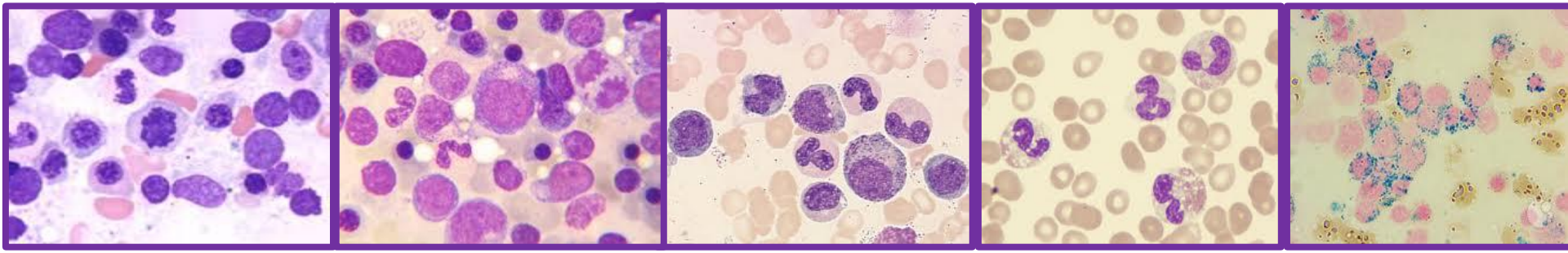
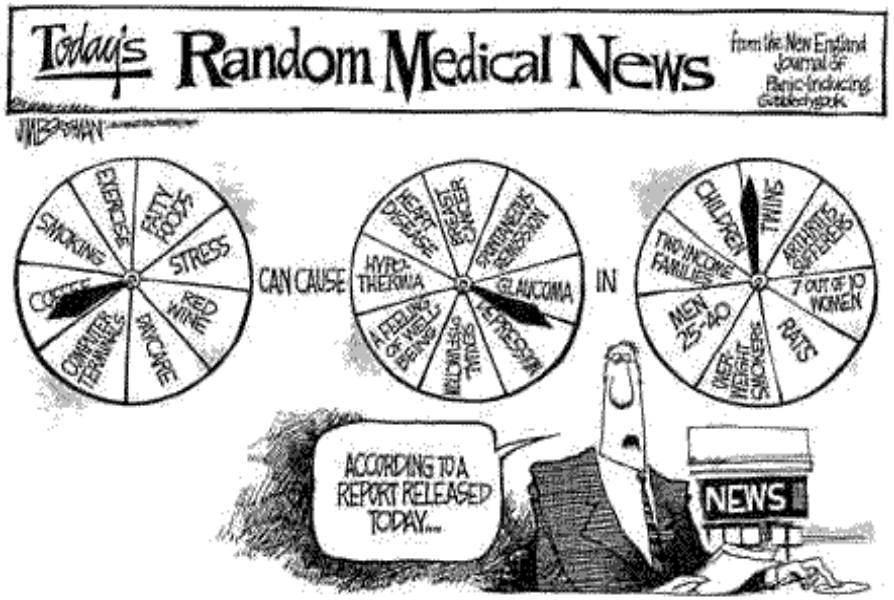
ΝΕΟΤΕΡΑ ΠΡΟΓΝΩΣΤΙΚΑ ΜΟΝΤΕΛΑ ΣΤΑ ΜΥΕΛΟΔΥΣΠΛΑΣΤΙΚΑ ΣΥΝΔΡΟΜΑ- ΘΕΡΑΠΕΥΤΙΚΕΣ ΕΦΑΡΜΟΓΕΣ



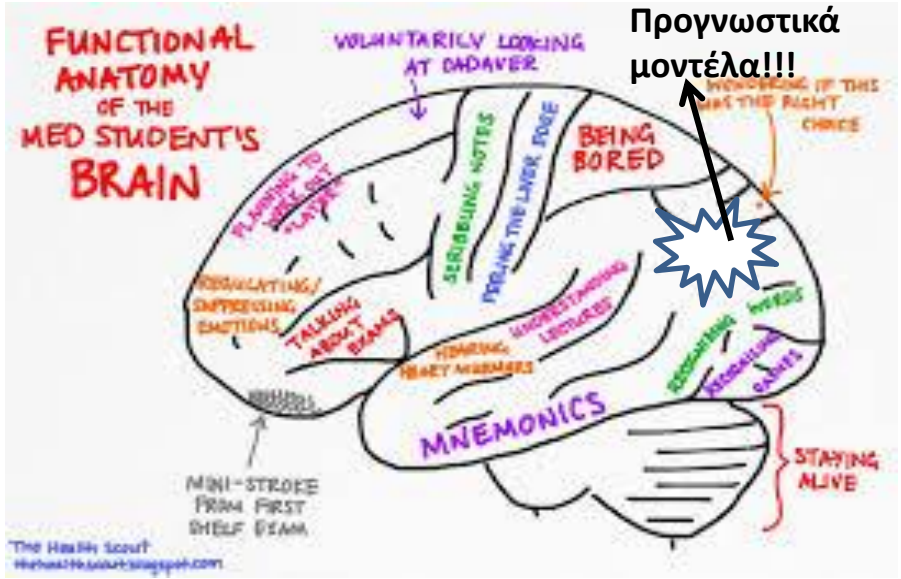
Θεώνη Κανελλοπούλου

ΓΝΑ Ευαγγελισμός, 03 Ιούνη 2014

ΕΙΝΑΙ ΣΗΜΑΝΤΙΚΑ :::



…ή δημιουργούν σύγχυση???!!!

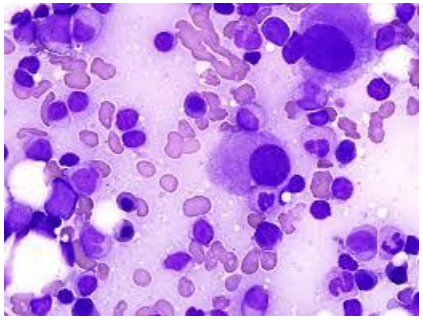


Προγνωστικά μοντέλα!!!

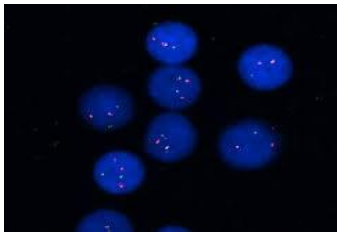
ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΣΤΑΤΙΚΩΝ

- Γυναίκα 60 ετών
- Αναιμία <8g/dL από διμήνου που χρήζει μεταγγίσεων ανά 2 εβδομάδες
- Λευκά και αιμοπετάλια εντός ΚΦ τιμών
- Λοιπό ιστορικό ελεύθερο

- Μυελός Βλ<2%



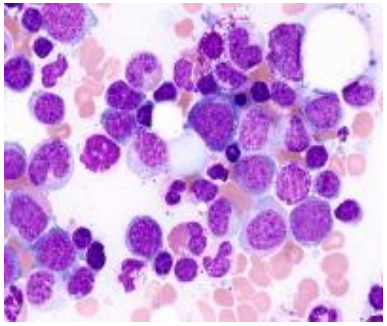
- FISH 5q(-)



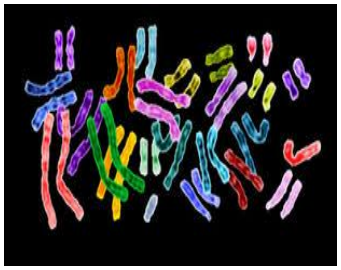
Επιβίωση > 5 έτη
Κίνδυνος εξέλιξης σε ΟΜΛ 10 έτη

- Άνδρας 60 ετών
- Εμπύρετο, δύσπνοια, καταβολή δυνάμεων
- Πανκυτταροπενία

- Μυελός Βλ.15%



- Καρυότυπος 44ΧΥ,-7,-5



Επιβίωση < 6 μήνες
Κίνδυνος εξέλιξης σε ΟΜΛ 2.5 μήνες

ΤΑ ΠΡΟΓΝΩΣΤΙΚΑ ΜΟΝΤΕΛΑ ΕΙΝΑΙ ΣΗΜΑΝΤΙΚΑ…

- **Κλινική ετερογένεια**
  - ✓ **ποιοι ασθενείς θα μεταπέσουν σε ΟΜΛ;**

- **Ανάγκη ομαδοποίησης**
  - ✓ **Χαρακτηριστικά νόσου**

    κυτταροπενίες, εξέλιξη σε ΟΜΛ, ίνωση μυελού, βιοχημικοί δείκτες
    - *IPSS, WPSS, MDACC, LR-PSS, IPSS-R*
  - ✓ **Χαρακτηριστικά ασθενών**

    ηλικία, ECOG, συννοσηρότητα
    - *MDS-CI*

- **Ενημέρωση ασθενών**

- **<u>Θεραπευτικές αποφάσεις</u>**

blood 1997 89: 2079-2088

IPSS

International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes

Peter Greenberg, Christopher Cox, Michelle M. LeBeau, Pierre Fenaux, Pierre Morel, Guillermo Sanz, Miguel Sanz, Teresa Vallespi, Terry Hamblin, David Oscier, Kazuma Ohyashiki, Keisuke Toyama, Carlo Aul, Ghulam Mufti and John Bennett

	Βαθμός (score)				
ΠΡΟΓΝΩΣΤΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ	**0**	**0.5**	**1.0**	**1.5**	**2.0**
βλάστες μυελού	< 5%	5% -10%	--	11% - 20%	21% - 30%
καρυότυπος*	Καλός	Ενδιάμεσος	Κακός	--	--
κυτταροπενίες†	0-1	2-3	--	--	--

	0	**0.5**	**1.0**	**1.5**	**2.0**	**≥ 2.5**
Ομάδα κινδύνου	**Χαμηλός**	**Ενδιάμεσος I**		**Ενδιάμεσος II**		**Υψηλός**
Διάμεση επιβίωση, έτη	5.7	3.5		1.2		0.4
Εξέλιξη σε ΟΜΛ, έτη	9.4	3.3		1.1		0.2

*καλός = φυσιολογικός, -Y, del(5q), del(20q); ενδιάμεσος = άλλες ανωμαλίες; κακός = σύνθετος (≥ 3 ανωμαλίες) ή ανωμαλίες στο χρωμόσωμα 7.
†Hb < 10 g/dL; ANC < 1800/μL; PLT < 100,000/μL.

A)

Prognostic Category	IPSS Prognostic Score Value				
	0	0.5	1	1.5	2
Cytogenetics	Good	Intermediate	Poor		
BM blasts, %	< 5	5-10		11-20	21-30
Cytopenias	0/1	2/3			

Cytogenetic groups

Good: normal, -Y, del(5q), del(20q)

Intermediate: any not considered good or poor

Poor: complex (≥ 3 abnormalities), chromosome 7 abnormalities

Cytopenias definitions

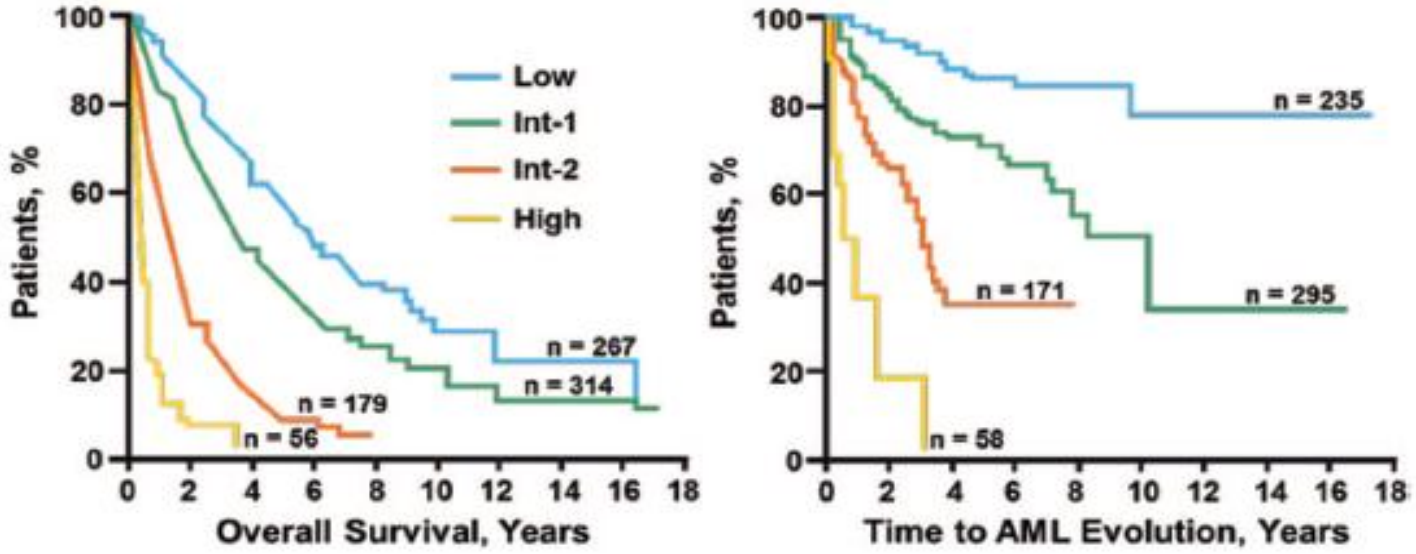
Hemoglobin: <10 gm/dL

Neutrophils: < 1800^9/L

Platelets: < 100×10^9/L

Risk Category	Risk Score
Low	0
Int-1	0.5-1.0
Int-2	1.5-2.0
High	≥ 2.5

B)



ΜΕΙΟΝΕΚΤΗΜΑΤΑ IPSS

- **Μεγαλύτερη βαρύτητα στο ποσοστό των βλαστών από τις κυτταρογενετικές ανωμαλίες**
  - ✓ Κατηγοριοποίηση με βάση το φαινόμενο και όχι το αίτιο

- **Δε διαφοροποιείται η βαρύτητα των κυτταροπενιών**
- Δε λαμβάνεται υπόψη η ανάγκη για μεταγγίσεις

- Εφαρμογή μόνο σε de novo ΜΔΣ
  - Κατάταξη κατά FAB
  - Περιλαμβάνονται περιστατικά ΟΜΛ, ΧΜΜΛ

- **Όχι κατάλληλο μοντέλο στα χαμηλού κινδύνου ΜΔΣ**

10 χρόνια αργότερα …

VOLUME 25 · NUMBER 23 · AUGUST 10 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

WPSS

Time-Dependent Prognostic Scoring System for Predicting Survival and Leukemic Evolution in Myelodysplastic Syndromes

Luca Malcovati, Ulrich Germing, Andrea Kuendgen, Matteo G. Della Porta, Cristiana Pascutto, Rosangela Invernizzi, Aristoteles Giagounidis, Barbara Hildebrandt, Paolo Bernasconi, Sabine Knipp, Corinna Strupp, Mario Lazzarino, Carlo Aul, and Mario Cazzola

Score	WHO κατάταξη	Καρυότυπος (1)	Ανάγκη μεταγγίσεων (2)
0	RA, RARS, 5q-	Καλός	Όχι
1	RCMD	Ενδιάμεσος	Ναι
2	RAEB-1	Κακός	-
3	RAEB-2	-	-

(1) Καρυότυπος : Καλός = ΚΦ, -Y, del(5q-), del(20q-). Κακός = σύνθετος (≥3 ανωμαλίες), ή ανωμαλίες στο χρωμόσωμα 7. Ενδιάμεσος = όλοι οι υπόλοιποι.
(2) Ανάγκη μεταγγίσεων ορίζεται το λιγότερο μία μονάδα κάθε 8 εβδομάδες για περίοδο 4 μηνών.

