SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori

Istituto di Ricovero e Cura a Carattere Scientifico

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

MYELODYSPLASTIC SYNDROMES: CHAOS AND ORDER

Del (5q) Syndrome

Dr Valeria Di Battista

October 26, 2018
IRST, Meldola

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DISCLOSURE
I have no relevant financial relationships to disclose.

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Del(5q) Syndrome

CLINICAL FEATURES

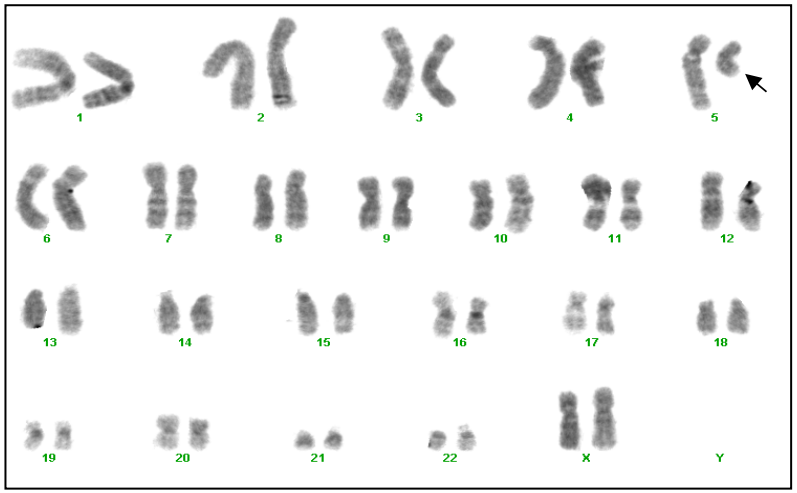
- Old age
- Female gender
- Low rate of leukemia transformation

