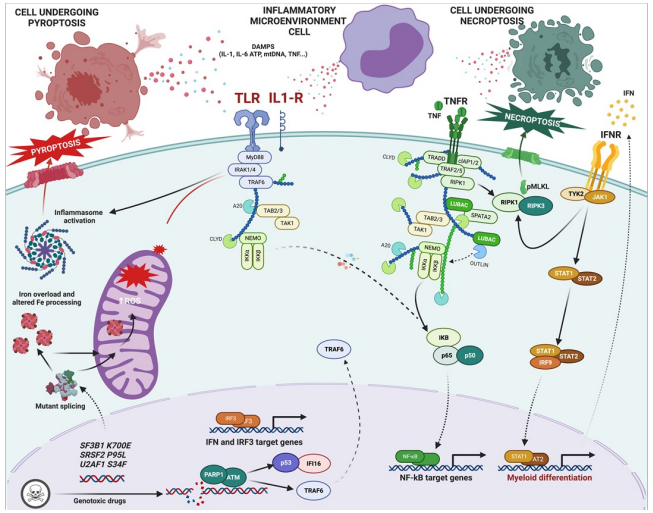
Department of Leukemia
The University of Texas MD Anderson Cancer Center

*** An IL-1 Beta inhibitor**

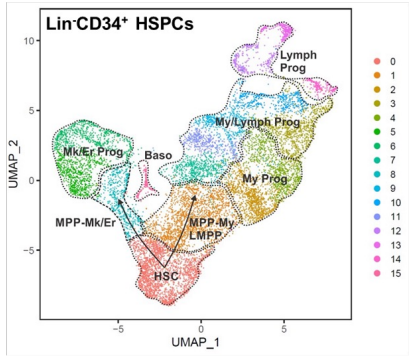
Abstract #858; *Session: 637. Myelodysplastic Syndromes — Clinical and Epidemiological I; ASH Meeting 2022*

IL-1β Signaling Activates NF-κB Pathway and Amplifies Inflammation

- IL-1β binding to IL1R1 activates NF-$_K$B pathway
- NF-$_K$B pathway activation induces the production of other cytokines (e.g., TNFα) that amplify the inflammatory response from the microenvironment

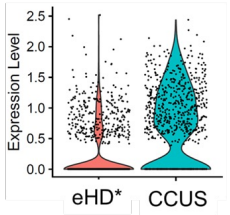


IL1-β is highly expressed in HSCs of patients with clonal cytopenia of undetermined significance (CCUS)



*eHD=elderly healthy donors

***IL1-β* in HSCs**



$P=1.7x10^{-71}$

Chronic exposure to IL1-β induces HSC metabolic activation and myeloid differentiation
(Pietras et al. Nat Cell Biol, 2016)

K. Chien, I. Gomez-Gomez, and S. Colla; unpublished data

Novità dal Meeting della Società Americana di Ematologia

Milano, 2-3-4 Febbraio 2023

Canakinumab in Lower risk MDS: Objectives and Design

- **Primary objectives:** safety and clinical activity by IWG-06*
- **Secondary objectives:**
  - Rate of transfusion independency
  - Duration of response
  - Progression
  - TFR, correlative studies

- **Phase I** (cohorts, n=3): 3+3 design starting 150mg SC daily q28 days and escalating to 300mg
- **Next Steps:**
  - Expansion cohort #1 (n=20): Transfusion dependent LR-MDS after at east one line of therapy. Stopping rules for toxicity.
  - Other planned: #2: TD LR-MDS no prior therapy; #3: TI LR-MDS and #4: CCUS

Eligibility Criteria

- Age ≥ 18 years old
- MDS
- Risk:
  - IPSS: low or int-1 risk
  - IPSS-R ≤ 3.5 points
- At least one prior line of therapy
- Symptomatic anemia or transfusion dependence
- Adequate renal and hepatic functions or performance status

n. 25

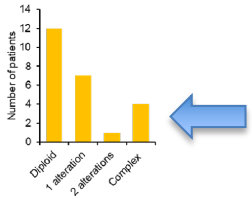
IWG, International Working Group; TFR, Treatment-free remission; LR, low risk; TD, transfusion dependence; TI, transfusion independence

Patients' Characteristics: CBC, Cytogenetics, NGS and Risk Score

Median age, years (range)	74.5 (58-87)
Sex, female n (%)	9 (37%)
CBC, median (range)	
Hemoglobin g/L	8.1 (6.5-10.4)
WBC x10^9/L	3.05 (0.8-11.2)
ANC x10^9/L	1.76 (0.5-9.8)
Platelets x10^9/L	128 (15-430)
Bone marrow (BM)	
BM Blast % (range)	2 (1-6)

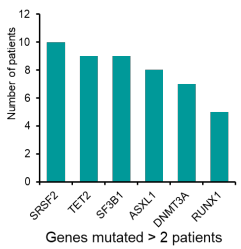
Median PRBC units at baseline 8 weeks (range)	3.5 (0-21)
Number prior treatment, median (range)	2 (1-5)
IPSS/IPSS-R risk score, median (range)	
IPSS risk score	0.5 (0-1)
IPSS-R risk score	3 (1-5.5)

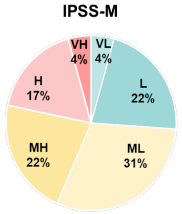
Cytogenetics



Molecular Landscape:

Median number of mutations: 3 (range 1-8)

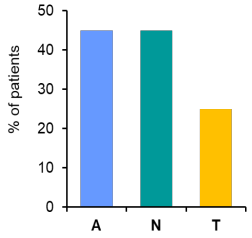




Patients' Characteristics: Toxicity and Responses

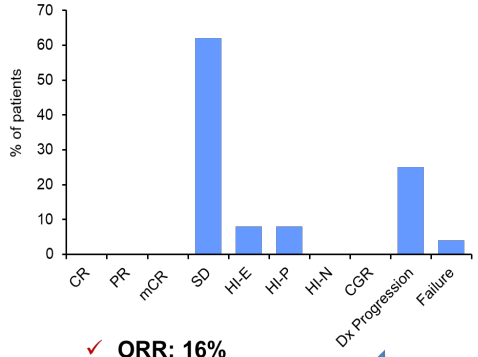
Treatment Related Toxicity

- Grade 1 related toxicity n=1
  (soft tissue necrosis at the site of injection)
- Grade 3 or 4 toxicity in ≥ 20% of patients



A, Anemia (n=11)
N, Neutropenia (n=11)
T, Thrombocytopenia (n=6)

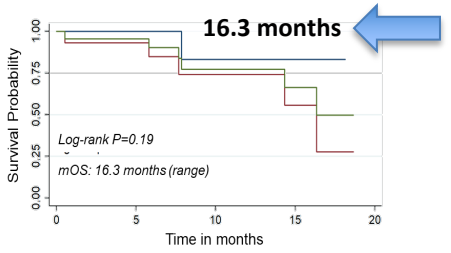
Modified IWG 06 Response



- ✓ **ORR: 16%**
- ✓ **HI-P: 2 patients**
- ✓ **TI: 2 patients**

Patient's Characteristics: Overall Survival & Event Free Survival

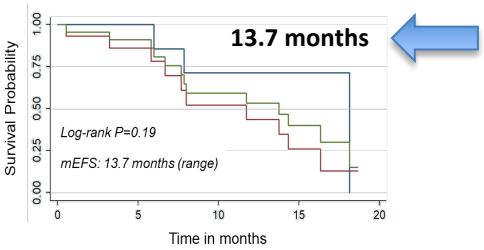
Overall Survival



Number at risk

MH, H, VH*	8	7	5	2	0
L, ML**	16	11	6	3	0
All patients	24	18	11	5	0

Event Free Survival



Number at risk

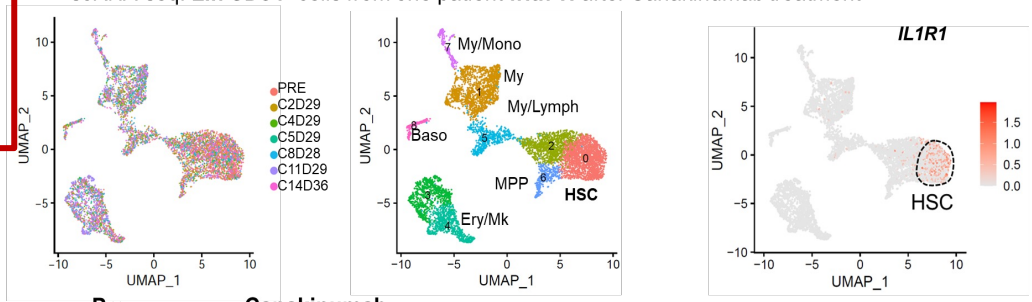
MH, H, VH*	8	7	5	2	0
L, ML**	16	11	6	3	0
All patients	24	18	11	5	0

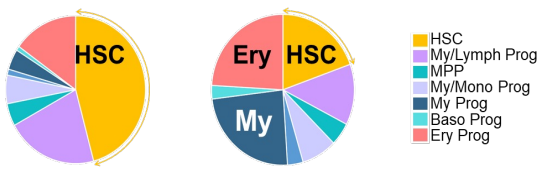
**IPSS-M: MH, Moderate High; H, High; VH, Very High; **IPSS-M: L, Low; ML, Moderate Low; mOS, Median overall survival; mEFS: Median event free survival*

Single-cell RNA sequencing

Canakinumab Treatment Response: HSPCs

- scRNA-seq: **Lin⁻CD34⁺** cells from one patient **with TI** after Canakinumab treatment



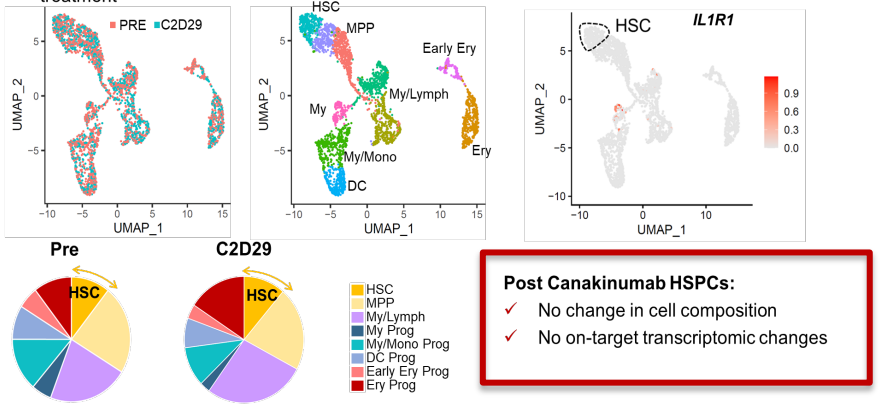


Post Canakinumab HSPCs:
- ✓ Increased HSC differentiation

DNMT3A, TET2 mutant

Canakinumab Treatment no Response and Disease Progression: HSPCs

- scRNA-seq: **Lin⁻CD34⁺** cells from 1 patient with MDS-MLD-RS **with no response** to Canakinumab treatment

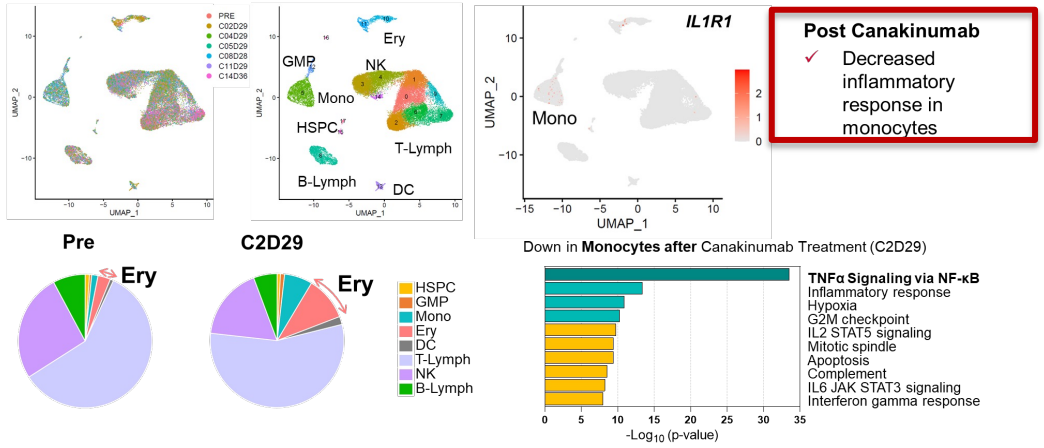


Post Canakinumab HSPCs:
- ✓ No change in cell composition
- ✓ No on-target transcriptomic changes

TET2, DNMT3A, SF3B1 mutant

Canakinumab Treatment: BM MNC Changes

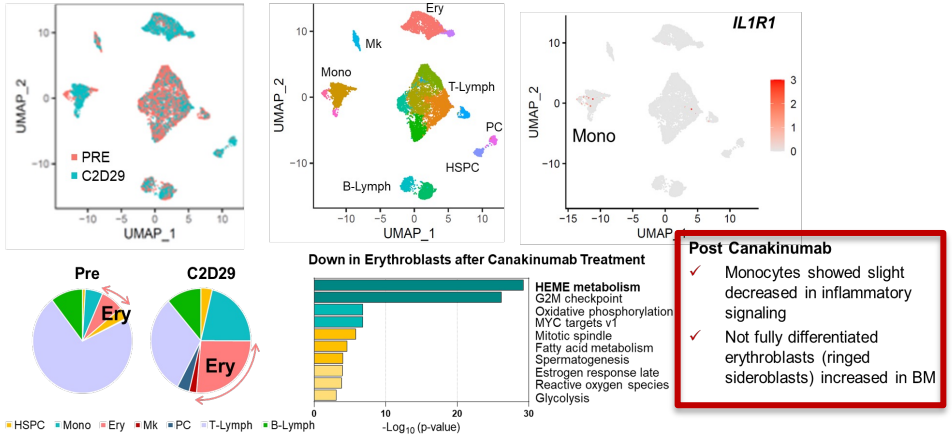
- scRNA-seq: **BM MNCs** cells from one patients **with TI** after Canakinumab treatment



