MDS ad alto rischio: un caso clinico

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Novembre 2012

LA DIAGNOSI

- Maschio, 83 anni
- BMI = 24.2

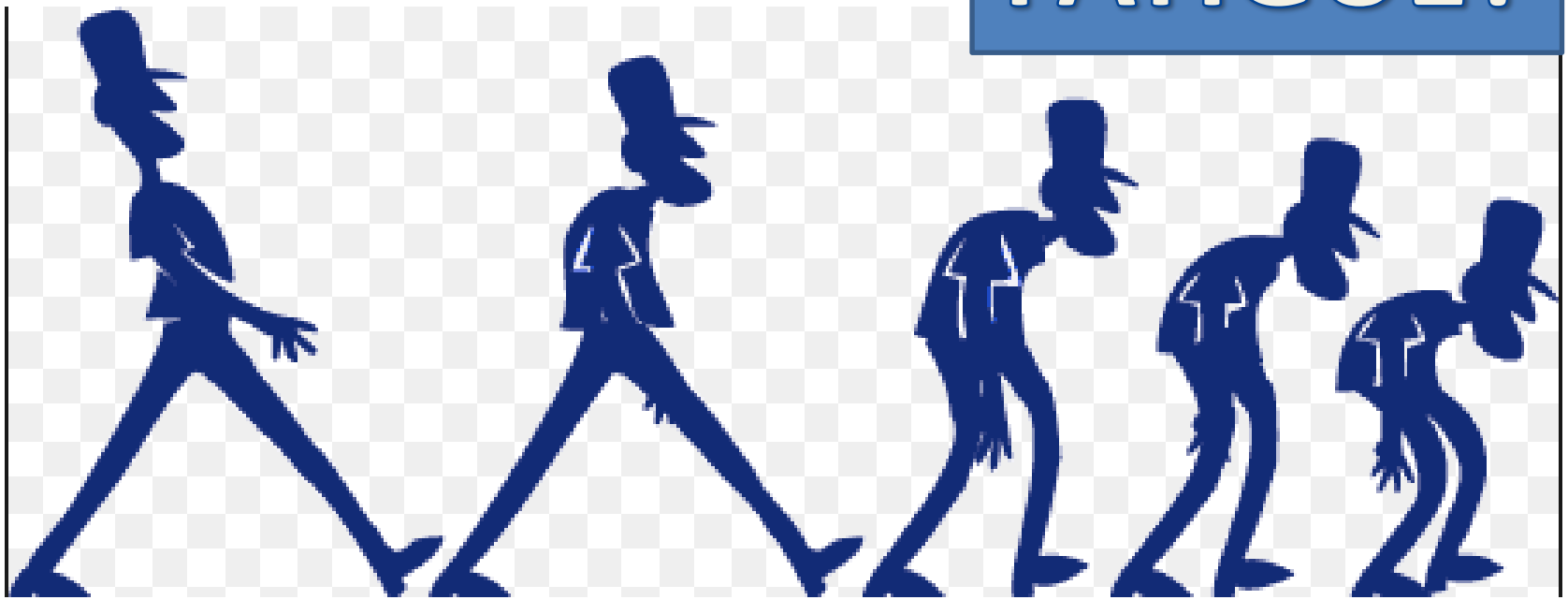
- **Comorbilità:** dislipidemia, fibrillazione atriale (buona FE), aortosclerosi
- **Terapia domiciliare:** ASA, statina, warfarin

Novembre 2012

LA DIAGNOSI

- buon performance status

FATIGUE?

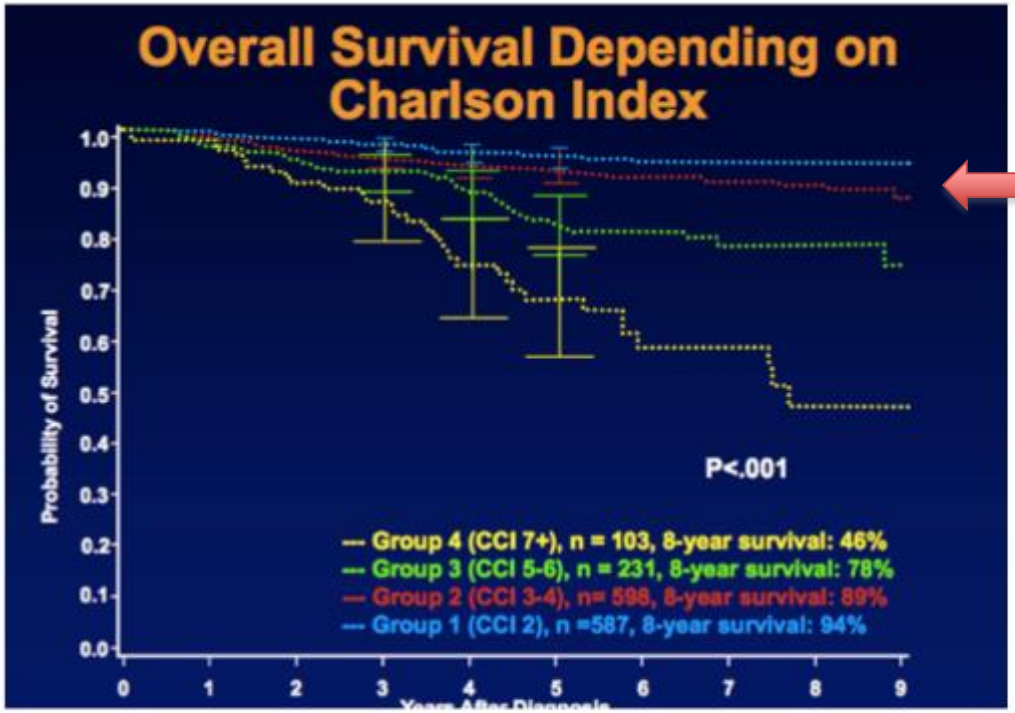


D1 . “pensate a questo anziano come…”

