57° CONGRESSO NAZIONALE SIGG
Società Italiana di Gerontologia e Geriatria

MILANO

21/11/2012 - 24/11/2012

Nuove terapie per le sindromi mielodisplastiche e le smoldering leukemie dell'anziano

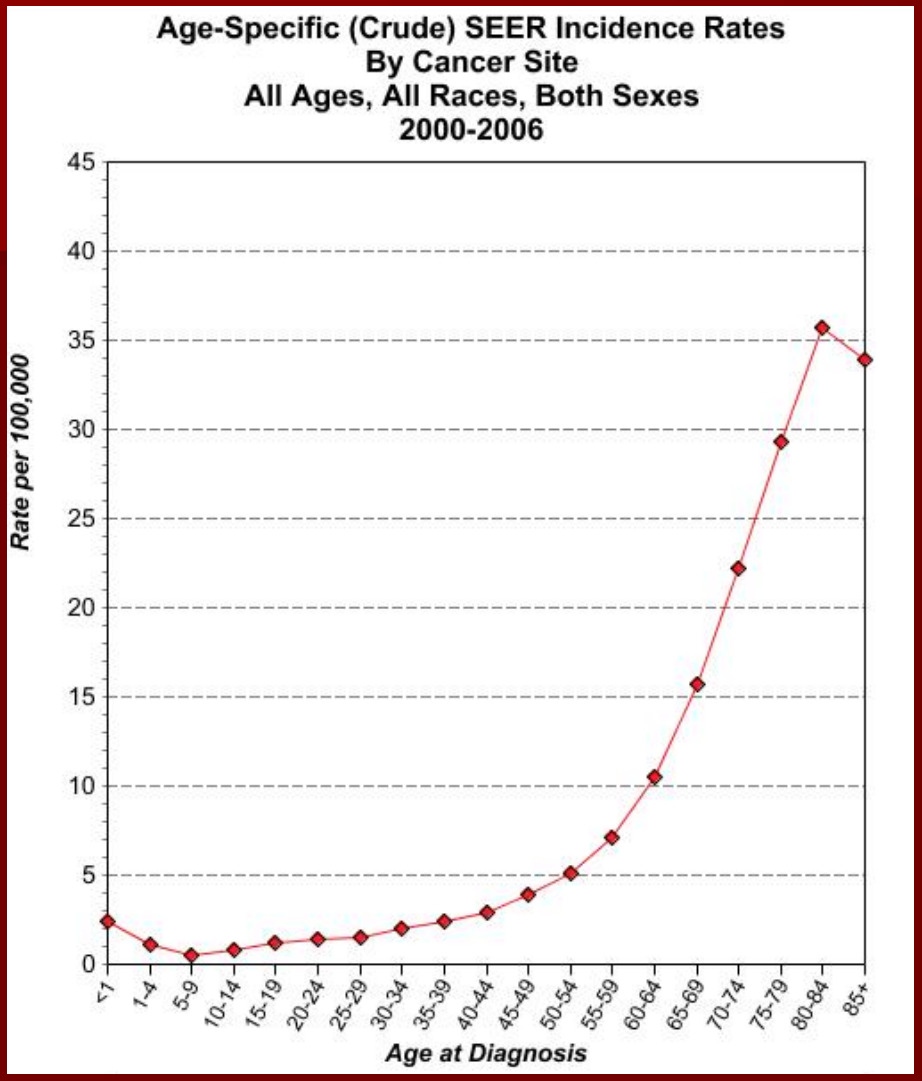
Milano

Saturday, 21-24 November 2012

Giovanni Martinelli, MD

Istituto "Seragnoli" Bologna

AML: a disease of the elderly



- Estimated new cases in 2009: 12.800
- Median age: 67 years
- Age-adjusted incidence rate: 3.5×10^5 x year
  - <65y: 1.7×10^5 x year
  - >65y: 15.5×10^5 x year

Reasons for lack of progress

- Poor tolerance for intensive Rx
  - Poor PS and comorbidities
- Inherent chemoresistance
  - Adverse biology
- Lack of accrual to clinical trials
  - Therapeutic nihilism

4 (5) models leukemias

PML-RARa
NPM+

(CD33+)

CURED

Come si presenta una Sindrome Mieloproliferativa Acuta (APL)

Le **Sindromi Mieloproliferative acute** (APL) si presentano:

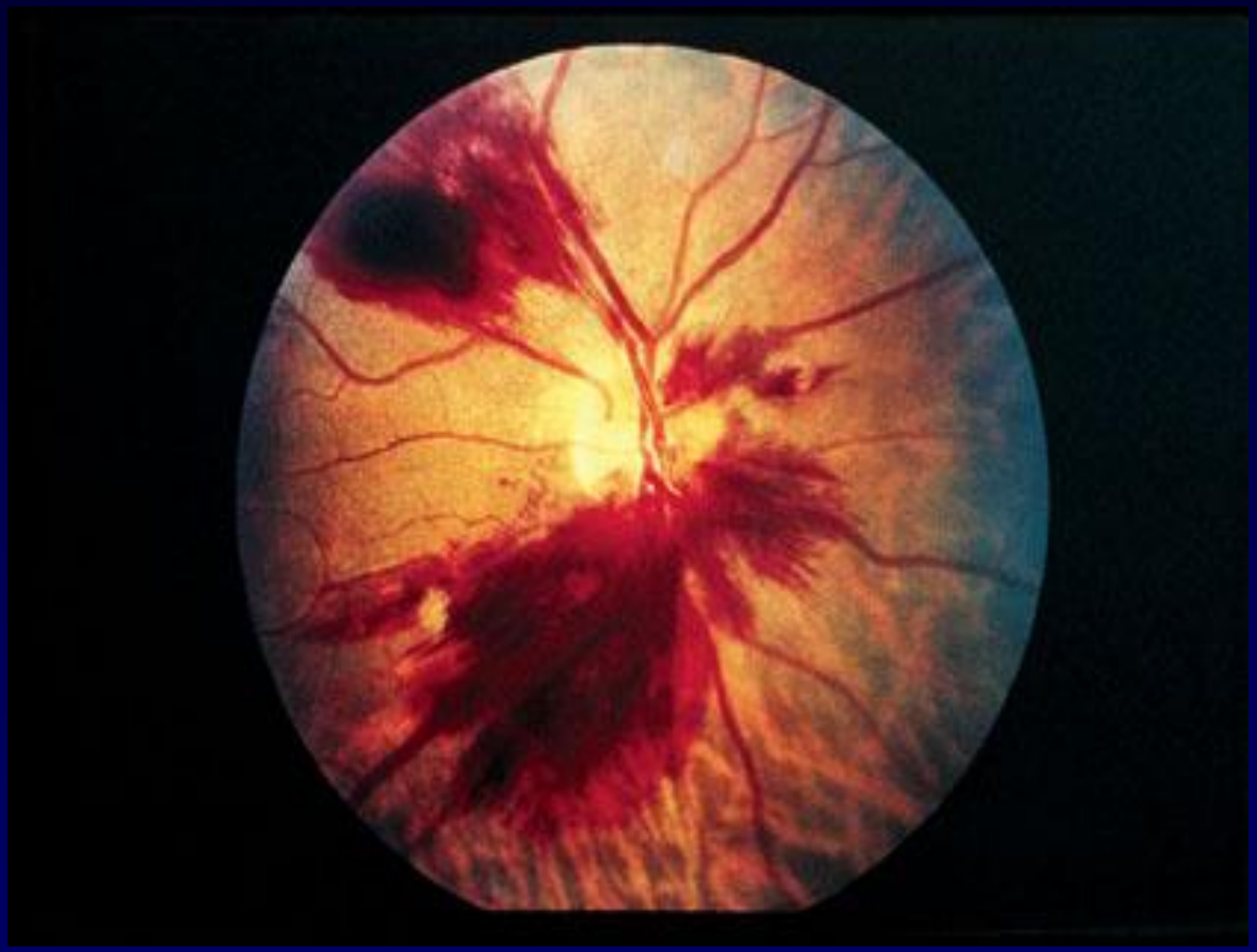
Sul piano clinico-laboratoristico sono caratterizzate da:

1. Anemia, (severissima, Halitosis sanguinis)
2. Leucopenia, neutropenia, o leucocitosi (blasti) anche elevatissima
3. Severa piastrinopenia singola o combinate associata invariabilmente a DIC (diffuse intravascular coagulopathy)laboratoristica e clinica
4. Quadri midollari in genere ipocellulati con sostituzione midollare totale da parte della popolazione leucemica.

ANEMIA

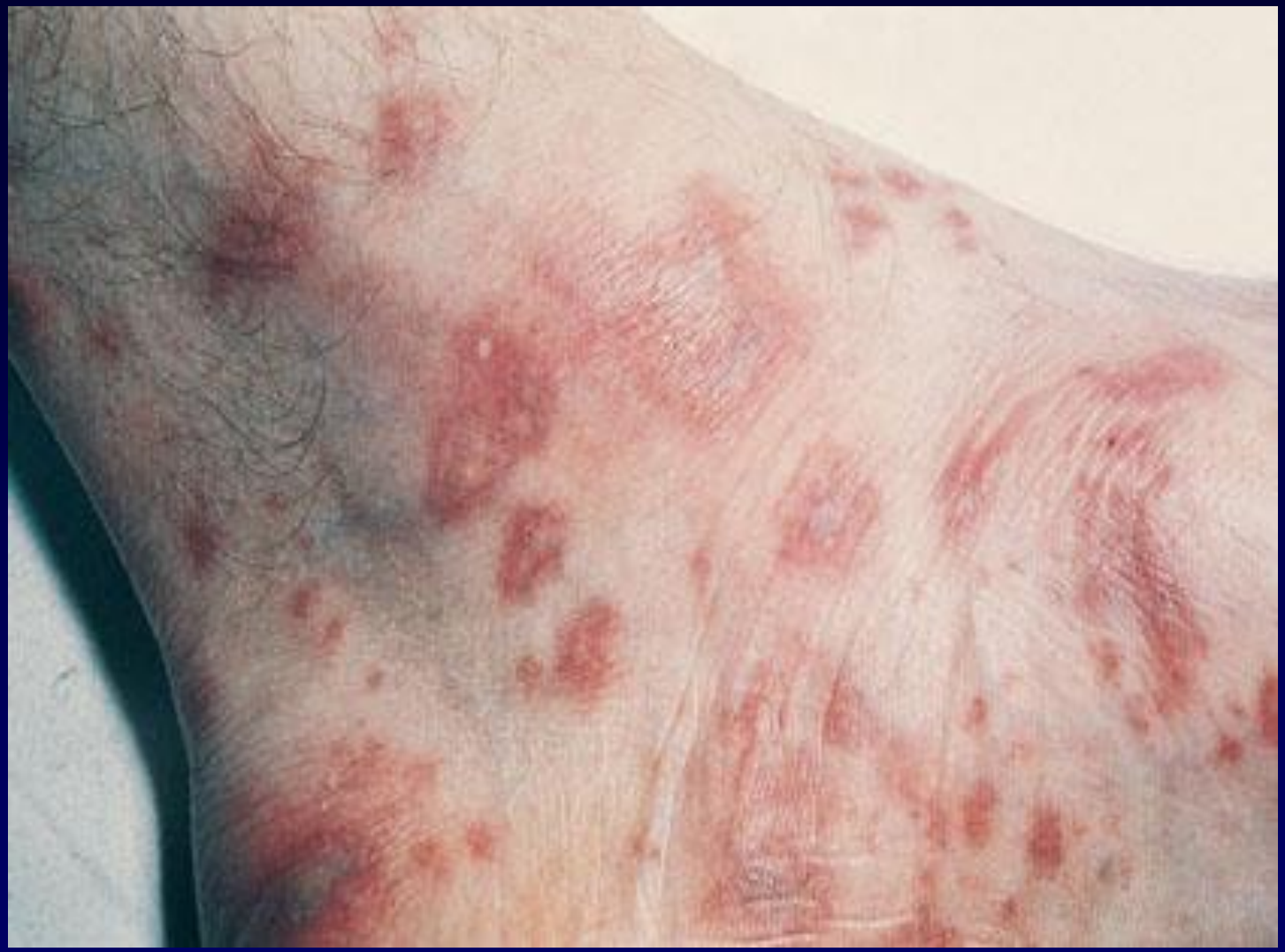
1. Tachicardia
2. Tachipnea
3. Soffio sistolico
4. Pallore mucoso-cutaneo
5. Astenia
6. Angina
7. Etc.

PIASTRINOPENIA



Emorragia retinica in un paziente con LEUCEMIA MIELOIDE ACUTA APL con importante trombocitopenia.

PIASTRINOPENIA + CID + infezione

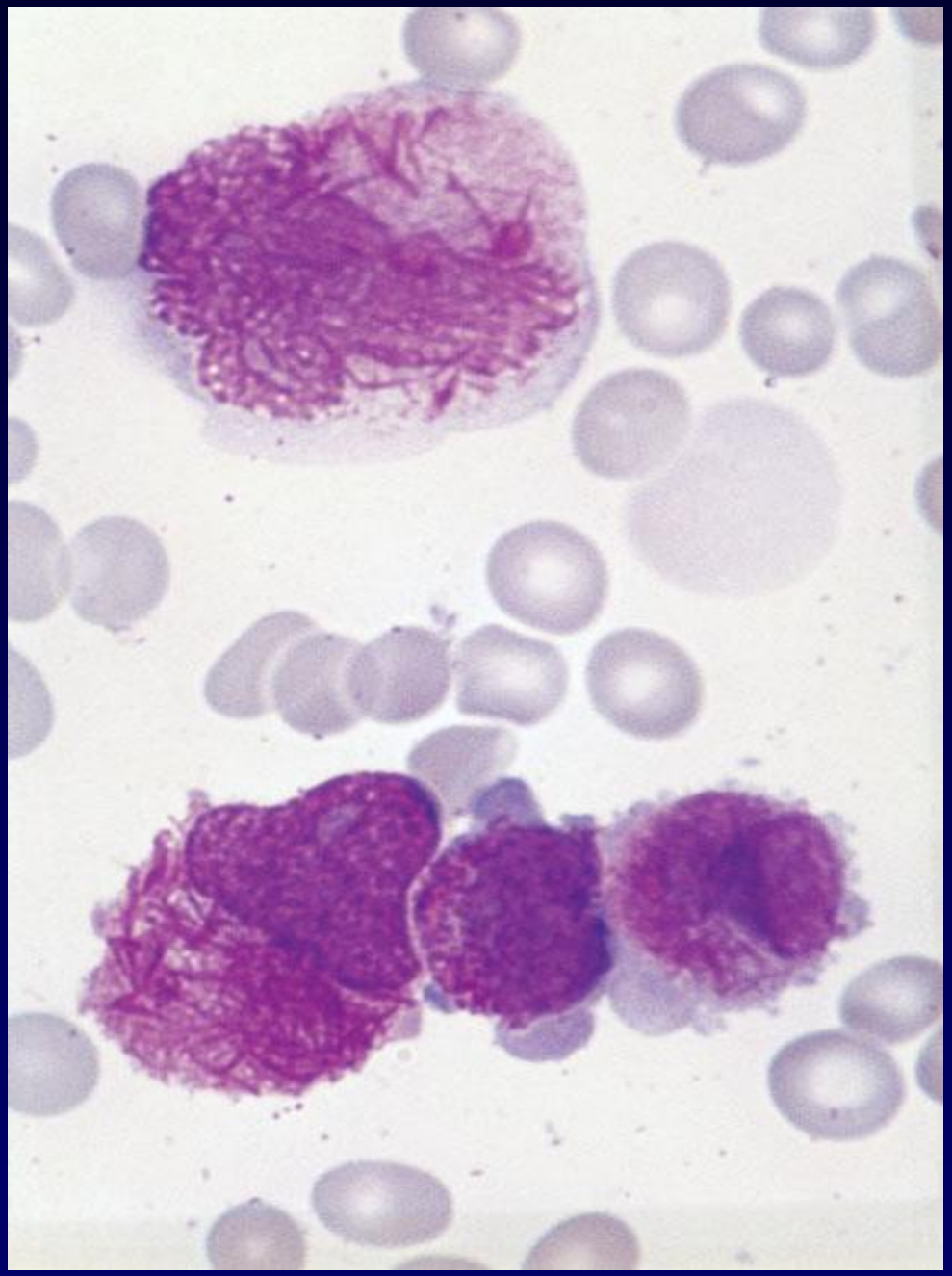


Setticemia da meningococco: tipiche lesioni cutanee purpuriche intorno alla caviglia in malattia acuta fulminante con coagulazione intravascolare disseminata