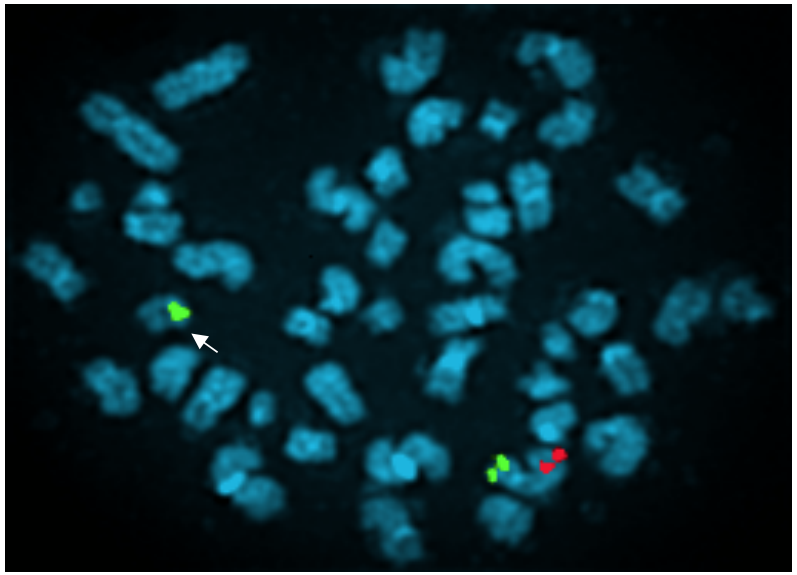
BLOOD COUNT

- Macrocytic anemia
- Mild leukopenia
- Normal or increased platelet count

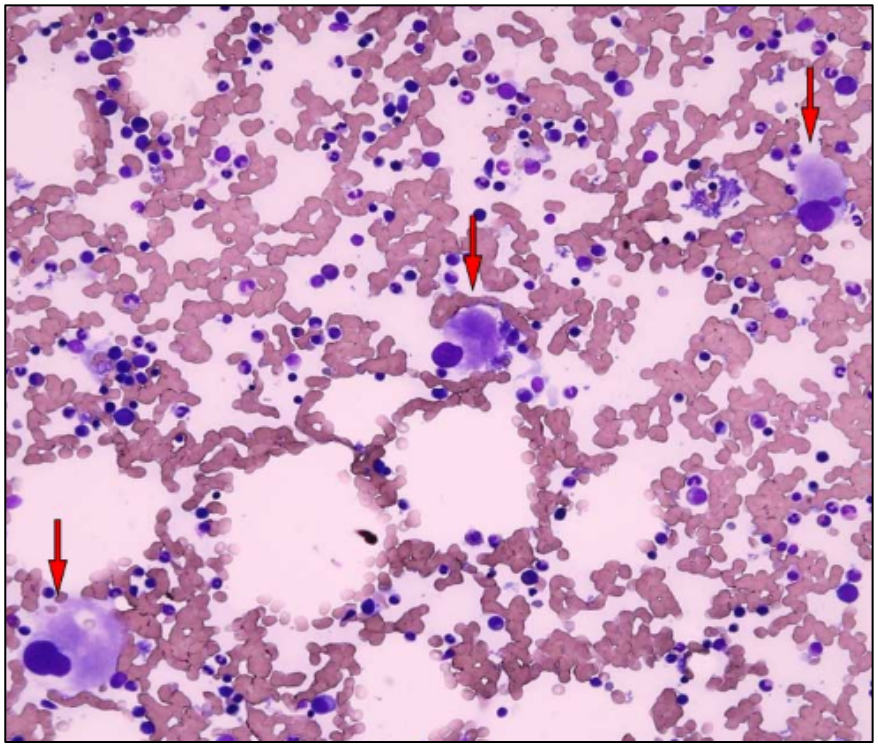
CYTOGENETIC ANALYSIS

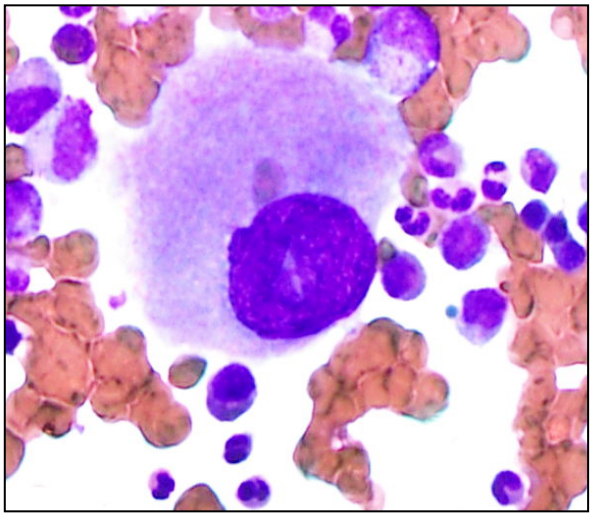
- Isolated interstitial deletion of 5q

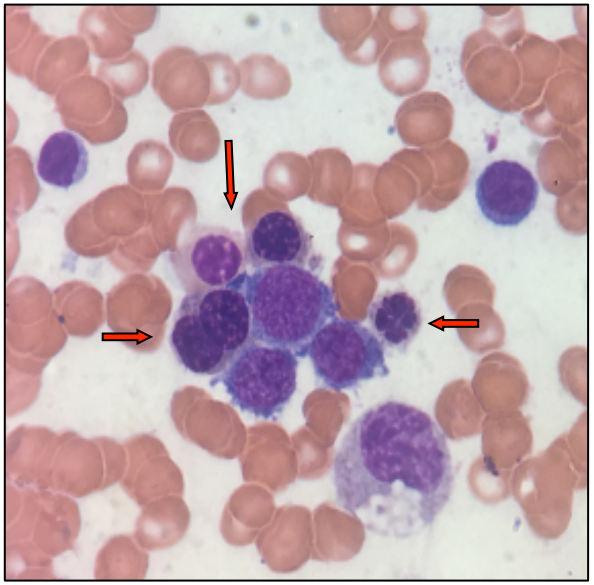




Del(5q) Syndrome: Morphology

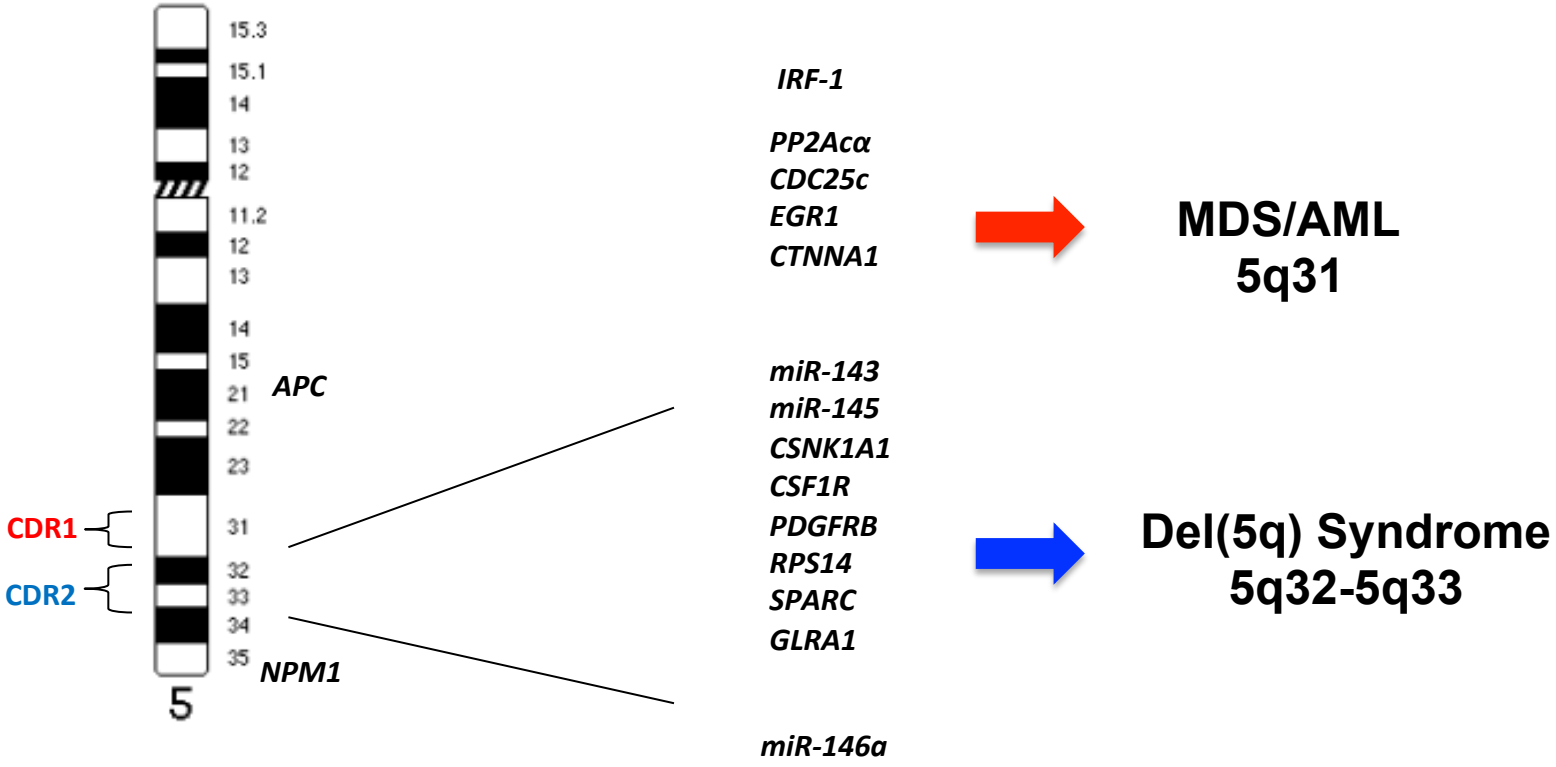






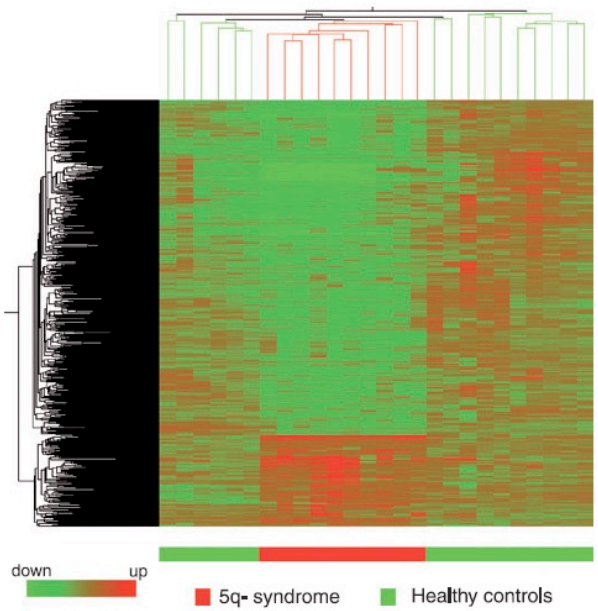
- normal/increased megakaryocytes with hypo or non lobated nuclei
- erythroid hypoplasia
- <5% myeloblasts

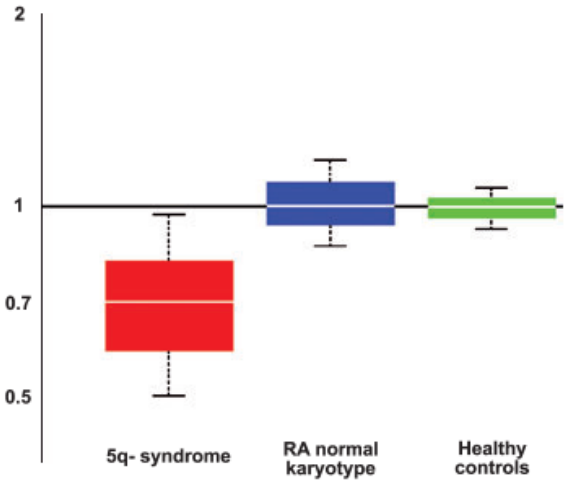
Del(5q) Syndrome: identification of the CDR



Boultwood et al, Blood 2002

Del(5q) Syndrome: GEP in CD34+ cells



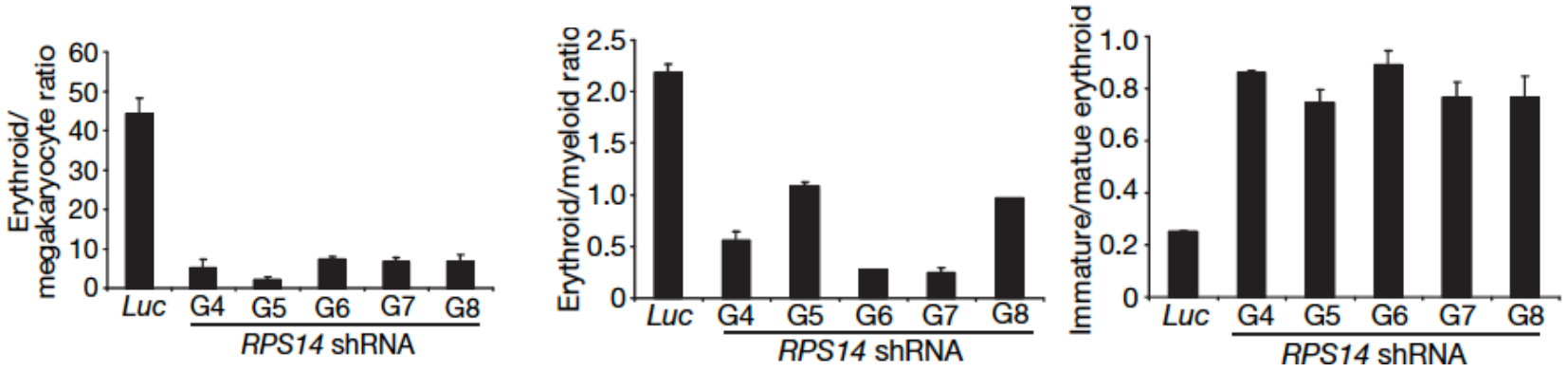


Most of the genes within the distal CDR are downregulated in 5q-syndrome:
RPS14, *CSNK1A1*, *SPARC, RBM22…*

Boultwood et al, BJH 2007

RPS14 haploinsufficiency and anemia

- Component of the 40S ribosomal subunit
- RNA interference (RNAi)-based screen knocked down *RPS14* inducing a block in erythroid differentiation with relative preservation of megakaryocytic and myeloid differentiation