Score	Ομάδα κινδύνου	Διάμεση επιβίωση, μήνες	Εξέλιξη σε ΟΜΛ, 2 έτη
0	**Πολύ χαμηλός**	141	3%
1	**Χαμηλός**	66	6%
2	**Ενδιάμεσος**	48	21%
3 - 4	**Υψηλός**	26	38%
5 - 6	**Πολύ υψηλός**	9	80%

A)

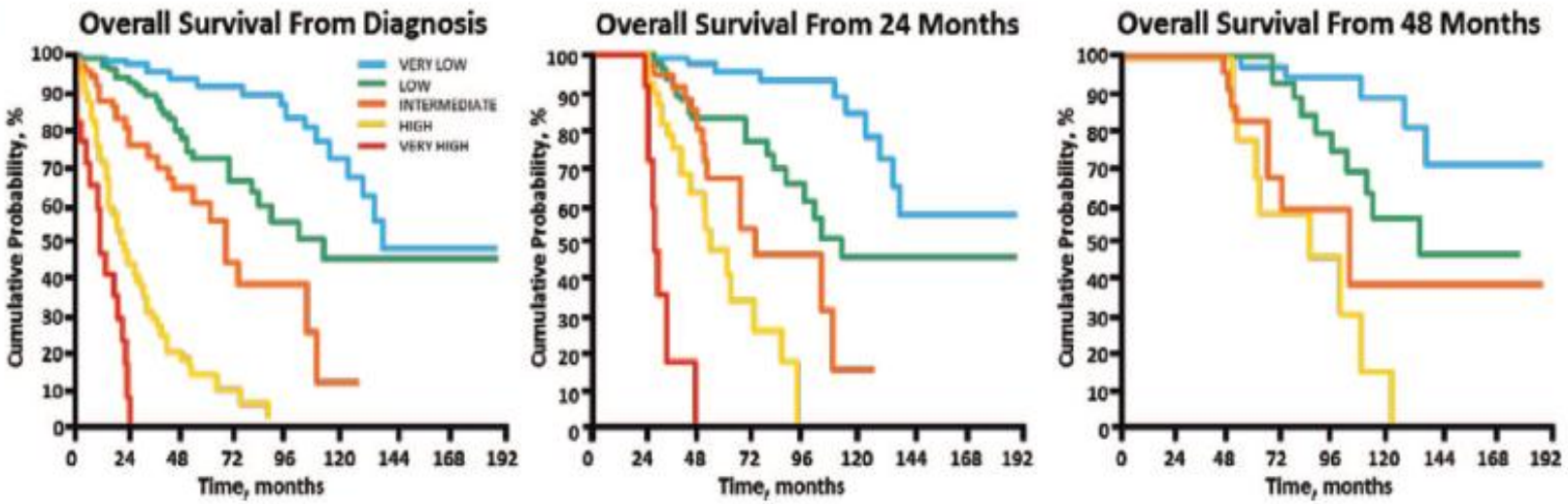
Prognostic Category	WPSS Prognostic Score Value			
	0	1	2	3
WHO category	RCUD, RARS, MDS with isolated del(5q)	RCMD	RAEB-1	RAEB-2
Cytogenetics	Good	Intermediate	Poor	
Severe anemia	Absent	Present		

Cytogenetics are based on IPSS groups

Severe anemia defined as hemoglobin < 9 g/dL in males or < 8 g/dl in females

Risk Category	Risk Score
Very low	0
Low	1
Intermediate	2
High	3-4
Very high	5-6

B)



WPSS

- **Δυναμικό σύστημα**.
- Επιβίωση και εξέλιξη σε ΟΜΛ σε οποιαδήποτε στιγμή της ζωής του ασθενούς
- Ιδιαίτερο χρήσιμο για την πρόγνωση ασθενών χαμηλού κινδύνου και του σωστού χρόνου για μεταμόσχευση

- Δεν υπολογίζεται η βαρύτητα της ουδετεροπενίας – θρομβοπενίας
- Δε μπορεί να εφαρμοστεί στα ΜΥΝ/ΜΔΣ

blood 2012 120: 2454-2465
doi:10.1182/blood-2012-03-420489 originally published online June 27, 2012

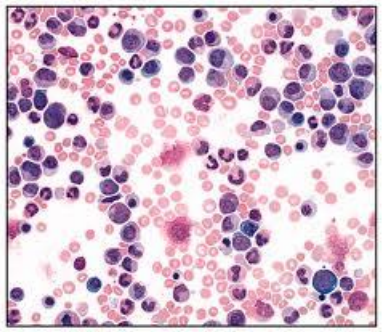
Revised International Prognostic Scoring System for Myelodysplastic Syndromes

Peter L. Greenberg, Heinz Tuechler, Julie Schanz, Guillermo Sanz, Guillermo Garcia-Manero, Francesc Solé, John M. Bennett, David Bowen, Pierre Fenaux, Francois Dreyfus, Hagop Kantarjian, Andrea Kuendgen, Alessandro Levis, Luca Malcovati, Mario Cazzola, Jaroslav Cermak, Christa Fonatsch, Michelle M. Le Beau, Marilyn L. Slovak, Otto Krieger, Michael Luebbert, Jaroslaw Maciejewski, Silvia M. M. Magalhaes, Yasushi Miyazaki, Michael Pfeilstöcker, Mikkael Sekeres, Wolfgang R. Sperr, Reinhard Stauder, Sudhir Tauro, Peter Valent, Teresa Vallespi, Arjan A. van de Loosdrecht, Ulrich Germing and Detlef Haase

IPSS-R

Προγνωστικές υποομάδες	Καρυοτυπικές ανωμαλίες	Διάμεση επιβίωση, έτη	Κίνδυνος εξέλιξης σε ΟΜΛ, έτη	HR OS/AML
Πολύ καλή	-Y, del(11q)	5.4	NR	0.7/0.4 -0.5/0.5
Καλή	ΚΦ, del(5q), del(12p), del(20q), 2 ανωμαλίες που περιλαμβάνουν del(5q)	4.8	9.4	1/1
Ενδιάμεση	del(7q), +8, +19, i(17q), άλλοι μονοί ή διπλοί ανεξάρτητοι κλώνοι	2.7	2.5	1.5/1.8 – 1.6/2.2
Κακή	-7, inv(3)/t(3q)/del(3q), 2 ανωμαλίες με -7/del(7q), σύνθετος: 3 ανωμαλίες	1.5	1.7	2.3/2.3 – 2.6/3.4
Πολύ κακή	Σύνθετος: >3 ανωμαλίες	0.7	0.7	3.8/3.6 – 4.2/4.9

	Score						
Προγνωστικοί παράγοντες	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**3.0**	**4.0**
Καρυότυπος	Πολύ καλός	--	Καλός	--	Ενδιάμεσος	Κακός	Πολύ κακός
Βλάστες μυελού %	≤ 2	--	> 2 και < 5	--	5-10	> 10	--
Hb, g/dL	≥ 10	--	8 έως < 10	<8	——	——	——
PLT, x 10^9/L	≥ 100	50 - 100	< 50	——	——	——	——
ANC, x 10^9/L	≥ 0.8	< 0.8	--	——	——	——	——



ΚΙΝΔΥΝΟΣ	**Score**
Πολύ χαμηλός	≤ 1.5
Χαμηλός	> 1.5 έως 3
Ενδιάμεσος	> 3.0 έως 4.5
Υψηλός	> 4.5 έως 6.0
Πολύ υψηλός	> 6

I P S S - R

C)

Prognostic Category	IPSS-R Prognostic Score Value						
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good		Good		Int	Poor	Very poor
BM blasts, %	≤ 2		> 2-< 5		5-10	> 10	
Hemoglobin, g/dL	≥ 10		8-< 10	< 8			
Platelets, × 10^9/L	≥ 100	50-< 100	< 50				
ANC, × 10^9/L	≥ 0.8	< 0.8					

Cytogenetic groups

Very good: –Y, del(11q)

Good: normal, del(5q), del(12p), del(20q), del(5q) + 1 additional

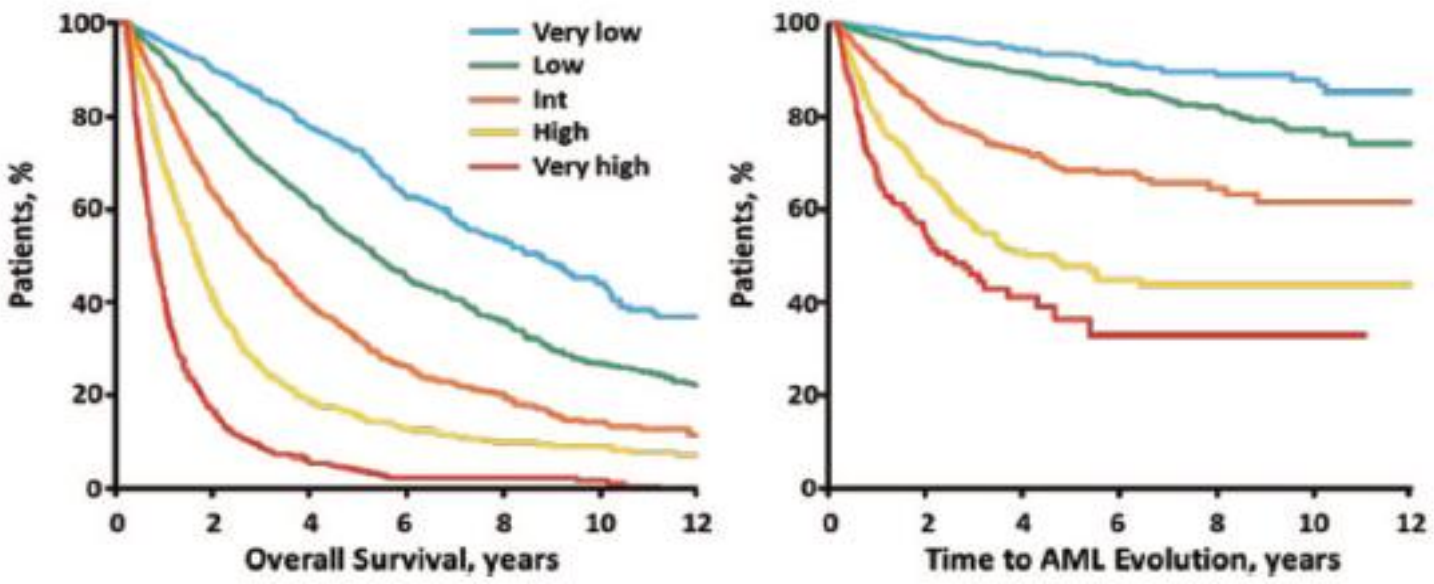
Intermediate: del(7q), +8, +19, i(17q), other abnormalities not in other groups

Poor: -7, inv(3)/t(3q)/del(3q), -7/del(7q) + 1 additional, complex (3 abnormalities)

Very poor: complex (> 3 abnormalities)

Risk Category	Risk Score (for age 70)
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

D)



ΘΕΡΑΠΕΥΤΙΚΟΙ ΑΛΓΟΡΙΘΜΟΙ, NCCN 2014:

IPSS, WPSS, IPSS-R

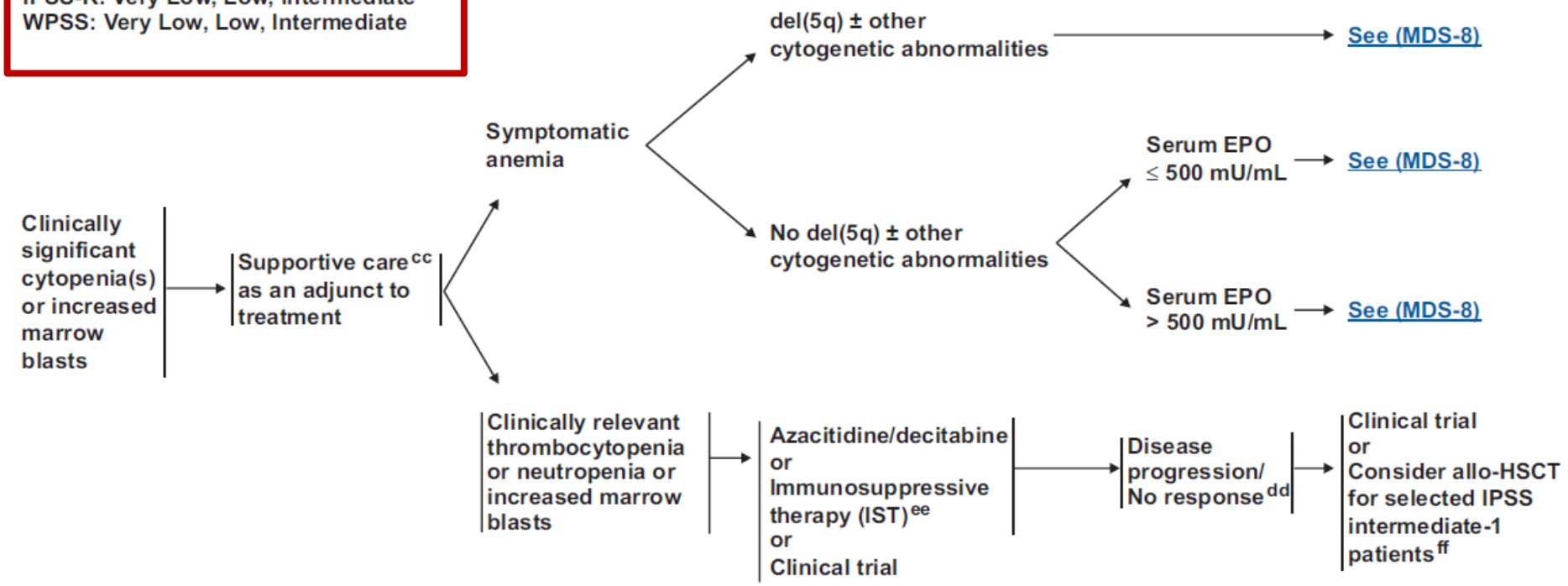
NCCN Guidelines Version 2.2014
Myelodysplastic Syndromes

NCCN Guidelines Index
MDS Table of Contents
Discussion

PROGNOSTIC CATEGORY[aa]

IPSS: Low/Intermediate-1
IPSS-R: Very Low, Low, Intermediate[bb]
WPSS: Very Low, Low, Intermediate

TREATMENT



[aa] Presence of comorbidities should also be considered for evaluation of prognosis (See references 128-133 in the Discussion section).

[bb] IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending upon additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels. If patients initially are managed as lower risk but fail to respond, move to higher risk management strategies.

[cc] See Supportive Care (MDS-B).

[dd] Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

[ee] Patients generally ≤ 60 y, and ≤ 5% marrow blasts or those with hypocellular marrows, HLA-DR15 positivity, or PNH clone positivity.

[ff] IPSS Intermediate-1, IPSS-R and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HSCT (hematopoietic stem cell transplant): Allogeneic-matched sibling transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).

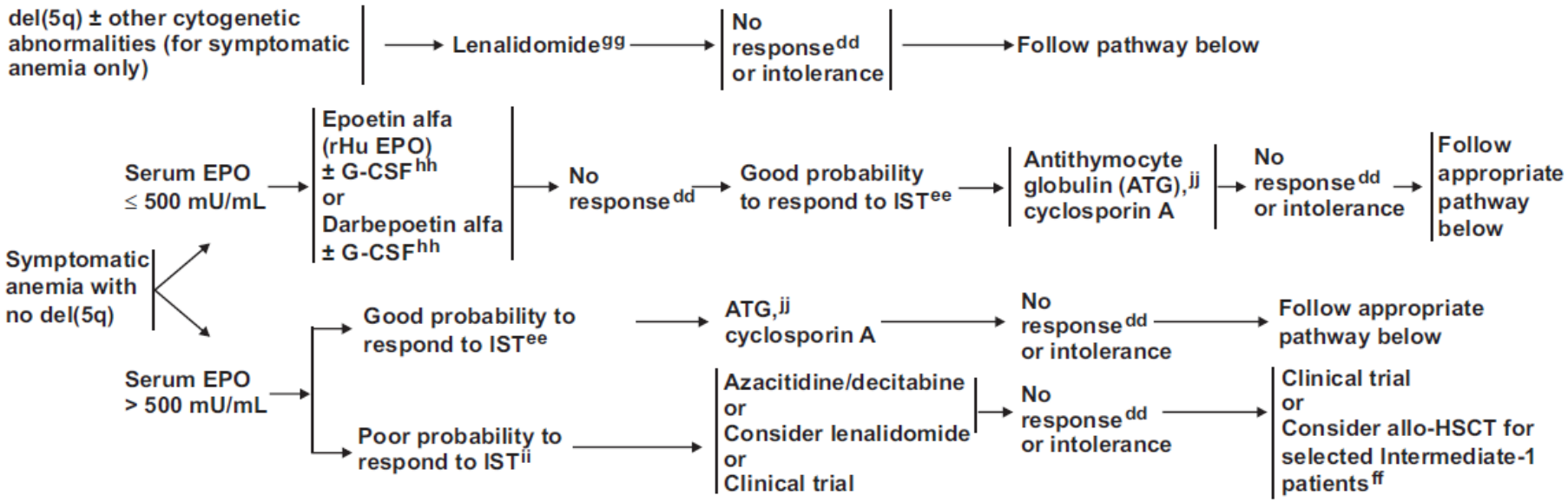
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 2.2014
Myelodysplastic Syndromes

NCCN Guidelines Index
MDS Table of Contents
Discussion

PROGNOSTIC CATEGORY[aa]
IPSS: Low/Intermediate-1
IPSS-R: Very Low, Low, Intermediate[bb]
WPSS: Very Low, Low, Intermediate

TREATMENT



[aa] Presence of comorbidities should also be considered for evaluation of prognosis (See references 128-133 in the Discussion section).

[bb] IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending upon additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels. If patients initially are managed as lower risk but fail to respond, move to higher risk management strategies.

[dd] Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

[ee] Patients ≤ 60 y, or those with hypocellular marrows, HLA-DR15 positivity, or PNH clone positivity.

[ff] IPSS Intermediate-1, IPSS-R and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HSCT (hematopoietic stem cell transplant): Allogeneic-matched sibling transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).

[gg] Except for patients with low neutrophil counts or low platelet counts. Recommended initial dose is: 10 mg/d for 21 out of 28 days monthly for 2-4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤ 500 mU/mL.

[hh] See dosing of hematopoietic cytokines (MDS-10).