Post Canakinumab
- ✓ Decreased inflammatory response in monocytes

Canakinumab Treatment: BM MNCs

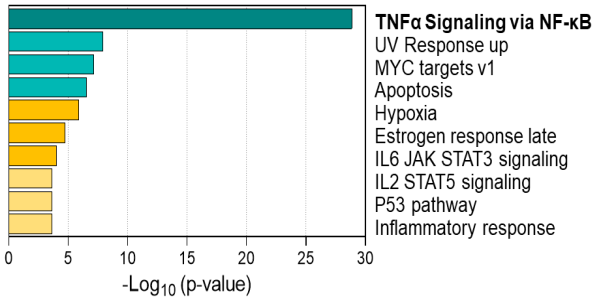
- scRNA-seq: **BM MNCs** from 1 MDS patient with **no response** to Canakinumab treatment



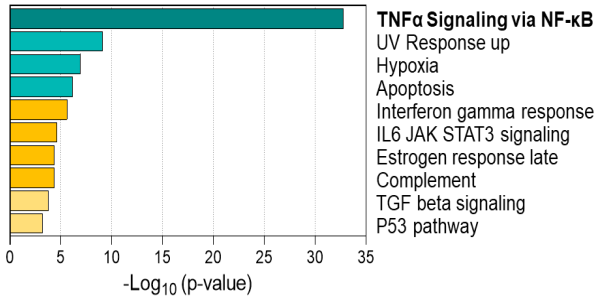
Post Canakinumab
- ✓ Monocytes showed slight decreased in inflammatory signaling
- ✓ Not fully differentiated erythroblasts (ringed sideroblasts) increased in BM

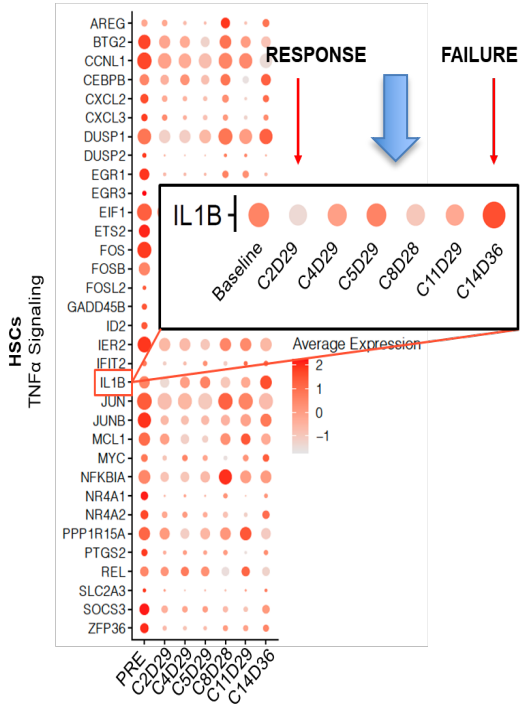
Canakinumab Treatment Induces Transcriptomic Changes in HSPCs

Down in HSCs during Canakinumab Treatment at C2D29



Down in Myeloid HSPCs at C2D29

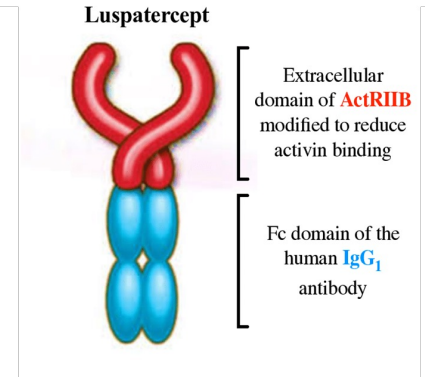




Conclusions

- Canakinumab is safe in lower risk MDS
- Limited clinical activity in transfusion dependent LR MDS after at least one line of therapy
- Single cell analysis showed that canakinumab targets IL-1β signaling in HSPCs and monocytes from patients with *DNMT3A*/*TET2* mutations
- Canakinumab has no effect in *SF3B1*-mutant MDS-RS because of different biological mechanisms driving the disease
- Next Steps: include earlier stage MDS and CCUS

Luspatercept *is a first-in-class, modified activin II receptor (ActRIIB)/Human IgG1 Fc domain recombinant* ***fusion protein,*** *acting as a* ***trap*** *for the* ***transforming growth factor beta (TGF-beta) superfamily ligands*** *(i.e. GDF11), that* ***suppress aberrant erythroid inhibitory Smad2/3 signaling*** *and* ***enhances late stage erythropoiesis*** *in MDS models*



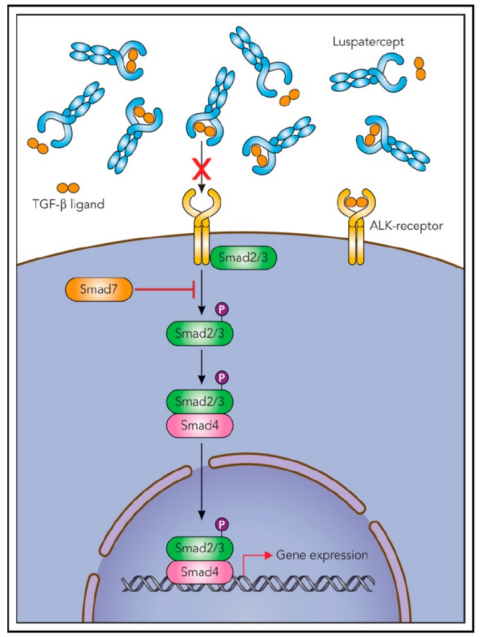


Figure 4. Regulators of erythropoiesis. EPO-R, EPO receptor. Professional illustration by Patrick Lane, ScEYEnce Studios.

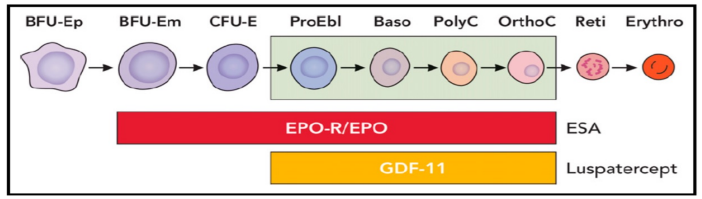


Table 2. Completed clinical trials of luspatercept in MDS

Luspatercept trials					No. of erythroid responses		
Phase	Trial name	NCT no.	Patient population	End point	Luspatercept	Placebo	Dosing, mg/kg
1		NCT01432717	Postmenopausal, healthy women (age 45-75 years)	Mean hemoglobin change at day +15	24	8	0.0625-0.25
2	PACE-MDS	NCT01749514	IPSS low or intermediate-1 risk, anemia with or without transfusion dependence	HI-E, RBC-TI ≥ 8 weeks	32 (HI-E, 63%); 16 (RBC-TI, 38%)	—	0.125-1.75
3	MEDALIST	NCT02631070	IPSS-R very low, low, or intermediate risk, ≥15% RS or ≥5% RS with SF3B1 mutation, R/R ESA or serum EPO >200 U/L, transfusion dependence (≥2 units once every 8 weeks)	HI-E, RBC-TI ≥ 8 weeks	81 (HI-E, 53%); 58 (RBC-TI, 38%)	9 (HI-E, 12%); 10 (RBC-TI, 13%)	1.0-1.75

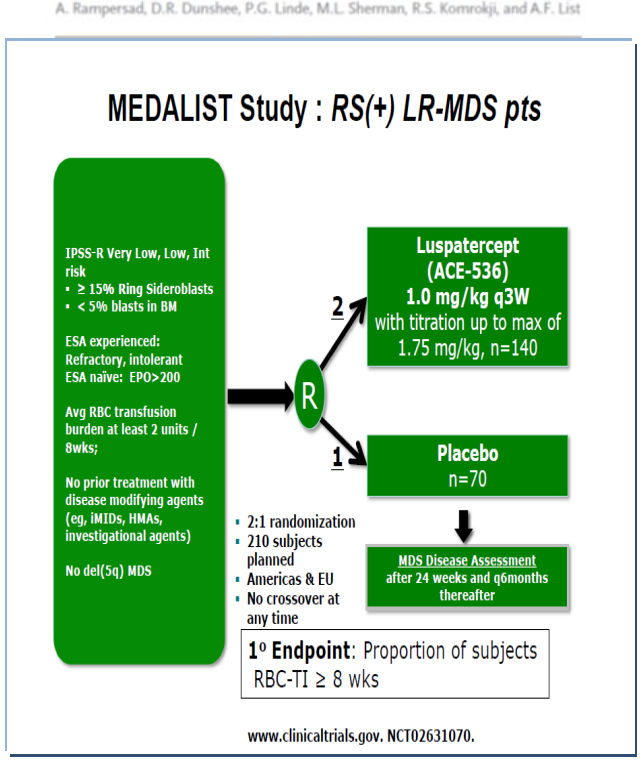
R/R, relapsed or refractory.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes

P. Fenaux, U. Platzbecker, G.J. Mufti, G. Garcia-Manero, R. Buckstein, V. Santini, M. Díez-Campelo, C. Finelli, M. Cazzola, O. Ilhan, M.A. Sekeres, J.F. Falantes, B. Arrizabalaga, F. Salvi, V. Giai, P. Vyas, D. Bowen, D. Selleslag, A.E. DeZern, J.G. Jurcic, U. Germing, K.S. Götze, B. Quesnel, O. Beyne-Rauzy, T. Cluzeau, M.-T. Voso, D. Mazure, E. Vellenga, P.L. Greenberg, E. Hellström-Lindberg, A.M. Zeidan, L. Adès, A. Verma, M.R. Savona, A. Laadem, A. Benzohra, J. Zhang, A. Rampersad, D.R. Dunshee, P.G. Linde, M.L. Sherman, R.S. Komrokji, and A.F. List



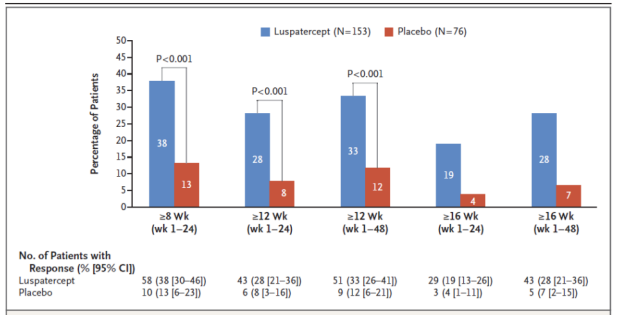


Figure 1. Independence from Red-Cell Transfusion.
Shown are the percentages of patients who had independence from red-cell transfusion (defined as the absence of a red-cell transfusion) for the indicated time periods in each trial group. In the analysis of the primary end point (transfusion independence for ≥8 weeks during weeks 1 through 24), the odds ratio for luspatercept as compared with placebo was 5.07 (95% confidence interval [CI], 2.28 to 11.26). For the key secondary end point of transfusion independence for 12 weeks or longer, the odds ratio was 5.07 (95% CI, 2.00 to 12.84) for the analysis period of weeks 1 through 24 and 4.05 (95% CI, 1.83 to 8.96) for the analysis period of weeks 1 through 48. P values were determined with the use of a Cochran–Mantel–Haenszel test with stratification for average baseline red-cell transfusion burden (≥6 units per 8 weeks vs. <6 units per 8 weeks) and baseline Revised International Prognostic Scoring System score (very low or low risk vs. intermediate risk). An analysis that applied the new International Working Group 2018 response criteria[33] with transfusion independence for 16 weeks or longer was also conducted.

Table 2. Erythroid Response and Increase in Mean Hemoglobin Levels.

End Point	Luspatercept (N=153)	Placebo (N=76)
Erythroid response during wk 1–24*		
No. of patients (% [95% CI])	81 (53 [45–61])	9 (12 [6–21])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	52/107 (49)	8/56 (14)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	29/46 (63)	1/20 (5)
Erythroid response during wk 1–48*		
No. of patients (% [95% CI])	90 (59 [51–67])	13 (17 [9–27])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	58/107 (54)	12/56 (21)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	32/46 (70)	1/20 (5)
Mean increase in hemoglobin level of ≥1.0 g/dl — no. (% [95% CI])§		
During wk 1–24	54 (35 [28–43])	6 (8 [3–16])
During wk 1–48	63 (41 [33–49])	8 (11 [5–20])

* Analysis was based on the proportion of patients meeting the modified criteria for erythroid response (also called hematologic improvement–erythroid) according to International Working Group 2006 criteria[34] sustained over a consecutive 56-day period during the indicated treatment period: for patients with baseline red-cell transfusion burden of at least 4 units per 8 weeks, a transfusion reduction of at least 4 red-cell units per 8 weeks; and for patients with baseline red-cell transfusion burden of less than 4 units per 8 weeks, a mean increase of hemoglobin of at least 1.5 g per deciliter.
† Analysis was based on the number of patients with baseline red-cell transfusion burden of at least 4 units per 8 weeks.
‡ Analysis was based on the number of patients with baseline red-cell transfusion burden of less than 4 units per 8 weeks.
§ Analysis was based on the proportion of patients with an increase from baseline of at least 1 g per deciliter (>14 days after the last red-cell transfusion or within 3 days before the next red-cell transfusion) that was sustained over any consecutive 56-day period in the absence of red-cell transfusions.

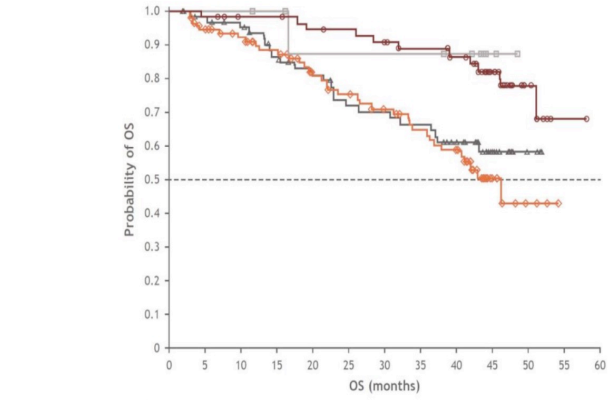
1774 Overall Survival and Progression-Free Survival of Patients Following Luspatercept Treatment in the MEDALIST Trial poster

Valeria Santini, MD, PhD[1*], *Pierre Fenaux*[2], *Amer M. Zeidan, MD*[3], *Rami S. Komrokji*[4], *Rena Buckstein*[5], *Esther Natalie Oliva, MD*[6], *Xianwei Ha*[7*], *Dimana Miteva*[8*], *Aylin Yucel, PhD*[7*], *Jose Alberto Nadal*[8*] *and Uwe Platzbecker, MD*[9]
[1]*University of Florence, Florence, Italy*

Conclusions:

- Although the MEDALIST trial was not specifically powered to assess OS or PFS, these data show that achieving response with luspatercept treatment increased OS probability.
- Luspatercept was associated with **increased 36-mo OS probability for pts with IPSS-R Very low-risk MDS** and **36-mo PFS probability in pts with a BL serum EPO level of 100 to ≤ 200 U/L.**
- Therefore, pts with LR-MDS with these BL characteristics may derive greater survival benefit from luspatercept.