1. GO-GO
2. SLOW-GO
3. NO-GO

L'ANZIANO SECONDO L'EMATOLOGO…

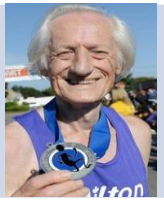
CHARLSON COMORBILITY INDEX = 2



Saussele, ASH 2013

L'ANZIANO SECONDO L'EMATOLOGO…

Category	Parameter
Go-go / fit	No functional dependence in ADL No functional dependence in IADL No relevant comorbidities No geriatric syndromes[a]
Slow-go / vulnerable	No functional dependence in ADL Dependence in one or more IADL Comorbidity present but not life-threatening Mild memory disorder and depression No geriatric syndromes[a]
No-go / frail	Age ≥85 years[b] ≥3 grade 3 comorbidities (cumulative illness rating scale for geriatrics) or ≥3 comorbidities with constant limitation in daily life One or more geriatric syndromes[a]



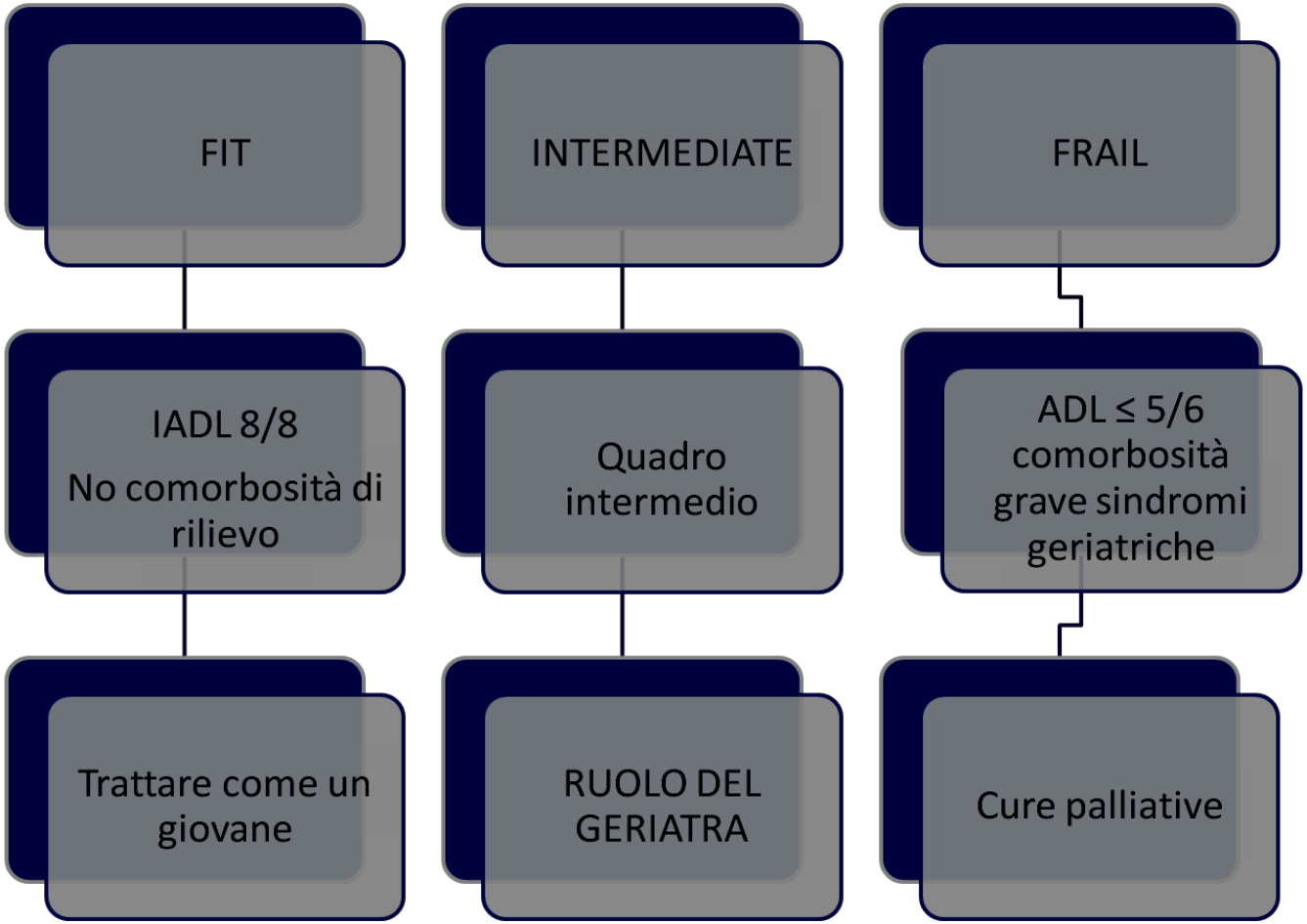
[a]Geriatric symptoms: dementia, delirium, depression, deterioration, neglect or abuse, osteoporosis, falls and incontinence
[b]A higher upper age limit might be considered

L'ANZIANO SECONDO IL GERIATRIA…

IL PUNTO DI VISTA DEL GERIATRA

- Livello funzionale
- Valutazione supporto sociale
- Comorbidità e terapia in corso
- Screening cognitivo?
- Screening tono dell'umore
- Test di performance fisica

