

Elena Crisà MD, PhD

INOC - Istituto Nazionale Oncologico Candiolo (Torino)

Disclosures of Elena Crisà

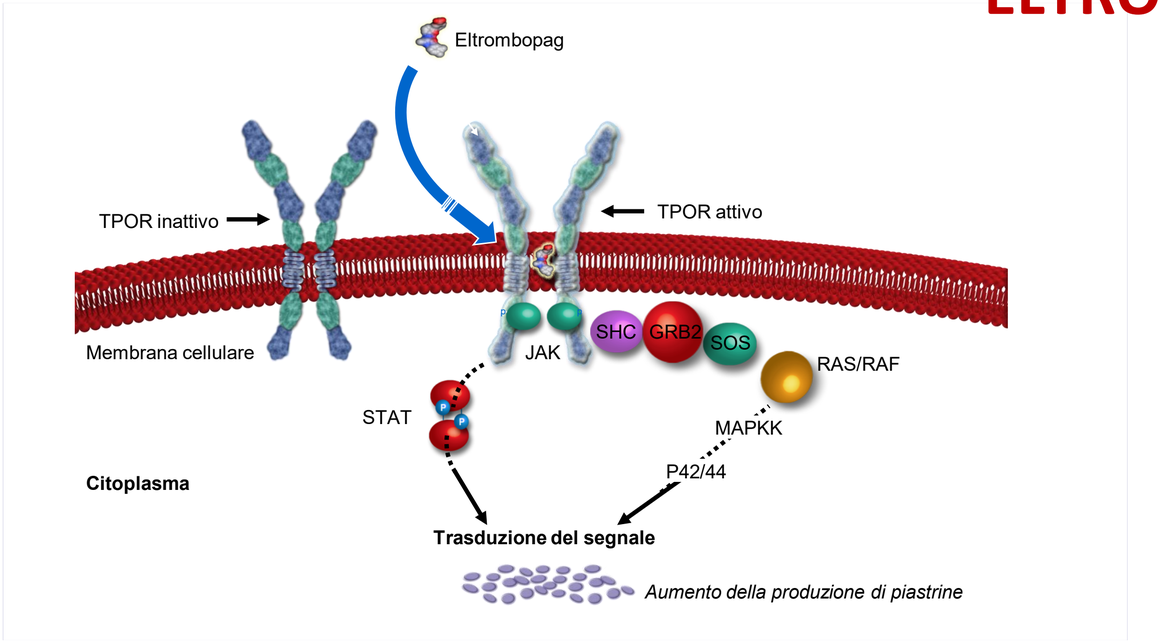
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GSK						X	
JANSSEN	X						
BMS					X	x	
Ascentage						x	

AGENDA

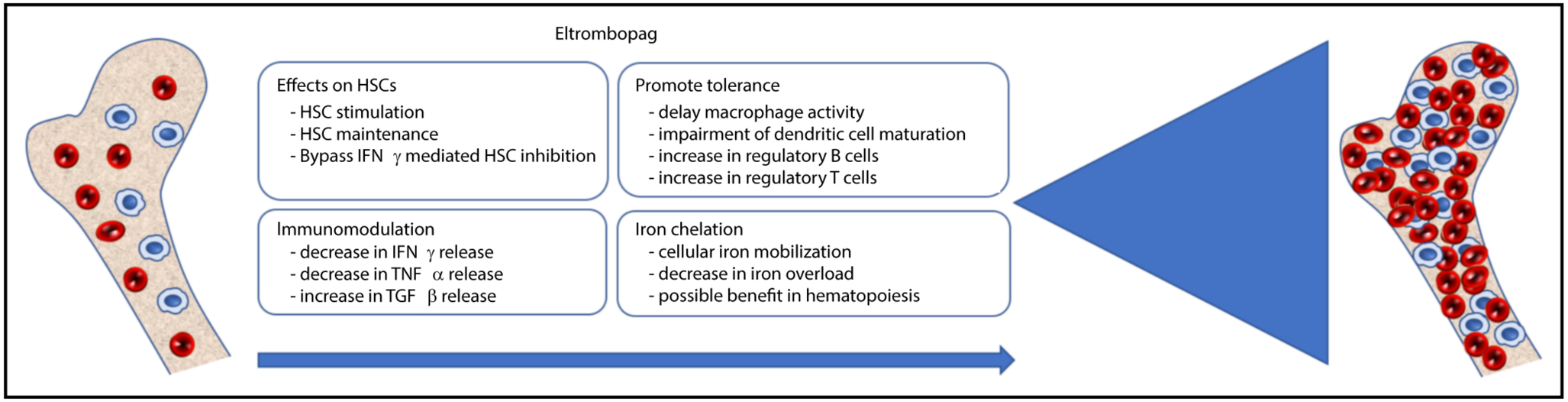
- **Observational study on eltrombopag in hypocellular myelodysplastic neoplasm (FISiM-Eltrombopag-hMDS)**

- **Phase 2 randomized trial of lenalidomide discontinuation versus continuous therapy in patients with del(5q) myelodysplastic neoplasm (LEN STOP trial)**

ELTROMBOPAG



thrombopoietin-receptor agonist, first approved in patients with idiopathic thrombocytopenic purpura, then in severe AA



Eltrombopag in low- and int-1-risk MDS

Phase 1

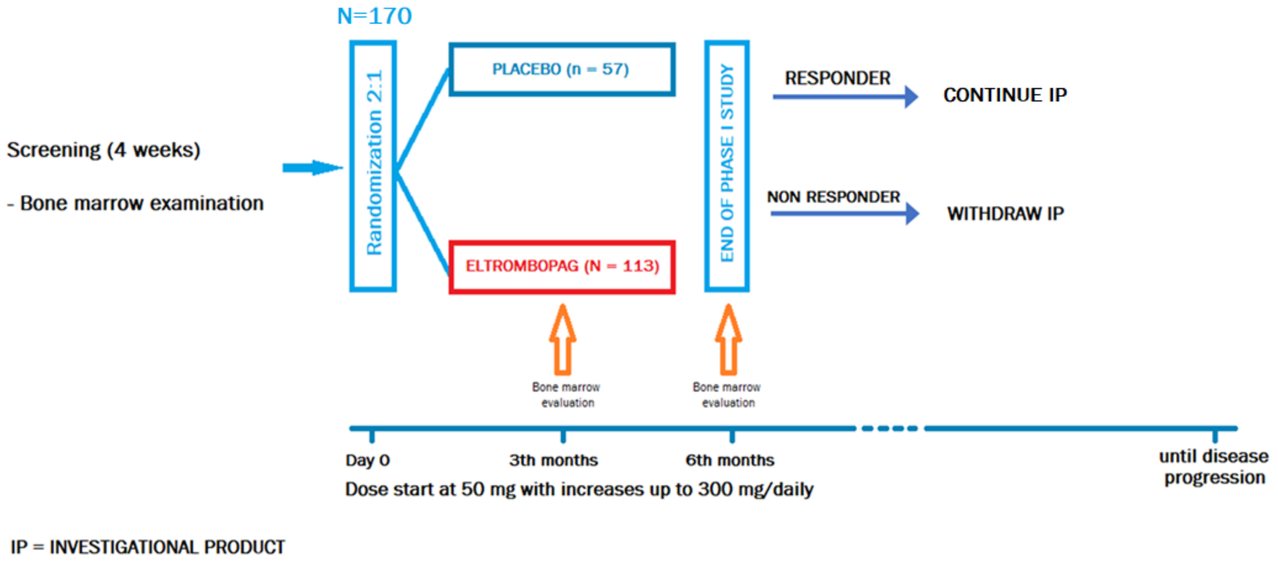
To determine the efficacy and safety of eltrombopag in the first 6 months