Figure 1A. Kaplan–Meier estimates of OS by response and treatment arms

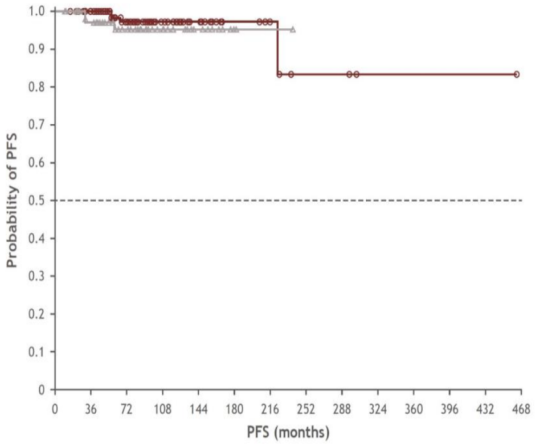


No. of patients at risk													
Luspatercept responders	58	57	54	54	51	50	47	44	39	23	9	1	0
Luspatercept non-responders	95	87	78	71	59	54	48	42	36	9	3	0	0
Placebo responders	10	10	10	9	7	7	7	7	6	2	0	0	0
Placebo non-responders	66	62	58	50	45	39	38	36	29	15	3	0	0

Luspatercept responders (events 11/58), median NA months (95% CI 51.1–NA)
Luspatercept non-responders (events 36/95), median 46.1 months (95% CI 36.3–NA)
Placebo responders (events 1/10), median NA months (95% CI 16.6–NA)
Placebo non-responders (events 23/66), median NA months (95% CI 37.0–NA)
Luspatercept responders vs placebo responders: HR 1.58 (95% CI 0.20–12.27), $P = 0.7595$
Luspatercept non-responders vs placebo non-responders: HR 1.25 (95% CI 0.74–2.11), $P = 0.4288$
Luspatercept responders vs luspatercept non-responders: HR 0.319 (95% CI 0.16–0.63), $P = 0.0003$

Data cut: Jan 15, 2021.
OS was defined as time from randomization to death from any cause.
Responders are defined as patients with an absence of any red blood cell transfusion ≥ 8 weeks during first 24 weeks of double-blind treatment.
CI, confidence interval; HR, hazard ratio; NA, not applicable; OS, overall survival.

Figure 1B. Kaplan–Meier estimates of PFS by treatment arms in the intent-to-treat population



No. of patients at risk													
Luspatercept	153	143	96	41	19	10	7	3	3	1	1	1	1	0
Placebo	76	68	48	21	9	2	1	0	0	0	0	0	0	0

Luspatercept (events 4/153), median NA months (95% CI 223.57–NA)
Placebo (events 3/76), median NA months (95% CI NA–NA)
Luspatercept vs placebo: hazard ratio 0.48 (95% CI 0.10–2.36), $P = 0.3514$

Data cut: Jan 15, 2022.
PFS was defined as time from MDS diagnosis to acute myeloid leukemia progression.
The plot was generated with a stratified Cox proportional hazards model.
CI, confidence interval; NA, not applicable; PFS, progression-free survival.

3098 Multiple Episodes of Transfusion Independence with Luspatercept Treatment and the Impact of Dose Escalation in Patients with Lower-Risk Myelodysplastic Syndromes from the MEDALIST Study

Uwe Platzbecker, MD[1], *Valeria Santini, MD, PhD*[2*], *Rami S. Komrokji*[3], *Amer M. Zeidan, MD*[4], *Guillermo Garcia-Manero, MD*[5], *Rena Buckstein*[6], *Esther Natalie Oliva, MD*[7], *Veronika Pozharskaya*[8*], *Xianwei Ha*[8*], *Jose Alberto Nadal, PhD, MSc*[9*], *Dimana Miteva*[9*] *and Pierre Fenaux*[10]

[1]*Department for Hematology, Cell Therapy and Hemostaseology, University of Leipzig Medical Center, Leipzig, Germany*
[2]*University of Florence, Florence, Italy*

Conclusions:

- Patients who were **Low Transfusional Burden (LTB) at baseline experienced more periods of RBC-TI response than ITB and HTB patients.**
- **LTB patients were more likely to respond to lower doses** of luspatercept, whereas**. almost half of ITB and HTB patients required escalation to the maximum dose level to respond and might be expected to wait longer for a second response**
- Importantly, many patients experienced multiple RBC-TI response periods with luspatercept, emphasizing the value of measuring cumulative response duration as well as the benefit of continuing luspatercept treatment.

Figure. RBC-TI ≥ 8 weeks response periods per patient by baseline transfusion burden

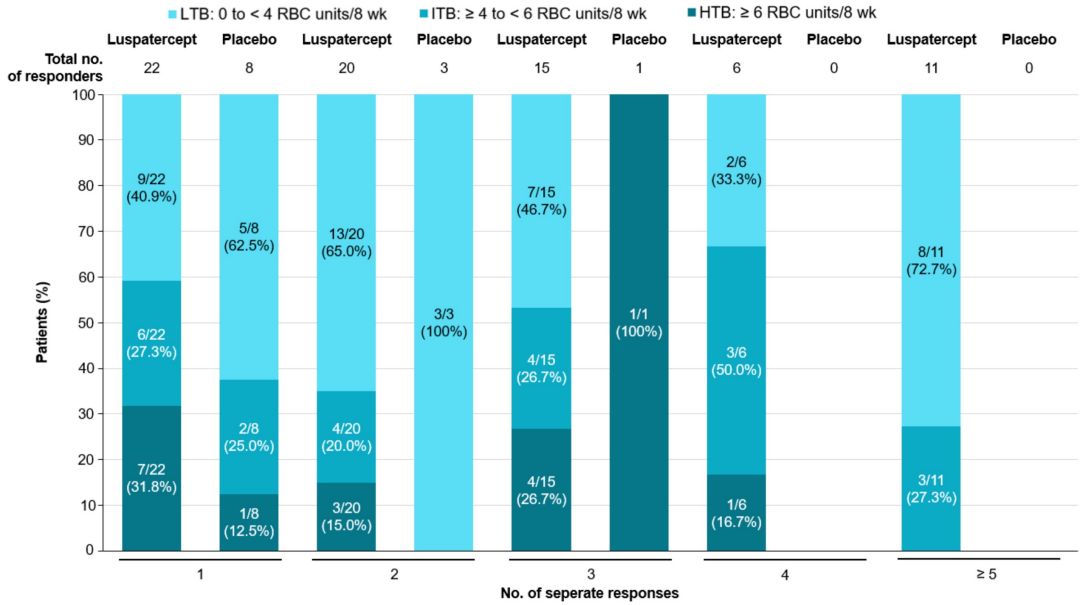


Table. Responders at different luspatercept dose levels

	ITT population		LTB at baseline		ITB at baseline		HTB at baseline	
	Luspatercept (n = 74)	Placebo (n = 12)	Luspatercept (n = 39)	Placebo (n = 8)	Luspatercept (n = 20)	Placebo (n = 2)	Luspatercept (n = 15)	Placebo (n = 2)
Responders at dose level,[a] n (%)								
1.0 mg/kg	55 (74.3)	9 (75.0)	37 (94.9)	7 (87.5)	12 (60.0)	1 (50.0)	6 (40.0)	1 (50.0)
1.33 mg/kg[b]	28 (37.8)	3 (25.0)	13 (33.3)	2 (25.0)	9 (45.0)	0	6 (40.0)	1 (50.0)
1.75 mg/kg[b]	31 (41.9)	3 (25.0)	14 (35.9)	1 (12.5)	10 (50.0)	1 (50.0)	7 (46.7)	1 (50.0)

[a]Response at a given dose defined as last dose prior to or on the start date of one response episode, with response episode defined as the absence of any RBC transfusion during any consecutive 56 days period during the entire treatment period. Treatment period end date is the earliest of: the last dose + 20 days; study discontinuation; data cutoff; or death. Dose level refers to the dose received at the time of response. [b]Can include responders who had previous response at lower dose levels, lost response and escalated to the next level.
HTB, high transfusion burden; ITB, intermediate transfusion burden; LTB, low transfusion burden; No., number; RBC-TI, RBC transfusion independence; wk, weeks.

4408 Characterization of Patients with Lower-Risk Myelodysplastic Syndromes Experiencing Long-Term Responses with Luspatercept in the MEDALIST Study

Uwe Platzbecker, MD[1], *Valeria Santini, MD, PhD*[2*], *Rami S. Komrokji*[3], *Amer M. Zeidan, MD*[4], *Guillermo Garcia-Manero, MD*[5], *Rena Buckstein*[6], *Esther Natalie Oliva, MD*[7], *Dimana Miteva*[8*], *Veronika Pozharskaya*[9*], *Xianwei Ha*[9*], *Jose Alberto Nadal, PhD, MSc*[8*] *and Pierre Fenaux*[10]

[1]*Department for Hematology, Cell Therapy and Hemostaseology, University of Leipzig Medical Center, Leipzig, Germany*
[2]*University of Florence, Florence, Italy*
[10]*Service d'Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, France*

Conclusions:

- Patients **continuing treatment for > 48 weeks were younger and had lower baseline TB, SF, and EPO levels.**
- **Higher rates of RBC-TI and mHI-E response led to longer durations of treatment** and **the maximum luspatercept dose level**
- **There were no safety signals** in terms of progression to AML/HR-MDS occurring

Table 1. Baseline characteristics by duration of luspatercept treatment received

Characteristic	Duration of treatment			
	0 to 24 weeks (n = 45)	> 24 to 48 weeks (n = 26)	> 48 to 144 weeks (n = 45)	> 144 weeks (n = 37)
Age, mean (SD), years	71.8 (6.11)	71.3 (10.06)	70.8 (8.01)	67.8 (10.61)
Sex, female, n (%)	18 (40.0)	6 (23.1)	18 (40.0)	17 (45.9)
Time since MDS diagnosis > 2 to 5 years,[a] n (%)	13 (28.9)	11 (42.3)	18 (40.0)	20 (54.1)
Time since MDS diagnosis, mean (SD), months[a]	76.8 (81.04)	42.9 (24.67)	50.4 (48.17)	54.1 (39.28)
Transfusion burden < 6 RBC units/8 weeks over 16 weeks, n (%)	20 (44.4)	11 (42.3)	32 (71.1)	24 (64.9)
RBC transfusions/8 weeks, mean (SD), units	6.5 (2.82)	6.1 (2.42)	4.7 (2.55)	4.9 (2.76)
Serum ferritin, mean (SD), µg/L	1641.1 (1159.76)	1471.4 (1116.6)	1230.3 (913.53)	1048.1 (474.25)
SF3B1 mutated, n (%)	39 (86.7)	23 (88.5)	42 (93.3)	37 (100.0)
Serum EPO < 100 U/L,[b] n (%)	10 (22.2)	10 (38.5)	13 (28.9)	18 (48.6)
Prior ESA treatment < 6 months,[c] n (%)	19 (42.2)	8 (30.8)	15 (33.3)	6 (16.2)
Hemoglobin, mean (SD),[d] g/dL	7.7 (0.93)	7.5 (0.84)	7.8 (0.77)	7.7 (0.80)
Platelets > 400 × 10^9/L,[e] n (%)	2 (4.4)	1 (3.8)	5 (11.1)	9 (24.3)
Platelets, mean (SD),[e] × 10^9/L	237.9 (132.63)	220.0 (93.49)	280.5 (103.03)	287.3 (140.86)

[a]Time since MDS diagnosis is defined as the number of years from the date of original diagnosis to the date of informed consent.
[b]Baseline EPO (efficacy) is defined as the highest EPO value within 35 days of the first dose of IP.
[c]ESA population.
[d]Time from end of prior ESA to start of study is defined as the number of months from the date of the end of prior ESA to the date of C1D1. When C1D1 is missing, the randomization date is used.
[e]Baseline platelet (efficacy) is defined as the lowest platelet value within 35 days of the first dose of IP.
C, cycle; D, day; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; IP, investigational product; MDS, myelodysplastic syndromes; RBC, red blood cell; SD, standard deviation; *SF3B1*, splicing factor 3b subunit 1.

Table 2. RBC-TI and mHI-E response rates

Response	Duration of treatment			
	0 to 24 weeks (n = 45)	> 24 to 48 weeks (n = 26)	> 48 to 144 weeks (n = 45)	> 144 weeks (n = 37)
RBC-TI ≥ 8 weeks responders,[a] n (%)	5 (11.1)	6 (23.1)	31 (68.9)	32 (86.5)
95% CI	(3.71–24.05)	(8.97–43.65)	(53.35–81.83)	(71.23–95.46)
RBC-TI ≥ 16 weeks responders,[b] n (%)	0	1 (3.9)	18 (40.0)	29 (78.4)
95% CI	(NA–NA)	(0.10–19.64)	(25.70–55.67)	(61.79–90.17)
mHI-E responders,[c] n (%)	10 (22.2)	11 (42.3)	37 (82.2)	36 (97.3)
95% CI	(11.20–37.09)	(23.35–63.08)	(67.95–92.00)	(85.84–99.93)

[a]Defined as the absence of any RBC transfusion during any consecutive 56-day period during the entire treatment period = min (death date, study discontinuation date, last dose date + 20, data lock date).
[b]Defined as the absence of any RBC transfusion during any consecutive 112-day period during the entire treatment period = min (death date, study discontinuation date, last dose date + 20, data lock date).
[c]Defined as the proportion of subjects meeting the modified HI-E criteria per the International Working Group sustained over any consecutive 56-day period during the treatment period defined as the time for treatment initiation to the earliest of: last dose date + 20 days; study discontinuation; data cutoff; or death
CI, confidence interval; mHI-E, modified hematologic improvement–erythroid; NA, not applicable; RBC, red blood cell; RBC-TI, RBC transfusion independence.