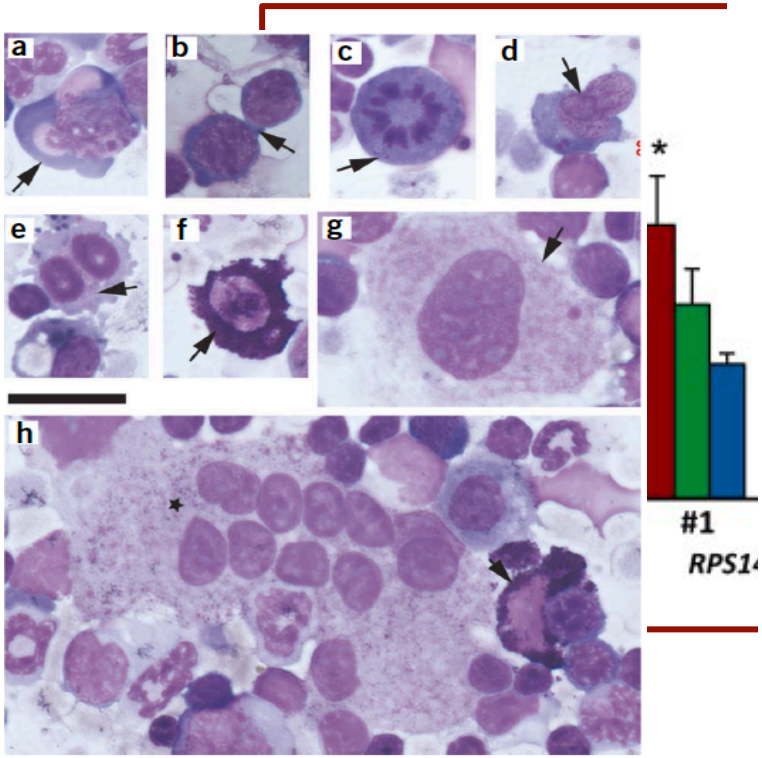


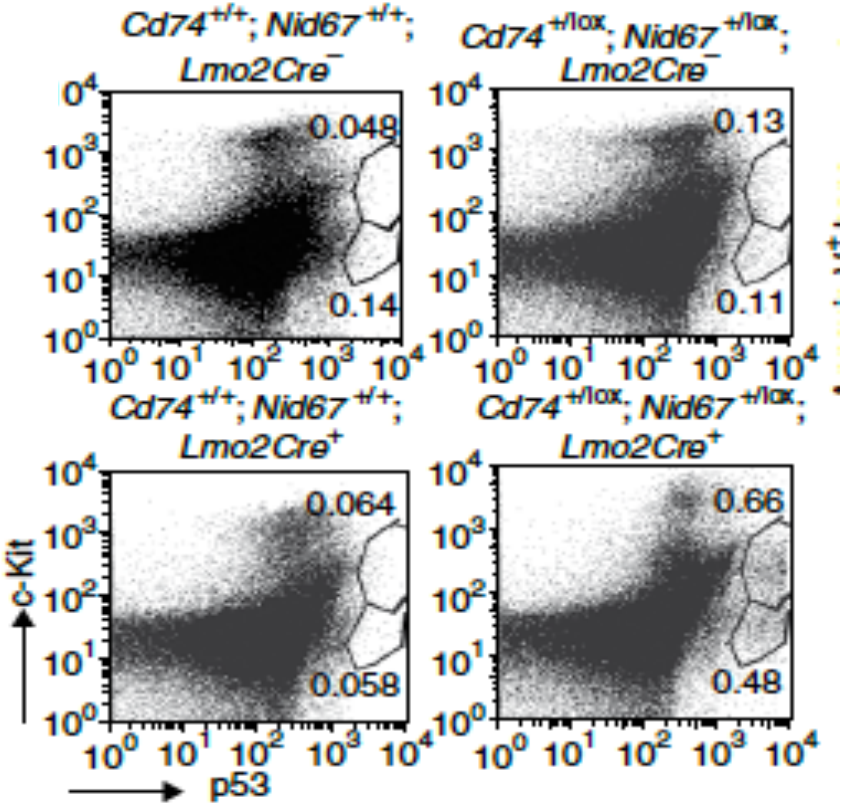
- Forced expression of *RPS14* in primary bone marrow cells from 5q- syndrome patients rescued the phenotype

Ebert et al, Nature 2008

RPS14 haploinsufficiency and p53

- Synthenic mouse model for human 5q- syndrome by allelic deletion of CDR *(RPS14)*
- p53 expression and apoptosis
- Intercrossing of these mice with p53-deficient mice rescues the progenitor deficit
- Lineage specific p53 accumulation in human erythroid cells



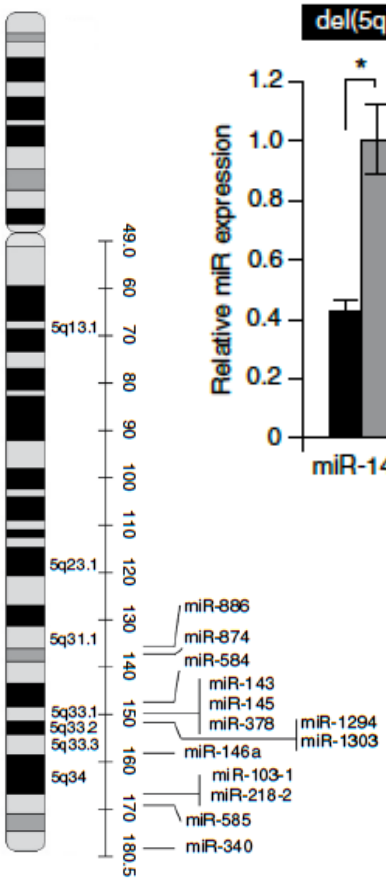


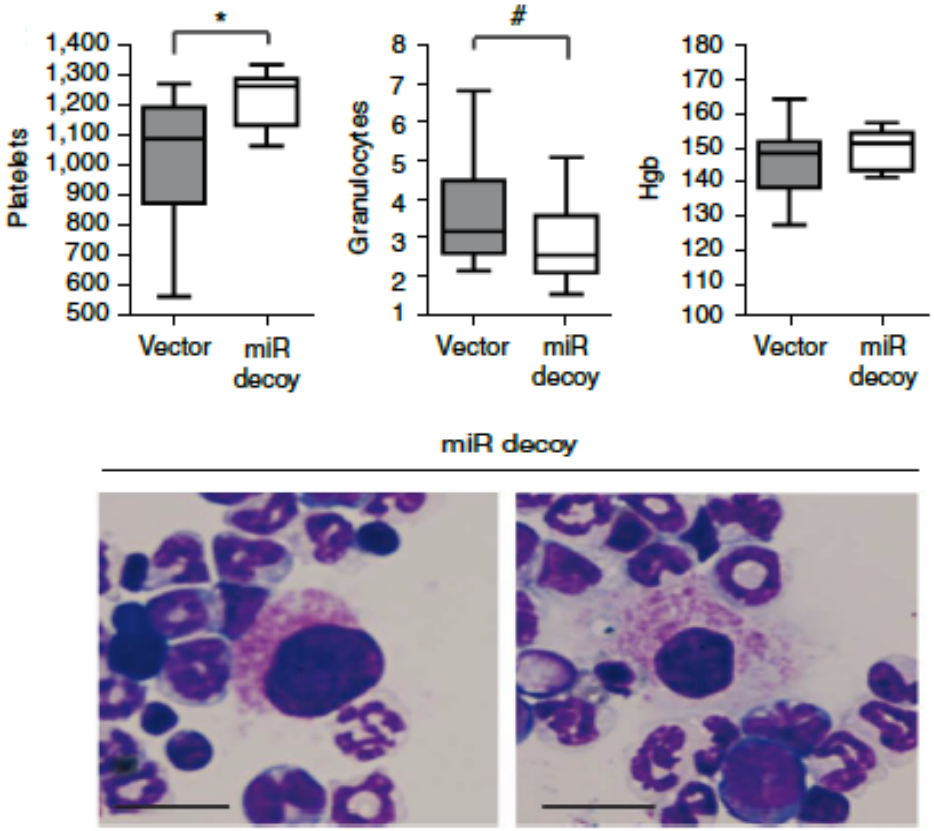
Barlow et al, Nat Med 2009

Dutt et al, Blood 2011

miR145 and miR146a in thrombocytosis

Low expression of *miR-145* (5q33.1) and *miR-146a* (5q33.3)
KD of *miR-145 and miR-146a* or overexpression of *TRAF6* in mouse HSPC recapitulate thrombocytosis, characteristic dysmegakaryopoiesis and variable neutropenia