IL PUNTO DI VISTA DEL GERIATRA



IL PUNTO DI VISTA DEL GERIATRA

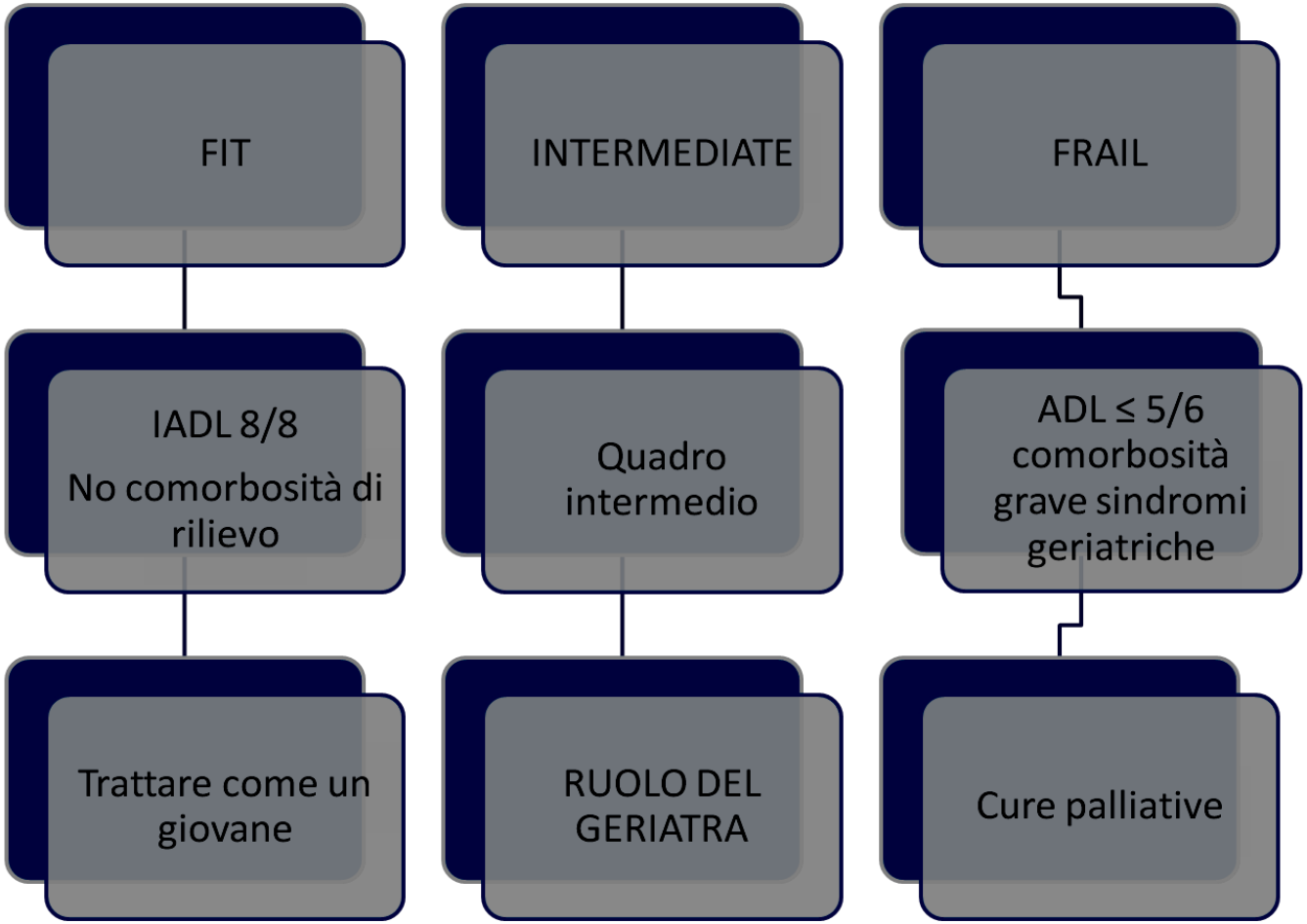
GO-GO?

IL PUNTO DI VISTA DEL GERIATRA

SLOW-GO?

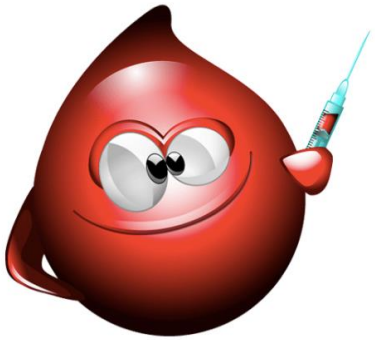
IL PUNTO DI VISTA DEL GERIATRA

IL PUNTO DI VISTA DEL GERIATRA



Novembre 2012

LA DIAGNOSI

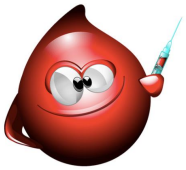


EMOCROMO

- GB 2130
- N 190
- Hb 10.1
- MCV 104
- PLT 193000

Novembre 2012

LA DIAGNOSI



ESAMI

- CM IgA-k
- IgA 643 (<400)
- K siero 373 (<370)
- Beta2 2.050 (<2)
- Albumina 3.8