Leucemia mieloide acuta, sottotipo M_3:

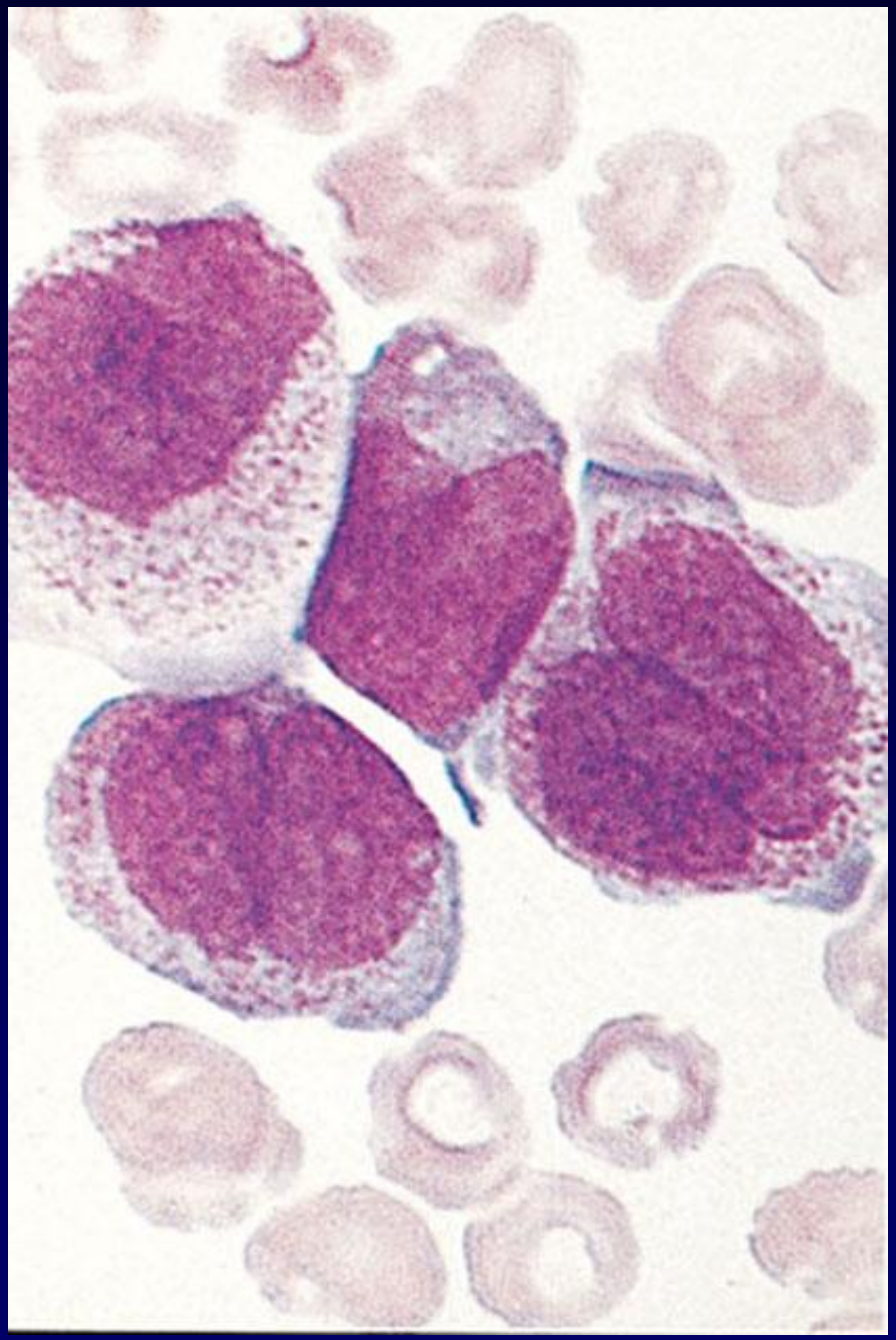
promielociti che contengono grossolani granuli azzurrofili e ammassi di corpi di Auer (fastelli) in (a). I nuclei contengono uno o due nucleoli.

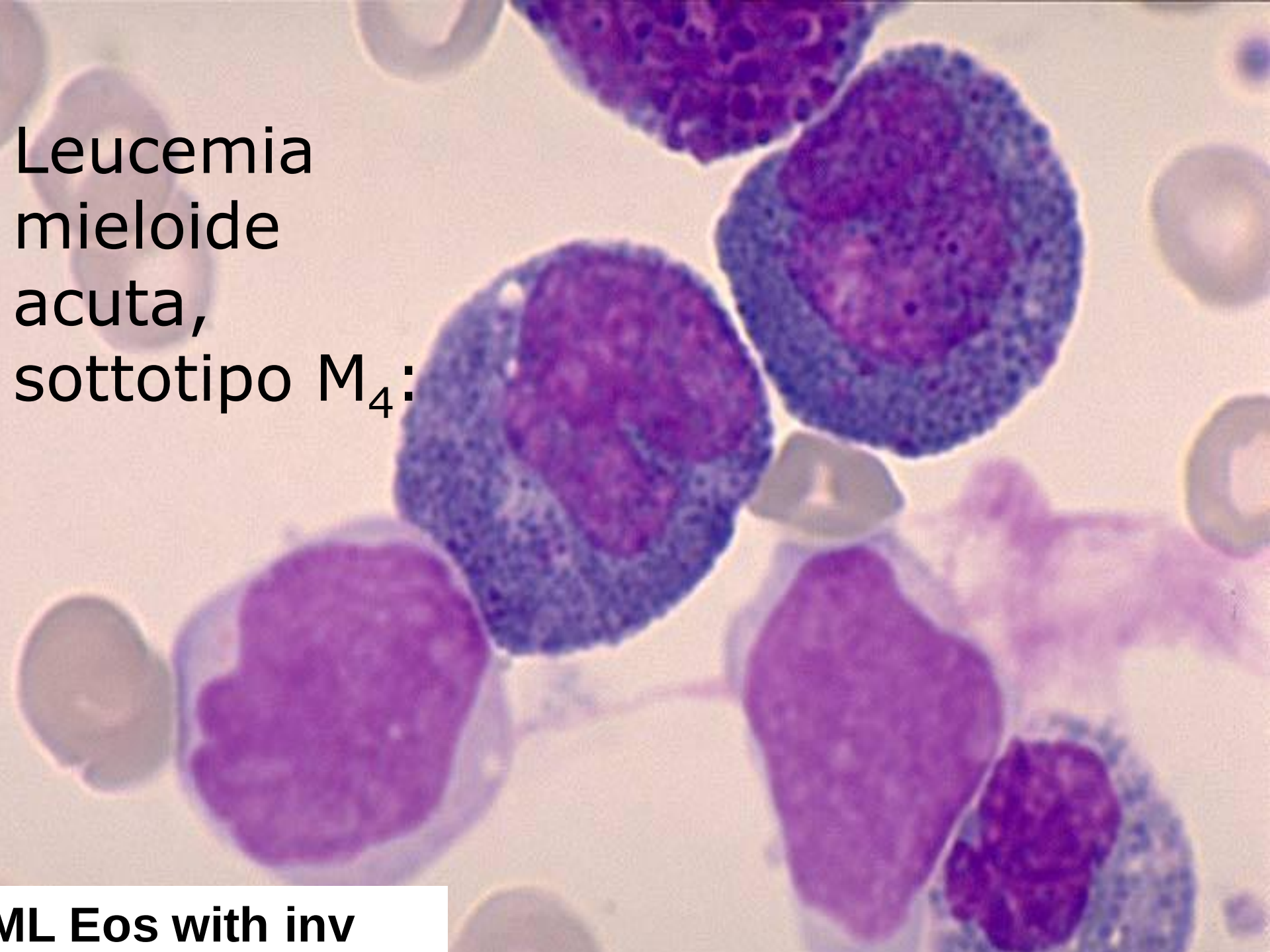
Il sottotipo è associato con la traslocazione cromosomica 15;17



Leucemia mieloide acuta, sottotipo M_3:

variante microgranulare. Le tipiche cellule bilobate contengono numerosi piccoli granuli azzurrofili.

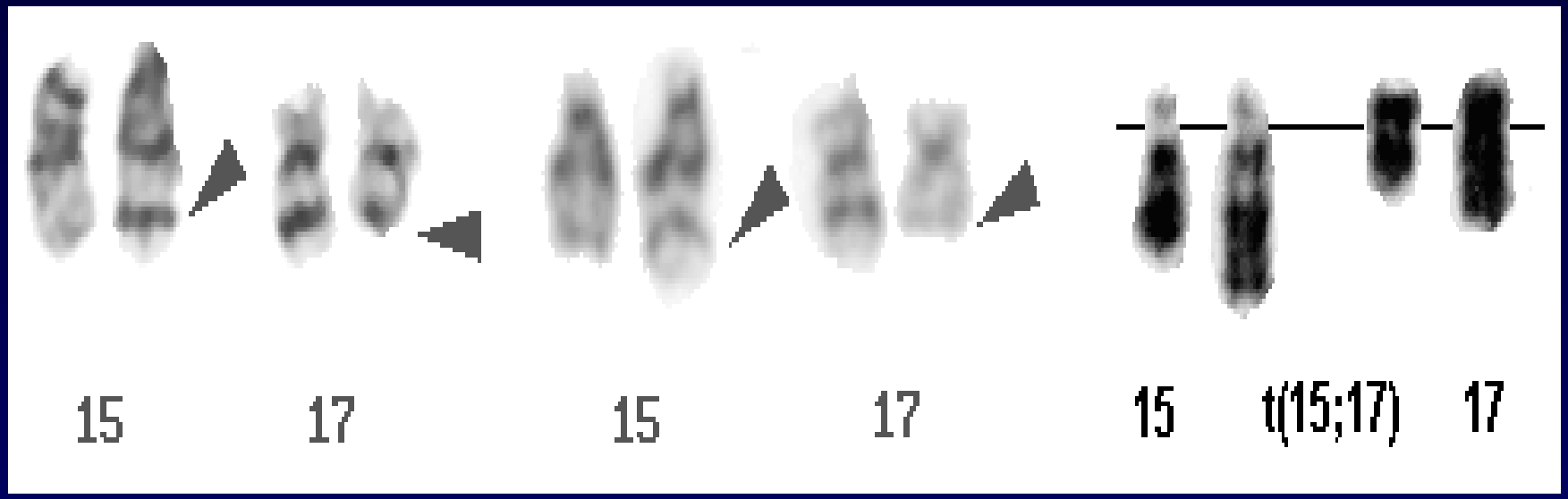



Leucemia mieloide acuta, sottotipo M_4:
ML Eos with inv

Leucemia M3 APL O PROMIELOCITICA

t(15;17)(q22;q21)

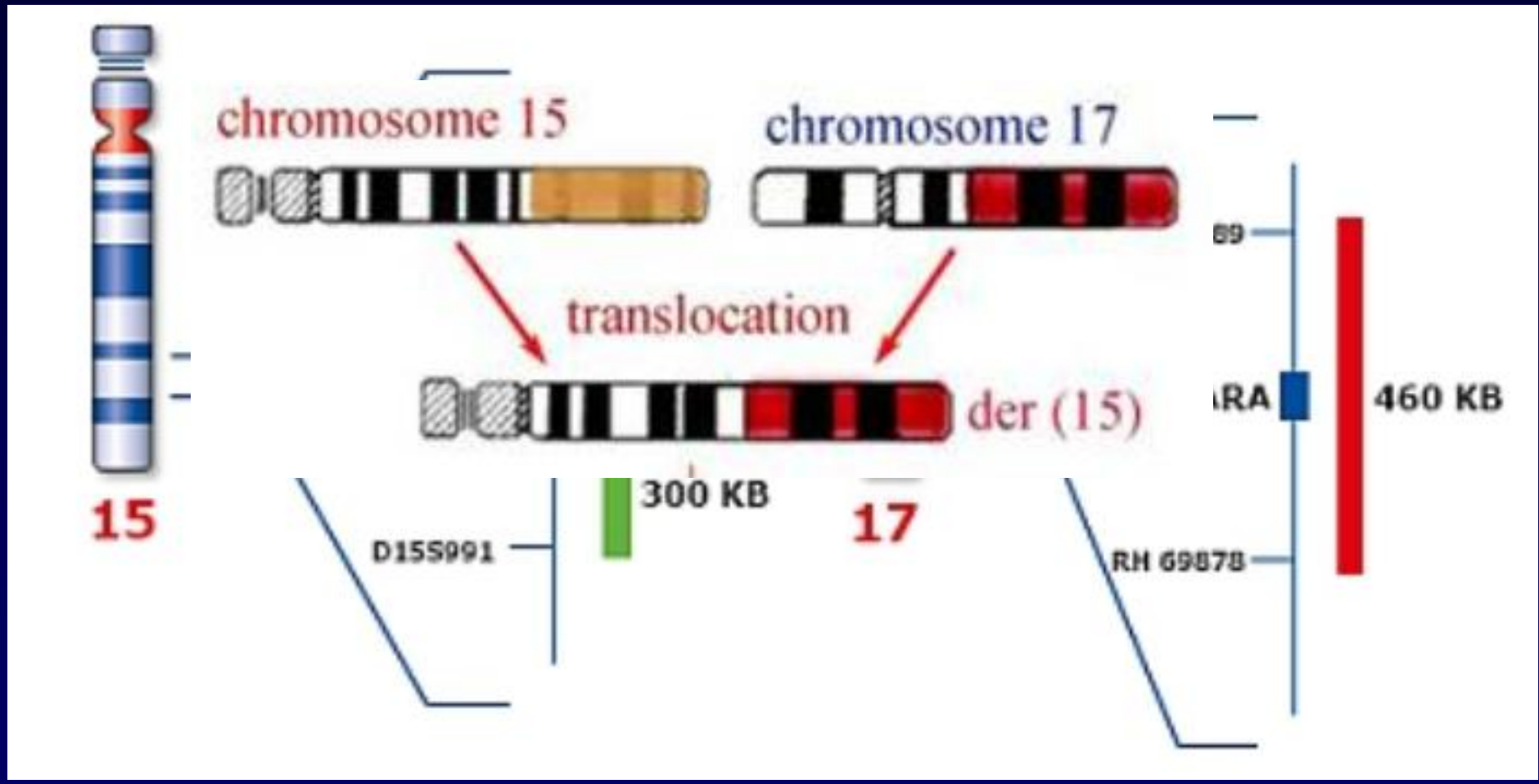
IDENTITA'



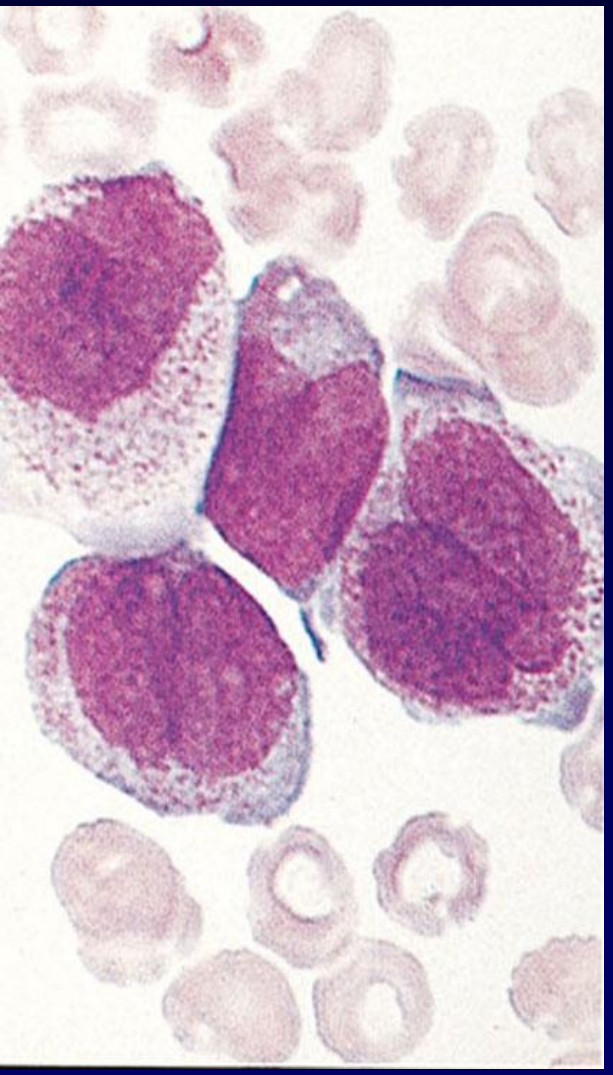
t(15;17)(q22;q21) G- banding (sinistra e centro)

