LENALIDOMIDA EN EL SMD 5Q-

EXPERIENCIA ESPAÑOLA

M. Díez Campelo

Hematología
HOSPITAL UNIVERSITARIO
SALAMANCA

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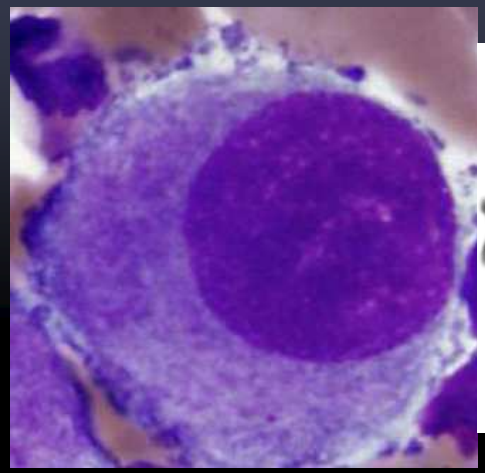
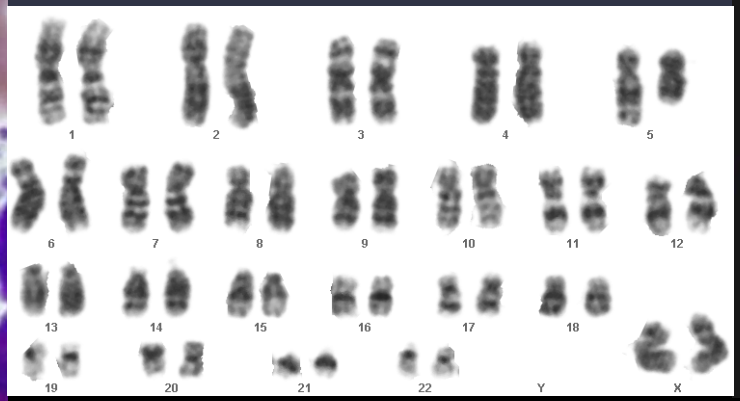
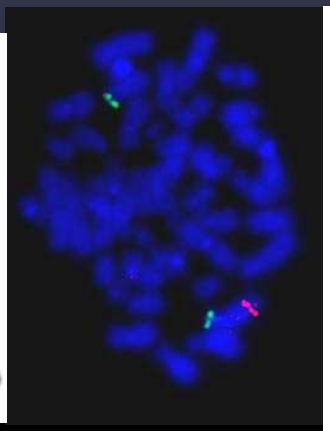
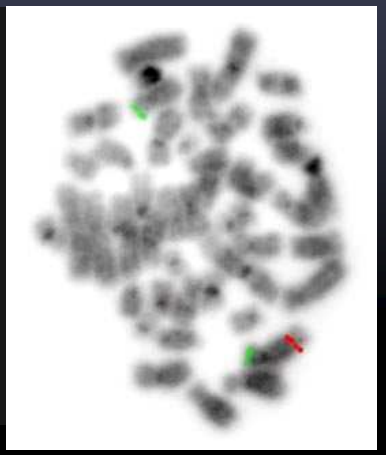
15-30% MDS









Sole anomaly or in addition to 1 cytogenetics aberrations ⇧ OS[1]

Anemia[2] (78%)

Transfusion dependency (40%): Lenalidomide

Transfusion independency (60%)

[1]Mallo et al, 2011

[2]Germing et al, 2012

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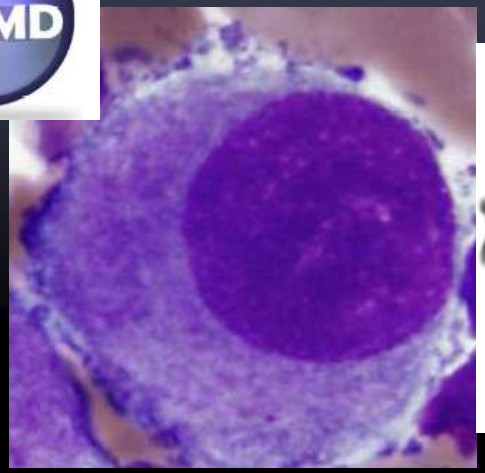

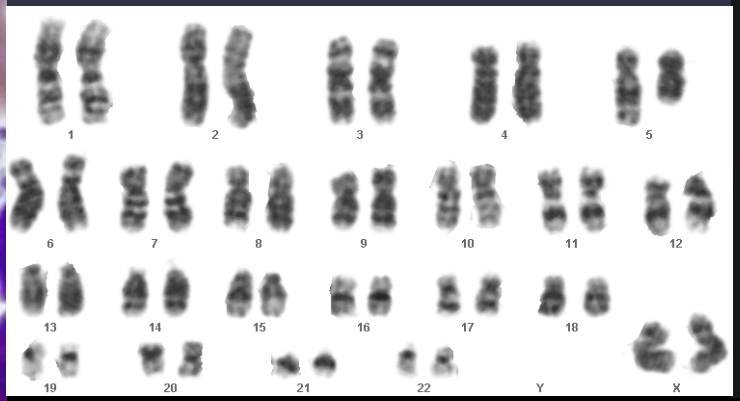

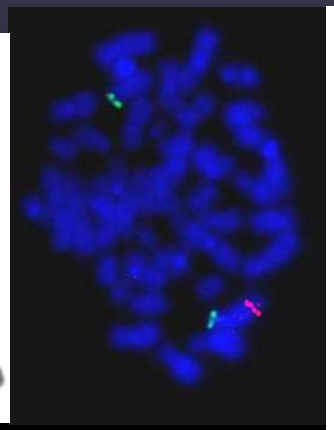

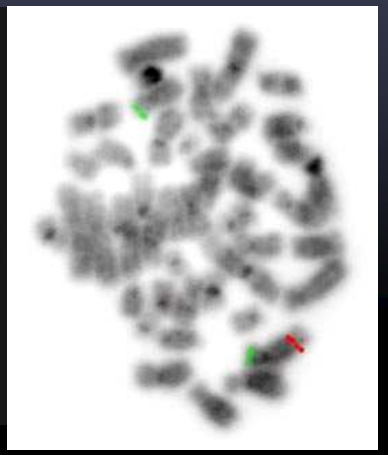

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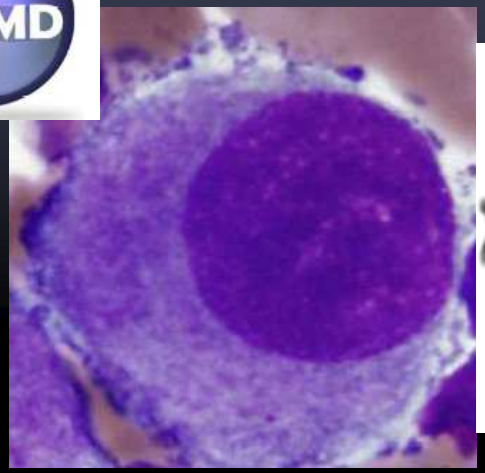

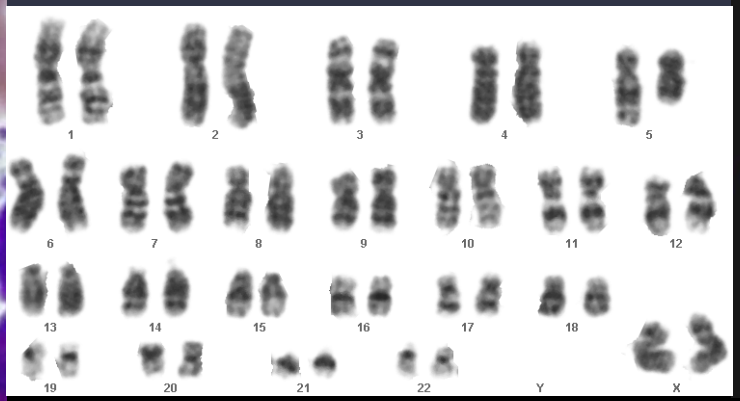

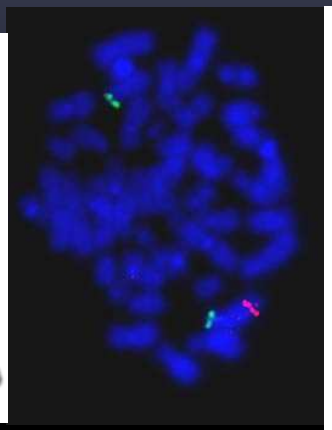

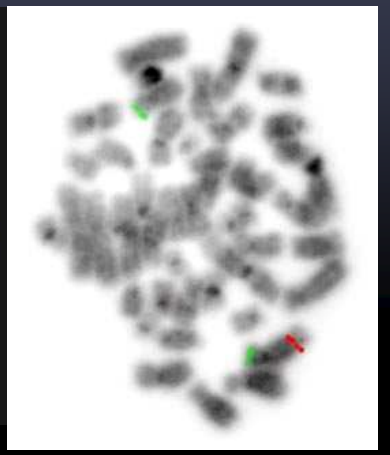

Lenalidomide and predictors of response in MDS del(5q)

Clinical predictors[1]: platelets, time from diagnosis to Lena

Genetic: *TP53 mutations*[2, 3] and lower complete cytogenetic responses

No other genetic predictors of response

[1]Fenaux et al, 2012

[2]Jädersten et al, 2011

[3]Bally et al, 2012

bjh research paper

Response to lenalidomide in myelodysplastic syndromes with del(5q): influence of cytogenetics and mutations

Mallo et al, 2013

Aims

- Molecular characterization (by conventional cytogenetics, SNP arrays and sequencing) of MDS with 5q- for those who will receive lenalidomide treatment

- To determine genetic and clinical differences between responders and non responders

Patients

- **52 samples with 5q deletion by cytogenetics or FISH**
- **DNA sample at diagnosis or prior treatment:**
  - **Tumoral:**
    - Bone marrow (n=49)
    - Peripheral blood (PB) (n=3)
  - **Control:**
    - CD3+ lymphocytes from PB (n=29)
- **Response evaluation:**
  - Hematological response (n=48, 92.3%):
    - **Responder** (complete or partial), n=37 **(77%)**
    - **Non responder** (non response/stable disease or progression), n=11 **(33%)**
  - Cytogenetics response (n=38, 73.1%):
    - Complete, n=12 **(31%)**
    - Partial, non response, progression, n=26

Mallo et al, 2013

Methods

- **Genomic array (n=52):**
  - Genome-Wide Human SNP Array 6.0 (Affymetrix®)
- **Mutational screening (n=43-45)** for:
  - *CBL* (exons 8-9; n=43)
  - *TET2* (exons 4-11; n=44)
  - *ASXL1* (exon 12; n=43)
  - *IDH1* (exon 4; n=44)
  - *IDH2* (exon 4; n=43)
  - *TP53* (exons 5-8; n=45)
- **Clinical data:** age, sex, PB counts, BM blasts, FAB and WHO 2001 diagnosis, lenalidomide treatment response, overall survival (OS), AML evolution

Results (cytogenetic analysis)

	Conventional cytogenetics	SNP *array*
Isolated 5q-	38	32
5q- + 1	6	10
Complex (5q- + ≥2)	4	10
Normal*	2	0
No metaphases*	2	0

Additional alterations in 26.3%

*FISH 5q positive

Most losses were verified by **FISH** with hand-made (BACs) or commercial probes

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Results (cytogenetics *vs.* response)

- **Conventional cytogenetics**

	Responder	Non responder	
0-1 alterations	33	5	***P*=0.020***
≥ 2 alterations	4	6	

- **Genomic SNP microarray**

	Responder	Non responder	
0-1 alterations	25	5	***P*=0.288***
≥ 2 alterations	12	6	

- Neither of them related to AML progression

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Results (mutations *vs.* response)

- **Mutational screening**

	Mutated cases
CBL	1 (2.3%)
IDH1	0 (0.0%)
IDH2	1 (2.3%)
ASXL1	0 (0.0%)
TET2	8 (18.2%)
TP53	5 (11.1%)

Mallo et al, 2013

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TP53	5 (11.1%)

- ***TET2***
  - No correlation with hematological or cytogenetics response
  - No related with OS or progression

- ***TP53***
  - Trend to correlation with hematological response (***P*=0.061**)
  - No relation with cytogenetics response (*P*=0.150). None of the mutated cases achieved complete cytogenetics response
  - No correlation with karyotypic complexity, OS or AML evolution

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Predictors of response in Lena TD patients

Table I. Clinical data for the global series, lenalidomide responders and non-responders patients.