ESAMI

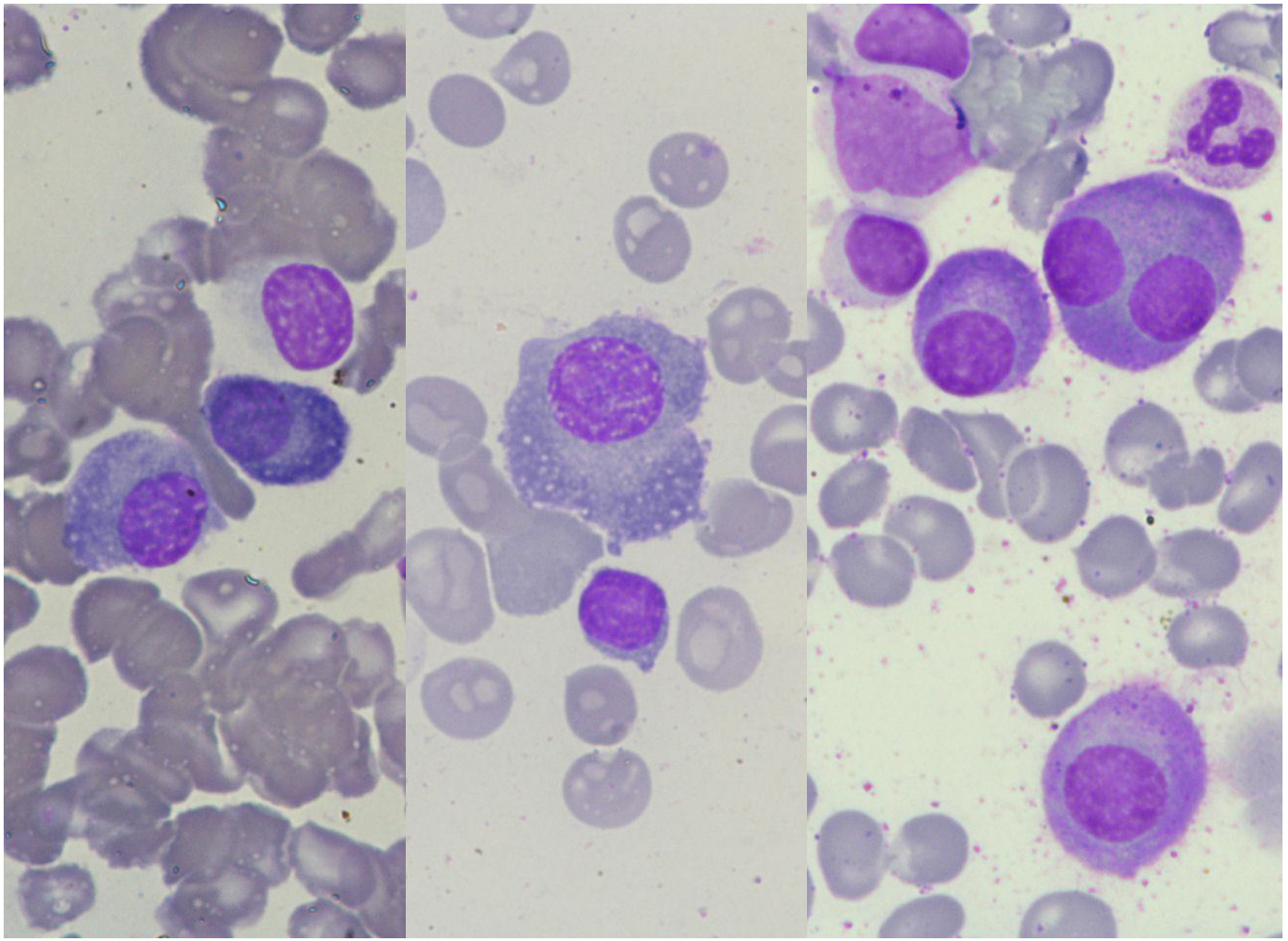
- Ca
- creatinina
- SGOT, SGPT
- ferritina

LA DIAGNOSI

MIELOASPIRATO

- le 3 linee emopoietiche appaiono **iporappresentate, ipomaturanti…**
- **blasti** indifferenziati, verosimilmente non linfoidi **18%**
- **Plasmacellule** plurinucleate ed anomale **20%**