Istituto di Ematologia e Oncologia Medica "Seràgnoli", Università di Bologna

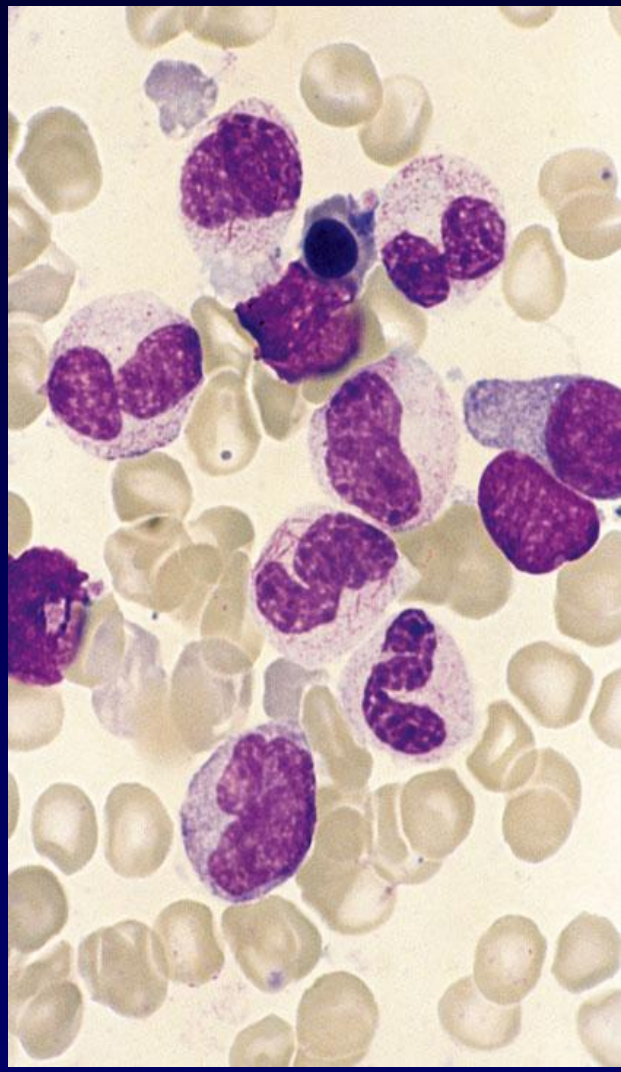
Leucemia M3 APL O PROMIELOCITICA
PML-RAR alpha fusion transcript



LEUCOPENIA (M3) - LEUCOCITOSI



(ATRA)



Cosa abbiamo imparato dalla APL ?

Trials multicentrici in corso sulla terapia di prima linea della leucemia promielocitica

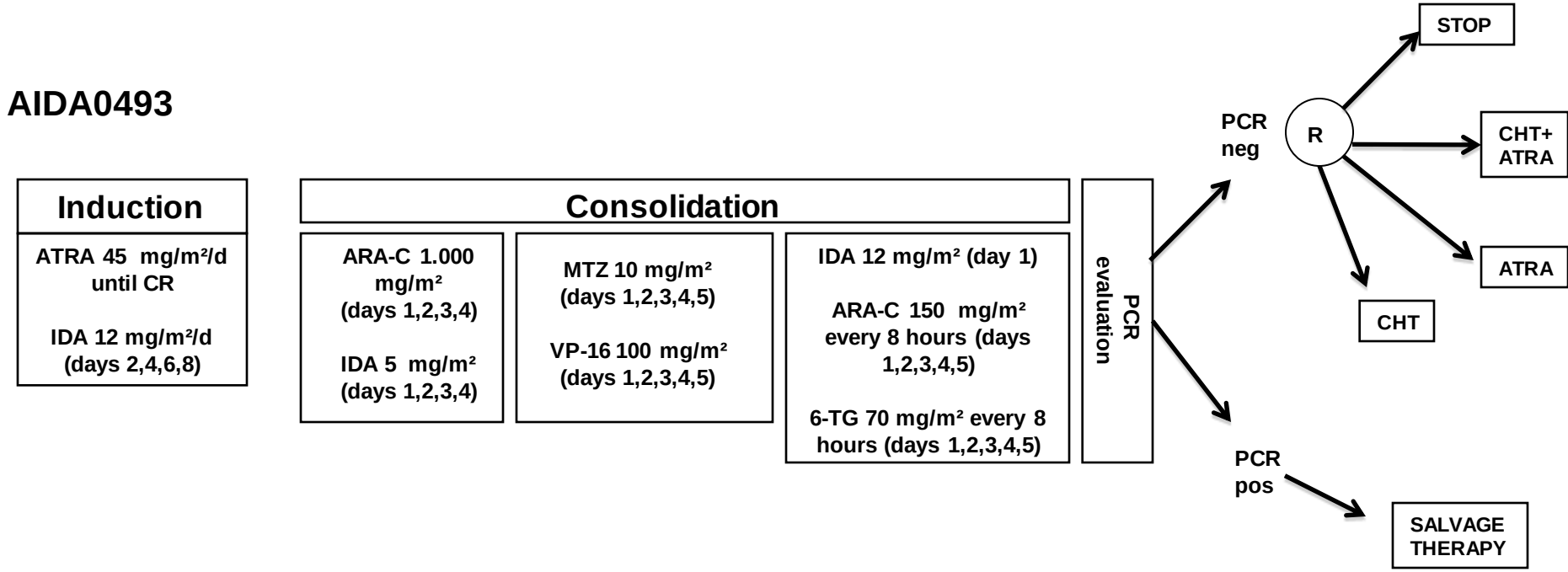
Patients with APL may be stratified into 3 risk categories:

1. Low risk WBC count < 10,000/µL and a platelet count > 40,000/µL;

2. intermediate risk is a WBC count < 10,000/µL and a platelet count < 40,000/µL;

3. high risk is a WBC count > 10,000/µL.

Gimema	AIDA	Risk-adapted	NR
Pethema	AIDA	Risk-adapted	NR


AIDA0493
Induction
ATRA 45 mg/m²/d until CR
IDA 12 mg/m²/d (days 2,4,6,8)
Consolidation
ARA-C 1.000 mg/m² (days 1,2,3,4)
IDA 5 mg/m² (days 1,2,3,4)
MTZ 10 mg/m² (days 1,2,3,4,5)
VP-16 100 mg/m² (days 1,2,3,4,5)
IDA 12 mg/m² (day 1)
ARA-C 150 mg/m² every 8 hours (days 1,2,3,4,5)
6-TG 70 mg/m² every 8 hours (days 1,2,3,4,5)
PCR evaluation
PCR neg
R
STOP
CHT+ ATRA
ATRA
CHT
PCR pos
SALVAGE THERAPY

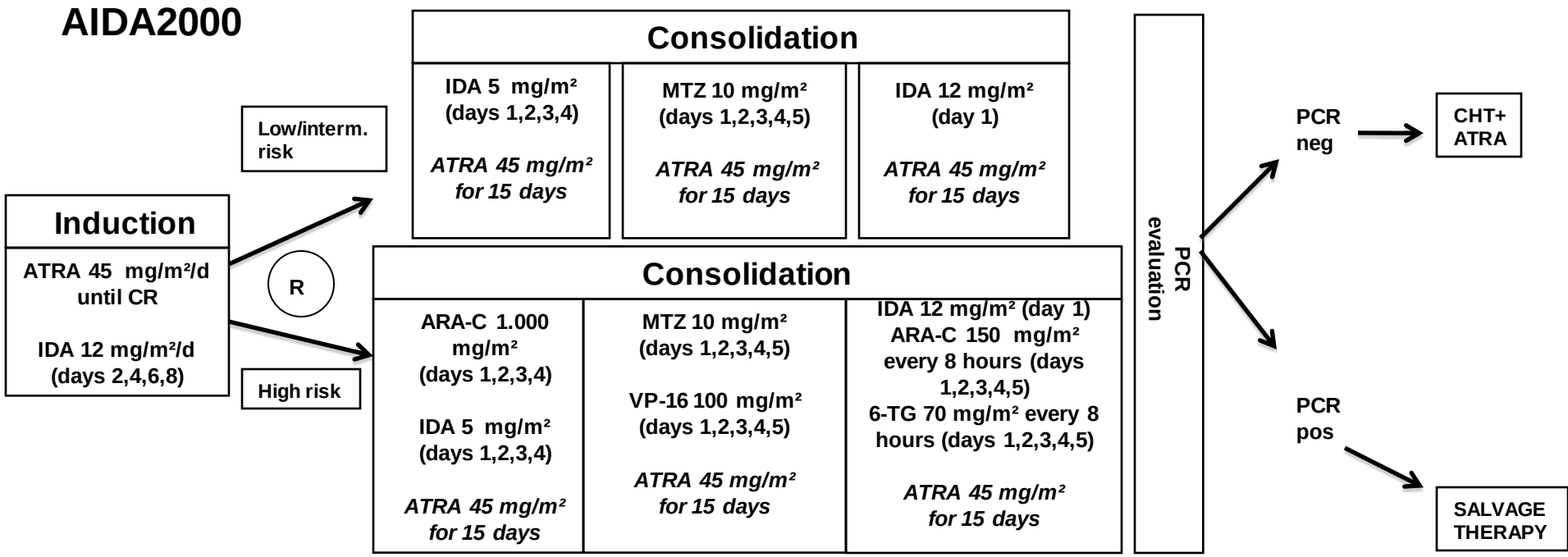
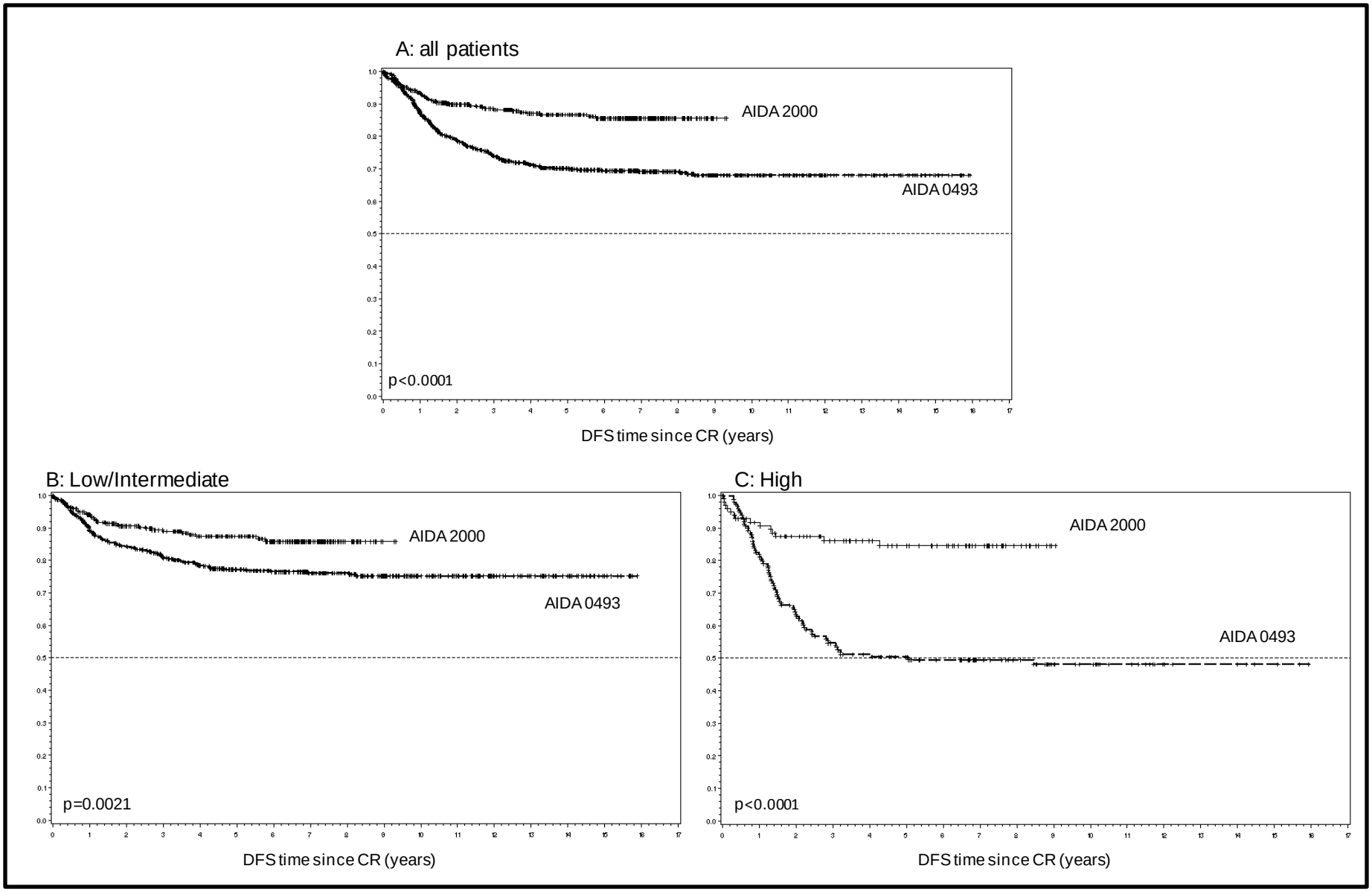

AIDA2000
Induction
ATRA 45 mg/m²/d until CR
IDA 12 mg/m²/d (days 2,4,6,8)
R
Low/interm. risk
High risk
Consolidation
IDA 5 mg/m² (days 1,2,3,4)
ATRA 45 mg/m² for 15 days
MTZ 10 mg/m² (days 1,2,3,4,5)
ATRA 45 mg/m² for 15 days
IDA 12 mg/m² (day 1)
ATRA 45 mg/m² for 15 days
Consolidation
ARA-C 1.000 mg/m² (days 1,2,3,4)
IDA 5 mg/m² (days 1,2,3,4)
ATRA 45 mg/m² for 15 days
MTZ 10 mg/m² (days 1,2,3,4,5)
VP-16 100 mg/m² (days 1,2,3,4,5)
ATRA 45 mg/m² for 15 days
IDA 12 mg/m² (day 1)
ARA-C 150 mg/m² every 8 hours (days 1,2,3,4,5)
6-TG 70 mg/m² every 8 hours (days 1,2,3,4,5)
ATRA 45 mg/m² for 15 days
PCR evaluation
PCR neg
CHT+ ATRA
PCR pos
SALVAGE THERAPY

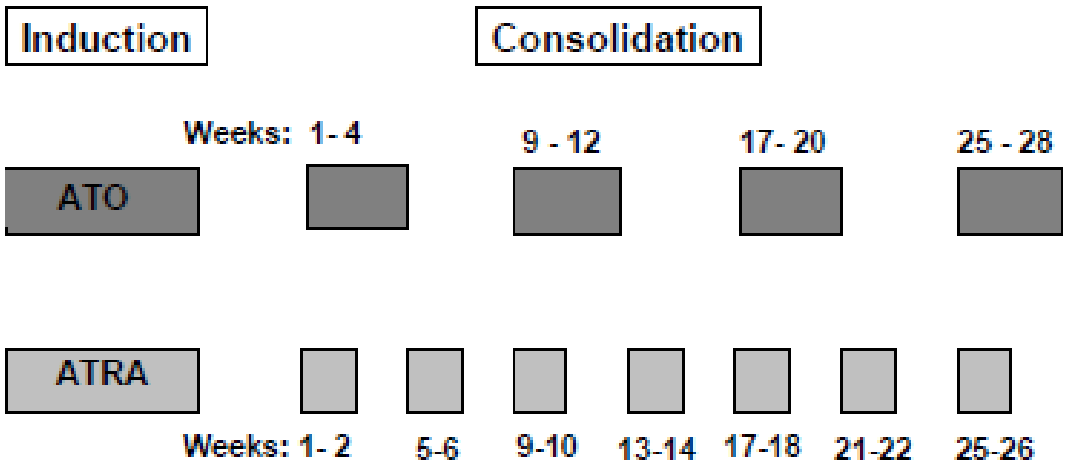
FIGURE 3. Disease-free survival according to protocol