Characteristic	Global series (n = 52)	Responders (n = 37)	Non-responders (n = 11)	P value
Age, median, Q1–Q3 (years)	75·5 (60·0–80·0)	75·0 (62·5–80·0)	60·0 (47·0–80·0)	0·424
Sex, male/female	13/39	9/28	3/8	1·000
FAB subtype				
RA	43	30	11	0·442
RARS	2	2	0	
RAEB	7	5	0	
WHO subtype (2001)				
RA and '5q- Syndrome'	35	27	5	0·144
RCMD/RCMD-RS/RAEB-1	17	10	6	
Haemoglobin, median, Q1–Q3 (g/l)	93 (79–103)	95 (81–102)	91 (80–108)	0·659
Absolute neutrophil count, median, Q1–Q3 ($\times 10^9$/l)	1·9 (1·3–2·6)	2·0 (1·4–2·6)	1·1 (0·9–2·9)	0·167
Platelet count, median, Q1–Q3 ($\times 10^9$/l)	295·5 (181·8–361·8)	314·0 (205·5–438·5)	240·0 (120·0–274·0)	**0·023**
Bone marrow blast count, median, Q1–Q3 (%)	2·0 (1·0–4·0)	2 (1–4)	2 (0–4)	0·693
IPSS risk group				
Low/Int-1	48	33	11	1·000
Int-2/High	1	1	0	
Duration of MDS before treatment, median, Q1–Q3 (months)	5·5 (1·8–19·1)	5·7 (1·8–19·9)	5·0 (1·5–10·7)	0·540
Number of aberrations by CC				
Normal/NM/5q-	42	33	6	**0·020**
5q- + ≥1	10	4	5	
Aberrant metaphases, median, Q1–Q3 (%)	78·6 (42·1–93·0)	74·7 (45·3–91·7)	80·0 (42·1–88·0)	0·953
Number of aberrations by SNP-A				
5q-	32	25	5	0·288
5q- + ≥1	20	12	6	
TET2 status				
Mutated	8	6	1	1·000
Unmutated	36	26	7	
TP53 status				
Mutated	5	2	3	0·061
Unmutated	40	30	6	
5q deletion size, median, Q1–Q3 (Mb)	69·7 (62·3–73·7)	69·8 (63·6–76·0)	70·6 (58·9–71·0)	0·854

Mallo et al, 2013

Predictors of response in Lena TD patients

Table III. Clinical data according to transfusion independence achievement.

Characteristic	TI – responders (n = 29)	TI – non-responders (n = 8)	P value
Age, median, Q1–Q3 (years)	78·0 (72·5–80·0)	61·5 (47·0–79·0)	0·088
Sex, male/female	5/24	3/5	0·332
FAB subtype			
RA	25	8	1·000
RARS	1	0	
RAEB	3	0	
WHO subtype (2001)			
RA and '5q- Syndrome'	26	7	0·235
RCMD/RCMD-RS/RAEB-1	0	1	
Haemoglobin, median, Q1–Q3 (g/l)	87 (81–99)	87 (76–102)	0·796
Absolute neutrophil count, median, Q1–Q3 ($\times 10^9$/l)	2·2 (1·5–2·9)	2·4 (1·1–3·3)	0·970
Platelet count, median, Q1–Q3 ($\times 10^9$/l)	322 (239·5–379·5)	177·5 (73·5–241·5)	**0·018**
Bone marrow blast count, median, Q1–Q3 (%)	2·0 (1·0–4·0)	2·0 (1·0–4·0)	0·969
IPSS risk group			
Low/Int-1	26	7	0·235
Int-2/High	0	1	
Duration of MDS before treatment, median, Q1–Q3 (months)	10·7 (2·5–21·3)	1·95 (1·3–5·5)	0·101
Number of aberrations by CC			
Normal/NM/5q-	26	4	**0·027**
5q- + ≥1	3	4	
Aberrant metaphases, median, Q1–Q3 (%)	69·4 (40·0–84·1)	85·7 (42·8–100·0)	0·185
Number of aberrations by SNP-A			
5q-	20	3	0·215
5q- + ≥1	9	5	
TET2 status			
Mutated	6	0	0·553
Unmutated	19	5	
TP53 status			
Mutated	2	1	0·501
Unmutated	22	5	
5q deletion size, median, Q1–Q3 (Mb)	69·4 (61·0–73·3)	70·7 (69·5–78·5)	0·090

Mallo et al, 2013

Predictors of response in Lena TD patients

Multivariante analysis

Outcome	Variables	OR (95% CI)	*P* value
Haematological response	Karyotypic complexity ($\geq$2 aberrations vs. 0–1)	4·4 (0·8–23·7)	0·088
	Platelet count ($\leq 280 \times 10^9$/l vs. $>280 \times 10^9$/l)	6·2 (1·1–35·0)	0·040
Transfusion independence	Karyotypic complexity ($\geq$2 aberrations vs. 0–1)	7·5 (0·9–58·7)	0·056
	Platelet count ($\leq 240 \times 10^9$/l vs. $>240 \times 10^9$/l)	8·4 (1·2–59·0)	0·032

Mallo et al, 2013

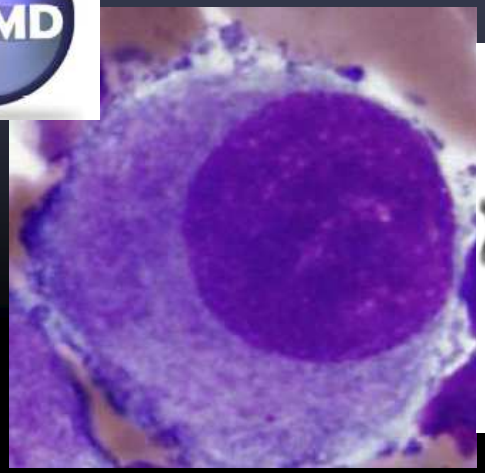
Conclusions

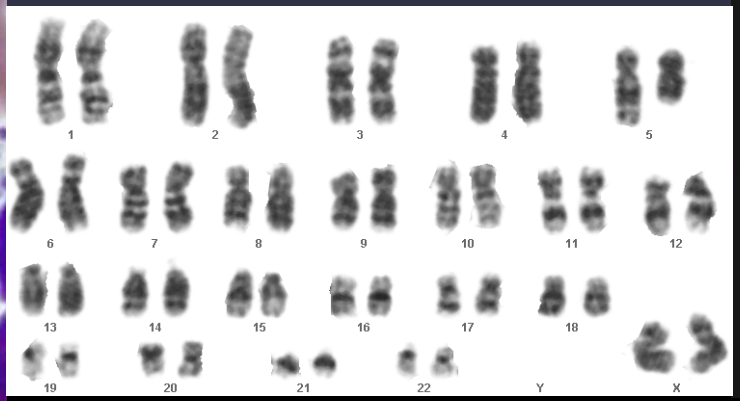
- Platelet baseline count below 280x10^3/L is related with treatment failure
- Karyotype complexity (by conventional cytogenetics) inversely correlates with hematological response to lenalidomide treatment

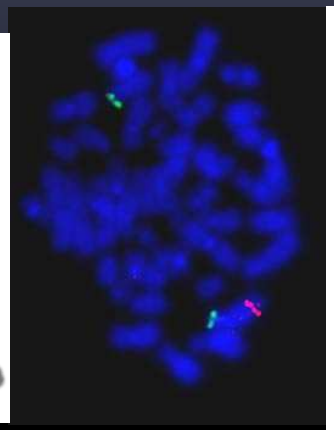
- SNP array detected additional alterations in 26.3% of cases with isolated 5q- (by conventional cytogenetics)
- Inclusion of defects by SNP array did not allow for better separation of responders and non responders
- *TP53* mutations showed a trend (*P*=0.061) to treatment failure. None of the mutated cases achieved complete cytogenetics response

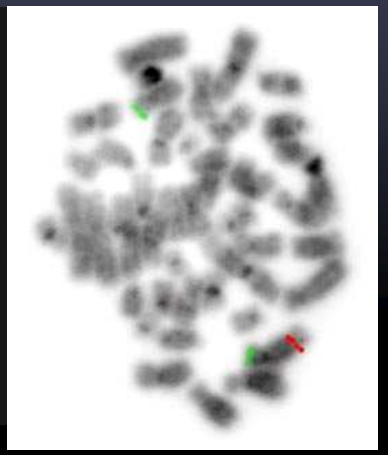
Mallo et al, 2013

15-30% MDS









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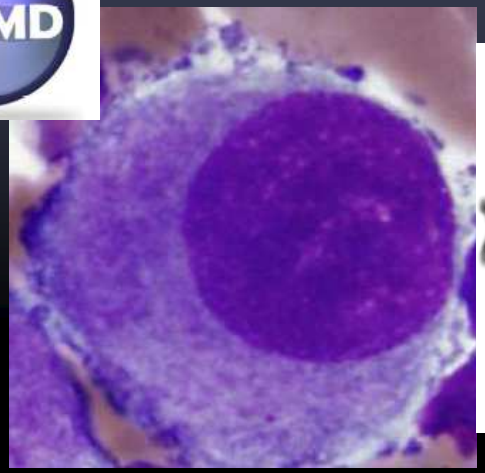
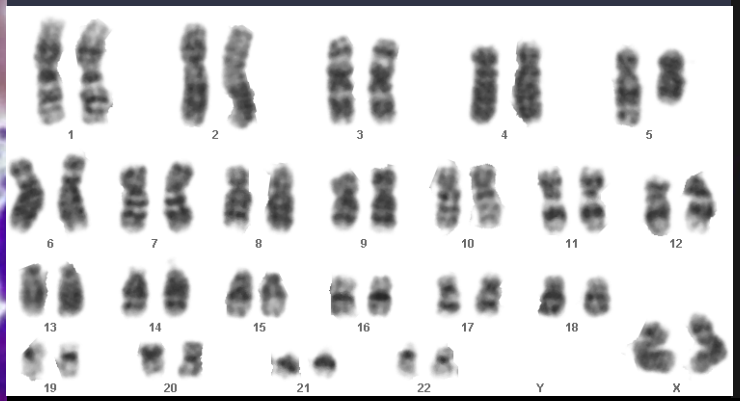
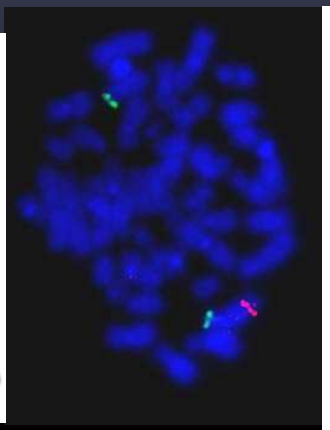
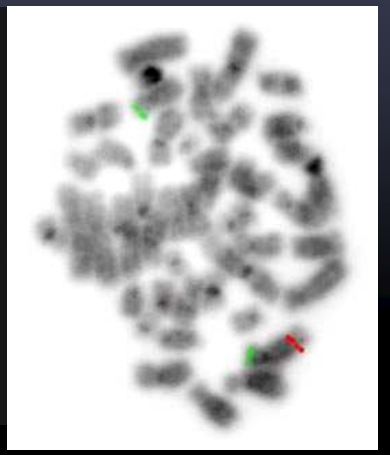








Lenalidomide and outcome in MDS del(5q)

high rates of RBC transfusion independece[1] (TI)

cytogenetic response[1] (CyR)

Outcome?

TI[1]: ⇧ OS and ⇩ AML evolution

AML evolution[2]: ⇧ if no erythroid or cytogenetic response

Similar[3,4] OS and AML evolution to no Lena TD patients

[1]Fenaux et al, 2011

[2]Göhring et al, 2010

[3]Adès et al, 2012

[4]Kuendgen et al, 2013

A retrospective time-dependent comparative analysis of the impact of lenalidomide on outcomes in lower risk MDS with chromosome 5q deletion

J. Sánchez-García, C. Del Cañizo, E. Such, B. Nomdedeu, E. Luño, R. De Paz, B. Xicoy, D. Valcárcel, S. Brunet, V. Marco, M. García, S. Osorio, M. Tormo, A. Bailen, C. Cervero, A. Torres-Gómez, F. Ramos, M. Diez-Campelo, M. Belkaid, B. Arrizabalaga, G. Azaceta, J. Bargay, M.J. Arilla, M. Caballero, J. Falantes and G. Sanz (Spanish Registry of MDS and Grupo Andaluz of MDS)

11th International Symposium on Myelodysplastic Syndromes
Edinburgh, UK. May 18-21, 2011

Sánchez-García & Sanz et al, *submitted* 2013

Aim of the Study

- To evaluate in a large series of patients with low risk MDS (IPSS low or Interemdiate-1) and deletion 5q included in the Spanish MDS registry database the impact of lenalidomide treatment on OS and LFS using a time-dependent analysis.