3088 Efficacy and Safety of Luspatercept in Adult Patients with Transfusion-Dependent Anemia Due to Very Low, Low and Intermediate Risk Myelodysplastic Syndromes (MDS) with Ring Sideroblasts, Who Had an Unsatisfactory Response to or Are Ineligible for Erythropoietin-Based Therapy: A Retrospective Multicenter Study By Fondazione Italiana Sindromi Mielodisplastiche (FiSiM ETS)

Luca Lanino[1*], Prassede Salutari, MD[2*], Alessandra Perego, MD[3*], Bruno Fattizzo, MD[4*], Marta Riva, MD[5*], Marta Ubezio, MD[1*], Pellegrino Musto, MD[6], Daniela Cilloni, MD[7*], Esther Natalie Oliva, MD[8], Maria Teresa Voso, MD[9], Anna Maria Pelizzari, MD[10*], Antonella Poloni, PhD, MD[11*], Isabella Capodanno, MD[12*], Chiara Elena, MD[13*], Claudio Fozza, MD[14*], Fabrizio Pane, MD[15], Massimo Breccia, MD[16*], Marco De Gobbi, MD, PhD[17*], Francesco Di Bassiano, MD[18*], Daniela Barraco, MD[19*], Elena Crisà, MD[20*], Dario Ferrero, MD[21*], Chiara Frairia, MD[22*], Antonella Vaccarino, MD[23*], Davide Griguolo, MD[24*], Stefania Paolini, MD, PhD[25*], Martina Quintini, MD[26*], Mariarosaria Sessa, MD[27*], Mauro Turrini, MD[28*], Monica Bocchia, MD[29*], Nicola Di Renzo, MD[30*], Elisa Diral, MD[31*], Cristina Foli, MD[32*], Alfredo Molteni, MD[33*], Ubaldo Occhini, MD[34*], Giulia Rivoli, MD[35*], Carmine Selleri, MD[36], Roberto Bono, MD[37*], Anna Calvisi, MD[38*], Andrea Castelli, MD[39*], Eros Di Bona, MD[40*], Ambra Di Veroli, MD[41*], Luana Fianchi, MD[42*], Sara Galimberti, MD[43*], Daniele Grimaldi, MD[44*], Monia Marchetti[45*], Marianna Norata, MD[46*], Alessandro Rambaldi, MD[47], Ilaria Tanasi, MD[48*], Patrizia Tosi, MD[49*], Ilaria Naldi, PhD[50*], Valeria Santini, MD, PhD[51*] and Matteo G. Della Porta, MD[1*]

[1]Cancer Center, IRCCS Humanitas Research Hospital & Humanitas University, Rozzano - Milan, Italy
[50]Fondazione Italiana Sindromi Mielodisplastiche FISiM-ETS, Firenze, Italy
[51]Department of Experimental and Clinical Medicine, MDS Unit, Hematology, AOU Careggi - University of Florence, Firenze, Italy

Demographics and Baseline Disease Characteristics

	FiSiM Study (n = 201)	Medalist Trial(n = 153)
Age, median (range), years	74 (31-89)	**71 (40–95)**
≤ 64 years, n (%)	31 (15.4)	29 (19.0)
65 to 74 years, n (%)	76 (37.8)	72 (47.1)
≥ 75 years, n (%)	94 (46.8)	52 (34.0)
Male, n (%)	**129 (63.5)**	**94 (61.4)**
ECOG performance status, n (%)		
0	77 (37.9)	54 (35.3)
1	110 (54.2)	91 (59.5)
2	14 (6.9)	8 (5.2)
Time since diagnosis, median (range), months	**42 (2-234)**	**44 (3-421)**
≤ 2 years, n (%)	64 (31.8)	40 (26.2)
2 to 5 years, n (%)	70 (34.8)	62 (40.5)
≥ 5 years, n (%)	67 (33.4)	51 (33.3)
Time since first RBC transfusion, median, months	**21 (2-156)**	**NR**
IPSS-R risk category		
Very Low, n(%)	8 (3.9)	18 (11.8)
Low, n (%)	151 (74.4)	109 (71.2)
Intermediate, n (%)	42 (20.7)	25 (16.3)
High, n (%)	0	1 (0.7)

n. 201 n. 153

Demographics and Baseline Disease Characteristics

	FiSiM Study (n = 201)	Medalist Trial (n = 153)
Comorbidities that require ongoing treatment		
≥ 1, n (%)	134 (66.7)	NR
≥ 3, n (%)	43 (21.4)	
Renal comorbidity	14 (7.0)	
Gastrointestinal comorbidity	18 (9.0)	NR
Autoimmune comorbidity	9 (4.5)	
Prior ESA use	198 (98.5)	148 (96.7)
Baseline Serum EPO		
< 200 U/L, n (%)	67 (33.3)	88 (57.5)
≥ 200 U/L, n (%)	44 (21.9)	64 (41.8)
≥ 500 U/L, n (%)	18 (8.9)	NR
Missing values	90 (44.8)	
RBC transfusion burden, median (range), units/8 weeks	7 (2 - 22)	5 (1–15)
≥ 6 units/8 weeks, n (%)	130 (64.6)	66 (43.1)
4 to < 6 units/8 weeks, n (%)	51 (25.4)	41 (26.8)
< 4 units/8 weeks, n (%)	20 (10.0)	46 (30.1)
≤ 4 units/8 weeks, n (%)	53 (26.1)	
5-7 units/8 weeks, n (%)	57 (28.1)	NR
> 8 units/8 weeks, n (%)	91 (44.8)	
Pre-transfusion Hb, median (range), g/dL	7.9 (5.5-9.6)	7.6 (6–10)

Primary Endpoint

	FiSiM Study (n = 201)	MEDALIST (n = 153)
RBC-TI ≥ 8 weeks during Weeks 1–24, n (%)	**61 (30.3)**	**58 (37.9)**
Baseline transfusion requirements		
≥ 6 units/8 weeks, n (%)	27 (20.8)	6/66 (9.0)
4-5 units/8 weeks, n (%)	19 (37.3)	15/41 (36.6)
< 4 units/8 weeks, n (%)	15 (75.0)	37/46 (80.4)
> 8 units/8 weeks, n (%)	15 (16.5)	
5-7 units/8 weeks, n (%)	19 (33.3)	NR
≤ 4 units/8 weeks, n (%)	27 (50.9)	
TI duration, median, weeks	**23.9**	**30.6**
Number of patients with multiple TI responses		
2 responses	11 (18.0)	23 (15.0)
≥3 responses	12 (19.7)	13 (8.5)

Median follow-up was 377 days

Secondary Endpoints

	FiSiM Study (n = 201)	MEDALIST (n = 153)
RBC-TI ≥ 8 weeks during weeks 1–48, n (%)	79 (39.3)	69 (45.1)
RBC-TI ≥ 12 weeks during weeks 1–24, n (%)	38 (18.9)	43 (28.1)
RBC-TI ≥ 12 weeks during weeks 1–48, n (%)	59 (29.4)	51 (33.3)

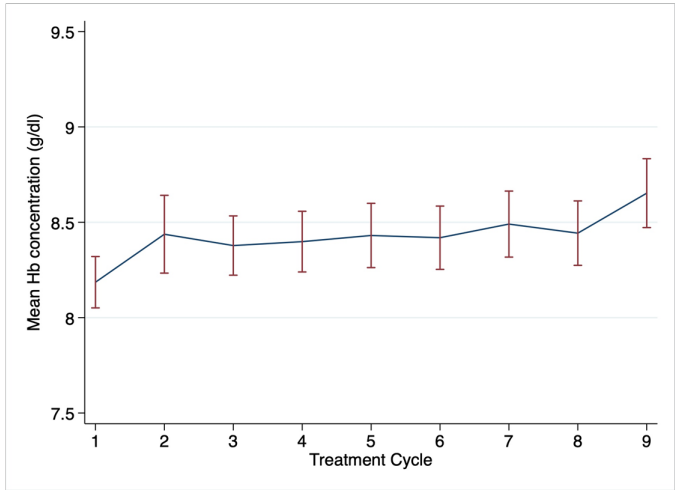
Erythroid Response

	FiSiM Study (n = 201)	MEDALIST (n = 153)
Weeks 1-24		
Reduction ≥4 RBC U/8wk (baseline burden ≥4 U/8wks)	66/181 (36.4)	52/107 (48.6)
Hb increase ≥1.5 g/dl (burden <4 U/8wks)	5/20 (25.0)	29/46 (63.0)
Weeks 1-48		
Reduction ≥4 RBC U/8wk (baseline burden ≥4 U/8wks)	71/181 (39.2)	58/107 (54.2)
Hb increase ≥1.5 g/dl (baseline burden <4 U/8wks)	10/20 (50.0)	32/46 (69.6)

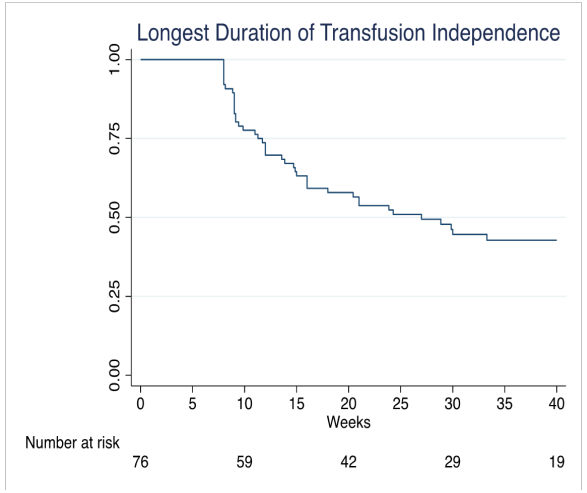
Novità dal Meeting della Società Americana di Ematologia

Milano, 2-3-4 Febbraio 2023

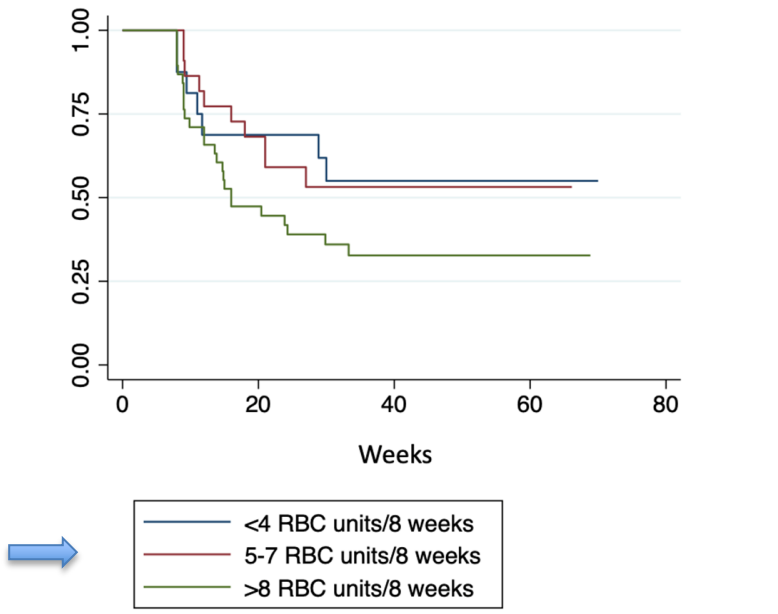
Mean increase in Hb concentration



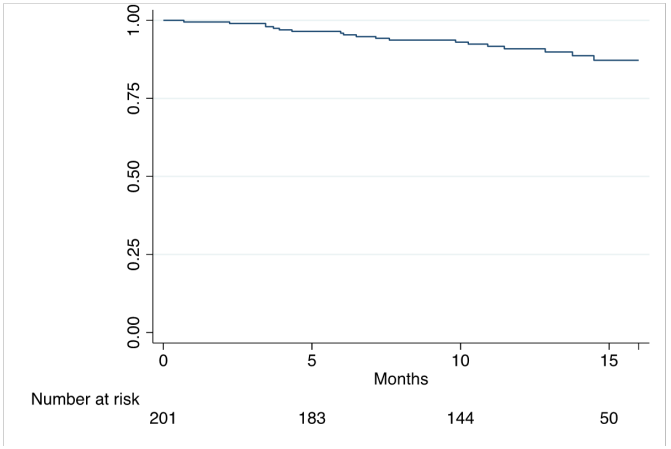
Longest Duration of Transfusion Independence



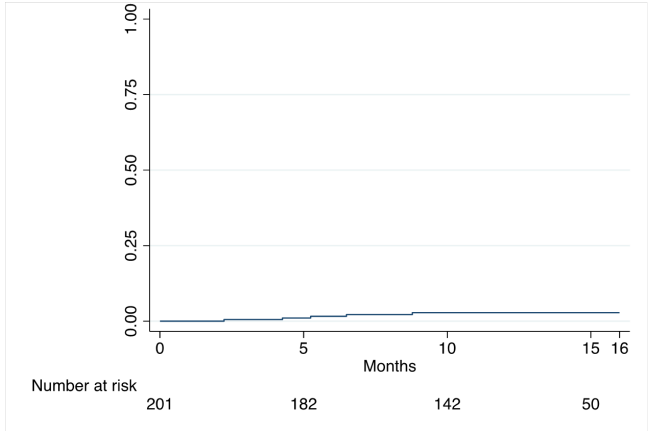
Duration of Transfusion Independence Stratified by Baseline Transfusion Burden



Overall Survival



Acute Myeloid Leukemia Evolution



Treatment Exposure

Treatment duration, median (range), weeks	42.1
Completed ≥ 24 weeks of treatment, n (%)	143 (71.1)
Completed ≥ 48 weeks of treatment, n (%)	83 (41.3)
Number of doses received, median (range)	14 (2-25)
Maximum dose escalation, n (%)	
1.0 mg/kg	13 (6.5)
1.33 mg/kg	23 (11.4)
1.75 mg/kg	165 (82.1)
Patients discontinued from treatment, n (%)	87 (43.3)
AML	5
Lack of benefit	56
Patient withdrawal	4
Death	13
Other	11

Iron Overload Outcomes

Patients previously on Iron Chelation Therapy, n (%)	15 (7.5)
Patients currently on Iron Chelation Therapy, n (%)	121 (60.2)
Mean change in ferritin concentration across C2-C6 (95% C.I.)	-205 µg/L (-454;42)
Mean change in ferritin concentration across C7-C12 (95% C.I.)	-518 µg/L ((-801;-235)

