Groupe Français des Myelodysplasies

Sindromes mielodisplasticos: biologia y tratamiento

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Sindromes Mielodisplasticos (SMD)

- Trastornos clonales de los proyenitores hematopoieticos caracterizados por:
  - Hematopoiesis ineficaz resultando en citopenias
  - Alto riesgo de progresion en LMA (35%)
- Edad mediana: 65 - 70 anos
- Incidencia de 3 a 5/100000 personas/ano

Myelodysplastic syndromes (MDS)

- Epidemiologia
- Clasificacion y factores pronosticos
- Biologia
  - apoptosis, angiogenesis
  - Citogenetica, genetica and epigenetica
  - Anomalias Immunologicas
- Tratamiento

Myelodysplastic syndromes (MDS)

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MDS: etiology

Generally unknown, except:

-Inherited disorders:Down's syndrome, Fanconi, neurofibromatosis,

-Exposures : chemotherapy (alkylating rather than anthracyclines or VP 16), radiotherapy, benzene

-Association to immune disorders (relapsing polychondritis , vasculitis, seronegative arthritis, Crohn)

MDS: occupational and environmental exposures

(Cardiff, Lille, MD Anderson)

Exposure to:

- oil derivatives
- Compounds used in agriculture
- Smoking

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MDS: FAB Classification

Classification	BM Blasts (%)	PB Blasts (%)
RA, RARS	<5	<1
RAEB	5–20	<5
RAEB-t	21–29	Auer rods
CMML	0–20	Monocytes

PB = peripheral blood; RAEB-t = RAEB in transformation.

WHO classification

FAB	WHO
• RA • RARS	• RA • RCMD • RARS • RCMD-RS • 5q- syndrome
• RAEB	• RAEB-1 • RAEB-2
RAEB-t CMML	• AML • MDS/MPD

Indice pronostico International (IPSS)

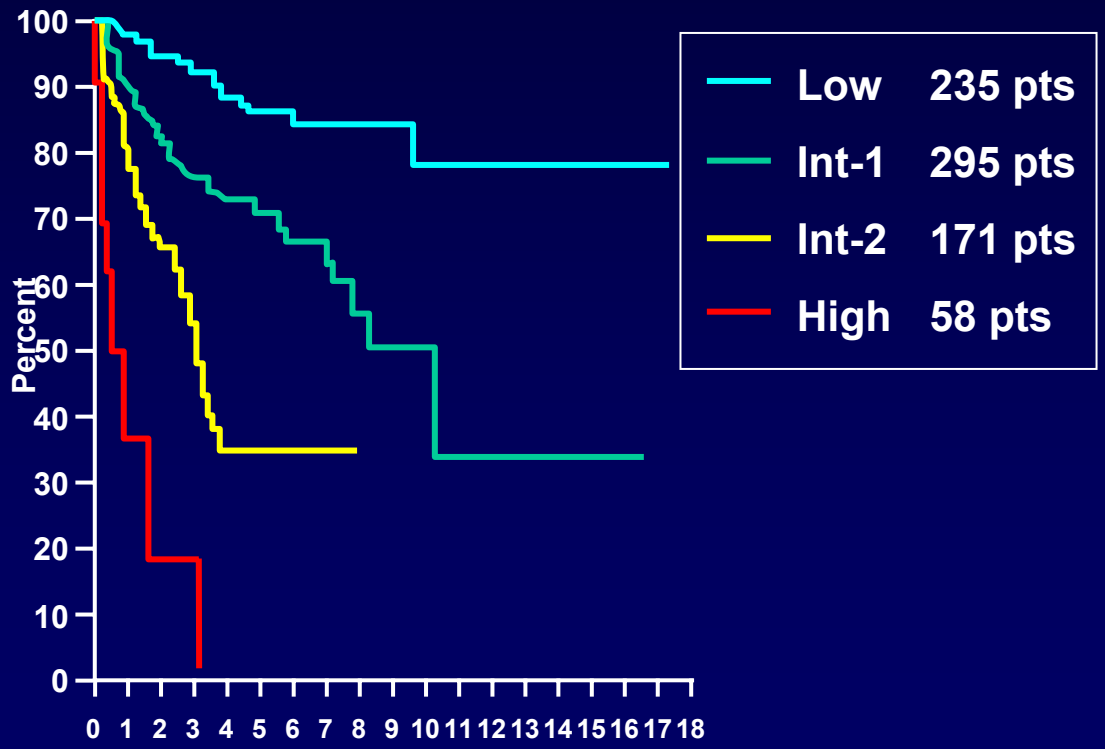
	Score Value				
Prognostic variable	0	0.5	1.0	1.5	2.0
BM blasts, %	<5	5–10	—	11–20	21–30
Karyotype*	Good	Interm.	Poor		
Cytopenias	0/1	2/3	—		

Scores	puntuation
Low	0
Int-1	0.5–1.0
Int-2	1.5–2.0
High	≥2.5

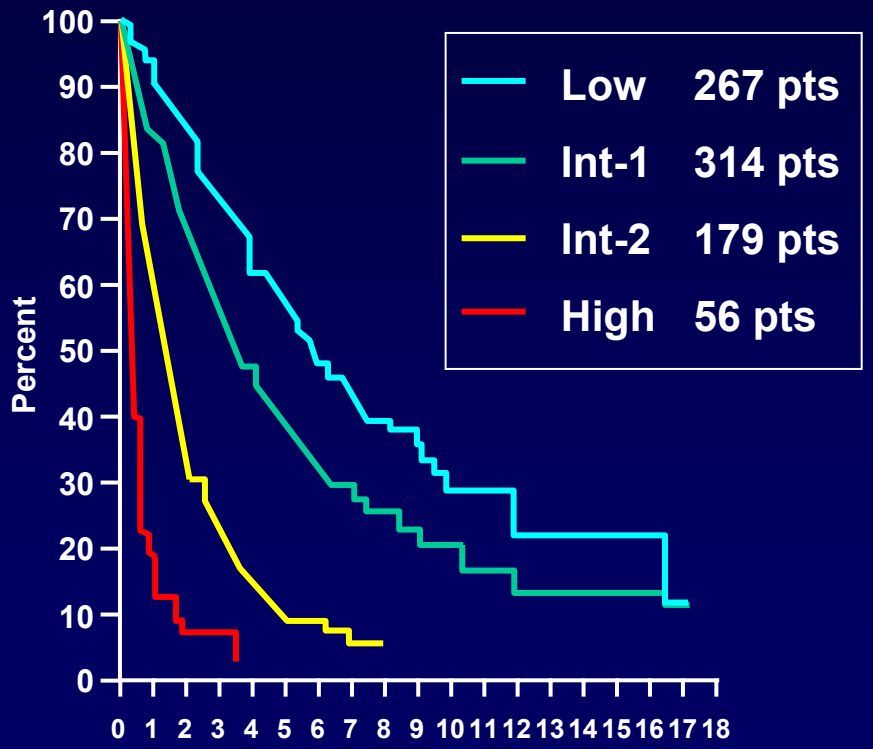
Cytogenetics	
Good	Normal –y del(5q) del(20q)
Poor	Complex (≥3 abn)
Chr.	7 abn
Int.	Other

IPSS

AML Evolution



Survival



Greenberg P et al. *Blood*. 1997;89:2079-2088.

MDS: other prognostic factors than IPSS ?

- Multilineage dysplasia
- Myelofibrosis
- ALIP ?
- RBC Transfusion requirement
- Genetic mutations (ras, p53, AML 1)

Are they independent ?

Role of WPSS (multilineage dysplasia and RBC transfusion requirement) (Pavia group) ?

SMD: riesgo « alto » vs « bajo »

- **Riesgo bajo**
  - IPSS intermedio-2 or elevado
  - (blastos en la MO >10%)
- **Riesgo alto**
  - IPSS bajo o intermedio-1
  - (blastos en la MO <5%)

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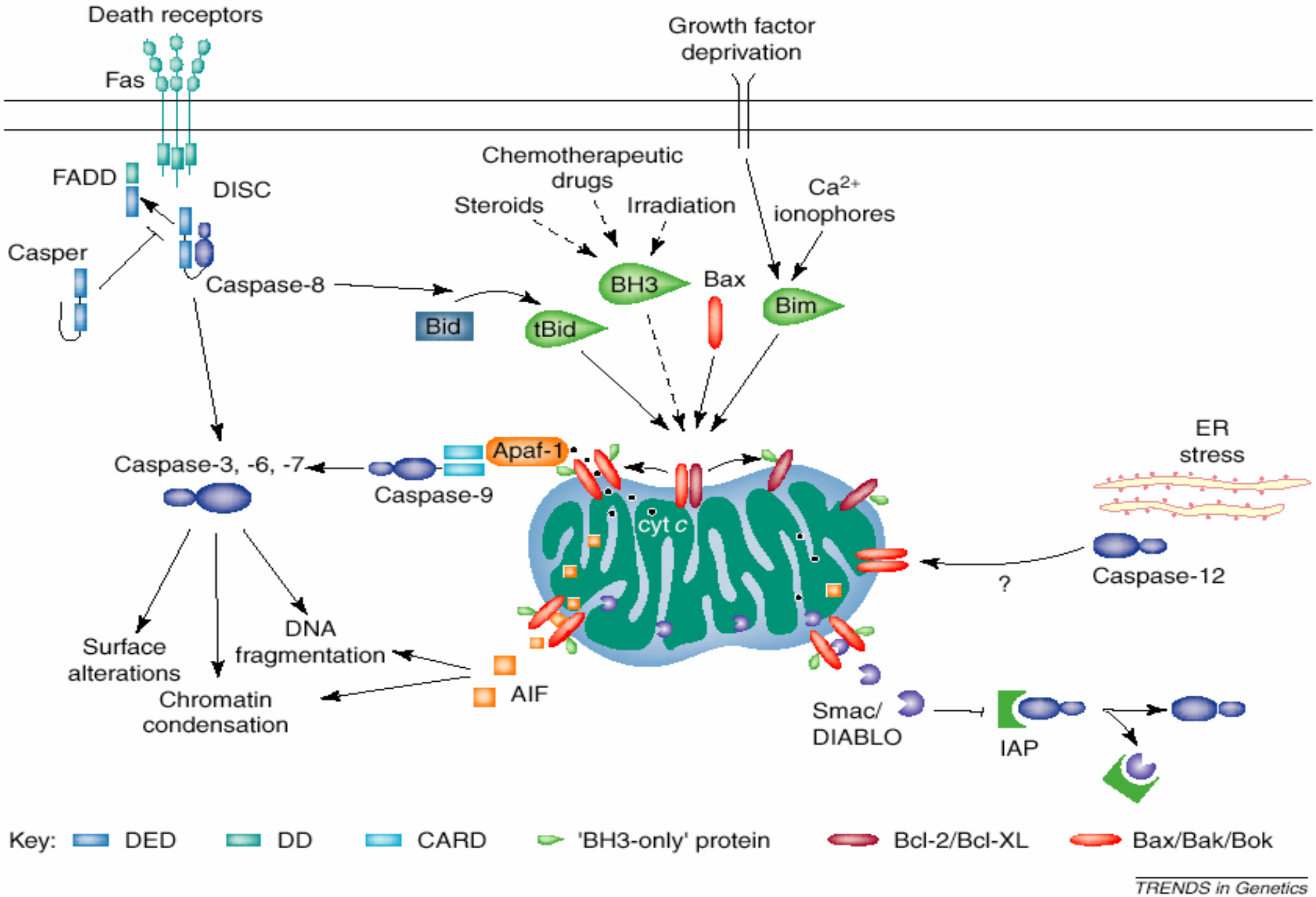
MDS: pathophysiology

- **Early stage** (no or limited excess of marrow blasts): increased apoptosis of marrow progenitors leading to blood cytopenias

Mechanisms of incresed apoptosis:

- Activation of « death » receptors (FAS….)
- mitochondrial Activation (with impaired iron metabolism?)


Death receptors
Fas
Growth factor deprivation
FADD
DISC
Chemotherapeutic drugs
Steroids
Irradiation
Ca2+ ionophores
Casper
Caspase-8
Bid
tBid
BH3
Bax
Bim
Caspase-3, -6, -7
Caspase-9
Apaf-1
cyt c
ER stress
Caspase-12
?
Surface alterations
Chromatin condensation
DNA fragmentation
AIF
Smac/ DIABLO
IAP
Key:
DED
DD
CARD
'BH3-only' protein
Bcl-2/Bcl-XL
Bax/Bak/Bok
TRENDS in Genetics

Role of the iron transporter ABCB7 in RARS (Boultwood, PLoS 2008)

- Partial inactivating mutations of ABCB7 gene in X linked sideroblastic anemias
- Reduced expression of ABCB7 gene (without detectable mutations) in RARS

MDS: increased angiogenesis

- ↑ density of bone marrow microvessels[1,2]
- ↑ circulating angiogeneic factors (particularly VEGF)[2,3]

MDS: pathophysiology

- **Later stage** :progressive maturation arrest with worsening of cytopenias and increase in marrow blasts

Mechanisms:(oncogene activation?) tumor suppressor or other gene inactivation by

- Chromosome abnormalities(-7, +8)
- Gene mutations (ras, p53)
- Gene hypermethylation (p15)
- NF kappa B activation

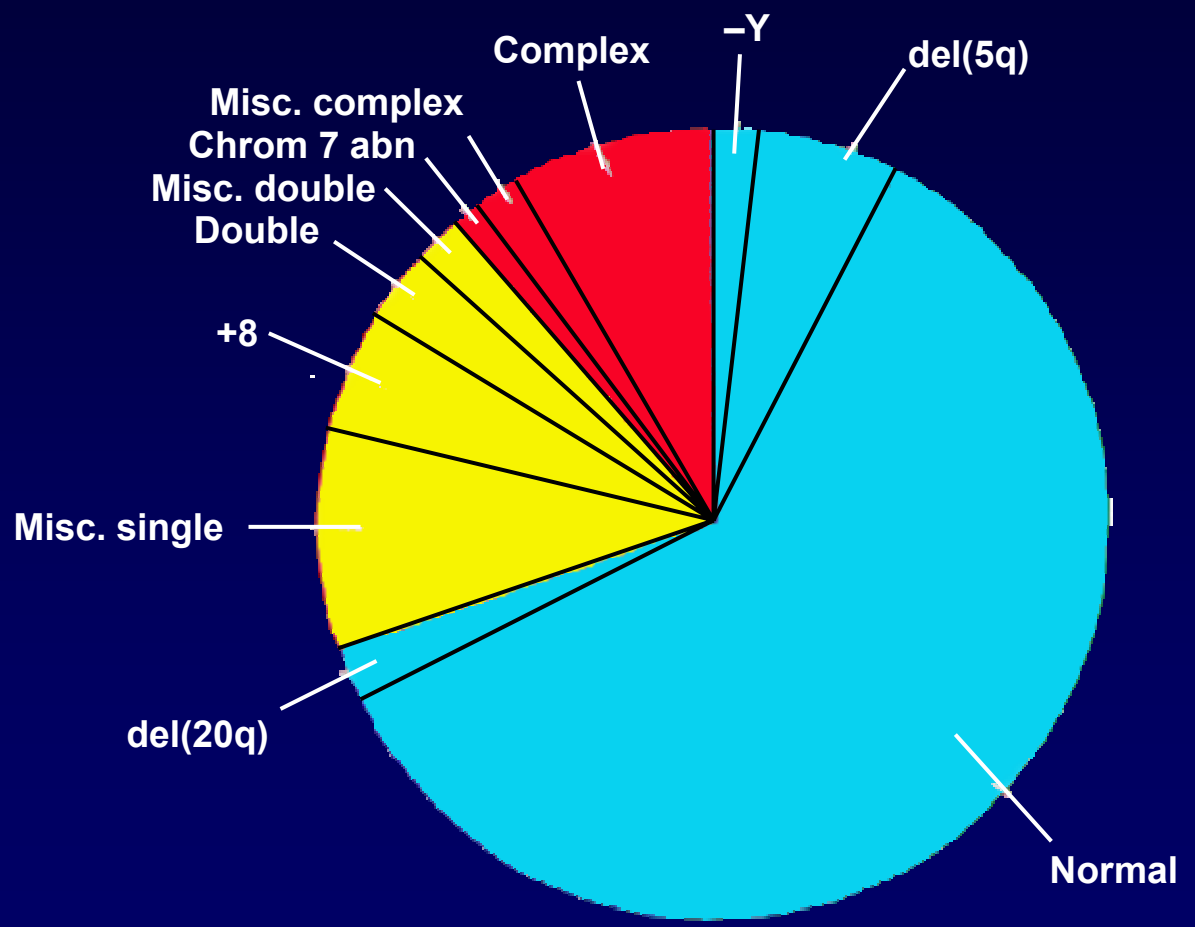
Main cytogenetic abnormalities in MDS (50%)

- **Deletions (40%):**
  partial : del 5q, del 20q,
  complete: -7,-Y
- **Chromosome gain (20%):** +8
- **Unbalanced translocations(15%):** t(1;7),t(5;17)
- **Balanced translocations(1-2%)**
  t(3;3),t(3;5),t(5;12)

- **Complex abnormalities(30%)**

Cytogenetic Abnormalities in MDS

	No. of patients	(%)
–Y	17	(2)
del(5q)	48	(6)
Normal	489	(60)
del(20q)	16	(2)
Misc. single	74	(9)
+8	38	(5)
Double	29	(3)
Misc. double	14	(2)
Chrom 7 abn	10	(1)
Misc. complex	15	(2)
Complex	66	(8)



Greenberg P et al. *Blood*. 1997;89:2079-2088.

Less frequent Cytogenetic abnormalities in MDS (Haase, Blood ,2008)

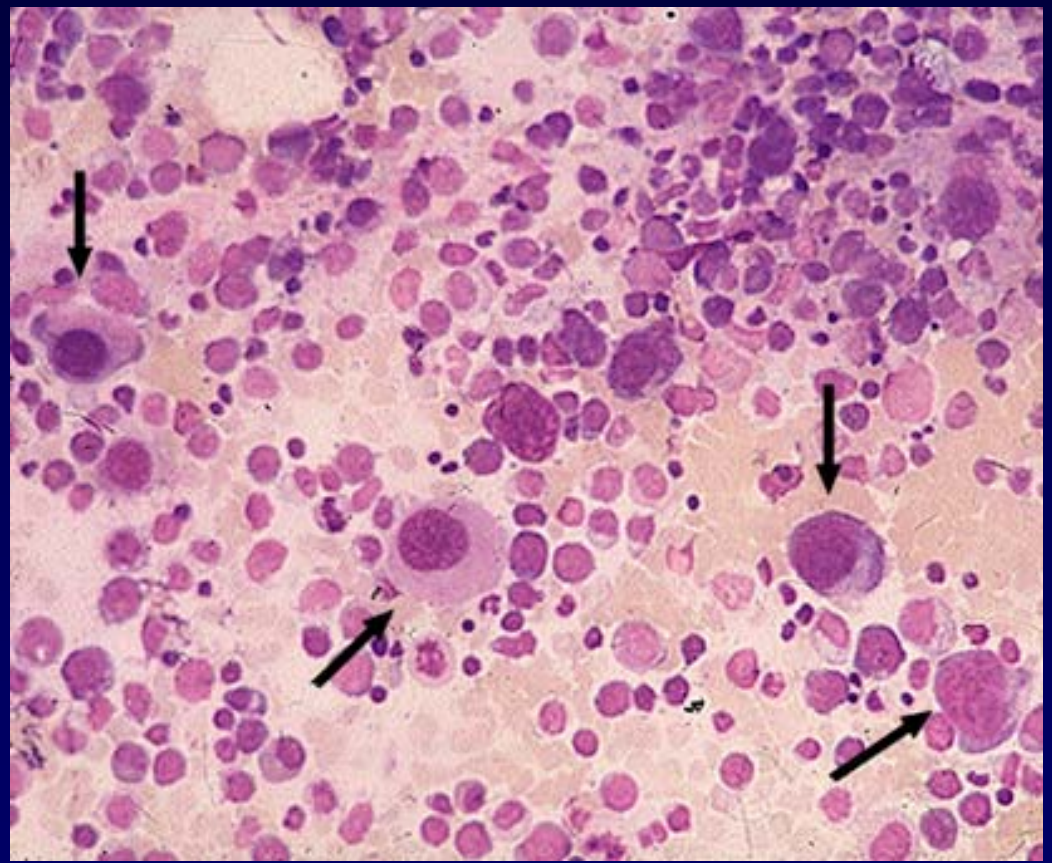
Based on > 2500 cases

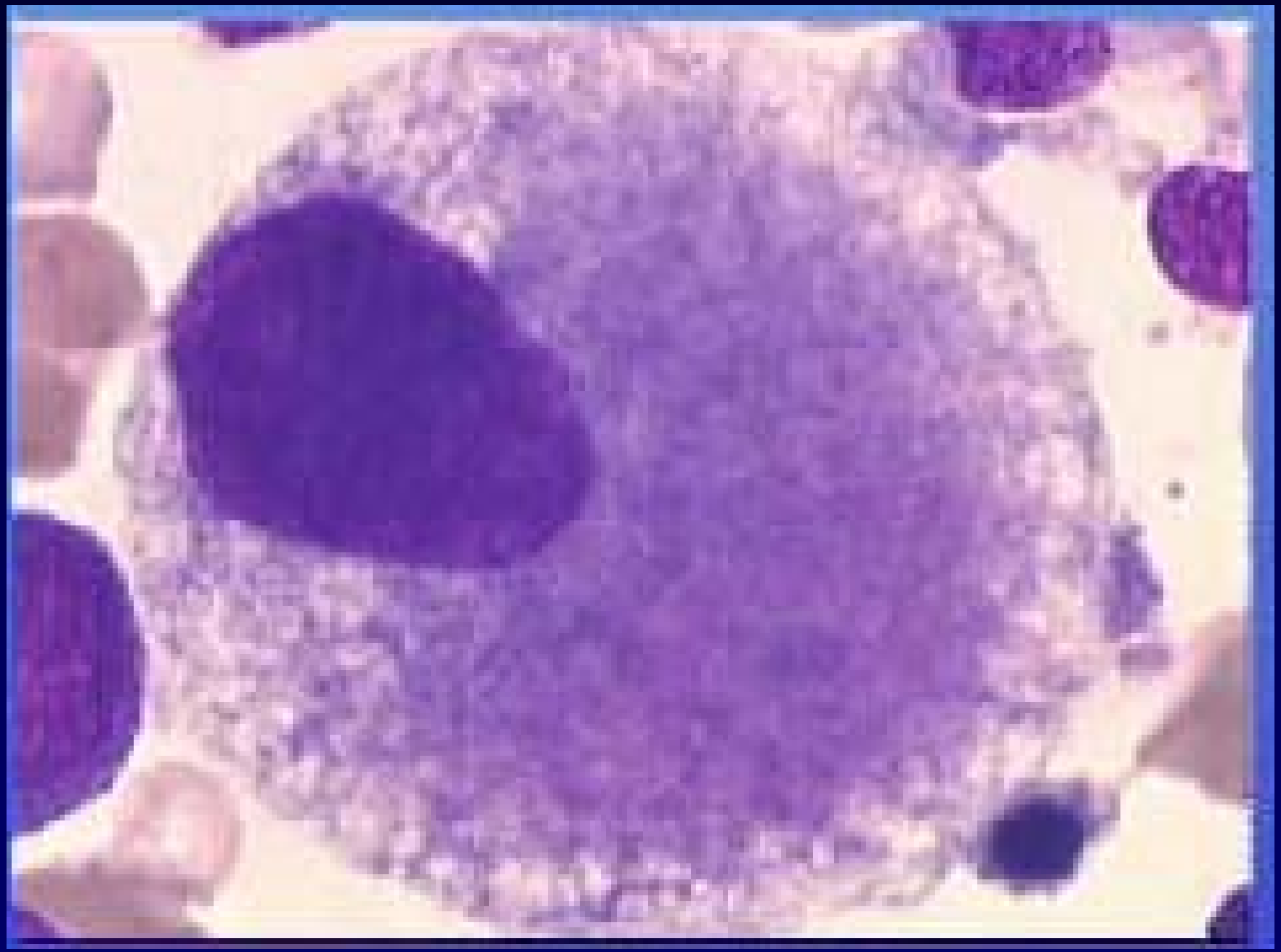
13 rare abnormalities identified :