MIELOASPIRATO alla DIAGNOSI 1



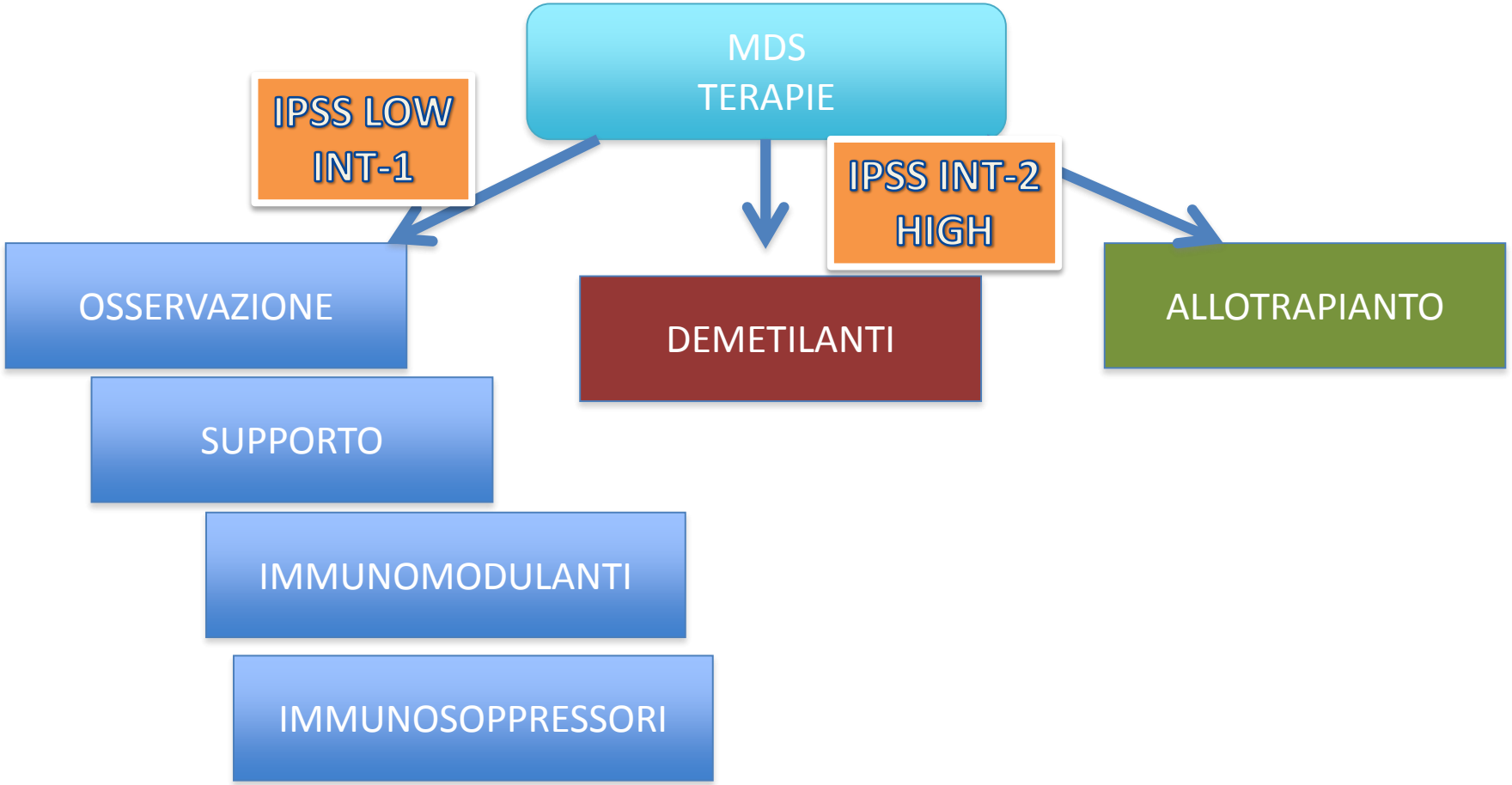
LA DIAGNOSI

IMMUNOFENOTIPO

- **PLASMACELLULE:** CD45-, CD138+/CD38+/CD56+
- **BLASTI:** CD34+, CD117+, CD13+ (15%)

CITOGENETICA (CARIOTIPO + FISH chr 5, PDGFRa, PDGFRb, 17)

- **46, XY**
- FISH negative


MDS
TERAPIE
IPSS LOW
INT-1
IPSS INT-2
HIGH
OSSERVAZIONE
SUPPORTO
IMMUNOMODULANTI
IMMUNOSOPPRESSORI
DEMETILANTI
ALLOTRAPIANTO

CITOGENETICA & IPSS

VARIABILE PROGNOSTICA	0	0,5	1,0	1,5	2,0
BLASTI BM	<5%	5-10%		10-20%	20-30%
CITOGENETICA	Good: Normal del (5q) del (20q) -y	Intermediate Others	Poor: -7 del (7q) Complex		
CITOPENIE Hb <10gr/dL Pmn <1,8x10^9/L Plt < 100x10^9/L	0/1	2/3			

Low Score 0	Intermediate -1 Score 0,5-1,0	Intermediate -2 Score 1,5-2,0	High Score ≥2,5

IPSS

Prognostic Variable	Score Value				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts, %	< 5	5-10	--	11-20	21-30
Karyotype*	Good	Intermediate	Poor	--	--
Cytopenias†	0/1	2/3	--	--	--

Prognostic Variable	Total Score					
	0	0.5	1.0	1.5	2.0	≥ 2.5
Risk	Low	Intermediate I		Intermediate II		High
Median survival, yrs	5.7	3.5		1.2		0.4

IPSS

LA DIAGNOSI

BIOLOGIA MOLECOLARE

- **WT1: 303** (vs <250)
- **ASXL1, IDH1/2, EZH2: wild-type**
- **TET2: mutato**
- **IgH** (PCR qualitativa): clonale

D2 . pensate valga la pena di trattare il nostro professore”?