Sánchez-García & Sanz et al, *submitted* 2013

Patients & Methods (1)

- Retrospective multicenter study
- 215 patients from 4980 cases of Spanish MDS registry fulfilled the following inclusion criteria
  - Deletion of long-arm chromosome 5 alone or in combination with other abnormalities by conventional cytogenetics
  - Low or Int-1 IPSS at diagnosis
  - Low or Int-1 IPSS at lenalidomide treatment
  - Complete information available
  - At least 3-months follow-up for alive patients
- 86 patients had received lenalidomide (Lena-group) and 129 patients did not (no-Lena group)

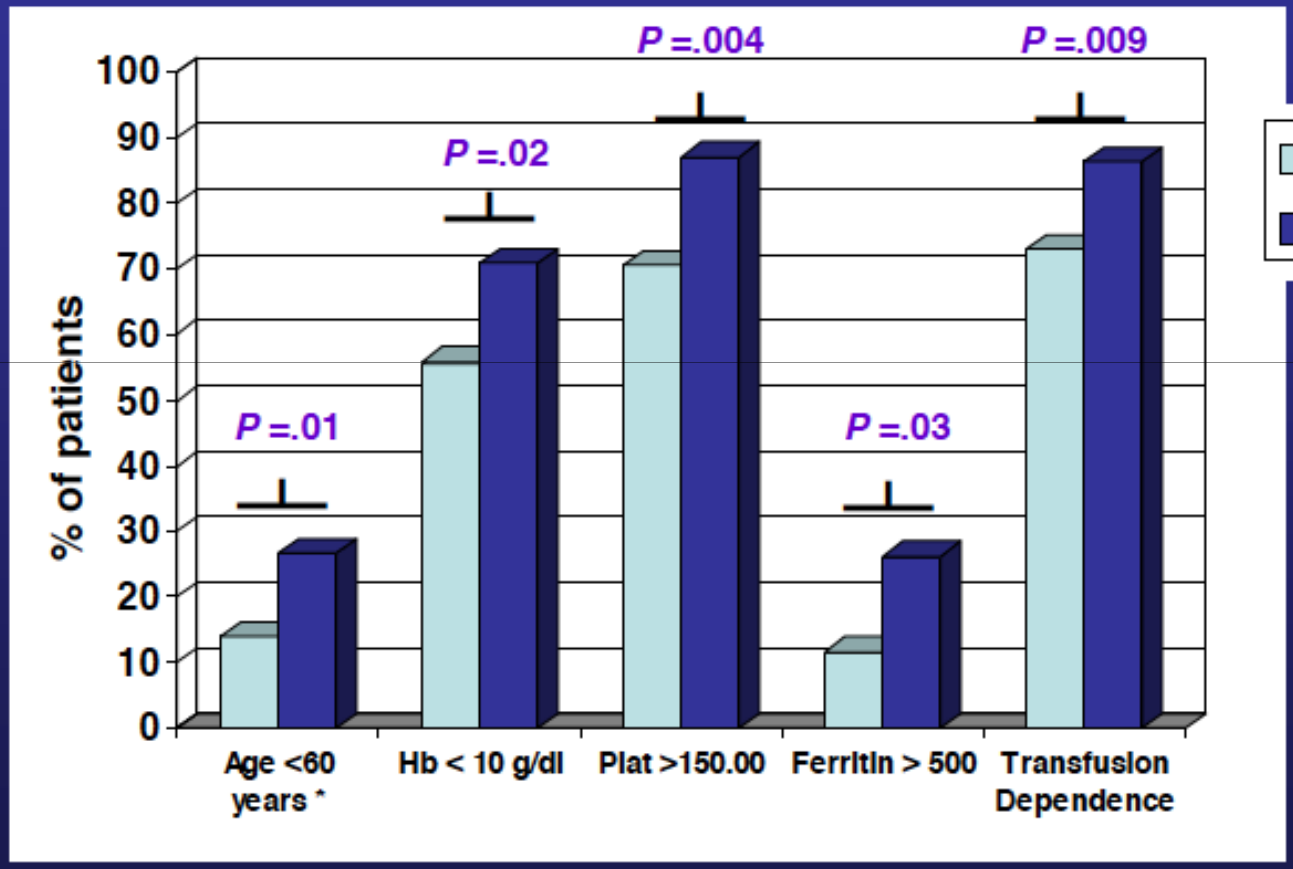
Sánchez-García & Sanz et al, *submitted* 2013

Patients & Methods (2)

- Study endpoints:
  - Overall survival (OS)
  - Leukemia-free survival (LFS)
- Univariate analyses:
  - Actuarial curves plotted by Kaplan–Meier method (covariates at diagnosis) and Simon–Makuch method (time–dependent covariates)
  - Comparison of actuarial curves: log rank test
- Multivariate analyses
  - Cox proportional hazards regression method with lenalidomide treatment treated as a time–dependent covariate

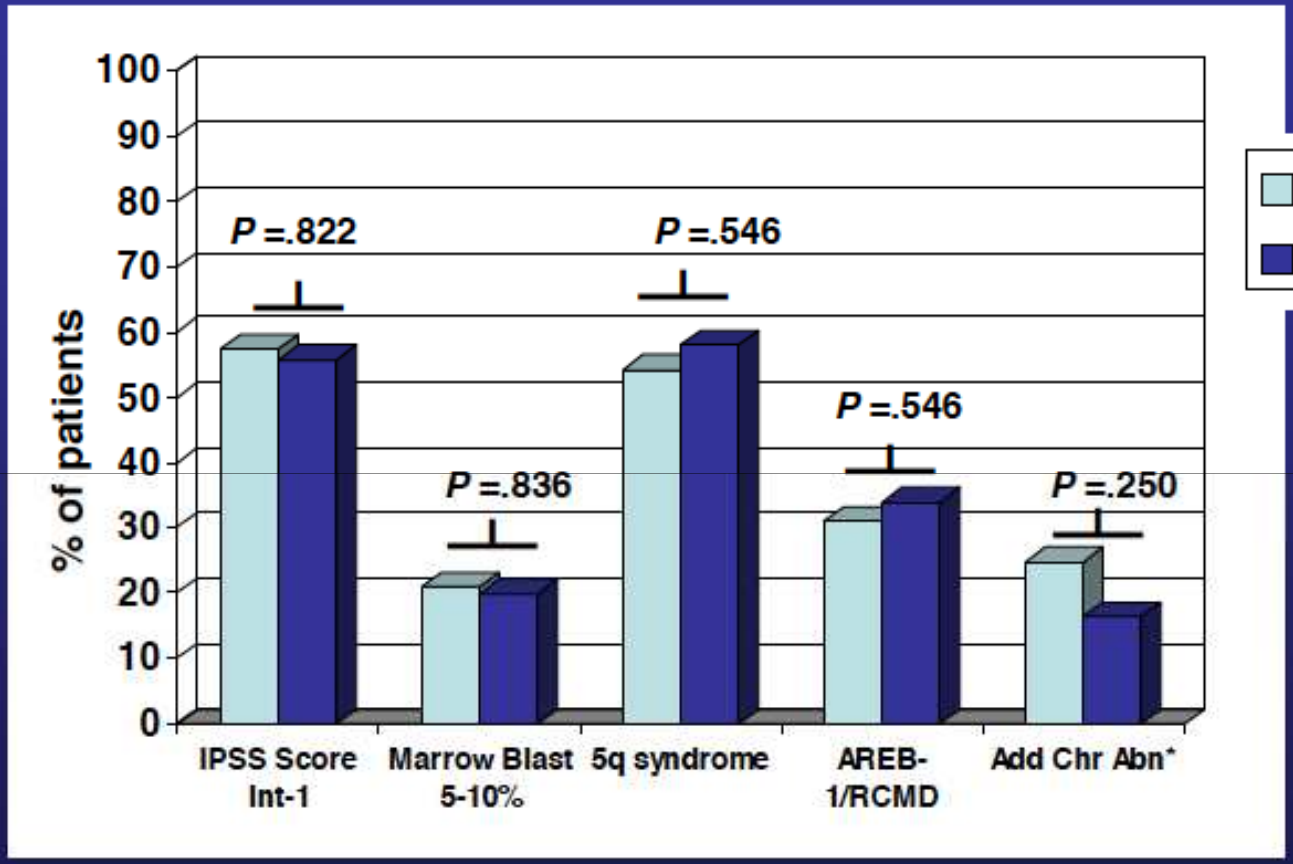
Sánchez-García & Sanz et al, *submitted* 2013

Characteristics of Patients (1)



Sánchez-García & Sanz et al, *submitted* 2013

Characteristics of Patients (2)



* Additional Chromosomal Abnormalities	No-Lena Group N (%)	Lena Group N (%)	
Del(5q) alone	97 (75.2)	72 (83.7)	0.250
+2 Abnormalities	19 (14.7)	10 (11.6)	
+3 or complex	13 (10.1)	4 (4.7)	

Sánchez-García & Sanz et al, *submitted* 2013

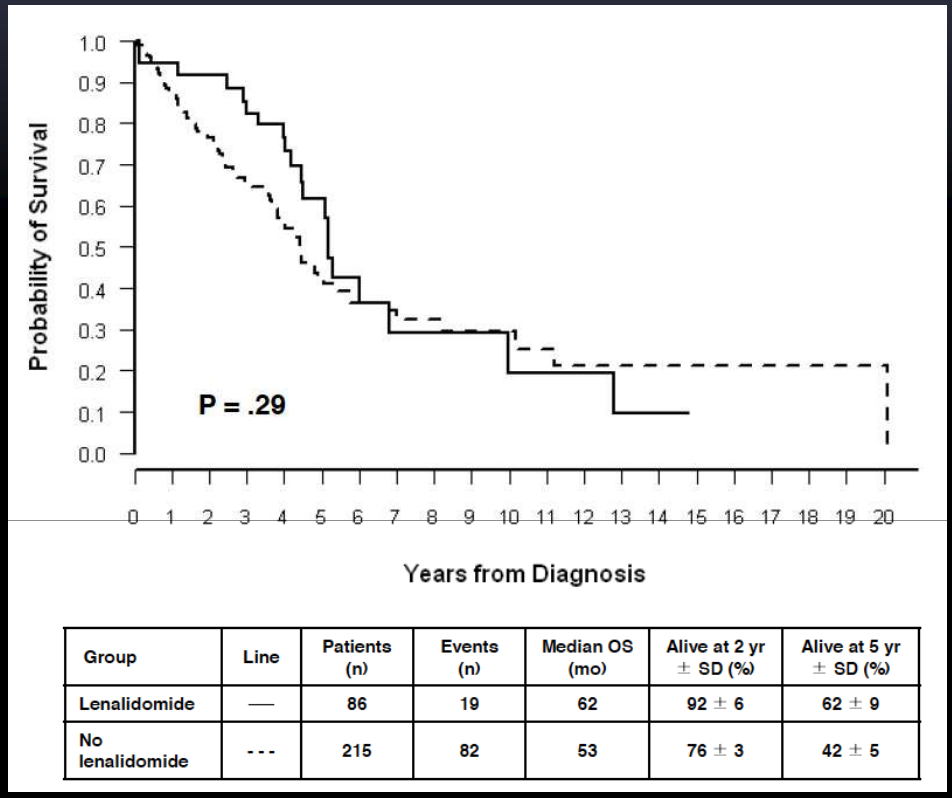
Characteristics of Patients (3)

- Median time from diagnosis and lenalidomide treatment was 11.6 mo (range 0.1 – 149 mo)
- Lena-Group patients received lenalidomide 10 mg (n=80) or 5 mg (n = 6) for 21 d every 28 d (median treatment duration, 13 mo; range, 1 – 42 mo)
- Sustained and transient transfusion independence (TI) was achieved in 51% and 28% respectively
- Median follow-up after starting lenalidomide was 22 mo (range, 3 – 55 mo)
- Median follow-up for No-Lena and Lena groups was 32 mo (range, 4 – 156 mo) and 40 (6 – 177 mo) respectively