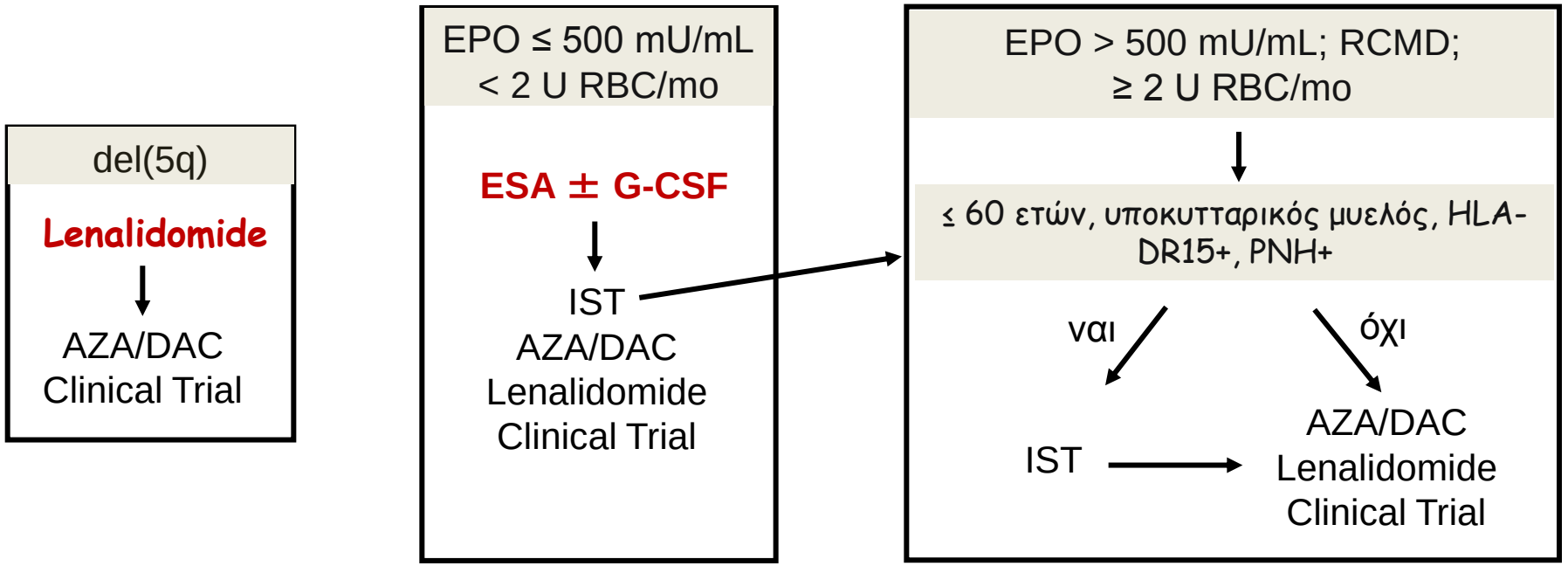
[ii] Patients lack features listed in footnote dd.

[jj] Both equine and rabbit ATG have been used in patients with MDS (See Discussion).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ΘΕΡΑΠΕΥΤΙΚΟΣ ΑΛΓΟΡΙΘΜΟΣ ΑΝΑΙΜΙΑΣ

Χαμηλού ή ενδιάμεσου Ι κινδύνου MDS



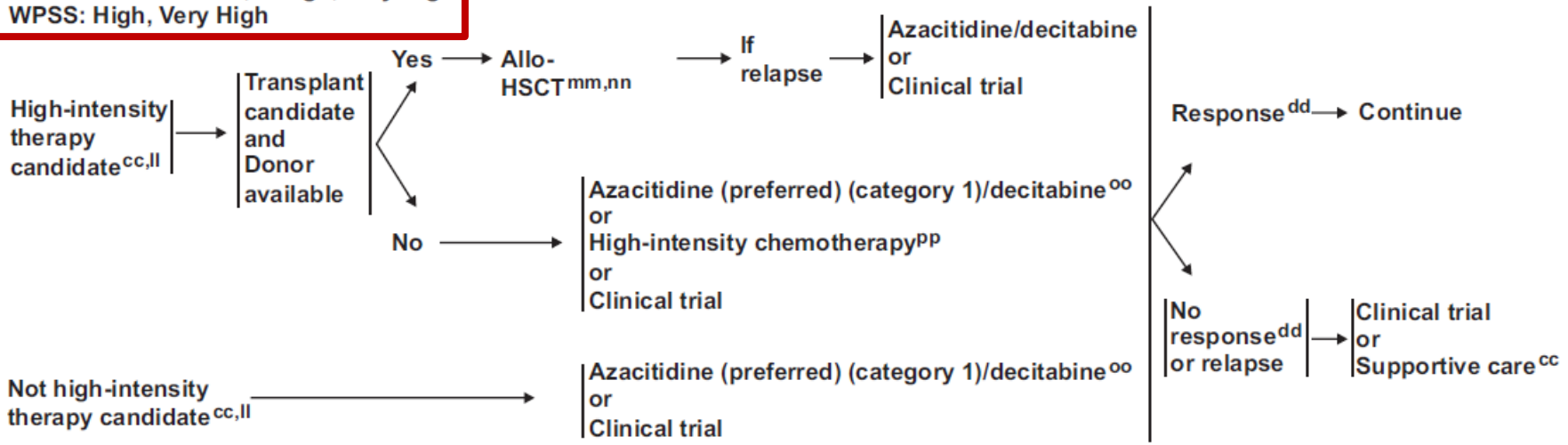
NCCN Guidelines Version 2.2014
Myelodysplastic Syndromes

NCCN Guidelines Index
MDS Table of Contents
Discussion

PROGNOSTIC CATEGORY[aa]

IPSS: Intermediate-2, High[ee]
IPSS-R: Intermediate,[kk] **High, Very High**
WPSS: High, Very High

TREATMENT



[aa] Presence of comorbidities should also be considered for evaluation of prognosis (See references 128-133 in the Discussion section).

[cc] See Supportive Care (MDS-B).

[dd] Response should be evaluated based on IWG criteria: Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood 2006;108:419-425.

[ff] IPSS Intermediate-1, IPSS-R and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HSCT (hematopoietic stem cell transplant): Allogeneic-matched sibling transplant including standard and reduced-intensity preparative approaches or matched unrelated donor (MUD).

[kk] IPSS-R Intermediate patients may be managed as very low/low risk or high/very high risk depending upon additional prognostic factors such as age, performance status, serum ferritin levels, and serum LDH levels.

[ll] Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken immediately to transplant or bridging therapy should be used to decrease marrow blasts to an acceptable level prior to transplant.

[mm] Azacitidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability. However, these agents should not be used to delay available HSCT.

[nn] Hematopoietic stem cell transplant (HSCT): Allogeneic-matched sibling including standard and reduced-intensity preparative approaches or MUD.

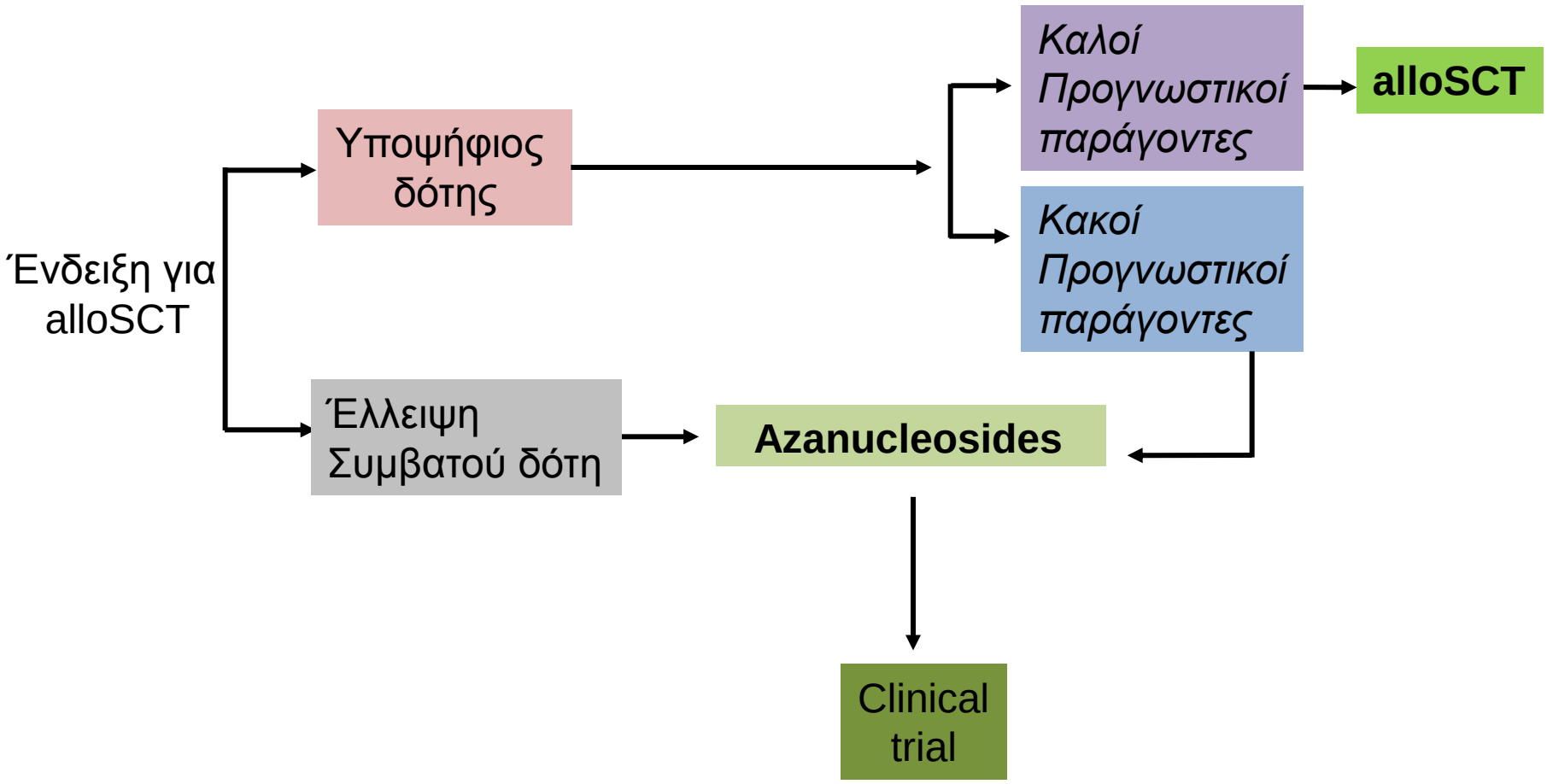
[oo] While the response rates are similar for both drugs, survival benefit from a Phase III randomized trial is reported for azacitidine and not for decitabine

[pp] High-intensity chemotherapy:

- Clinical trials with investigational therapy (preferred), or
- Standard induction therapy if investigational protocol is unavailable or if it is used as a bridge to HSCT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ΘΕΡΑΠΕΥΤΙΚΟΣ ΑΛΓΟΡΙΘΜΟΣ
Ενδιαμέσου-2 ή υψηλού κινδύνου MDS



Όμως…

Υπάρχουν ασθενείς <u>χαμηλού κινδύνου</u> κατά IPSS, IPSS-R που έχουν πολύ κακή κλινική πορεία και έκβαση παρά την ενδεδειγμένη θεραπεία

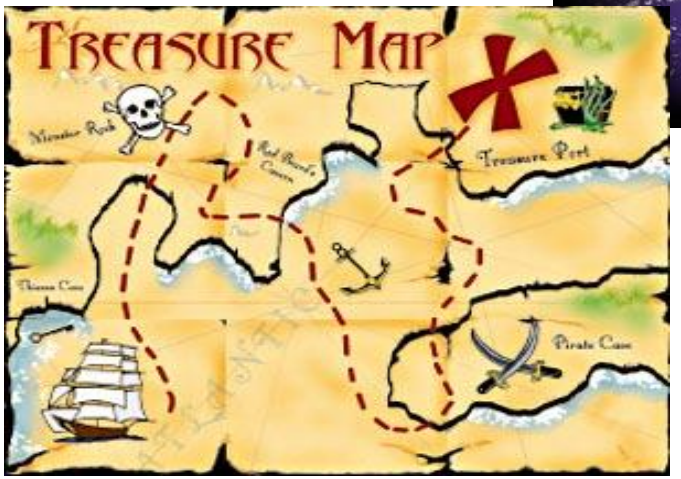
- **Ανάγκη για νέα προγνωστικά μοντέλα**
- **Στοχευμένες θεραπείες σε αυτή την ομάδα ασθενών**
- **Παρακολούθηση MRD**

ΝΕΑ ΠΡΟΓΝΩΣΤΙΚΑ ΜΟΝΤΕΛΑ

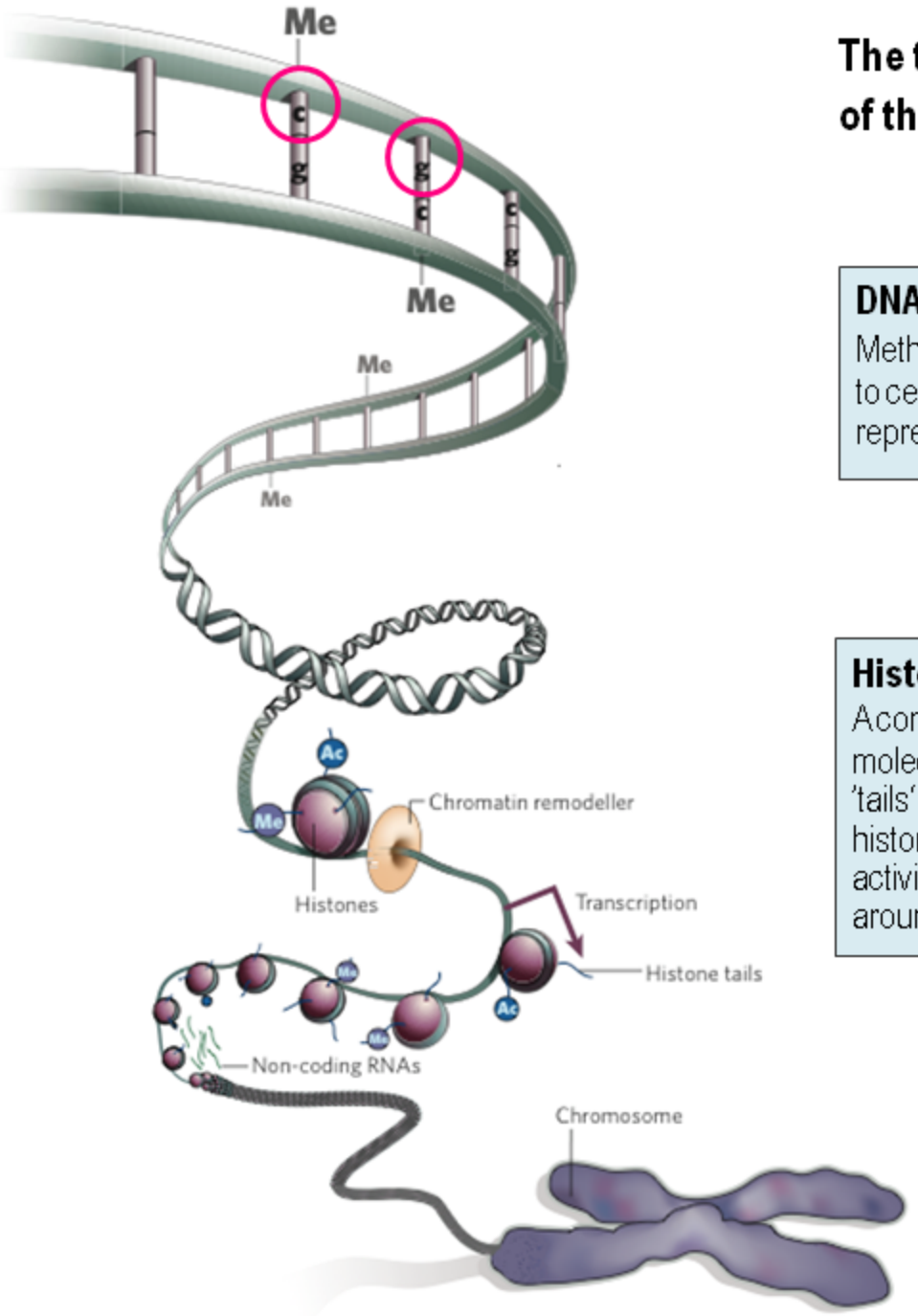
- 50% των ασθενών έχουν φυσιολογικό καρυότυπο
- <15% δεν ανευρίσκεται βλάβη στα γονίδια

- Ασθενείς με πανομοιότυπο καρυότυπο παρουσιάζουν ετερογένεια

ΤΟ ΜΥΣΤΙΚΟ ΕΙΝΑΙ ΣΤΑ ΓΟΝΙΔΙΑ!!!



The two main components of the epigenetic code



DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of DNA wrapped around them.