Phase 2

To assess the long-term response and safety

Inclusion criteria

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



IP = INVESTIGATIONAL PRODUCT

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

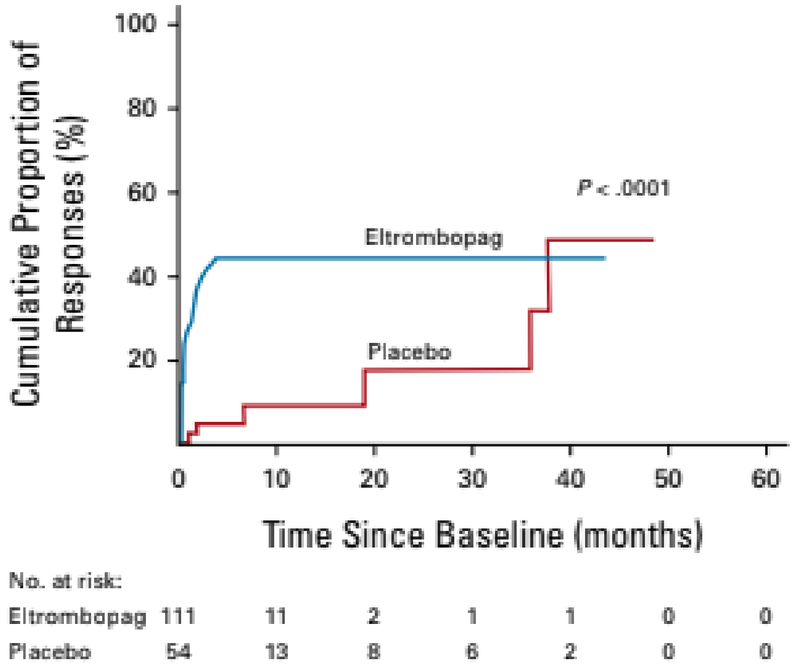
Platelet response P<0.0001

Placebo	Eltrombopag
6/54	47/111
11%	42%

Platelet transfusion independance

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

OR 5.9, 95% CI: 2.3–14.9, p<0.001



Oliva EN, et al. Journal of Clinical Oncology, 2023

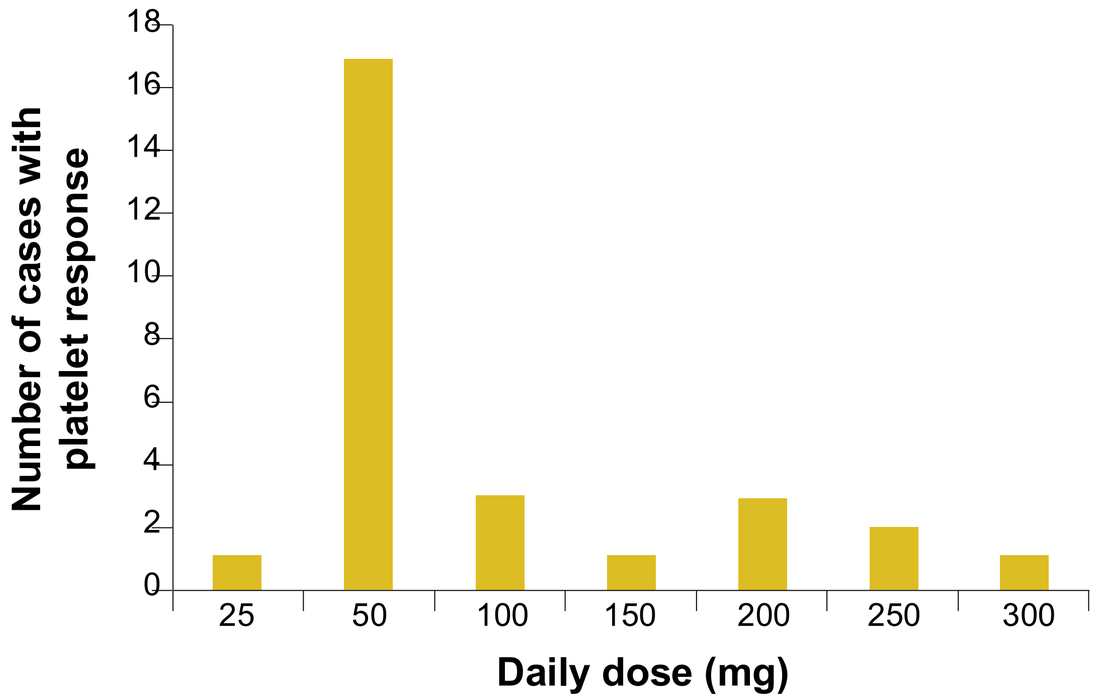
EQoL-MDS: Platelet response

Factors **not** associated with response:

- Gender,
- MDS duration
- WHO classification
- IPSS, IPSS-R
- Cytogenetics
- Bleeding
- PLT transfusions
- **Hypoplasia**
- fibrosis

Median daily dose at response

50 mg (IQR 50-150 mg)



AML evolution and/or disease progression occurred in 17% (for both) of eltrombopag and placebo patients with no difference in survival times