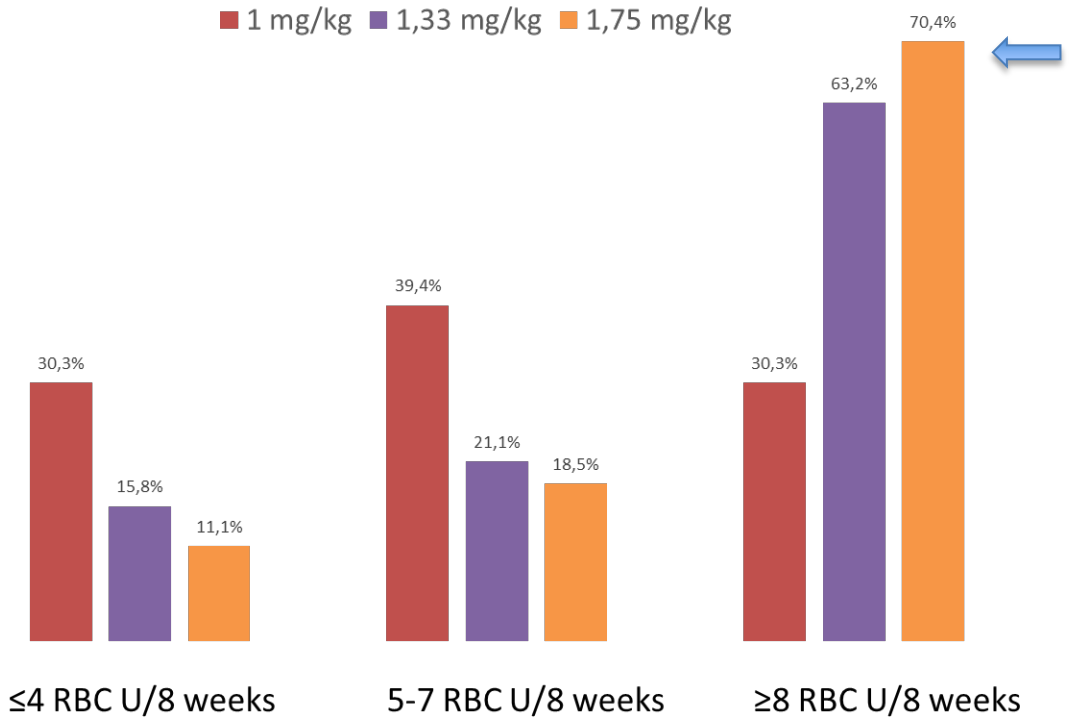
Response Rate according to IWG 2018 Criteria in FiSiM cohort

Low Transfusion Burden	
HI-E (16 weeks TI) during weeks 1-24, n(%)	8 (40.0)
HI-E (16 weeks TI) during weeks 1-48, n(%)	10 (50.0)
High Transfusion Burden	
Major response (16 weeks TI) during weeks 1-24, n(%)	22 (12.2)
Major response (16 weeks TI) during weeks 1-48, n(%)	32 (17.2)
Minor response, n(%)	76 (42.0)
Platelets Response, n(%)	5/17 (29.4)
Neutrophil Response, n(%)	3/18 (16.6)

Safety Outcomes

AML Evolution, n (%)	5 (2.5)
Time to AML, median in months	5.2
Patients with ≥ 1 SAEs, n (%)	35 (17.4)
SAE - Bone Fractures	4
SAE - Cardiac	11
SAE - Renal	1
SAE - Infections	10
SAE - COVID19	4
Death on treatment, n (%)	13 (6.5)
Death overall, n (%)	20 (9.9)

Dose at First Response by Baseline Transfusion Burden



Summary

- In the 2022 real life, patients with MDS-RS are characterized by older age and increased transfusion burden with respect to MEDALIST population
- Luspatercept is effective for the treatment of transfusion-dependent anemia in MDS-RS in a real-life setting.
- The benefit extended beyond the achievement of TI and produced a significant reduction in the number of RBC transfusions.
- Higher baseline transfusion burden was associated with a reduced probability to achiever TI; in these patients, the reduction of transfused RBC units appears a more reliable treatment target.
- In patients with high transfusion burden, high dose of luspatercept (1.75 mg/kg) is expected to be required to induce a clinical benefit

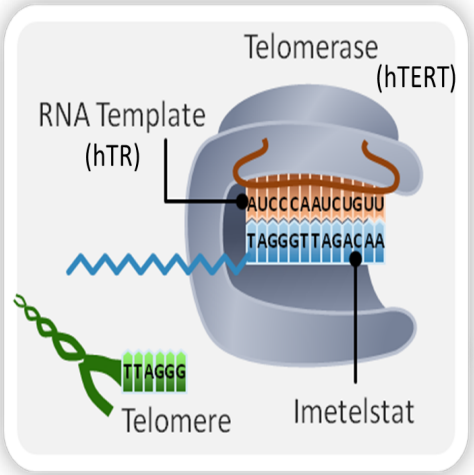
Imetelstat Achieved Prolonged, Continuous Transfusion Independence in Patients With Heavily Transfused Non-Del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis Stimulating Agents Within the IMerge Phase 2 Study

Uwe Platzbecker, MD,[1] Rami Komrokji, MD,[2] Pierre Fenaux, MD, PhD,[3] Mikkael A. Sekeres,[4] Michael Robert Savona,[5] Yazan F. Madanat, MD,[6] Koen Van Eygen, MD,[7] Azra Raza, MD,[8] Ulrich Germing, MD,[9] Laurie Sherman, BSN,[10] Tymara Berry, MD,[10] Souria Dougherty, MBA,[10] Sheetal Shah, PhD,[10] Libo Sun, PhD,[10] Ying Wan, MD, PhD,[10] Fei Huang, PhD,[10] Annat Ikin, PhD,[10] Faye Feller, MD,[10] Amer Zeidan, MHS,[11] and Valeria Santini[12]

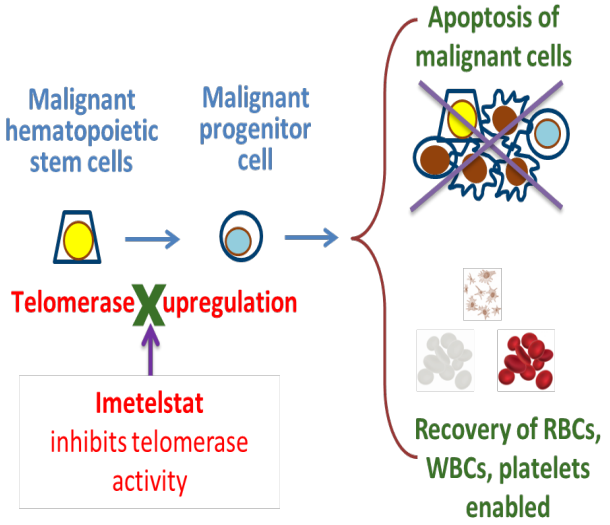
[1]University Clinic Leipzig, Leipzig, Germany; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]Hôpital Saint-Louis, Université Paris Diderot, Paris, France; [4]Sylvester Cancer Center, University of Miami, Miami, FL, USA; [5]Vanderbilt University Medical Center, Nashville, TN, USA; [6]University of Texas Southwestern Medical Center, Dallas TX, USA; [7]Algemeen Ziekenhuis Groeninge, Kortrijk, Belgium; [8]Columbia University Medical Center, New York, NY, USA; [9]Klinik für Hämatologie, Onkologie, and Klinischelmmunologie, Universitätsklinik Düsseldorf, Heinrich-Heine-Universität, Düsseldorf, Germany; [10]Geron Corporation, Parsippany, NJ, USA; [11]Yale School of Medicine, New Haven, CT, US; [12]MDS Unit, AOU Careggi-University of Florence, Florence, Italy

Imetelstat: First-in-Class Telomerase Inhibitor

- Imetelstat is a direct and competitive inhibitor of telomerase activity[1,2]



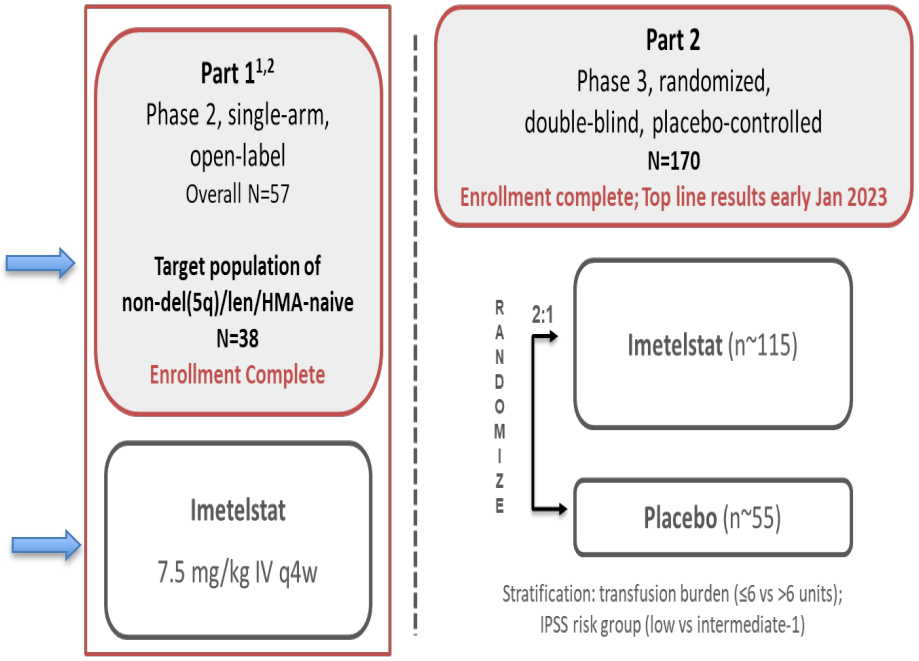
- Imetelstat has disease-modifying potential to selectively kill malignant stem and progenitor cells, enabling recovery of blood cell production[3,4]



hTERT, human telomerase reverse transcriptase; hTR, catalytic component; RBC, red blood cell; WBC, white blood cell.

1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939; 2. Herbert BS, et al. *Oncogene.* 2005;24(33):5262-5268; 3. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467; 4. Wang X at al. *Blood Adv.* 2018;25;2(18):2378-2388.

IMerge (MDS3001; NCT02598661) Phase 2/3 Study Design



Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent

Pre-medication: diphenhydramine, hydrocortisone 100-200mg (or equivalent)

Supportive care: transfusions, myeloid growth factors per local guidelines

- **Patients with LR-MDS**[1,2]
  - IPSS low or intermediate-1
  - Relapsed/refractory to ESA or sEPO >500 mU/mL
  - Transfusion dependent: ≥4 units RBC/8 weeks over the 16-week prestudy period
  - Non-del5(q), len/HMA-naive
- **Primary endpoint**: ≥8-week RBC TI
- **Key secondary endpoints**: safety, ≥24-week TI rate, HI-E, OS, PFS, and time to progression to AML

AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IV, intravenous; len, lenalidomide; LR, lower-risk; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; q4w, every 4 weeks; RBC, red blood cell; sEPO, serum erythropoietin; TI, transfusion independence.

1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 3113.

Meaningful and Durable TI With Imetelstat Treatment

- Of 57 patients treated in the phase 2 study, 38 patients were non-del(5q) and lenalidomide/HMA naive (target patient population)[1,2]
  - Longer duration of TI was seen in the target population (median, 88 weeks) vs all 57 treated patients (median, 65 weeks)

Efficacy parameters	Target population N=38[2]
8-week TI, n (%)	16 (42)
Median duration of TI, weeks (95% CI)[a]	88.0 (23.1-140.9)
24-week TI, n (%)	12 (32)
TI ≥1 year, n (%)	**11 (29)**

- **The analysis in this presentation describes the characteristics and clinical benefits of the 11 patients within the target patient population who had continuous TI for ≥1 year while on imetelstat after 57 months of follow-up**
- The 29% of patients who achieved sustained TI ≥1 year[2] represent:
  - 69% of the ≥8-week TI responders
  - 92% of the ≥24-week TI responders
  - 37% (10 of 27) of MDS-RS+ patients treated

[a]Based on the Kaplan Meier method. HMA, hypomethylating agent; MDS, myelodysplastic syndromes; RS+, ring sideroblast-positive; TI, transfusion independence.

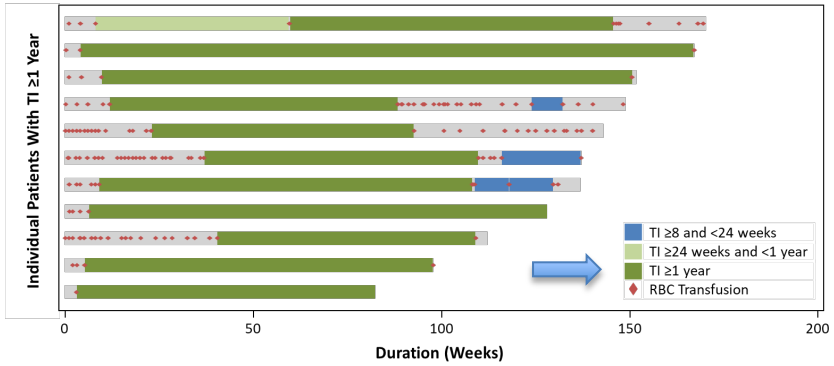
1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 658.