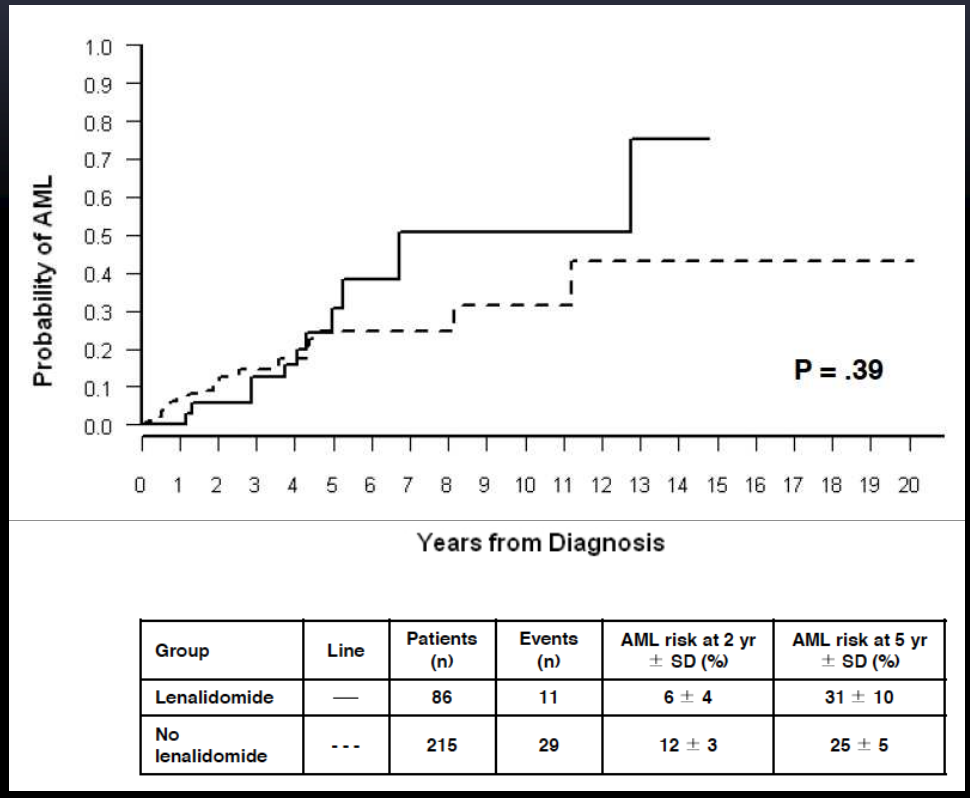
Sánchez-García et al, *submitted* 2013

Lena, impact on outcome in TD patients

All patients



Group	Line	Patients (n)	Events (n)	Median OS (mo)	Alive at 2 yr ± SD (%)	Alive at 5 yr ± SD (%)
Lenalidomide	—	86	19	62	92 ± 6	62 ± 9
No lenalidomide	- - -	215	82	53	76 ± 3	42 ± 5



Group	Line	Patients (n)	Events (n)	AML risk at 2 yr ± SD (%)	AML risk at 5 yr ± SD (%)
Lenalidomide	—	86	11	6 ± 4	31 ± 10
No lenalidomide	- - -	215	29	12 ± 3	25 ± 5

	Global	Lena	No Lena
Median OS (mo)	59	62	53
2 years	81%	92%	76%
5 years	48%	62%	42%

	Global	Lena	No Lena
AML	19%	13%	23%
2 years	13%	6%	12%
5 years	32%	31%	25%

Sánchez-García & Sanz et al, *submitted* 2013

Lena, impact on outcome in TD patients

All patients

Table 2. Multivariate analysis of long-term outcomes with lenalidomide tretament as time-dependent covariate and forced to enter into the models.

Variable (categories and codes)	Overall survival			Risk of progression to AML		
	Beta coefficient (SE)	Hazard ratio (95% CI)	P value	Beta coefficient (SE)	Hazard ratio (95% CI)	P value
Lenalidomide treatment (no = 0, yes = 1)	- 0.21 (.26)	0.82 (0.49 – 1.37)	0.45	0.37 (0.37)	1.45 (0.71 – 2.98)	0.31
Platelet count, × 10^9/L (<150 = 0, ≥150 = 1)	- 0.85 (.22)	0.43 (0.28 – 0.66)	< 0.001	- 1.0 (0.37)	0.37 (0.20 – 0.87)	0.005
Age, yr (< 60 = 0, ≥ 60 = 1)	0.54 (0.28)	1.72 (0.99 – 2.97)	0.051	- 0.69 (0.34)	0.50 (0.26 – 0.98)	0.043
Chromosomal abnormalities (del(5q) alone = 0, del(5q) + 1 additional abnormality = 1, and del(5q) + ≥2 additional abnormalities =2)	0.47 (0.25)	1.59 (0.98 - 2.58)	0.058	0.87 (0.35)	2.39 (1.14 – 4.99)	0.020
Blasts in bone marrow, % (<5 = 0, ≥5 = 1)	-	-	NS	0.23 (0.08)	1.26 (1.07 – 1.49)	0.006

SE denotes standard error; yr, years; and NS, not statistically significant (P > .20)

Sánchez-García & Sanz et al, *submitted* 2013

Lena, impact on outcome in TD patients

Transfusion dependent patients

	mFU	mOS*	2y AML evolution*
51 patients (78%) TI	26 mo	NR	3%
14 patients (22%) TD		31 mo	23%
		p<0.001	p<0.001

Median TI duration 36 mo

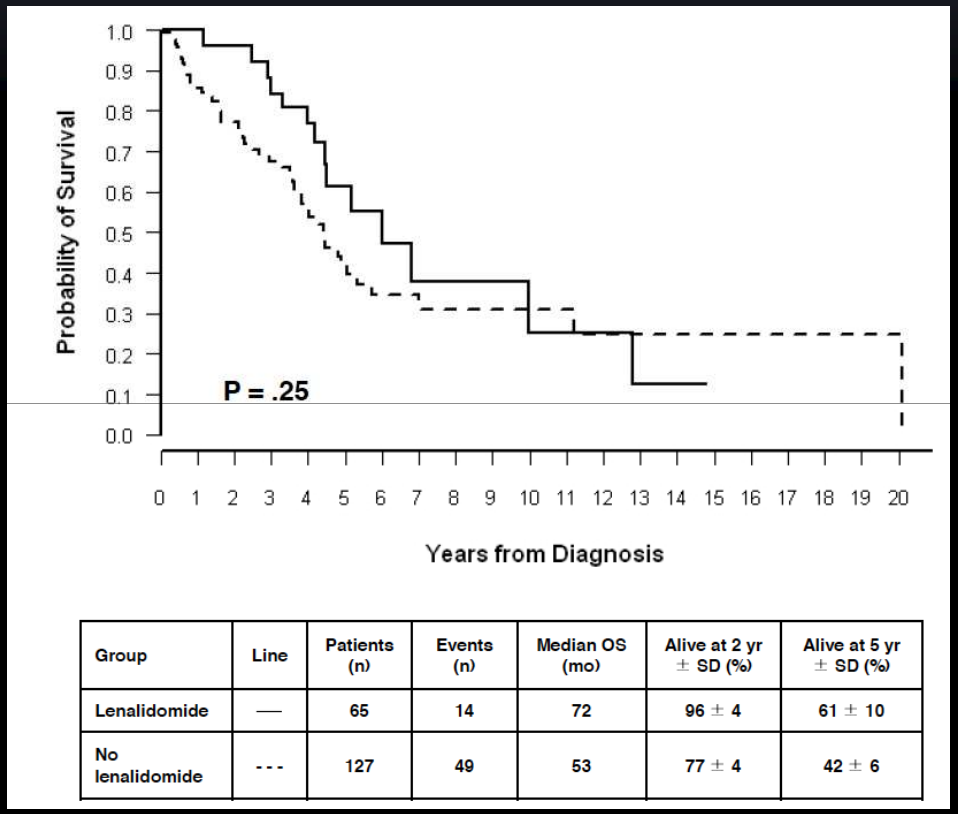
OS estimated at 18 mo after TI failure 51%

*Desde inicio Lena,

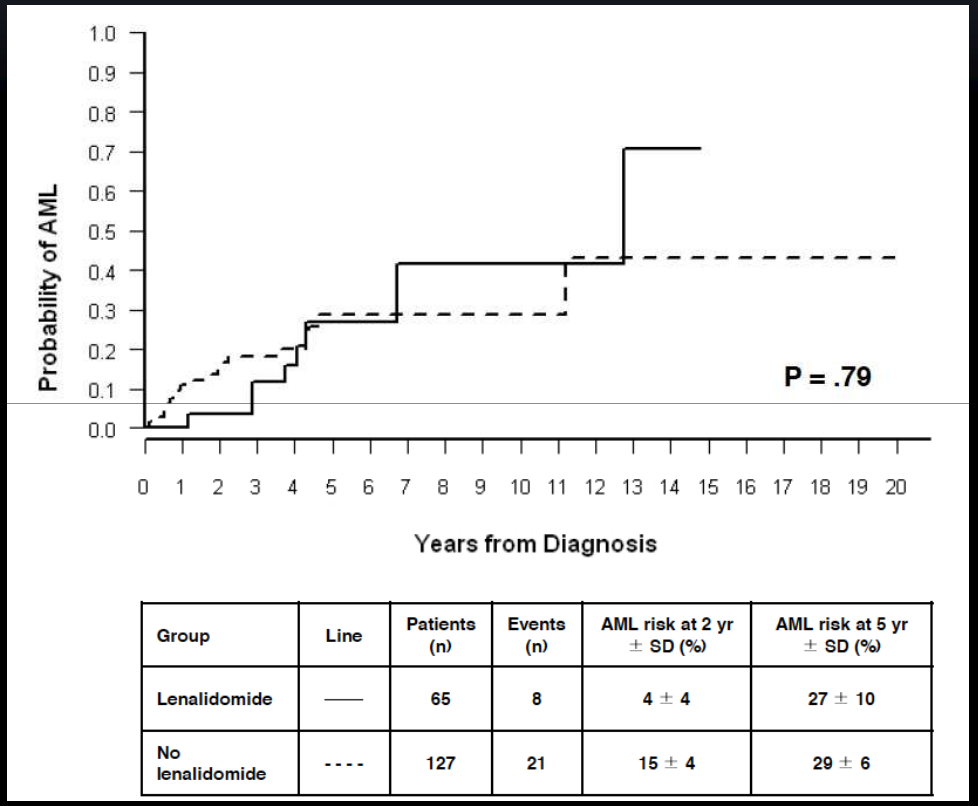
Sánchez-García & Sanz et al, *submitted* 2013

Lena, impact on outcome in TD patients

Transfusion dependent patients



Group	Line	Patients (n)	Events (n)	Median OS (mo)	Alive at 2 yr ± SD (%)	Alive at 5 yr ± SD (%)
Lenalidomide	——	65	14	72	96 ± 4	61 ± 10
No lenalidomide	- - -	127	49	53	77 ± 4	42 ± 6

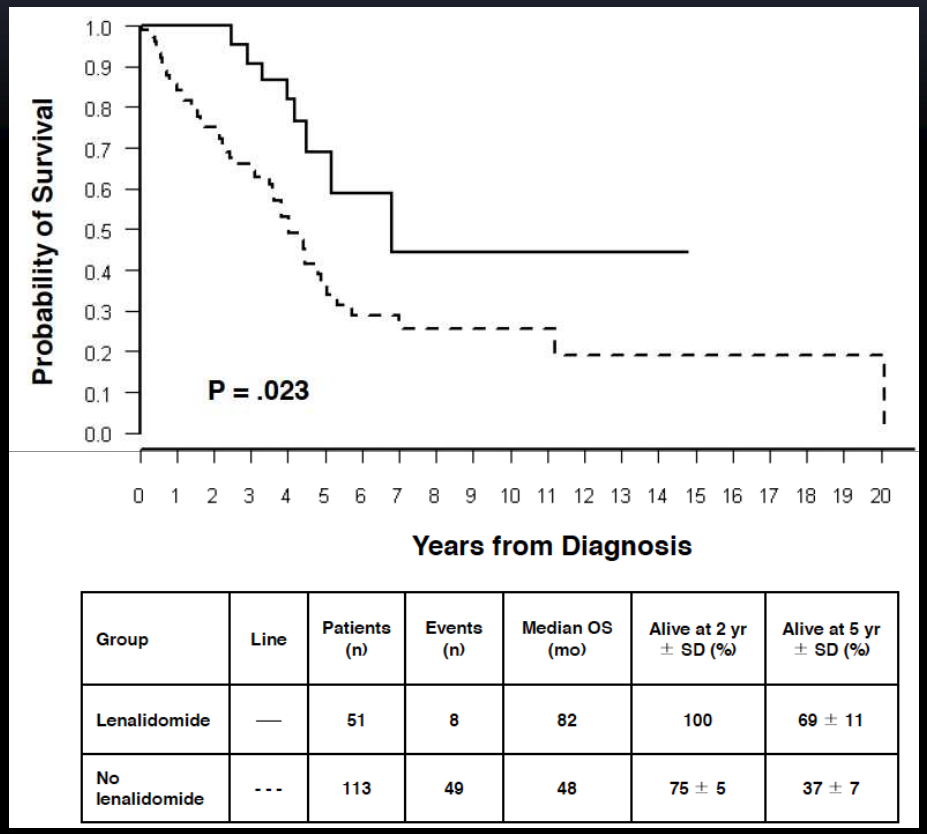


Group	Line	Patients (n)	Events (n)	AML risk at 2 yr ± SD (%)	AML risk at 5 yr ± SD (%)
Lenalidomide	——	65	8	4 ± 4	27 ± 10
No lenalidomide	- - - -	127	21	15 ± 4	29 ± 6