- good (+1/+1q, t(1q), t(7q), del(9q), del(12p), chromosome 15 anomalies, t(17q), monosomy 21, trisomy 21, and –X)
- intermediate :del(11q), chromosome 19 anomalies
- Poor: t(5q)

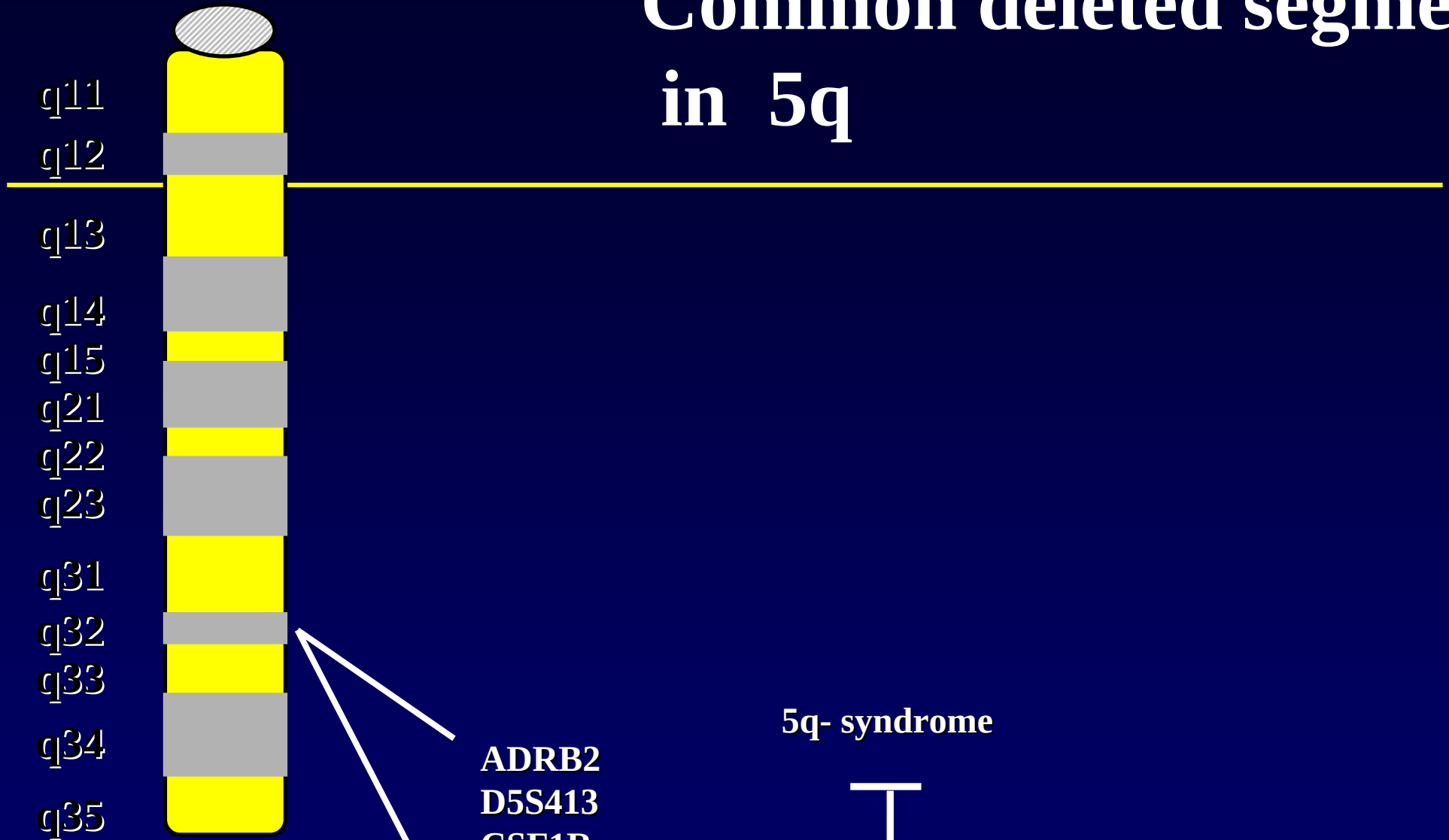
The 5q-syndrome

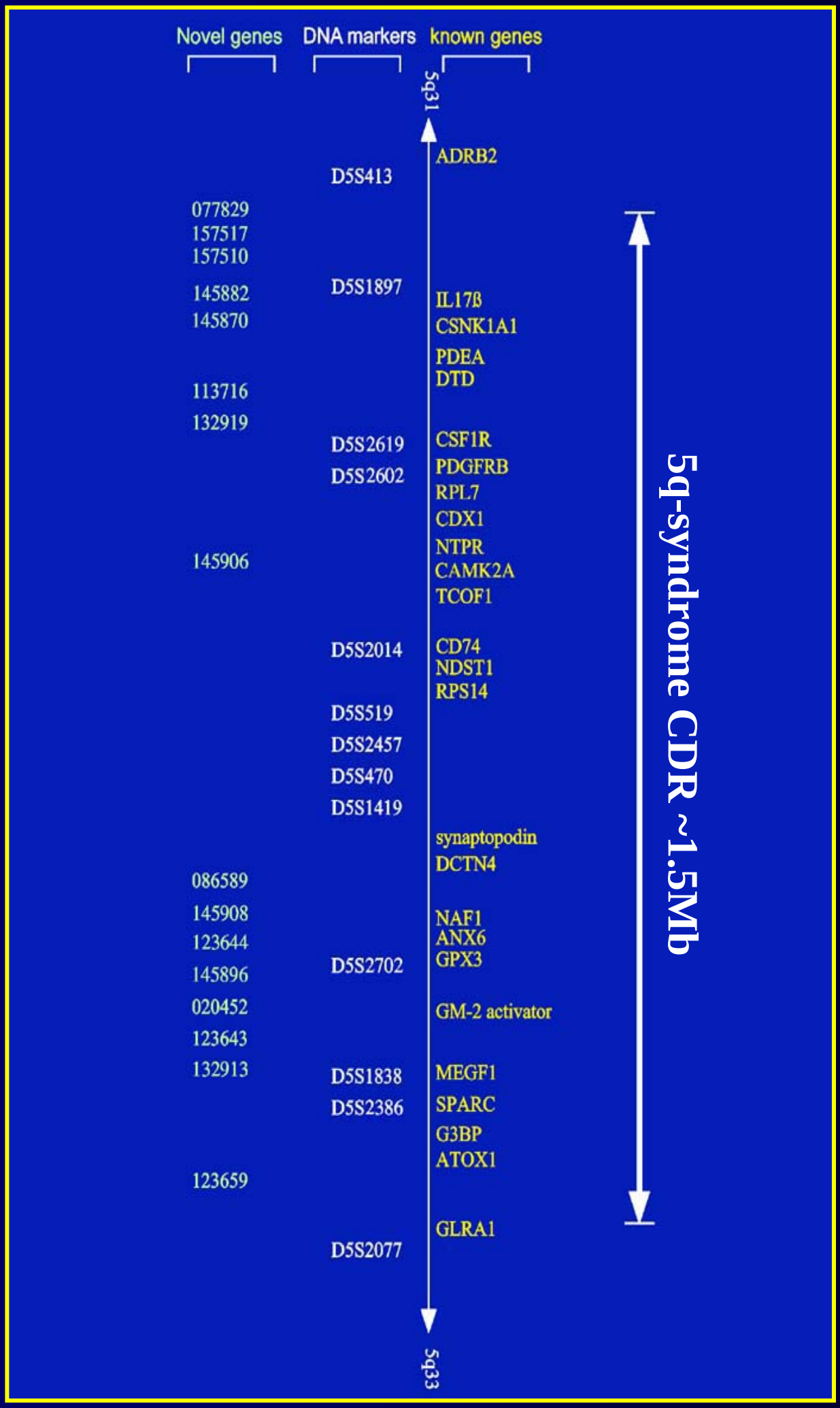
- Interstitial del(5q) including band q31
- Mononuclear megakaryocytes
- Macrocytic anemia
- Thrombocytosis
- Elderly females





Common deleted segment in 5q




Novel genes
DNA markers
known genes
5q31
5q33
ADRB2
D5S413
077829
157517
157510
145882
145870
D5S1897
IL17ß
CSNK1A1
PDEA
DTD
113716
132919
D5S2619
CSF1R
D5S2602
PDGFRB
RPL7
CDX1
NTPR
145906
CAMK2A
TCOF1
D5S2014
CD74
NDST1
RPS14
D5S519
D5S2457
D5S470
D5S1419
synaptopodin
DCTN4
086589
145908
123644
145896
D5S2702
NAF1
ANX6
GPX3
020452
123643
GM-2 activator
132913
D5S1838
MEGF1
D5S2386
SPARC
G3BP
ATOX1
123659
GLRA1
D5S2077
5q-syndrome CDR ~1.5Mb

RPS14 gene: involved in the 5q- syndrome (Ebert, Nature, 2008)

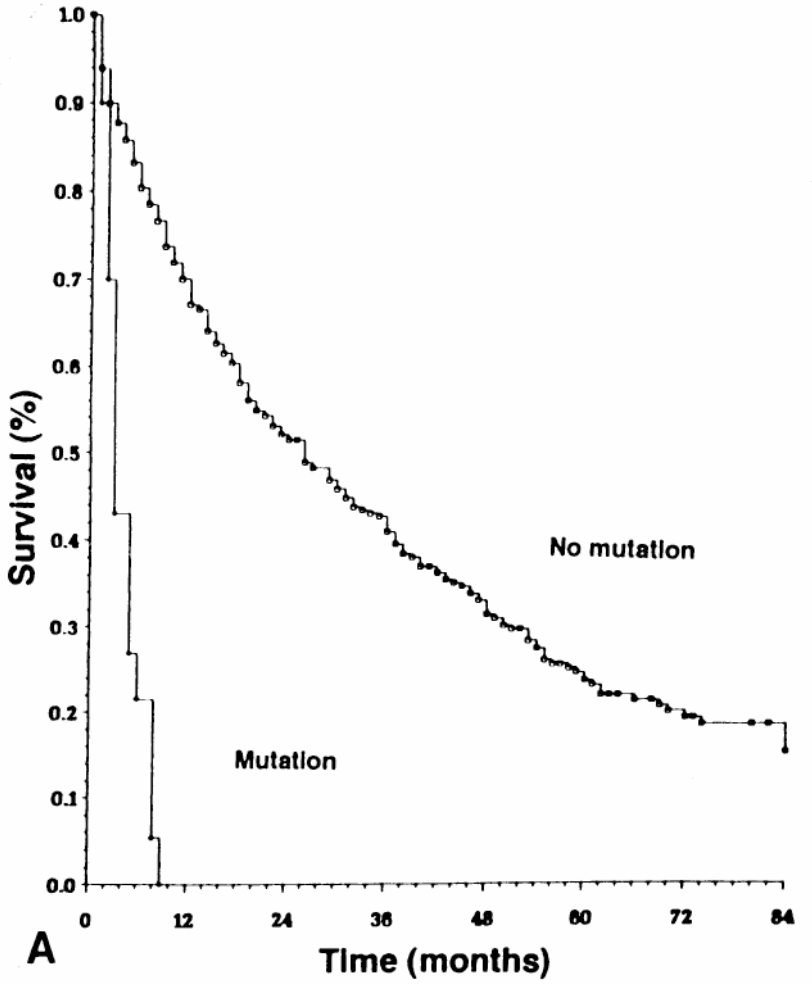
- Inhibition by si RNA lentiviral vectors of each of the 41 genes of the CDR
- Functional KO of only one of them, RSP14, recapitulates the 5q- phenotype (erythroid maturation blockade, apoptosis)
- Reversion of the phenotype by forced expression of RPS14 in primary cells from del 5q patients

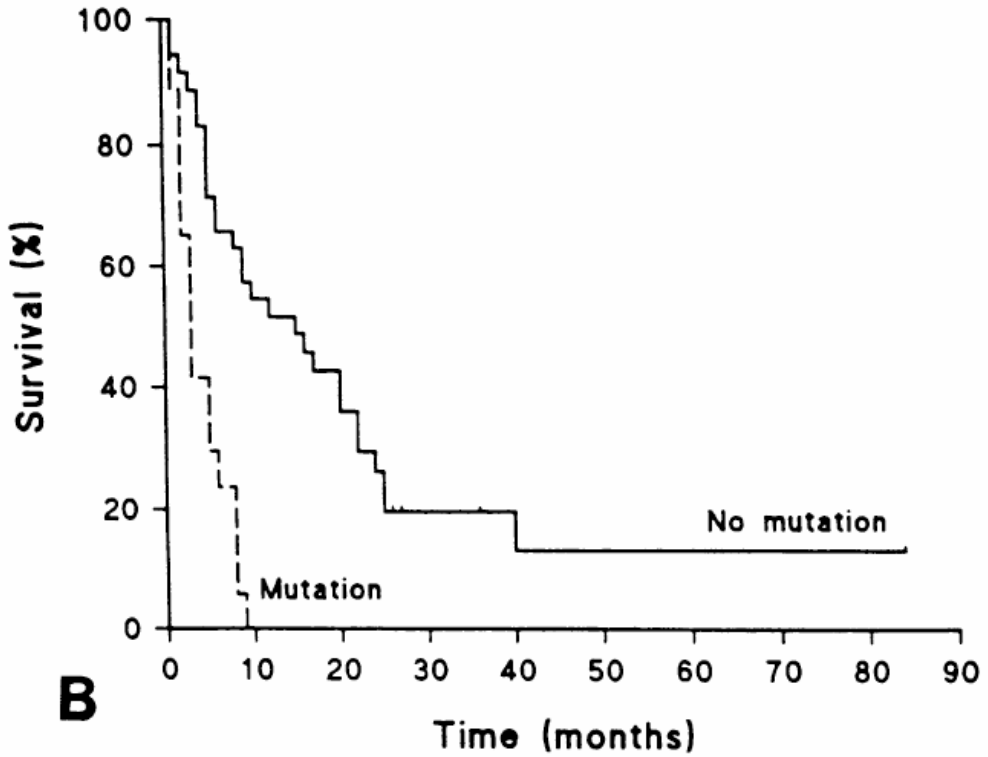
RPS14 gene: involved in the 5q- syndrome (Ebert, Nature, 2008)

- RPS14= member of the Ribosomal Protein Family (S 40 ribosomal subunit)
- Other members of this family: RPS 19 and RPS 24, haploinsufficient in 25% of patients with Blackfan Diamond Syndrome
- defective ribosomal assembly in both diseases

Acquired Gene Mutations in adult MDS

- *ras* mutations
- *p53* mutations
- AML 1 mutations



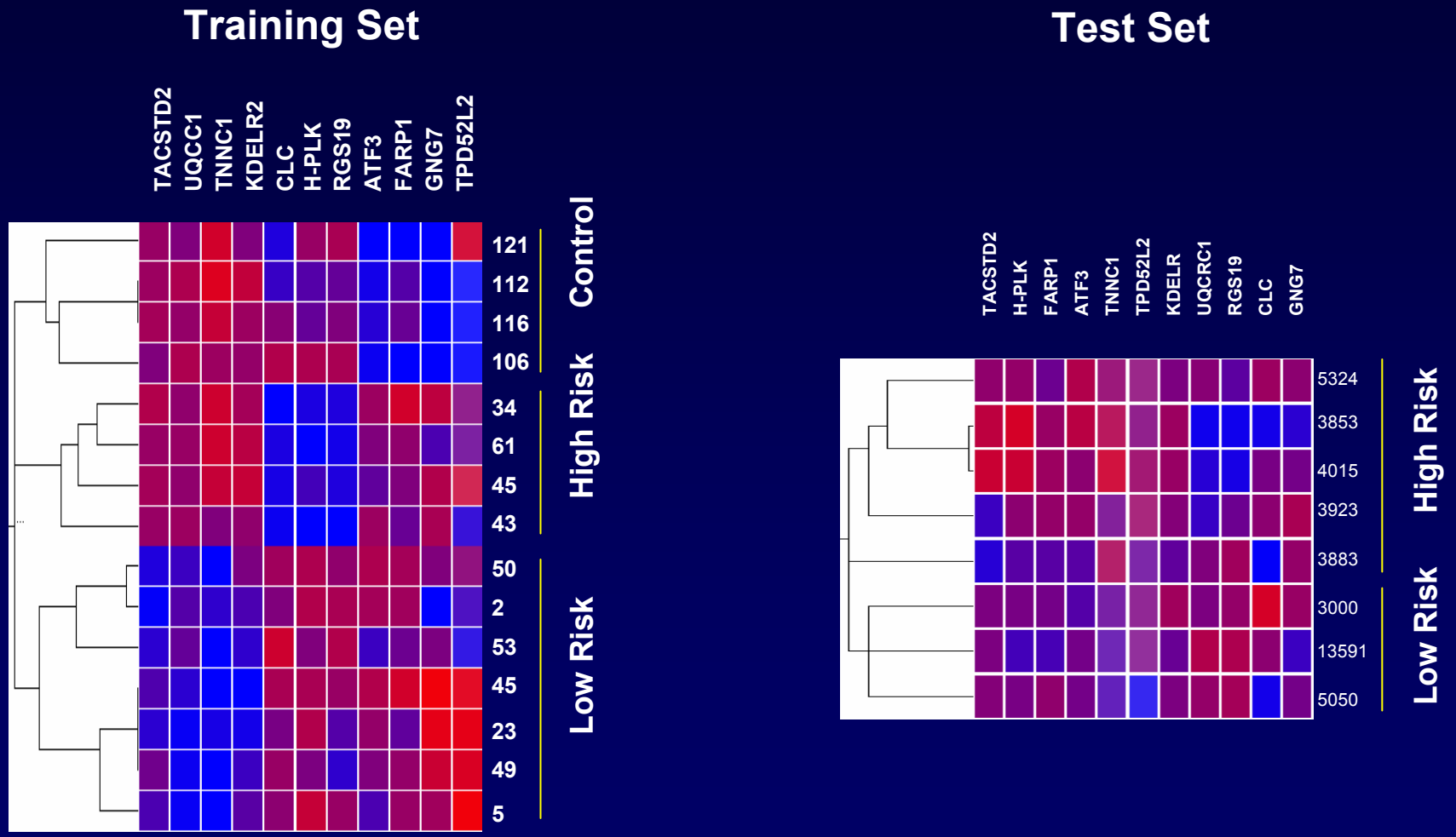


(A) Actuarial survival of the 182 MDS cases (treated or untreated); mutated cases (n = 20) versus nonmutated (n = 162) cases ($P < 10^{-5}$). (B) Actuarial survival of the 51 MDS patients who received chemotherapy; mutated cases (n = 13) versus nonmutated cases (n = 38) ($P < 10^{-5}$).