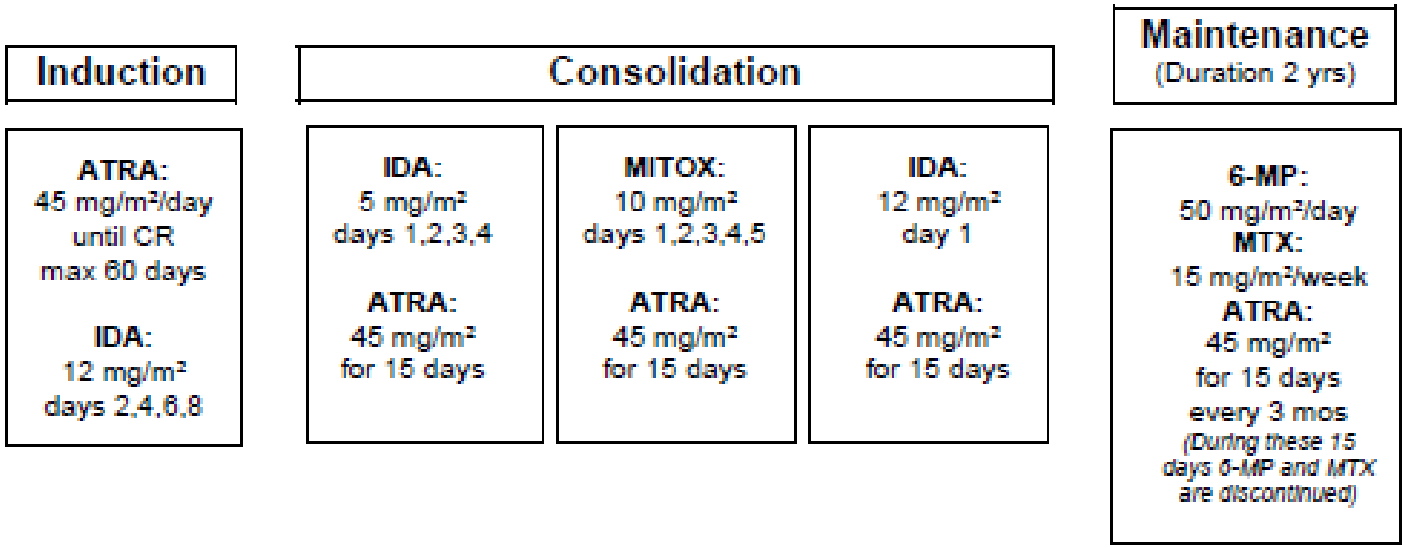
GIMEMA
Gruppo Italiano Malattie EMatologiche dell'Adulto

Schema del trattamento

ARM A



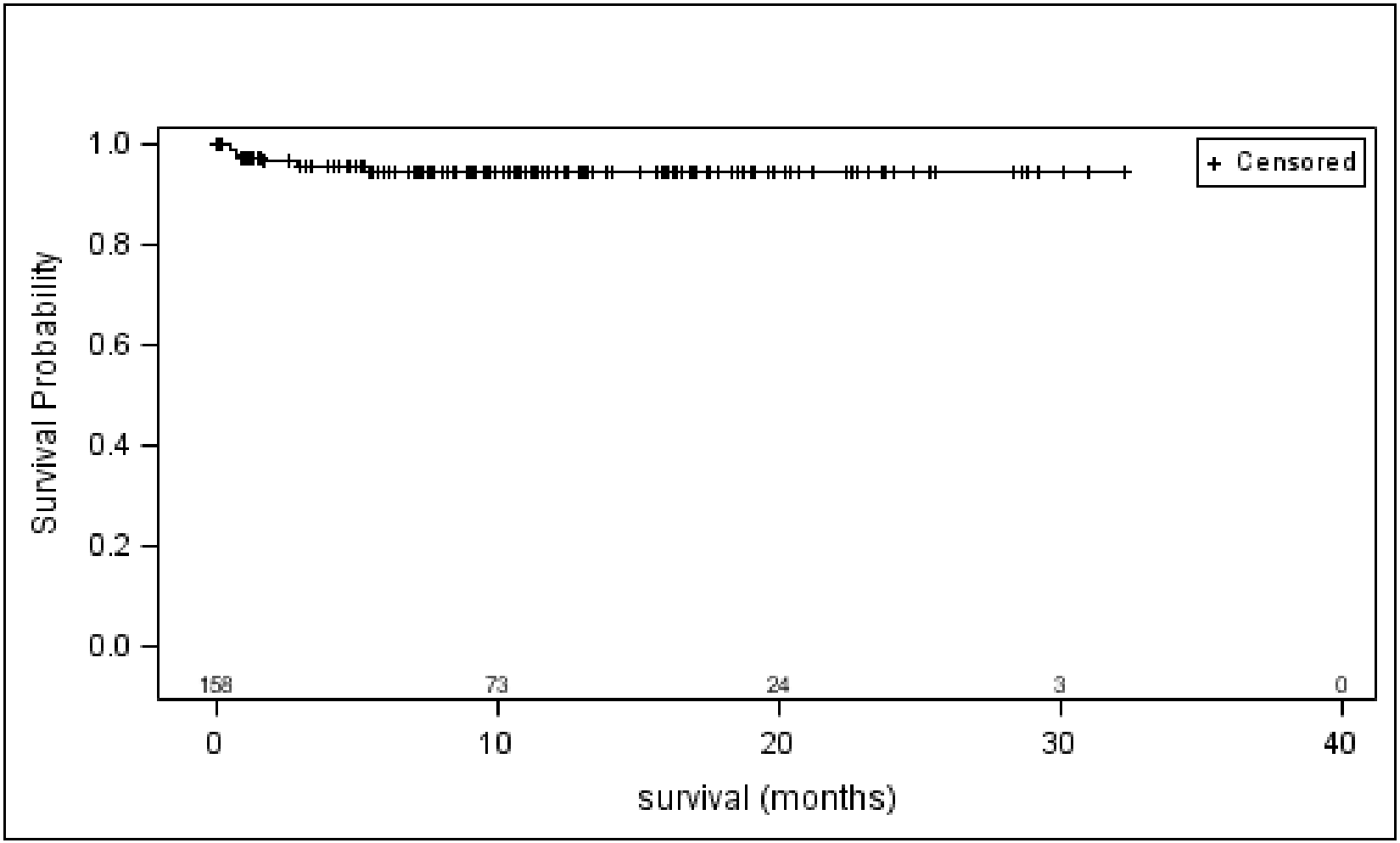
ARM B



Pazienti arruolati per random

ARM	Frequency
A	82 (50.6%)
B	80 (49.4%)

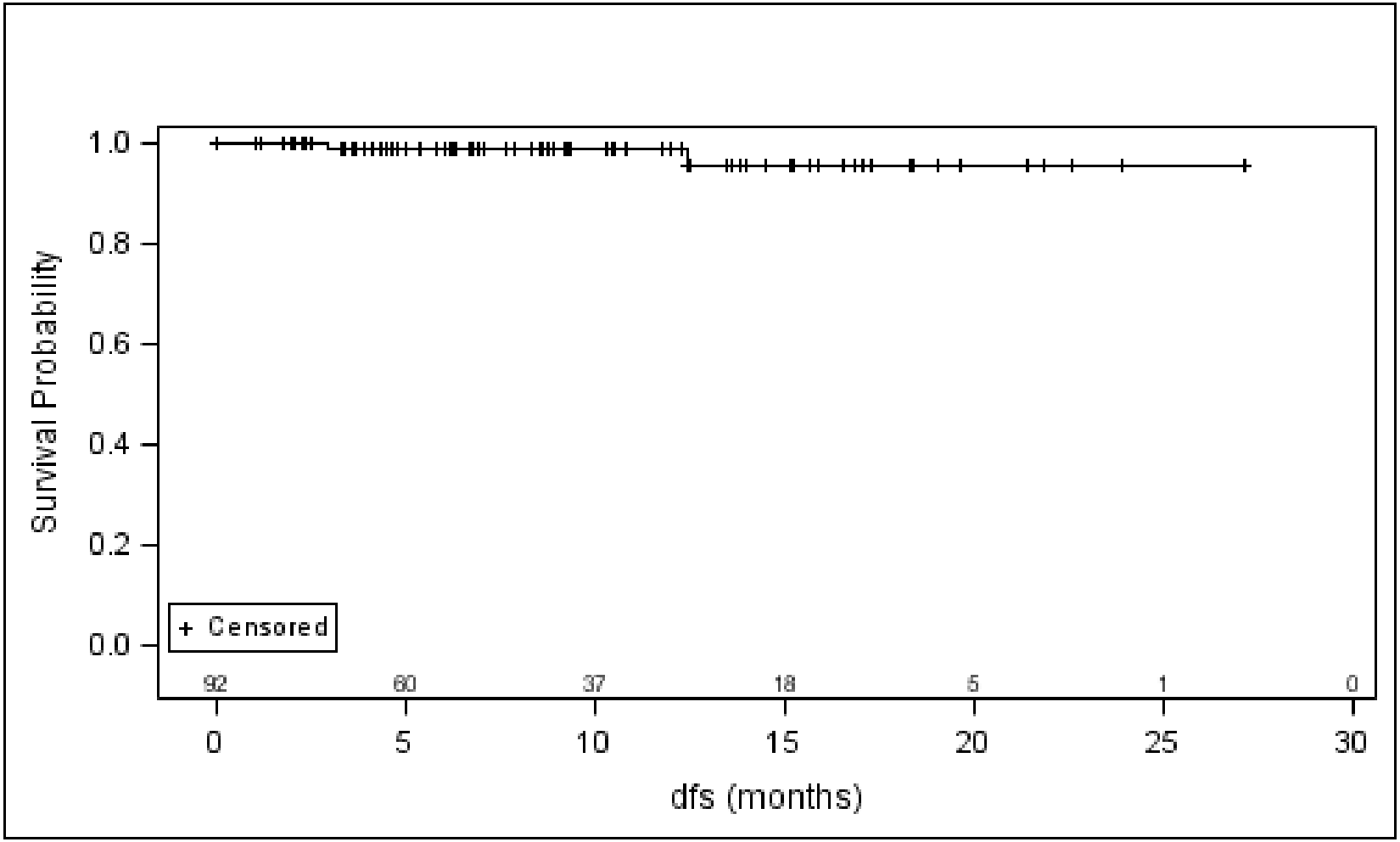
Overall Survival



*L' analisi è stata condotta su **158** pazienti (dei 162 arruolati, 2 sono risultati non eleggibili e 2 sono usciti per violazione).

GIMEMA
Gruppo Italiano Malattie EMatologiche dell'Adulto

Disease Free Survival



4 models leukemias

PML-RARa
NPM+

(CD33+)

CURED

CBFs +

(MDR low)

CURED

4 models leukemias

PML-RARa
NPM+

(CD33+)

CURED

CBFs +

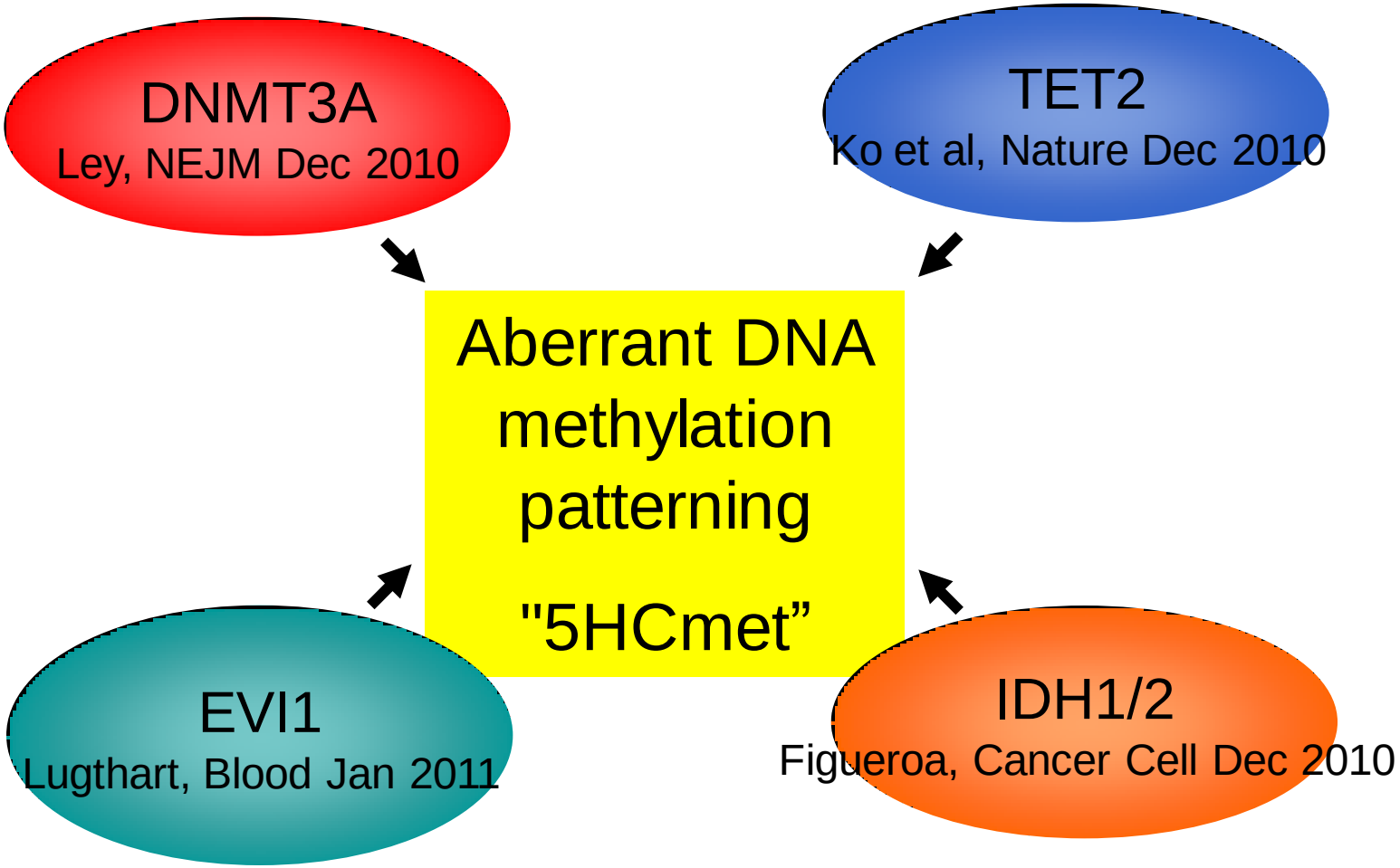
(MDR low)

Mostly CURED

RTK+
(FLT3+)

CURED

AML: frequent alterations at key epigenetic regulators



4 models leukemias

PML-RARa
NPM+

(CD33+)

CURED

CBFs +

(MDR low)

CURED

RTK+
(FLT3+)

CURED ?