Genetic lesion		Putative biologic role	Clinical phenotype
Splicing machinery	*SF3B1*	Altered RNA splicing	Associated with ring sideroblasts
	U2AF1	Altered RNA splicing, cell cycle arrest	Higher risk of progression to sAML
	SRSF2	Altered RNA splicing	Shorter overall survival, higher risk of progression to sAML
	SF3A1, ZRSR2, PRPF40B, U2AF2, SF1	Altered RNA splicing	
Epigenetic regulation	*TET2*	Impaired conversion of 5-methylcytosine to 5-hydroxymethylcytosine, increased self-renewal	
	DNMT3A	Impaired CpG site de novo methylation, increase in self-renewal and loss of differentiation capacity	Shorter overall survival, higher risk of progression to sAML
	IDH1/2	Production of oncometabolite 2-hydroxyglutarate, inhibition of TET2 function	
	ASXL1	Epigenetic dysregulation	Poor prognosis
	ATRX	Decreased H3K27me3	Severe anemia, acquired α-thalassemia
	EZH2	Decreased H3K27me3	Poor prognosis
Transcription factor	*RUNX1*	Impaired differentiation	Blasts high, low platelets, poor prognosis
	ETV6	Impaired differentiation	Poor prognosis
Kinase signalling	*JAK2*	Activation of kinase signaling	Frequent in RARS-T and MDS/MPN overlap syndrome
	NRAS/KRAS	Activation of kinase signaling	Elevated blast counts, low platelets, higher risk of progression to AML
	MPL	Activation of kinase signaling	
	c-CBL	Activation of kinase signaling by loss of ubiqitination mediated degradation of signaling pathway members	More common in CMML
DNA damage pathway	*TP53*	Impaired DNA damage response, genomic instability, associated with complex karyotype and chromothripsis	Elevated blasts, thrombocytopenia, poor prognosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Effect of Point Mutations in Myelodysplastic Syndromes

Rafael Bejar, M.D., Ph.D., Kristen Stevenson, M.S., Omar Al
Naomi Galili, Ph.D., Björn Nilsson, M.D., Ph.D., Guillermo G
Hagop Kantarjian, M.D., Azra Raza, M.D., Ross L. Le
Donna Neuberg, Sc.D., and Benjamin L. Ebert, M.

N Engl J Med 2011;364:2496-506.

IPSS

χαμηλού, ενδ.1 κινδύνου 66%

Καρυότυπος

ΚΦ 58% - σύνθετος 13%

- **Στο 51.5% υπήρχε έστω και μία μεταλλαγή !!!**
- 18% ≥2 μεταλλαγές

Table 1. Frequency of Mutation and Association with Median Survival.*

Mutated Gene	No. of Samples (%)	Median Survival (95% CI)	P Value
		yr	
All samples	439 (100)	1.86 (1.60–2.14)	
TET2	90 (20.5)	1.88 (1.26–2.55)	0.48
ASXL1	63 (14.4)	1.33 (0.96–1.88)	0.003
RUNX1	38 (8.7)	1.16 (0.77–1.53)	<0.001
TP53	33 (7.5)	0.65 (0.44–1.10)	<0.001
EZH2	28 (6.4)	0.79 (0.67–1.40)	<0.001
NRAS	16 (3.6)	1.03 (0.44–1.98)	0.006
JAK2	13 (3.0)	2.14 (1.02–3.12)	0.96
ETV6	12 (2.7)	0.83 (0.62–2.29)	0.04
CBL	10 (2.3)	1.52 (0.14–1.71)	0.02
IDH2	9 (2.1)	1.58 (0.50–2.14)	0.03
NPM1	8 (1.8)	2.18 (0.59–2.74)	0.43
IDH1	6 (1.4)	3.30 (0.35–9.52)	0.52
KRAS	4 (0.9)	0.89 (0.36–7.44)	0.54
GNAS	3 (0.7)		
PTPN11	3 (0.7)		
BRAF	2 (0.5)		
PTEN	1 (0.2)		
CDKN2A	1 (0.2)		

* Median survival is listed for specific mutations present in at least 4 of the 439 samples (1%). A patient could have multiple mutations. The P values are for median survival in the group of patients with a mutated gene versus the group of patients without a mutation in that gene. CI denotes confidence interval.

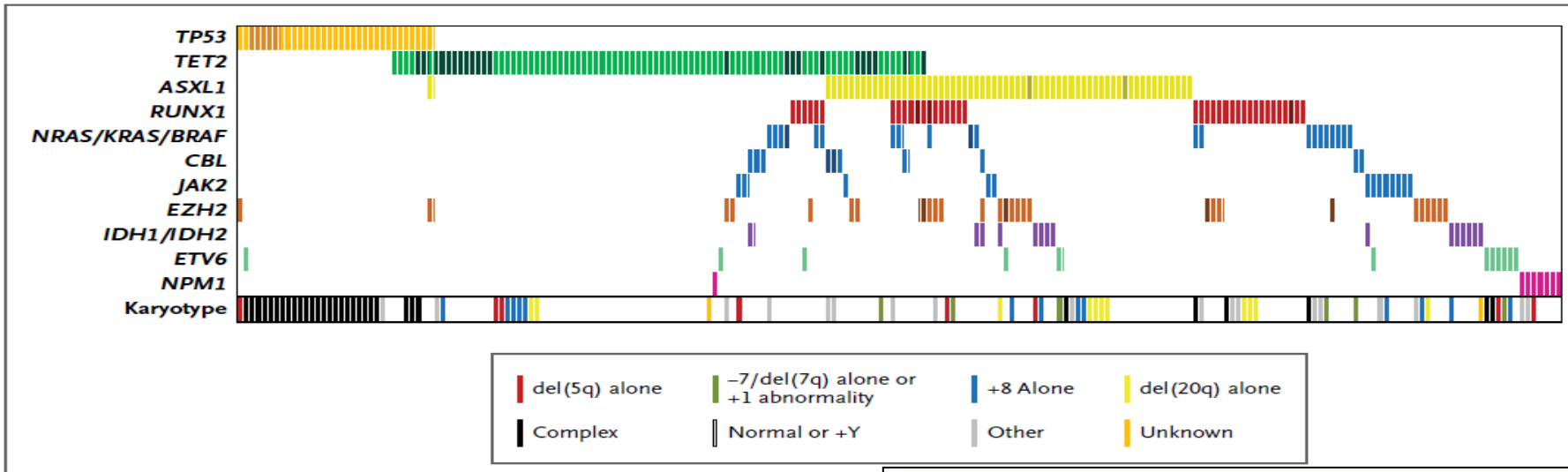


Figure 1. Mutations and Cytogenetic Abnormalities in 223 Samples with at l

Mutations in the 11 most frequently mutated gene groups are shown by col a mutation in one or more of the genes listed. Darker bars indicate sample karyotype of each of the 223 samples is also shown.

- **Συσχέτιση μεταλλαγών με παράγοντες κινδύνου**
  - ✓ Καρυότυπος, βλάστες, κυτταροπενίες

Table 2. Hazard Ratios for Death in a Multivariable Model.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Age ≥55 yr vs. <55 yr	1.81 (1.20–2.73)	0.004
IPSS risk group		
Intermediate-1 vs. low	2.29 (1.69–3.11)	<0.001
Intermediate-2 vs. low	3.45 (2.42–4.91)	<0.001
High vs. low	5.85 (3.63–9.40)	<0.001
Mutational status		
TP53 mutation present vs. absent	2.48 (1.60–3.84)	<0.001
EZH2 mutation present vs. absent	2.13 (1.36–3.33)	<0.001
ETV6 mutation present vs. absent	2.04 (1.08–3.86)	0.03
RUNX1 mutation present vs. absent	1.47 (1.01–2.15)	0.047
ASXL1 mutation present vs. absent	1.38 (1.00–1.89)	0.049

* The model was generated from a stepwise Cox regression model that included the International Prognostic Scoring System (IPSS) risk category (based on the percentage of blasts in bone marrow, the karyotype, and the number of cytopenias [see Table 2 in the Supplementary Appendix]), age, sex, and mutation status for genes that were mutated in 1% or more of the 428 samples for which the IPSS classification was recalculated. Age was included in the analysis as a categorical variable on the basis of a best-split algorithm showing a significant difference in overall survival between patients less than 55 years of age and those 55 years of age or older (see Table 8 in the Supplementary Appendix).

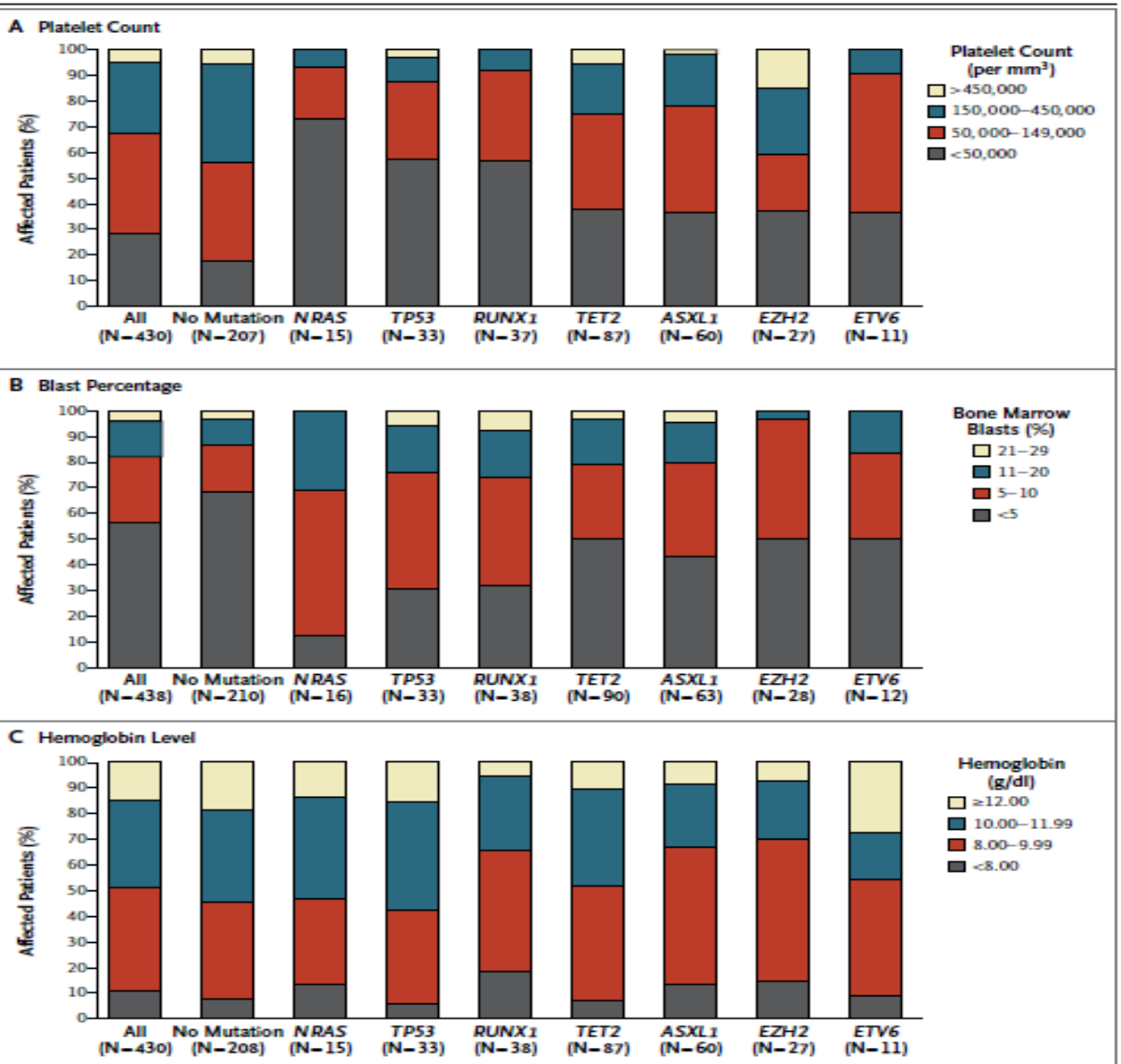
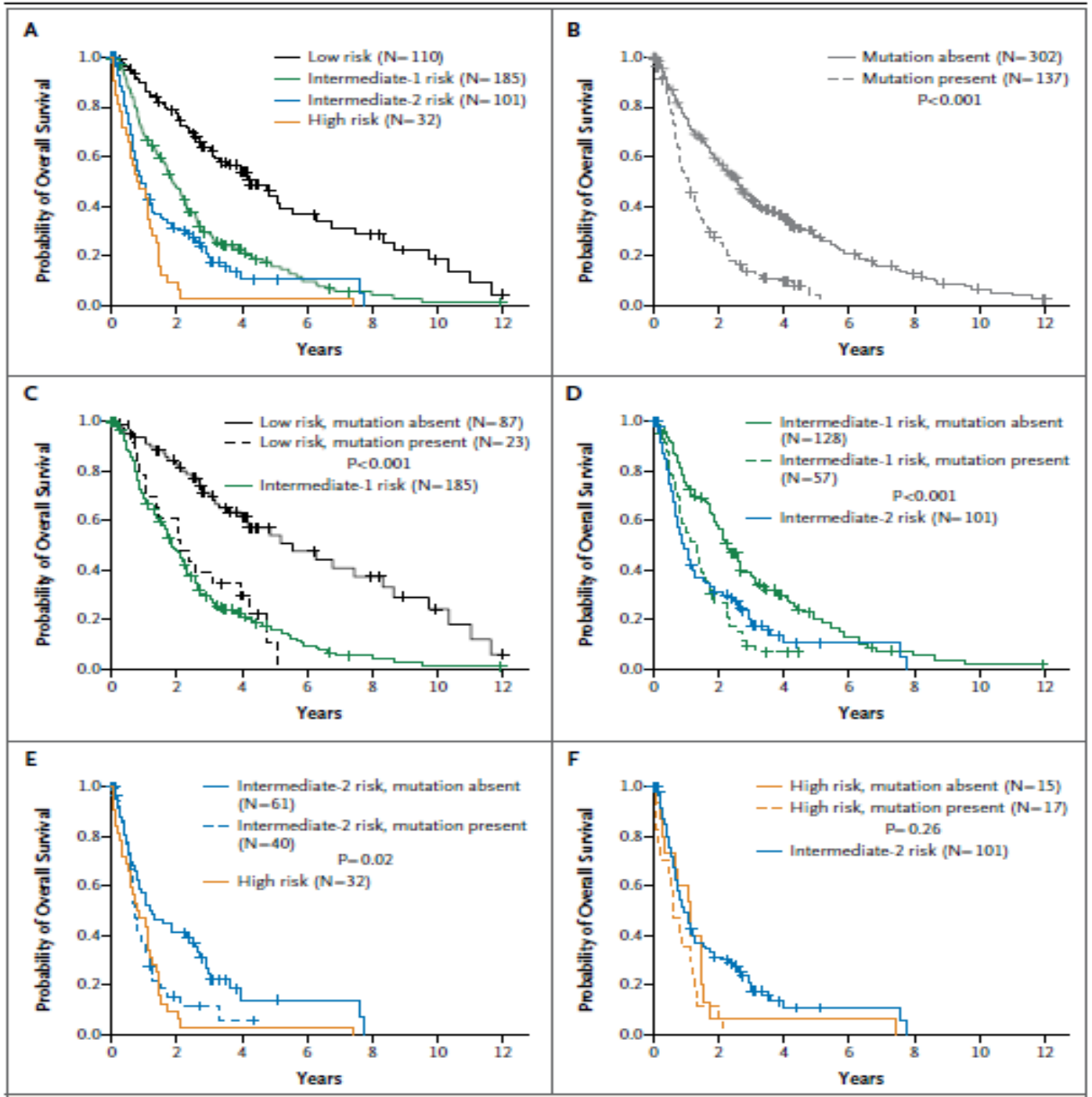


Figure 3. Proportions of Patients with Mutations, According to Platelet Count, Blast Percentage, and Hemoglobin Level.