PROGNOSTIC VALUE OF P 53 MUTATIONS IN AML AND MDS ***Wattel et al, Blood 1994, 84, 3148***

Risk Prediction (11 Genes) in MDS

(Hoffmann et al,2003)



SNP array technology in MDS

- Can detect microdeletion, micro amplification, including « copy number variation » (CNV), « uniparental disomy » (UPD)

SNP array technology in MDS
(Mohamedali, Blood, 2007)

- 119 low risk MDS
- 125 regions of UPD identified
- UPD= 46%, microdeletions: 10%, microamplifications: 8%
- Chromosomes most involved: 4,1,6,2,3
- microdeletions associated to poor prognosis

SNP array technology in MDS(Gondek, Blood, 2008)

- 174 pts
- UPD in 35% (undetectable by cytogenetics)
- 6p21, 11q13, 4q23, 7q22
- UPD in 7q in the absence of detectable del 7q has poorer prognosis

High resolution CGH analysis in MDS (Starczynowski, Blood, 2008)

- 44 pts, 16 with abnormal karyotype
- 36 with CVN
- Presence of genetic anomaly >3 Mb associated with poorer outcome

NFkappa B and MDS (U 848 Inserm)

- **NF kappa B activated during progression of MDS (Braun, Blood, 2006)**
- **Inhibition of NEMO induces apoptosis in higher risk MDS (Carvalho, Oncogene,2007)**
- **NF kappa inhibition induces cell death in higher risk MDS (Fabre, Oncogene, 2007)**
- **FLT3 receptor inhibition reduces constitutive NF kappa B activation in higher risk MDS (Grosjean, Apopotosis 2008)**

NFkappa B and MDS (U 848 Inserm)

- **Hypomethylating agents and HDAC inhibitors inhibit NF kappa in higher risk MDS (Fabre, Cell Cycle, 2008)**

Genetic and epigenetic changes

genetic:
(=irreversible)

- **mutations**
- **deletions**
- **gene rearrangements**

Epigenetic:
(=potentially reversible)

- **DNA methylation**
- **histone deacetylation**

DNA methylation, Histone acetylation and Active / inactive chromatin

histones HYPERACETYLATED +
DNA NOT METHYLATED → Gene transcription

histones NOT ACETYLATED +
DNA METHYLATED → Gene silencing

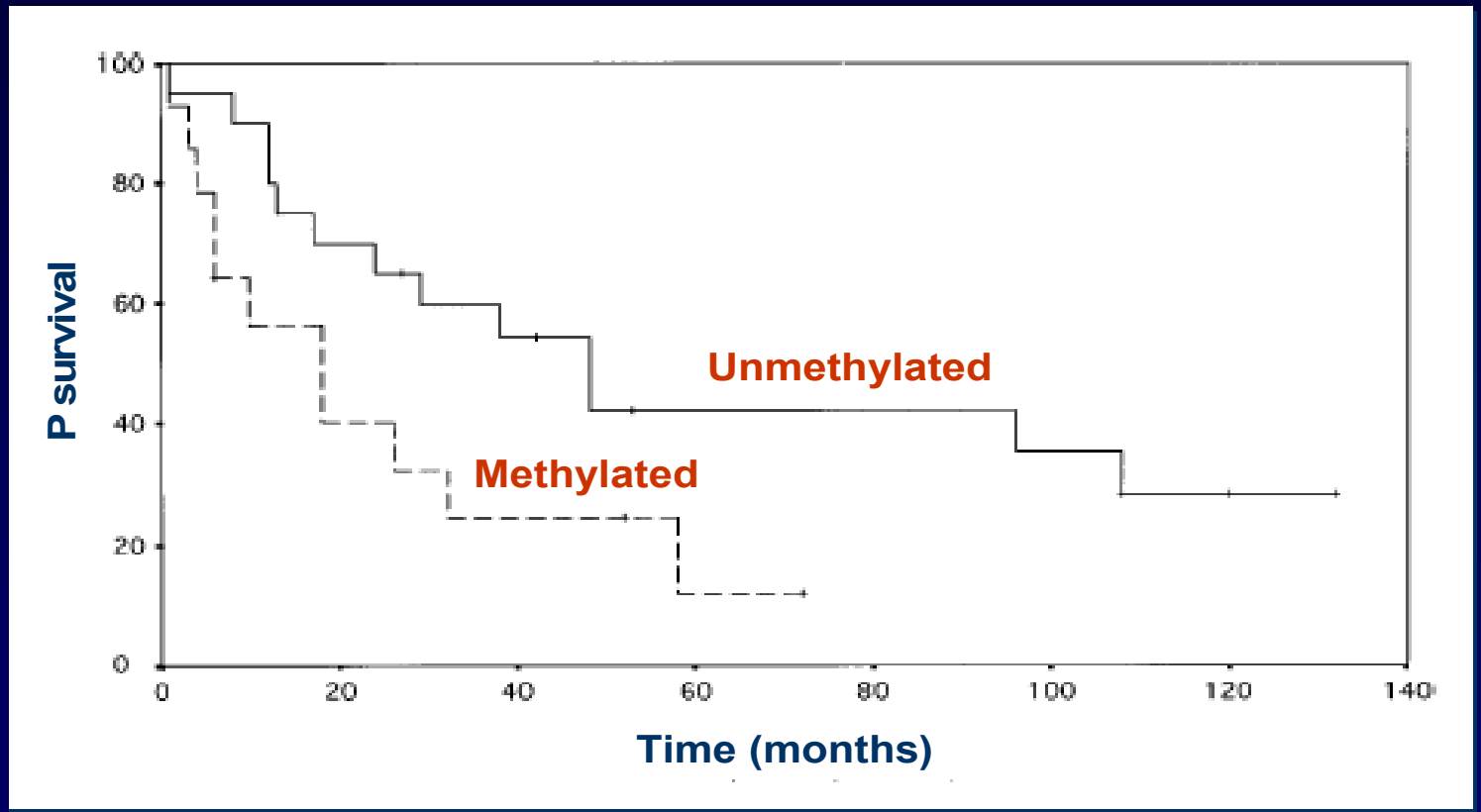
Hypermethylated genes in MDS

- P15 (~65%) – cell cycle regulation
- DAPkinase (~47%) – apoptosis
- SOCS1 – cytokine regulation
- E-cadherin – cell adhesion
- Calcitonin – calcium and phosphorus metabolism
- Alpha catenin (del 5q)

Particularly in high risk MDS and MDS with "unfavorable" karyotype

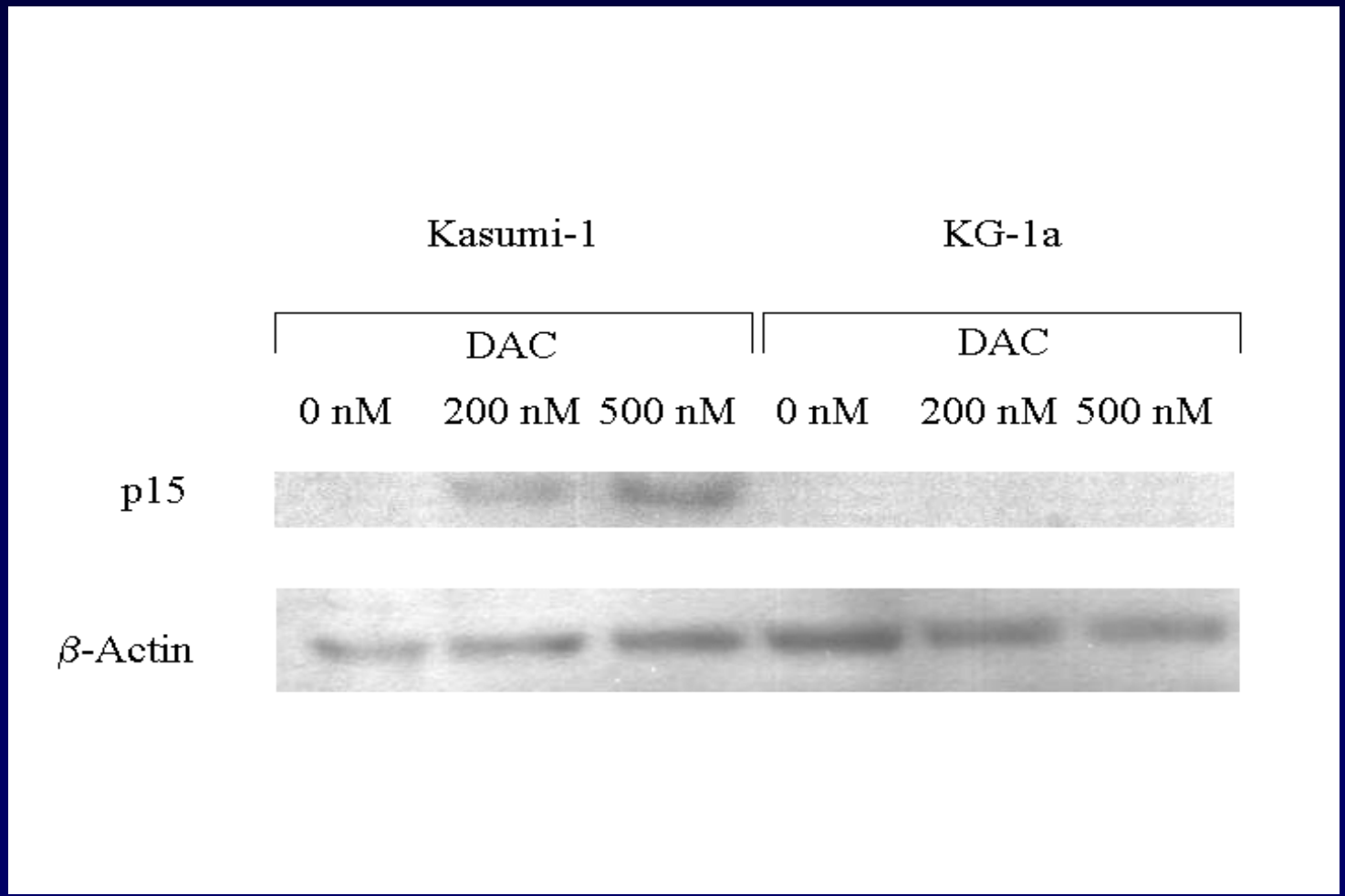
Increases during progression

Survival in patients with MDS according to p15 gene methylation status (Quesnel, Blood , 1995)

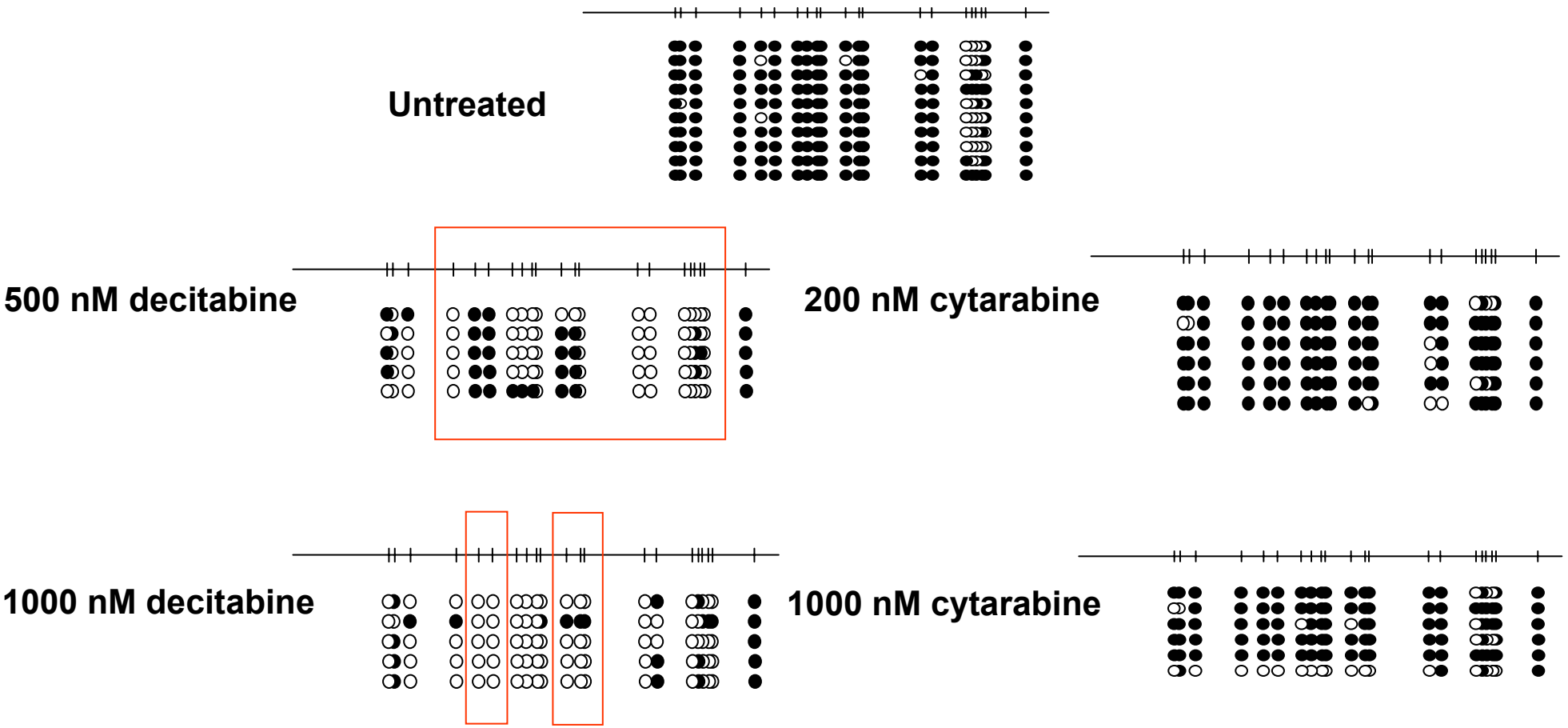


Quesnel *et al. Blood* 1998;91:2985–90

Demethylation of p15 promoter by DAC is associated with p15 protein reexpression

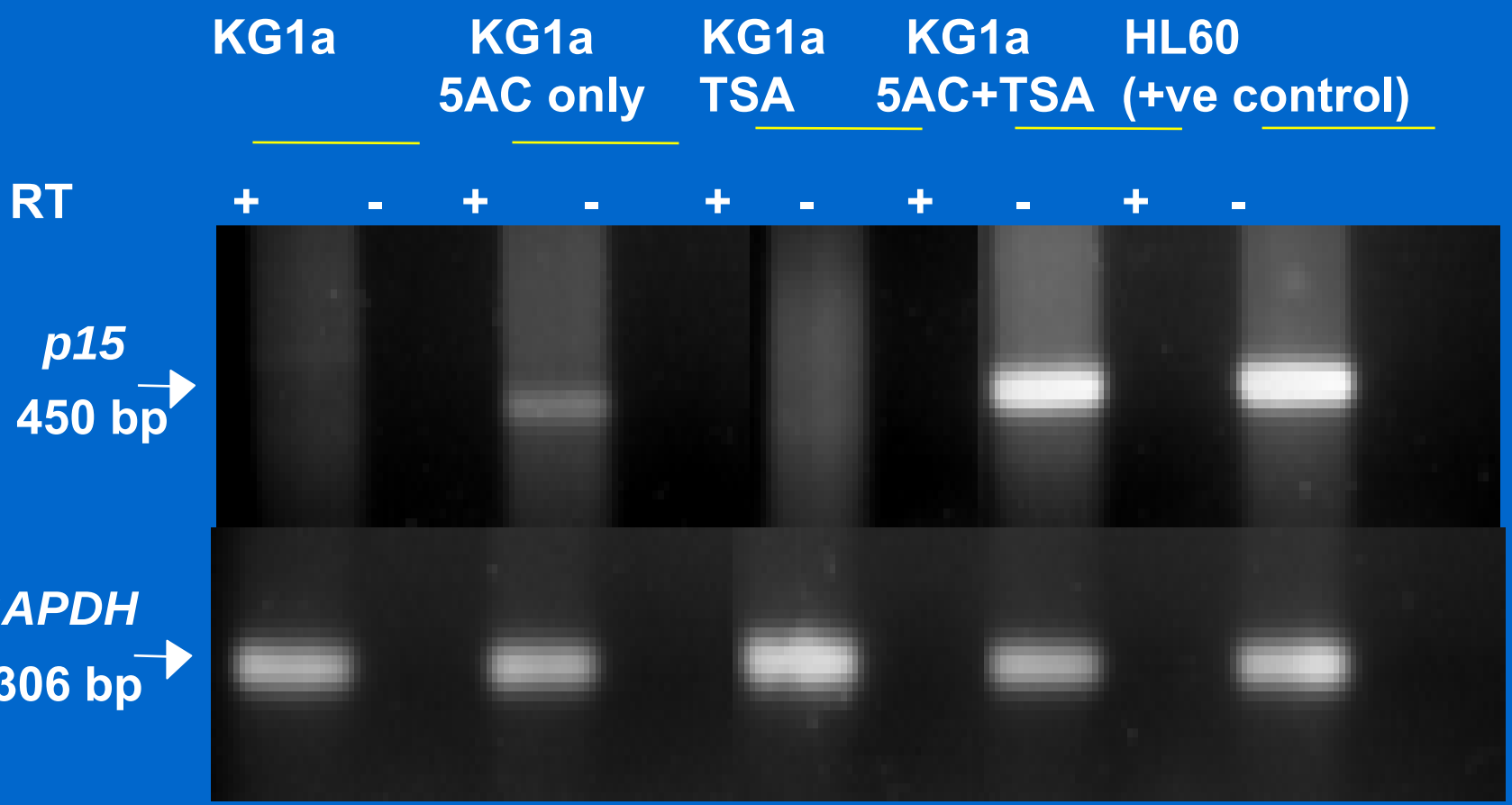


p15 promoter Hypomethylation by treatment of myeloid cells with decitabine but not cytarabine(KG1)



Berg *et al. Leuk Res* 2007;31:497–506

Gene Re-expression through Sequential Methyltransferase and Histone Deacetylase Inhibition



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Immune abnormalities and MDS

- oligoclonal expansion of T cell populations in some MDS (Nakamura) with inhibitory effect on CFU-GM (Molldrem)
- possible correction by immunosuppressive (ATG) (Molldrem, Sloand, Lim)

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SMD: riesgo « alto » vs « bajo »

Groupe Français des Myelodysplasies

- **Riesgo alto**
  - IPSS intermedio-2 or elevado
  - (blastos en la MO >10%)
- **Riesgo bajo**
  - IPSS bajo o intermedio-1
  - (blastos en la MO <5%)

Treatment Objectives

- **Delay disease progression**
- **Prolong survival**
- **Improve blood cell deficiencies**
- **Improve quality of life**

Treatment Objectives (High risk MDS)

- **Delay disease progression**
- **Prolong survival**
- **Improve blood cell deficiencies**
- **Improve quality of life**

Treatment Objectives (low risk MDS)

- **Delay disease progression**
- **Prolong survival**
- **Improve blood cell deficiencies**
- **Improve quality of life**

Treatment of higher risk MDS

Treatment of high risk MDS

- Allogeneic stem cell transplantation
- Chemotherapy (intensive or not)
- Hypomethylating agents
- Others (clinical trials)

Treatment of high risk MDS

- **Allogeneic stem cell transplantation**
- Chemotherapy (intensive or not)
- Hypomethylating agents
- Others (clinical trials)

MDS: « classical » allogeneic SCT

- Requires
  - HLA identical donor
  - Age<50-55

- **Results:**
  - 50% cure
  - 25% relapses
  - 25% transplant related mortality

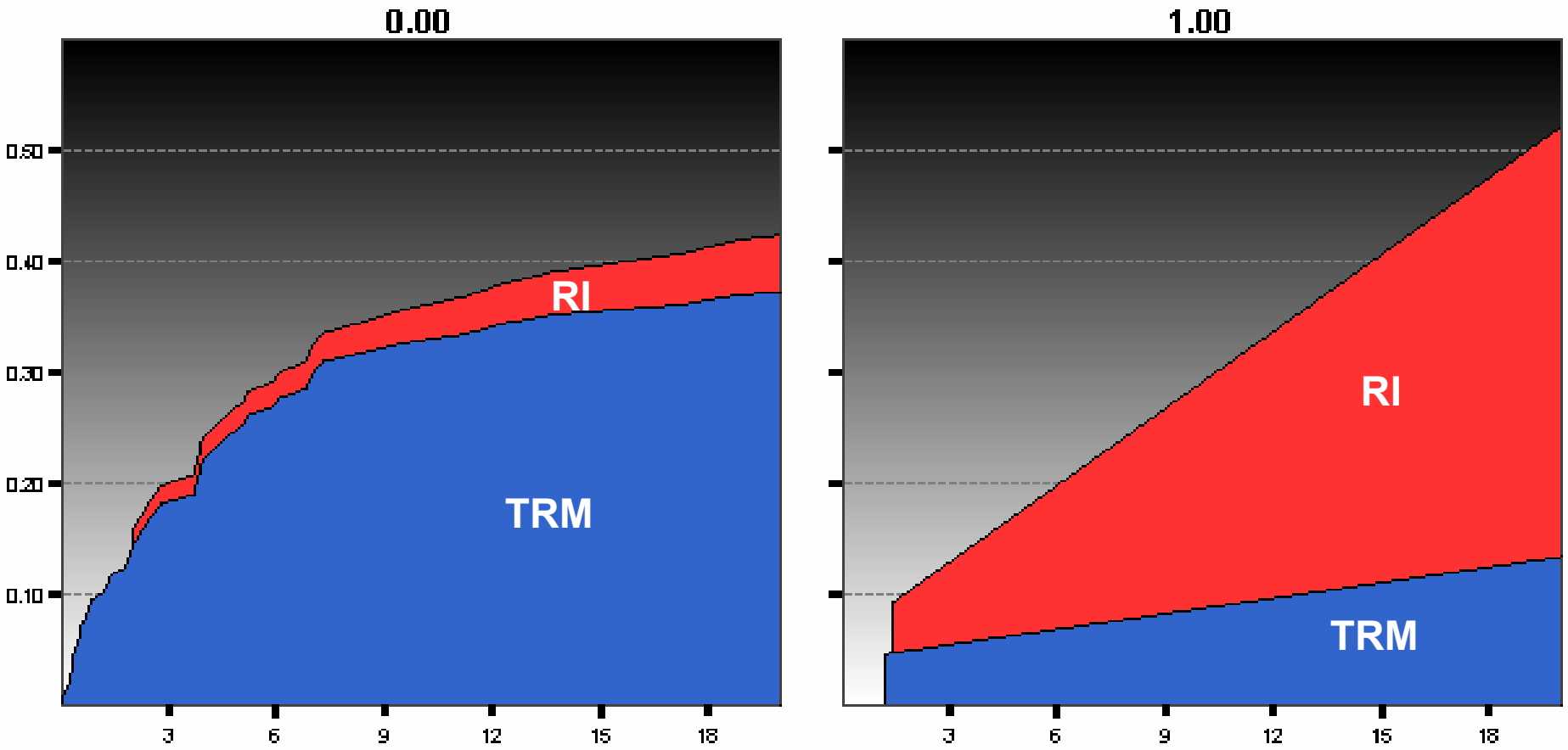
MDS non myeloablative allo SCT

- extend indication to 65-70 years
- less toxicity…but more relapses

Outcome of allogeneic SCT in MDS

"standard"

Non myeloblative



Allo SCT: chemotherapy or hypomethylating agents before transplant?

