FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

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Interruzione terapia Lenalidomide in MDS del5q

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Is it possible to stop lenalidomide in MDS del(5q) responding patients?

ARTICLE

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Transfusion independence after lenalidomide discontinuation in patients with del(5q) myelodysplastic neoplasm: a HARMONY Alliance study

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Lenalidomide (LEN) can induce red blood cell-transfusion independence (RBC-TI) in 60–70% of del(5q) myelodysplastic neoplasm (MDS) patients. Current recommendation is to continue LEN in responding patients until failure or progression, with likelihood of toxicity and a high cost for healthcare systems. This HARMONY Alliance study investigated the outcome of MDS del(5q) patients who discontinued LEN while RBC-transfusion independent. We enrolled 118 patients with IPSS-R low-intermediate risk. Seventy patients (59%) discontinued LEN for intolerance, 38 (32%) per their physician decision, nine (8%) per their own decision and one (1%) for unknown reasons. After a median follow-up of 49 months from discontinuation, 50/118 patients lost RBC-TI and 22/30 who underwent cytogenetic re-evaluation lost complete cytogenetic response. The median RBC-TI duration was 56 months. In multivariate analysis, RBC-TI duration after LEN discontinuation correlated with low transfusion burden before LEN therapy, treatment ≥ 12 LEN cycles, younger age and higher Hb level at LEN withdrawal. Forty-eight patients were re-treated with LEN for loss of response and 28 achieved again RBC-TI. These data show that stopping LEN therapy in MDS del(5q) patients who reached RBC-TI allows prolonged maintenance of TI in a large subset of patients.

Leukemia; https://doi.org/10.1038/s41375-024-02360-1

Is it possible to stop lenalidomide in MDS del(5q) responding patients?

WHO?

WHEN?

Retrospective study of lenalidomide discontinuation in patients with myelodysplastic syndrome harboring del(5q).

Aim of the study

To investigate the outcome of patients with del(5q) MDS RBC-TI who discontinue lenalidomide in RBC-TI response

Primary end point

RBC-TI duration

Secondary end point

- Event free survival (events included RBC-TI loss, disease progression, lenalidomide re-start or death)
- overall survival
- progression free survival
- time to acute myeloid leukemia
- response rate to lenalidomide re-challenge
- biological and clinical predictors of response duration after discontinuation

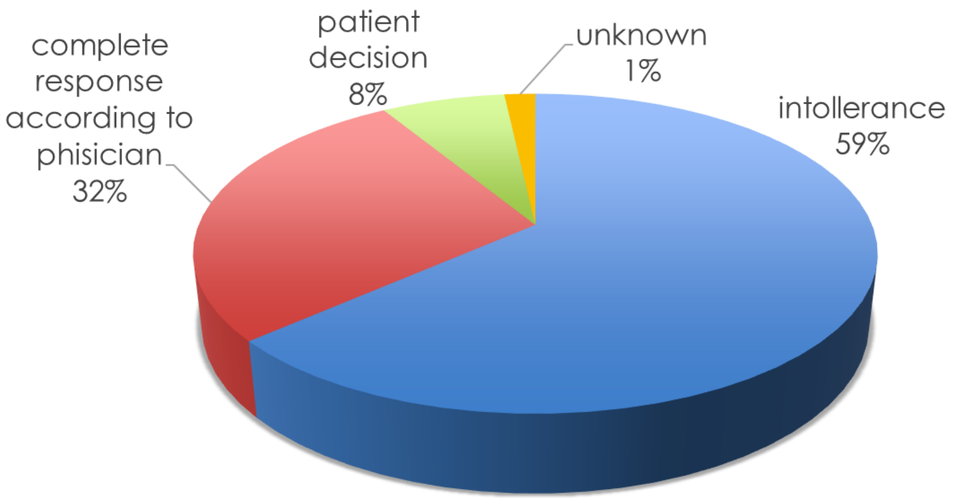
Patients characteristics			
At lenalidomide start			
		N°	**%**
Patients		118	
Gender	Male	24	20%
	Female	94	80%
Age (years)	median (range)	77 (42-93)	
IPSS	low	59	56%
	intermediate I	46	44%
IPSS-R	very low	26	22%
	low	68	58%
	Intermediate I	24	20%
Bone marrow blasts %	median (range)		2 (0-5)
RBC-transfusion burden >4 units/8 wks	no	21	17%
	yes	97	82%
N of lenalidomide cycles	median (range)	12 (1-72)	
At lenalidomide discontinuation			
Age (years)	median (range)	77 (33-97)	
Absolute Neutrophils Count x10^9/l	median (range)	1.51 (0.19-5.1)	
Hemoglobin g/dl	median (range)	12 (7.8-15.5)	
Platelets x10^9/l	median (range)	150 (3-386)	
Bone marrow blasts %	median (range)	1(0-5)	
RBC transfusion-dependence		0	0 %
Cytogenetic response	CCyR (95 evaluable patients)	45	47%
	PCyR (92 evaluable patients)	15	16%