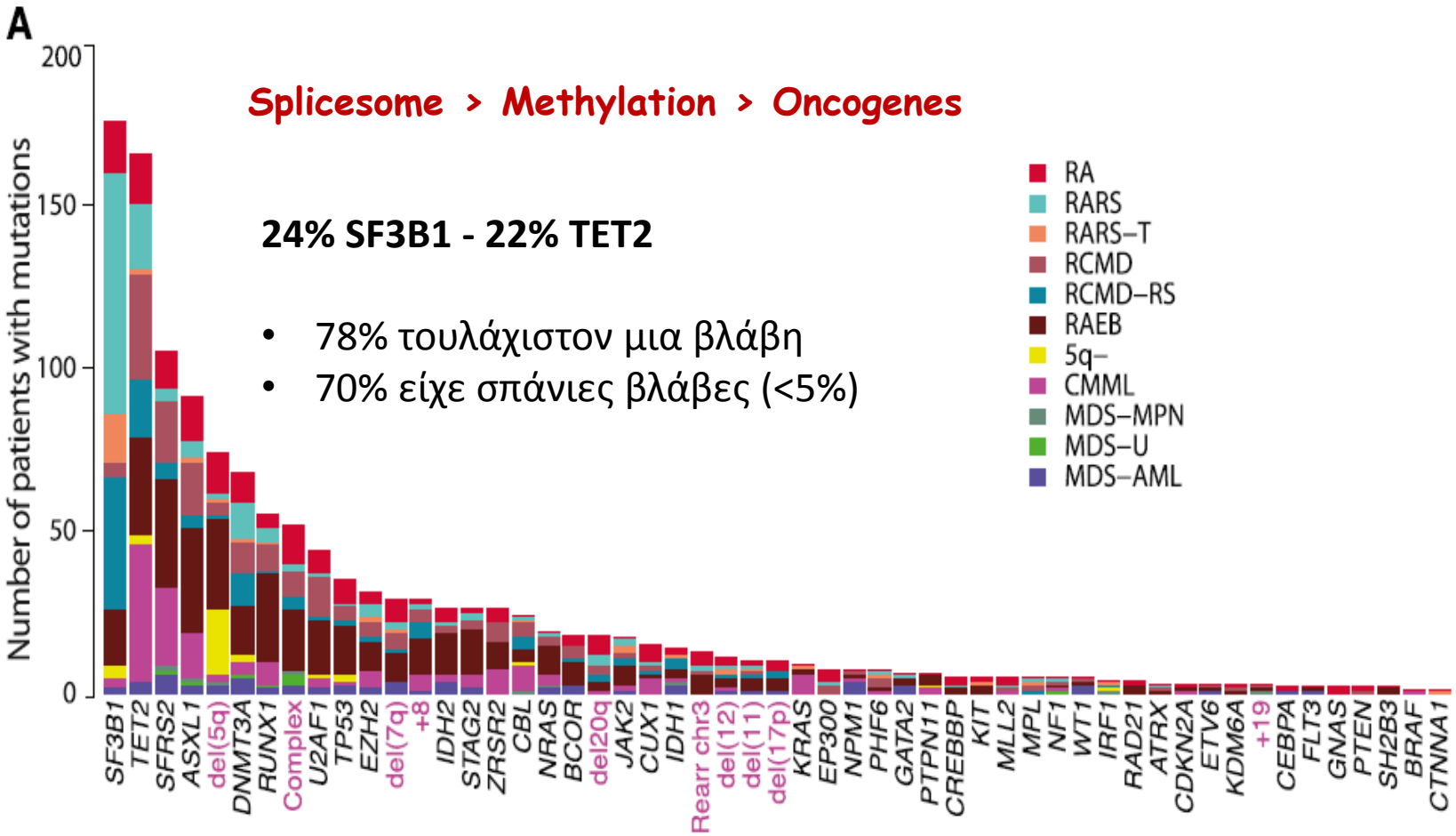
Data are shown for the platelet count (Panel A), percentage of blasts in bone marrow aspirate (Panel B), and hemoglobin level (Panel C) at the time of bone marrow sample collection. The numbers in parentheses along the x axis indicate the number of patients with a mutation in the gene (patients could have >1 mutated gene). Mutations in *NRAS*, *TP53*, and *RUNX1* were significantly associated with severe thrombocytopenia (defined as <50,000 platelets per cubic millimeter) ($P<0.001$ for each comparison) (Panel A) and elevated blast percentage (defined as ≥5%) ($P<0.001$, $P=0.005$, and $P=0.003$ for mutations in the three genes, respectively) (Panel B).


A
Probability of Overall Survival
Low risk (N=110)
Intermediate-1 risk (N=185)
Intermediate-2 risk (N=101)
High risk (N=32)
Years
B
Probability of Overall Survival
Mutation absent (N=302)
Mutation present (N=137)
P<0.001
Years
C
Probability of Overall Survival
Low risk, mutation absent (N=87)
Low risk, mutation present (N=23)
P<0.001
Intermediate-1 risk (N=185)
Years
D
Probability of Overall Survival
Intermediate-1 risk, mutation absent (N=128)
Intermediate-1 risk, mutation present (N=57)
P<0.001
Intermediate-2 risk (N=101)
Years
E
Probability of Overall Survival
Intermediate-2 risk, mutation absent (N=61)
Intermediate-2 risk, mutation present (N=40)
P=0.02
High risk (N=32)
Years
F
Probability of Overall Survival
High risk, mutation absent (N=15)
High risk, mutation present (N=17)
P=0.26
Intermediate-2 risk (N=101)
Years

blood
2013 122: 3616-3627
doi:10.1182/blood-2013-08-518886 originally published online September 12, 2013

Clinical and biological implications of driver mutations in myelodysplastic syndromes

Elli Papaemmanuil, Moritz Gerstung, Luca Malcovati, Sudhir Tauro, Gunes Gundem, Peter Van Loo, Chris J. Yoon, Peter Ellis, David C. Wedge, Andrea Pellagatti, Adam Shlien, Michael John Groves, Simon A. Forbes, Keiran Raine, Jon Hinton, Laura J. Mudie, Stuart McLaren, Claire Hardy, Calli Latimer, Matteo G. Della Porta, Sarah O'Meara, Ilaria Ambaglio, Anna Galli, Adam P. Butler, Gunilla Walldin, Jon W. Teague, Lynn Quek, Alex Sternberg, Carlo Gambacorti-Passerini, Nicholas C. P. Cross, Anthony R. Green, Jacqueline Boultwood, Paresh Vyas, Eva Hellstrom-Lindberg, David Bowen, Mario Cazzola, Michael R. Stratton and Peter J. Campbell



Splicesome > Methylation > Oncogenes

24% SF3B1 - 22% TET2

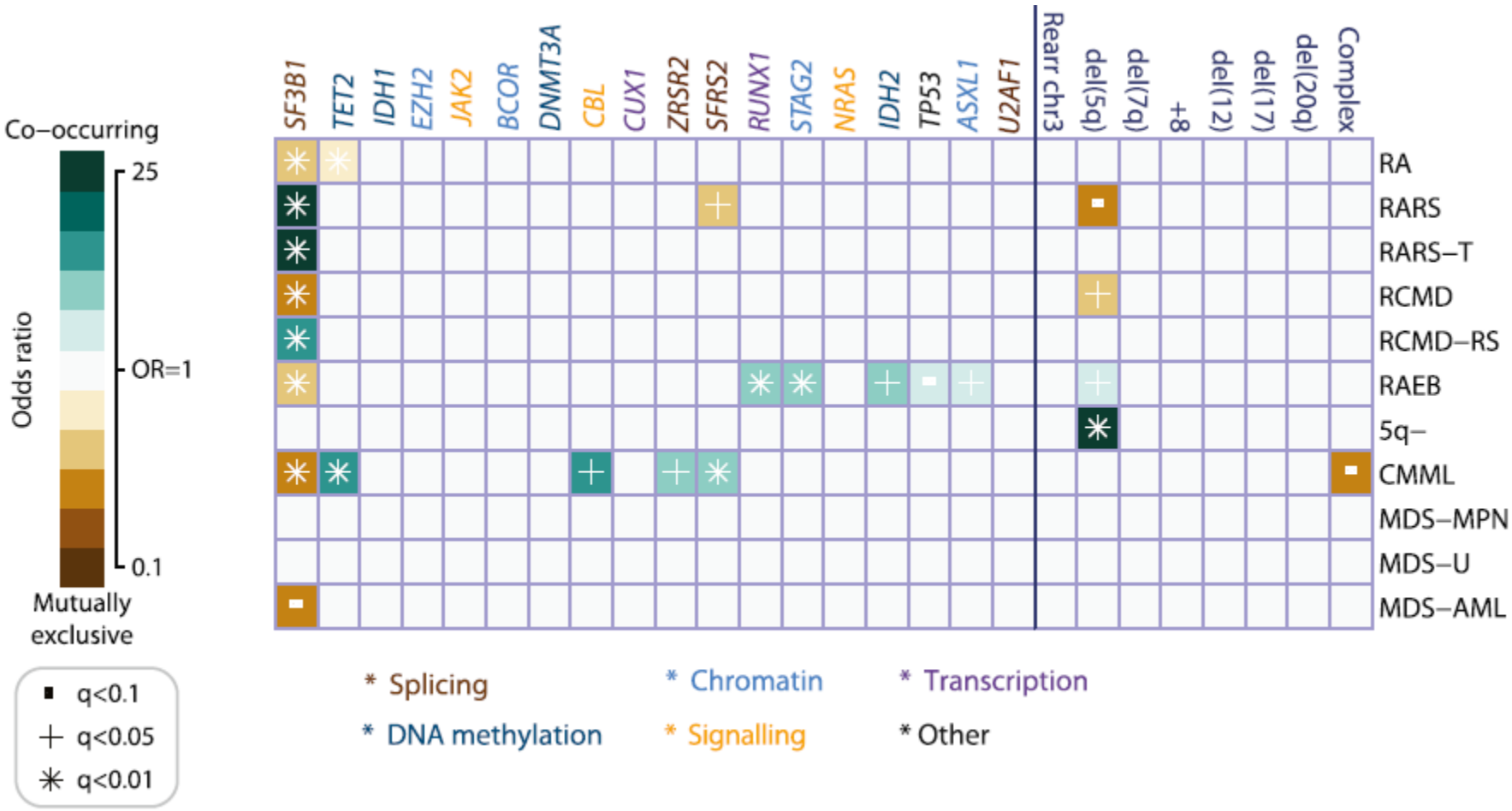
- 78% τουλάχιστον μια βλάβη
- 70% είχε σπάνιες βλάβες (<5%)

738 pts, 111 genes

blood
2013 122: 3616-3627
doi:10.1182/blood-2013-08-518886 originally published online September 12, 2013

Clinical and biological implications of driver mutations in myelodysplastic syndromes

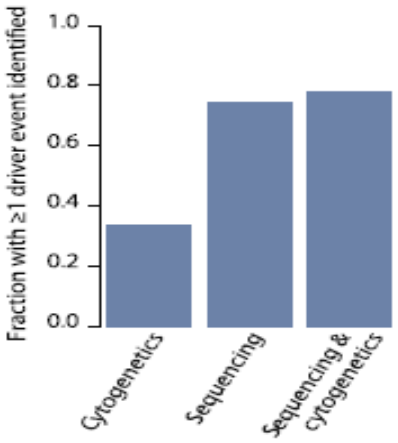
Elli Papaemmanuil, Moritz Gerstung, Luca Malcovati, Sudhir Tauro, Gunes Gundem, Peter Van Loo, Chris J. Yoon, Peter Ellis, David C. Wedge, Andrea Pellagatti, Adam Shlien, Michael John Groves, Simon A. Forbes, Keiran Raine, Jon Hinton, Laura J. Mudie, Stuart McLaren, Claire Hardy, Calli Latimer, Matteo G. Della Porta, Sarah O'Meara, Ilaria Ambaglio, Anna Galli, Adam P. Butler, Gunilla Walldin, Jon W. Teague, Lynn Quek, Alex Sternberg, Carlo Gambacorti-Passerini, Nicholas C. P. Cross, Anthony R. Green, Jacqueline Boultwood, Paresh Vyas, Eva Hellstrom-Lindberg, David Bowen, Mario Cazzola, Michael R. Stratton and Peter J. Campbell

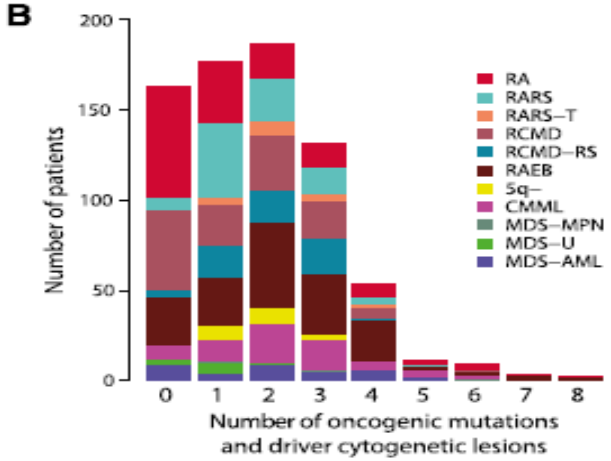


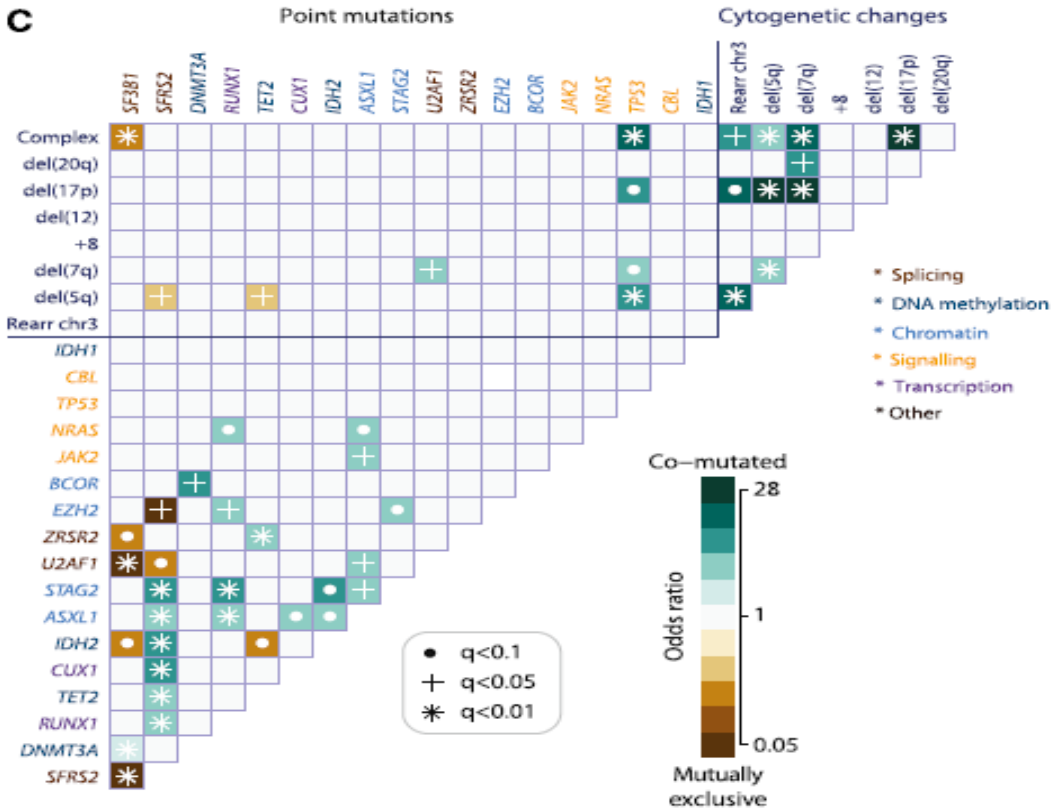
blood
2013 122: 3616-3627
doi:10.1182/blood-2013-08-518886 originally published online September 12, 2013

Clinical and biological implications of driver mutations in myelodysplastic syndromes

Elli Papaemmanuil, Moritz Gerstung, Luca Malcovati, Sudhir Tauro, Gunes Gundem, Peter Van Loo, Chris J. Yoon, Peter Ellis, David C. Wedge, Andrea Pellagatti, Adam Shlien, Michael John Groves, Simon A. Forbes, Keiran Raine, Jon Hinton, Laura J. Mudie, Stuart McLaren, Claire Hardy, Calli Latimer, Matteo G. Della Porta, Sarah O'Meara, Ilaria Ambaglio, Anna Galli, Adam P. Butler, Gunilla Walldin, Jon W. Teague, Lynn Quek, Alex Sternberg, Carlo Gambacorti-Passerini, Nicholas C. P. Cross, Anthony R. Green, Jacqueline Boultwood, Paresh Vyas, Eva Hellstrom-Lindberg, David Bowen, Mario Cazzola, Michael R. Stratton and Peter J. Campbell