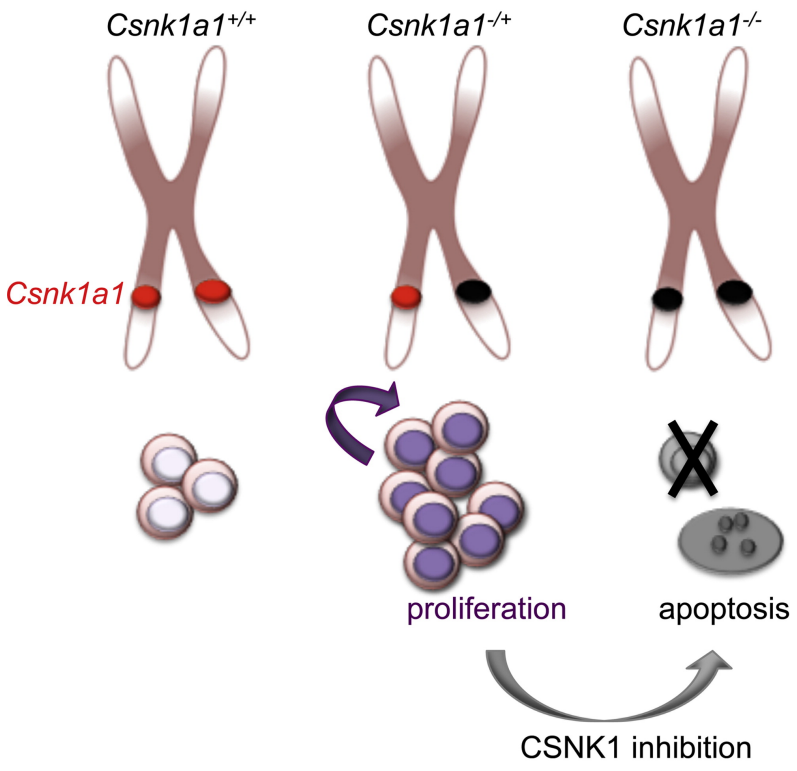


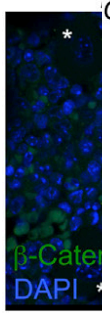


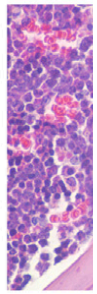
Starczynowski DT et al, Nat Med 2011

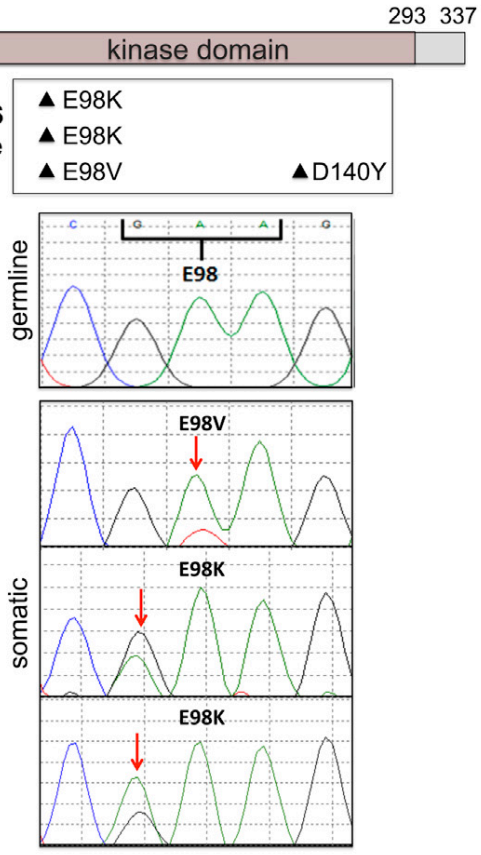
CSNK1A1: a critical role in clonal advantage

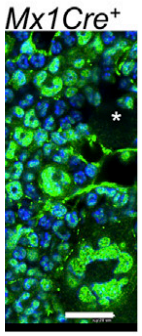
- Heterozygous inactivation causes cell expansion and B-catenin activation
- Mutated in 7% of 5q- syndrome

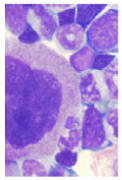


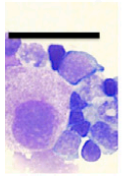






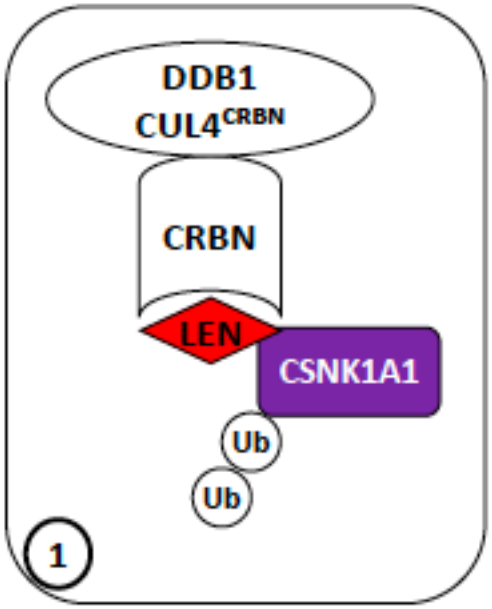


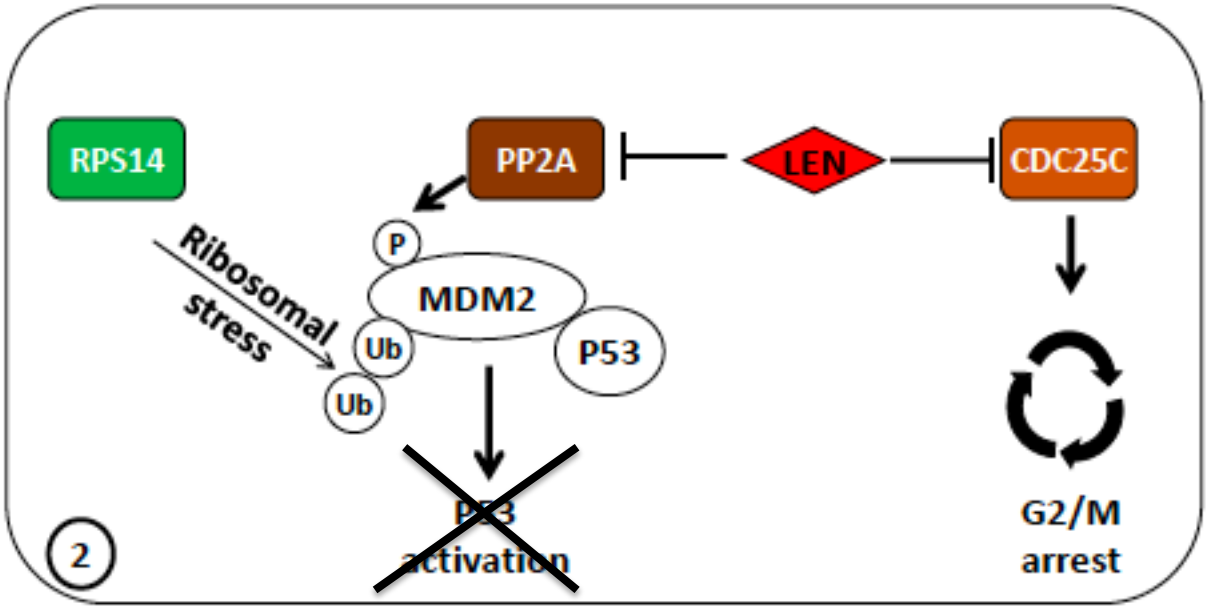




Schneider RK et al, Cancer Cell 2014

Lenalidomide: mechanisms of action





Homozygous loss of *CSNK1A1* causes *p53* induction
Ubiquitination of target proteins: *IKZF1, IKZF3*

Primary Resistence to Lenalidomide:
TP53 (*CSNK1A1*?) mutations
Overexpression of *PP2A*
Decrease of *CRBN* mRNA

Adapted from Loiseau et al, Exp Hematol. 2015

Lenalidomide History: MDS-001/3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Lenalidomide in Myelodysplastic Syndromes

Alan List, M.D., Sandy Kurtin, C.N.P., M.S., Denise J. Roe, Dr.P.H., Andrew Buresh, M.D., Daruka Mahadevan, M.D., Ph.D., Deborah Fuchs, M.D., Lisa Rimsza, M.D., Ruth Heaton, B.S., Robert Knight, M.D., and Jerome B. Zeldis, M.D.