Oliva EN, et al. Journal of Clinical Oncology, 2023

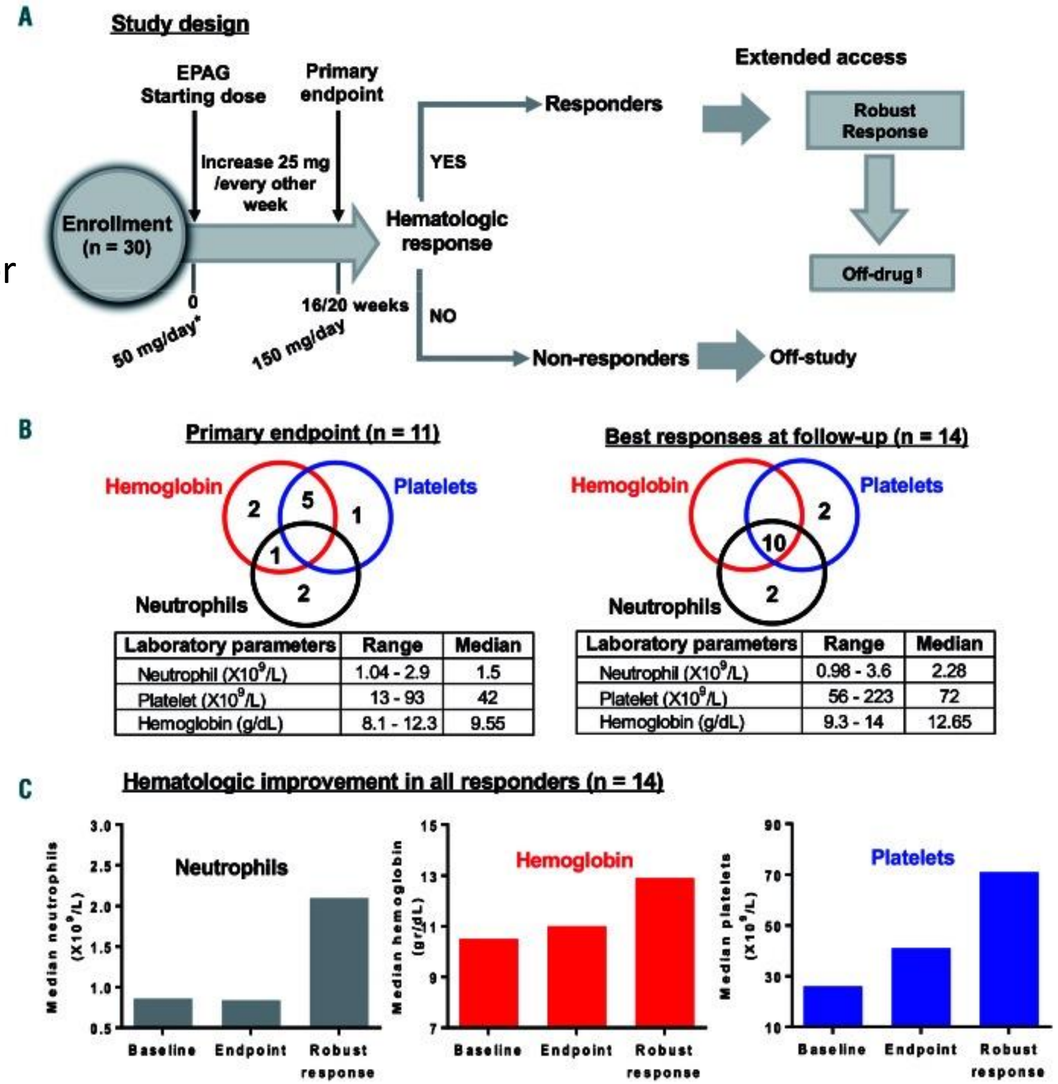
Eltrombopag monotherapy can improve hematopoiesis in patients with IPSS-R very low to intermediate risk MDS

Patients population

- 25 LR-MDS patients
- **any cytopenia**(hemoglobin ≤9.0 g/dL or RBC-TD (at least 4 units of red blood cells at 8 weeks prior to enrollment); platelet counts ≤30x10^9/L or platelet TD; or absolute neutrophil count (ANC) ≤0.5x10^9/L).
- Th.related MDS excluded.

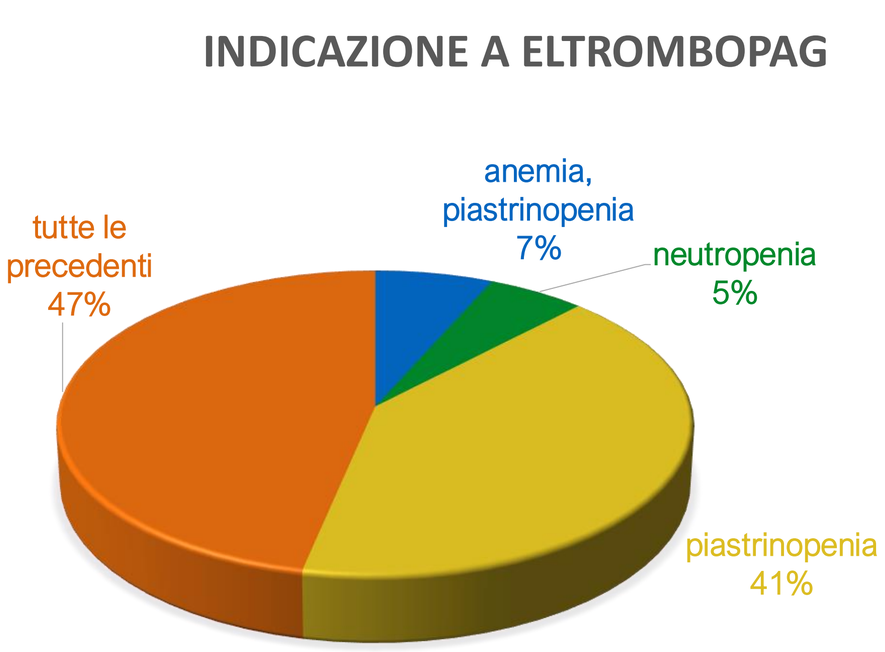
→ **bilineage response in 44% of patients**

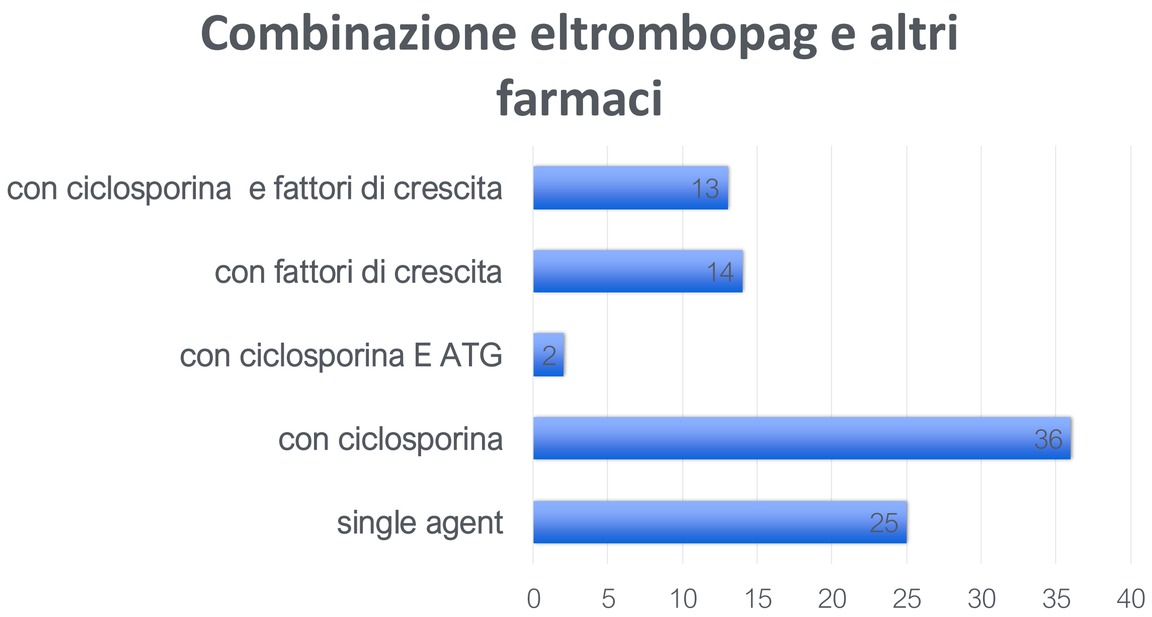
- **hypocellularity a predictor of response**
- In 25/30 (83%) patients eltrombopag was escalated to the maximum dose
- most frequent TAE: nausea and vomiting (20%), skin lesions (20%), headaches (17%), and discoloration of the sclerae (17%)
- No AML progression



Vicente, A., et al., Haematologica 2020

FISIM survey: 108 patients





FISiM-Eltrombopag-hMDS

RATIONALE

- Limited real-world evidence for eltrombopag in h-MDS, alone or combined with immunosuppressive therapy (IST).
- Previous phase II data suggest hematologic activity; hypocellularity may predict response.