- 85 patients (71%) had experienced hematological or non-hematological treatment-related AEs during treatment.
- Seventy-nine (67%) AEs were grade1-2 and 59 (50%) were grade 3-4

WHO? Patients characteristics

Inclusion criteria

- Diagnosis of MDS according to 2008 or 2016 WHO classification with isolated del(5q) or a del(5q) with 1 additional abnormality, excluding chromosome 7 abnormalities
- IPSS-r very low, low or intermediate at lenalidomide treatment start
- RBC-TI achievement with lenalidomide
- Lenalidomide stop in RBC-TI



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WHO? Patients characteristics

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	yes	97	82%
During treatment			
Best response to lenalidomide	RBC-TI	55	47%
	RBC-TI +CCyR	48	40%
	RBC-TI +PCyR	15	13%
Hematological toxicity	Grade 1-2/3-4	36/27	30/23%
Non-hematological toxicity	Grade 1-2/3-4	43/32	36/27%
Dose reduction		42	36%
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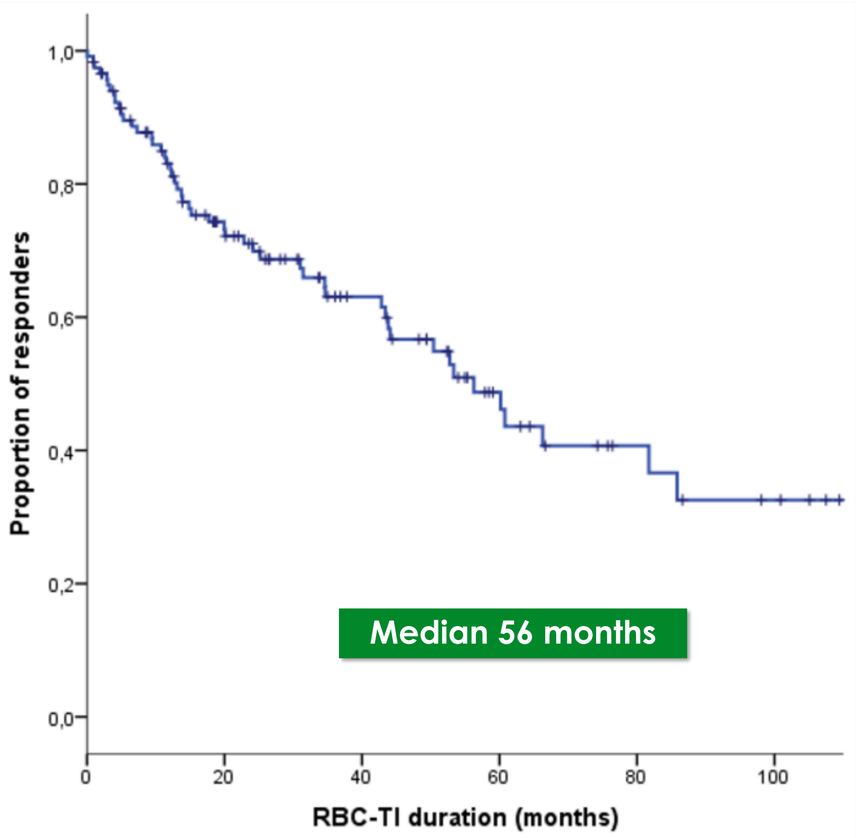
Median FUP from lenalidomide stop: 49 months

A.