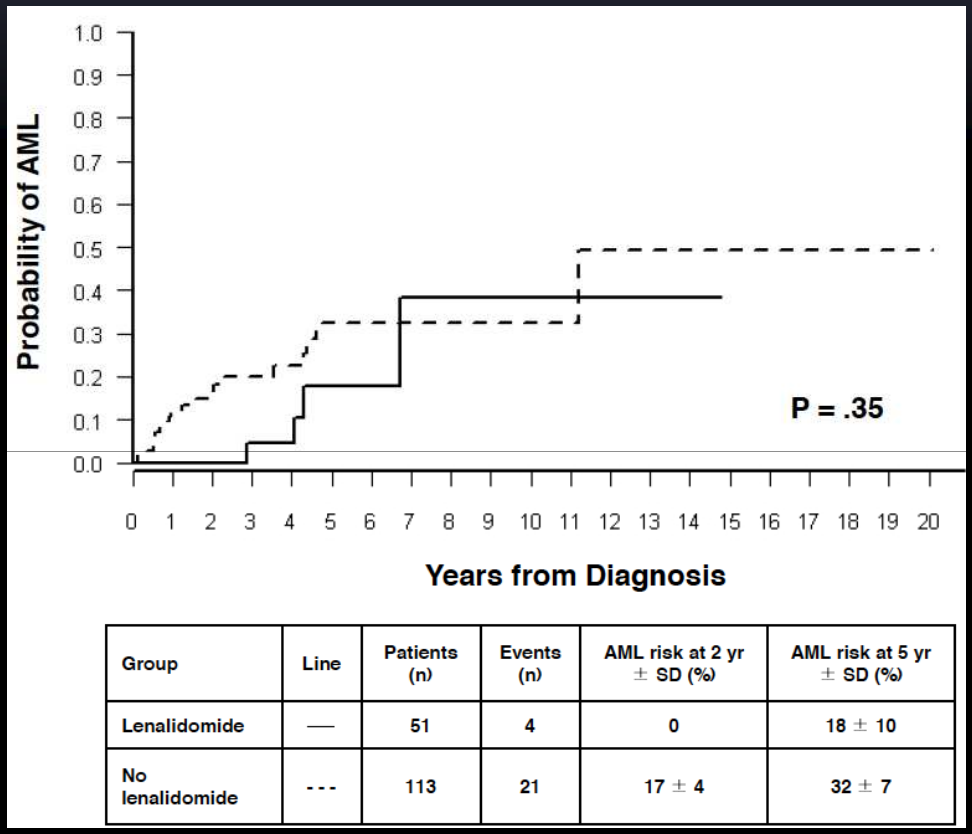
Sánchez-García & Sanz et al, *submitted* 2013

Lena, impact on outcome in TD patients

Transfusion dependent patients, impact of TI



Group	Line	Patients (n)	Events (n)	Median OS (mo)	Alive at 2 yr ± SD (%)	Alive at 5 yr ± SD (%)
Lenalidomide	——	51	8	82	100	69 ± 11
No lenalidomide	- - -	113	49	48	75 ± 5	37 ± 7

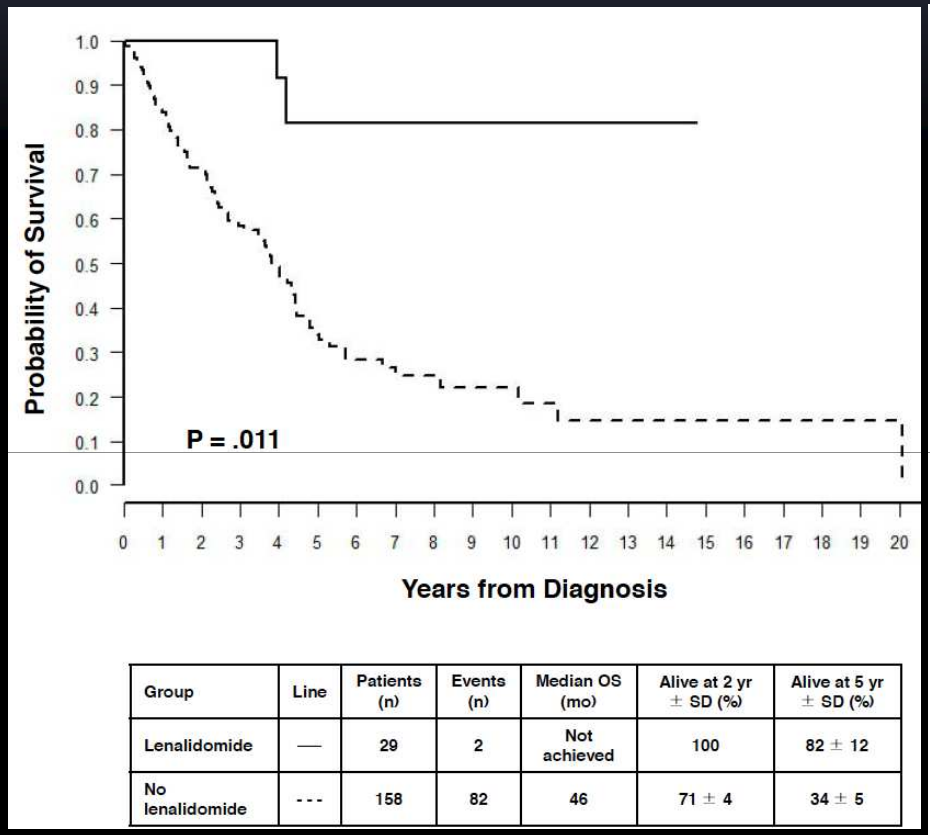


Group	Line	Patients (n)	Events (n)	AML risk at 2 yr ± SD (%)	AML risk at 5 yr ± SD (%)
Lenalidomide	——	51	4	0	18 ± 10
No lenalidomide	- - -	113	21	17 ± 4	32 ± 7

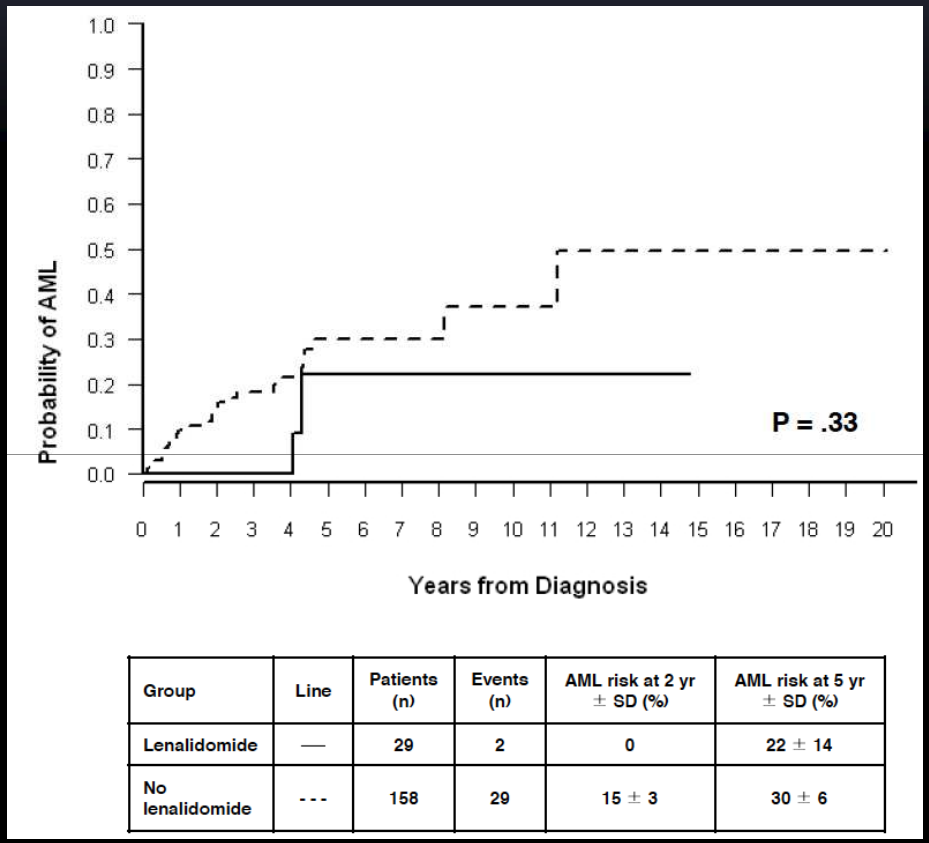
Sánchez-García & Sanz et al, *submitted* 2013

Lena, impact on outcome in TD patients

Cytogenetic response



Group	Line	Patients (n)	Events (n)	Median OS (mo)	Alive at 2 yr ± SD (%)	Alive at 5 yr ± SD (%)
Lenalidomide	—	29	2	Not achieved	100	82 ± 12
No lenalidomide	---	158	82	46	71 ± 4	34 ± 5



Group	Line	Patients (n)	Events (n)	AML risk at 2 yr ± SD (%)	AML risk at 5 yr ± SD (%)
Lenalidomide	—	29	2	0	22 ± 14
No lenalidomide	---	158	29	15 ± 3	30 ± 6

49 patients assessed:

- 19 (39%) complete cytogenetic response
- 10 (20%) partial cytogenetic response
- 20 (41%) no response

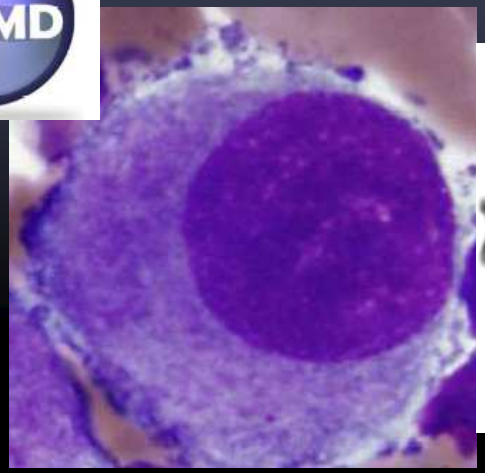
Sánchez-García & Sanz et al, *submitted* 2013

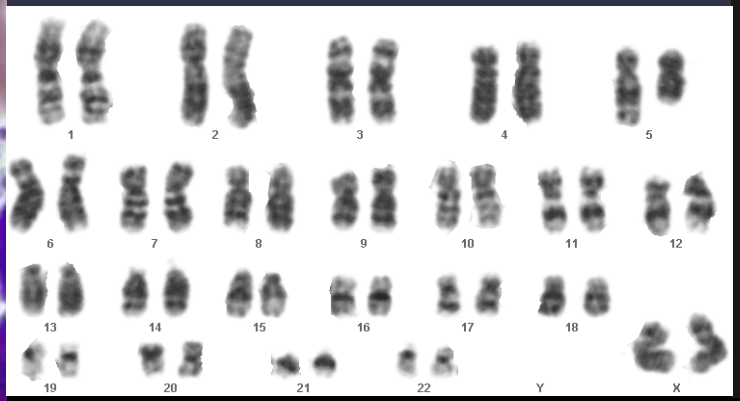
CONCLUSIONS

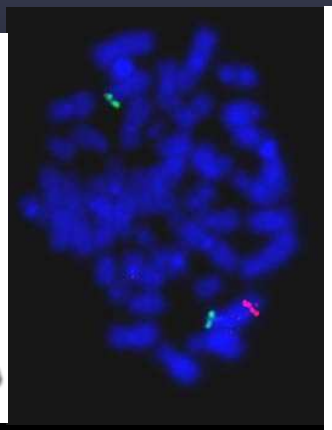
- Lena in TD patients improve
  - OS
  - AML evolution among patients who reach TI
- Lena in the overall population improve,
  - OS among patients who reach TI and CyR
- *Poor prognosis* after relapse/no response to Lena

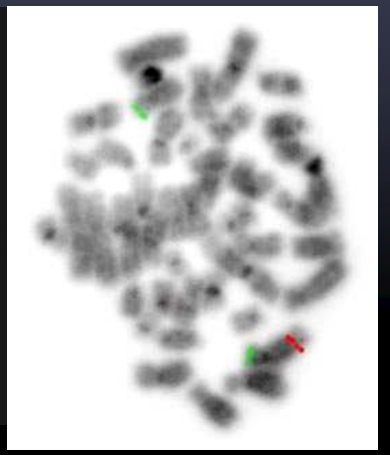
Sánchez-García & Sanz et al, *submitted* 2013

15-30% MDS









Sole anomaly or in addition to 1 cytogenetics aberrations OS[1]

Anemia[2] (78%)

Transfusion dependency (40%): Lenalidomide

Transfusion independency (60%): ¿Lenalidomide?