STUDY DESIGN

- Multicenter, retrospective–prospective observational study .
- Adults with WHO 2022 h-MDS, IPSS-R very low–intermediate risk.
- Off-label eltrombopag, alone or with IST, at any treatment line.

~100 patients | 26 participating FISiM centers | Cases: Jan 2016–Dec 2026

FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

FISiM-Eltrombopag-hMDS

Primary Objective

- Evaluate effectiveness of eltrombopag treatment (off-label) in patients with hypocellular myelodysplastic neoplasms

Secondary Objectives

- Confirm h-MDS diagnosis through central bone marrow biopsy revision
- Describe molecular landscape and correlate mutations with treatment response
- Assess response according to addition of immunosuppressive drugs
- Evaluate duration of response, safety profile, and overall survival
- Determine time to AML progression
- Identify predictors of treatment response

FISiM-Eltrombopag-hMDS

PRIMARY ENDPOINT

Overall response rate (ORR) according to IWG 2006 and 2018 criteria.

KEY SECONDARY ENDPOINTS

- confirm MDS-h diagnosis vs AA through central pathology revision and correlation with cytogenetic and molecular data
- Response with concomitant IST and duration of response
- Safety, overall survival and AML progression
- Molecular landscape and predictors of response

HI-E: Erythroid Response

2018 Criteria: Transfusion independence ≥8 weeks (LTB/HTB patients) or Hb increase ≥1.5 g/dL for ≥8 weeks (NTD patients)

2006 Criteria: Hb increase ≥1.5 g/dL or reduction ≥4 RBC units/8 weeks

HI-P: Platelet Response

Absolute increase of 30×10^9/L (baseline $>20\times10^9$/L) or increase from $<20\times10^9$/L to $>20\times10^9$/L with ≥100% rise

HI-N: Neutrophil Response

≥100% increase and absolute increase $>0.5\times10^9$/L for patients with baseline ANC $<1.0\times10^9$/L

FISiM-Eltrombopag-hMDS

Patient population

Inclusion Criteria

- Age ≥18 years at diagnosis
- h-MDS diagnosis per WHO 2022 classification
- IPSS-R risk: very-low to intermediate
- De novo or therapy-related MDS
- Bone marrow sample available for central review
- Treatment with eltrombopag (monotherapy or with IST) as first-line or subsequent therapy

Exclusion Criteria

- Unavailability of bone marrow sample for central pathological revision

The sample size is based on feasibility, with an estimated enrollment of approximately 100 patients from 30 Italian FISiM member centers, covering the period January 2016 to December 2025.

FISiM-Eltrombopag-hMDS

Data Collection

CENTRAL PATHOLOGY REVIEW

Bone marrow biopsy review to confirm h-MDS diagnosis (Padova Prof. Pizzi).

- Scanned images
- Unstained slides

DATA COLLECTION

Clinical, cytogenetic and NGS data; treatment and outcomes collected through the FISiM registry.

SAMPLE COLLECTION

Only for prospective patients (BM and/or peripheral blood)

FISiM-Eltrombopag-hMDS

Study Timeline updated

November 2026

Study initiation and ethics approval completion

1

2

November2026- Decembrer 2027

Active data collection period across 26 FISiM centers

3

Gennaio 2028

Final report and statistical analysis completion

Coordinator PI

Elena Crisà
INOC - Istituto Nazionale Oncologico Candiolo

Sponsor

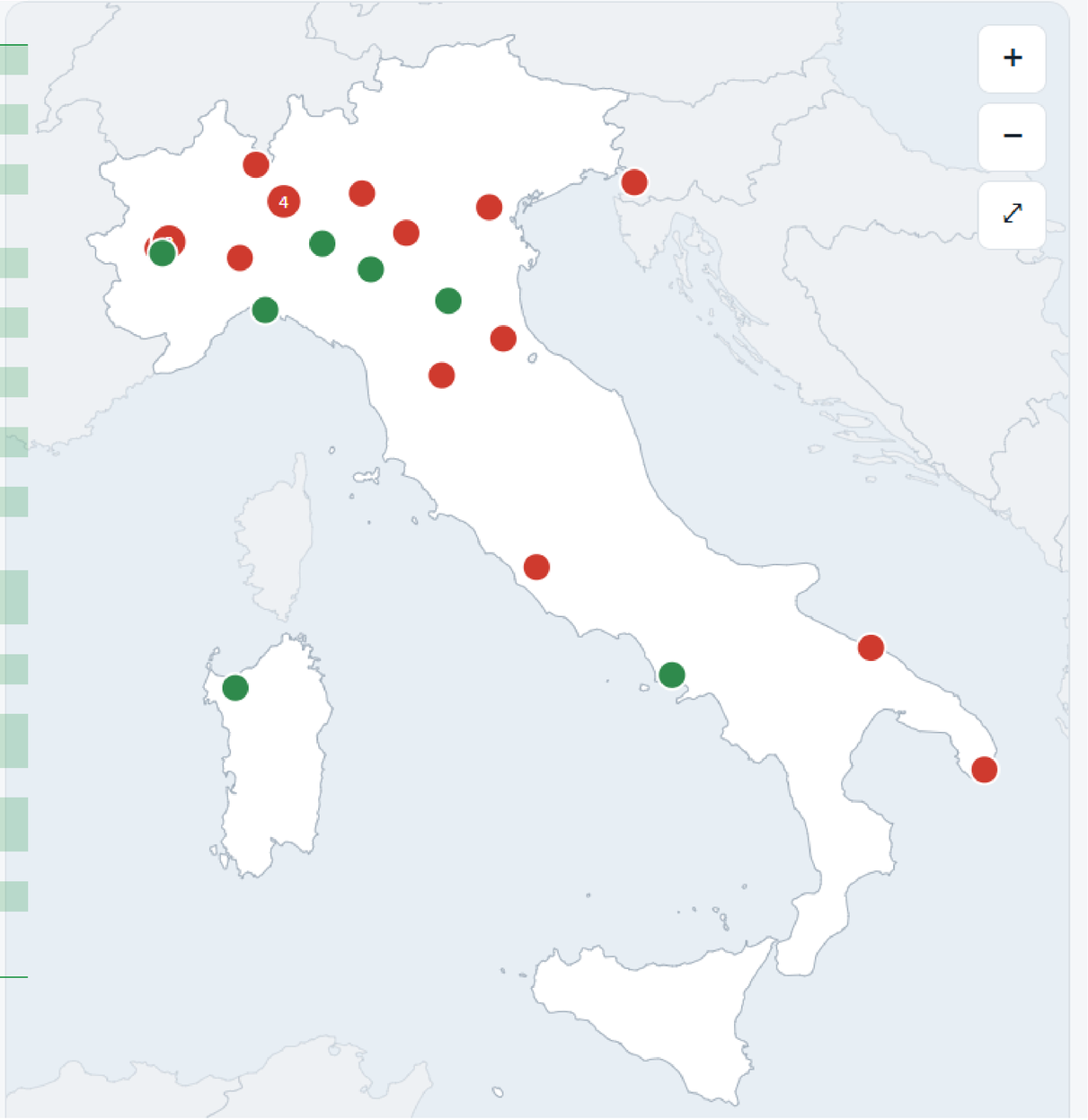
FISiM-ETS Fondazione Italiana Sindromi Mielodisplastiche