- High risk of relapse post transplant if marrow blasts:
  - >10% (classical allo)
  - > 5% (NMA allo)

- intensive chemo before allo? Yes if normal karyotype
- If abnormal karyotype: : hypomethylating agent ?

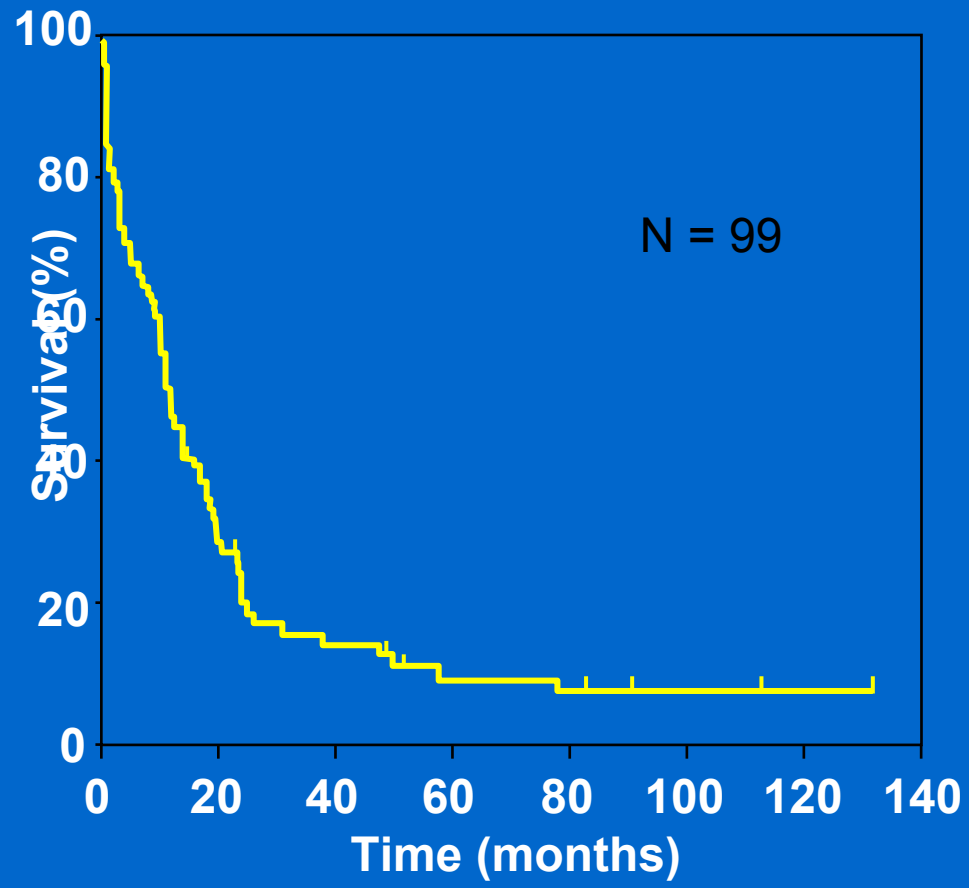
Treatment of high risk MDS

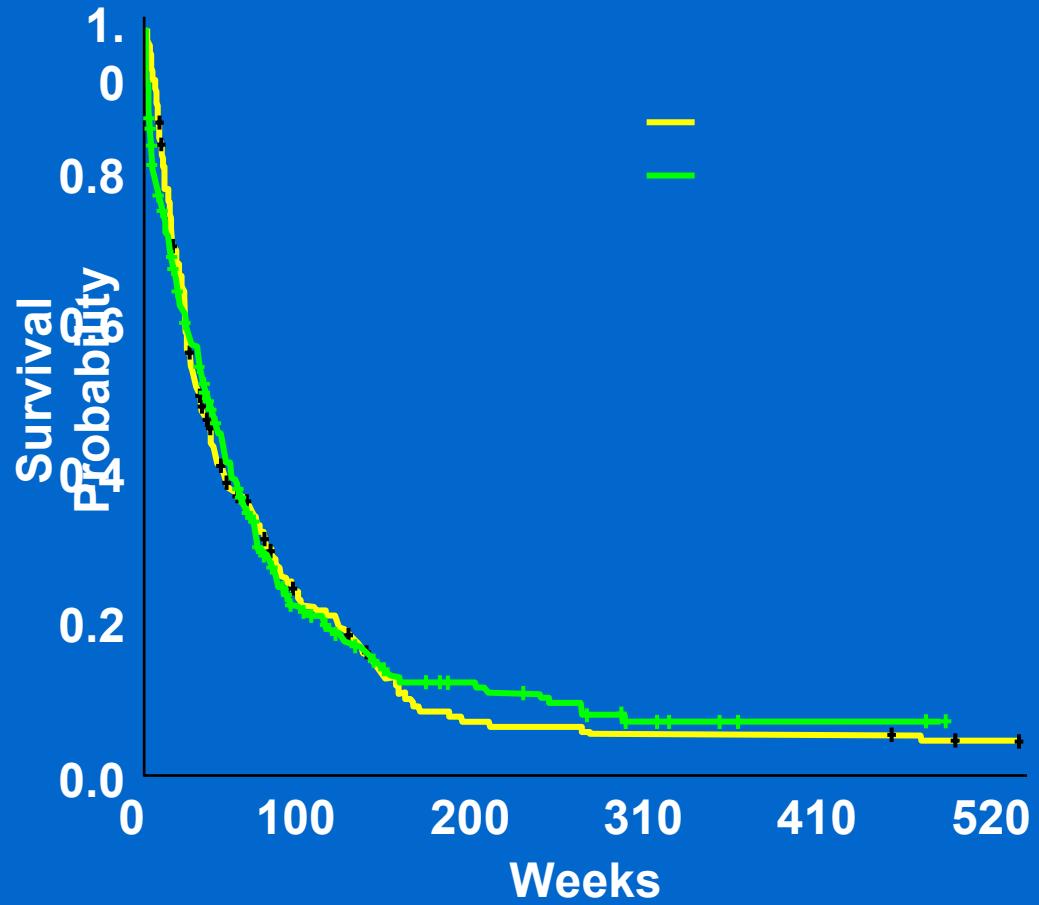
- Allogeneic stem cell transplantation
- Chemotherapy (intensive or not)
- Hypomethylating agents
- Others (clinical trials)

Intensive chemotherapy

- Mainly anthracycline-AraC (like in AML)
- Generally restricted to patients <65 y
- CR rates: 40-60%
- Short CR (median < 1 y)
- Major prognostic factor: karyotype

Kaplan-Meier Estimate of Survival with Intensive Chemotherapy





Wattel E. et al.

Br J Haematology. 1997;98:983-991.

With Permission of E Estey, MD

Clofarabine in MDS (Gandhi, ASH 2006; Faderl, 2008)

- **Gandhi (2006):** Clofarabine 15 to 30 mg/m2 /d x5 IV

  5/ 9 CR in MDS but myelotoxic

- **Faderl (2008):** 40 % CR; better results with addition of LD AraC

A Phase II Study of Maintenance with Azacitidine in MDS patients achieving CR or PR after Intensive Chemotherapy (C Gardin)

azacitidine

- sc 60 mg / m2 / day x for 5 days
- every 4 weeks
- For 24 months

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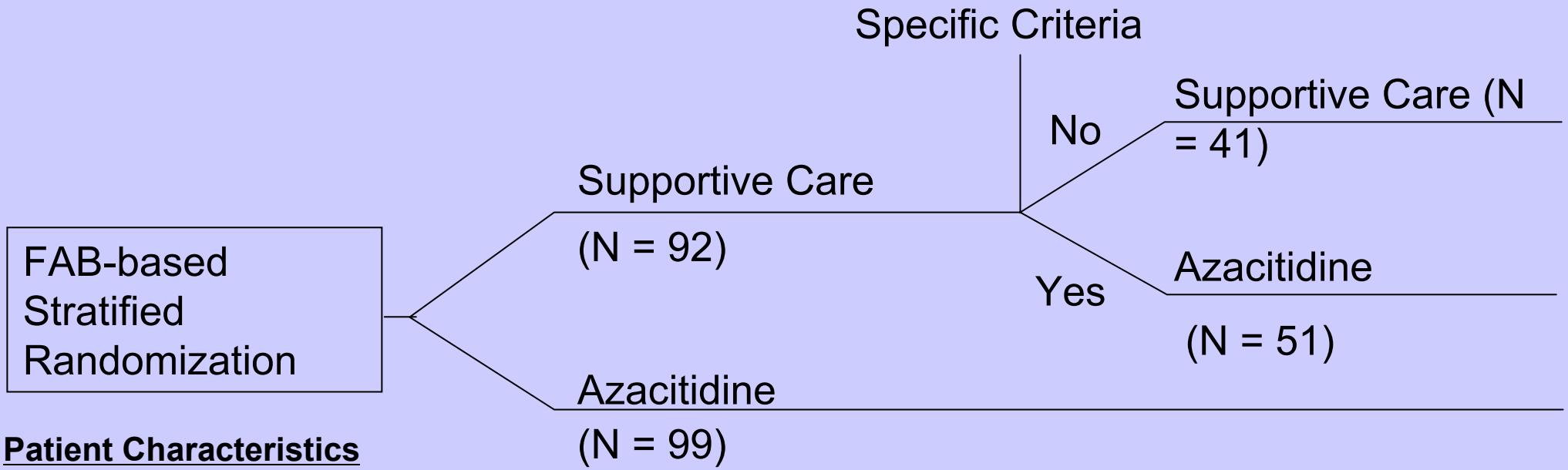
MDS :low dose chemotherapy: LD AraC

- LD AraC : 20mg/m2/d
- 15% RC, 20% RP, 20% HI
- Fairly myelotoxic
- +++responses only in the absence of unfavorable karyotype
- Effect on survival in MDS:
  - not better than BSC (Miller, 1992)
  - not as good as azacytidine (Fenaux, 2008))

Treatment of high risk MDS

- Allogeneic stem cell transplantation
- Chemotherapy (intensive or not)
- Hypomethylating agents
- Others (clinical trials)

CALGB 9221: A Randomized Phase III study with azacytidine



Patient Characteristics

Median age (yrs) = 67

% RAEB or RAEB-T = 54

% Transfusion dependent = 70

MDS Clinical Studies: Phase III

Efficacy Results: Response

Response Category	Aza %	BSC %	Cross-over %
Total responses	**60[1]**	**5**	**47**
CR	**7[2]**	**0**	**10**
PR	**16[1]**	**0**	**4**
Improved	**37[1]**	**5**	**33**
Transfusion Elimination	**45**		

Note: Statistical analysis does not include data obtained after cross – over

[1] $p<0.001$ vs BSC [2] $p<0.01$ vs BSC

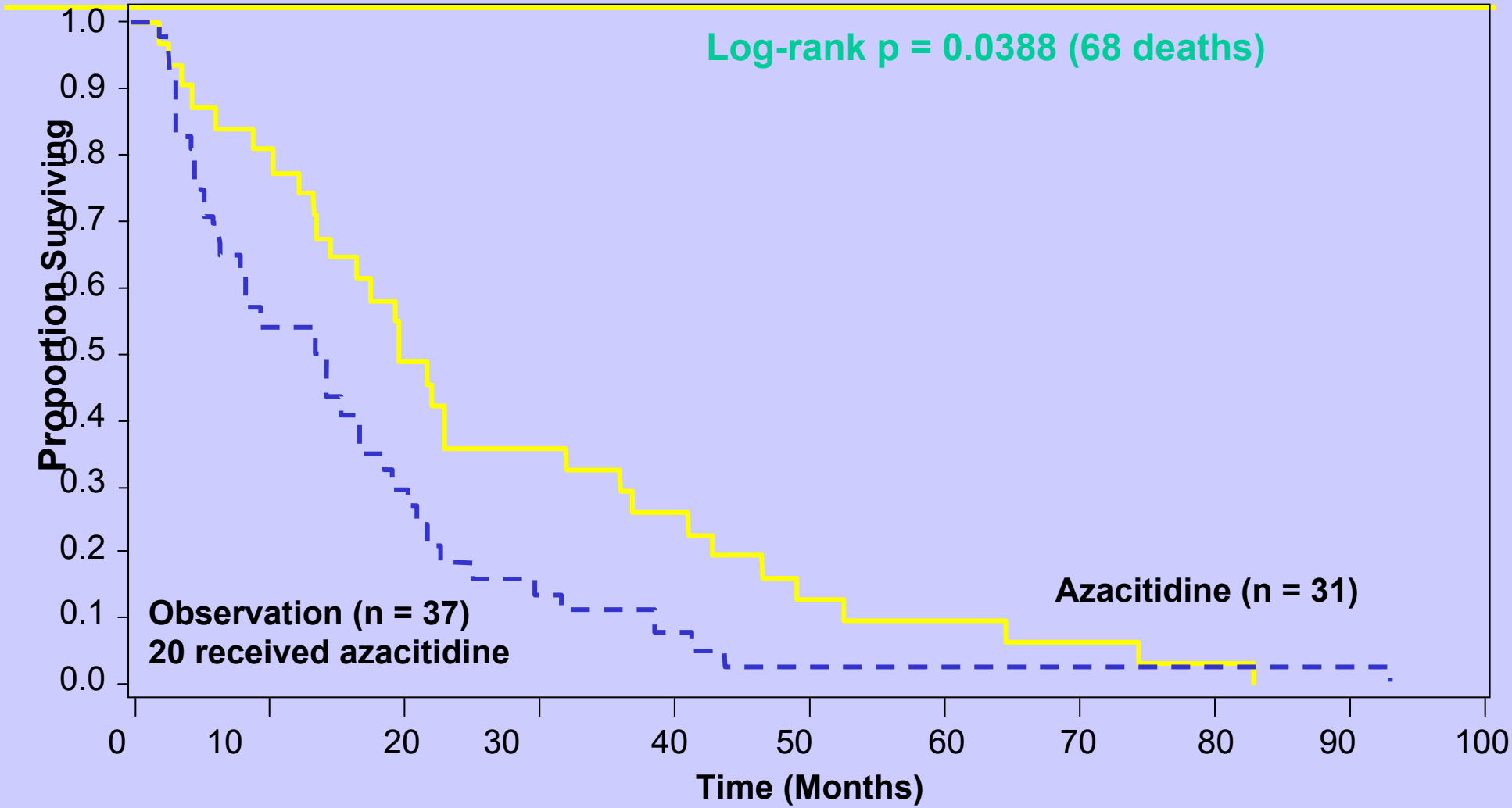
MDS Clinical Studies: Phase III

Parameter	Aza	BSC
Median survival	**20 months[1]**	**14 months**

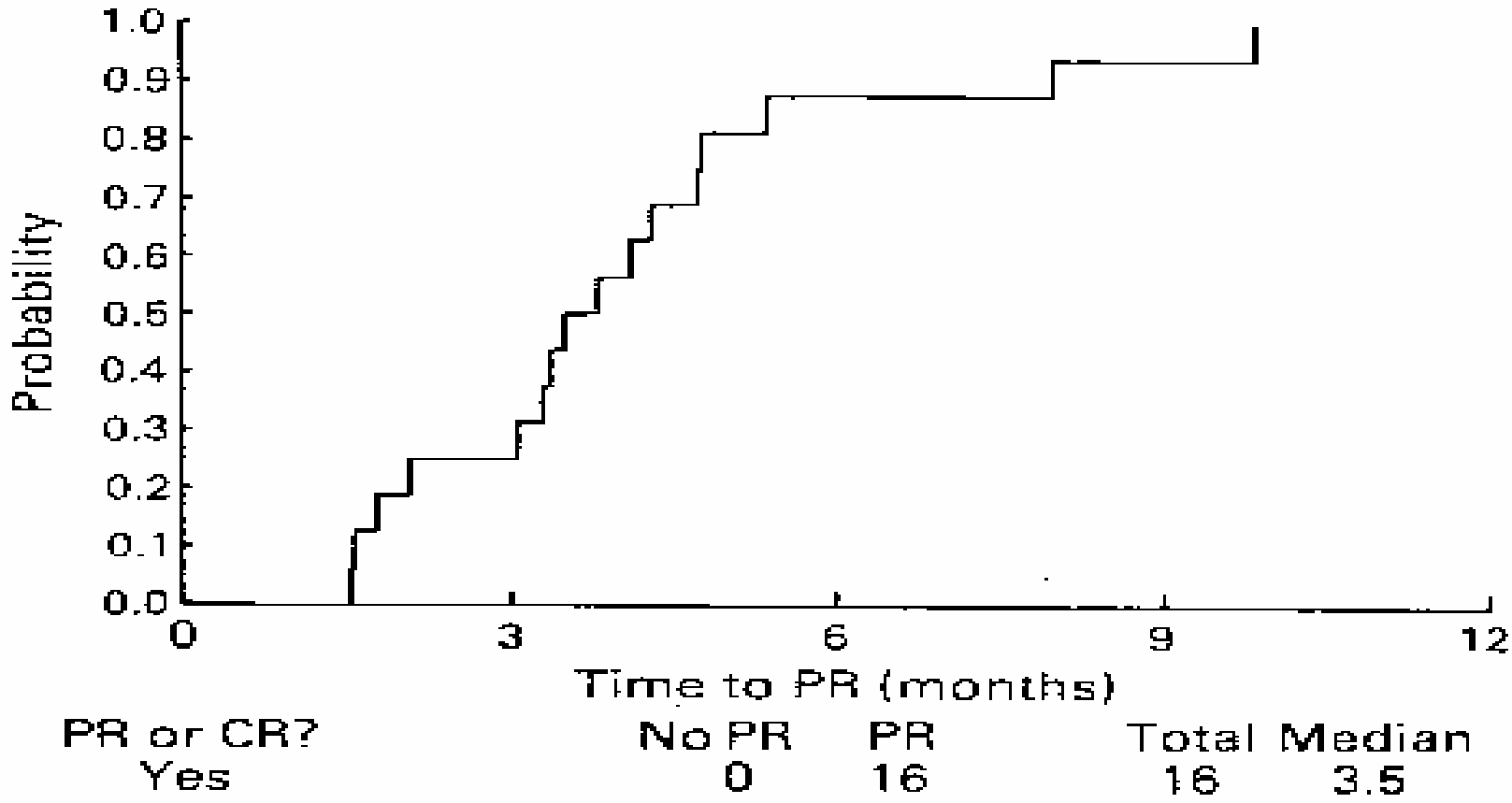
[1] p= 0.1 vs BSC

(Silverman, JCO, May 2002)

Survival (ITT)
restricted to RAEB and RAEB-T

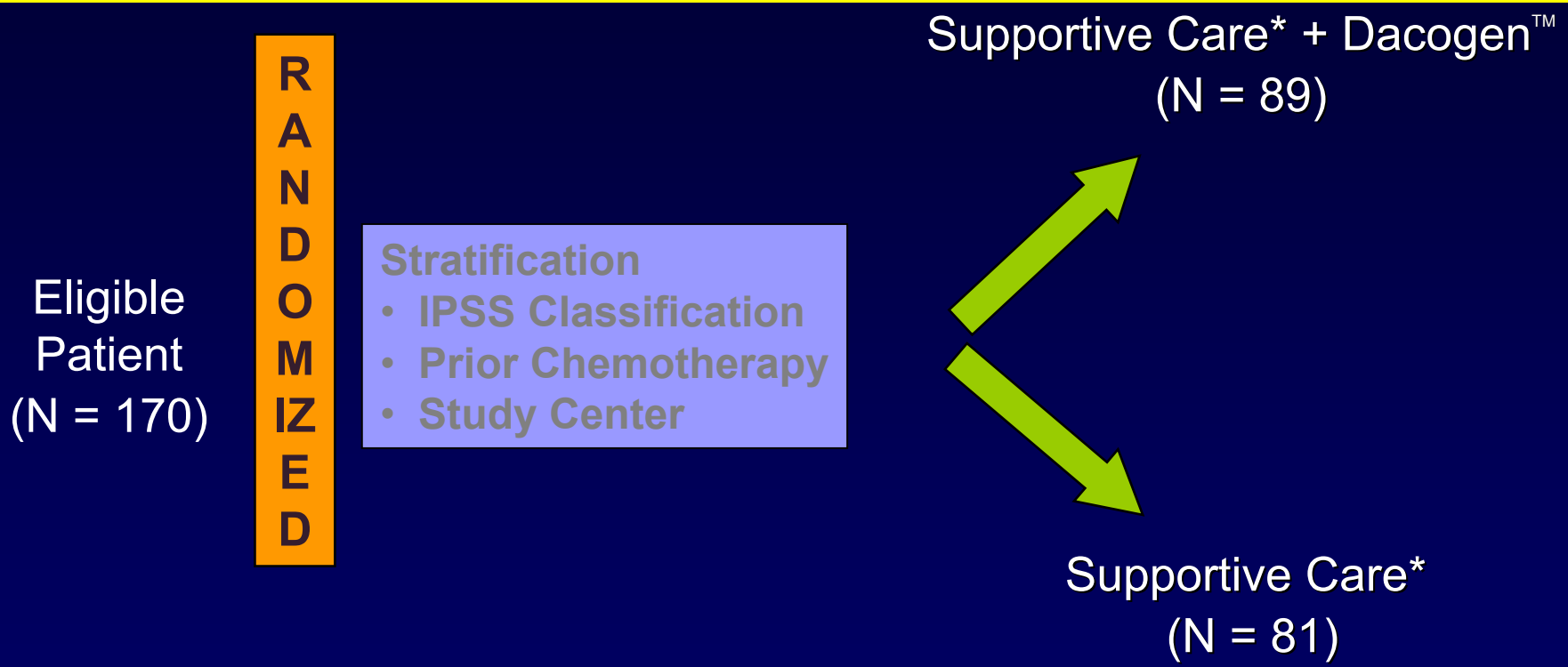


Demethylating agents are slow-acting drugs: patience is needed.