- Phase I/II
- 43 trasfusion dependent MDS
- 25 mg or 10 mg (21 or 28 day-cycles)
- 10/12 (83%) major ER
- 9/10 (75%) complete CyR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

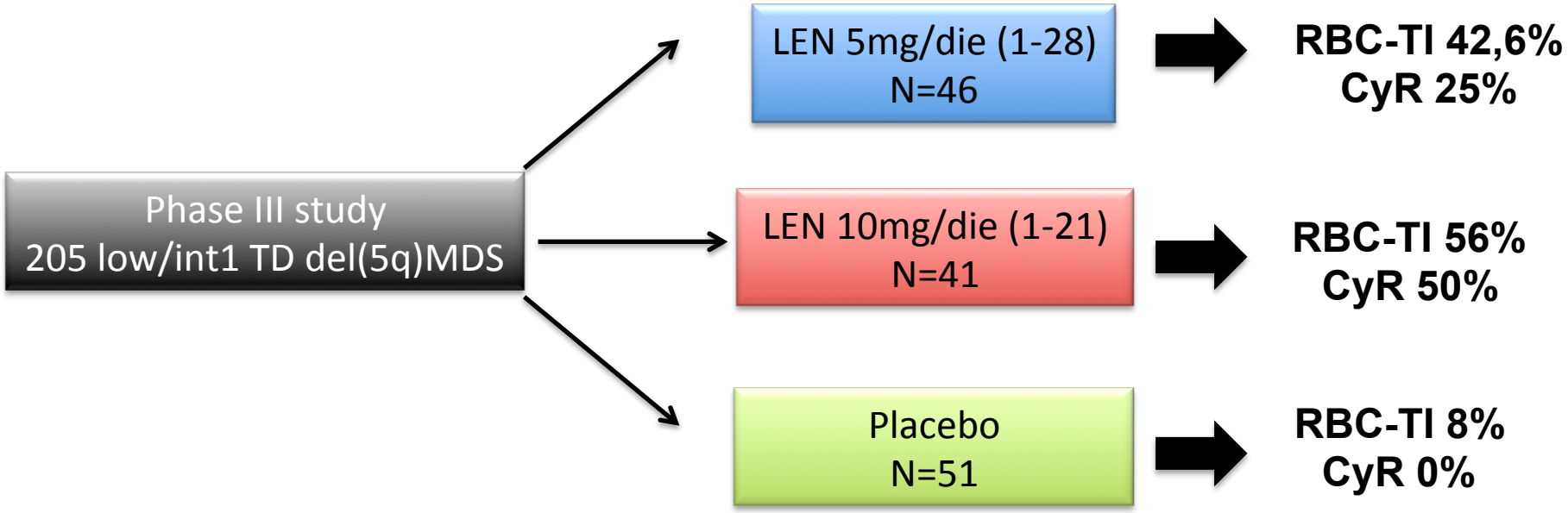
Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

Alan List, M.D., Gordon Dewald, Ph.D., John Bennett, M.D., Aristotle Giagounidis, M.D., Azra Raza, M.D., Eric Feldman, M.D., Bayard Powell, M.D., Peter Greenberg, M.D., Deborah Thomas, M.D., Richard Stone, M.D., Craig Reeder, M.D., Kenton Wride, M.S., John Patin, M.S., Michele Schmidt, R.N., Jerome Zeldis, M.D., and Robert Knight, M.D., for the Myelodysplastic Syndrome-003 Study Investigators*

- Multicenter phase II
- 148 low-risk del(5q) MDS
- 10 mg (21 or 28 day-cycles)
- 67% TI
- 73% CyR (45% complete)

List A et al, NEJM 2005/2006

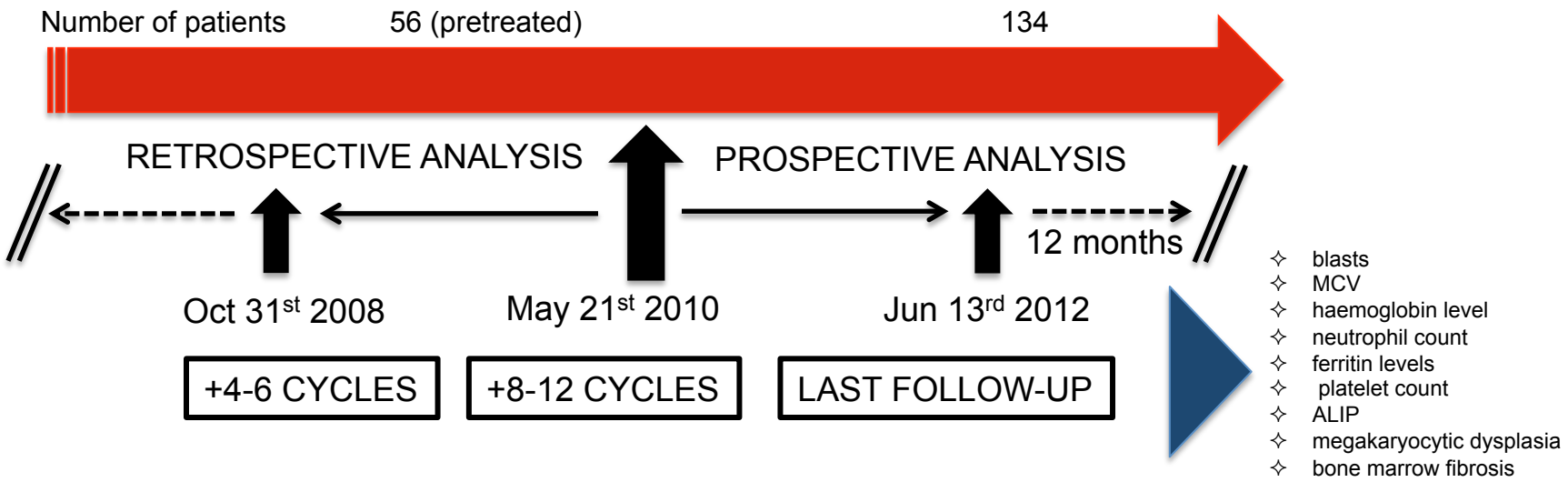
Lenalidomide Approval in Europe: MDS-004



- 10 mg dose is the most active
- Manageable safety profile
- No increase in AML progression
- Platelet count >150000/mmc predictive of RBC-TI

Fenaux P et al, Blood 2011

MO.RE Study: MOnotoring REvlimid
The Use of Lenalidomide In Italy



PRIMARY ENDPOINTS

- **to assess erythroid and cytogenetic responses**
- **to determine prescription and administration appropriateness**

SECONDARY ENDPOINTS

- **to monitor cytogenetic and haematological changes**
- **to identify prognostic subgroups**
- **to monitor LEN safety**

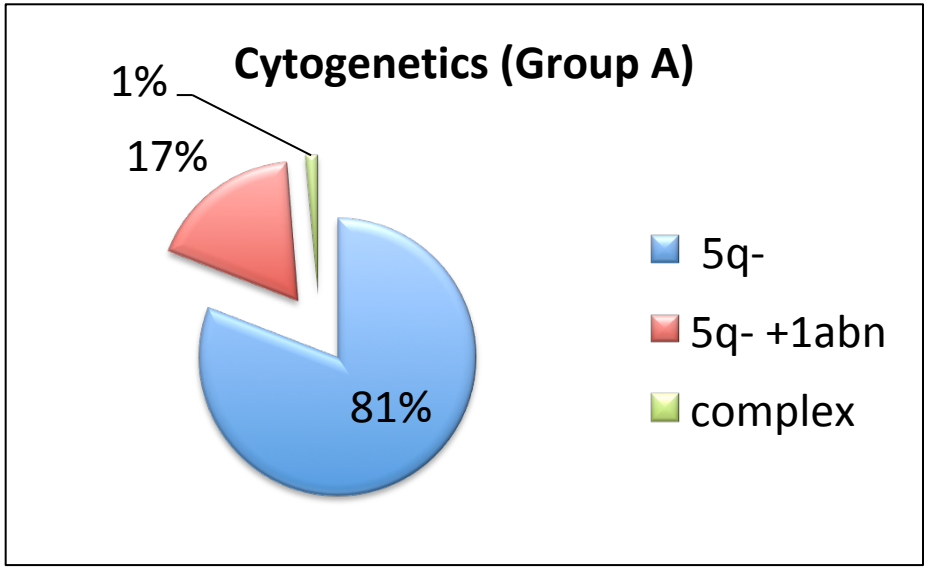
Arcioni F, Roncadori A, Di Battista V….Mecucci C, EJH 2018