Baseline Characteristics of ≥1-Year TI Imetelstat-Treated Patients Compared to the Overall Target Population

Baseline characteristic	Patients with TI ≥1 year (n=11)	Target population (N=38)
≥2 years since initial diagnosis, n (%)	10 (90.9)	28 (73.7)
IPSS category, n (%)		
Low	5 (45.5)	24 (63.2)
Intermediate-1 risk	6 (54.5)	14 (36.8)
MDS-RS+, n (%)	10 (90.9)	27 (71.1)
Normal karyotype, n (%)	7 (63.6)	28 (73.7)[a]
Mutations at baseline, n (%)		
SF3B1	11 (100)	27 (71.1)[b]
Other	4 (36.4)	13 (34.2)[b]
Prior ESA, n (%)	11 (100)	34 (89.5)
Prior luspatercept, n (%)	2 (18.2)	6 (15.8)
Median prior RBC transfusion burden (over 8 weeks) prior to study treatment, units (range)	6.0 (4-14)	8.0 (4-14)

[a]Thirty-four patients had karyotyping results. [b]Baseline mutation samples were collected in 31 patients, 28 out of 31 (90.3%) had a mutation detected. ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System;

LR-MDS Patients Treated With Imetelstat Achieved Sustained, Continuous TI ≥1 Year



- Median onset of 8-week TI was 9.29 weeks (range, 3.3-40.7)

Data cutoff: October 13, 2022.
LR, lower-risk; MDS, myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

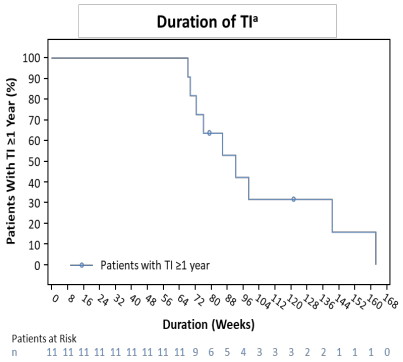
Disposition and Treatment Exposure for Imetelstat-Treated Patients With TI ≥1 Year

	Patients with TI ≥1 year (n=11)
Median time on study,[a] months (range)	57.3 (19.0-57.8)
Median treatment duration, weeks (range)	126.1 (70.1-168.1)
Median treatment cycles, n (range)	27.0 (18-40)
Median relative dose intensity,[b] % (range)	98.9 (85.5-102.4)

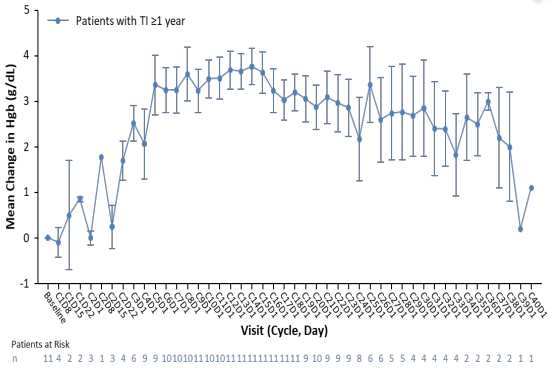
Data cutoff: October 13, 2022.
[a]Defined as the interval between study day 1 and the date of death (censored) or last day on the trial; based on the Kaplan-Meier method. [b]Defined as the total actual dose/total planned dose.
TI, transfusion independence.

Durable TI Accompanied by Substantial Increase in Hgb in TI ≥1-Year Responders

Median TI duration: 92.4 weeks[a]
(95% CI, 69.57-140.86)



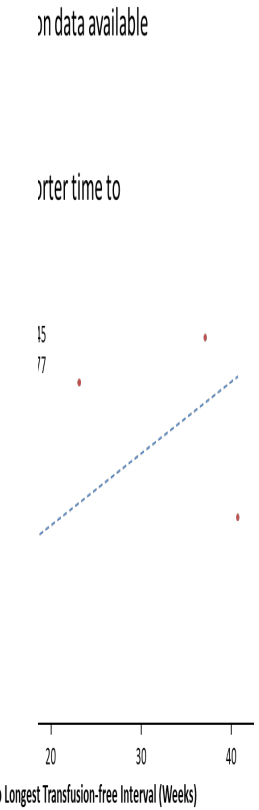
Mean Change in Hgb[b] **> 3 g/dl**



Data cutoff: October 13, 2022.
[a]Based on the Kaplan Meier method. [b]The mean changes from the minimum hgb of the values in the 8 weeks prior to the first dose date are shown and values that within 14 days of RBC transfusions were excluded. This plot does not include the values from unscheduled visits.
Hgb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

Robust PFS and Survival of Imetelstat-Treated Patients With TI ≥1 Year

Reduction in *SF3B1* VAF in Imetelstat-Treated Patients With TI ≥1 Year Correlated



Data cutoff: October 13, 2022.
TI, transfusion independence; VAF, variant allele frequency.

Conclusions

- Imetelstat demonstrated ≥1 year sustained, continuous TI in 29% of patients with transfusion dependent, non-del(5q) LR-MDS relapsed/refractory to ESAs and lenalidomide/HMA naive
  - Attainment of 24-week TI was indicative of the likelihood to achieve TI ≥1 year
- Strong evidence of disease-modifying activity for imetelstat mechanism of action:
  - Durable TI with median duration of TI of 92.4 weeks and robust increase in Hgb by ≥3 g/dL
  - Notable survival post-ESA (median OS, 56 months)
  - Meaningful reduction in mutational burden that correlated with longer TI and shorter time to onset of TI
- Safety findings were consistent with those of the overall target population and previous reports
- Enrollment is complete for the phase 3 part of IMerge, a randomized (2:1), double-blind, placebo-controlled trial to compare efficacy of imetelstat versus placebo in transfusion dependent, ESA-relapsed/refractory, non-del(5q), lenalidomide/HMA-naive LR-MDS
  - Results from the primary analysis are expected in early January 2023

ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin; HMA, hypomethylating agent; LR, lower risk; MDS, myelodysplastic syndromes; OS, overall survival; TI, transfusion independence.

4 weeks (consistent with target population)

- Events were manageable with dose holds (n= 10/11) and reduction (n=7/11) as specified in the protocol with limited clinical consequences
- Imetelstat-related cytopenias are on-target effects based on the selective reduction of malignant cells through telomerase inhibition[2]

Data cutoff: October 13, 2022.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TI, transfusion independence.
1. Steensma DP, et al. *J Clin Oncol*. 2021;39(1):48-56. ; 2. Mascarenhas J, et al. Presented at: EHA Annual Meeting 2021; Abstract EP0116.

Press release, January, 4th, 2023

- Trial met primary 8-week transfusion independence (TI) endpoint and key secondary 24-week TI endpoint with highly statistically significant and clinically meaningful improvements
- Median TI duration approaching one year for imetelstat 8-week TI responders and 1.5 years for imetelstat 24-week TI responders
- Statistically significant and clinically meaningful efficacy results achieved across key MDS subtypes, including ring sideroblast (RS+/RS-) status, high and very high transfusion burden and Low and Intermediate-1 IPSS risk categories
- Safety results consistent with prior imetelstat clinical experience with no new safety signals
- Clinical and molecular evidence support the potential for MDS disease modification
- Request for rolling submission of U.S. New Drug Application (NDA) granted and 2023 plans on target for regulatory submissions in the U.S. and EU
- Conference call with Geron management scheduled at 8 a.m. ET this morning

	Imetelstat (n=118)	Placebo (n=60)	P-value*
8-week TI, n (%)	47 (39.8)	9 (15.0)	<0.001
95% confidence interval	(30.9, 49.3)	(7.1, 26.6)	
24-week TI, n (%)	33 (28.0)	2 (3.3)	<0.001
95% confidence interval	(20.1, 37.0)	(0.4, 11.5)	

8-Week TI	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
Transfusion burden				
4-6 units	28/62 (45.2)	7/33 (21.2)	23.9 (1.9, 41.4)	0.027
>6 units	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

ASTX727-03: Phase 1 Study Evaluating Oral Decitabine/Cedazuridine (ASTX727) Low-Dose (LD) in Lower-Risk Myelodysplastic Syndromes (LR-MDS) Patients

On behalf of the ASTX727-03 Investigators Team

Guillermo Garcia-Manero[1], Kimo Bachiashvili[2], Harshad Amin[3], Elie Traer[4], Daniel A. Pollyea[5], David Sallman[6], Aref Al-Kali[7], Larry Cripe[8], Jesus Berdeja[9], Elizabeth A. Griffiths[10], Sanjay Mohan[11], Yuri Sano[12], Aram Oganesian[12], Harold Keer[12], Abdulraheem Yacoub[13]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; [3]Boca Raton Cancer Research, Boca Raton, FL; [4]Oregon Health and Science University, Portland, OR; [5]University of Colorado Cancer Center, Denver, CO; [6]Moffitt Cancer Center, Tampa, FL; [7]Mayo Clinic, Rochester, Rochester, MN; [8]Indiana University Health, Indianapolis, IN; [9]Sarah Cannon Research Institute, Nashville, TN; [10]Roswell Park Comprehensive Cancer Center, New York, NY; [11]Vanderbilt-Ingram Cancer Center, Nashville, TN; [12]Astex Pharmaceuticals, Inc., Pleasanton, CA; [13]The University of Kansas Clinical Cancer Research Center

Abstract # 461 presented at the ASH Annual Meeting.
New Orleans, LA Dec. 10 - 13, 2022 22US-ASTX_PPT727(117)

Introduction (1): HMAs in Lower-Risk MDS

Hypomethylating agents (HMAs) are standard therapies in higher risk MDS but use in lower-risk disease (Int-1/LR) is less clear

- A prior study of low-dose decitabine (20 mg/m^2 vs. azacitidine 75 mg/m^2 x 3 q 28 d) suggested clinical benefit[1,2] leading to inclusion in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
- A recent randomized study of an oral formulation of azacitidine (CC-486) showed no difference in survival (median OS 17.3 vs. 16.2 months) compared to placebo
  - CC-486 exposure and schedule are different than parenteral azacitidine
  - Survival impacted by early infectious deaths in first 56 days (16 [15%] in CC-486 vs 6 [5.5%] placebo)[3]
- Optimizing dosing regimen for LR MDS is critical to balance clinical response with risk of myelosuppression

Int - Intermediate; OS - overall survival

[1]Jabbour, et al. Blood 2017 Sep 28; 130(13):1514-1522 [NCT01720225]
[2]Sasaki, et al. NEJM Evid 2022 Aug 9; 1(10) [NCT01720225]
[3]Garcia-Manero, et al. JCO 2021 May 1; 39(13): 1426-1436 [NCT01566695]

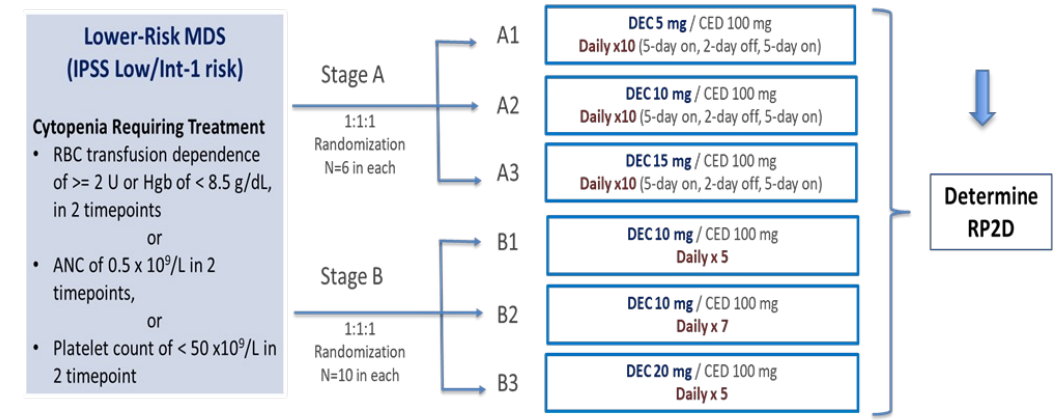
Introduction (2): Oral Decitabine/Cedazuridine

- Oral decitabine/cedazuridine (ASTX727)
  - fixed-dose (FDC) combination of 35 mg decitabine (DEC) and the cytidine deaminase (CDA) inhibitor cedazuridine (100 mg, C) produces equivalent PK AUC exposure compared to IV decitabine[1]
- ASCERTAIN: Phase 3 study led to the approval of oral DEC-C
  - LR MDS subjects who received the standard dose (SD) of ASTX727 for 5 days and demonstrated clinical benefit[2]
- Study ASTX727-03 (*NCT03502668*):
  - Phase 1 investigated multiple dosing regimens of oral DEC-C in LR MDS
  - With the Objective of obtaining clinical responses while avoiding myelotoxicity in patients who are expected to receive long-term treatment

AUC – are under the curve; IV – intravenous

[1]Savona, et al, [ASH 2020 Abstract 1230]
[2]Garcia-Manero, et al, [ASH 2021 Abstract 66]

Phase 1 Study Design



Major Entry Criteria:

- Cytopenia requiring treatment
- ECOG PS 0-2
- Adequate organ function
- Prior treatment with HMA is allowed
- Exclude CMML

Primary Endpoint

- Safety as determined by incidence of drug-related Grade ≥3 AEs or DLTs

Secondary Endpoint

- Hematologic Improvement (HI) based on modified 2016 IWG criteria
- Transfusion Independence
- Overall Survival (OS), Leukemia Free Survival (LFS)

IPSS – International Prognostic Scoring System; RBC – red blood cell; ANC – absolute neutrophil count; RP2D – recommended phase 2 dose; ECOG – Eastern Cooperative Oncology Group; PS – performance status; CMML – chronic myelomonocytic leukemia; AEs – adverse events; DLTs – dose-limiting toxicities; IWG – International Working Group

71

DLT frequency for each regimen

Stage	Ph1 Stage A			Ph1 Stage B		
Cohort	A1	A2	A3	B1	B2	B3
Regimen	5mg 10-day	10mg 10-day	15mg 10-day	10mg 5-day	10mg 7-day	20mg 5-day
DLT /Evaluable subject #	3/10	4/4	-	3/11	7/10	7/11

- All DLTs were related to grade 4 neutropenia (last longer than 10 days in Cycle 1)
- Cohort A3 was closed with no enrollment due to the high incidence of DLT observed in cohort A2
- The DLT incidences were proportional to the dose intensity (total DEC dose per cycle) and number of days of study drug administration

76

Patient Demographics/ Disease Characteristics n. 47

Characteristics		Total Treated N=47
Age in years (median, range)		76 (51-88)
Sex: Male/Female		30 (65%) / 17(35%)
Median weight, kg (range)/Median BSA, m2 (range)		80 (52-136) / 1.9 (1.5 – 2.5)
MDS, IPSS classification	Low-risk / Int-1	15 (32%) / 32 (68%)
Cytogenetics	Good	33 (70%)
	Intermediate	8 (17%)
	Poor	4 (9%)
Prior treatment for MDS		27 (57%)
ECOG PS	0/1/2	10(21%) / 34 (72%) / 3(6%)