5HCmet+

(TET2, DMT3+,
IDH2+, Evi1+)

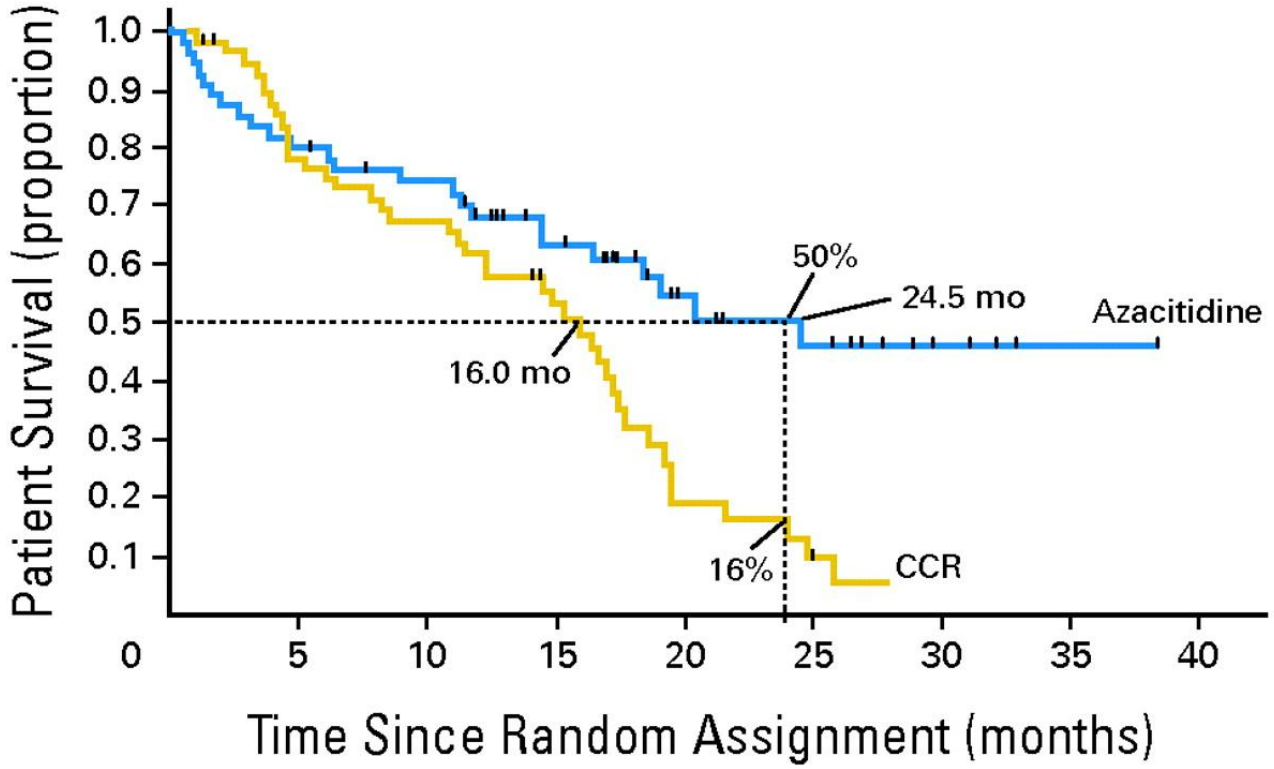
Resistant to CT
Potentially sensitive to 5AZA

Hypomethylating agents in AML

	N	CR %	OR %
Azacytidine (CALGB)	103	9-12	35-48
Decitabine (phase 3) (20 mg/m^2 x5)	242		18

Silverman et al, JCO 2006; Lubbert et al, ASH 2007; Cashen et al, JCO 2010; Blum et al, PNAS 2010; Thomas et al, ASCO 2011

AZA prolongs OS in WHO AML



No. of patients at risk

Azacitidine	55	43	38	26	15	10	4	1	0
CCR	58	43	36	22	6	3	0	0	0

Fenaux et al, JCO 2010

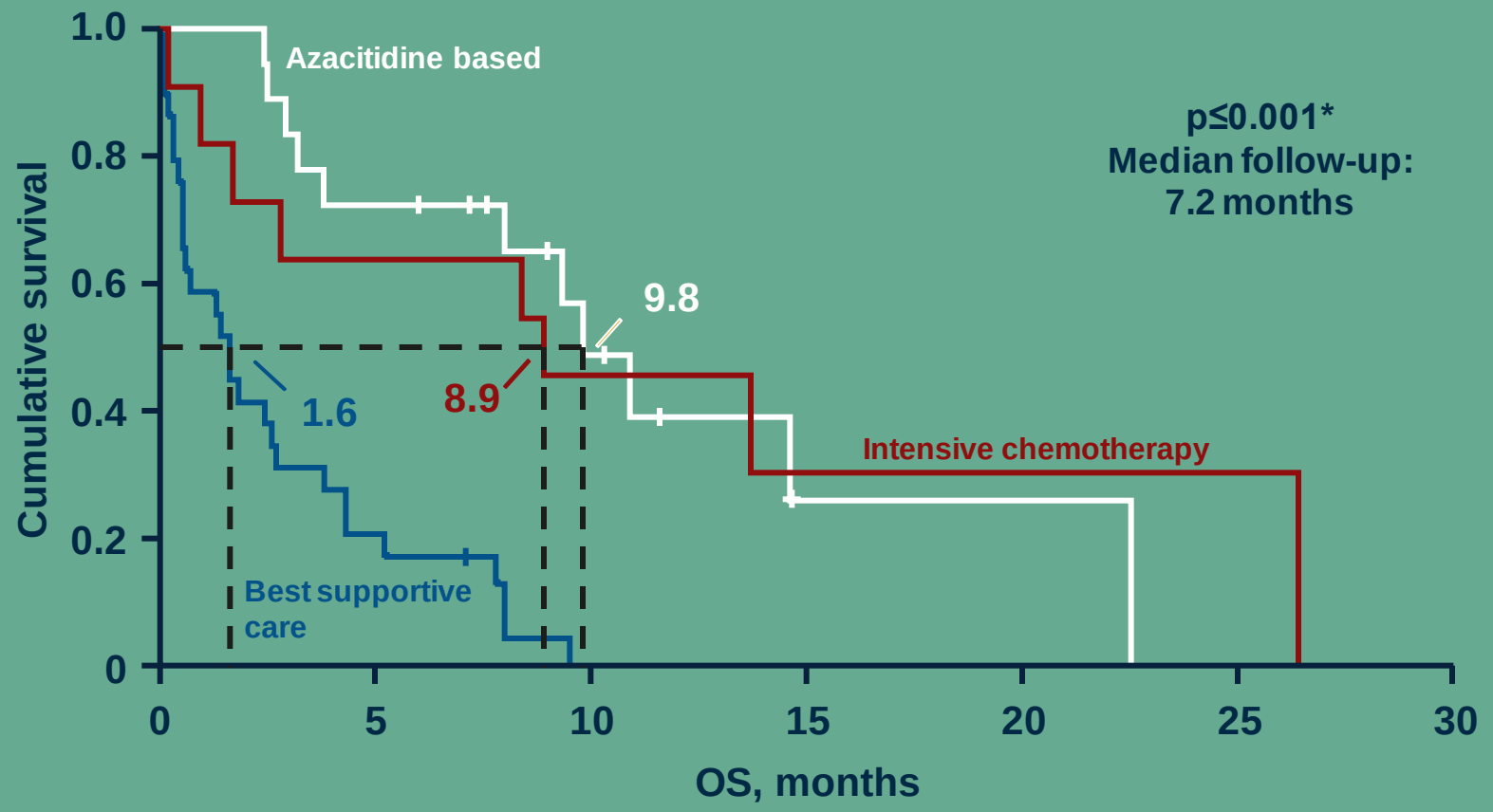
Come possiamo inserire la Vidaza in un algoritmo terapeutico, ora, delle AML?

INDICAZIONI VIDAZA*SC 1FL 100 MG 25MG/ML

Pazienti adulti non eleggibili al trapianto di cellule staminali emopoietiche con:

- MDS a rischio intermedio 2 e alto secondo IPSS,
- CMMoL con il 10-29% di blasti midollari senza disordine mieloproliferativo,
- **LMA con 20-30% di blasti e displasia multilineare, secondo WHO**

Azacitidine versus IC or BSC in elderly patients with AML – survival



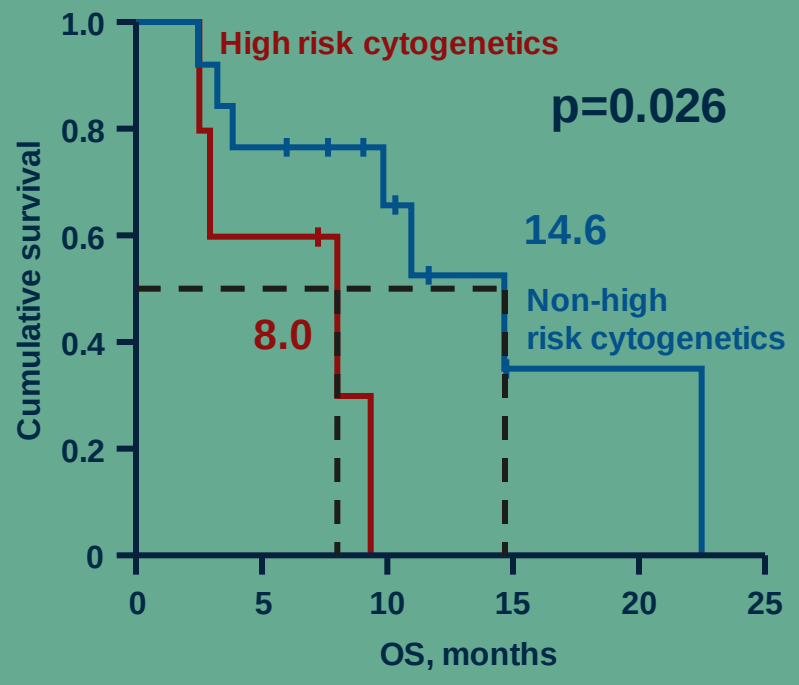
OS was similar in patients treated with azacitidine and IC, although patients who received IC were younger overall

*AZA vs BSC

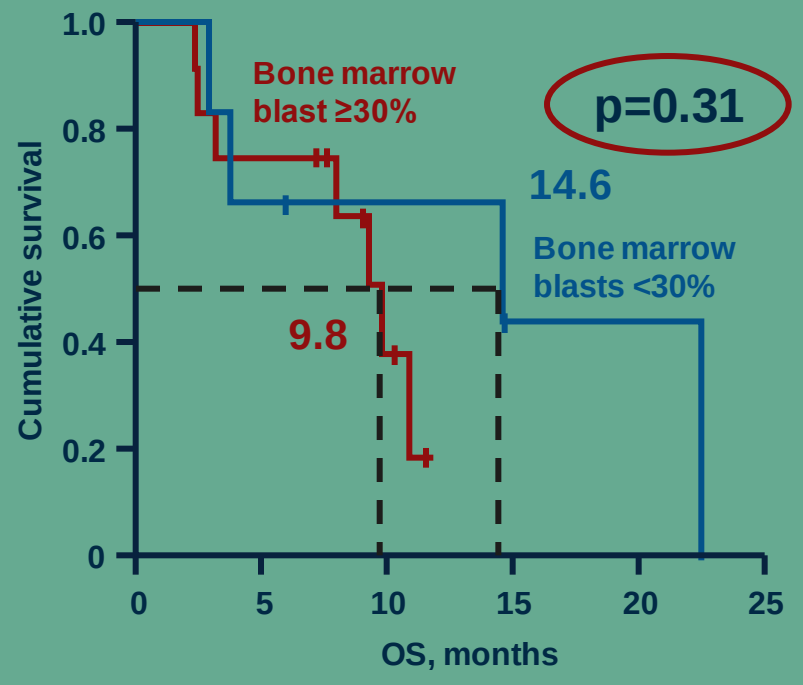
Lao Z, et al. Poster presentation at EHA 2012. Abstract 0657

Azacitidine versus IC or BSC in elderly patients with AML – survival of azacitidine-treated patients

OS of AZA-treated pts by cytogenetic risk



OS of AZA-treated pts by BM blasts



OS differed significantly according to cytogenetic risk but not between patients with <30% and ≥30% blasts

Lao Z, et al. Poster presentation at EHA 2012. Abstract 0657

Azacitidine versus IC or BSC in elderly patients with AML – hospitalisations and infections

	AZA	IC	p-value
Median inpatient days, n	46	80	0.043
Infective episodes*, n	1.5	3.0	0.015
Median ICU days, n	0	2	0.005

*defined as febrile illness that required inpatient stay or intravenous antibiotics

Azacitidine was associated with significantly fewer hospitalisations and infections compared with IC

Lao Z, et al. Poster presentation at EHA 2012. Abstract 0657

Baseline ferritin levels as a prognostic indicator in patients with MDS/AML treated with azacitidine – ORR

ORR*, %	Serum ferritin level			p value
	<500ng/ml (n=49)	500–1,000ng/ml (n=46)	>1,000ng/ml (n=95)	
Overall	71.4	82.6	24.2	<0.0001
At 4 months	75.3	87.0	22.1	<0.0001
At 6 months	89.8	100.0	48.4	<0.0001

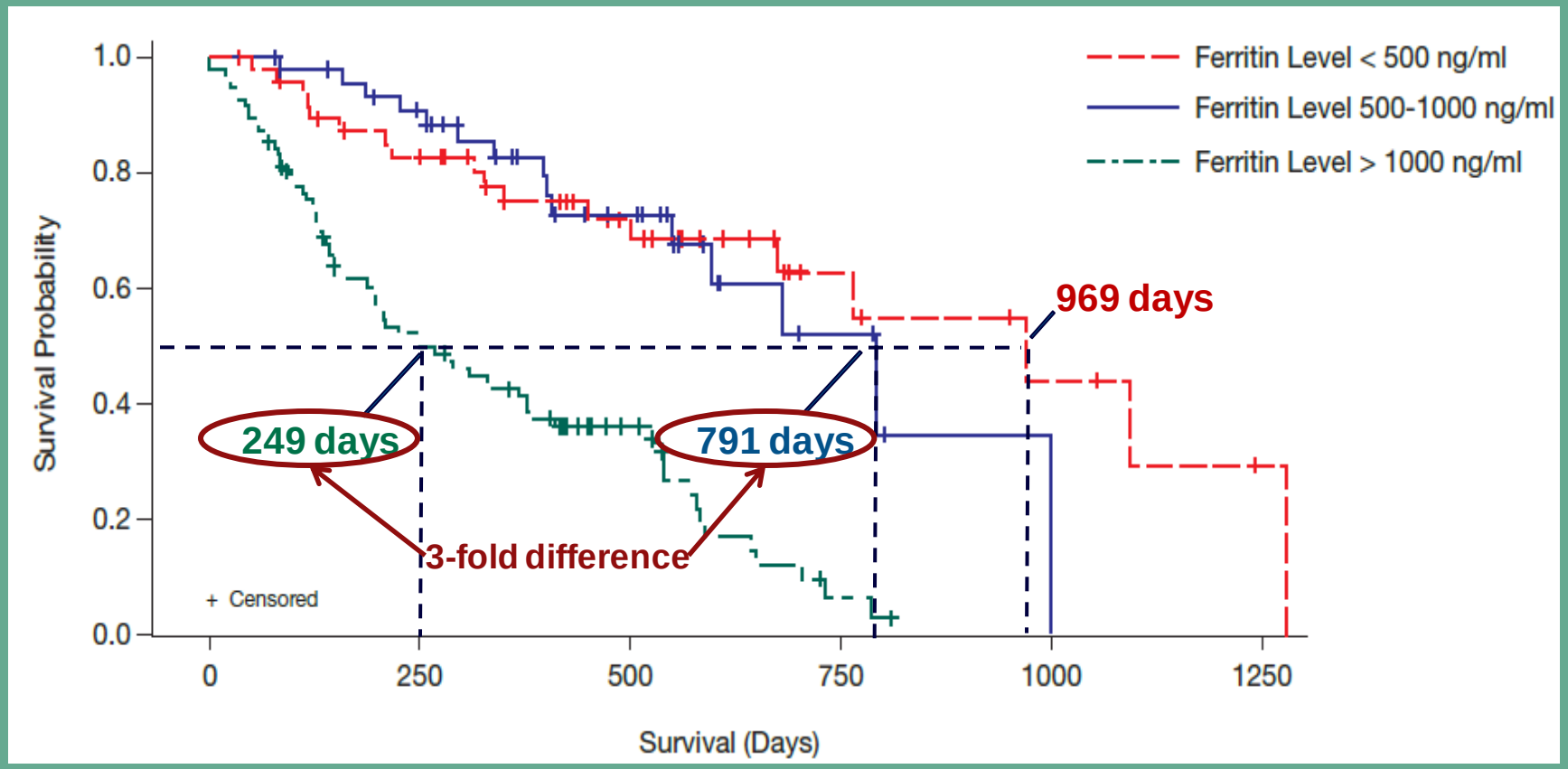
*defined as mCR + CR + PR + HI

Baseline serum ferritin levels were significantly correlated with response to azacitidine

mCR = marrow complete response

Garcia R, et al. Poster presentation at EHA 2012. Abstract 0882

Baseline ferritin levels as a prognostic indicator in patients with MDS/AML treated with azacitidine – OS

