IMPACT IN RESPONSES AND OUTCOMES OF SOMATIC MUTATIONS IN PATIENTS WITH DEL(5Q) MDS TREATED WITH LENALIDOMIDE PRIOR TO TRANSFUSION DEPENDENCY – MOLECULAR RESULTS FROM THE SINTRAREV CLINICAL TRIAL

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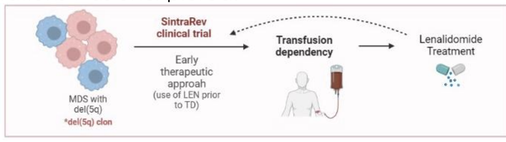
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Introduction

Lenalidomide (Len) is the **standard treatment** for patients with **myelodysplastic syndromes and deletion 5q** (del(5q)-MDS) who are red blood cell **transfusion dependent** (TD).

Background

A phase 3 clinical trial (**SintraRev**) demonstrated better efficacy of **early treatment** with **Len** in **anemic del(5q)-MDS patients** prior to TD, but the impact of somatic mutations was unexplored.



Objectives

Analyze the **mutational profiles** of **non-TD del(5q)-MDS patients** treated with **Lenalidomide** or Placebo (Pcb).

Study the **impact of somatic mutations** on patients **responses** and **outcomes.**

Methods

SintraRev trial

Phase III trial
Multicenter
Randomized & Double blind
Placebo-controlled

61 patients with MDS-del(5q)

Patients diagnosis between 2010 to 2018
Bone marrow samples at inclusion, Week 12 and every 24 weeks until last follow-up
Median follow-up was **60.6 months**

Molecular profile analysis by Next Generation Sequencing (NGS)

Genetic Sequencing

Molecular data available from **47 patients**
Collected **data** of **TD occurrence, AML-progression** and **death.**
SPSS Statistics v25 and **R v4.0.2** for analyses

Molecular results and statistical analyses

Data Analysis

Results

Clinical and molecular features of the SintraRev trial patients are shown in ***Table 1.*** At baseline, **41 somatic mutations** were detected (24 in Len arm and 17 in Pcb, with comparable clinical and molecular features).

The most frequent mutated genes were ***SF3B1*** (25,5%, n=12) and ***TP53*** (21,3%, n=10). The main characteristics of these patients are shown in ***Table 2***.

Results in terms of **responses**, **TD** and **AML-transformation** for these two groups are shown in ***Table 3.***

Summary

Treatment with **low-dose Len** in **transfusion independent del(5q)-MDS** achieved **cytogenetic** and **erythroid responses** in all ***SF3B1* mutated** patients and **lower incidence** of **TD** and **AML- transformation.**

***TP53* mutation** was associated with **lower response rates** to Len but with **similar incidence** of **AML-transformation** than in Pcb group.

Conclusion

Early administration of **Len** in **del(5q)-MDS** patients **without TD** may be an **effective therapeutic approach** with a manageable **safety** profile **regarding clonal evolution.**

	Placebo (n=21)	Lenalidomide (n=40)
Gender, n (Female/Male)	18/3	32/8
Age (years), median (range)	71.9 (64.7-80.7)	72.2 (65-82.4)
Hb, g/dL	9.8 (8.9-10.2)	9.8 (9.3-10.7)
Platelets, x10^9/L	272 (200-327)	238 (171-312)
Neutrophils, x10^9/L	2.2 (1.5-2.7)	2.1 (1.5-3.2)
Bone marrow blasts, %	2 (0-3)	1.5 (0.6-3)
WHO 2017, n (%)		
MDS-EB-1	1 (4.8%)	2 (4.9%)
MDS del(5q)	20 (95.2%)	38 (95.1%)
IPSS		
Low	14 (66.7%)	29 (72.5%)
Intermediate 1	7 (33.3%)	11 (27.5%)
IPSS-M		
Very low	3 (16.7%)	5 (17.2%)
Low	13 (72.2%)	20 (69%)
Moderate low	2 (11.1%)	2 (6.9%)
Moderate high	0 (0%)	2 (6.9%)
Cytogenetic abnormalities, n (%)		
Isolated del(5q)	19 (90.4%)	35 (87.5%)
Del(5q) plus additional abnormalities	2 (9.6%)	5 (12.5%)
NGS data at baseline		
NGS at BSL	18 (85.7%)	29 (72.5%)
Median mutation per patient, n (range)	1 (0-3)	1 (0-3)
patients without mut, n (%)	7 (38.9%)	10 (34.5%)
patients with 1 mut, n (%)	6 (33.3%)	15 (51.7%)
patients with 2 or more mut, n (%)	5 (27.8%)	4 (13.8%)
TP53 mutated patients, n (%)	5 (27.8%)	5 (17.2%)
SF3B1 mutated patients, n (%)	4 (22.2%)	8 (27.6%)
DNMT3A mutated patients, n (%)	2 (11.1%)	7 (24.1%)