Steering Committee

Elena Crisà, Gianni Binotto, Mara Memoli, Annamaria Pellizzari, Daniela Barraco, Emanuela Messa, Monica Crugnola, Carlo Finelli

FISiM-Eltrombopag-hMDS

N°	CENTRO	PI
1	Università di Napoli Federico II	Mara Memoli
2	Policlinico di S. Orsola, IRCCS AOU di Bologna	Stefania Paolini
3	IRCCS Istituto Romagnolo per lo Studio dei Tumori Dino Amadori	Marianna Norata
4	AOU Parma	Monica Crugnola
5	Ospedale Guglielmo da Saliceto	Costanza Bosi
6	Ospedale Maggiore, ASU Giuliano Isontina	Davide Griguolo
7	Ospedale S. Eugenio, ASL Roma 2	Pasquale Niscola
8	IRCCS Ospedale Policlinico San Martino	Giulia Rivoli
9	Spedali Civili di Brescia	Annamaria Pelizzari
10	Ospedale di Circolo e Fondazione Macchi, ASST Sette Laghi	Daniela Barraco
11	Ospedale Carlo Poma, ASST di Mantova	Francesco Frattini
12	IRCCS Ospedale San Raffaele	Elisa Diral
13	Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico	Bruno Fattizzo
14	PO Fatebenefratelli, ASST Fatebenefratelli Sacco	Livia Leuzzi
15	PO San Paolo, ASST Santi Paolo e Carlo	Gian Marco Podda
16	AOU San Luigi Gonzaga, Università degli Studi di Torino	Federico Itri
17	AOU Città della Salute e della Scienza, Università degli Studi di Torino	Giuseppe Lanzarone
18	AOU Città della Salute e della Scienza	Valentina Giai
19	AO SS. Antonio e Biagio e Cesare Arrigo	Monia Marchetti
20	AO Ordine Mauriziano, Università degli Studi di Torino	Daniela Cilloni
21	Candiolo Cancer Institute, IRCCS Fondazione del Piemonte per l'Oncologia	Elena Crisà
22	Pia Fondazione di Culto e Religione Card. G. Panico	Anna Mele
23	AOU Consorziale Policlinico, Università degli Studi Aldo Moro	Pellegrino Musto
24	Università degli Studi di Sassari	Claudio Fozza
25	AOU Careggi	Valeria Santini
26	AOU di Padova	Gianni Binotto



Phase 2, multicenter, prospective,randomized study on lenalidomide discontinuation

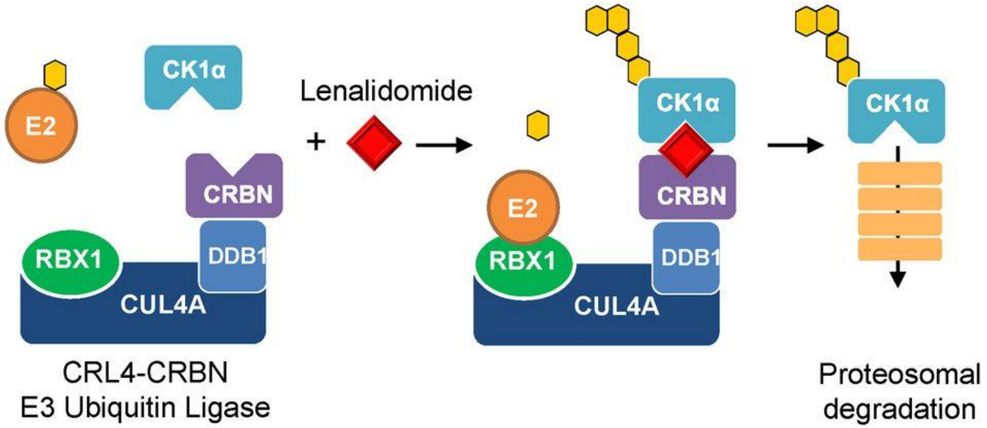
Sponsor: INOC Istituto Nazionale Oncologico Candiolo

Coordinating PI: Elena Crisà

Funder : AIFA, programma di Ricerca Indipendente Malattie Rare 2025

Partnership: FISiM and QOL-ONE

Lenalidomide in del(5q) MDS



Lenalidomide can lead to red blood cell-transfusion independence (RBC-TI) in 60 - 70% of del(5q) RBC-transfusion dependent MDS patients, and to complete cytogenetic response (CCyR) in 30-40% o the cases.