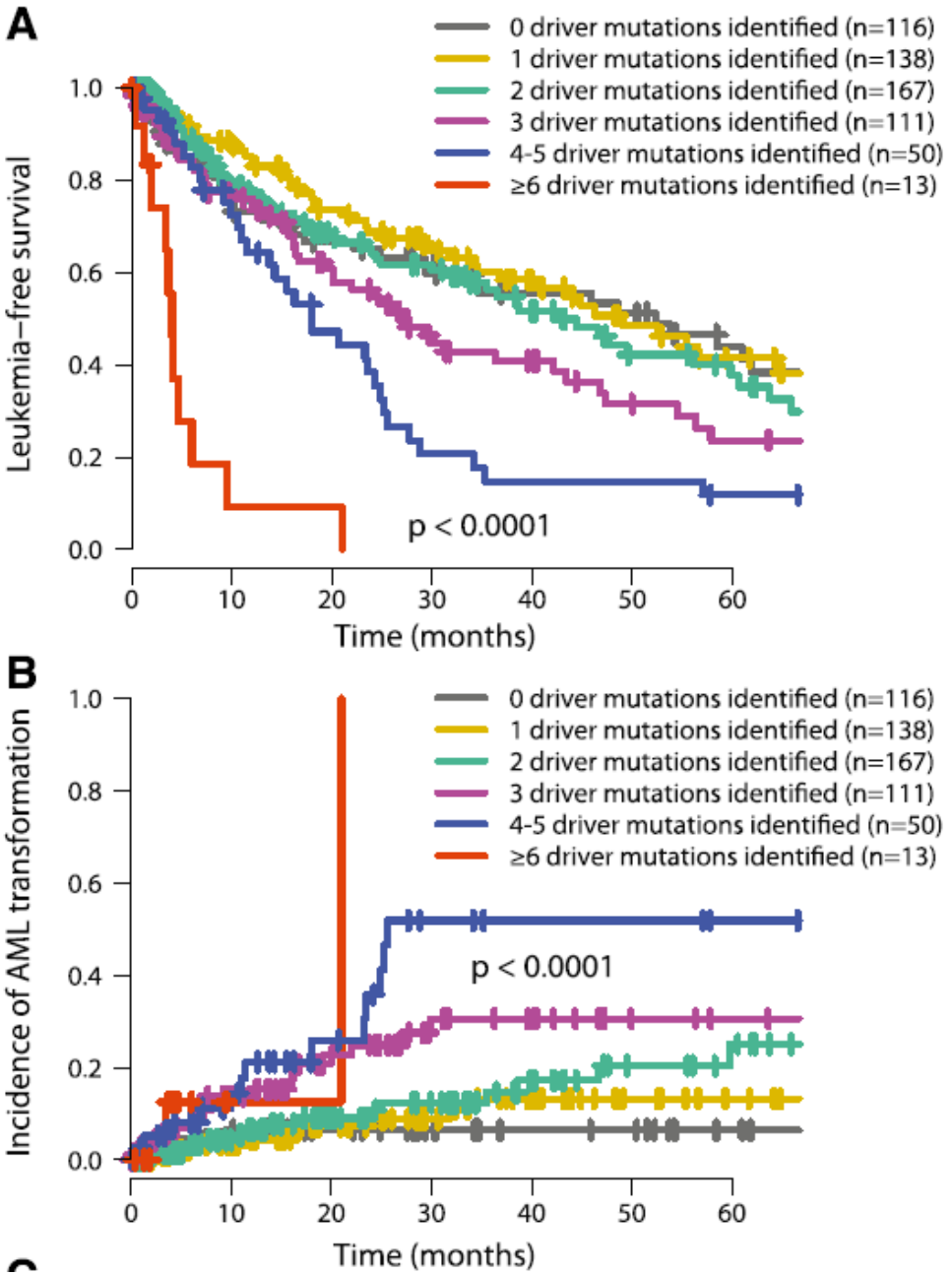




blood
2013 122: 3616-3627
doi:10.1182/blood-2013-08-518886 originally pu
online September 12, 2013

Clinical and biological implications of driver mutations in myelodysplastic syndromes

Elli Papaemmanuil, Moritz Gerstung, Luca Malcovati, Sudhir Tauro, Gunes Gundem, Peter
Chris J. Yoon, Peter Ellis, David C. Wedge, Andrea Pellagatti, Adam Shlien, Michael John
Simon A. Forbes, Keiran Raine, Jon Hinton, Laura J. Mudie, Stuart McLaren, Claire Hardy,
Latimer, Matteo G. Della Porta, Sarah O'Meara, Ilaria Ambaglio, Anna Galli, Adam P. Butle
Walldin, Jon W. Teague, Lynn Quek, Alex Sternberg, Carlo Gambacorti-Passerini, Nichola
Cross, Anthony R. Green, Jacqueline Boultwood, Paresh Vyas, Eva Hellstrom-Lindberg, D
Bowen, Mario Cazzola, Michael R. Stratton and Peter J. Campbell



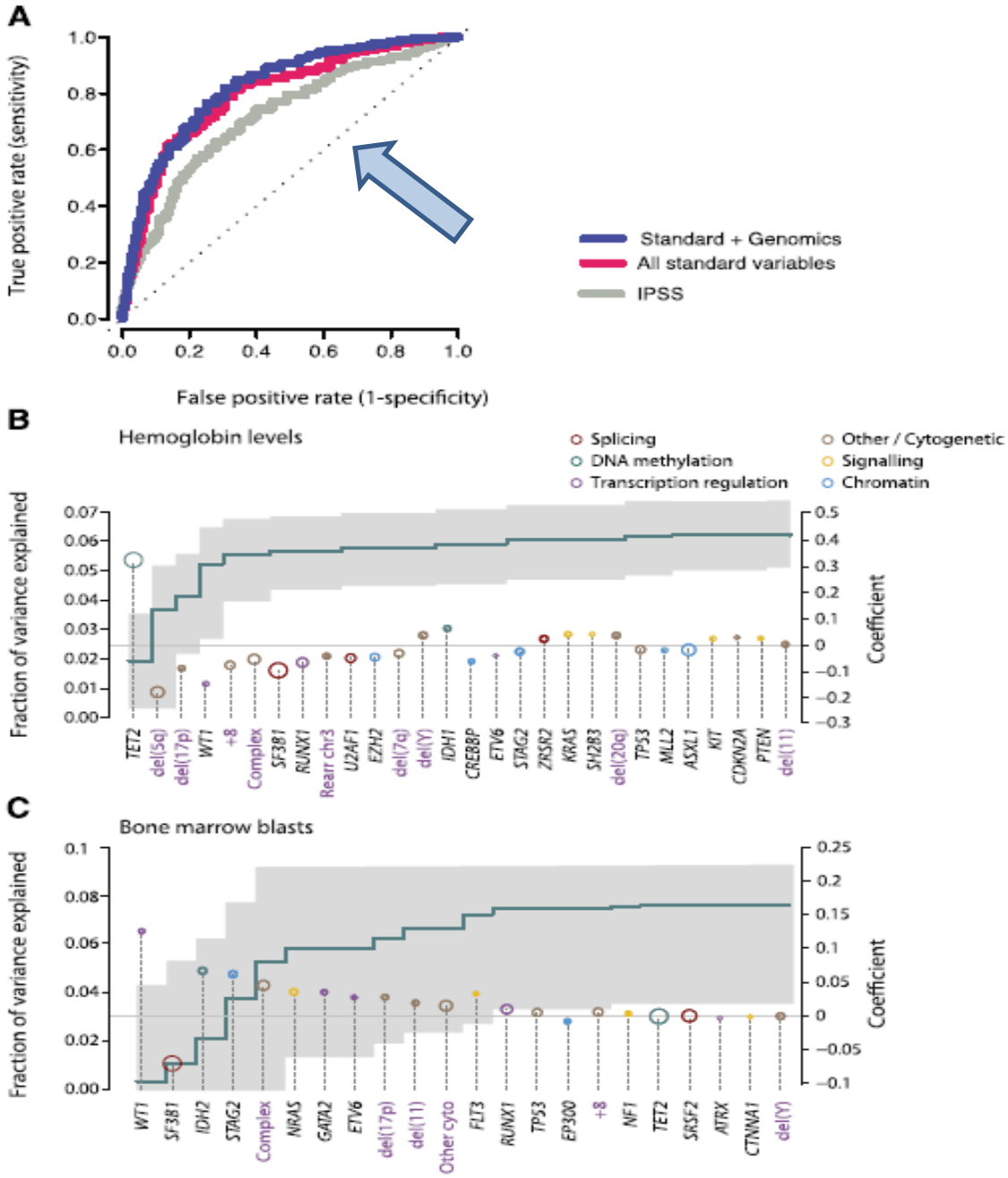


Figure 6. Predicting leukemia-free survival. (A) Receiver operating characteristic curves on cross-validation subsets for leukemia-free survival using 3 variable datasets: IPSS (gray); standard variable predictions made using all variables available from peripheral blood counts bone marrow evaluation, cytogenetics, and demographics (red); and sequencing in combination with all standard variables (blue). The further the curve deviates from the diagonal, the more informative the prognostic model is. (B) Multivariate model to predict hemoglobin levels from driver mutations. The green step curve shows the cumulative proportion of variance (left y-axis) in hemoglobin levels explained by each of the genetic variables as one proceeds from left to right along the x-axis. The gray shaded area represents the 95% CI for this curve. Coefficient estimates for each gene in the model including all variables (right y-axis) are shown as circles, colored by biological pathway and sized by the number of patients with the given lesion. Coefficients above 0 indicate positive correlation with hemoglobin levels. (C) Multivariate model to predict bone marrow blast count from driver mutations, as for panel B.

Στην κλινική πράξη :::

Γνωρίζουμε ότι εάν…

- **5q-**

lenalidomide

VOLUME 29 · NUMBER 15 · MAY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

TP53 Mutations in Low-Risk Myelodysplastic Syndromes With del(5q) Predict Disease Progression

Martin Jädersten, Leonie Saft, Alexander Smith, Austin Kulasekararaj, Sabine Pomplun, Gudrun Göhring, Anette Hedlund, Robert Hast, Brigitte Schlegelberger, Anna Porwit, Eva Hellström-Lindberg, and Ghulam J. Mufti

- **Ασθενείς χαμηλού κινδύνου με del(5q) έχουν μεταλλαγές TP53 που τους κατατάσσουν σε υψηλού κινδύνου για εξέλιξη σε ΟΜΛ.**
- **Ο αριθμός των μεταλλαγμένων κυττάρων αυξάνει κατά την εξέλιξη της νόσου.**
- **Ο κλώνος TP53 πιθανόν να είναι ανθεκτικός στη θεραπεία με λεναλιδομίδη και σταδιακά αυξάνει παρά τη δραστικότητα στα υπόλοιπα κύτταρα**
- **Γενετική αστάθεια – νέες καρυοτυπικές ανωμαλίες**

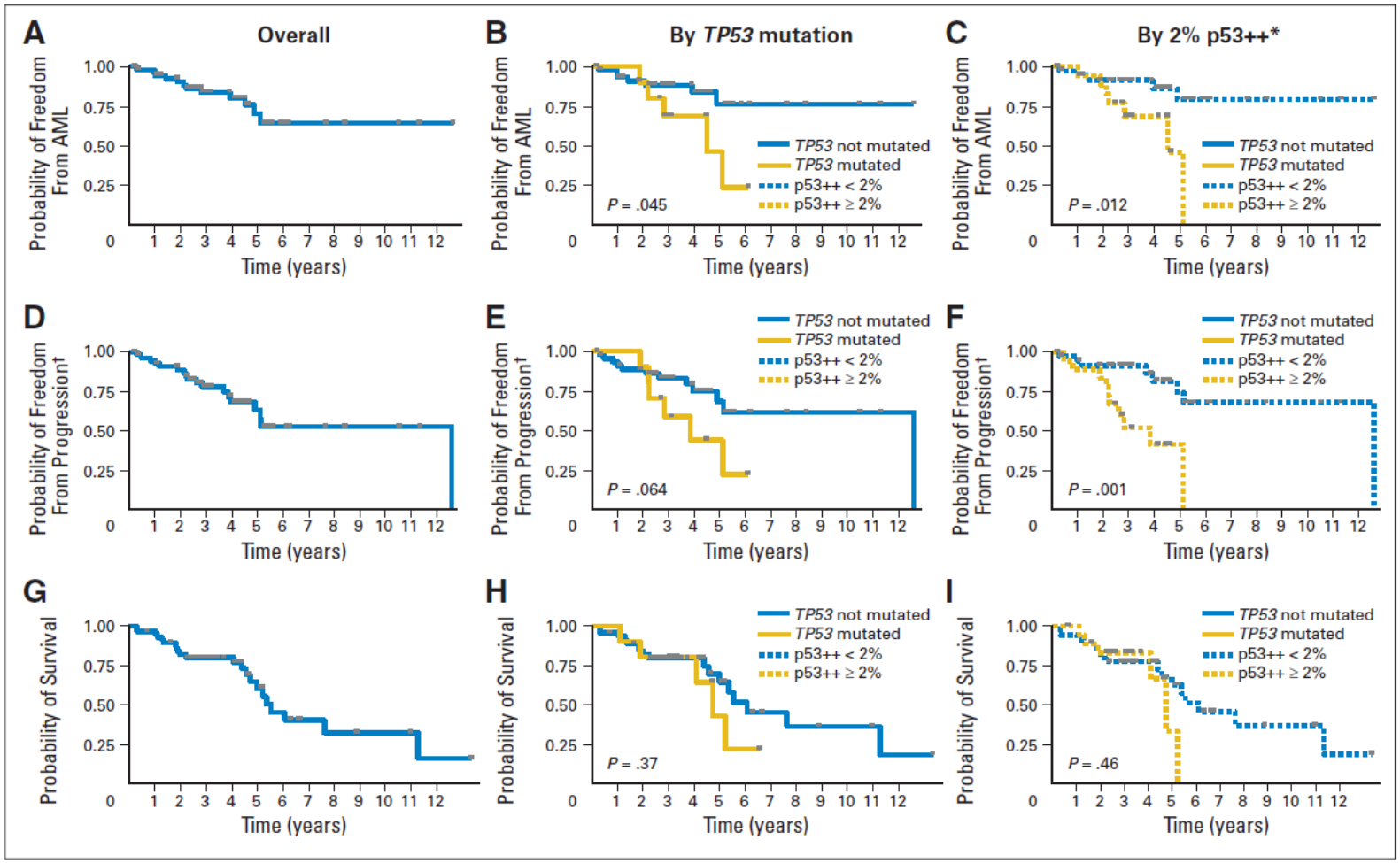
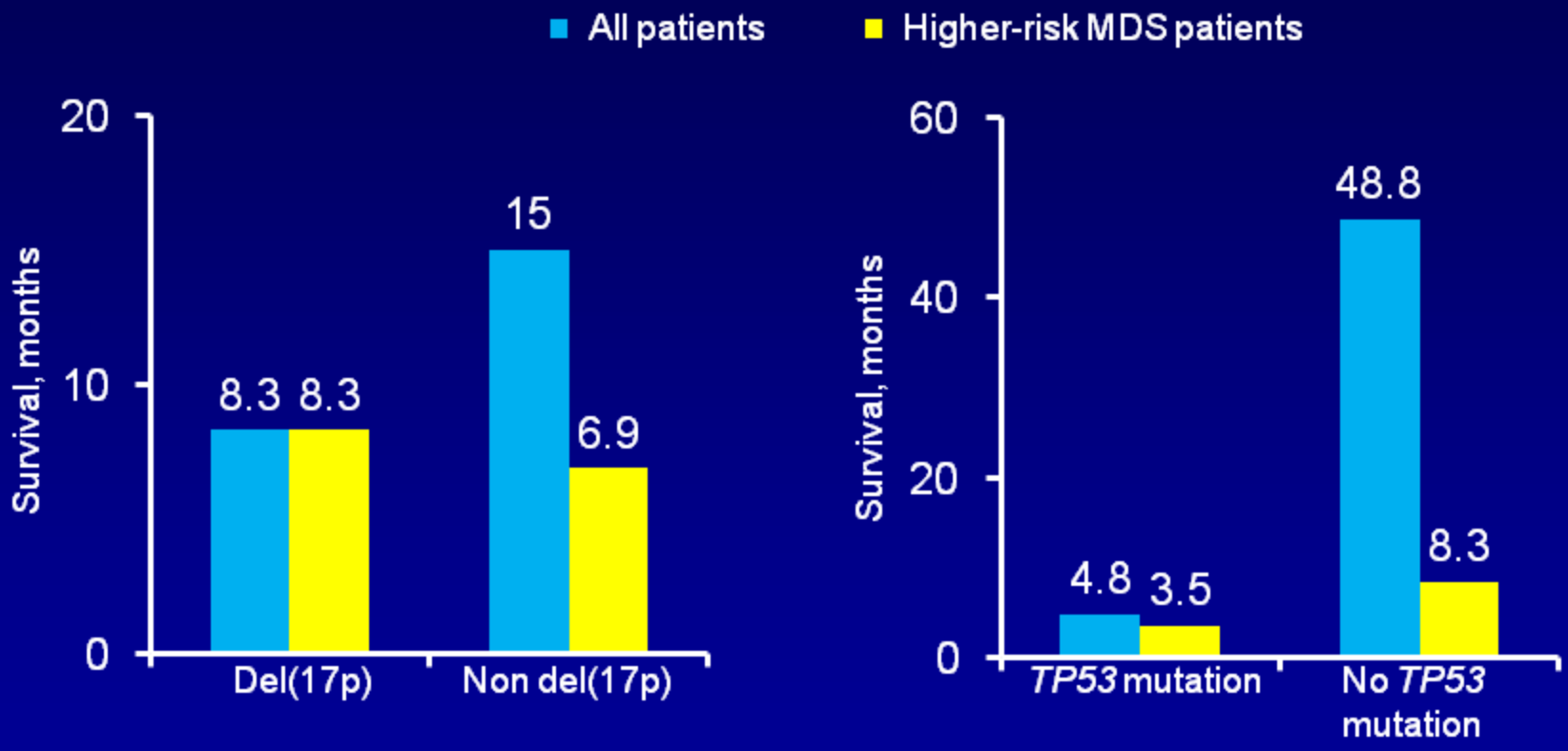


Fig 2. *TP53* mutations predict outcome in del (5q) myelodysplastic syndrome and are related to p53 status. (*) p53++, proportion of marrow cells with strong p53 staining by immunohistochemistry. (†) Progression is defined as marrow blast increase from 10% to 19% or acquisition of complex karyotype. AML, acute myeloid leukemia.