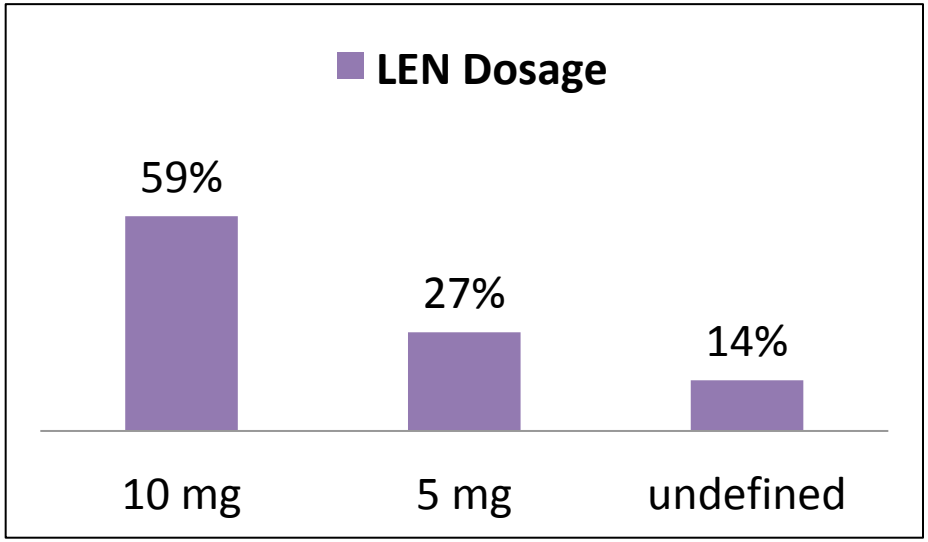
MO.RE Study: MOnitoring REvlimid

Eligible patients: 190/213;
M:F 1:2

	Group A Cy	Group B FISH
Patients (n)	149	41
Age (range)	38-95	41-87
Gender		
male	44	16
female	105	25
IPSS		
Low	69	20
Int1	80	21

Inclusion criteria:
1) LOW or INT-1 MDS;
2) transfusion-dependent anaemia;
3) 5q deletion, whether isolated or not





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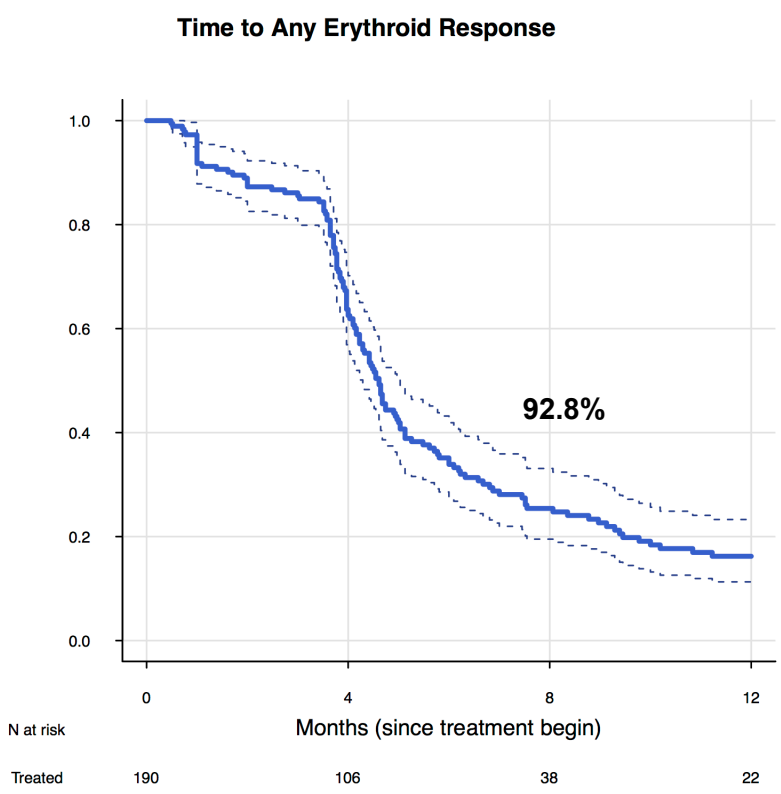
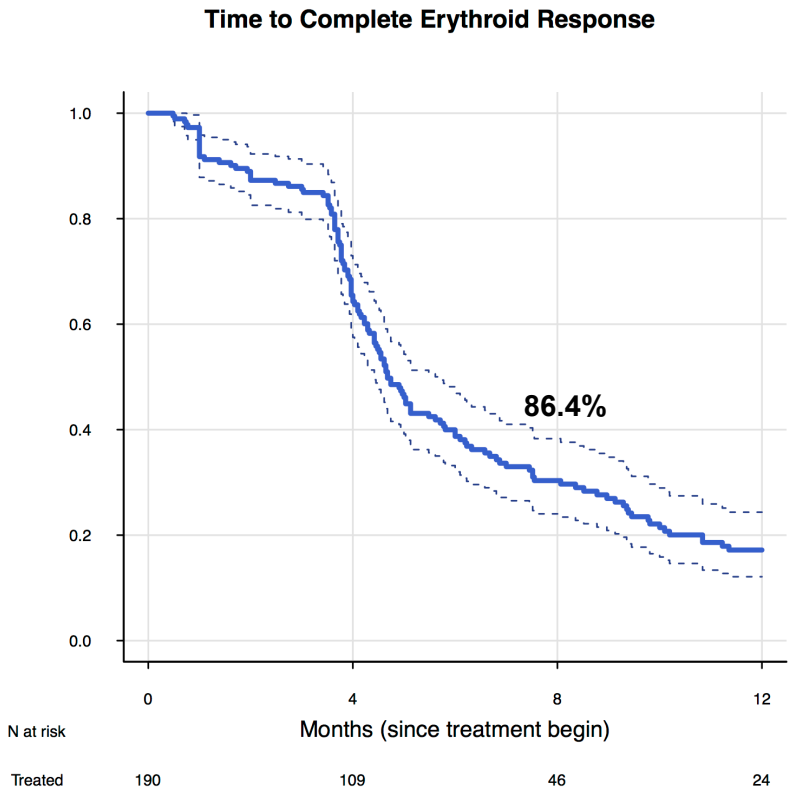
MO.RE Study: Erythroid response