- Median time to reponse 4-6 weeks

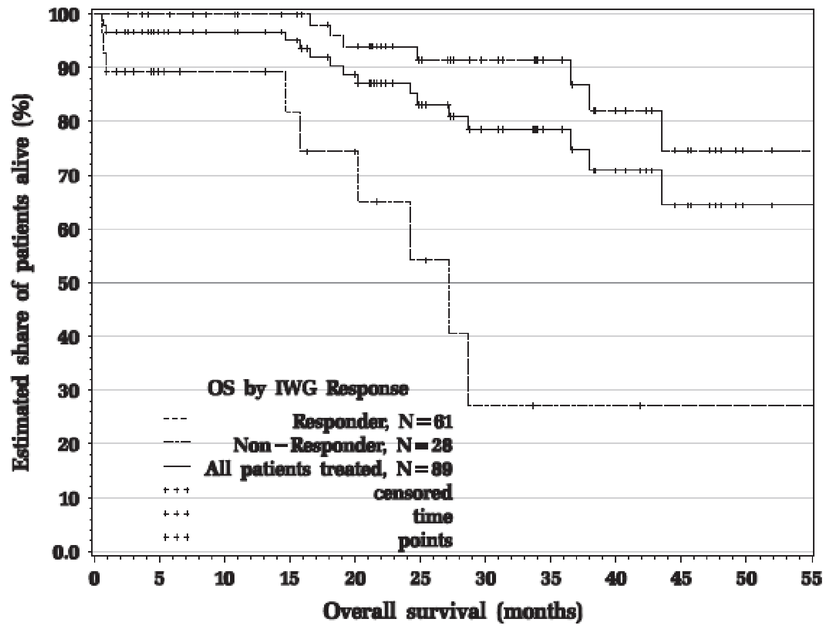
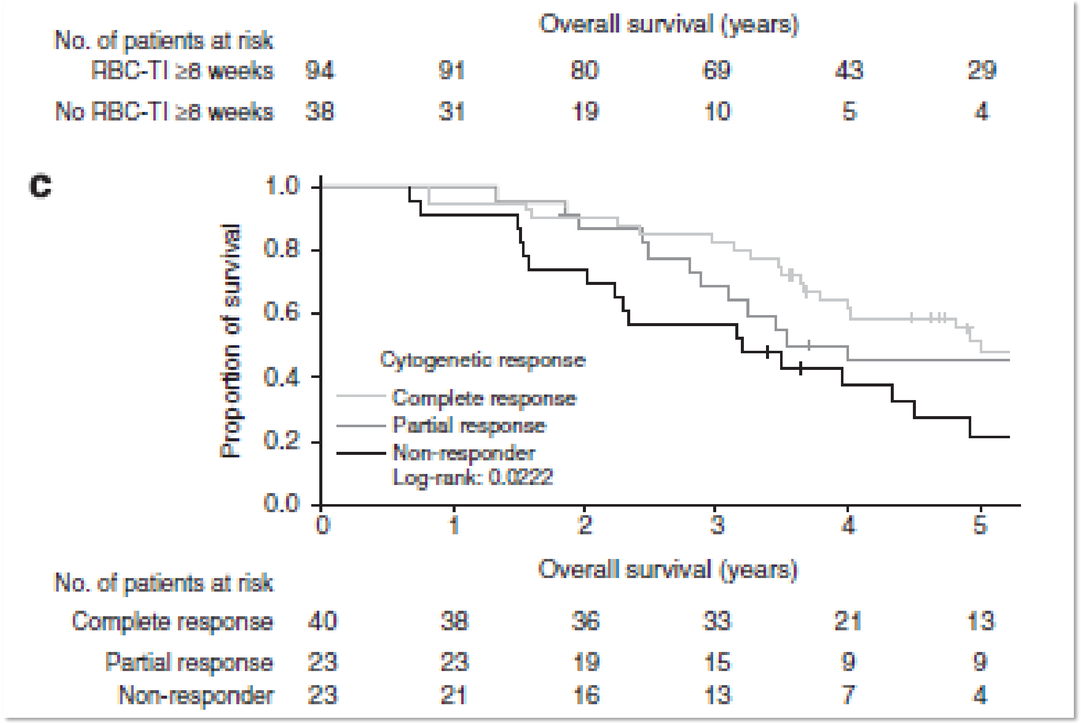


Figure 1. Kaplan–Meier plot showing overall survival of all patients treated and IWG-responders vs IWG-nonresponders.

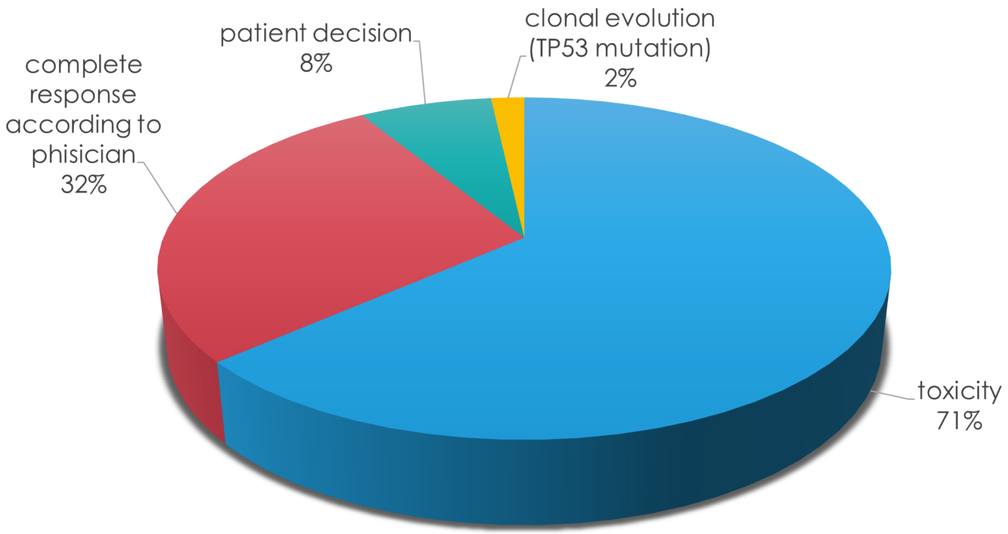
LE-MON 5 *Schuler E. et al. Leukemia 2016*



MDS 003 List et al, Leukemia 2014

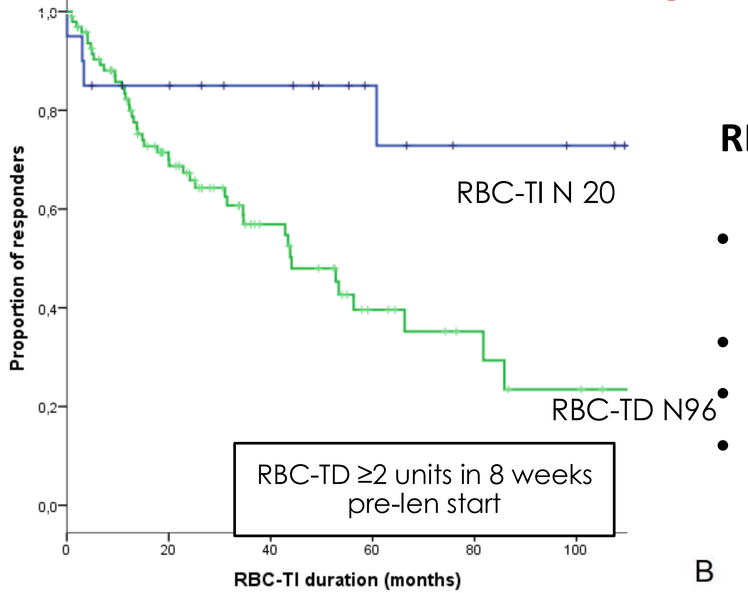
Retrospective study of lenalidomide discontinuation in patients with MDSdel(5q). A HARMONY Alliance study

Reason for lenalidomide discontinuation



46 patients were re-treated with lenalidomide for response loss and 56% achieved at least a hematological response (3 also a CCyR)

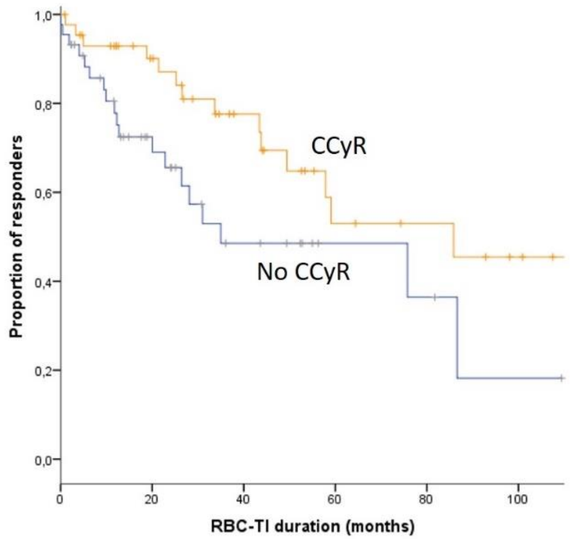
Median FUP from lenalidomide stop: 40 months (range 2-213)