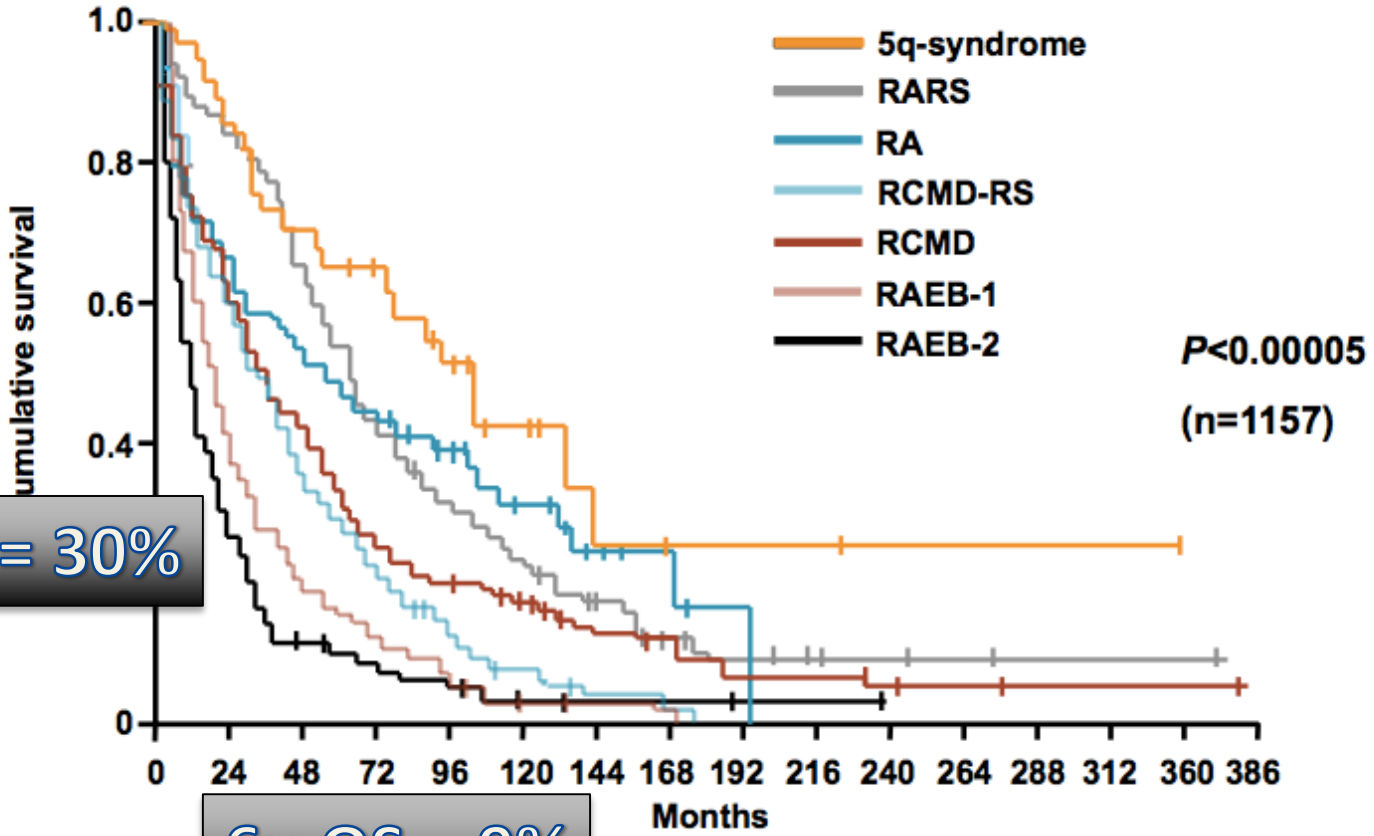
1. No
2. Sì
3. Non so

Attesa di vita nella popolazione generale

Table 3. Differences in Remaining Life Expectancy in Older Persons Between the General Population and Individuals with Selected Geriatric Syndromes

		Geriatric Syndromes							
Age	Remaining Life Expectancy in the General Population	Multiple Morbidities (>3 Diseases)	Inflammation (High C-Reactive Protein)	Frailty (Phenotype)	Cognitive Impairment (Mini-Mental State Examination Score <24)	Frailty (Accumulation Deficit)	Low Body Mass Index	Allostatic Load	Disability in Activities of Daily Living
65	18.4	−2.2	−2.8	−3.2	−2.5	−1.1	−5.4	−10.3	−3.9
70	14.9	−2.0	−2.5	−2.8	−2.2	−1.0	−4.8	−8.9	−3.4
75	11.7	−1.7	−2.1	−2.5	−1.9	−0.9	−4.1	−7.5	−3.0
80	8.9	−1.4	−1.8	−2.1	−1.6	−0.7	−3.4	−6.0	−2.5
85	6.5	−1.1	−1.4	−1.6	−1.3	−0.6	−2.7	−4.7	−2.0
90	4.6	−0.8	−1.1	−1.2	−1.0	−0.4	−2.0	−3.5	−1.5
95	2.8	−0.5	−0.6	−0.7	−0.6	−0.2	−1.2	−2.2	−0.9
100	0.4	−0.1	−0.1	−0.1	−0.1	−0.1	−0.2	−0.4	−0.2