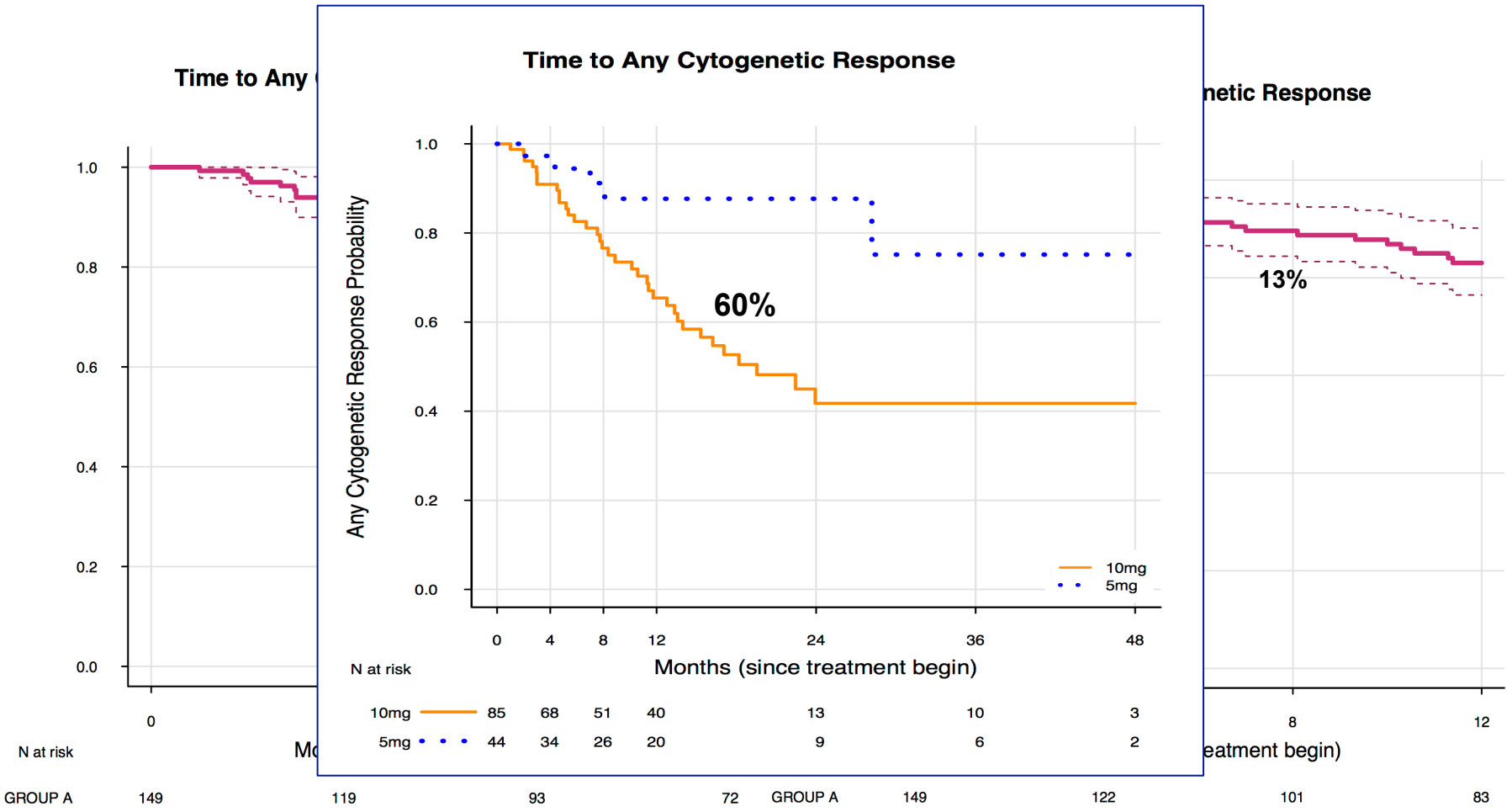




- Only the number of cycles >6 reached the statistical significance (P < .001).
- Platelet count (>100.000/mmc) was significant only in univariate analysis.
- No differences emerged in two treatment schedules.

Arcioni F, Roncadori A, Di Battista V….Mecucci C, EJH 2018

MO.RE Study: Cytogenetic response



Only the starting dosage at 10 mg LEN daily significantly correlated with overall cytogenetic response (P < .001)

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MO.RE Study: Disease progression

UPN	A/B	S/A	Diagnosis	Diagnosis (evolution)	Time from diagnosis to registry inclusion (months)		Registry observation period (months)	N° cycles	PLT	K (diagnosis)	K (evolution)	Cy Resp	Erythroid Resp
					Morph	Cy							
49259	B	M/65	RAEB1	AML	46	46	42	30 (7)	220000	/	Complex	/	Complete
50266	A	F/80	AR	AML	9	7	7	1	232000	Isolated 5q-	Complex	No	No
51081	A	F/65	RAEB 1	AML	60	0,42	6	4 (1)	88000	Isolated 5q-	Complex	No	No
52149	A	F/63	AR	AML	48	48	19	7 (1)	208000	Isolated 5q-	Isolated 5q-	No	Complete
52961	A	F/74	AR	AML	2	1	41	27	737000	Isolated 5q-	Isolated 5q-	No	Complete
54021	A	F/82	RAEB 1	AML	7	7	27	5	130000	5q- + 1 abn	Complex	No	No
59751	A	F/64	AR	AML	2	2	8	7	695000	Isolated 5q-	Isolated 5q-	No	No
80601	A	F/71	AR	AML	20	20	35	14	358000	Isolated 5q-	Isolated 5q-	No	No
81684	A	F/72	AR	AML	13	13	25	16	473000	Isolated 5q-	Complex	No	No
82594	B	M/73	AR	AML	2	1	8	8	17100	/	/	/	No
828													o
106													plete
122													o
140													o
158													o
171													o
114													o
159635	A	F/75	AR	AML	24	1	10	10	21400	Isolated 5q-	Isolated 5q-	No	Complete
48876	A	M/72	AR	RAEB1	10	42	33	35 (2)	122000	Isolated 5q-	Abnormal without 5q-	No	Complete
49105	A	F/66	RAEB1	RAEB2	29	7	14	8	154000	Isolated 5q-	Isolated 5q-	No	No
49570	A	M/67	AR	RAEB1	36	6	40	33 (2)	298000	Isolated 5q-	Isolated 5q-	No	Complete
49634	A	F/61	AR	RAEB2	36	10	20	6	237000	Isolated 5q-	Isolated 5q-	No	Complete
49974	B	M/61	AR	RAEB1	60	4	39	56 (17)	87000	/	/	/	Complete
50185	A	F/74	AR	RAEB1	54	27	31	29 (1)	55000	5q- + 1 abn	5q- + 1 abn	No	Complete
50368	A	M/58	AR	RAEB2	12	8	31	23 (1)	45000	Isolated 5q-	5q- + 1 abn	No	Complete
51948	B	F/71	RAEB1	RAEB2	6	35	7	4	201000	/	Isolated 5q-	/	No
71655	A	M/67	AR	RAEB1	84	25	12	17 (5)	121000	Isolated 5q-	Isolated 5q-	No	No
132971	A	M/89	AR	RAEB2	36	8	26	22	243000	Isolated 5q-	Isolated 5q-	No	Complete
145855	B	F/76	AR	RAEB2	24	2	8	7	157000	/	/	/	No
157011	A	F/68	AR	RAEB1	53	14	17	17	88000	5q- + 1 abn	5q- + 1 abn	No	Complete

9,5% AML evolution

AML evolution is associated to complex karyotype in 53% of cases, whereas complex cytogenetics and new cytogenetic aberrations never appeared when MDS evolved towards a higher risk category

6,1% HR MDS progression

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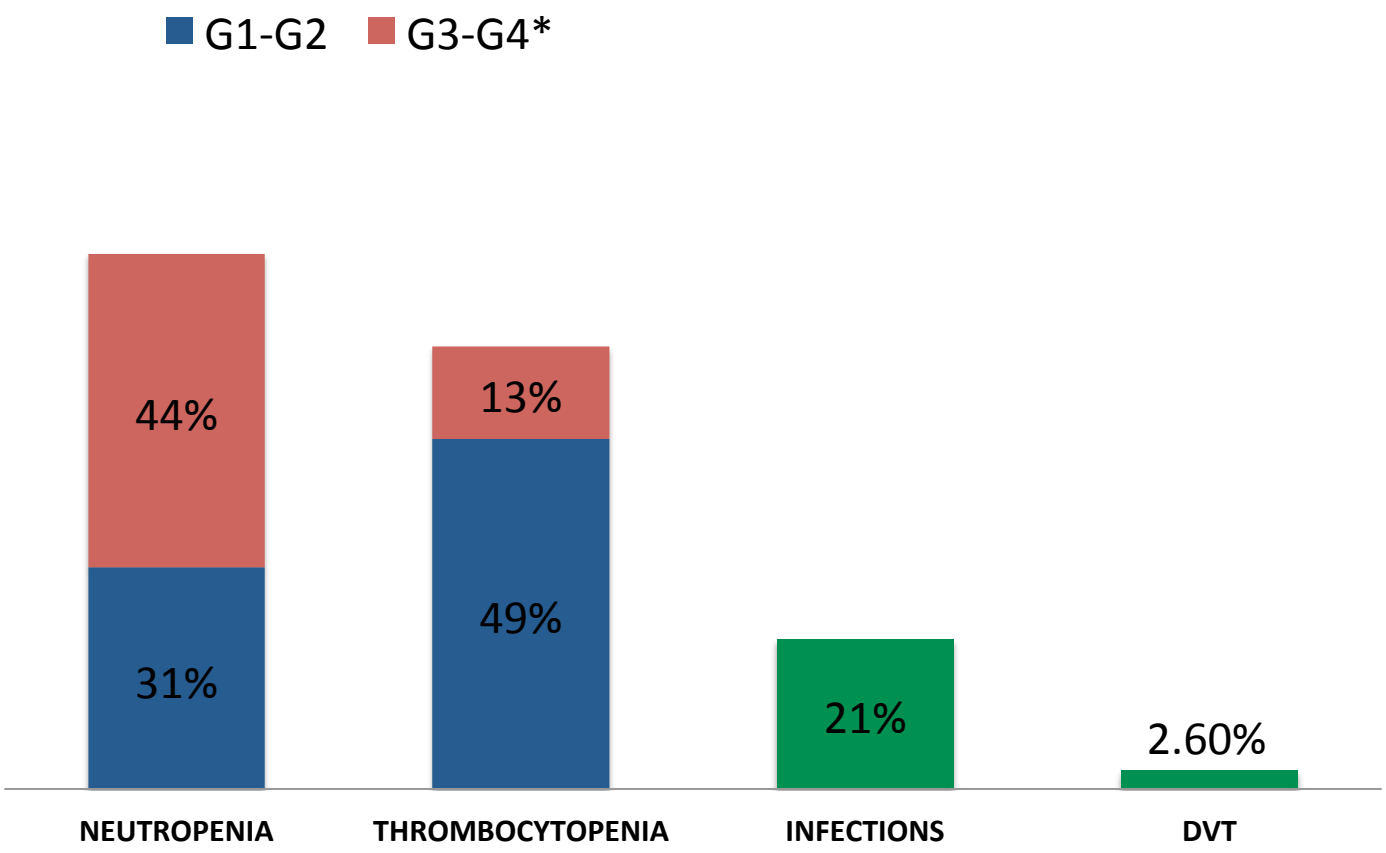
MO.RE Study: Adverse events