[1]Mallo et al, 2011

[2]Germing et al, 2012

RE-SMD

SINTRA-REV

SPANISH STUDY WITH LENALIDOMIDE IN *5Q- MDS PATIENTS* WITH *TRANSFUSION INDEPENDENT ANEMIA*

María Díez Campelo MD, PhD

Hematología
HOSPITAL UNIVERSITARIO SALAMANCA

IBSAL
Instituto de Investigación Biomédica de Salamanca

- Rationale of the study
- Spanish MDS Registry data on del(5q) patients
- Clinical trial

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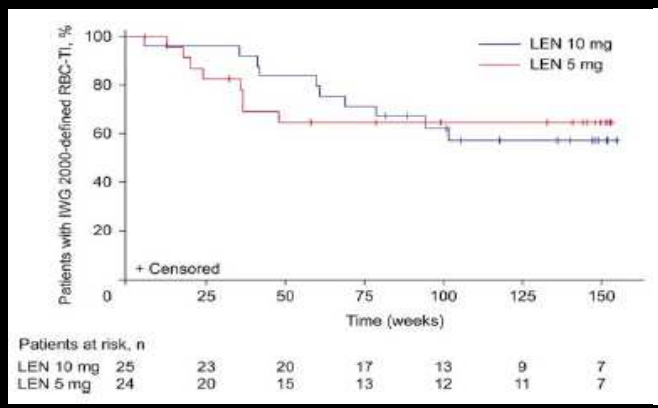
MDS and del(5q)

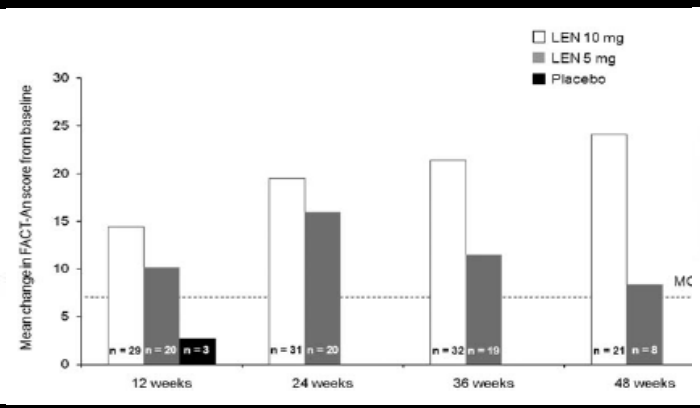
Low risk MDS

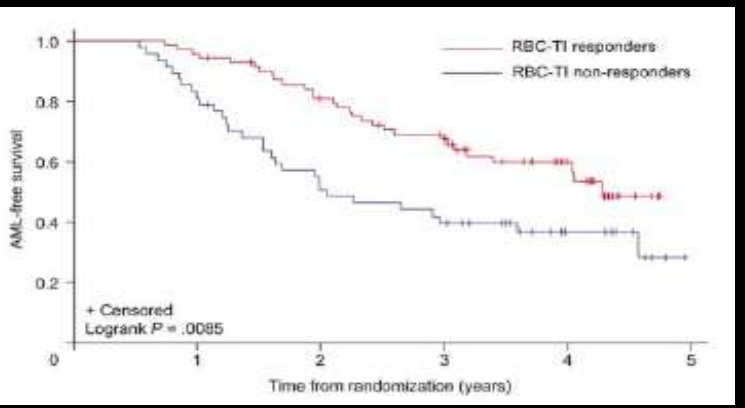
Anemia

Poor response to ESAs

Transfusion requirements → LENALIDOMIDE





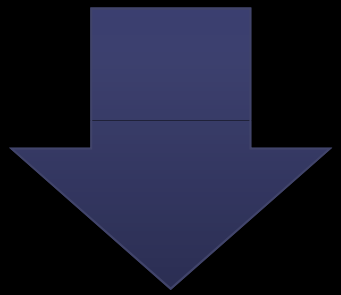


Adés et al. Haematologica 2012
Kelaidi et al, Leuk Res 2008
Le Bras et al, Leuk Res 2011
Fenaux, Blood 2011

MDS and del(5q) at presentation, 381 untreated patients

68% developed anemia

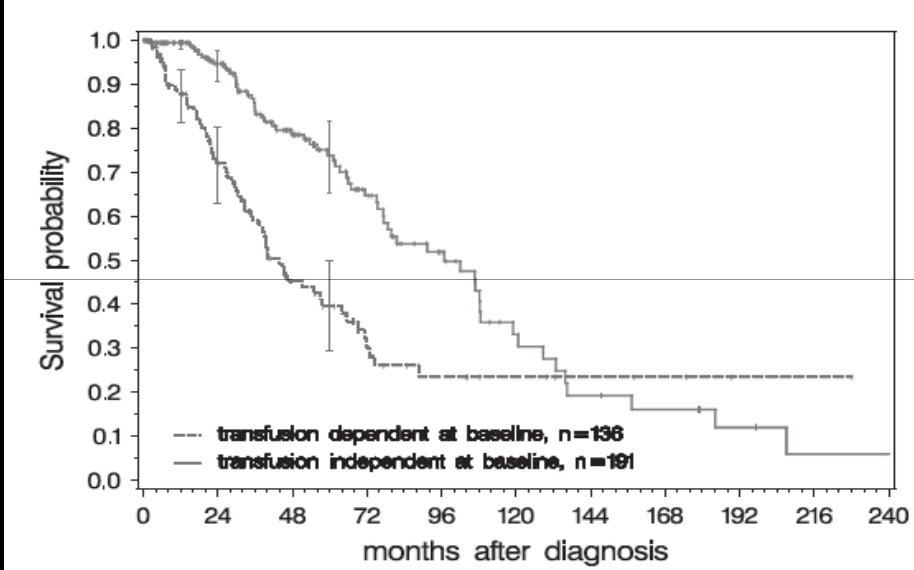
42% transfusion requirements

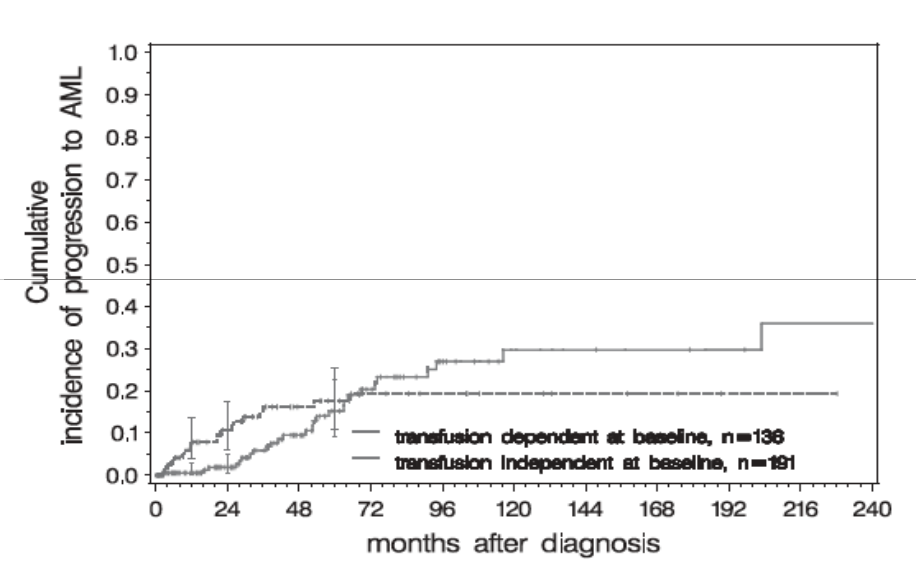


LENALIDOMIDE?

Germing et al. Leukemia 2012

MDS and del(5q) at presentation, 381 untreated patients





Germing et al. Leukemia 2012

TRANSFUSION DEPENDENCY IN MDS

- Poor prognosis (WPSS)
- Advanced Disease
- Risk of AML evolution

Could prolong the time until transfusion dependency?

LENALIDOMIDE?

SINTRA-REV

- Rationale of the study
- Spanish MDS Registry data on del(5q) patients
- Clinical trial

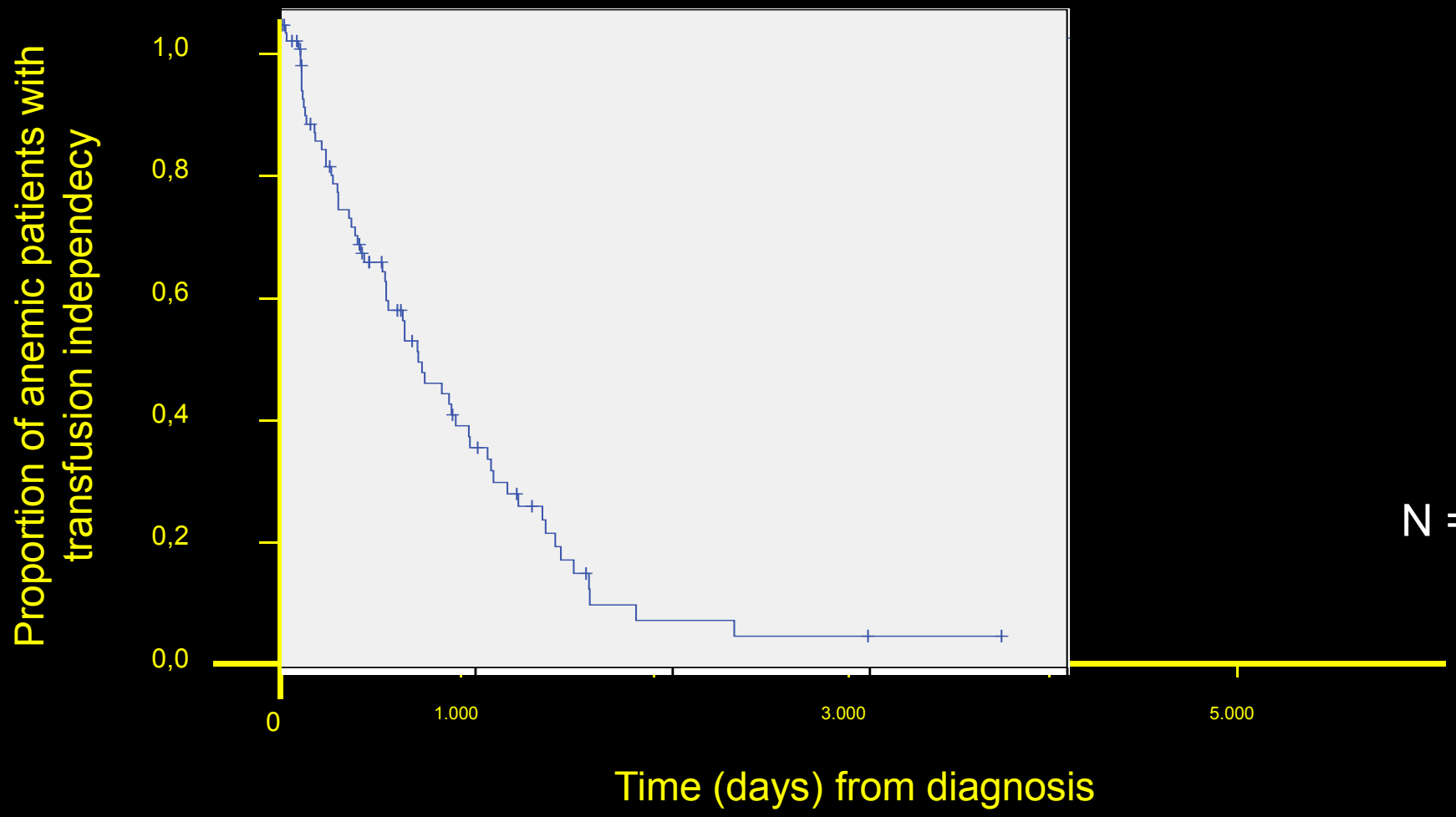
MDS and del(5q) at presentation

Spanish Registry on 150 MDS patients

AT DIAGNOSIS:

- 94% developed anemia (Hb<12 g/dL)
- Median 10.4 g/dL (7.4-13.9 g/dL)
- N=84 with information available on TD
- 73% developed transfusion requirements (61/84)

MDS and del(5q) evolution



- Rationale of the study
- Spanish MDS Registry data on del(5q) patients
- Clinical trial

SINTRA-REV: Title

"Multicenter, randomized, double-blind, phase III study of REVLIMID (Lenalidomide) versus placebo in patients with low risk myelodysplastic syndrome (low and intermediate-1 IPSS) with alteration in 5q- and anemia without transfusion dependency"

SINTRA-REV: Objectives

The main objective of the study is efficacy:

- To assess if treatment with Revlimid (Lenalidomide) *prolongs* the period until *disease progression* (transfusion dependency).
- Revlimid will be *compared* to current standard treatment for patients with low risk MDS associated with the loss of 5q with transfusion independent anamia, which is *observation* and *monitoring* until disease progression.