Incidence of del(17p) and *TP53* mutations in patients with del(5q) MDS/AML treated with lenalidomide – survival



***TP53* mutations were correlated with shorter survival independent of IPSS risk in patients with del(5q) MDS/AML**

Sebaa A, et al. Poster presentation at EHA 2012. Abstract 0338 (Eclache-Saudreau V, et al.)

TP53 mutations in MDS and their impact on patient outcomes

Retrospective analysis of the incidence and prognostic impact of *TP53* mutations in patients with del(5q) using next-generation sequencing

Patient characteristics (n=318)

- Median age, years (range): 65 (17–72)
- IPSS risk, n (%)
  - low: 71 (24)
  - int-1: 101 (32)
  - int-2: 58 (18)
  - high: 29 (9)
- 40 patients (12%) received BM transplant, IC, azacitidine or lenalidomide

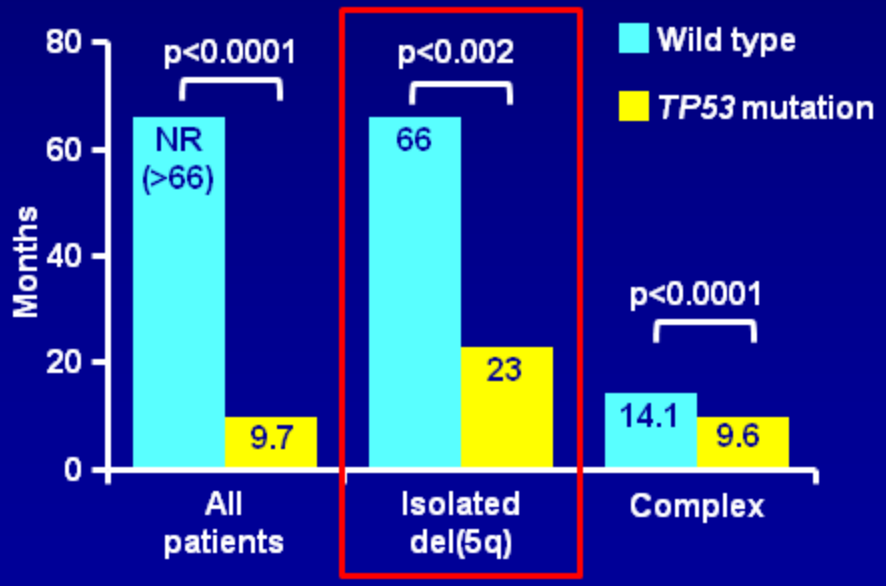
Multivariate analysis†: *TP53* mutational status was the strongest predictor for OS and PFS (p<0.0001 for both)

***TP53* mutations are an independent prognostic marker in patients with del(5q) MDS**

_TP53_ mutational status

- Patients with mutation, n (%): 30 (9.4)
- Median clone size, % (range): 42 (2.5–93)

OS by *TP53* mutational status*

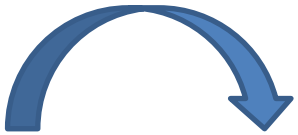


*Survival analysis was censored at treatment date
†Co-variables: age, sex, WHO subtype, IPSS risk, ±mutations; progression free survival

Kulasekararaj AG, et al. Oral presentation at ASH 2011. Abstract 792

ΣΤΗΝ ΚΛΙΝΙΚΗ ΠΡΑΞΗ ;;;

5q- & TP53 mutated



Πιο επιθετική θεραπεία;;;

ΣΤΗΝ ΚΛΙΝΙΚΗ ΠΡΑΞΗ ;;;

- **Non5q-**
  - TP53, EZH2, ETV6, RUNX1, ASXL1 κακής πρόγνωσης
  - Είναι σωστό να επιλέξουμε πιο επιθετική θεραπεία ;;;
  - Ποιοι ασθενείς θα ωφεληθούν;;;

ΣΤΗΝ ΚΛΙΝΙΚΗ ΠΡΑΞΗ ;;;

- ***TET2, DNMT3A, IDH1/IDH2***
  - Εμπλέκονται στη μεθυλίωση DNA,
  - Μεθυλίωση CpG νησίδων…

- Ανταποκρίνονται καλύτερα οι ασθενείς σε DNMT αναστολείς;;;

Leukemia (2011) 25, 1147–1152

www.nature.com/leu

ORIGINAL ARTICLE

Impact of *TET2* mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias

R Itzykson[1,12], O Kosmider[2,12], T Cluzeau[3], V Mansat-De Mas[4], F Dreyfus[5], O Beyne-Rauzy[6], B Quesnel[7], N Vey[8], V Gelsi-Boyer[9], S Raynaud[10], C Preudhomme[11], L Adès[1], P Fenaux[1] and M Fontenay[2] on behalf of the Groupe Francophone des Myelodysplasies (GFM)

Table 3 Response to azacitidine and response duration, according to *TET2* gene status

	Overall	*TET2 mutated*	*TET2 WT*	P[a]
Patients (*n*)	86	13	73	
CR	20 (23%)	5 (38%)	15 (21%)	0.17
PR	1 (1%)	0 (0%)	1 (1%)	
mCR	11 (13%)	4 (31%)	7 (10%)	
SD with HI	13 (15%)	2 (15%)	11 (15%)	
SD without HI	23 (27%)	1 (8%)	22 (31%)	
Progression	15 (17%)	1 (8%)	14 (19%)	
Early death (<4 cycles)	3 (4%)	0 (0%)	3 (4%)	
Overall response (CR, PR, mCR)	32 (37%)	9 (69%)	23 (31%)	0.01
Overall response including SD with HI	45 (52%)	11 (85%)	34 (47%)	0.01
Response duration, mos	9.3 (1.7–29.0)	9.2 (2.0–28.2)	7.1 (1.7–29.0)	0.7

Abbreviations: CR, complete remission; HI, hematological improvement; mCR, marrow CR; mos, months; PR, partial remission; SD, stable disease; TET2, ten-eleven-translocation 2.
Results are reported as *n* (%) or median.
[a]*TET2* mutated versus WT.

Leukemia (2014) 28, 78–87

www.nature.com/leu

ORIGINAL ARTICLE

Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms

F Traina[1,2,3], V Visconte[1], P Elson[4], A Tabarroki[1], AM Jankowska[1], E Hasrouni[1], Y Sugimoto[1], H S
MA Sekeres[5], AS Advani[5], M Kalaycio[5], EA Copelan[5], Y Sauntharajah[1], ST Olalla Saad[2], JP Mac

Table 2. Differences in treatment response based on mutational status

Mutational status	*Total, n = 92 (%)*	*Non-responders, n = 70 (%)*	*CR, mCR, PR, SD with HI, n = 22 (%)*	*P-value*[a]
TET2				
Wild type	75 (82)	58 (77)	17 (23)	
Mutant	17 (18)	12 (71)	5 (29)	0.54
DNMT3A				
Wild type	84 (91)	66 (79)	18 (21)	
Mutant	8 (9)	4 (50)	4 (50)	0.09
IDH1/IDH2				
Wild type	85 (92)	66 (78)	19 (22)	
Mutant	7 (8)	4 (57)	3 (43)	0.35
TET2/DNMT3A				
Neither mutated	68 (74)	55 (81)	13 (19)	
One or both mutated	24 (26)	15 (62)	9 (38)	0.09
TET2/DNMT3A/IDH1/IDH2				
None mutated	64 (70)	51 (80)	13 (20)	
1 gene mutated	24 (26)	18 (75)	6 (25)	
2 genes mutated	4 (4)	1 (25)	3 (75)	0.06[b]
ASXL1				
Wild type	68 (74)	53 (78)	15 (22)	
Mutant	24 (26)	17 (71)	7 (29)	0.58
CBL[c]				
Wild type	88 (97)	66 (75)	22 (25)	
Mutant	3 (3)	3 (100)	–	1.0
RAS[c]				
Wild type	89 (98)	67 (75)	22 (25)	
Mutant	2 (2)	2 (100)	–	1.0
CBL/RAS[c]				
Wild type	86 (95)	64 (74)	22 (26)	
CBL or *NRAS* mutant	5 (5)	5 (100)	–	0.33
SF3B1				
Wild type	80 (87)	61 (76)	19 (24)	
Mutant	12 (13)	9 (75)	3 (25)	1.0

Abbreviations: CR, complete remission; HI, hematological improvement; mCR, marrow CR; PR, partial remission; SD, stable disease. [a]Unless otherwise noted, Fisher's exact test for categorical factors with 2 levels; chi-square test for factors with >2 levels; Wilcoxon rank sum test for measured factors. [b]Cochran-Armitage trend test. [c]DNA was not available for Sanger sequencing in one patient.

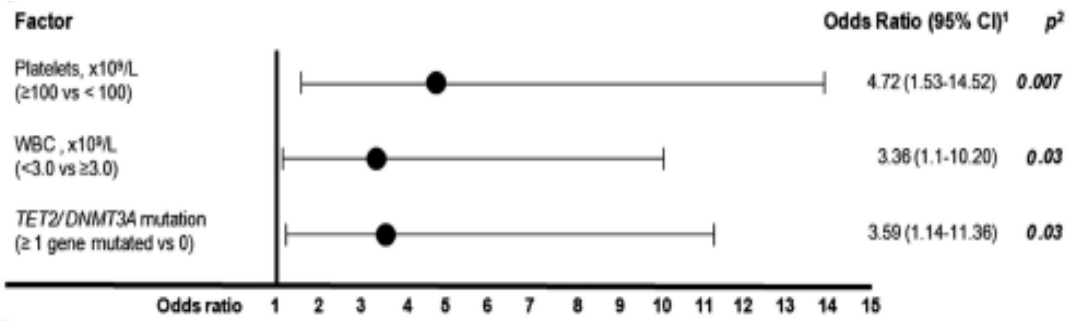
Leukemia (2014) 28, 78–87

www.nature.com/leu

ORIGINAL ARTICLE

Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms

F Traina[1,2,3], V Visconte[1], P Elson[4], A Tabarroki[1], AM Jankowska[1], E Hasrouni[1], Y Sugimoto[1], H Szpurka[1], H Makishima[1], CL O'Keefe[1], MA Sekeres[5], AS Advani[5], M Kalaycio[5], EA Copelan[5], Y Sauntharajah[1], ST Olalla Saad[2], JP Maciejewski[1,5] and RV Tiu[1,5]



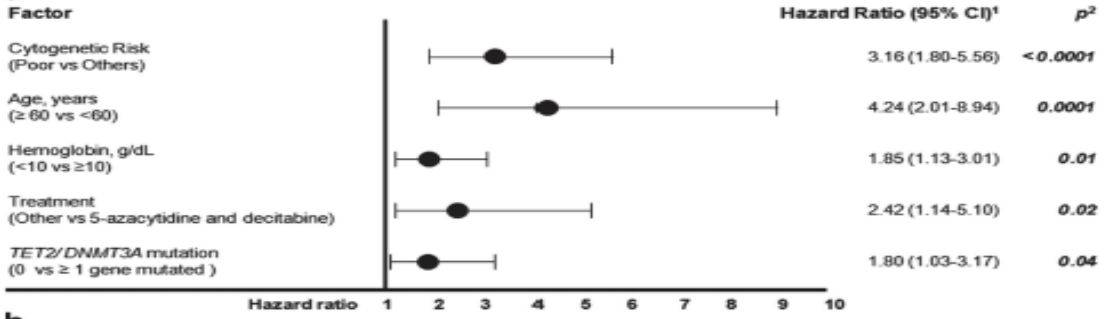
b

Feature	Category	Score
Platelets, x10⁹/L	≥100	0
	< 100	1
WBC , x10⁹/L	<3.0	0
	≥3.0	1
TET2/DNMT3A mutation	One or both genes mutated	0
	Both genes wild type	1

Total Score	Risk Group	N (%)	N (%) Response	p³
0 or 1	Favorable	23 (25%)	10 (43%)	
2	Intermediate	52 (57%)	12 (23%)	
3	Unfavorable	16 (18%)	-0-	**0.002**

Figure 1. Multivariate analysis results of clinical and laboratory parameters on response to 5-azacytidine and/or decitabine. (**a**) Multivariate analysis for favorable treatment response (CR, mCR, PR and SD with HI) identified platelet counts $\geqslant 100 \times 10^9$/l, white blood cell (WBC) count $< 3 \times 10^9$/l and *TET2* and/or *DNMT3A* mutation as predictive factors of favorable response. Odds ratios and confidence intervals (CI) are indicated with a black dot and a line, respectively. (**b**) A risk stratification score that predicts response was built. The score was based on counting the number of poor features present, where platelets $< 100 \times 10^9$/l, WBC $\geqslant 3.0 \times 10^9$/l, and $TET2^{WT}$ and $DNMT3A^{WT}$ each counted as one poor feature. The score identified three groups with significant differences in response to DNMT inhibitor treatment. [1]Feature with the better prognosis is listed first; [2]Wald test; [3]Cochran-Armitage trend test.

a



b

Feature	Category	Score
Cytogenetic Risk	Others Poor	0 7
Age	< 60 ≥ 60	0 10
Hemoglobin, g/dL	≥10 <10	0 4
Treatment	5-azacytidine and decitabine Other	0 6
TET2/*DNMT3A* mutation	One or both genes mutated Both genes wild type	0 5

Total Score	Risk Group	N (%)	Median Survival (months)	p[3]
<22	Favorable	56 (61%)	18.3	
≥22	Unfavorable	36 (39%)	5.0	**<0.0001**

c

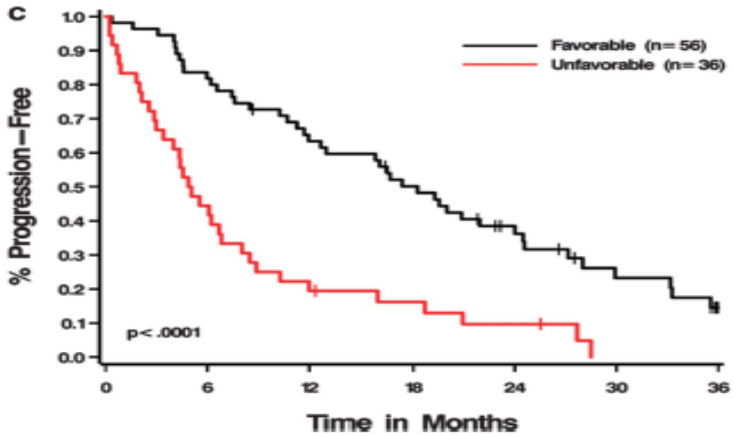
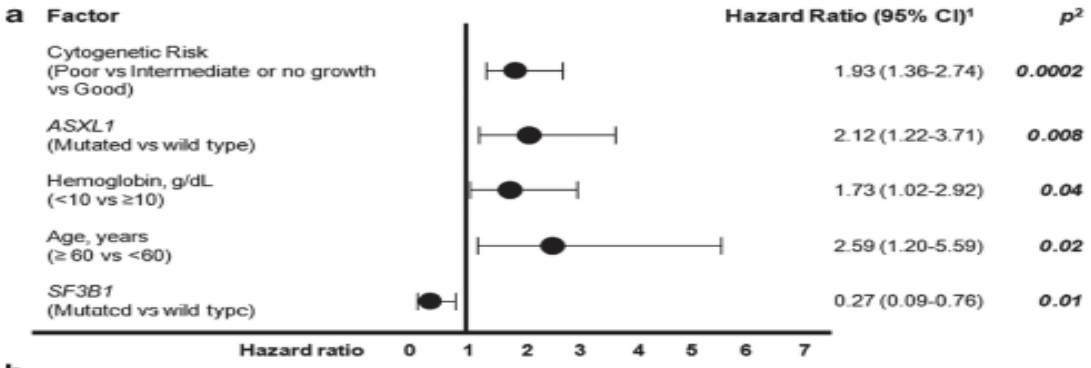


Figure 2. Multivariate analysis results of clinical and laboratory parameters on progression-free survival (PFS) of patients treated with 5-azacytidine and/or decitabine. (**a**) Multivariate analysis identified factors independently associated with shorter PFS: poor cytogenetic risk, age⩾60 years, hemoglobin < 10 g/dl, treatment with regimens other than both 5-azacytidine and decitabine, and $TET2^{WT}$ and $DNMT3A^{WT}$. Hazard ratios and confidence intervals (CI) are indicated with a black dot and a line, respectively. (**b**) A risk stratification score that predicts PFS was built by assigning points to each factor based on the parameter estimates of the final model. Summing these points, two distinct groups of patients were identified. (**c**) Kaplan–Meier curves for the two risk groups. [1]Feature with the poorer prognosis is listed first; [2]Wald test; [3]Logrank test.



b

Feature	Category	Score
Cytogenetic Risk	Good Intermediate or no growth Poor	0 2 5
ASXL1	Wild type Mutated	0 3
Hemoglobin, g/dL	≥10 <10	0 2
Age	< 60 ≥ 60	0 4
SF3B1	Mutated Wild type	0 8

Total Score	Risk Group	N (%)	Median Survival (months)	p[3]
<12	Favorable	49 (53%)	30.7	
≥12	Unfavorable	43 (47%)	7.9	<0.0001

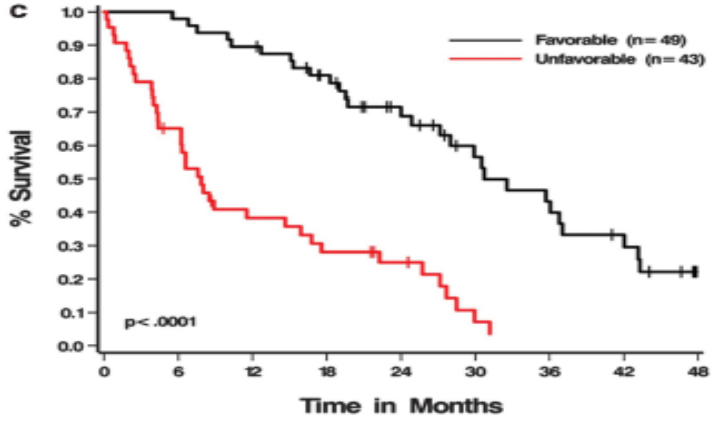


Figure 3. Multivariate analysis results of clinical and laboratory parameters on overall survival (OS) of patients treated with 5-azacytidine and/or decitabine. (**a**) Multivariate analysis identified factors independently associated with shorter OS: poorer cytogenetic risk, $ASXL1^{MUT}$, hemoglobin <10g/dl, age $\geqslant 60$ years and $SF3B1^{WT}$. Hazard ratios and confidence intervals (CI) are indicated with a black dot and a line, respectively. (**b**) A risk stratification score that predicts OS was built by assigning points to each factor based on the parameter estimates of the final model. Summing these points, two distinct groups of patients were identified. (**c**) Kaplan–Meier curves for the two risk groups. [1] Feature with the poorer prognosis is generally listed first (hazard ratios >1 indicate the first feature has the poorer outcome; ratios <1 indicate the first feature has the better outcome); [2] Wald test; [3] Logrank test.