(Silverman et al. 1993)

Decitabine) Phase III Study Design



*Antibiotics, Growth Factors and/or Transfusions

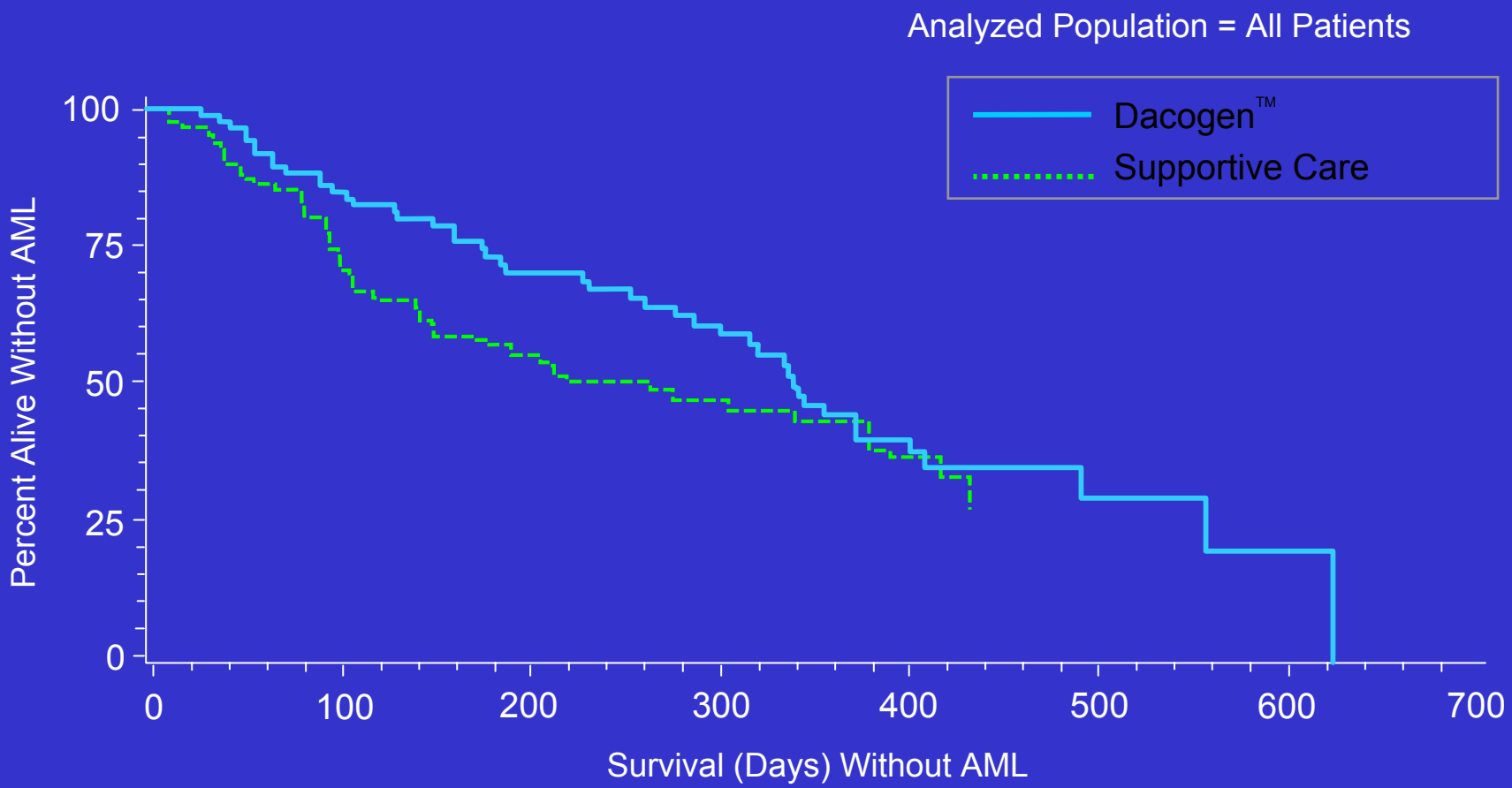
Investigator's Assessment of Best Response (All Patients)

Response	Dacogen™ (n = 89)	Supportive Care (n = 81)	p-value[3]
Complete Response	**10%**	**0**	**< 0.001**
Partial Response	**15%**	**0[2]**	
Hematologic Improvement	**10%**	**0**	
Stable Disease	**37%**	**47%**	
Progressive Disease	**16%**	**25%**	
Not Evaluable[1]	**12%**	**26%**	

1. Patients that withdrew from study prior to any response evaluation
2. Two patients had a partial response to Dacogen™ after progressing on supportive care
3. 2-sided Fisher's Exact Test for equal overall response rate (CR+PR)
4. **Not reflective of adjudicative data set**

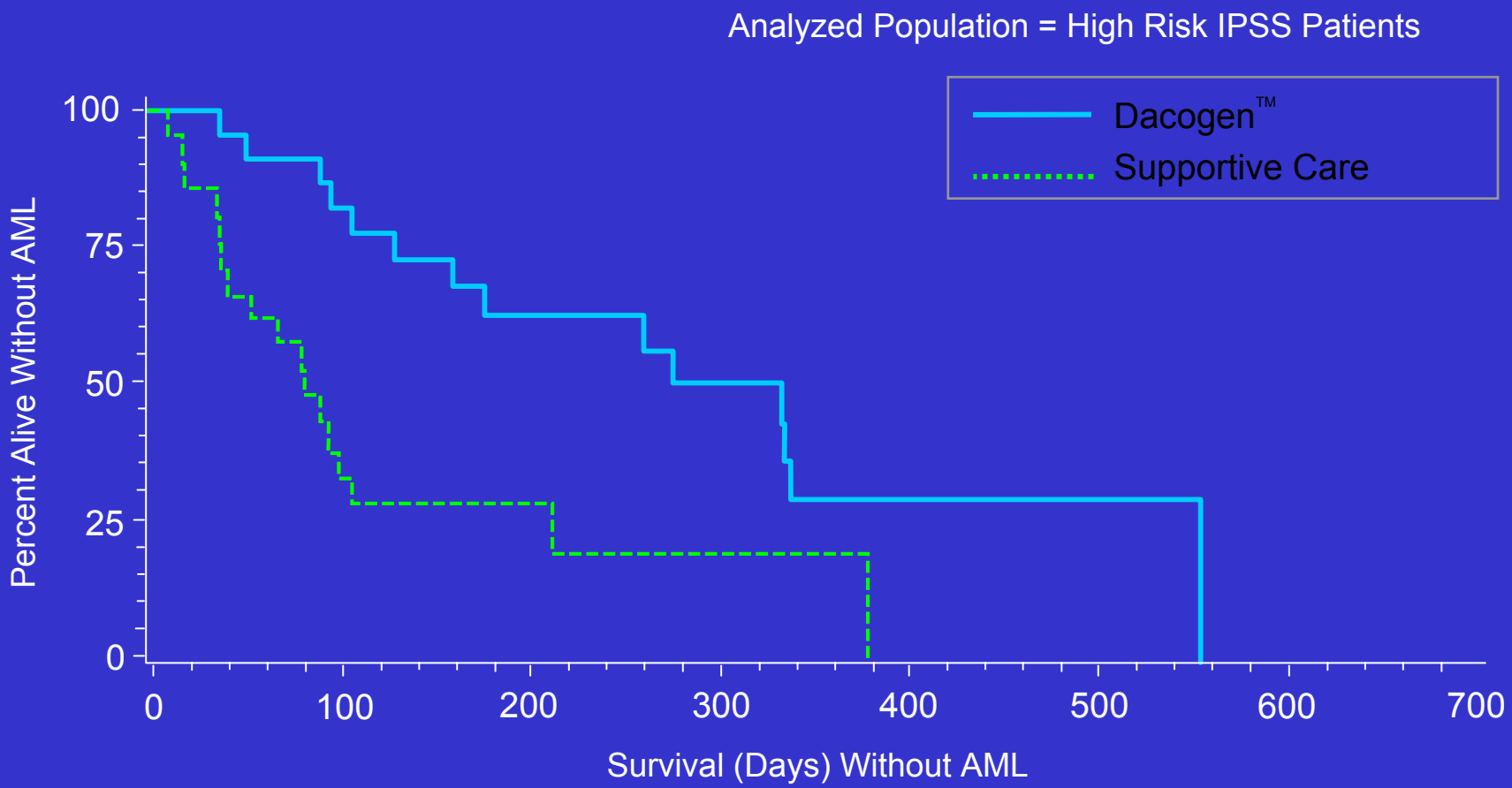
Time to AML or Death

(All Patients)



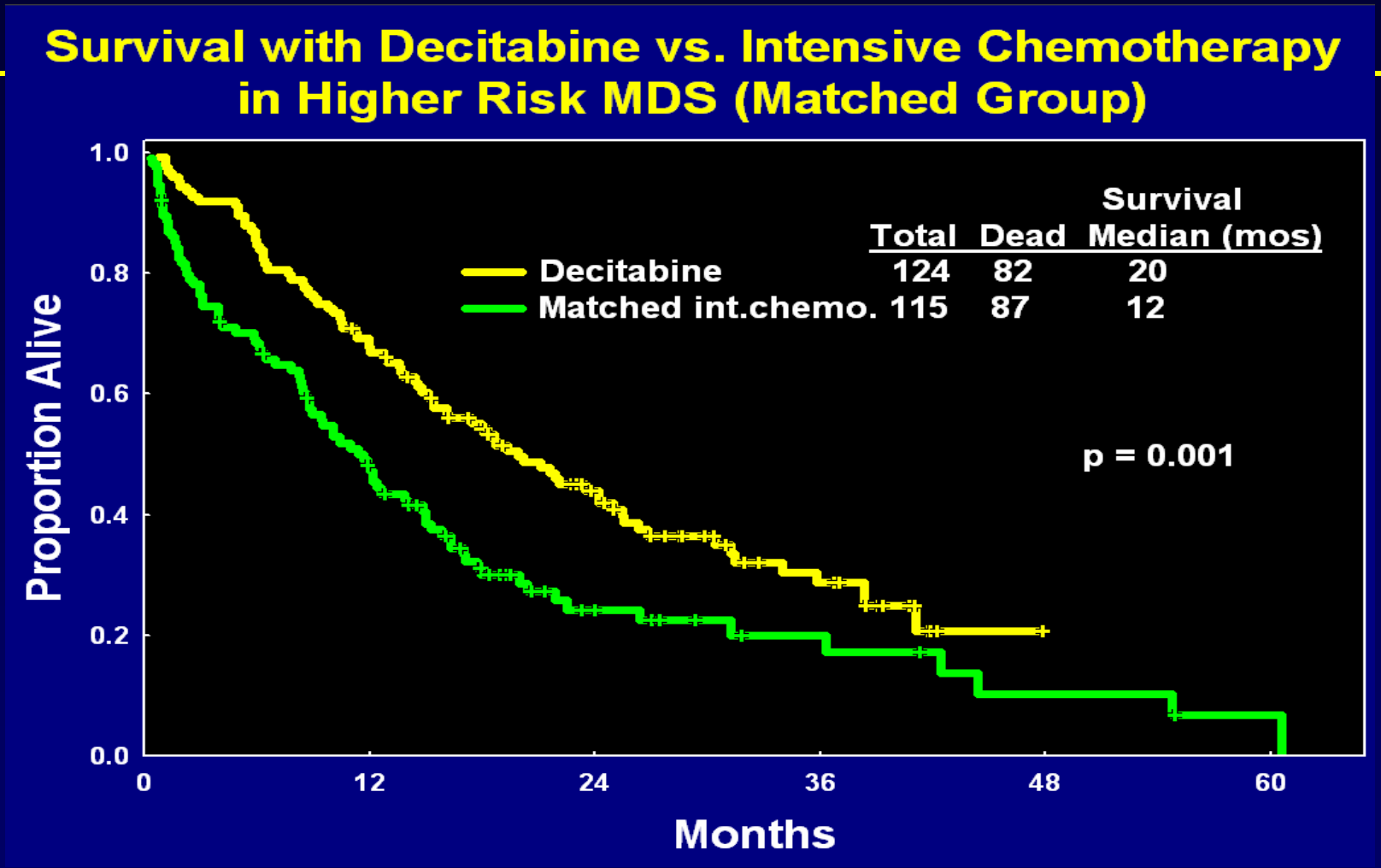
2-sided Wilcoxon test for homogeneity of survival distributions p = 0.042
2-sided Log-rank test for homogeneity of survival distributions p = 0.198
Reflects cut-off after 92 events. 3 Patients crossing over or never receiving randomized treatment are censored
Based on treatment schema, median treatment = ~ 3 cycles (168 days)

Time to AML or Death
High Risk Patients
(n = 44)



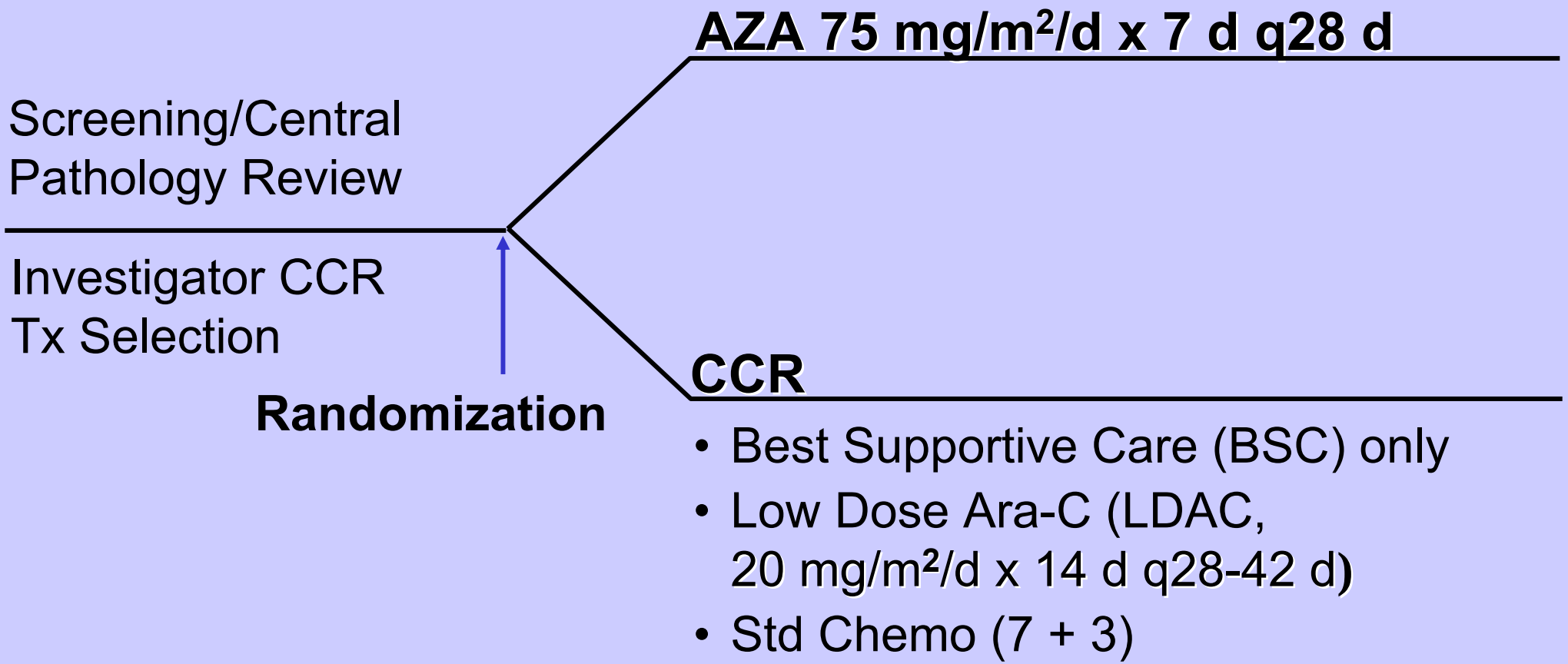
2-sided Wilcoxon test for homogeneity of survival distributions $p < 0.001$
2-sided log-rank test for homogeneity of survival distributions $p = 0.004$

Superviviencia Decitabina vs Quimio intensiva : 20 vs 12 meses



Kantarjian et al. Cancer (2007) 109 : 1133-1137

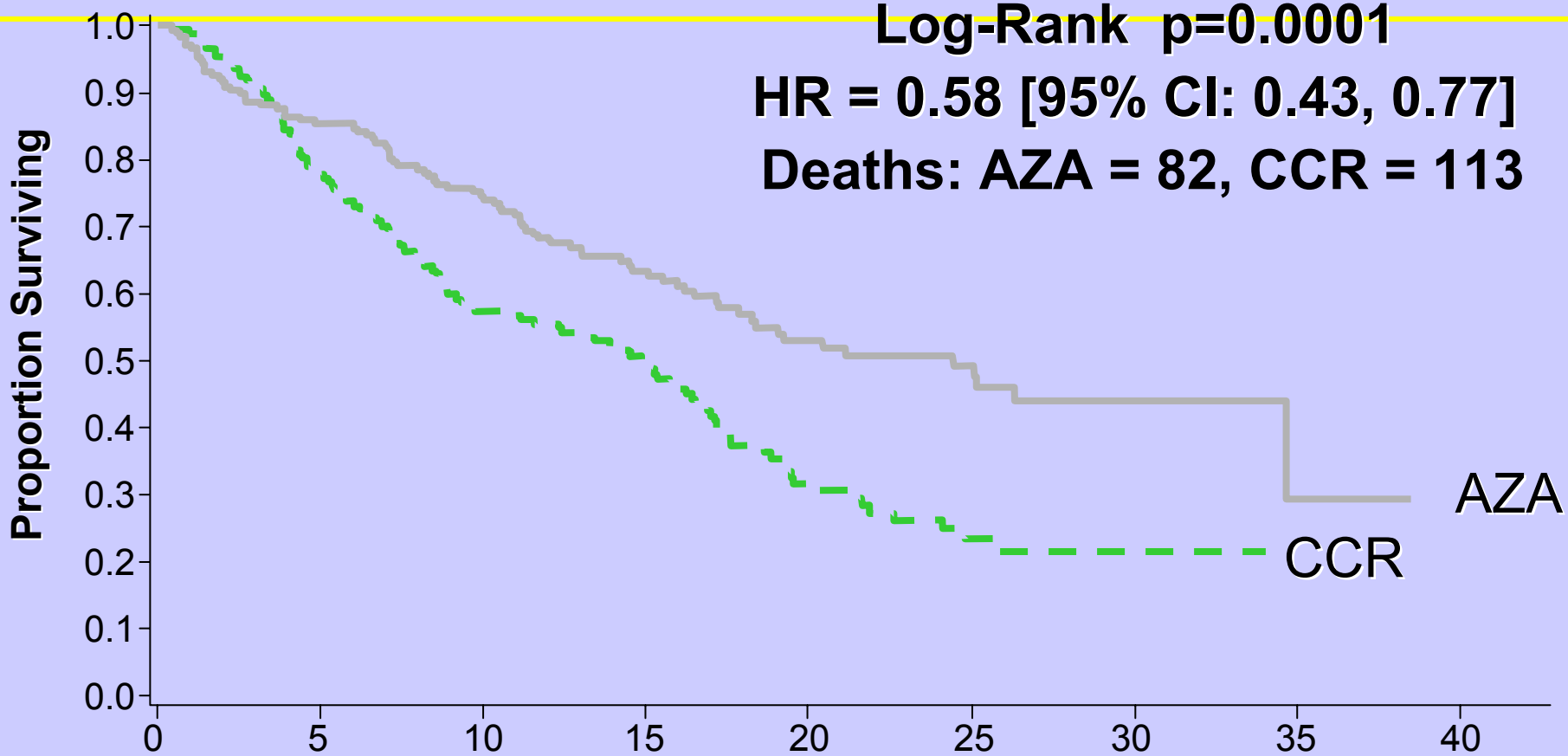
Azacitidine Survival Study



BSC was included with each arm

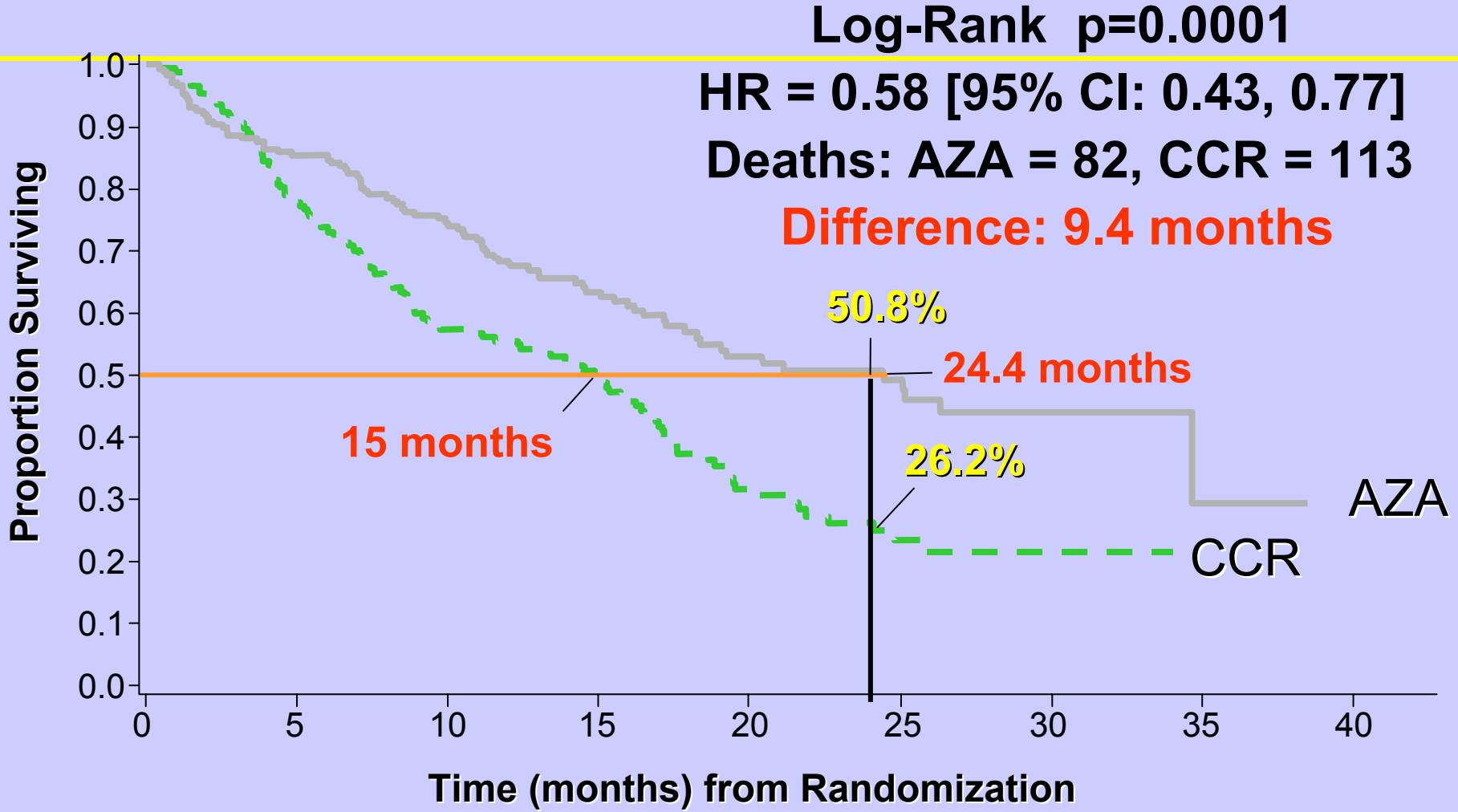
Tx continued until unacceptable toxicity or AML transformation or disease progression