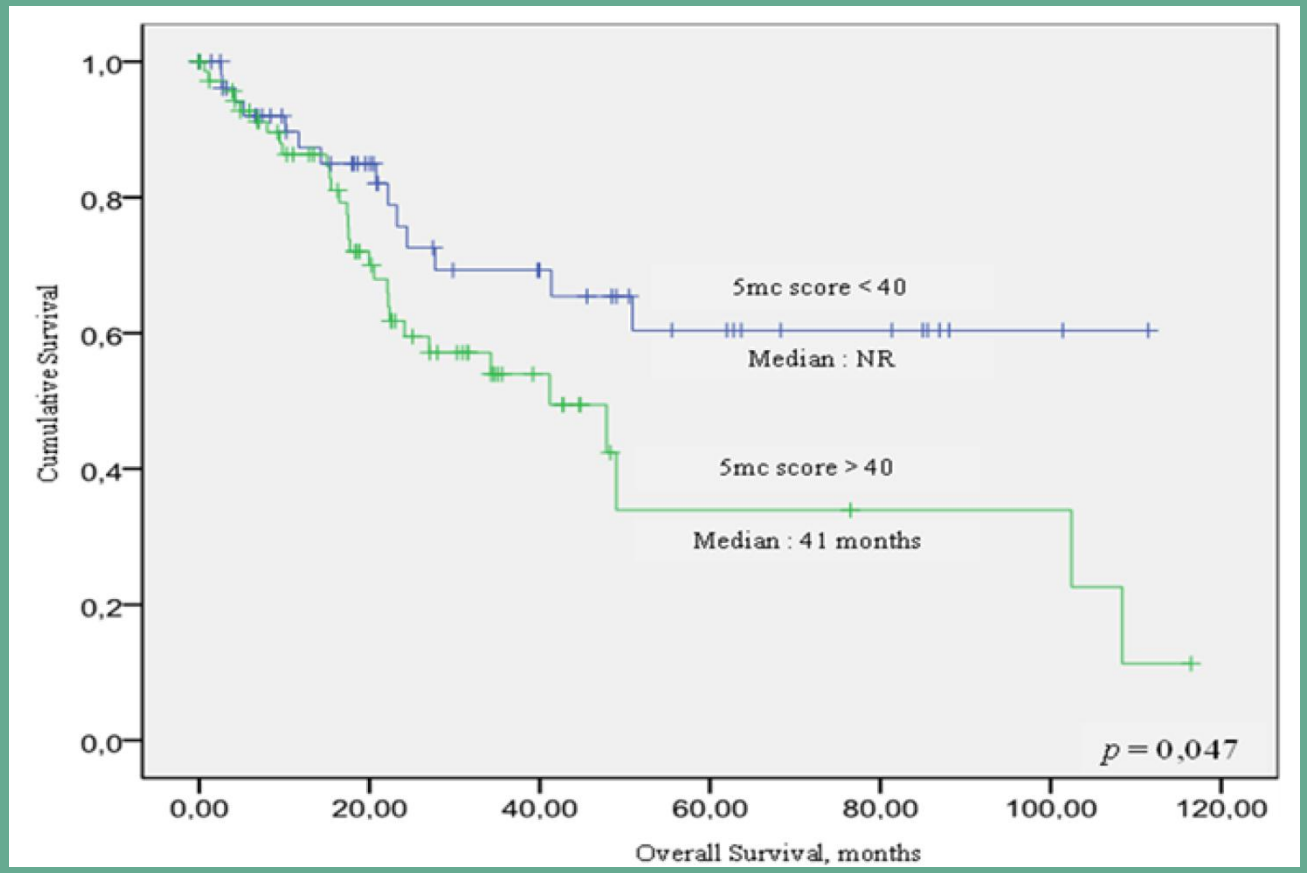


There was a strong correlation between baseline ferritin levels and OS (p<0.0001); authors speculate that avoiding high ferritin levels can improve OS in MDS patients treated with AZA

Garcia R, et al. Poster presentation at EHA 2012. Abstract 0882

Global DNA methylation predicts OS and response to azacitidine in high-risk MDS – OS

OS by H-score* (n=128)

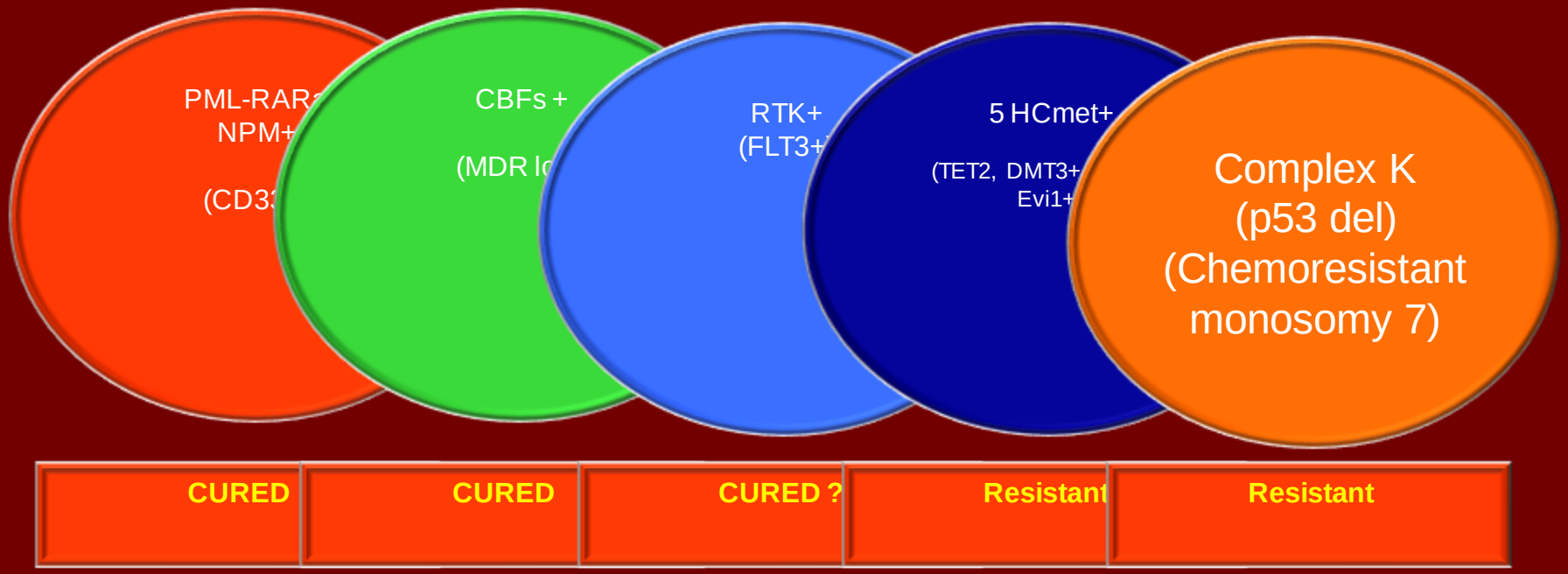


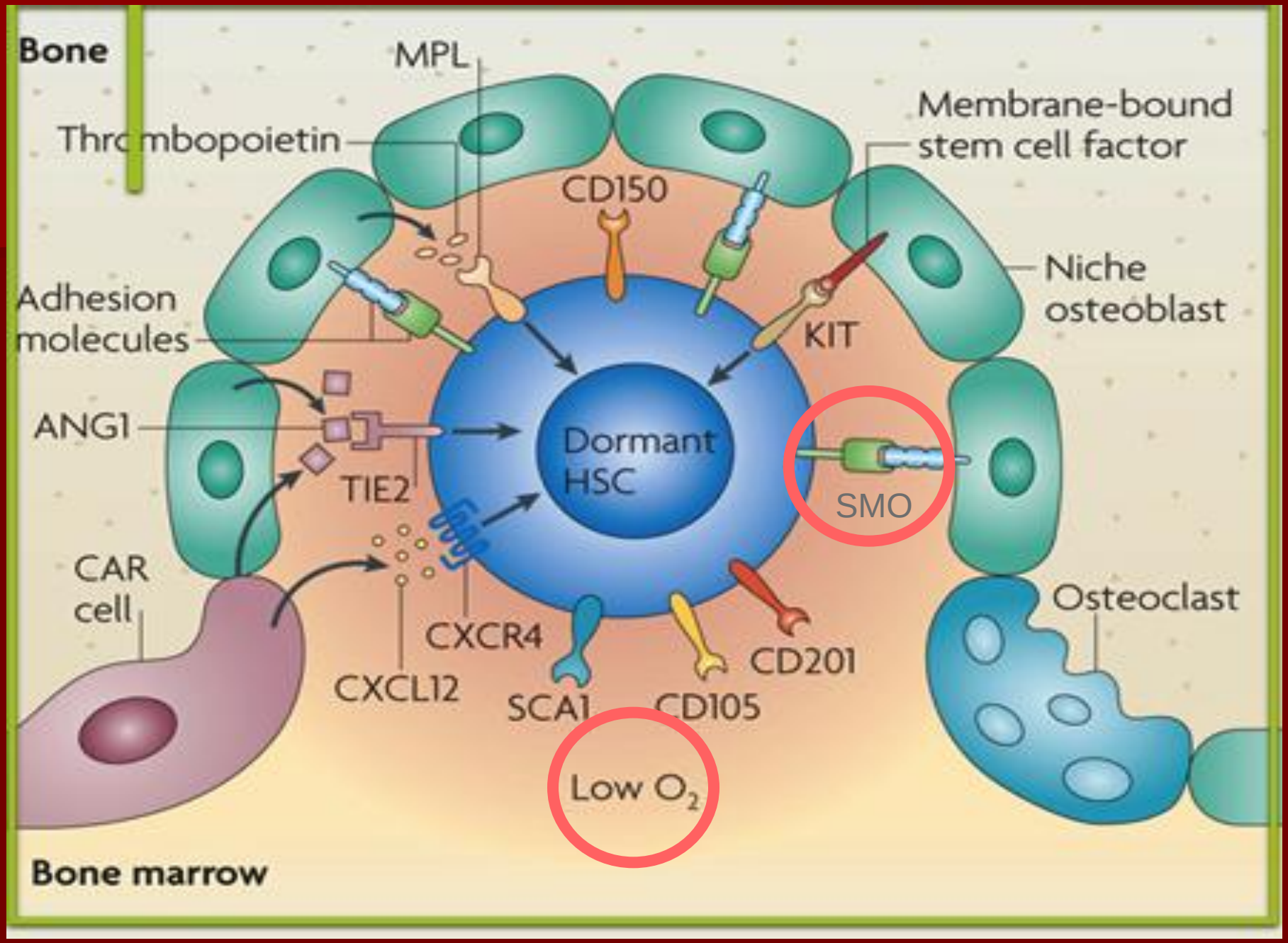
An H-score of <40 was associated with worse OS than an H-score of ≥40

*percentage of positive cells x intensity score

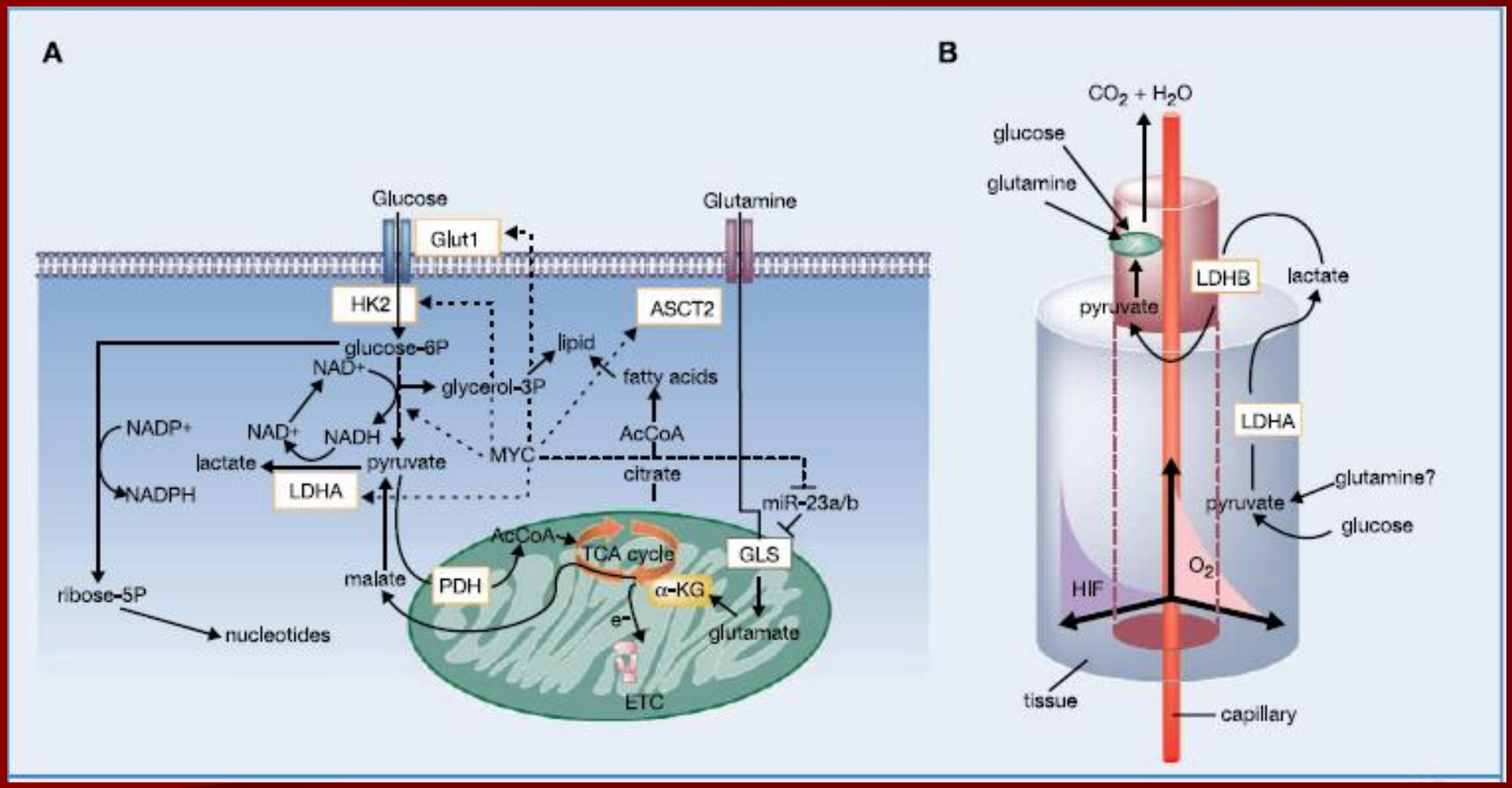
Poloni A, et al. Poster presentation at EHA 2012. Abstract 0332

5 models leukemias ?




Bone
MPL
Thrombopoietin
Membrane-bound
stem cell factor
CD150
Niche
osteoblast
Adhesion
molecules
KIT
ANG1
Dormant
HSC
TIE2
SMO
CAR
cell
Osteoclast
CXCR4
CD201
CXCL12
SCA1
CD105
Low O_2
Bone marrow

Glucose and Glutamine intake are increased in LSC



Cancer Research 2011

The ones to watch….