Υπάρχουν καλής πρόγνωσης μεταλλαγές ;;;

blood
2011 118: 6239-6246
doi:10.1182/blood-2011-09-377275 originally published online October 12, 2011

Clinical significance of *SF3B1* mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms

Luca Malcovati, Elli Papaemmanuil, David T. Bowen, Jacqueline Boultwood, Matteo G. Della Porta, Cristiana Pascutto, Erica Travaglino, Michael J. Groves, Anna L. Godfrey, Ilaria Ambaglio, Anna Gallì, Matteo C. Da Vià, Simona Conte, Sudhir Tauro, Norene Keenan, Ann Hyslop, Jonathan Hinton, Laura J. Mudie, James S. Wainscoat, P. Andrew Futreal, Michael R. Stratton, Peter J. Campbell, Eva Hellström-Lindberg, Mario Cazzola and on behalf of the Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium and of the Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative

Table 1. Proportion of patients carrying somatic mutations of *SF3B1* in the study population

WHO category	No. of patients studied	No. of sequencing failures*	No. of evaluable patients	No. (%) of patients carrying SF3B1 mutations
MDS				
RA	135	13	122	14 (11.5)
RARS	107	2	105	83 (79.0)
RCMD	102	6	96	6 (6.3)
RCMD-RS†	54	2	52	30 (57.7)
RAEB-1	87	4	83	7 (8.4)
RAEB-2	57	4	53	6 (11.3)
MDS del(5q)	22	0	22	4 (18.2)
MDS total	564	31	533	150 (28.1)
MDS/MPN				
CMML	67	5	62	4 (6.5)
RARS-T	18	0	18	12 (66.7)
MDS/MPN, U	3	0	3	0
AML secondary to MDS	40	2	38	2 (5.3)
All patients studied	692	38	654	168 (25.7)

*Failure was the result of insufficient sequence coverage.
†RCMD-RS was a separate MDS category in the 2001 WHO classification of myeloid neoplasms[21] but was incorporated into RCMD in the 2008 WHO classification.[2,3]

Συνοπτικά …

Ανάγκη σχεδιασμού προοπτικών μελετών

Rank	Status	Study

1 **Recruiting** **Collection of Biological Data With Potential Prognostic Relevance in Patients With MYELODYSPLASTIC SYNDROMES**

Condition: Myelodysplastic Syndrome

Collection of Biological Data With Potential Prognostic Relevance in Patients With MYELODYSPLASTIC SYNDROMES (O-MDS-Protocol)

This study is currently recruiting participants. (see Contacts and Locations)
Verified February 2011 by Fondazione Amelia Scorza Onlus

Sponsor:
Fondazione Amelia Scorza Onlus

Information provided by:
Fondazione Amelia Scorza Onlus

ClinicalTrials.gov Identifier:
NCT01291745

First received: February 7, 2011
Last updated: NA
Last verified: February 2011
History: No changes posted

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The present study is designed to determine the mutational status of markers (**TET2** and PLCb2, cytogenetic aberrations) together with methylation status of the above genes using bone marrow and matched buccal cell samples from MDS patients who necessitate to start a treatment (i.e. EPO, Lenalidomide, Azacytidine). All patients included in the study will be followed for at least 2 years.

Condition
Myelodysplastic Syndrome

3 **Completed** **Prognostic Molecular Markers in Patients With Myelodysplastic Syndrome**

Condition: Myelodysplastic Syndrome
Intervention: Genetic: spliceosome

Prognostic Molecular Markers in Patients With Myelodysplastic Syndrome

This study has been completed.

Sponsor:
Samsung Medical Center

Information provided by (Responsible Party):
Jun Ho Jang, Samsung Medical Center

ClinicalTrials.gov Identifier:
NCT02060409

First received: February 10, 2014
Last updated: February 11, 2014
Last verified: February 2014
History of Changes

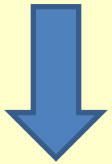
Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

In the era of hypomethylating agent in **MDS** treatment, the investigators aimed to investigate the prognostic impact of mutations in spliceosome machinery genes (SRSF2, U2AF1, and ZRSR2) on the outcomes of 1st line decitabine treatment in **MDS**.

Condition	Intervention
Myelodysplastic Syndrome	Genetic: spliceosome

Ανάγκη σχεδιασμού προοπτικών μελετών



Δημιουργία προγνωστικών μοντέλων σύμφωνα με μοριακά πρότυπα

Biological pathways and genes	Frequency, %*	Timing of mutation acquisition†	Relationship between mutant gene and clinical phenotype	Prognostic or predictive relevance of mutant gene
RNA splicing				
SF3B1	15-30%	More often a founding mutation	Strictly associated with ring sideroblasts phenotype (RARS, RARS-T)	Associated with good overall survival and low risk of leukemic evolution
SRSF2	10-20%	More often a founding mutation	Associated with RCMD or RAEB, co-mutated with *TET2* in CMML	Associated with poor overall survival and high risk of leukemic evolution
U2AF1	<10%	More often a founding mutation	Mainly associated with RCMD or RAEB	Associated with high risk of leukemic evolution
ZRSR2	<10%	More often a founding mutation	Not defined	Not defined
DNA methylation				
TET2	20-30%	More often a founding mutation	Found in all MDS subtypes, high mutation frequency (50-60%) in CMML	No impact on overall survival, may predict response to hypomethylating agents
DNMT3A	~10%	More often a founding mutation	Found in all MDS subtypes, co-mutated with *SF3B1* in RARS	Associated with unfavorable clinical outcome (negative prognostic relevance mitigated by *SF3B1* co-mutation in RARS)
IDH1/IDH2	~5%	More often a founding mutation	Associated with RCMD or RAEB	Associated with unfavorable clinical outcome
Chromatin modification				
ASXL1	15-20%	More often a subclonal mutation	Associated with RCMD or RAEB, high mutation frequency (40%) in CMML	Associated with unfavorable clinical outcome in all myeloid neoplasms (MDS, MDS/MPN, MPN)
EZH2	~5%	More often a subclonal mutation	Associated with RCMD or RAEB	Associated with unfavorable clinical outcome in all myeloid neoplasms
Transcription				
RUNX1	~10%	Typical subclonal mutation	Associated with RCMD or RAEB	Associated with unfavorable clinical outcome
BCOR	<5%	Typical subclonal mutation	Associated with RCMD or RAEB	Associated with unfavorable clinical outcome
DNA repair control				
TP53	~5%	Typical subclonal mutation	Associated with advanced disease and complex karyotype, mutated in 20% of patients with MDS with del(5q)	Associated with poor overall survival and high risk of leukemic evolution, predicts poor response to lenalidomide in MDS with del(5q)
Cohesin				
STAG2	<10%	More often a subclonal mutation	Associated with RCMD or RAEB. Mutated in about 10% of patients with AML	Associated with unfavorable clinical outcome
RAS pathway				
CBL	<5%	More often a subclonal mutation	Found in different MDS subtypes, associated with JMML in children	Not defined in MDS
NRAS/KRAS	<5%	More often a subclonal mutation	Found in different MDS subtypes, associated with JMML in children	Not defined in MDS
NF1	<5%	More often a subclonal mutation	Found in different MDS subtypes, associated with JMML in children	Not defined in MDS
DNA replication				
SETBP1	<5%	More often a subclonal mutation	Found in 25% of patients with aCML and in subsets of patients with advanced MDS or CMML	Associated with poor overall survival and high risk of leukemic evolution
Receptors				
CSF3R	<1%	Founding driver mutation in CNL	Strictly associated with CNL, found in a subset of patients with aCML	Mutation type may predict response to specific inhibitors

*Approximate proportion of patients with MDS carrying the mutant gene reported in studies published so far.
†Based on values for mutant allele burden or variant allele frequency.

Ανάγκη σχεδιασμού προοπτικών μελετών

Δημιουργία προγνωστικών μοντέλων σύμφωμα με μοριακά πρότυπα

Περισσότερο στοχευμένες θεραπείες…

ΣΤΟΧΕΥΜΕΝΕΣ ΘΕΡΑΠΕΙΕΣ	
TET-2	Vidaza ???
IDH1 & IDH2	Vidaza ???
DNMT3a	Vidaza ???
MLL	Demethylating agents ? HIDACs ?
EZH2	?
ASXL1	?
FLT3	Midostaurin, Lestaurtinib, Tandutinib Sunitinib, Sorafenib
KIT	Dasatinib, Midostaurin
RAS	Farsenyl transferase inhibitors Sorafenib ?
CBL	TKIs, Sorafenib ?
CEBPA	?
NPM1	ATRA ???
RUNX1	?

MYELOID NEOPLASIA

CME Article

Clinical and biological implications of driver mutations in myelodysplastic syndromes

Elli Papaemmanuil,[1] Moritz Gerstung,[1] Luca Malcovati,[2] Sudhir Tauro,[3] Gunes Gundem,[1] Peter Van Loo,[1,4,5] Chris J. Yoon,[1] Peter Ellis,[1] David C. Wedge,[1] Andrea Pellagatti,[6] Adam Shlien,[1] Michael John Groves,[3] Simon A. Forbes,[1] Keiran Raine,[1] Jon Hinton,[1] Laura J. Mudie,[1] Stuart McLaren,[1] Claire Hardy,[1] Calli Latimer,[1] Matteo G. Della Porta,[2] Sarah O'Meara,[1] Ilaria Ambaglio,[2] Anna Galli,[2] Adam P. Butler,[1] Gunilla Walldin,[7] Jon W. Teague,[1] Lynn Quek,[8] Alex Sternberg,[8,9] Carlo Gambacorti-Passerini,[10] Nicholas C. P. Cross,[11] Anthony R. Green,[12,13] Jacqueline Boultwood,[6] Paresh Vyas,[7] Eva Hellstrom-Lindberg,[7] David Bowen,[14] Mario Cazzola,[2] Michael R. Stratton,[1] and Peter J. Campbell[1,12,13] on behalf of the Chronic Myeloid Disorders working group of the International Cancer Genome Consortium

[1]Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, United Kingdom; [2]Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico, Policlinico San Matteo, University of Pavia, Pavia, Italy; [3]Division of Medical Sciences, University of Dundee, Dundee, United Kingdom; [4]Center for the Biology of Disease, Vlaams Instituut voor Biotechnologie, Leuven, Belgium; [5]Department of Human Genetics, Katholieke Universiteit Leuven, Leuven, Belgium; [6]Nuffield Department of Clinical Laboratory Sciences, University of Oxford, Oxford, United Kingdom; [7]Department of Haematology, Karolinska Institute, Stockholm, Sweden; [8]Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom; [9]Department of Haematology, Great Western Hospital, Swindon, United Kingdom; [10]Department of Haematology, University of Milan Bicocca, Milan, Italy; [11]Faculty of Medicine, University of Southampton, Southampton, United Kingdom; [12]Department of Haematology, University of Cambridge, Cambridge, United Kingdom; [13]Department of Haematology, Addenbrooke's Hospital, Cambridge, United Kingdom; and [14]St. James Institute of Oncology, St. James Hospital, Leeds, United Kingdom

Medscape EDUCATION **Continuing Medical Education online**

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Medscape, LLC and the American Society of Hematology. Medscape, LLC is accredited by the ACCME to provide continuing medical education for physicians.

1. Based on the genetic study by Papaemmanuil and colleagues, which of the following statements about mutations in myelodysplastic syndromes (MDS) is ***most likely*** correct?

   - Mutations in patients with MDS have been found in only 5 genes
   - MDS genome sequencing has shown mutations in genes implicated in RNA splicing, DNA modification, chromatin regulation, and cell signaling
   - In this study, about one-quarter of patients had one or more oncogenic mutations
   - Findings of this study do not support a genetic "predestination" hypothesis

2. Your patient is a 62-year-old male with MDS. Which of the following statements about the association of mutations in MDS with prognosis and other clinical outcomes is ***most likely*** correct?

   - Clonal, but not subclonal, driver mutations were of great prognostic significance
   - Number of driver mutations was not associated with leukemia-free survival
   - The interconnections between the cancer genome and MDS biology shown in this study have considerable potential for clinical application
   - Mutations involving RNA splicing do not appear to affect disease course or outcomes

3. Based on the genetic study by Papaemmanuil and colleagues, which of the following statements about gene mutations in MDS and related neoplasms is ***most likely*** correct?

   - Among oncogenic mutations identified in 43 genes, *SRSF2* was the most frequently mutated in the cohort
   - *TET2* was mutated in 22% of the cohort
   - Mutations in well-known cancer genes not previously implicated in MDS were not observed
   - Oncogenic mutations were observed in *IRF1* but not in *CUX1*

4. Based on the genetic study by Papaemmanuil and colleagues, which of the following statements about clonal and subclonal mutations in MDS and related neoplasms, and their effects on prognosis, is ***most likely*** correct?

   - Of 24 genes mutated in 5 or more patients, 8 genes were associated with significantly worse leukemia-free survival if mutated
   - Mutations in *SF3B1* were associated with worse leukemia-free survival
   - The investigators found a significant difference in leukemia-free survival between clonal and subclonal mutations for the 6 genes with published survival effects in which ≥5 patients had subclonal driver mutations
   - Detecting subclonal driver mutations is not helpful in determining prognosis

1. Based on the genetic study by Papaemmanuil and colleagues, which of the following statements about mutations in myelodysplastic syndromes (MDS) is ***most likely*** correct?

   - Mutations in patients with MDS have been found in only 5 genes
   - MDS genome sequencing has shown mutations in genes implicated in RNA splicing, DNA modification, chromatin regulation, and cell signaling
   - In this study, about one-quarter of patients had one or more oncogenic mutations
   - Findings of this study do not support a genetic "predestination" hypothesis

2. Your patient is a 62-year-old male with MDS. Which of the following statements about the association of mutations in MDS with prognosis and other clinical outcomes is ***most likely*** correct?

   - Clonal, but not subclonal, driver mutations were of great prognostic significance
   - Number of driver mutations was not associated with leukemia-free survival
   - The interconnections between the cancer genome and MDS biology shown in this study have considerable potential for clinical application
   - Mutations involving RNA splicing do not appear to affect disease course or outcomes

3. Based on the genetic study by Papaemmanuil and colleagues, which of the following statements about gene mutations in MDS and related neoplasms is ***most likely*** correct?

   - Among oncogenic mutations identified in 43 genes, *SRSF2* was the most frequently mutated in the cohort
   - *TET2* was mutated in 22% of the cohort
   - Mutations in well-known cancer genes not previously implicated in MDS were not observed
   - Oncogenic mutations were observed in *IRF1* but not in *CUX1*

4. Based on the genetic study by Papaemmanuil and colleagues, which of the following statements about clonal and subclonal mutations in MDS and related neoplasms, and their effects on prognosis, is ***most likely*** correct?

   - Of 24 genes mutated in 5 or more patients, 8 genes were associated with significantly worse leukemia-free survival if mutated
   - Mutations in *SF3B1* were associated with worse leukemia-free survival
   - The investigators found a significant difference in leukemia-free survival between clonal and subclonal mutations for the 6 genes with published survival effects in which ≥5 patients had subclonal driver mutations
   - Detecting subclonal driver mutations is not helpful in determining prognosis