Median 56 months

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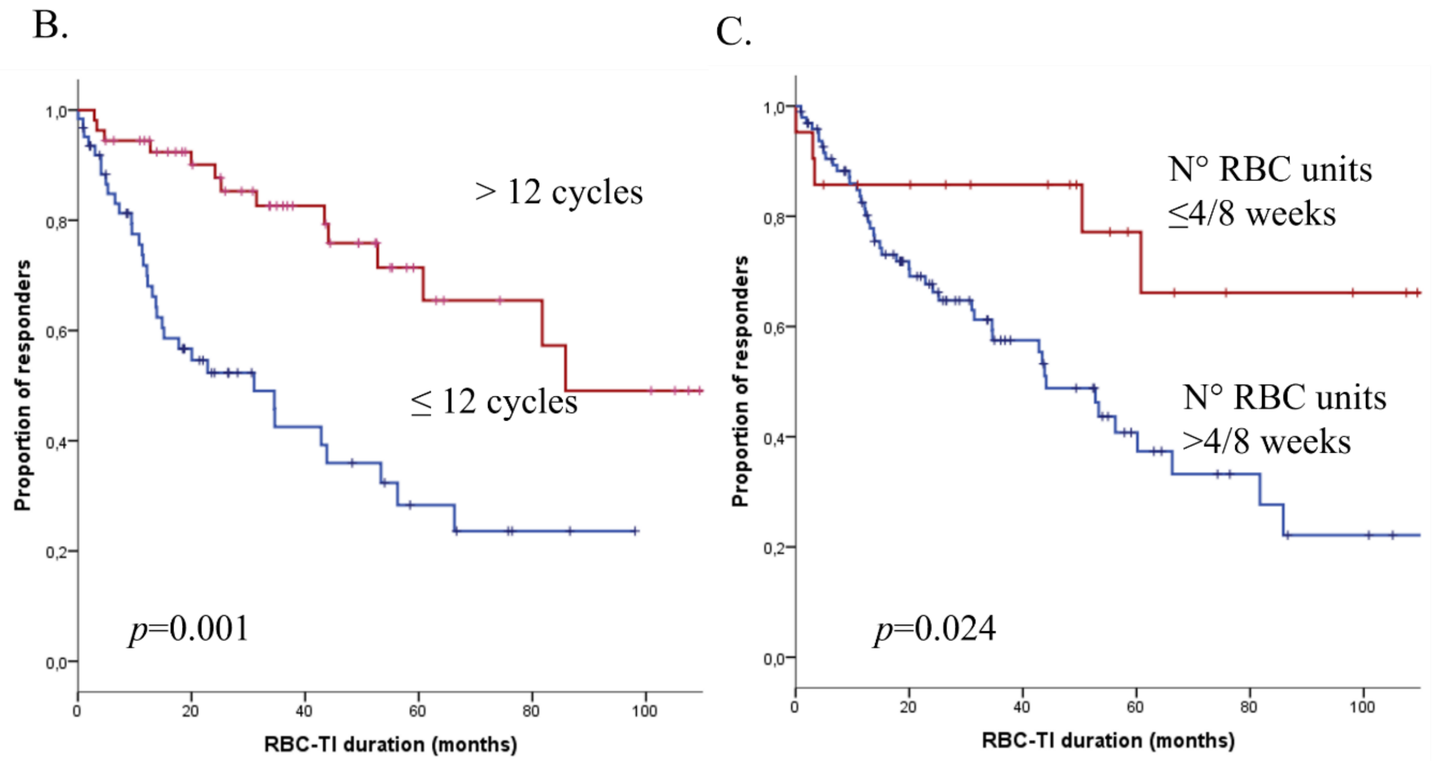
RBC-TI duration after lenalidomide discontinuation

50/118 patients lost RBC-TI



- 70% of the patients treated for >12 LEN cycles or with low transfusion burden at len start were still RBC-TI at 5 years.
- 67% (28/42) patients re-treated with lenalidomide for response loss achieved again RBC-TI