- CPX-351
  - CR/CRi 67%, ED 3%
- Laromustine
  - CR/CRp 32%, ED 14%
- **HD-Lenalidomide (50 x 28d)**
  - **CR/CRi 30%, ED 24%**
- Sapacitabine
  - CR/CRp 20%, ED 13%

Lancet et al, ASH 2010; Schiller et al, JCO 2010; Fehninger et al, Blood 2010; Kantarjian et al, ASH 2009

Lenalidomide plus LDAC in elderly patients with AML: an ongoing phase II, single-arm study – patients

Patient characteristics (n=33)

- Newly diagnosed non-del(5q) AML
- Median age, years (range): 77 (71–85)
- Median WBC, x10^9/L (range): 4.6 (0.8–46.8)
- Median Hb, g/dL (range): 8.9 (5.6–14.6)
- Median platelet count, x10^9/L (range): 30 (3–339)
- Cytogenetic risk, n
  - normal karyotype: 12
  - intermediate/ adverse: 19
  - not evaluable: 2
- AML, n
  - de novo: 13
  - secondary: 20

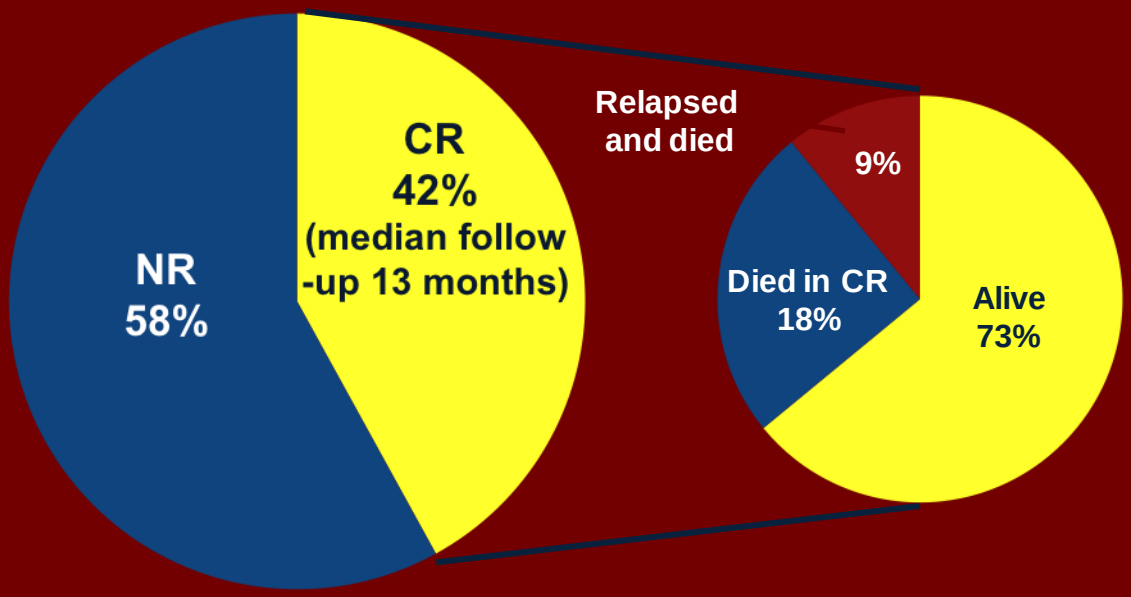
Treatment schedule

- Lenalidomide PO 10mg QD (days 1–21 of each 6-week cycle)
- Cytarabine SC 20mg/m^2 BID (days 1–15 of each 6-week cycle)

Visani G, et al. Poster presentation at EHA 2012. Abstract 0057

Lenalidomide plus LDAC in elderly patients with AML: an ongoing phase II, single-arm study – outcomes

Response (n=26)



Survival

Superior survival associated with baseline:

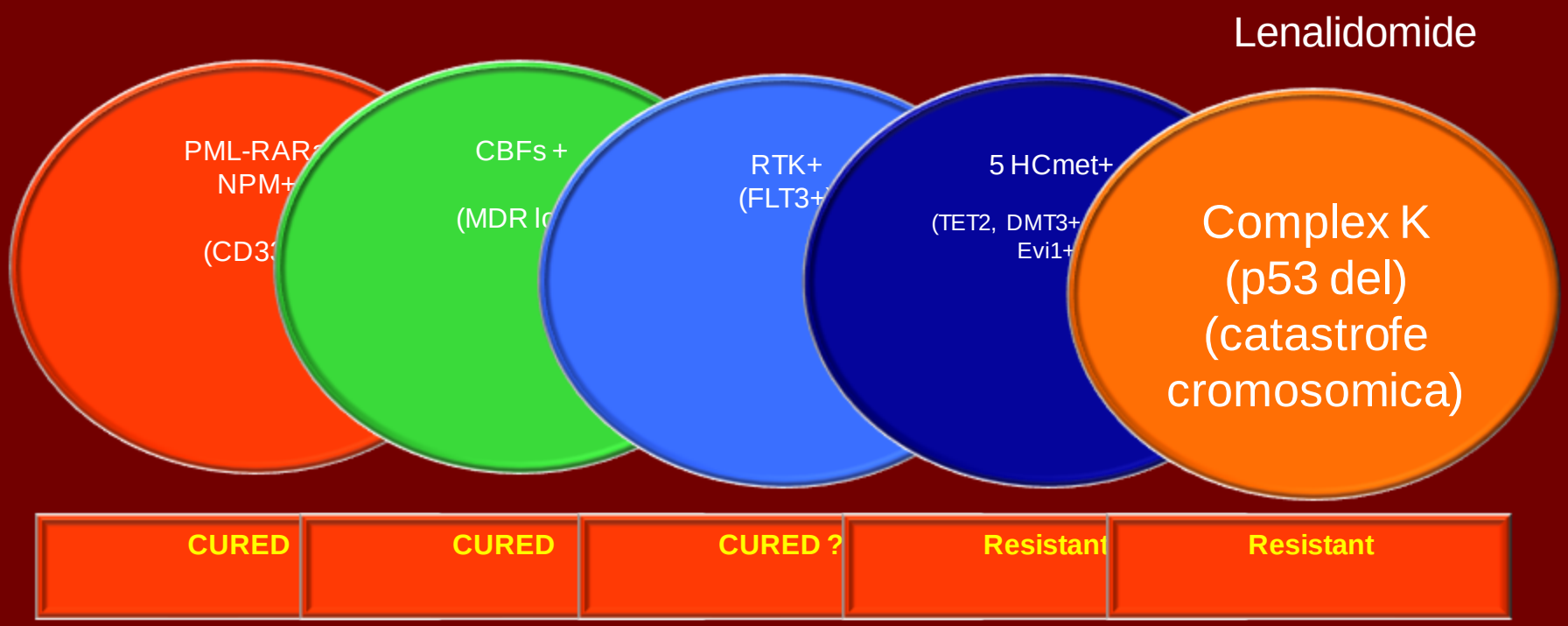
- **WBC <4.0 x10^9/L (p=0.04)**
- **Unfavourable cytogenetics (p=0.05)**

Low-dose lenalidomide + low-dose cytarabine show promising clinical activity in this subgroup of elderly AML patients with extremely poor prognosis

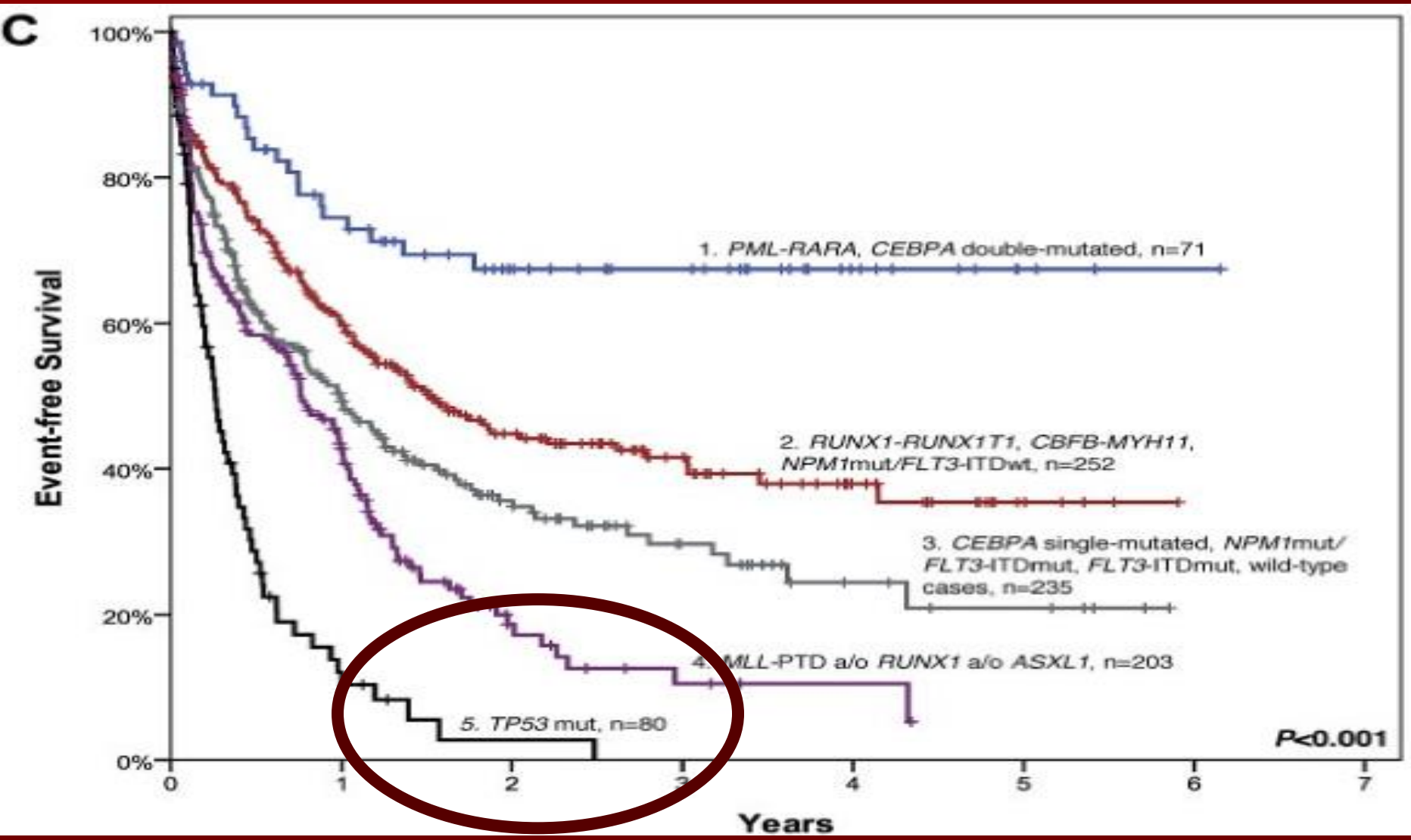
NR = no response

Visani G, et al. Poster presentation at EHA 2012. Abstract 0057

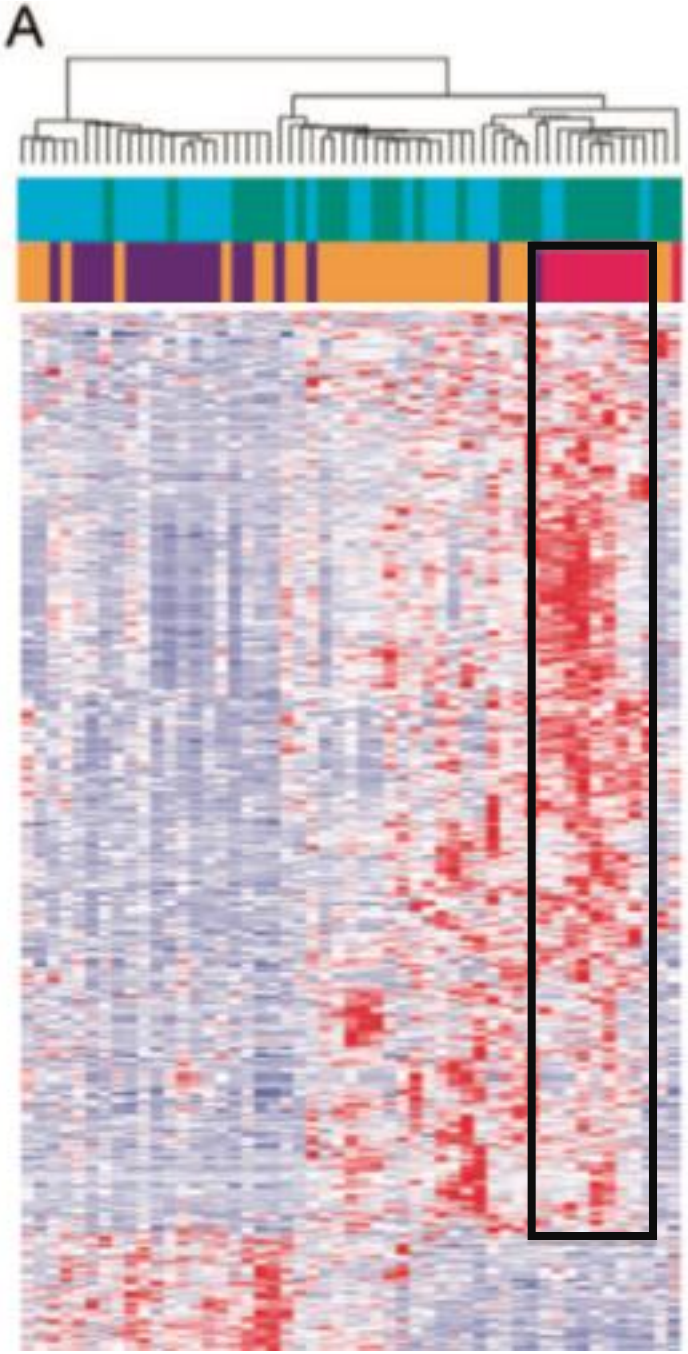
5 models leukemias ?