Baseline Hematology Parameter	Median (Range)
Bone marrow blasts (%)	2.0 (0 8)
Hemoglobin (g/L)	81 (62-145)
Platelets (10^9/L)	123.8 (5-509)
ANC (10^9/L)	1.9 (0-7)
RBC transfusion dependent (TD)	21 (45%)
Platelets TD	3 (6%)

- RBC TD: 21 (45%), N= 34 (71%) with Hgb <90 g/L
- Platelet TD: 3 (6%), N= 17 (35%) with Platelet < 75 X 10^9/L

- Low and Int-1 IPSS risk category were 32% and 68%, respectively; 29 (60%) had an IPSS-R score of 3.5 or less
- Prior treatment for MDS was primarily ESA 16 (34%) and 13 (28%) each were treated with lenalidomide or parenteral HMAs

Results: Pharmacokinetics (PK) Profile of Decitabine Exposure

Cohort	Daily Decitabine Dose (mg)	Cycle Cumulative Dose (mg)	% FDC Cycle Cumulative Dose	Total Cycle $_4AUC_{0\text{-}2h}$ (ng*hr/mL)	% FDC Total Cycle $AUC_{0\text{-}24h}$ (5 Days)
B1	10 x 5 days	50	29%	235	27%
B2	10 x 7 days	70	40%	269	31%
B3	20 x 5 days	100	57%	431	50%
Standard dose (SD)[1]	35 x 5 days	175	100%	856	100%

[1] ASTX727-02 phase 3 fixed-dose combination primary analysis (paired population): plasma decitabine results for AUC equivalence assessment; oral geometric least squares means

Total cycle $AUC_{0\text{-}24}$, is proportional to the total dose of decitabine per cycle

i. e. Cohort B1's cycle cumulative dose is 50 mg, which is 29% of the cycle cumulative dose of the SD of 35 mg over 5 days, and total cycle $AUC_{0\text{-}24h}$ is 27% of the total cycle $AUC_{0\text{-}24h}$ of the SD of 35 mg over 5 days

Efficacy Results: Hematologic Improvement (HI) and Transfusion Independence (TI)

	Phase 1 Stage A		Phase 1 Stage B			
	Cohort A1 5mg 10-day N=10	Cohort A2 10mg 10-day N=4	Cohort B1 10mg 5-day N=11	Cohort B2 10mg 7-day N=11	Cohort B3 20mg 5-Day N=11	Total
Total HI endpoint evaluable subjects	10	4	11	11	11	47
HI, n (%)	2 (20.0)	2 (50.0)	4 (36.4)	3 (27.3)	3 (27.3)	14 (29.8)
HI-E endpoint evaluable subjects, n	9	3	11	10	9	42
HI-E, n (%)	1 (11.1)	1 (33.3)	4 (36.4)	2 (20.0)	2 (22.2)	10 (23.8)
HI-P endpoint evaluable subjects, n	5	3	4	4	6	22
HI-P, n (%)	1 (20.0)	1 (33.3)	2 (50.0)	2 (50.0)	2 (33.3)	8 (36.4)
HI-N endpoint evaluable subjects, n	3	2	2	1	4	12
HI-N, n (%)	1 (33.3)	1 (50.0)	0	0	0	2 (16.7)
RBC TD at baseline, n	4	1	7	5	4	21
Post treatment RBC TI, n (%)	1 (25.0)	0	4 (57.1)	1 (20.0)	1 (25.0)	7 (33.3)
Platelet TD at baseline, n	0	1	1	0	1	3
Post-Treatment Platelet TI, n (%)	0	0	0	0	1 (100.0)	1 (33.3)

- All cohorts showed early emerging evidence of clinical activity (achieving HI and transfusion independence)

HI: Hematological Improvement based on IWG 2006 MDS response criteria
HI-E=erythroid response;
HI-N=neutrophil response;
HI-P=platelet response,
TD: Transfusion Dependence

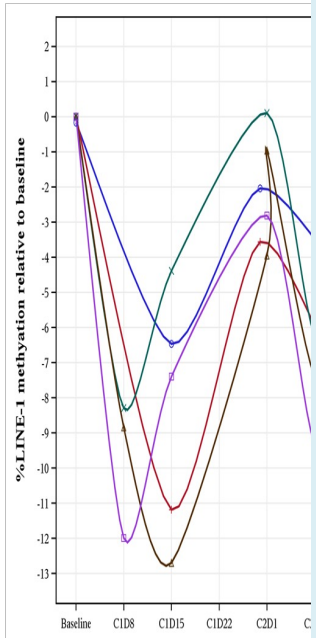
Safety Results: Treatment-Emergent Adverse Events in >20% of Patients (Independent of Attribution)

Preferred Term	Cohort A1 5mg 10-day (N=10)	Cohort A2 10mg 10-day (N=4)	Cohort B1 10mg 5-day (N=11)	Cohort B2 10mg 7-day (N=11)	Cohort B3 20mg 5-day (N=11)	Total (N=47)
Subjects with any AE	10 (100)	4 (100)	11 (100)	11 (100)	11 (100)	47 (100)
Total number of AEs	162	54	290	265	317	1093
Fatigue	6 (60.0)	2 (50.0)	4 (36.4)	5 (45.5)	4 (36.4)	21 (44.7)
Neutropenia	3 (30.0)	3 (75.0)	5 (45.5)	5 (45.5)	3 (27.3)	19 (40.4)
Neutrophil count decreased	1 (10.0)	2 (50.0)	2 (18.2)	5 (45.5)	8 (72.7)	18 (38.3)
Anaemia	1 (10.0)	2 (50.0)	5 (45.5)	3 (27.3)	5 (45.5)	16 (34.0)
Constipation	2 (20.0)	1 (25.0)	3 (27.3)	6 (54.5)	4 (36.4)	16 (34.0)
Diarrhoea	1 (10.0)	1 (25.0)	3 (27.3)	3 (27.3)	5 (45.5)	13 (27.7)
Decreased appetite	0	2 (50.0)	3 (27.3)	4 (36.4)	3 (27.3)	12 (25.5)
Cough	2 (20.0)	3 (75.0)	3 (27.3)	1 (9.1)	3 (27.3)	12 (25.5)
Pyrexia	3 (30.0)	1 (25.0)	4 (36.4)	2 (18.2)	1 (9.1)	11 (23.4)
Platelet count decreased	2 (20.0)	0	3 (27.3)	3 (27.3)	3 (27.3)	11 (23.4)
Oedema peripheral	2 (20.0)	1 (25.0)	4 (36.4)	1 (9.1)	3 (27.3)	11 (23.4)
Dyspnoea	0	2 (50.0)	4 (36.4)	2 (18.2)	2 (18.2)	10 (21.3)

- Safety profile consistent with that of standard (approved) DEC-C dosing
- No significant safety differences between the cohorts, with the exception of increase of AE frequency of decreased neutrophil counts observed in regiments with higher DEC doses per cycle (A2, B2, & B3)
- No clinically significant incidence of GI events at all the investigated doses were attributed to oral DEC-C

Results: Pharr

%LINE-1 Demethyl

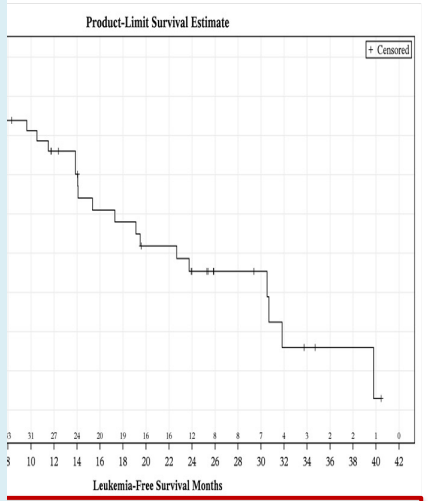


Conclusions

- Investigation of oral administration of various low-dose DEC-C regimens in IPSS Low/Int-1 risk MDS showed:
  - Safety profile consistent with standard dose of DEC-C
    - Treatment-emergent events were typically related to myelosuppression
    - Lower doses and shorter dosing regimens have fewer occurrences of neutropenia
    - No clinically significant GI adverse effects
  - All dosing cohorts demonstrated clinical activity
    - Endpoints evaluated: HI and transfusion independence, 31 months survival
    - Lower doses of decitabine administered orally appear to maintain clinical activity with lower levels of LINE-1 demethylation but less neutropenia
- Dose schedule 10 mg DEC/100 mg CED daily X 5 days (Cohort B1) was selected as the RP2D based on clinical efficacy and safety profile
- RP2D regimen is being currently compared to 35 mg DEC/100 mg CED for 3 days in a 28-day cycle in the ongoing Phase 2 study [*NCT03502668*]

Free

Curves of Leukemia-Free Survival



months 95% CI (14, 32 months)

64th ASH Annual Meeting

Evaluation of Lenalidomide (LEN) Vs Placebo in Non-Transfusion Dependent LR-MDS del(5q) patients: Final results of Sintra-REV

Phase III international multicenter clinical trial

Félix López-Cadenas, Eva Lumbreras, Teresa González, Blanca Xicoy, Joaquín Sánchez-García, Rosa Coll, Bohrane Slama, Jose Ángel Hernández-Rivas, Sylvain Thepot, Teresa Bernal, Agnés Guerci-Bresler, Guillermo Sanz, Joan Bargay, María Luz Amigo, Raquel de Paz Arias, Claude Preudhomme, Aristoteles Giagounidis, Uwe Platzbecker, Stefan Wickenhauser, Katharian S Goetze, Ali Arar, Jesus M Hernández-Rivas, Sofia M Toribio Castelló, Pierre Fenaux, Consuelo del Cañizo and María Díez-Campelo

M. Díez-Campelo, MD, PhD
mdiezcampelo@usal.es

Hematología
HOSPITAL UNIVERSITARIO SALAMANCA

Background and rationale

Low Risk MDS (LR-MDS) with del(5q)

- LR-MDS patients with del(5q):
  - Presented with anemia 68%, 42% transfusion dependency (TD)[1]
  - Median time to TD in anemic non-TD LR-MDS is 1.7y[2, 3]
- Len at 10 mg/d in patients with transfusion requirements:
  - Transfusion Independency (TI): 67%[4] and 61%[5]
  - Cytogenetic Responses (CyR): 73%[4] and 50%[5]
  - Improve outcome among responders[5, 6]: OS and AML evolution
  - Target clonal cells, nevertheless, did not eliminate malignant stem cells[7]

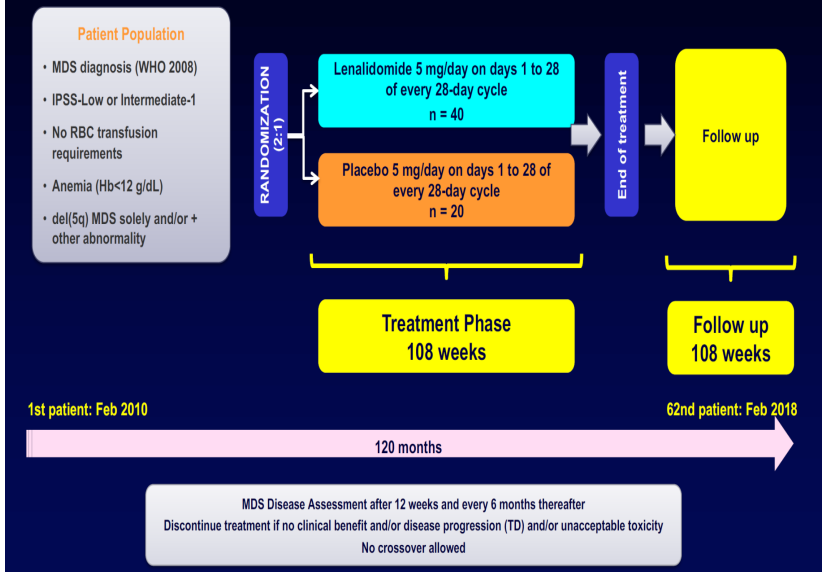
Could early Lenalidomide at low doses prolong time until TD and improve outcome?

1. Germing, Leukemia 2012
2. Rojas, Leuk Res 2014
3. López-Cadenas, ASH 2016
4. List, NEJM 2006
5. Fenaux, Blood 2011
6. List et al. Leukemia 2014
7. Tehranchi, NEJM 2010

Sintra-Rev Clinical Trial

Design

The Sintra-Rev trial is a phase 3, double-blind, randomized, placebo-controlled, multicenter study



Sintra-Rev Clinical Trial

Patient Characteristics (N=61)

	Len (%) N=40	Placebo (%) N=21
Gender (female)	32 (80)	18 (85.7)
Age (median)	72.2	71.9
WHO 2008		
RARS	0	1 (4.8)
RCUD	2 (5)	0
RCMD	10 (25)	5 (23.8)
RAEB-1	2 (5)	1 (4.8)
MDS with del(5q)	26 (65)	14 (66.7)
WHO 2017		
MDS-EB-1	2 (4.9%)	1 (4.8%)
MDS-del(5q)	38 (95.1%)	20 (95.2%)
IPSS		
Low	29 (72.5%)	14 (66.7%)
Int-1	11 (27.5%)	7 (33.3%)
Del(5q) abnormality		
Isolated	35 (85.5%)	19 (90.4%)
+ other abn*	5 (12.5%)	2 (9.6%)

	Len (median) N=40	Placebo (me) N=21
*Hb, g/dL	9.8	9.8
*ANC, x 10^9/L	2.1	2.2
*Plat, x 10^9/L	238	272
PB blasts, %	0	0
BM blasts, %	1.5	2
Time to Sintra-Rev	2.68 mo	4 mo

*Similar values at day 1 of Cycle 1
No differences between both arms

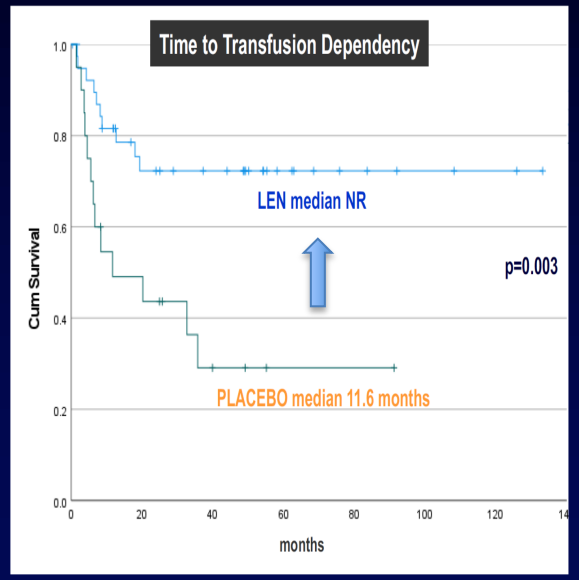
*Additional cytogenetic abnormalities: +8, t(1;13), -Y, -7, add(2) & del(11q), -Y
No significant differences between Len and Placebo arm