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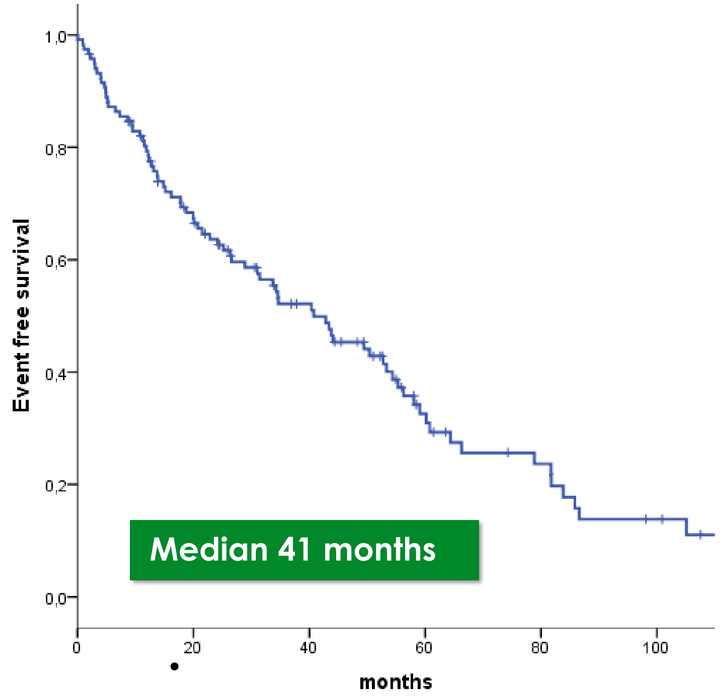
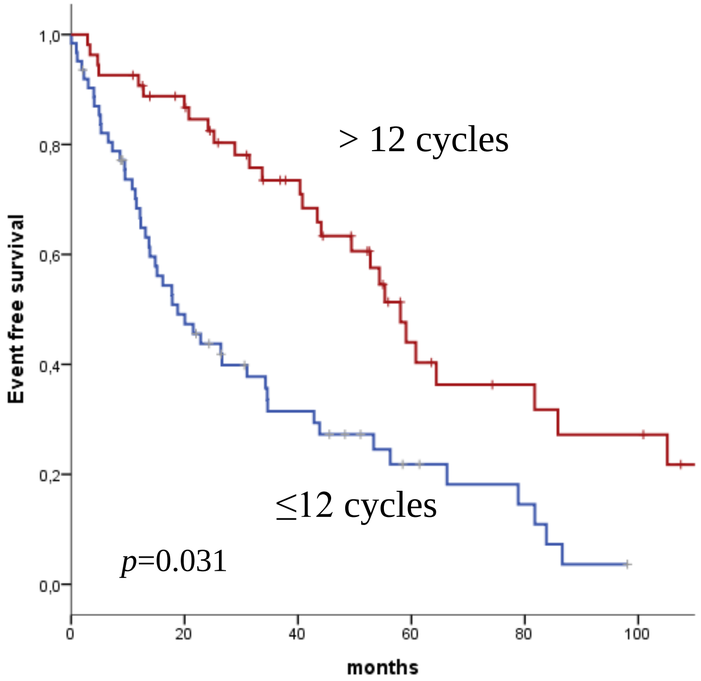
Event free survival (EFS) after lenalidomide discontinuation