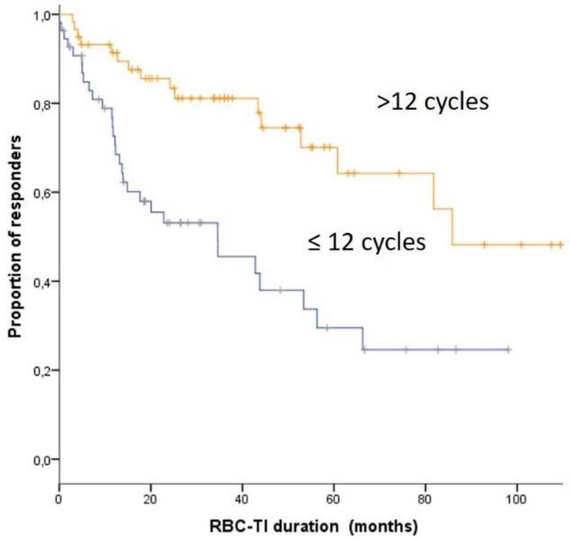


RBC-TI predictors In multivariate analysis:

- low transfusion burden before LEN start
- treatment ≥12 LEN cycles
- younger age
- higher Hb level at LEN withdrawal

B





median RBC-TI duration 56 months

Crisà et al., Leukemia 2024

RATIONALE

A prospective study is needed

- to assess the optimal duration of LEN treatment
- the depth of upfront response needed
- the presence/acquisition of somatic mutations during LEN treatment and after its discontinuation
- biological mechanism of maintenance of response after LEN discontinuation

TARGET POPULATION

Inclusion criteria

1.18 years of age or older

2.Eastern Cooperative Oncology Group (ECOG) 0-2

3.Diagnosis of MDS according to 2008 or 2016 WHO classification

4.**Cytogenetic analysis demonstrated an isolated del(5q) or a del(5q) with 1 additional abnormality, excluding chromosome 7 abnormalities**

5.IPSS-R very low, low or intermediate at lenalidomide treatment start

6.BM blast count at diagnosis and at study entry less than 5% , counted on BM aspirate.

7.Transfusion-dependent anemia before lenalidomide treatment

8.RBC-TI achievement with lenalidomide AND HB > 10 g/dl

9.Lenalidomide treatment duration >12 months

10.Adequate kidney function (creatinine clearance ≥30 mL/min)

11.Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study

12.Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening.

13.A signed informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.

Exclusion criteria

1.Diagnosis MDS with IPSS-R high or very high

2. Five per cent or more of blasts at (BM) aspirate at diagnosis or anytime during disease course

3. Peripheral blood (PB) blasts >1%

4. Del(5q) with more than 1 additional abnormalities, or chromosome 7 abnormalities, at diagnosis or anytime during disease course

5. Other treatments for MDS in addition to lenalidomide, excluding GCS-F for neutropenia induced by lenalidomide

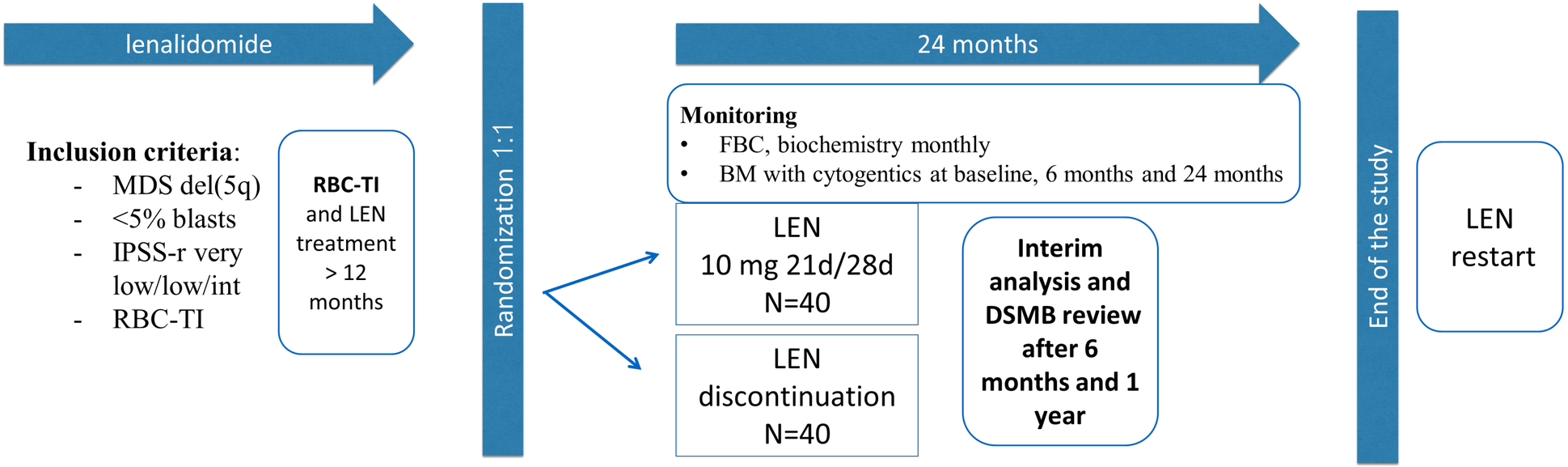
6. Prior chemotherapy or hypometilating agents for MDS

7.Pregnant or lactating female

Phase 2, multicenter, prospective,randomized study on lenalidomide discontinuation

Primary endpoint:
-RBC-TI duration+safety
Secondary endpoint:
- EFS, PFS , HRQoL, time to re-treatment

Exploratory endpoint:
-biological and clinical predictors of response duration after lenalidomide discontinuation
- clonal and microenvironment modifications during lenalidomide treatment and after discontinuation



Time plan

Expected duration of enrollment: 12-24 months
Experimental phase duration: 24 months (from randomization)
A subsequent follow-up will then continue until death for survival and disease progression monitoring.

Sponsor: INOC Candiolo • Coordinating PI: Elena Crisà Partnership: FISiM and QOL-ONE

PRIMARY END POINT

The study has two co-primary end points: RBC-TI rate at 2 years and safety.

-RBC TI rate at 2 years. We will compare the RBC-TI (absence of RBC transfusions in 8 consecutive weeks(24)) rate at 2 years in LEN continuation vs discontinuation arm. We hypothesize that the RBC TI rate at 2 years will be similar in the two arms of the trial by including only patients who received at least 12 cycles of LEN. RBC-transfusion need will be assessed monthly in both arms of the trial.

-Safety. Patients will be monitored for the occurrence of AEs (any hematological and non-hematological toxicity graded according to the NCI Common Toxicity Criteria, or disease progression) at every visit. We expect AEs to be less frequent in the discontinuation arm as compared to the continuation arm.