SINTRA-REV: Objectives

The secondary objectives of the study are:

- Erythroid response according to IWG 2006 criteria.
- Duration of RBC-TI.
- Change in Hb concentration.
- Cytogenetic response according IWG 2006 criteria.
- Bone marrow response according to IWG 2006 criteria.

- Variation in absolute platelet count.
- Variation in absolute neutrophil count.

- To assess the *safety and tolerability* of Lenalidomide, measured according to the incidence of clinical and laboratory toxicity.

- OS, EFS and transformation to AML.

SINTRA-REV: Design

- 60 patients with low risk del(5q-) MDS +/- other additional abnormality
- Anemia (Hb≤12g/dL) but without TD
- Randomized in a 2:1 ratio
- Treatment for 108 weeks or until disease progression: transfusion dependency (at least 2 RBC units/56 days with a minimum follow-up of 112 days), or unacceptable toxicity

SINTRA-REV: Scheme

Treatment phase

- 5 mg/day on days 1 to 28 of every 28-day cycle
- 108 weeks of treatment

Follow-up phase

- Observation and monitoring
- 108 weeks of follow-up

SINTRA-REV: Schedule/planning

Beginning 2010

2 years for recruitment: 2010-2011

2 years of follow-up: 2012-2013

Duration of the trial: 4 years

SINTRA-REV: preliminary results

PATIENTS INCLUDED: N=10
3 YEARS IN RECRUITMENT: 2.010-2.012

		DATE OF INCLUSION	Age (years)
H. Clínico de Salamanca	01-001	2/15/10	73
	01-002	3/18/10	83
	01-003	3/29/12	85
	01-004	5/31/12	74
	01-005	8/30/12	85
H. Son Llàtzer	02-001	6/22/11	70
H. Cruces	06-001	6/14/11	69
H. La Paz	08-001	9/7/11	56
H. Clínic de Barcelona	12-001	3/25/11	62
H. Germans Trias i Pujol	13-001	12/30/10	80

SINTRA-REV: preliminary results

DISEASE CHARACTERISTICS: CLASSIFICATION AND PROGNOSIS

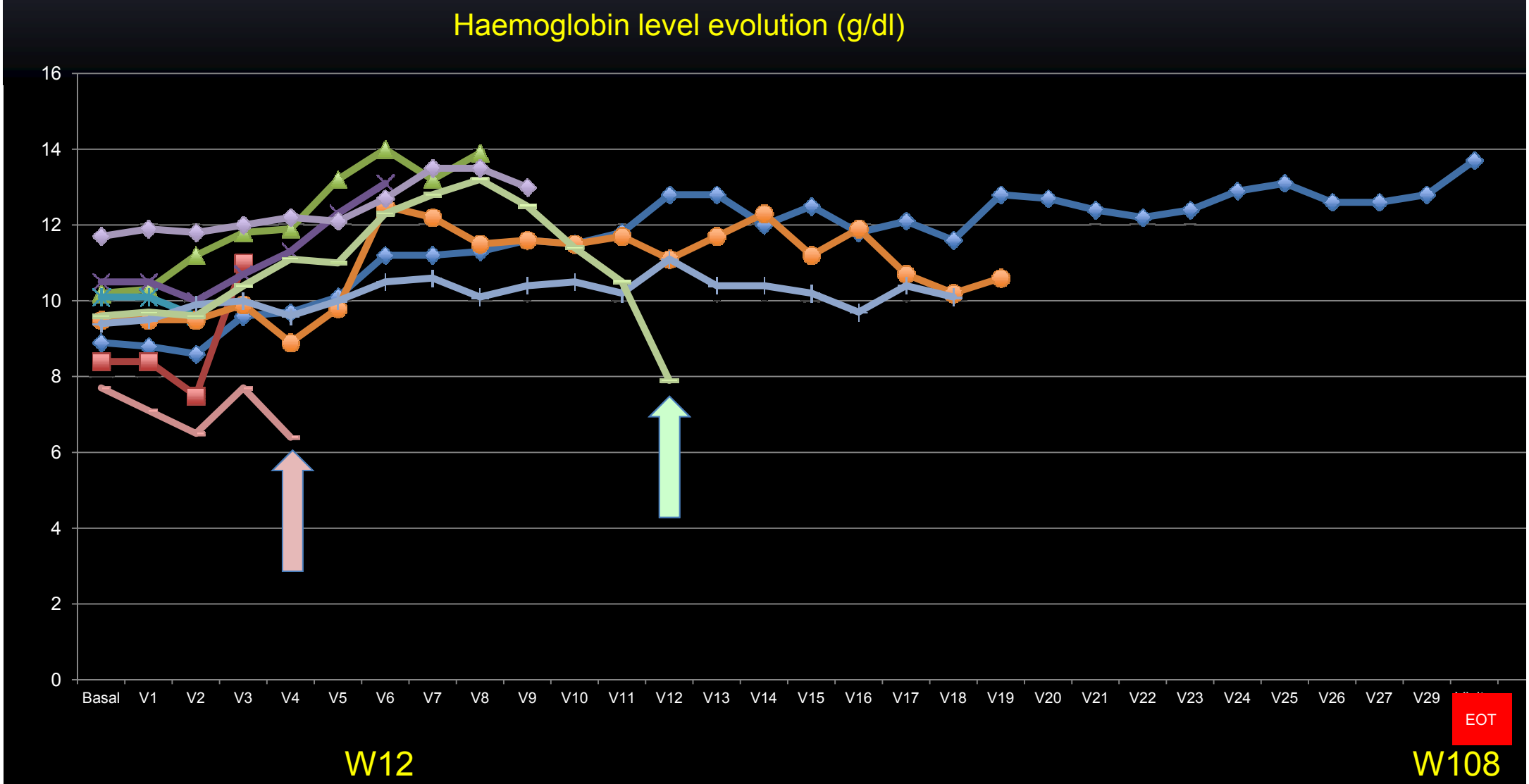
FAB	OMS 2008	IPSS
RA	RCMD	0
RA	RCMD	1
RA	RCMD	0
RA	MDS with 5q- abnormality	0
RA	MDS with 5q- abnormality	0
RARS	MDS with 5q- abnormality	0
RARS	RARS	0
RA	RCMD	1
RA	RCUD	0
RA	RARS	0

SINTRA-REV: preliminary results

STATUS OF THE PATIENTS

ACTIVE TREATMENT N=6	Week of treatment 12-108
WITHDRAWL N=5	TRANSFUSION DEPENDENCY N=2 Week 8 and 36 ADVERSE EVENTS N=3 Exanthema, week 2 Elevated lipase level, week 24 Solid tumor, week 40

SINTRA-REV: preliminary results



SINTRA-REV: preliminary results

ADVERSE EVENTS

SERIOUS ADVERSE EVENTS N=3	Exhantema N=1, grade 2 Increase in lipase level N=1, grade 3 Solid tumor N=1, grade 3
ADVERSE EVENTS N=13	Neutropenia N=3, grades 1-3 Thrombocytopenia N=1, grade 1 Asthenia N=2, grades 1 and 2 Dyspnoea N=1, grade 1 Constipation N=2, grades 1 and 2 Vomiting N=1, grade 2 Depression N=1, grade 1 Dental N=1, grade 2 Hypothyroidism N=1, grade 2