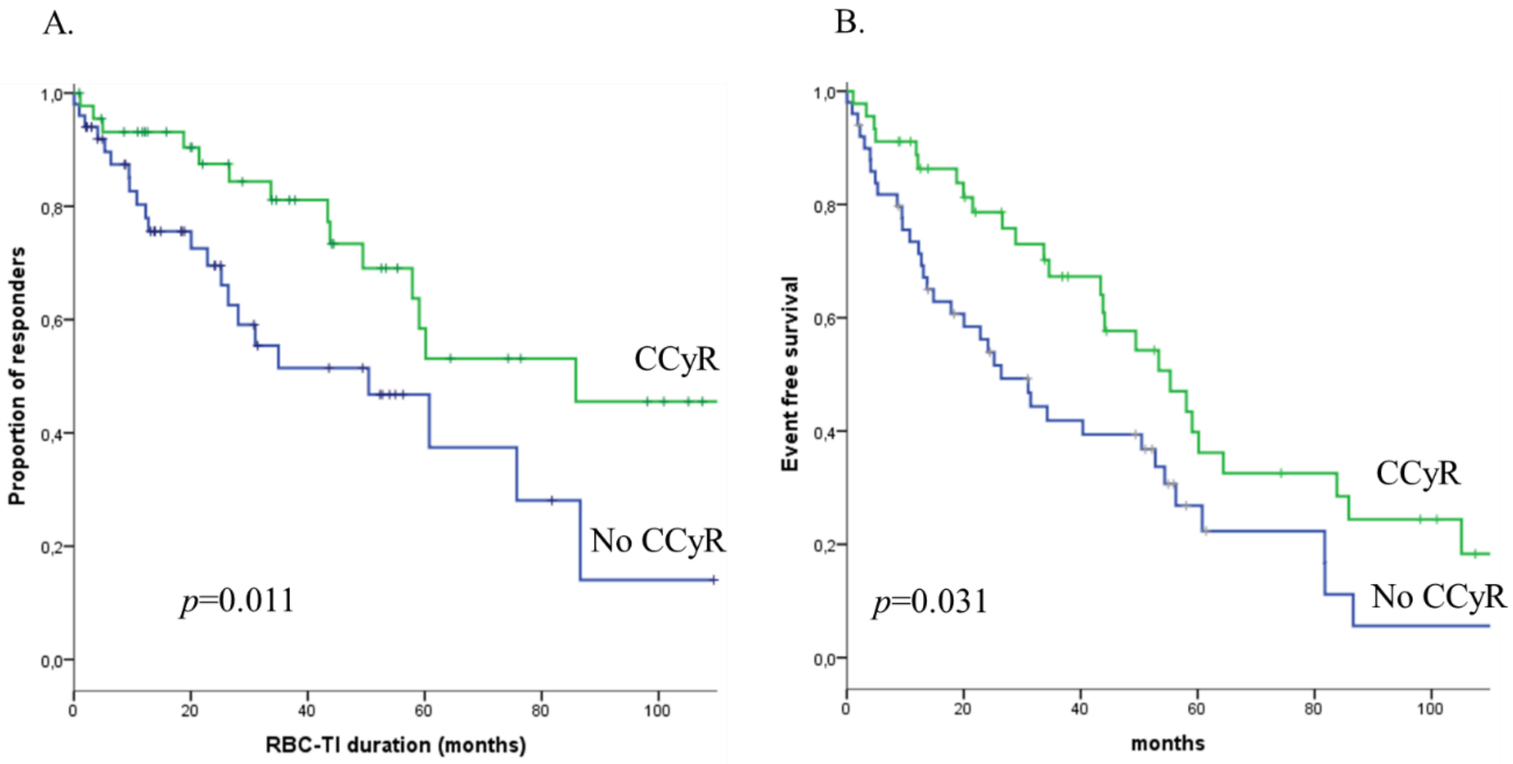
- **23 patients (19%) progressed to**
  - high risk MDS (n=15)
  - AML (n=8)

  ->5 years PFS rate was 83%.

- **44 patients (38,3%) died**

-> median OS after LEN discontinuation was 78.4 months

RBC-TI duration and EFS according to complete cytogenetic response



- Lack of longitudinal cytogentic data
- 22/30 who underwent cytogenetic re-evaluation lost complete cytogenetic response

Prognostic factors for RBC-TI loss and EFS on multivariate analysis

Prognostic factors for RBC-TI loss on multivariable analysis.

Variables	HR	95,0% CI		
		Lower	Upper	p value
Age *	1.04	1.00	1.07	0.024
RBC unit/8 weeks >4 at lenalidomide start	3.34	1.18	9.47	0.024
Lenalidomide cycles>12	0.34	0.18	0.65	0.001
Hemoglobin level at lenalidomide stop*	0.86	0.71	1.03	0.092

Prognostic factors for EFS on multivariable analysis.