*The incidence of neutropenia and thrombocytopenia was higher during the first 6 months of treatment

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MO.RE Study: Conclusions

- ✓ Correct patient selection and management of LEN administration
- ✓ Erythroid response results in line with literature and depends on the duration of therapy
- ✓ Cytogenetic response in the 10 mg group results in line with literature confirming the 10 mg dosage as the best
- ✓ A good response rate is observed even when an additional chromosomal change accompanied del(5q)
- ✓ Clonal cytogenetic evolution appears during AML evolution but not during progression into higher risk MDS
- ✓ **Limitations of the study:** heterogeneous dosages, no molecular investigation

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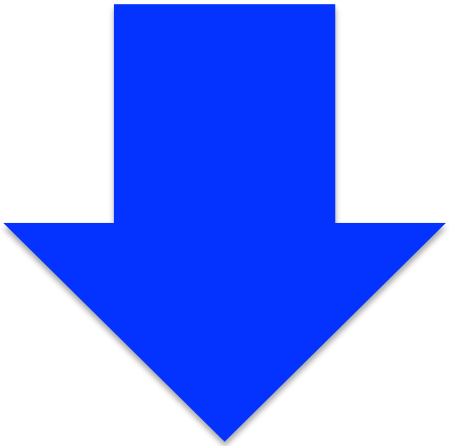
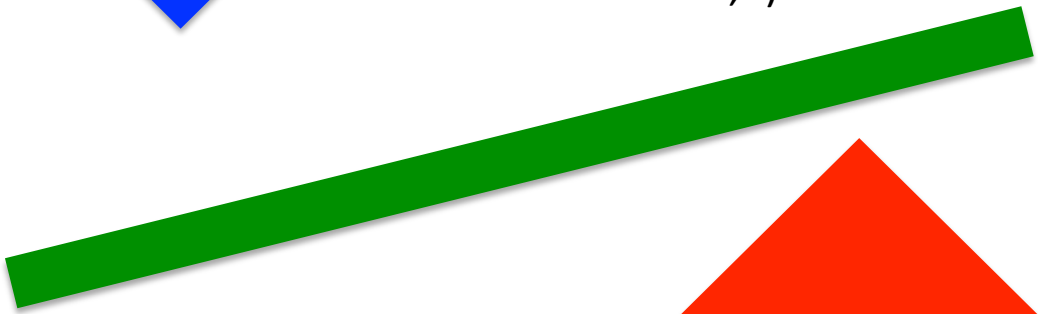
Del(5q) Syndrome: Chaos and Order



Chaos

- Early treatment
- Monitoring MRD (Karyotype/ FISH/cytofluorimetry?)
- ..and after Lenalidomide failure?
- New therapeutic options (dexamethasone, Cenersen, L-Leucine,..)

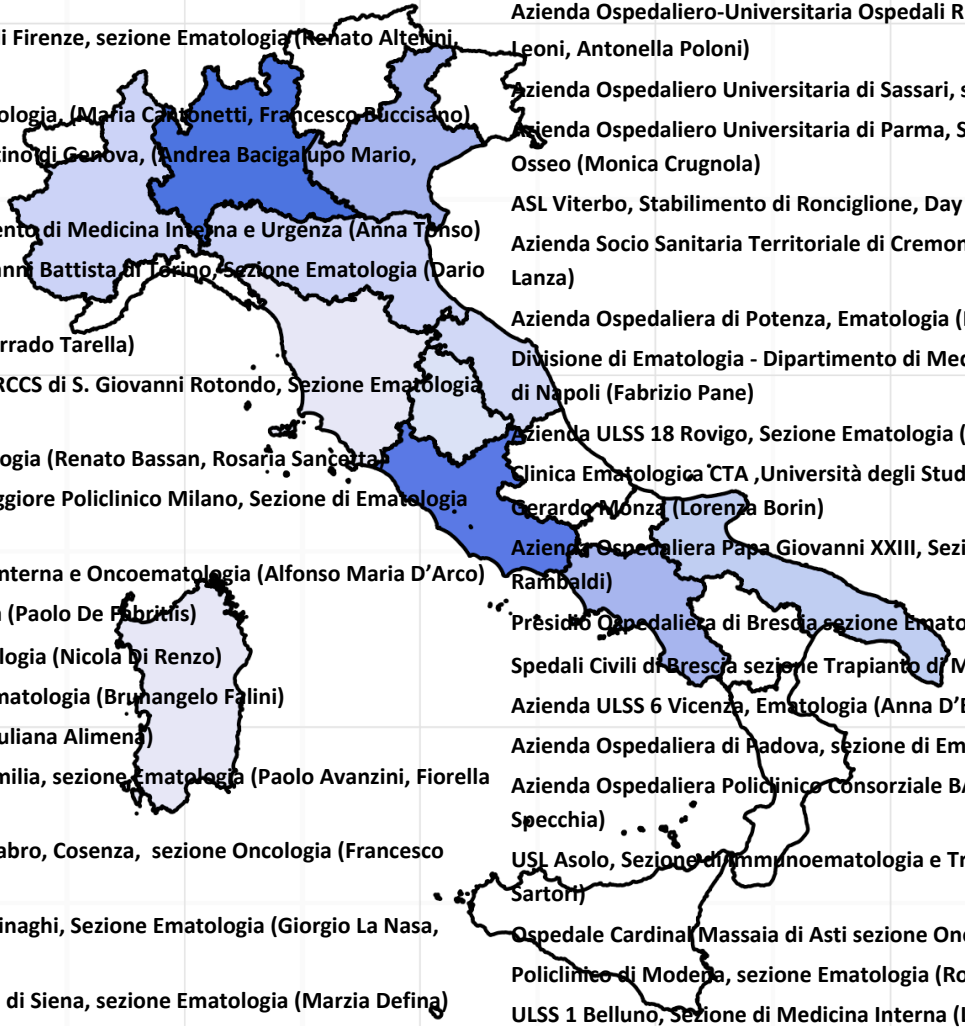


Order

- ESAs (if <500U/ML)
- Del(5q)± 1abn
- 10 mg dosage
- Mutational analysis (*TP53, CSNK1A*, ..)

Aknowledgements

MORE partecipating Centres



Azienda Ospedaliera Sant'Anna e San Sebastiano di Caserta, sezione di Oncoematologia (Antonio Abbadessa)

Azienda Ospedaliera Universitaria Careggi di Firenze, sezione Ematologia (Renato Altenini, Valeria Santini)

Policlinico Tor Vergata Roma, Sezione Ematologia, (Maria Cantonetti, Francesco Buccisano)

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