A novel hierarchical prognostic model of AML solely based on molecular mutations

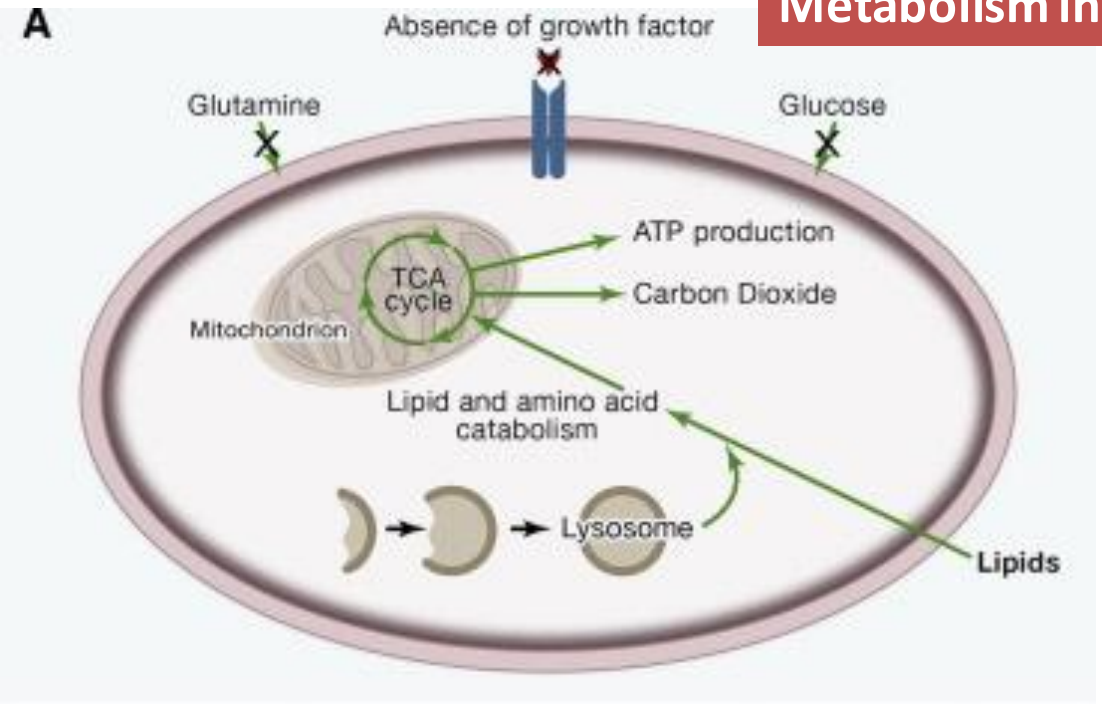


Monosomy 7



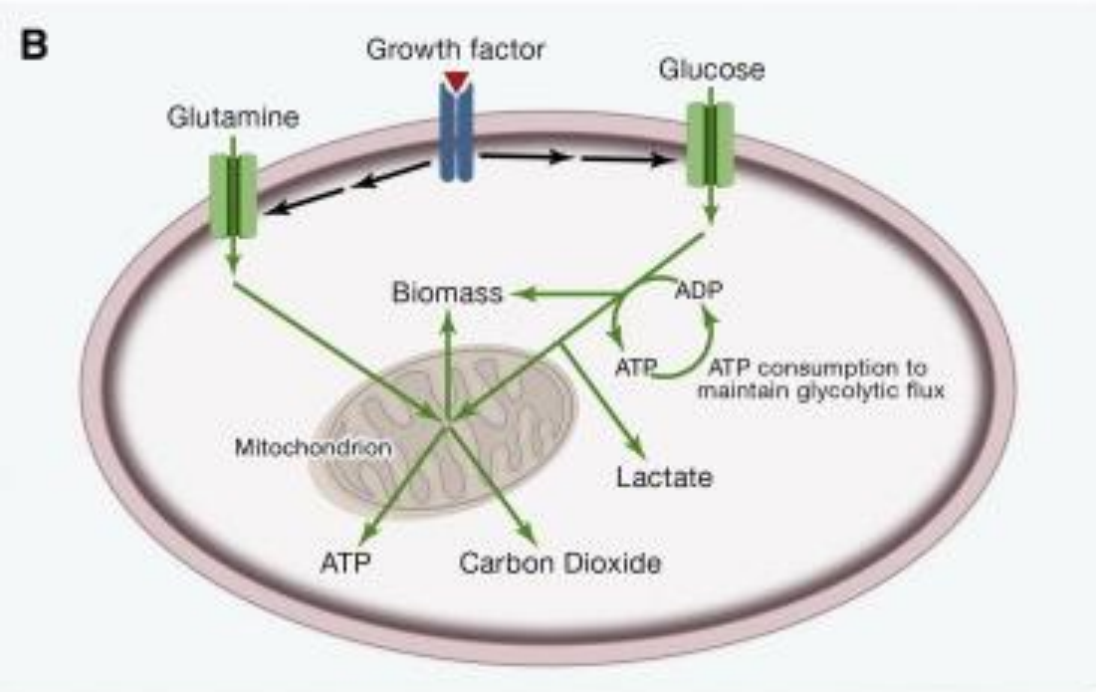
Iacobucci I. et Al. PlosOne 2012

Metabolism in Quiescent versus Proliferating Cells



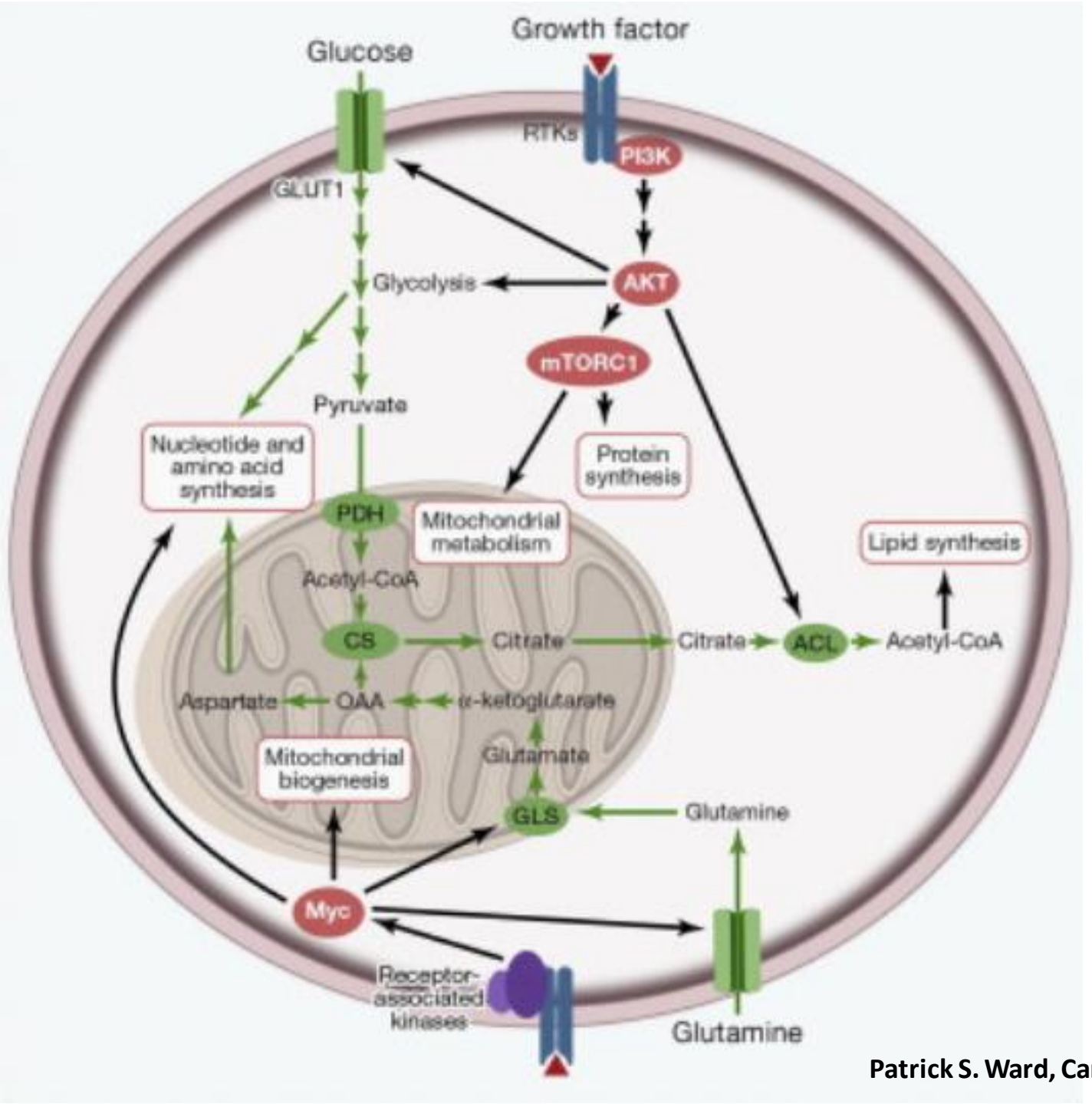
Quiescent Cells

Both Use Mitochondria

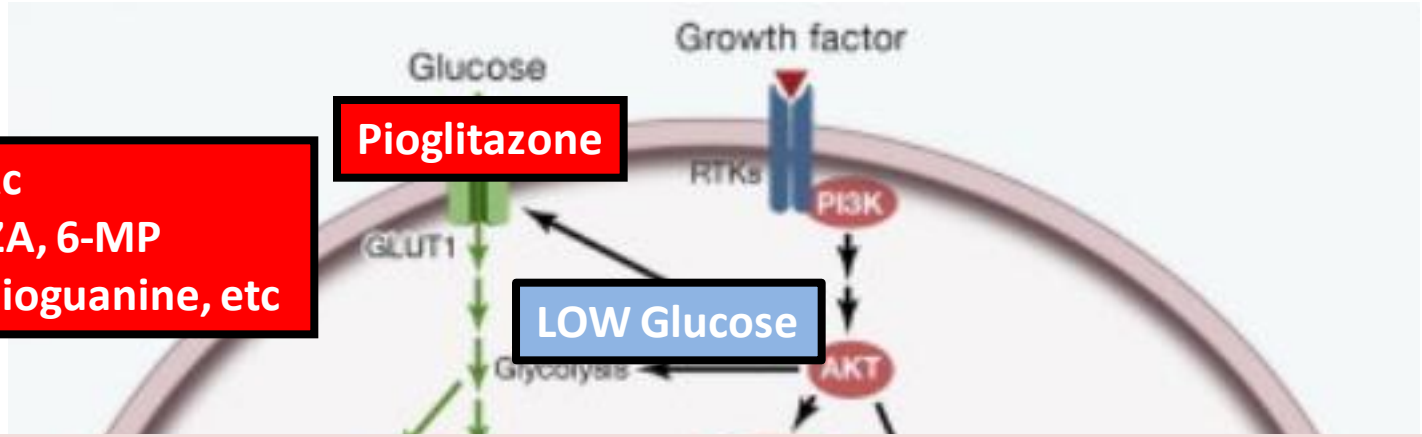


Proliferating Cells

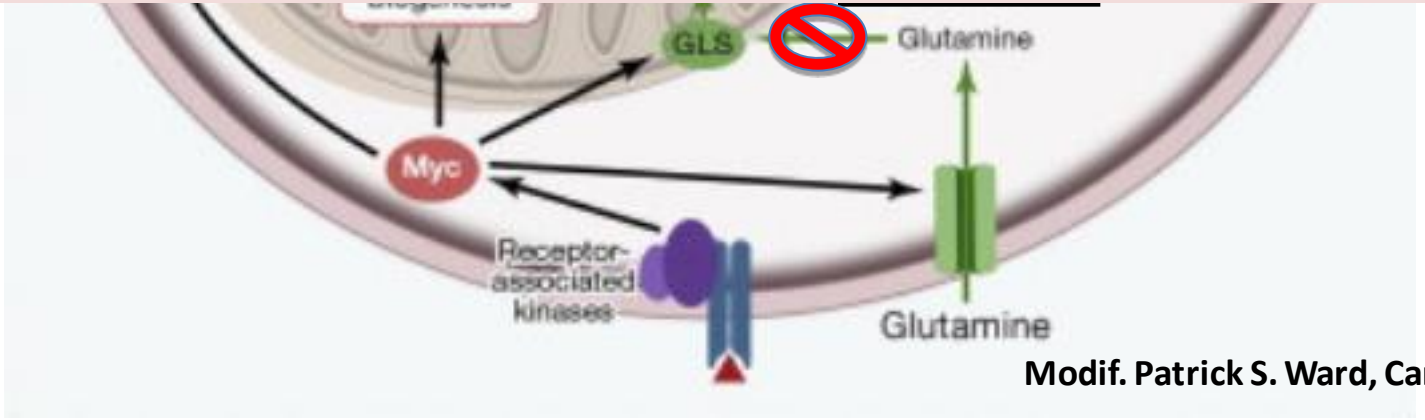
Patrick S. Ward, Cancer Cell 2012



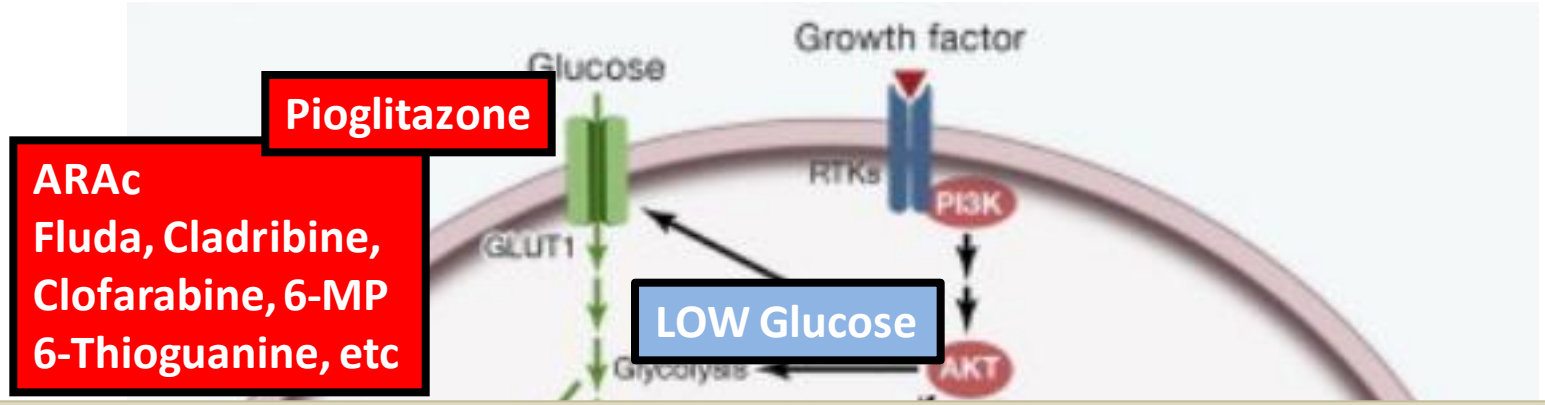
Patrick S. Ward, Cancer Cell 2012



Targeting the metabolic pathways of cancer



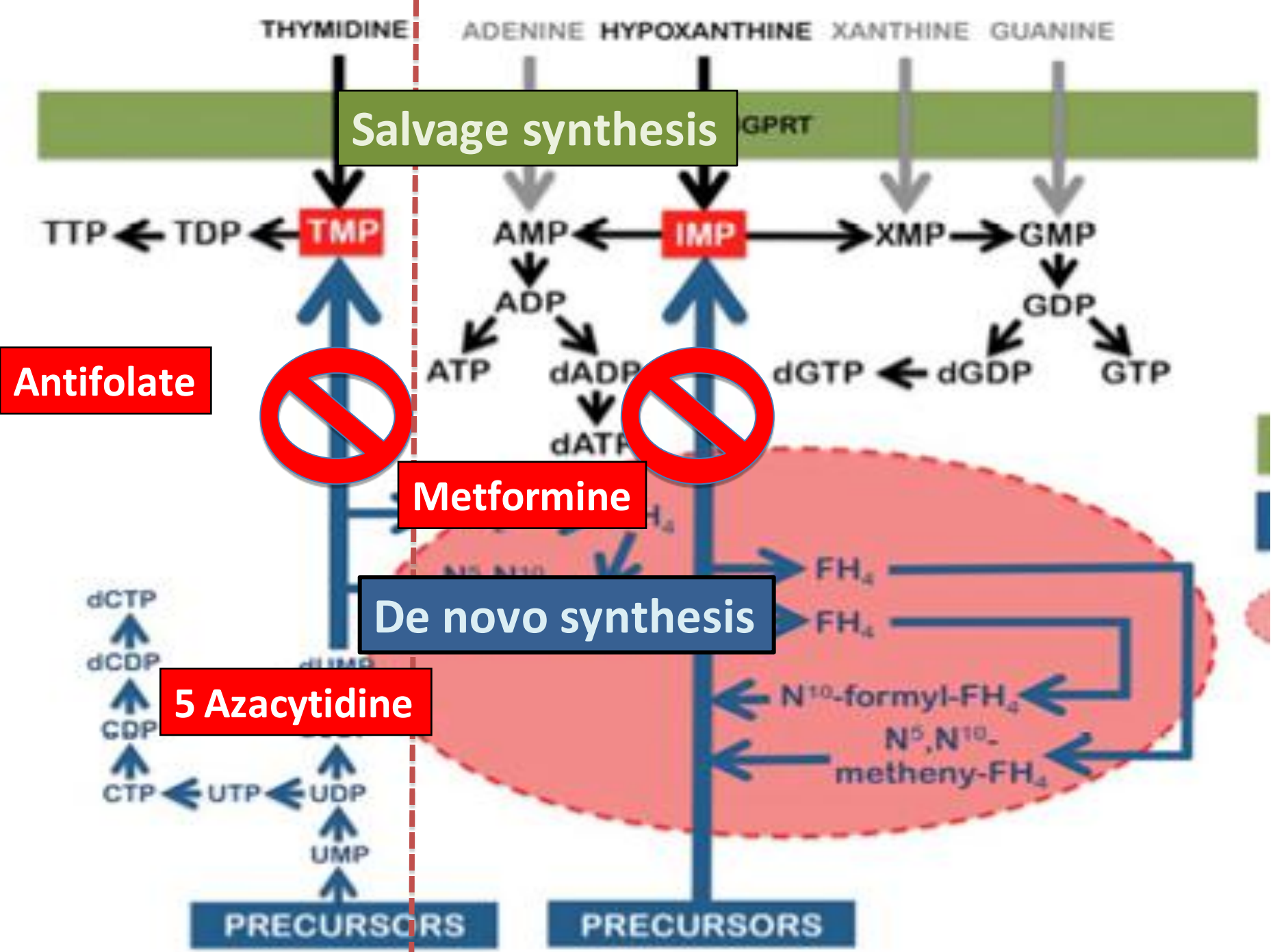
Modif. Patrick S. Ward, Cancer Cell 2012



"Biochemistry Therapy"

Targeting the metabolic pathways of complex K, including monosomy 7 or del 7 AMLs

Modif. From Patrick S. Ward, Cancer Cell 2012



Bruna Corominas-Faja1 AGING, July 2012, Vol. 4, No 7

Conclusions

PML-RARa
NPM+

(CD33+)

CURED

CBFs +

(MDR low)

CURED

RTK+
(FLT3+)

PI3K inhibition role?

5HCmet+
(Complex K)
(p53 del)
(TET2, DMT3+, IDH2+, Evi1+)

5 aza Have PI3K inhibition or p53 reactivation role?

Ringraziamenti

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NEXT GENERATION SEQUENCING for Targeted Personalized Therapy of Leukemia

2013 2015

10 partner internazionali uniscono le loro competenze per dar vita a un progetto di ricerca realmente innovativo e ambizioso: sequenziare il genoma dei malati di leucemia per individuare terapie efficaci e mirate.

SEVENTH FRAMEWORK PROGRAMME