Variables	HR	95,0% CI		
		Lower	Upper	p value
Age at diagnosis*	1.04	1.01	1.07	0.005
RBC unit/8 weeks >4 at lenalidomide start	1.28	1.05	1.56	0,013
IPSS-R very low vs low/intermediate	0.33	0,16	0.70	0.004
Lenalidomide cycles>12	0.55	0.32	0.95	0.031
Hemoglobin level at lenalidomide stop*	0.82	0.69	0.98	0.028

Variables included in the model were IPSSr, CCyR at len discontinuation, transfusion dependence before len start, number of len cycles received; only significant variables are shown

WHO?

- MDS del(5q) +/- one abnormality at IPSS-R very-low to intermediate
- Achievement of RBC-TI on lenalidomide
- better if early treatment with lenalidomide (low transfusion burden at len start)

WHEN?

- After at least 12 cycles of treatment
- After achievement of CCyR?

Open questions

- the optimal duration of LEN discontinuation
- 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

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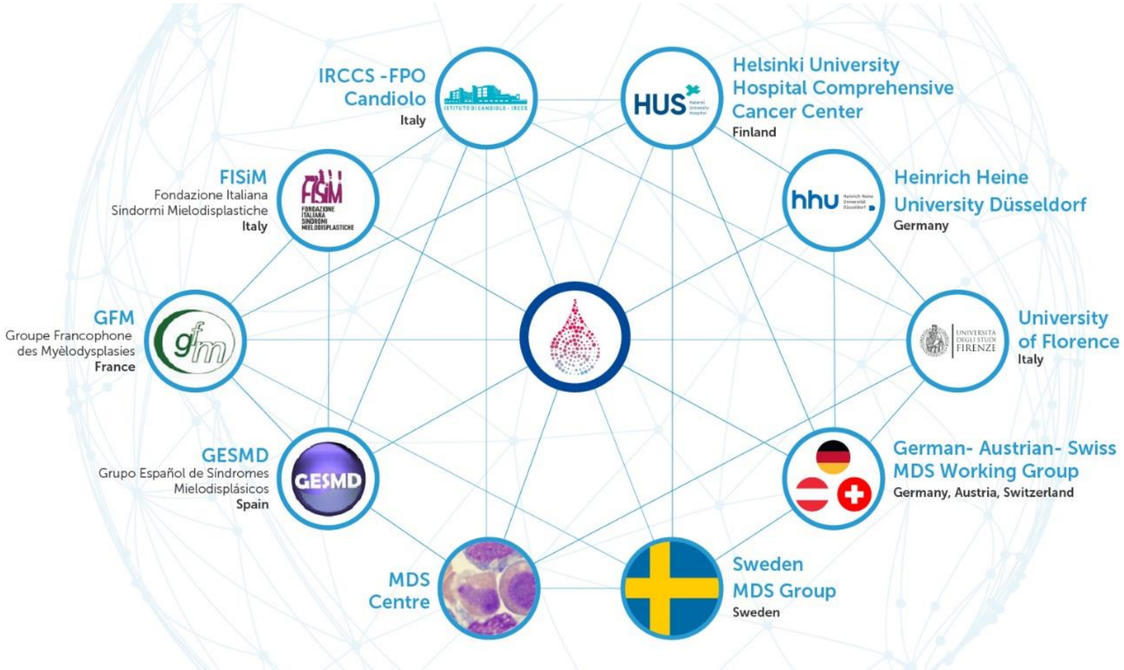
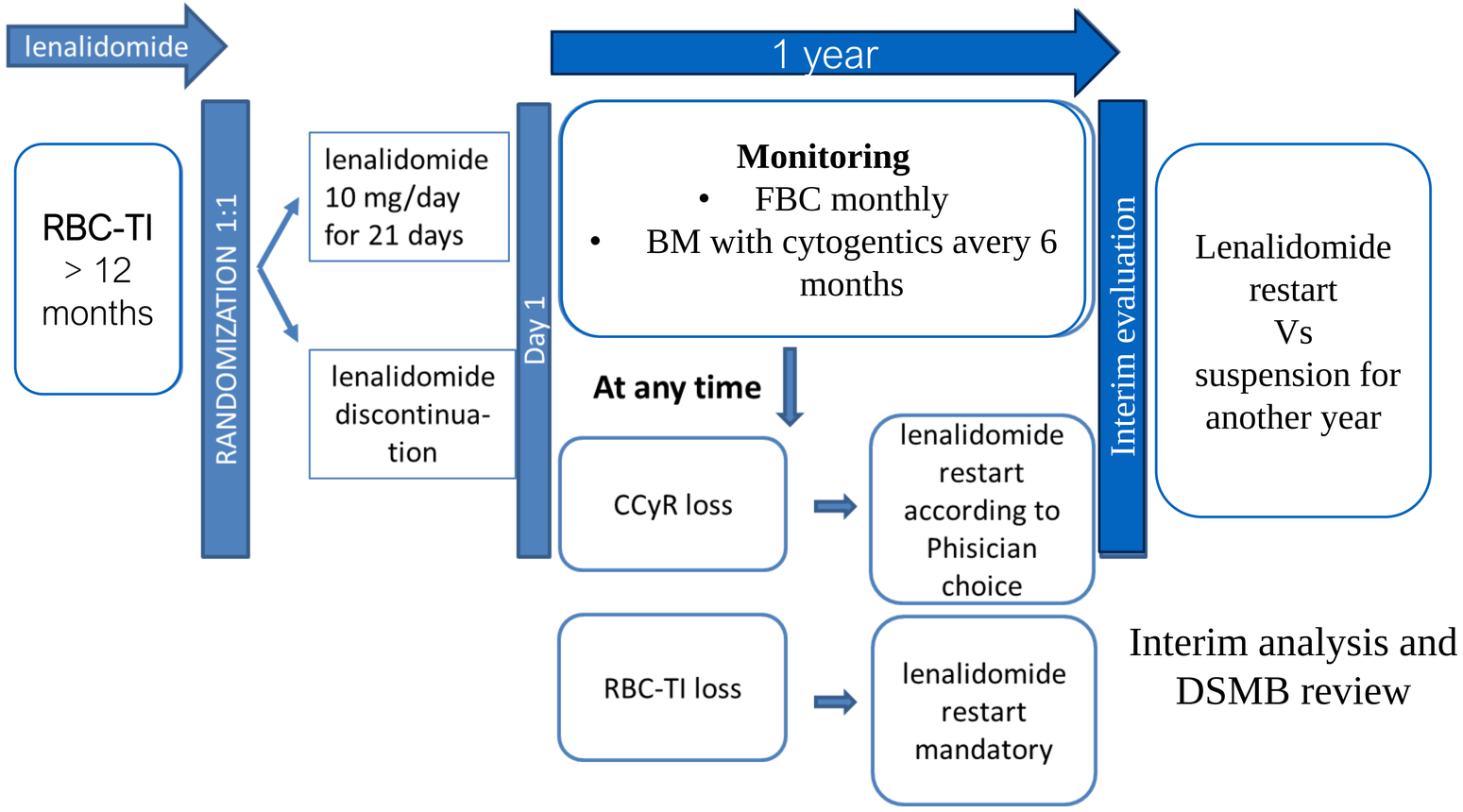


STUDY DESIGN: **Phase 2, multicenter, prospective,randomized study**

Primary endpoint: composite biological+clinical
-biological mechanism of disease control /clonal evolution (single cell RNA /WES)
-RBC-TI duration

Inclusion criteria:

- MDS del(5q)
- <5% blasts
- IPSS-r very low/low/int
- RBC-TI



Interim analysis and DSMB review

- Expected duration of enrollment: 36 months
- 80-100 patients

Comparison LEN continuation vs discontinuation with syntetic data

- Discontinuation arm: retrospective data already collected
- Continutaion arm: data from FISIM registry (102 patients del5q patients treated with LEN, response status to be checked)

-> balanced with syntetic data