SECONDARY END POINTS

-EFS and disease progression: we will compare in the 2 arms of the trial EFS, PFS and CCyR loss rate. To get sequential cytogenetic data and intercept disease progression during follow up BM aspiration with morphological, immunophenotype and cytogenetics analysis will be performed after 6 months, 24 months (end of the study) and in case of a hematologic relapse

-*Time to retreatment.* Patients who will lose response during LEN discontinuation could be retreated with LEN according to Physician choice and we will assess response rate to LEN re-treatment and time to retreatment.

-HRQoL modifications at 2 years. We will explore the impact of LEN treatment and the possible advantages in LEN discontinuation on HRQoL. HRQoL will be assessed by EQ-5D(34), QOL-E and by HM-PRO tools at screening, at randomization and at each study visit (25, 26). These validated patient-reported outcome tools designed specifically to assess the impact of haematological malignancies on patients' HRQoL and symptoms are tailored to capture both the disease burden and the treatment's effects from the patient’s perspective.

EXPLORATORY END POINTS

1.to search for biological and clinical predictors of response duration after lenalidomide discontinuation

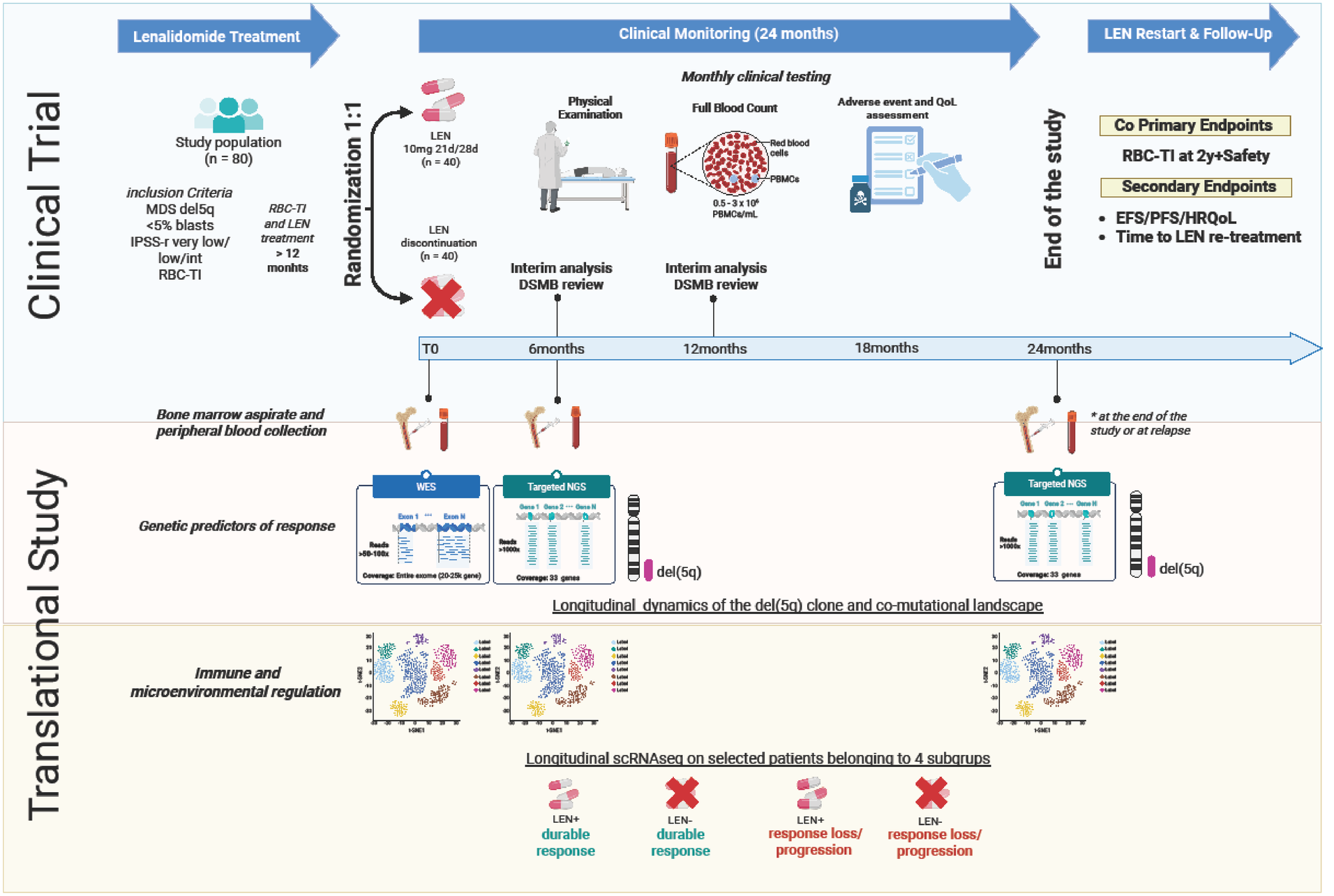
2.to explore clonal and microenvironment modifications during lenalidomide treatment and after discontinuation with correlative studies:

- whole exome sequencing (WES) on BM at baseline to identify potential predictors of the response duration at DNA level, outside the common alterations.

- NGS analysis on a panel of 30 genes commonly mutated in MDS on peripheral blood (PB) or bone marrow (BM) at baseline, 6 months and at the end of the study (24 months) to evaluate clonal evolution with or without lenalidomide

- Single cell RNA analysis on BM samples at baseline, 6 months and at the end of the study (24 months) to study microenvironment architecture and modifications during treatment and after lenalidomide discontinuation, and to assess changes in hemopoiesis both in del5q and WT clones.

- Study of cytokines and of changes in innate and adaptive immunity on peripheral blood during and after discontinuation of lenalidomide, comparing patients who maintain their response with those who lose response or experience disease progression



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Test/evaluation	Screening [a]	Baseline	Monthly +/-7 days	6 months +/- 1 month	24 months +/-1 month	Relapse [b]	End of study [c]
Informed consent	x						
demographics	x						
inclusion/exclusion criteria	x						
medical history	x						
concomitant medications	x	x	x	x	x	x	x
physical examination	x	x	x	x	x	x	x
ECOG	x	x	x	x	x	x	x
vital signs	x	x	x	x	x	x	x
CBC and differnetial	x	x	x	x	x	x	x
serum chemistry [d]	x	x	x	x	x		x
PB smear	x		x	x	x	x	x
Transfusion data collection	x	x	x	x	x	x	x
BM aspirate for morphology [e]	x			x	x	x	x
Immunophenotype on BM aspirate	x			x	x	x	x
BM cytogenetic [g]	x			x	x	x	x
NGS and correlative studies on PB	x			x	x	x	x
Single cell RNA analysis		x		x	x	x	x
QoL questionnaires	x	x	x	x	x	x	x
adverse event		x	x				x

1. Discontinuation from study treatment

- A patient in the continuation arm should discontinue lenalidomide treatment if any of the following occurs:
  - -inacceptable toxicity
  - -disease progression
- A patient in the discontinuation arm should restart lenalidomide treatment if any of the following occurs:
  - -Hemoglobin drop >2 g/dl or transfusion independence loss at any time after BM examination (to exclude disease progression)
  - - Loss of CCyR (according to Phisician choice)



Elena.crisa@inoc.it