Sintra-Rev Clinical Trial

Primary objective: 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



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

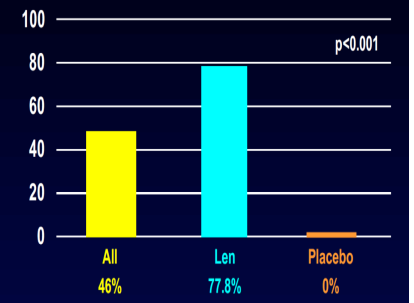
Sintra-Rev Clinical Trial

Secondary Objectives: Quality of responses

Low doses of Len reached Erythroid and Cytogenetic responses

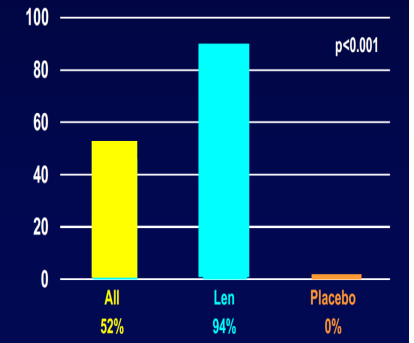
✓ Erythroid Response[1]

- ✓ Len (ITT Evaluable) 28/36 (77.8%)
  - ✓ Median Hb at EOT 12.4 g/dL (+2.7 g/dL)
- ✓ Placebo 0 (0%)



✓ Cytogenetic Response[1]

- ✓ Len (ITT Evaluable) 32/34 (94.1%):
  - ✓ 87.5% Complete (28/32)
  - ✓ 12.5% Partial (4/32)
- ✓ Placebo 0 (0%)



[1]IWG MDS 2006 criteria

Sintra-Rev Clinical Trial

Secondary objectives: Safety analysis (N=59)

Low doses of Len are safe and well tolerated

Non-Hematological	G1-2 Len	G1-2 Placebo	G3-4 Len	G3-4 Placebo
Gastrointestinal	18 (46.8%)	1 (4.8%)		
Vascular (PE/DVT)		2 (9.6%)	1 (2.6%)	
Asthenia	4 (10.5%)	2 (9.6%)		
Appetite	2 (5.3%)	1 (4.8%)		
Somnolence		1 (4.8%)		
Pruritus	4 (10.6%)	1 (4.8%)		
Rash	11 (28.6%)	3 (14.3%)	1 (2.6%)	
Hypothyroidism	1 (2.6%)			
2nd solid tumor			4 (10%)	1 (4.7%)

19 SAE (18L/1P) were documented: Vestibular Syndrome, Lung adenocarcinoma + Brain Metastasis, Respiratory failure (2), Cardiac insufficiency (3), Pulmonary Embolism, Neutropenic Fever, Pneumonia, Polyarthralgia, Carpal Arthritis, No consolidating respiratory infection, COPD (2) Blurred vision, Hypertensive crisis.
4 related to Len.

Sintra-Rev Clinical Trial

Secondary objectives: Safety analysis

Low doses of Len induced not clinically relevant neutropenia

Hematological	G1-2 Len	G1-2 Placebo	G3-4 Len	G3-4 Placebo
Anemia	3 (7.9%)	0	1 (2.6%)	0
Leucopenia	4 (10.6%)	0	0	0
Thrombocytopenia	5 (13.1%)	0	2 (5.3%)	0
Neutropenia	6 (15.8%)	3 (14.3%)	17 (44.7%)	1 (4.8%)
Febrile Neutropenia	0	0	1 (2.6%)	0
Pancytopenia	1 (2.6%)	0	0	0
Polycythemia	1 (2.6%)	0	0	0

19 SAE (18L/1P) were documented: Vestibular Syndrome, Lung adenocarcinoma + Brain Metastasis, Respiratory failure (2), Cardiac insufficiency (3), Pulmonary Embolism, Neutropenic Fever, Pneumonia, Polyarthralgia, Carpal Arthritis, No consolidating respiratory infection, COPD (2) Blurred vision, Hypertensive crisis.
4 related to Len.

Sintra-Rev Clinical Trial

Secondary objectives: outcome

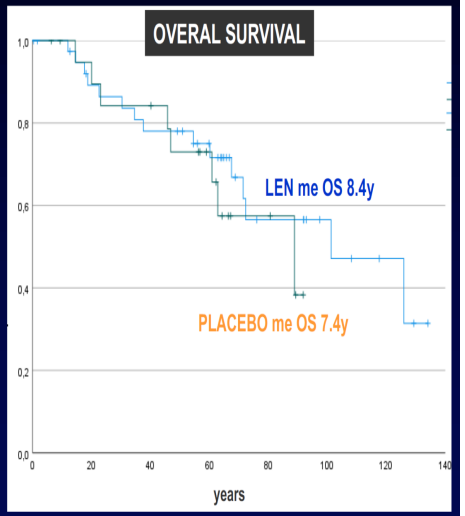
Low doses of Len did not increase AML evolution

✓ Similar median overall survival (no deaths related)

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

✓ 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



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

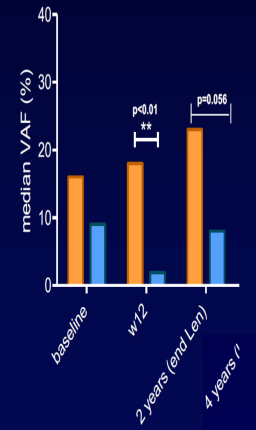
Sintra-Rev Clinical Trial

Secondary objectives: clonal safety (NGS)

Baseline → w12 → End of treatment → Long term FU

✓ Median VAF confirmed molecular responses in Len arm

- Len pts decrease VAF/clonal size
- Placebo pts remained stable and increased over time



ASH-Frank Toohey Abstract Achievement Award for Myelodysplastic Syndromes

Toribio-Castelló S, López-Cadenas F, et al. ASH 2022 Poster 4377 - Session 636

Sintra-Rev Clinical Trial

Secondary objectives: clonal safety (NGS)

Baseline → w12 → End of treatment → Long term FU

Low doses of Len did not promote clonal evolution

✓ *TP53* mut (N=6) at baseline also responded to Len

- 2/6 ER, median duration of response similar than *TP53* wt
- 4/6 CyR, median duration of response similar than *TP53* wt
- *TP53* clonal size decrease in 5/6 patients during treatment
- 2/6 (33.3%) AML at 62 mo (*SF3B1* co-mut) and 74 mo after inclusion

✓ *TP53* mut (N=5) at baseline in Placebo arm

- VAF remain stable in 4/5 and increased in 1/5
- 1/5 (20%) AML at 49 mo after inclusion (*SF3B1* co-mut)

ASH-Frank Toohey Abstract Achievement Award for Myelodysplastic Syndromes

Toribio-Castelló S, López-Cadenas F, et al. ASH 2022 Poster 4377 - Session 636

Sintra-Rev Clinical Trial

Summary

- Early treatment with Lenalidomide at low doses (5mg)
  - Prolongs the time to and decreased the risk of transfusion dependency
  - Reached erythroid responses in 77.8% of patients
  - Achieved cytogenetic responses in 94.1% of patients (87.5% completed)
  - Acceptable safety profile, hematological toxicities not clinically relevant
  - Did not promote clonal evolution, even in *TP53* mut patients

Safety of Deferiprone in Patients with Myelodysplastic Syndromes: Results from the Deferiprone US Safety Registry and a Compassionate Use Program

A Zeidan[1], C Fradette[2], A Rozova[2], N Toiber Temin[2], F Tricta[2]
[1]Yale University, New Haven, CT, USA [2]Chiesi Canada Corporation, Toronto, ON, Canada

Limited RCT Data on ICT in MDS

- Conducting randomized controlled trials (RCTs) on Iron chelation Therapy (ICT) in MDS have been challenging
- The only RCT conducted made the case for iron chelation use in patients with MDS
  - A phase II randomized double-blind study found a 36.4% reduction in the hazard ratio of an event with deferasirox compared to placebo (HR: 0.636; 95% CI: 0.42, 0.96)[1] **TELESTO**
- A meta-analysis of 9 prospective and retrospective observational studies found that iron chelation therapy in patients with lower-risk MDS had a longer median overall survival than those not receiving chelation therapy[2]

1. Angelucci, E., et al. *Annals Int Med.* 2020, 172(8):513–522. 2. Zeidan A.M., et al. *Annals of Hematology.* 2019;98:339-350.

NCCN Guidelines for ICT in MDS

- Daily iron chelation therapy (ICT) with deferoxamine or deferasirox should be considered if >20 to 30 blood transfusions have been received
  - Particularly for patients who have lower-risk MDS or are potential transplant candidates
- In iron overloaded patients (serum ferritin >2500 ng/mL), chelation therapy should aim to decrease levels to <1000 ng/mL
- Patients with decreased kidney function (creatine clearance <40 mL/min) should not be treated with deferasirox or deferoxamine

Deferiprone and MDS

Deferiprone (DFP) is an oral ICT approved for transfusional iron overload in thalassemia, sickle cell disease, and other anemias

- No contraindication or dosing adjustment based on renal function
- Requires close patient monitoring and laboratory testing, associated with severe neutropenia *(absolute neutrophil count <1.5x10^9/L) in 1% to 2% of pooled clinical trial patients*
- Previous studies of DFP in patients with thalassemia, sickle cell disease, and other anemias indicate a favorable efficacy and safety profile

Safety and Efficacy of DFP had not been established in MDS

- There is a limitation of use statement in the DFP label for MDS. MDS is associated with increased risk of neutropenia, including severe neutropenia/agranulocytosis, an AE associated with DFP
- As such, MDS was previously excluded in DFP controlled clinical trials resulting in limited data available on DFP in patients with MDS

AE adverse event; DFP, deferiprone; CT, iron chelation therapy; MDS, myelodysplastic syndromes.

Objectives and Methods

To evaluate the safety profile of DFP in patients with MDS who are participating in either the compassionate use program or safety registry

Deferiprone US Safety Registry

Established to meet FDA post-marketing requirements following DFP approval in the US in 2011

n. 115

Data collected:
December 5, 2011, to August 31, 2021

Compassionate Use Program (LA04)

The compassionate use program (LA04) included patients in the US and Canada

Data collected: **n. 15**
May 23,1996, to August 27, 2015

Both Programs

- Patients were chronically transfused and were identified through transfusion burden, ferritin level, or iron overload imaging studies. DFP administered at doses ranging from 75 – 99 mg/kg/day
- A central pharmacy handled data collection. Data was patient reported and there were no planned site visits and no lab data reported.
- All AEs were assessed and reported to the central pharmacy, irrespective of causal relationship, in all patients with MDS who received DFP, including any cases of agranulocytosis, neutropenia, and infection

Results: *Deferiprone US Safety Registry*

- The US safety registry included 115 adults with a mean age of 78 years; the majority were men (61.7%)
- Patient exposure to DFP ranged from 0 to 8 years, with the majority receiving DFP > 6 months (51.3%)

DFP, deferiprone; SD, standard deviation; US, United States.

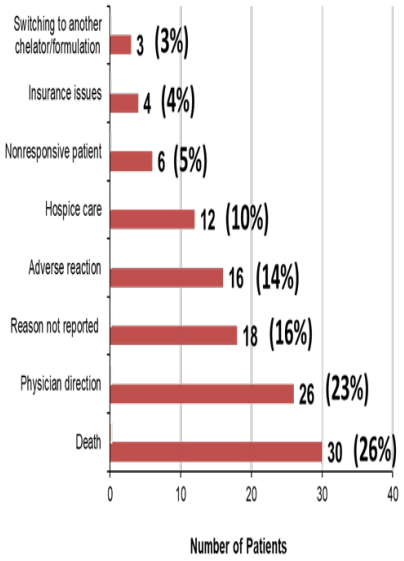
Patient Demographics and Medical History

	Overall (N = 115)
Demographics	
Mean age, years (SD)	77.7 (9.0)
Men, n (%)	71 (61.7)
Medical history	
DFP Exposure, mean years, [range]	1.1 (± 1.4) [0–7.9]
Receiving DFP > 6 months, n (%)	59 (51.3)
Receiving DFP > 12 months, n (%)	34 (29.6)

Results: *Deferiprone US Safety Registry*

Reason for discontinuation[a]

- None of the fatal outcomes were assessed as related to use of DFP
- Death (26%) was one of the most common reasons for dismissal from the registry
- In many cases the cause of death or circumstances surrounding death were not reported despite follow-up attempts



[a]Discontinuations were assigned by central pharmacy and may not correspond to number of corresponding events in safety database due to coding conventions and timing of occurrence (e.g., "death vs fatal outcome of an adverse event").
DFP, deferiprone; MDS, myelodysplastic syndromes.

Results: Com

- The compassionate use program included 15 adults with MDS and mean age of 68 years; the majority were men (60%)
- Mean patient exposure to DFP was 1 year **n. 115**
- 18 total patient-years of DFP exposure

DFP, deferiprone.

Conclusions

- This data indicate that the safety profile of DFP in patients with MDS appeared similar to thalassemia, sickle cell disease, and other anemias
  - No unexpected or new AEs reported
- There was no clear increase in the risk of reported neutropenia in patients with MDS based on this safety analysis
  - US Safety Registry: 4 (3.5%) patients reported severe neutropenia/agranulocytosis, 2 resolved, 1 unreported outcome, and 1 ongoing

DFP, deferiprone; ICT, iron chelation therapy; MDS, myelodysplastic syndromes; RCT, randomized controlled trial; RWE, real-world evidence.

a collection, limitations in
uncontrolled studies

elf reported data

s
medications
alues were collected (ie,

s, these types of RWE
orming patient care,
opulation with minimal

on chelation therapy; MDS, myelodysplastic syndromes.