LA DIAGNOSI: WHO

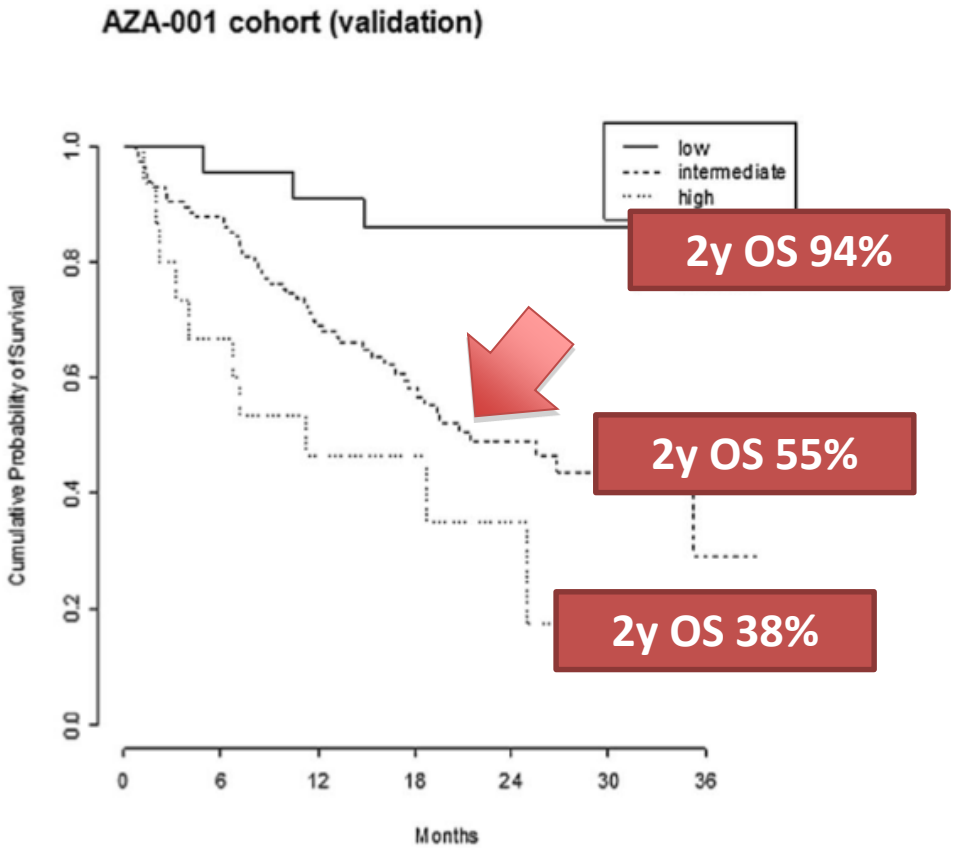


2y-OS = 30%

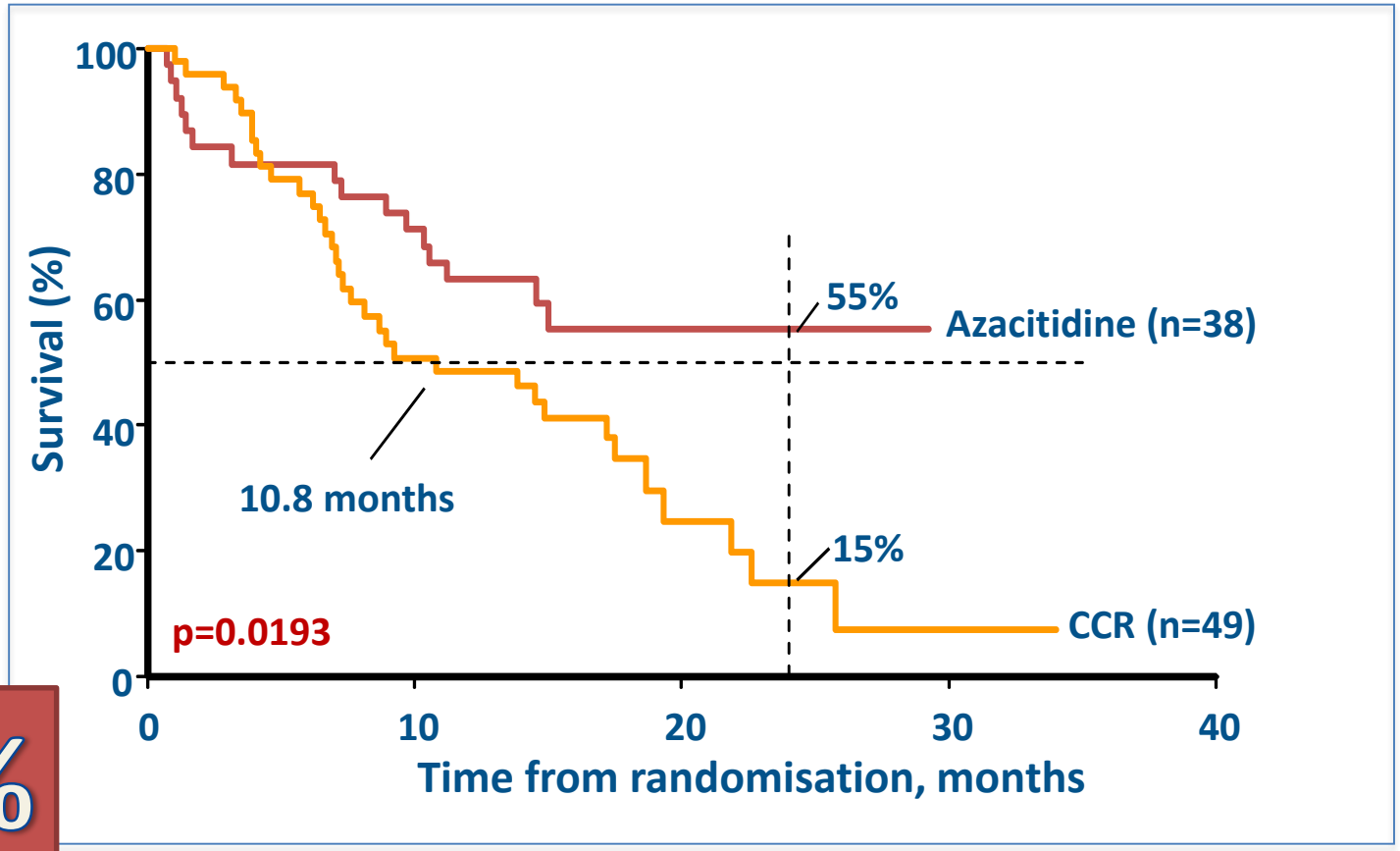
6y-OS = 9%

AZA SCORE

PS ≥2	1
PB blasti	1
Trasfusioni >4 in 8 sett	1
Rischio citogenetico intermedio alto	 1 2
LOW	0
INTERMEDIATE	1-3
HIGH	4-5



RISPOSTE e OS in AZA-001 >75y



+25%


MIELOMA?
MDS?

LA DIAGNOSI

- **RM RACHIDE e BACINO:** non lesioni osteolitiche, segni di artrosi con bulging discali multipli a livello lombare
- **FREE LIGHT CHAIN ratio** <100

Novembre 2012

LA TERAPIA

- **AZACITIDINA** 75 mg/mq

Lun-ven + lun-mart ogni 28gg

- **SOLDESAM** 20 mg/die

4 giorni al mese

Novembre 2012

LA TERAPIA

Parameters in Evaluable Pts,* n/N (%)	AZA 5-2-2†‡ 75 mg/m^2	AZA 5-2-5†‡ 50 mg/m^2	AZA 5d‡ 75 mg/m^2
Erythroid$_{Major}$	19/43 (44)	19/43 (44)	20/44 (46)
RBC-TI	12/24 (50)	12/22 (55)	15/25 (64)
Platelet$_{Major}$	12/28 (43)	8/30 (27)	11/22 (50)
Any HI	22/50 (44)	23/51 (45)	28/50 (56)
Neutrophil$_{Major}$	4/23 (17)	4/23 (17)	9/24 (38)