NCI CTCAE version 3,0

SINTRA-REV: preliminary results

PATIENT 1

RA, RCMD, IPSS 0, 74 year-old, woman

46 XX (del 5q) [20], FISH 45% +

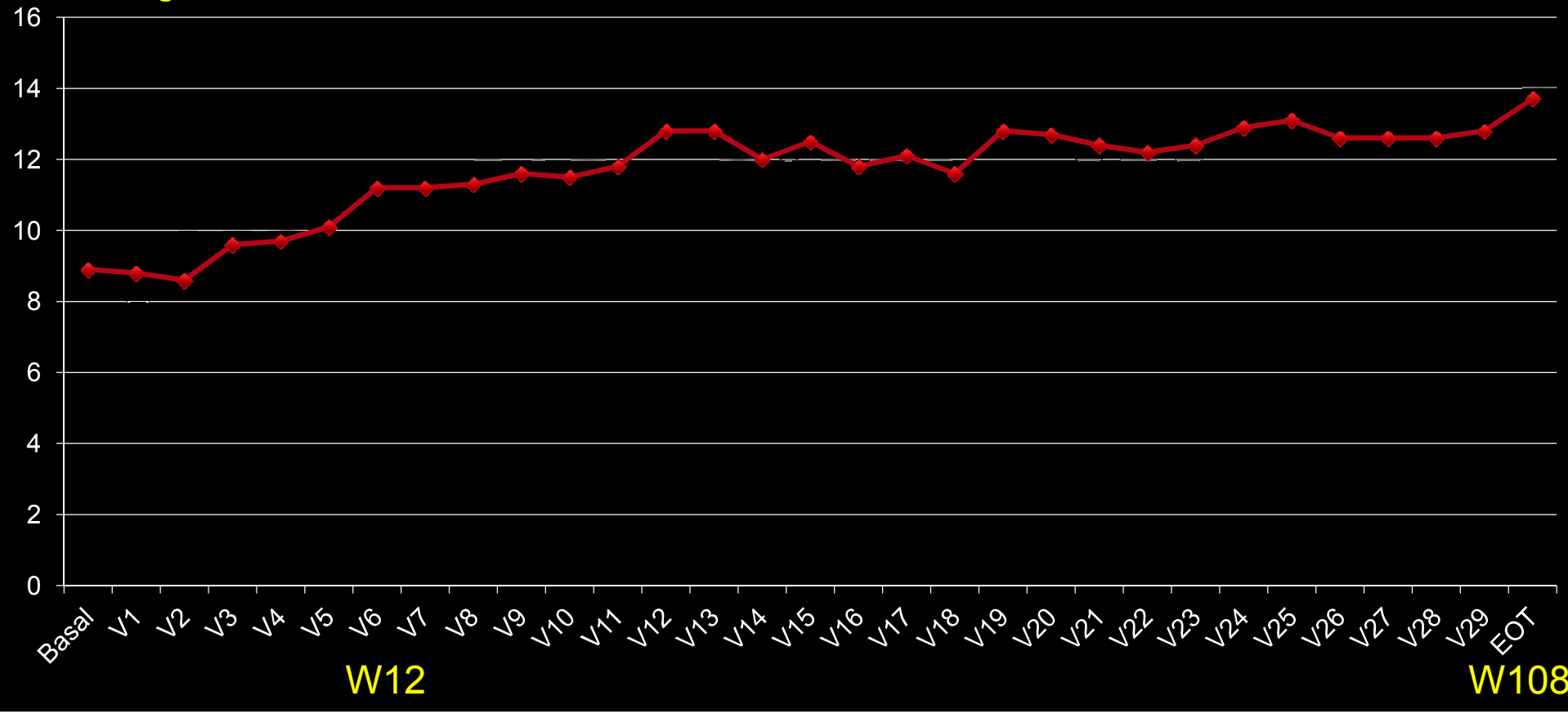
SINTRA-REV: preliminary results

PATIENT 1

RA, RCMD, IPSS 0, 74 year-old, woman

46 XX (del 5q) [20], FISH 45% +

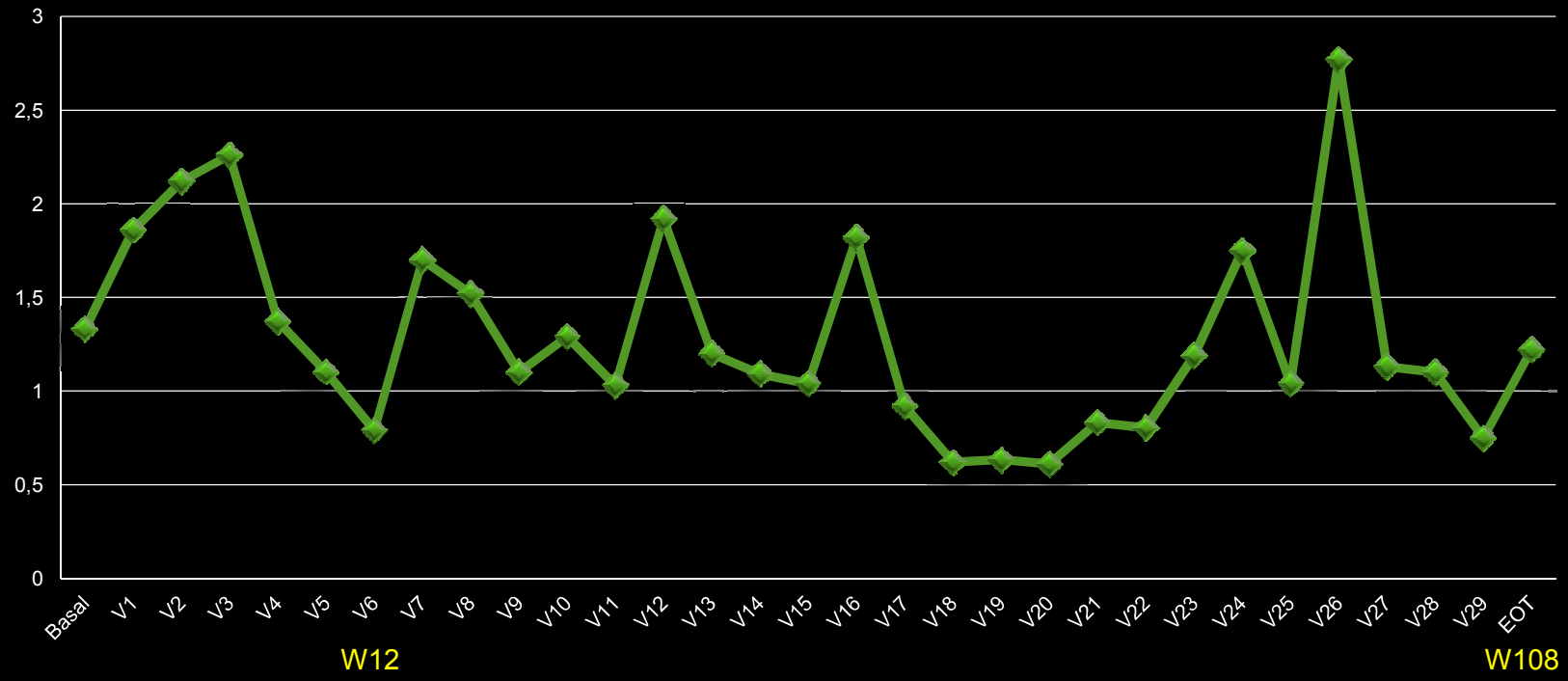
- Haemoglobin level



SINTRA-REV: preliminary results

PATIENT 1
RA, RCMD, IPSS 0, 74 year-old, woman
46 XX (del 5q) [20], FISH 45% +

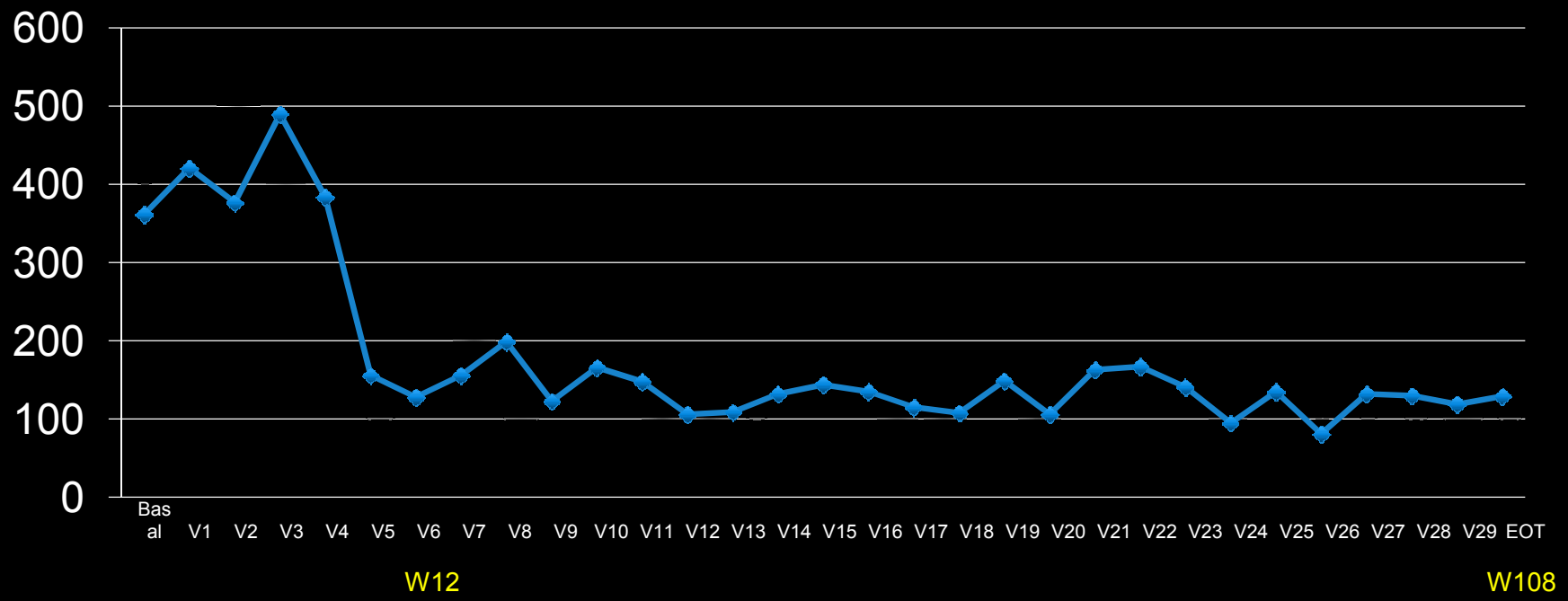
- Haemoglobin level
- Leukocytes



SINTRA-REV: preliminary results

PATIENT 1
RA, RCMD, IPSS 0, 74 year-old, woman
46 XX (del 5q) [20], FISH 45% +

- Haemoglobin level
- Leukocytes
- Platelets



SINTRA-REV: preliminary results

PATIENT 1
RA, RCMD, IPSS 0, 74 year-old, woman
46 XX (del 5q) [20], FISH 45% +

- Haemoglobin level
- Leukocytes
- Platelets
- NO other adverse events

SINTRA-REV: preliminary results

PATIENT 1
RA, RCMD, IPSS 0, 74 year-old, woman
46 XX (del 5q) [20], FISH 45% +

- Haemoglobin level
- Leukocytes
- Platelets
- Adverse Events
- Response at week 12
  - Erythroid response
  - Complete response in bone marrow
  - FISH negative

WITHDRAL at w108
6 mo FU

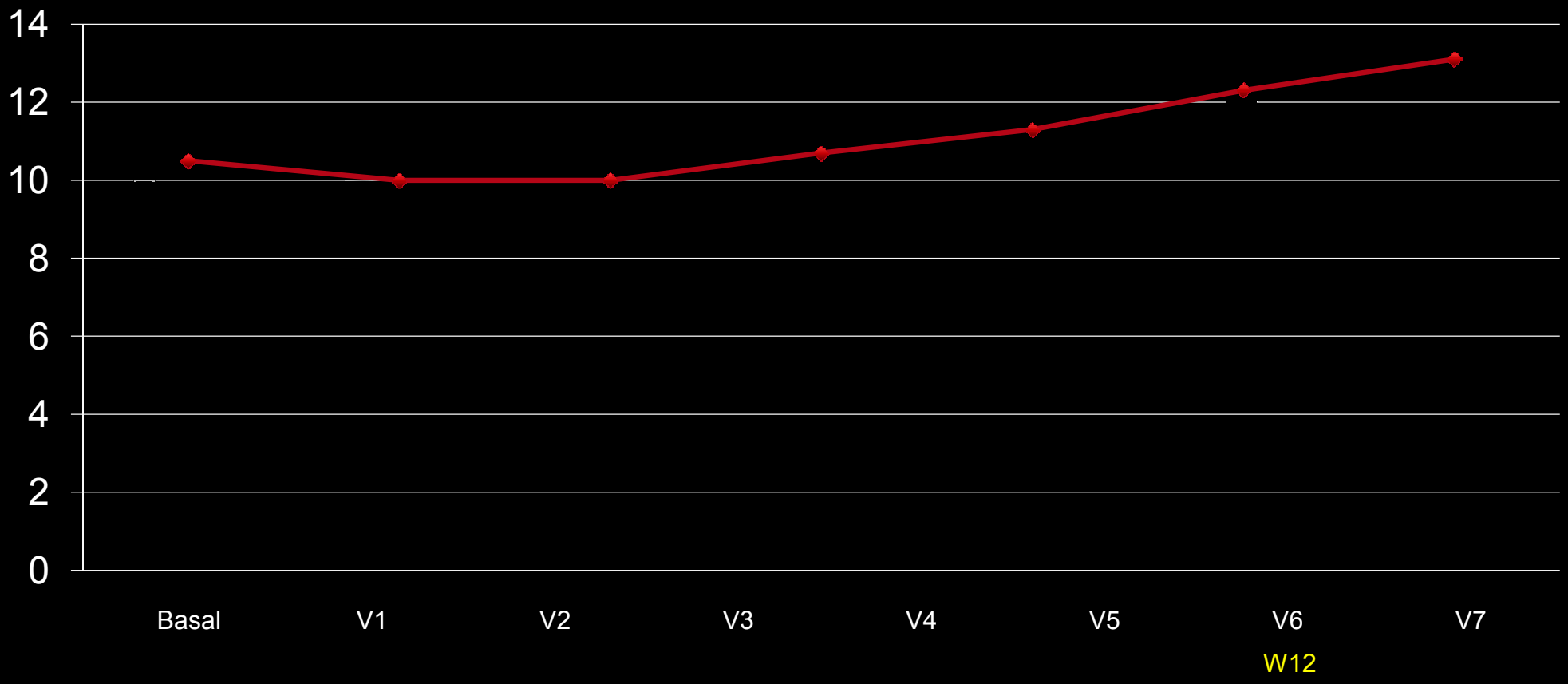
SINTRA-REV: preliminary results

PATIENT 4

RA, MDS 5q-, IPSS 0, 74 year-old, man, SEVERE COMORBIDITY (ISHCHEMIC CARDIOMIOPATHY)

46 XY (del 5q) [20], FISH 17% +

- Haemoglobin level



SINTRA-REV: preliminary results

PATIENT 4

RA, MDS 5q-, IPSS 0, 74 year-old, man, SEVERE COMORBIDITY (ISHCHEMIC CARDIOMIOPATHY)
46 XY (del 5q) [20], FISH 17% +

- Haemoglobin level
- NO cytopenias or adverse events

SINTRA-REV: preliminary results

PATIENT 4

RA, MDS 5q-, IPSS 0, 74 year-old, man, SEVERE COMORBIDITY (ISHCHEMIC CARDIOMIOPATHY)
46 XY (del 5q) [20], FISH 17% +

- Haemoglobin level
- NO cytopenias or adverse events
- Response at week 12
  - Erythroid response
  - Complete response in bone marrow
  - Cytogenetic response: 46 XY [21], FISH negative (4% +)

w24

SINTRA-REV: preliminary results

PATIENT 10

RA, MDS 5q-, IPSS 0, 80 year-old woman

46 XY (del 5q) [20], FISH NA

- Haemoglobin level

SINTRA-REV: preliminary results

PATIENT 10
RA, MDS 5q-, IPSS 0, 80 year-old woman
46 XY (del 5q) [20], FISH NA

- Haemoglobin level
- No cytopenias

SINTRA-REV: preliminary results

PATIENT 10
RA, MDS 5q-, IPSS 0, 80 year-old, woman
46 XY (del 5q) [20], FISH NA

- haemoglobin level
- No cytopenias
- Adverse events
  - G3 increase in lipase level, at w24 → WITHDRAWL

SINTRA-REV: preliminary results

PATIENT 10
RA, MDS 5q-, IPSS 0, 80 year-old woman
46 XY (del 5q) [20], FISH NA

- Haemoglobin level
- No cytopenias
- Adverse Events
- Response
  - Erythroid response at w12
  - Complete bone marrow response at w12
  - Complete cytogenetic response at w12

w108

SINTRA-REV: preliminary results

RESPONSE EVOLUTION

	HEMATOLOGICAL	BONE MARROW	CYTOGENETIC
Week 12 10 evaluable	8 Erythroid responses	6 CR 1 PR	3 CCyR 2 parcial CyR
Week 36 4 evaluable	2 Erythroid responses* 1 No response 1 Progression	2 CR* 1 Progression	2 CCyR* 1 Progression
Week 60 2 evaluable	2 Erythroid response*	2 CR*	2 CyCR*
Week 84-104 2 evaluable	2 Erythroid response*	2 CR*	2 CyCR*

* Patient withdrawal on week 24 due to elevated lipase level

ON GOING STUDIES

- Further investigation is needed on the *natural evolution on* MDS and del(5q) patients with no transfusion dependency
- The treatment in *this clinical trial* seems to be effective and safe

GESMD

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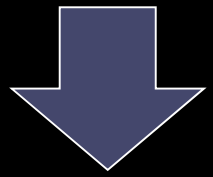
de SMD

RE-SMD

Registro Español
de SMD

TAKE HOME MESSAGES

Investigación clínica



Mejorar resultados

Ensayos clínicos