Overall Survival: Azacitidine vs CCR
ITT Population

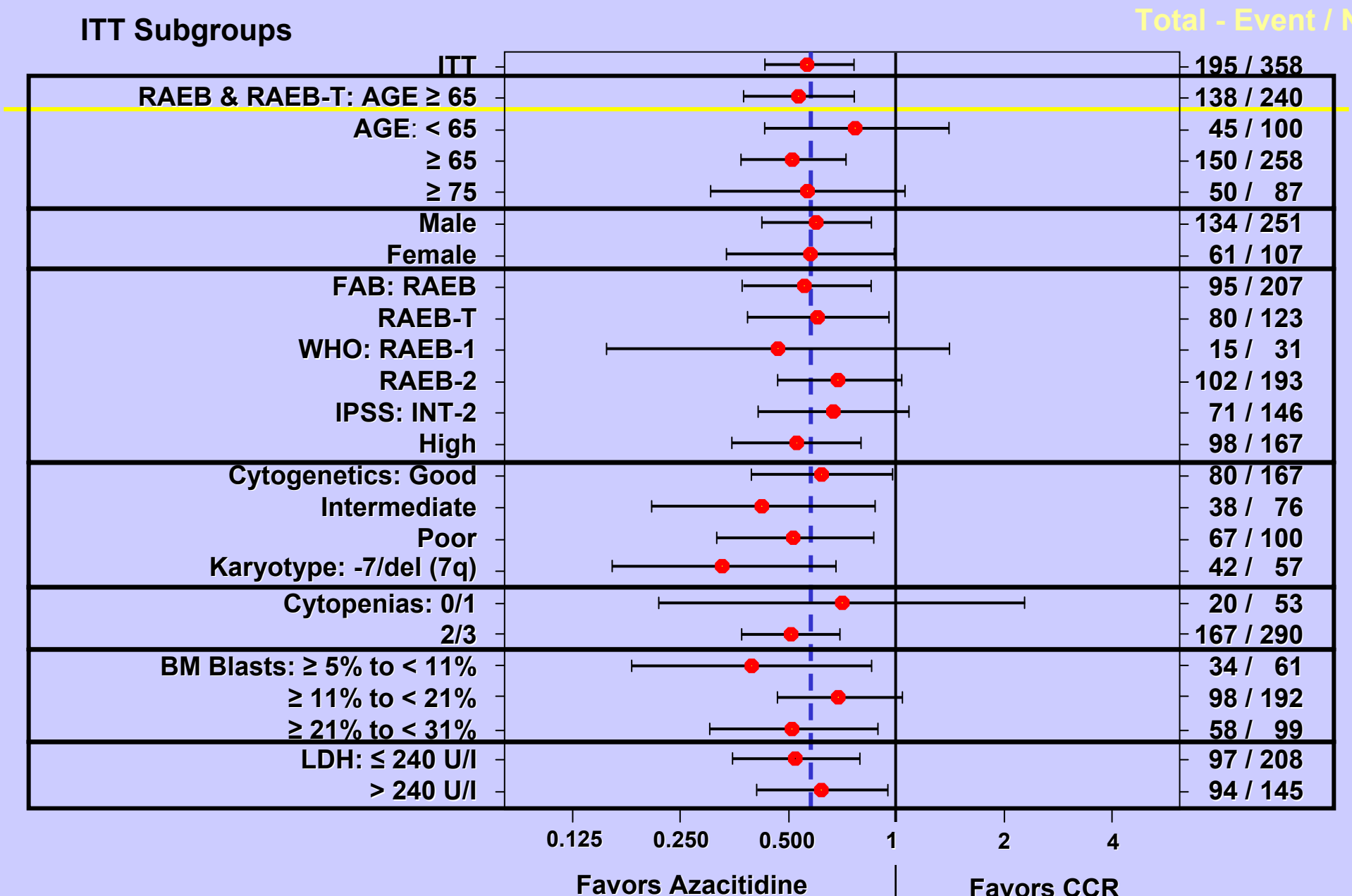


Number at risk								
AZA	179	152	130	85	52	30	10	1
CCR	179	132	95	69	32	14	5	0

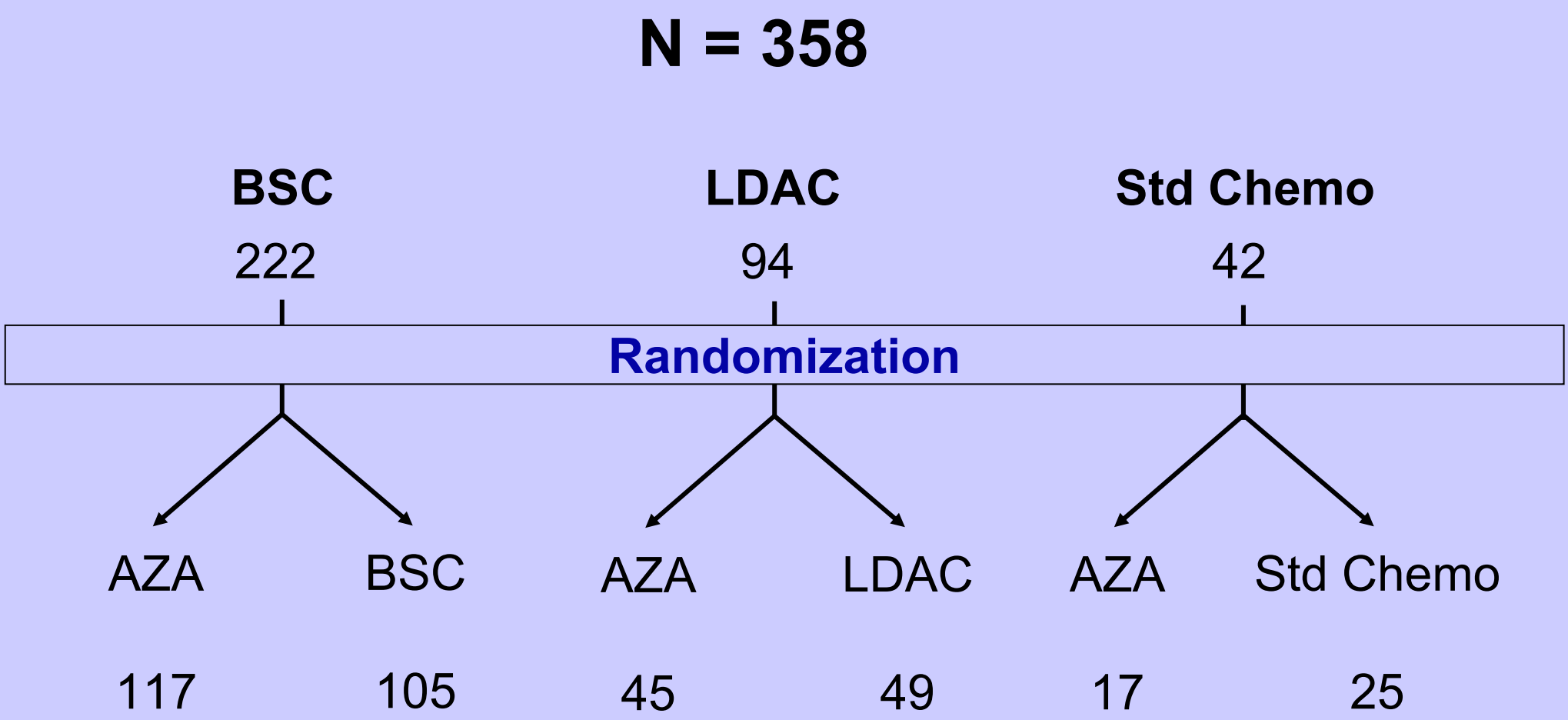
Overall Survival: Azacitidine vs CCR
ITT Population



Hazard Ratio and 95% CI for Overall Survival



Additional Analysis: Investigator Treatment Selection of CCR



Additional Analysis: Median OS by Investigator Selection

Treatment		Differences		
	K-M OS Time mos	K-M OS Time mos	Hazard Ratio	Log-rank P
AZA (N=117)	21.1			
vs				
BSC (N=105)	11.5	9.6	0.56	0.002
AZA (N=45)	24.5			
vs				
LDAC (N=49)	15.3	9.2	0.58	0.015
AZA (N=17)	25.1			
vs				
Stand Chemo (N=25)	15.7	9.4	0.87	0.75

Median Overall Survival per IPSS Cytogenetic Group

IPSS Group	Pts N=358 %	AZA OS (mos)	CCR OS (mos)	Diff. (mos)	p value
Good	**46**	**>25.1***	**17.1**	**>8.0**	**0.04**
Intermediate	**21**	**26.3**	**17.0**	**9.3**	**0.02**
Poor	**28**	**17.2**	**6.0**	**11.2**	**0.01**

* Median not reached

Median Overall Survival per frequent Cytogenetic abnormality

Karyotype	Pts N	AZA OS (mos)	CCR OS (mos)	Diff. (mos)	p value
-7/del 7q	**57**	**13.1**	**4.6**	**8.5**	**0.003**
+8	**25**	**26.3**	**6.6**	**19.7**	**0.003**

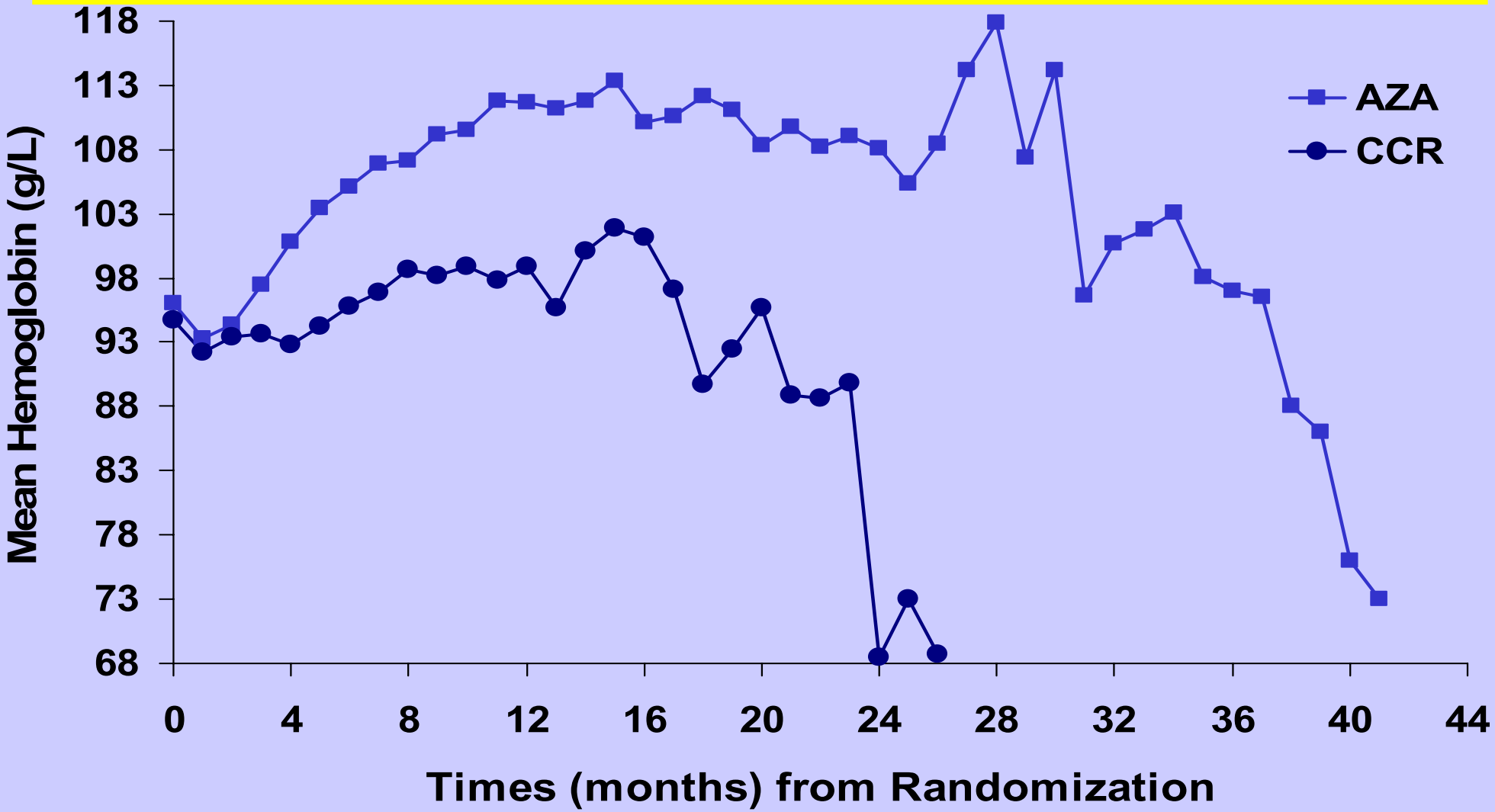
Secondary Endpoints

- **Time to AML**
  - 26.1 mos with AZA vs 12.4 with CCR, p=0.004
- **RBC Transfusion Independence**
  - 45% with AZA vs 11% with CCR, p<0.0001
- **Infections Requiring IV Antimicrobials**
  - Reduced by 33% with AZA vs CCR

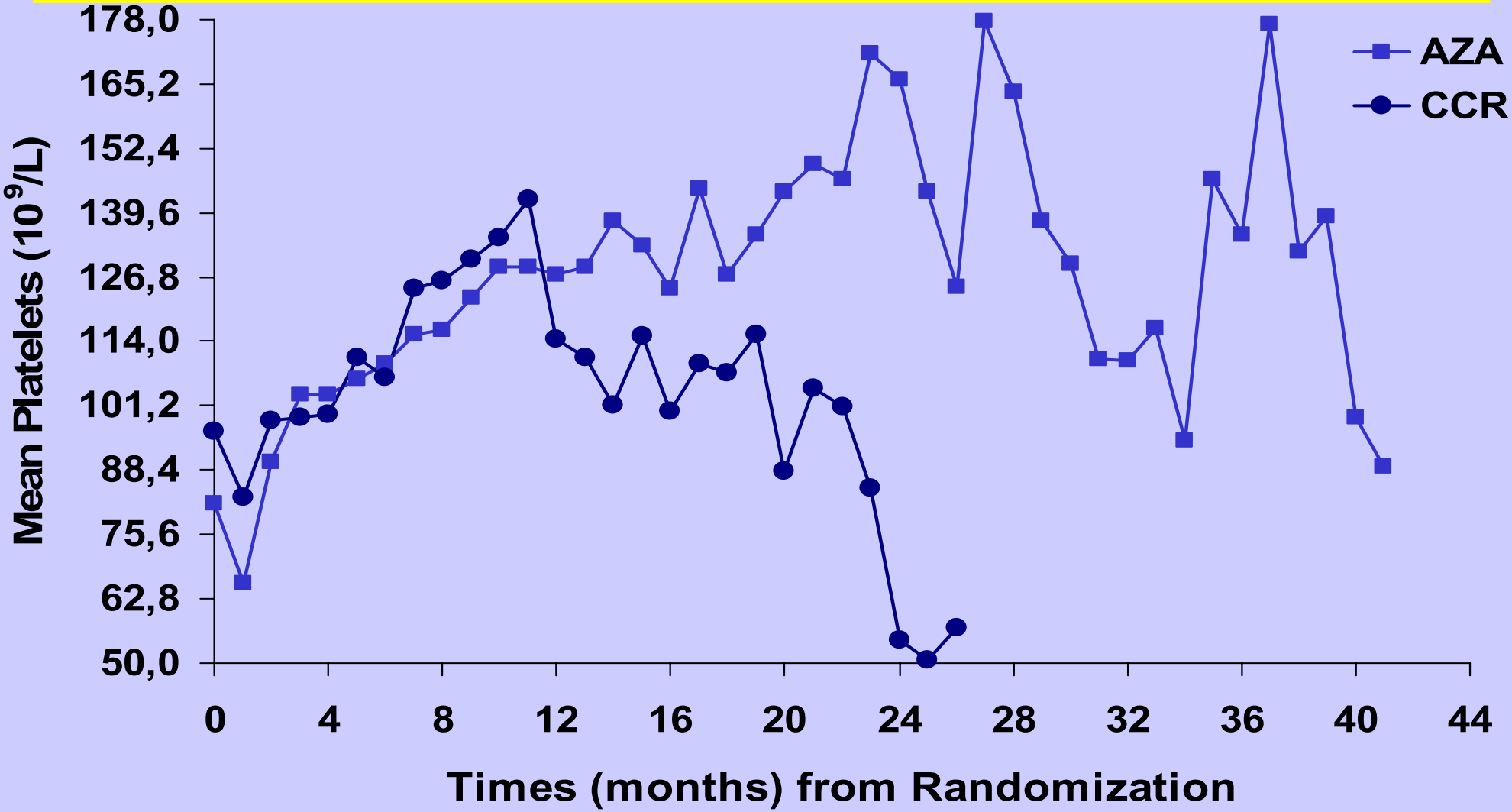
Hematologic Response & Improvement Rates Based on the IWG Criteria for MDS – ITT Population

Parameter	AZA N=179 %	Conventional Care Regimens (CCR) %				P-Value (AZA vs CCR)
		BSC Only N=105	LDAC N=49	Std Chemo N=25	CCR Total N=179	
IWG Hem. Resp.						
Overall (CR+PR)	**28.5**	**4.8**	**12.2**	**40.0**	**11.7**	**0.0001**
Complete Rem (CR)	**16.8**	**1.0**	**8.2**	**36.0**	**7.8**	**0.0150**
Partial Remission (PR)	**11.7**	**3.8**	**4.1**	**4.0**	**3.9**	**0.0094**
Stable Disease (SD)	**41.9**	**39.0**	**36.7**	**24.0**	**36.3**	**0.3297**

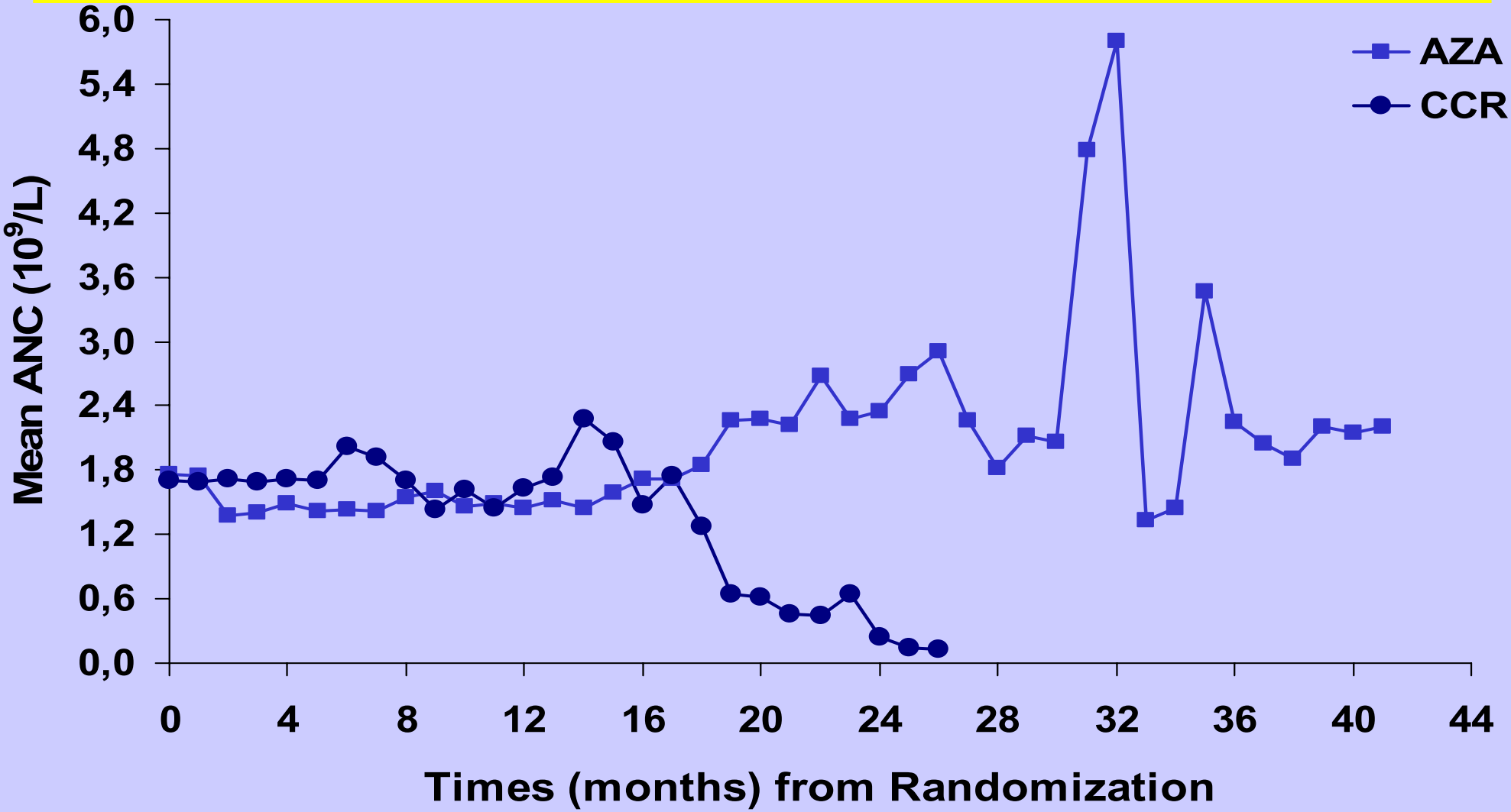
Mean Hemoglobin (g/L) for AZA vs CCR – ITT Population