Table 1*:* Clinical and molecular features of patients included in the SintraRev clinical trial.

Characteristics	Total (n=47)	SF3B1 Mut (n=12)	SF3B1 WT (n=35)	TP53 Mut (n=10)	TP53 WT (n=37)
Age (years), median (range)	72 (67-80)	71.5 (61.7-77.5)	72 (67-81)	**79 (77.5-82.2)**	71 (64.5-77)
Gender, n (Female/Male)	38/9	9/3	29/6	8/2	30/7
Time from diagnosis (months). Median (Range)	5 (2-15)	2.5 (2-16.5)	6 (1-15)	3.5 (2-11.5)	6 (1-17.5)
Ferritin (ng/ml), median (range)	169 (100-286)	**287 (114-396)**	155 (99-241)	178 (98-344)	163 (103-271)
Hb (g/dL), median (range)	9.9 (9-10,4)	9.9 (8.7-10.4)	9.9 (9.1-10.4)	**9.7 (9.1-10.2)**	10 (8.9-10.4)
Neutrophils, x10^9/L, median (range)	2.06 (1.48 -2.7)	1.86 (1.52-2.49)	2.1 (1.44-3.07)	**1.64 (1.27 – 2.5)**	2.1 (1.5-2.9)
Platelets, x10^9/L, median (range)	235 (177 – 323)	292 (228-350)	227 (171-299)	230 (191 – 331)	235 (175-324)
Bone marrow blasts, %, median (range)	1.78 (0 – 3)	2 (1-2)	1.5 (0-3)	1.5 (0-4)	2 (0-2.75)
Patients with RS in BM, n (%)	12 (35.3)	**6 (60)**	6 (25)	0	0
IPSS risk category, n (%)					
Low	34 (72.3)	6 (50)	28 (80)	7 (70)	27 (73)
Intermediate-1	13 (27.7)	6 (50)	7 (20)	3 (30)	10 (27)
IPSS-R risk category, n (%)					
Very Low	21 (44.7)	5 (41.7)	16 (45.7)	4 (40)	17 (45.9)
Low	24 (51.1)	7 (58.3)	17 (48.6)	5 (50)	19 (51.4)
Intermediate	2 (4.3)	0	2 (5.7)	1 (10)	1 (2.7)
Cytogenetics, n (%)					
Isolated del(5q)	42 (89.4)	11 (91.7)	31 (88.6)	8 (80)	34 (91.9)
Any other abnormalities with del(5q)	5 (10.6)	1 (8.3)	4 (11.4)	**2 (20)*** (del(11q) & -Y).	3 (8.1)

Table 2*:* Main characteristics of patients with ***SF3B1*** and ***TP53*** mutations compared to wild-type patients

Somatic mutations impact on response and outcomes

RESPONSES	*SF3B1* Mut	*TP53* Mut
Erythroid response	100%	40% ↓↓
Cytogenetic response	100%	60% ↓↓
Duration of response	Shorter than wild type	Similar than wild type
Transfusion Dependence	37,5% Len & 100% Pbo	80% Len & 60% Pbo
Time to Transfusion Dependence (median)	21.8 months Len & 6.3 months Pbo	12.6 months Len & 6.6 months Pbo
AML progression	25% Len & 50% Pbo	20% Len & 20% Pbo
Time to AML progression (median)	24 months Len % 16 months Pbo	NR/NR

Table 3*:* Results in terms of responses, TD and AML progression in ***SF3B1*** and ***TP53*** mutated patients.

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