Mean Platelets (10^9/L) for AZA vs CCR – ITT Population



Mean ANC (10^9/L) for AZA vs CCR – ITT Population



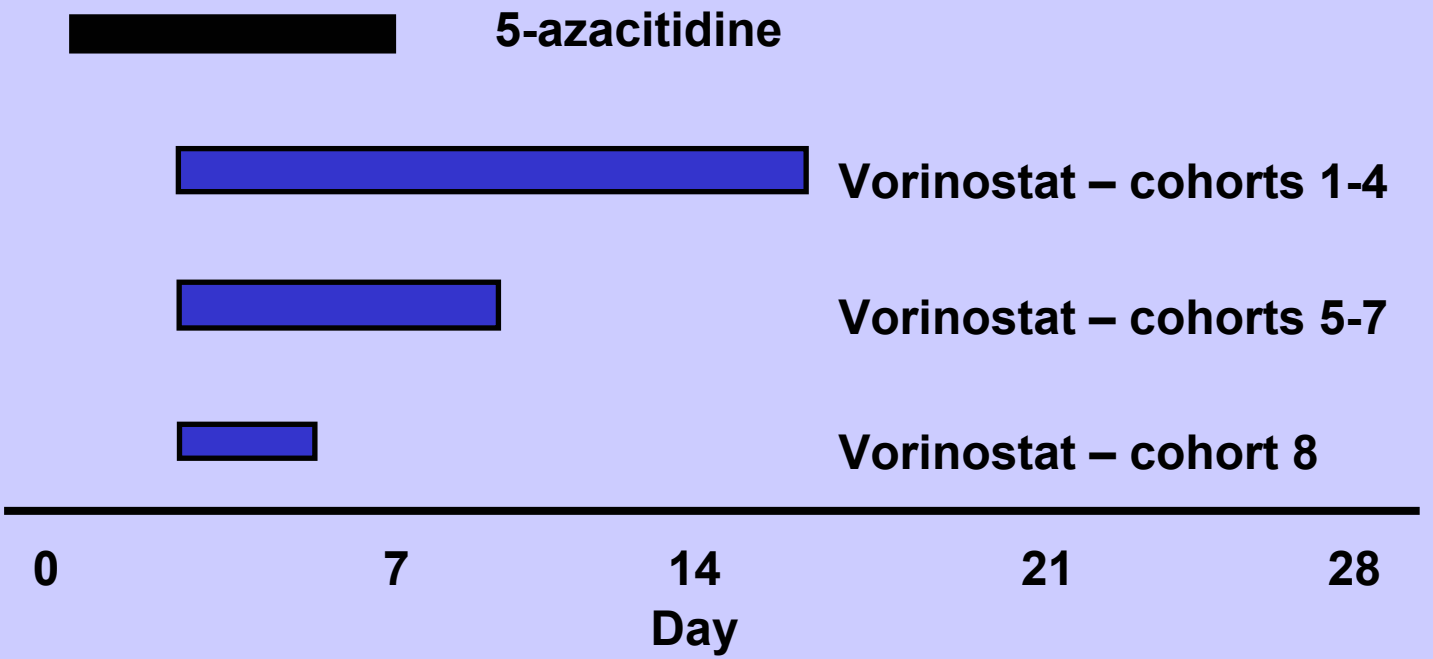
HDAC inhibitors

Short-chain fatty acids (SCFA)	Valproic acid
Hydroxamic acids	Vorinostat (SAHA)
Epoxyketone-containing cyclic tetrapeptides	LBH 589
Non-epoxyketone-containing cyclic tetrapeptides	
Benzamides	MGCD-0103, MS-275,

Phase I/II Study of 5-azacytidine, Valproic Acid and ATRA in Leukemia

VPA (mg/kg)	N	CR	CRp	BM	OR N (%)	Courses to response
50	40	10	3	6	19 (47)	1(1-3)
62.5	7	1	0	0	1 (14)	2
75	6	1	0	1	2 (33)	1
Total	**53**	**12**	**3**	**7**	**22 (42)**	**1 (1-3)**
Untreated	**33**	**11**	**3**	**3**	**17 (52)**	**1 (1-3)**
Previously Treated	**20**	**1**	**0**	**4**	**5 (25)**	**1(1-2)**

A Phase I/II study of vorinostat in combination with 5-azacitidine in patients with MDS



This represents 1 cycle. Cycles repeated every 28 days for a minimum of 4 cycles

Silverman et al. J Clin Oncol 26: 2008 (May 20 Suppl; abs 7000)

Response

Enrolled	23	
Evaluable for response	18	
Overall Response*	**15**	**(83.3%)**
CR	9	(50%)
CRi	2	(11%)
CR+CRi	11	(61%)
PR	0	
HI	4	(22%)
Stable	2	(11%)
NR	1	(6%)
Too Early	2	
IE for response	3	
Withdrew prior to Rx	1	
Transfusion Independence (n = 11)	9	(83%)

*IWG 2000 MDS
IWG 2006 MDS
IWG AML

Phase II trial combining Vorinostat and low dose AraC in higher risk MDS (T Prebet)

Vorinostat (SAHA): HDAC inhibitor

Low dose AraC

…has just started

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Treatment of high risk MDS

- Allogeneic stem cell transplantation
- Chemotherapy (intensive or not)
- Hypomethylating agents
- Others (clinical trials)
  - Arsenic
  - Farnesyl transferase inhibitors
  - Bortezomib
  - Lenalidomide (del 5q)

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LENALIDOMIDE IN HIGHER RISK MDS WITH DEL 5q
(phase I-II trial, GFM)
(L Ades)

- 43 patients evaluable (at least 1 cycle of treatment)
- Hematological response
  - 7 RC
  - 2 mCR
  - 3 HI-E
- Overall, 12 pts achieved RBC transfusion independance

Overall Response rate : 28%

Cytogenetic response : 9 patients :5 complete, 4 partial

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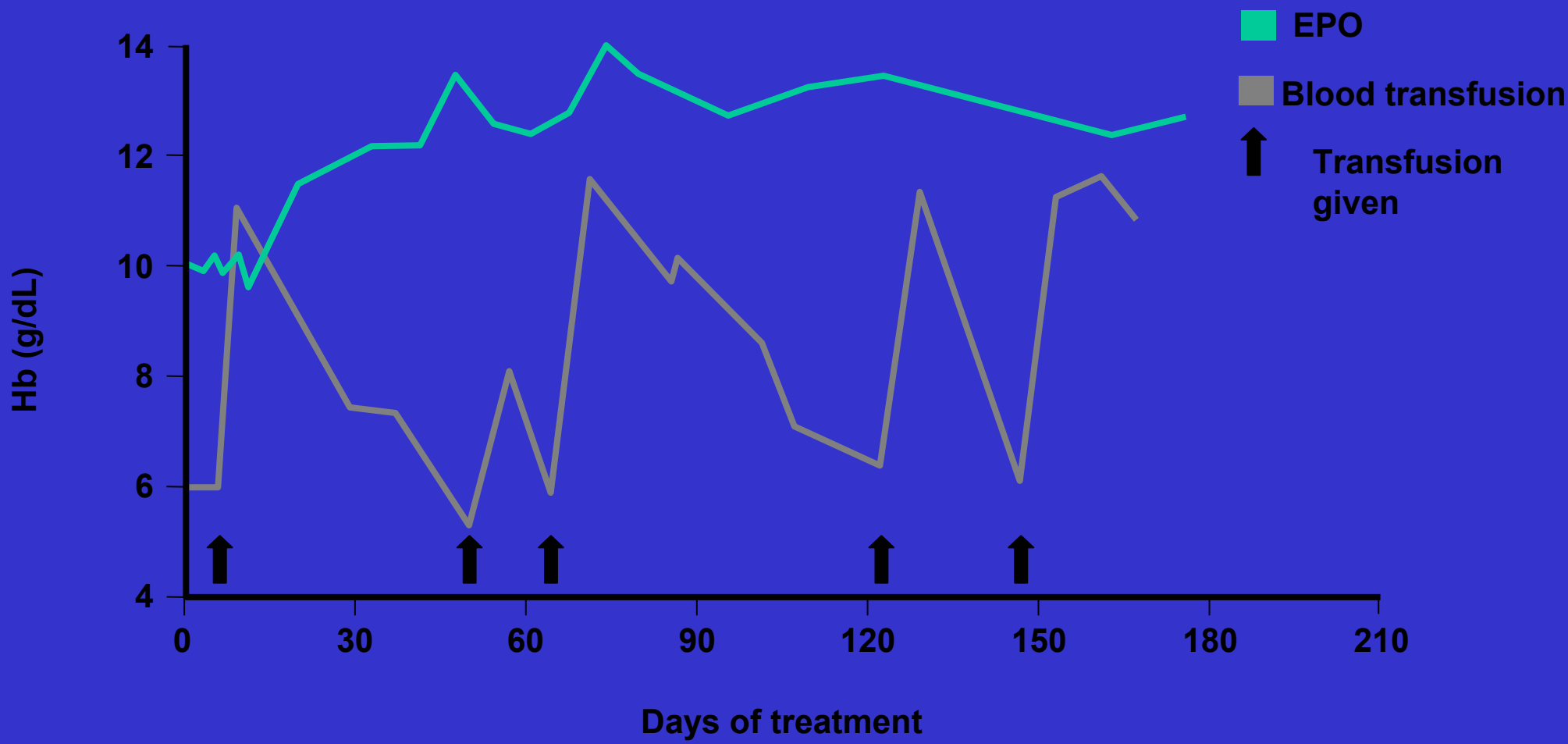
Treatment of lower risk MDS

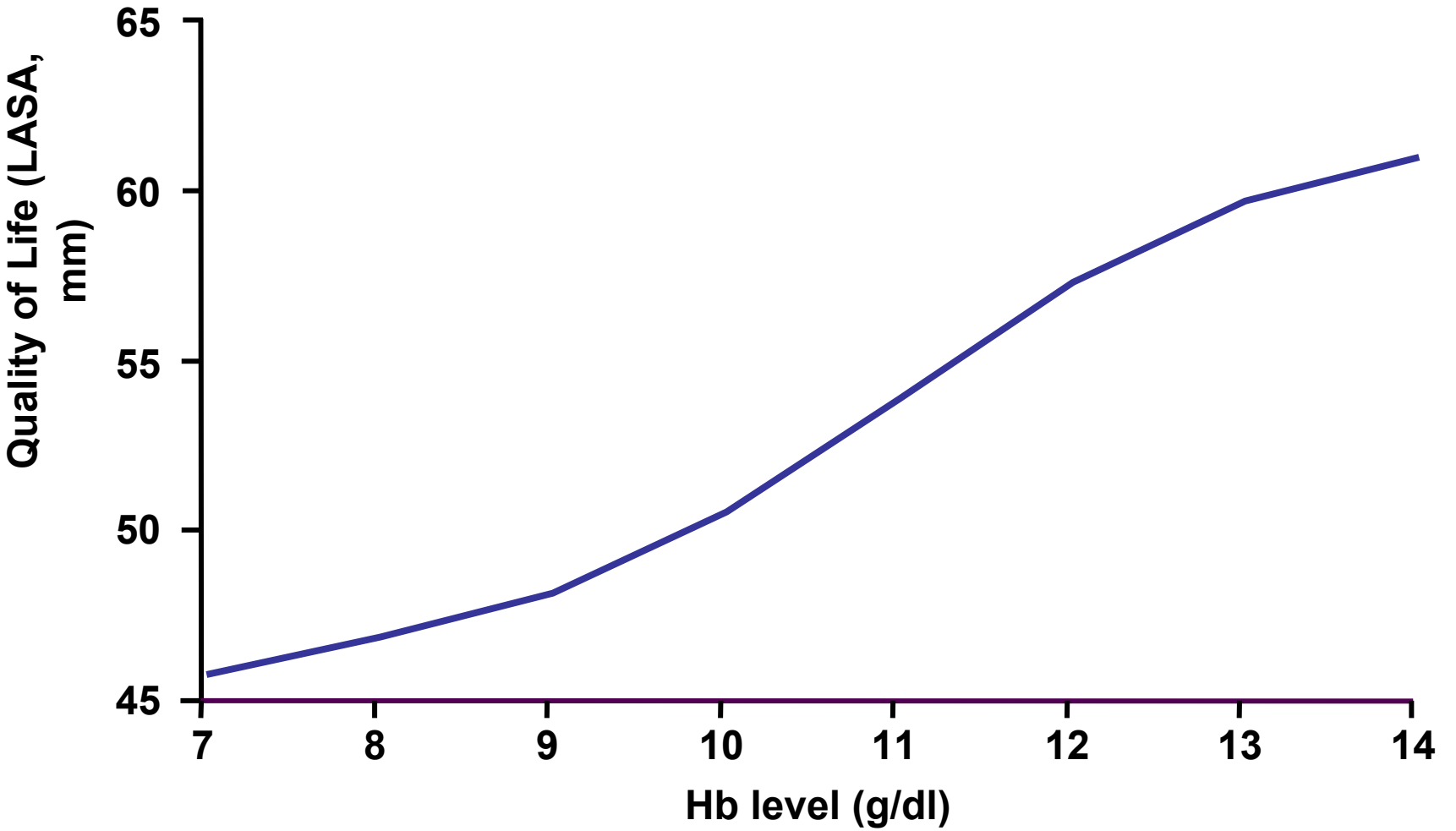
How to treat cytopenias in low risk MDS?

- **Anemia is the most prominent cytopenia:** **should it be treated just by transfusion or by trying to avoid it ?**

Hb level maintained by ESAs *versus* RBC transfusions



Quality of Life is correlated to Hb levels



LASA: Linear Analog Scale Assessment

Crawford et al. *Cancer* 2002; 95: 888–95

MDS and Transfusion

(Bardiaux, 2003)

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- 100 MDS requiring RBC transfusions
- Transfusion episodes / patient mean:11/year
- Cost/ patient mean:820 euros/month

How to prevent anemia recurrence in MDS ?

- ESAs (EPO and darbepoetin)
- ATG
- Thalidomide
- Lenalidomide
- Hypomethylating agents

EPO +/- G-CSF in MDS: prognostic factors of response

(Park , Kelaidi,Blood 2007)

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- N= 403 pts treated with EPO+/- G-CSF or Darbepoetin alpha
- Hb<10g/dl (54%transfused)
- 63% response (43% major, 20% minor)
- Median response duration: 22 months

EPO +/- G-CSF in MDS: prognostic factors of response (Park , Kelaidi,Blood 2007)

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Significantly higher response rate

- EPO <500 U/l
- IPSS low or int 1
- Transfusion < 2RBC concentrates /month

Significantly longer responses

- IPSS low or int 1
- No multilineage dysplasia

A simplified validated decision model for treatment of the anemia in MDS MDS with G-CSF + EPO

Predictive value of model : p<0.001

Variable	value	score	value	score
Transf. need	<2 U/m	0	≥2 U/m	1
Serum-epo	<500 U/l	0	≥500 U/l	1

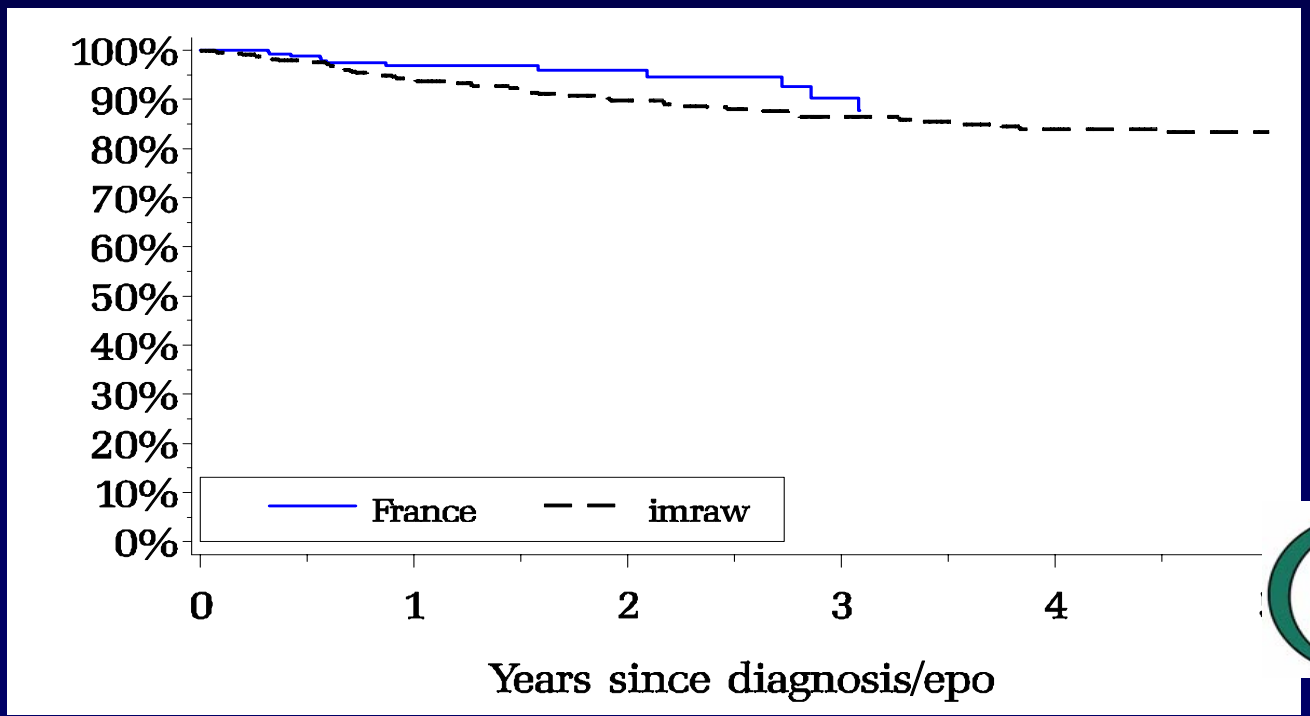
Probability of response:
Total score 0: 74%, score 1: 23%, score 2: 7%
QoL improved in responding patients

Hellstrom-Lindberg, et al, Br J Haem, 2003

Time to AML progression

Comparison between IMRAW and French-EPO cohort restricted to IPSS LOW INT1 patients without unfavorable karyotype (IMRAW n=447 patients, French-EPO= 284)

a) progression to AML , p= NS



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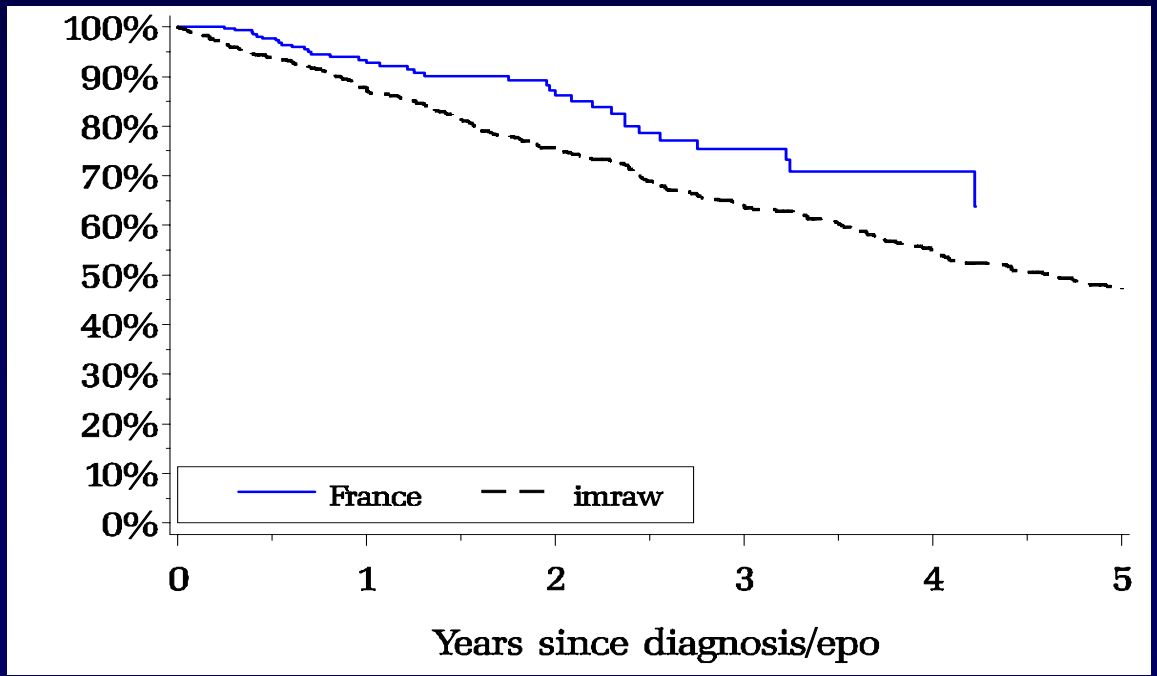
Overall survival

b) Overall survival, P=0.002



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ATG in MDS (Sloand, JCO, 2008)

- 129 pts
  - 24% response (CR+PR) to ATG
  - 48% response to ATG+ CsA
  - 8% response to CsA
- 31% of the responses complete (transfusion independence)

Factors affecting response to immunosuppression in MDS (Sloand, JCO, 2008)

- **Prognostic factors of response :**
  - Younger age (<60 y)
  - HLA DR 15
  - ATG+ CsA
  - IPSS low or int 1

- If compared to IPSS data base: immunosuppression improves survival in patients <60

THALIDOMIDE : RESULTS

	RESPONSE	
Raza A	16/51 at 12 weeks	15 Erythroid (11 MR ;4 mR) 1 Platelet (1mR)
Strupp C	19/30 at 8 weeks	9 Erythroid (3 MR;6mR) 6 Platelet (4 MR;2mR) 2 Neutrophil (1 MR;1mR)
Musto P	4/10 at 12 weeks	4 Erythroid (4 MR)
Moreno-Aspitia A	7/32 at 12 weeks	4 Erythroid (2 MR;2mR) 2 Platelet (1 MR;1 mR) 1Neutrophil (1 MR)
Bouscary D	13/47 at 16 weeks	

11 Erythroid (4 MR;7mR)
1 Platelet (1 MR)
2 Neutrophil (2 MR)

Thal: major side effects

side effect	% pts
. Sleepiness	72
. Constipation and dizziness	45
. Cutaneous reactions	33
. Headache	17
. Nausea	11
. Asthenia	8
. Paresthesia	7
. Worsening granulocytopenia	5
. Dyskinesia	4
. Oedema	2
. Others	5
. Thrombosis	0

Lenalidomide Erythroid Response: lower risk MDS with Del 5q

No . Patients	148
Erythroid Response	
Transf -Indep	
Minor (>50%↓)	99 (67%)
TI +Minor	13 (9%)
	112 (76%)
Time to Response	4.6 wks
	(1- 49)

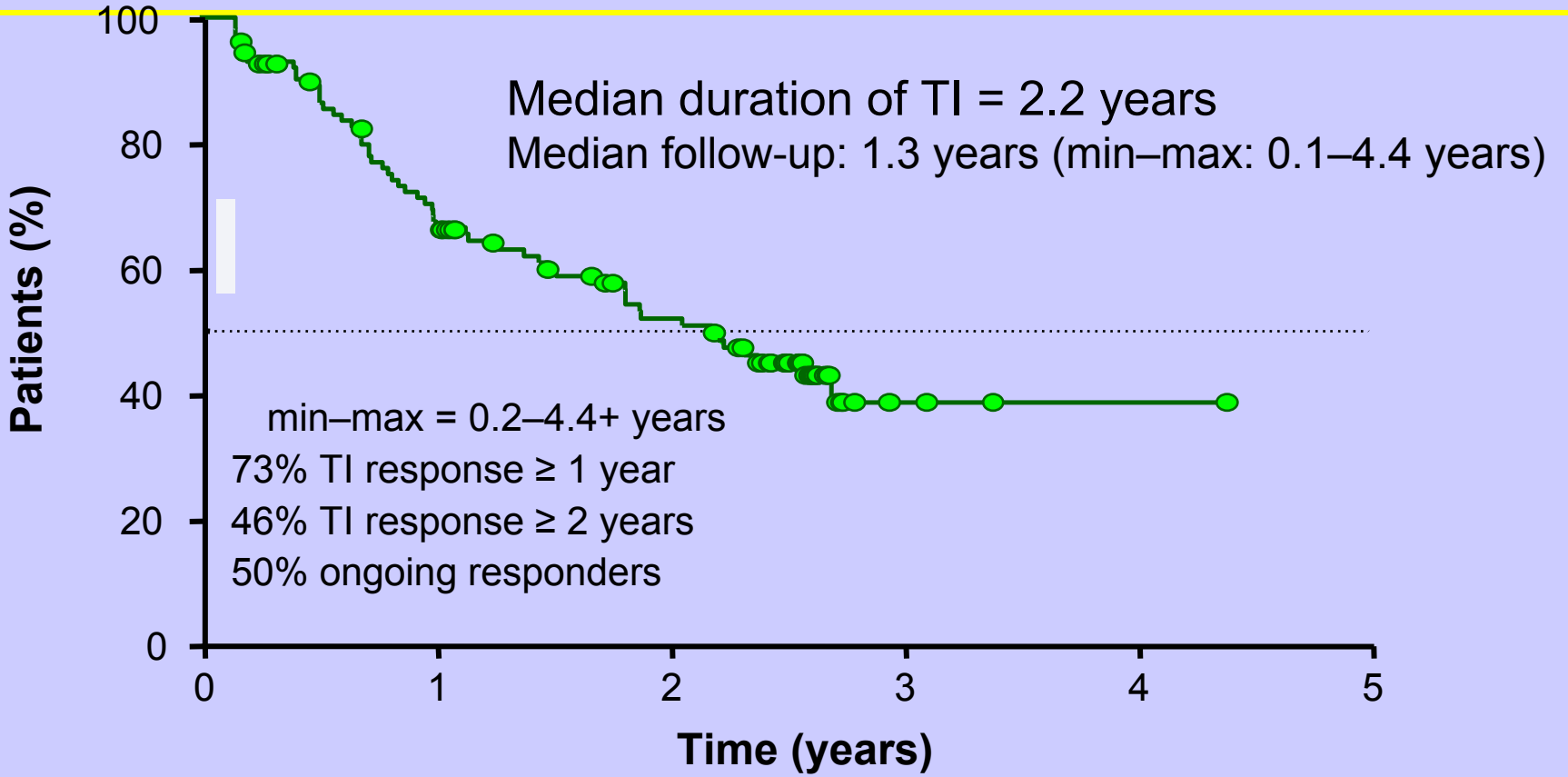
Cytogenetic response in patients with del 5q

Variable	n (%)
Evaluable	**104**
Cytogenetic response*	**75%**
Complete (CCR)	**48%**
Minor (≥ 50%↓)	**27%**

*All cytogenetic responders achieved an erythroid response.

List AF, et al. Updated data presented at ASH Annual Meeting, 2006 [Abstract 251].

Duration of major erythroid response in patients with del 5q (N = 168)



Data cutoff 4 Dec 2006 (N = 114).

Censored patients who remain TI at time of data cutoff or at time of study discontinuation.

List AF, et al. Updated data presented at ASH Annual Meeting, 2006 [Abstract 251].

Drug-Related Adverse Events

Adverse Event	All Grades	≥Grade 3 (%)
Thrombocytopenia	58%	54%*
Neutropenia	57%	55%**
Pruritus	32%	2%
Rash	28%	7%
Diarrhea	24%	2%
Fatigue	12%	3%

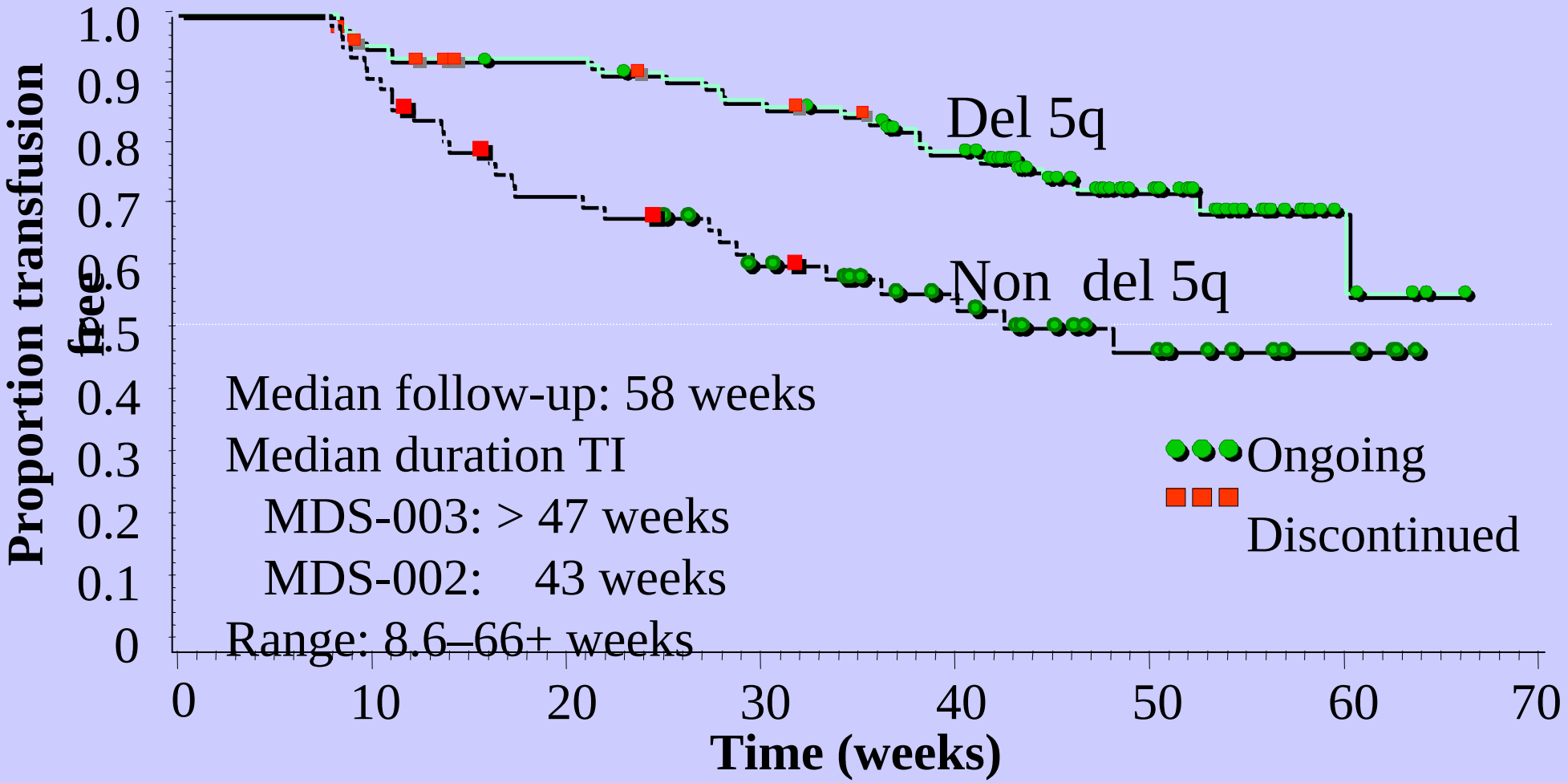
*

Lenalidomide erythroid response
non del 5q

Feature	Total
n	166
Erythroid response, n (%)	
major	**58 (27)**
Minor (> 50% ↓)	**36 (17)**
major + minor	**94 (44)**
Median time to response, weeks [range]	**4.5 [0.3–39.1]**

List AF, et al. Haematologica. 2005;90 Suppl 2:307.

Duration of transfusion independence



Hypomethylating agents in lower risk MDS

30 to 40% erythroid responses

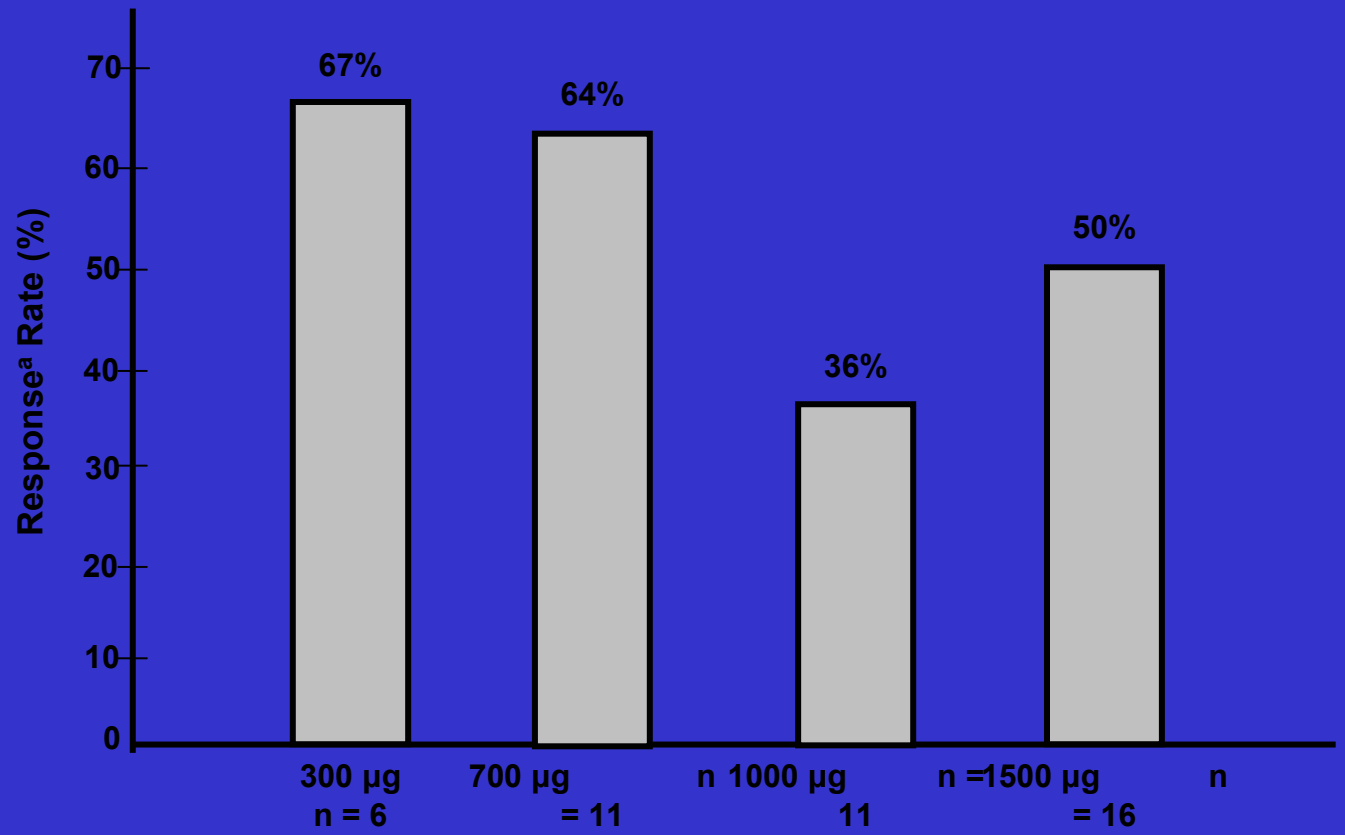
- **Azacytidine** (Silverman, 2002; Lyons, 2007)
- **Decitabine** (Wijermans, 2005; Kantarjian, 2007)

Treatment of thrombocytopenia

- Androgens
- (Interleukin 11)
- TPO agonist receptors
  - AMG 531 (Amgen)
  - Eltrombopag (GSK)

AMG 531 in lower risk MDS (Kantarjian, ASH 2007)

- Platelet response achieved in 52% of patients overall.



[a]: increase from baseline in platelet count by ≥30 x 109/L for patients starting with >20 x 109/L platelets, or an increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100%.[7]

Treatment of neutropenia

- +++ early treatment of infections(eg: Augmentin-Ciflox)
- No proven effect of G-CSF (except in acute situations?)

Chelation therapy in MDS

- **Indication (Nagasaki consensus):**
  - IPSS low and int 1 or int 2 or high with treatment increasing lifespan envisaged
  - >20- 30 concentrates, or Ferritin > 1000-1500

- **modalities:**
  - desferoxamine (SC, IV)
  - Deferiprone (oral)
  - Deferasirox(oral)

GFM study: chelation versus no chelation in heavily transfused lower risk MDS (n= 170) (Rose, ASH 2007)

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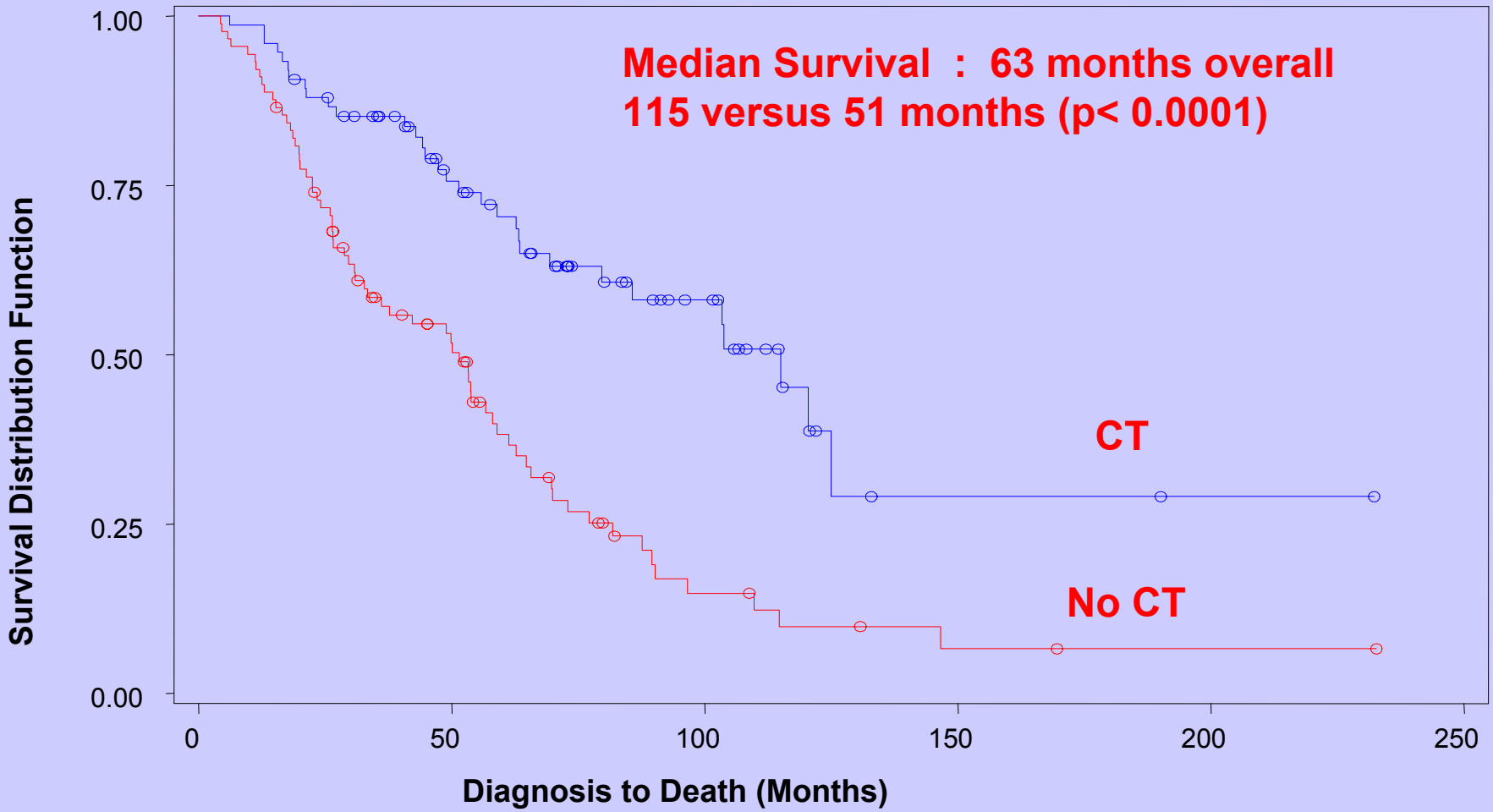

Recomendaciones para el tratamiento de los SMD: RIESGO ALTO

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Edad < 65-70

- con donante
  - Alo transplante
  - Precedido o no por QT intensiva o hipometilantes,basandose en
    - % blastos en MO
    - cariotipo

- sin donante
  - Cariotipo normal: QT intensiva o hipometilantes ?
  - ++++ Cariotipo desfavorable: hipometilantes

Recomendaciones para el tratamiento de los SMD: RIESGO ALTO

Groupe Français des Myelodysplasies

Edad > 65-70

- Cariotipo normal
  - AraC BD ?
  - +++Hipometilantes+/- otros
- Cariotipo desfavorable
  - ++++ hipometilantes+/- otros
  - Sino: tratamiento de soporte o protocol de investigacion

Recomendaciones para el tratamiento de los SMD: RIESGO BAJO

Groupe Français des Myelodysplasies

Anemia

- Primera linea
  - EPO or Darbepoietina
  - Lenalidomida en caso de del 5q

- Lineas ulteriores
  - GAL
  - Hipometilantes
  - Lenalidomida
  - (talidomida)

- +++ En caso de requerimiento transfusional: quelacion de hierro

Grupo Francofono de las Mielodisplasias

Groupe Français des Myelodysplasies

- Activa ensayos clinicos en los SMD (35 centros en Francia y Belgica
  + (recientemente) Suiza, Tunisia, Romania

- Website: www. gfmgroup.org , password 5q17p

- Registro Online registry de los SMD franceses

- Estrecha cooperacion con:
  - una asociacion de pacientes con SMD
  - la International MDS Foundation
  - el European Leukemia Net

Ensayos clinicos del GFM: Riesgo bajo

Groupe Français des Myelodysplasies

- **Primera linea:**
  - **Darbepoitina (no del 5q) (C Kelaidi)**
- **Secunda linea**
  - **AZA+/- EPO (S Boehrer)**
  - **LEN+/- EPO (F Dreyfus)**

Ensayos clinicos del GFM: Riesgo alto

Groupe Français des Myelodysplasies

- Primera linea
  - AZA (R Itzykson, S Thepot)
  - AZA en mantenimiento despues de QT (C Gardin)
  - AZA+ LEN (del 5q) (L Ades)
  - QT intensiva+ LEN (L Ades)
- LMMC
  - Decitabina (E Solary)
- Secunda linea
  - Vorinostat + LD AraC (T Prébet, N Vey)
  - Bevacizumab (L Legros)

Groupe SMD :Hopital Avicenne (Paris 13 University) and Institut Gustave Roussy (IGR)

- **Clinical department (Avicenne/Paris 13)**
- Claude Gardin
- Lionel Ades
- Claire Fabre
- Fatiha Chermat
- Rose Marie M'bida
- Natacha Hoarau
- Raphael Itzykson
- Sylvain Thépot
- Charikleia Kelaidi
- Blandine Bève
- Pierre Fenaux

- **INSERM U 848**
- Simone Bohrer
- Thorsten Braun
- Lionel Ades
- Claire Fabre
- Gabrielle Carvalho
- Pierre Fenaux
- Guido Kroemer

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- Virginie Eclache
- Florence Cymbalista