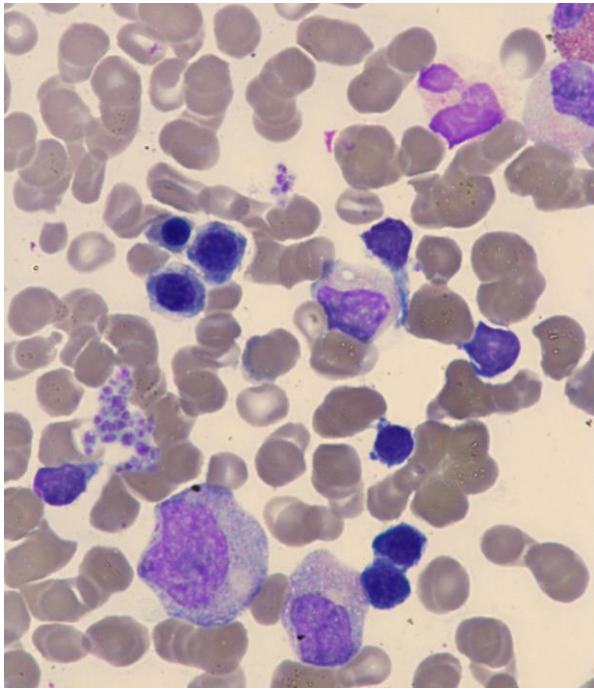
Lyons, JCO 2009

LA TERAPIA

Marzo 2013 (dopo 4 cicli)

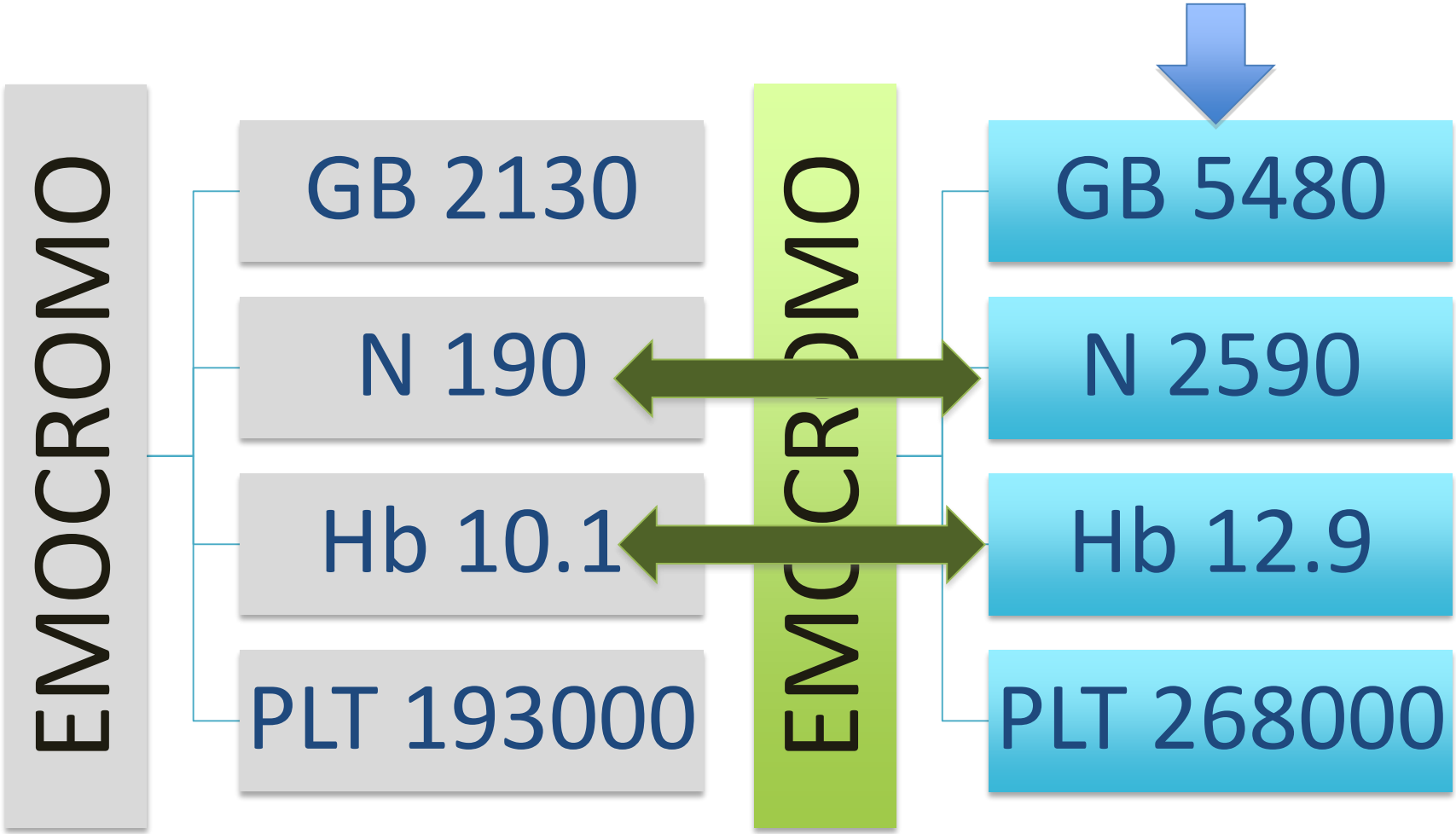
MIELOASPIRATO

- Modica diseritropoiesi, **blasti 2%**
- Linfociti e **plasmacellule nei limiti**
- WT1 **20 (normale)**
- IgH **clonale**



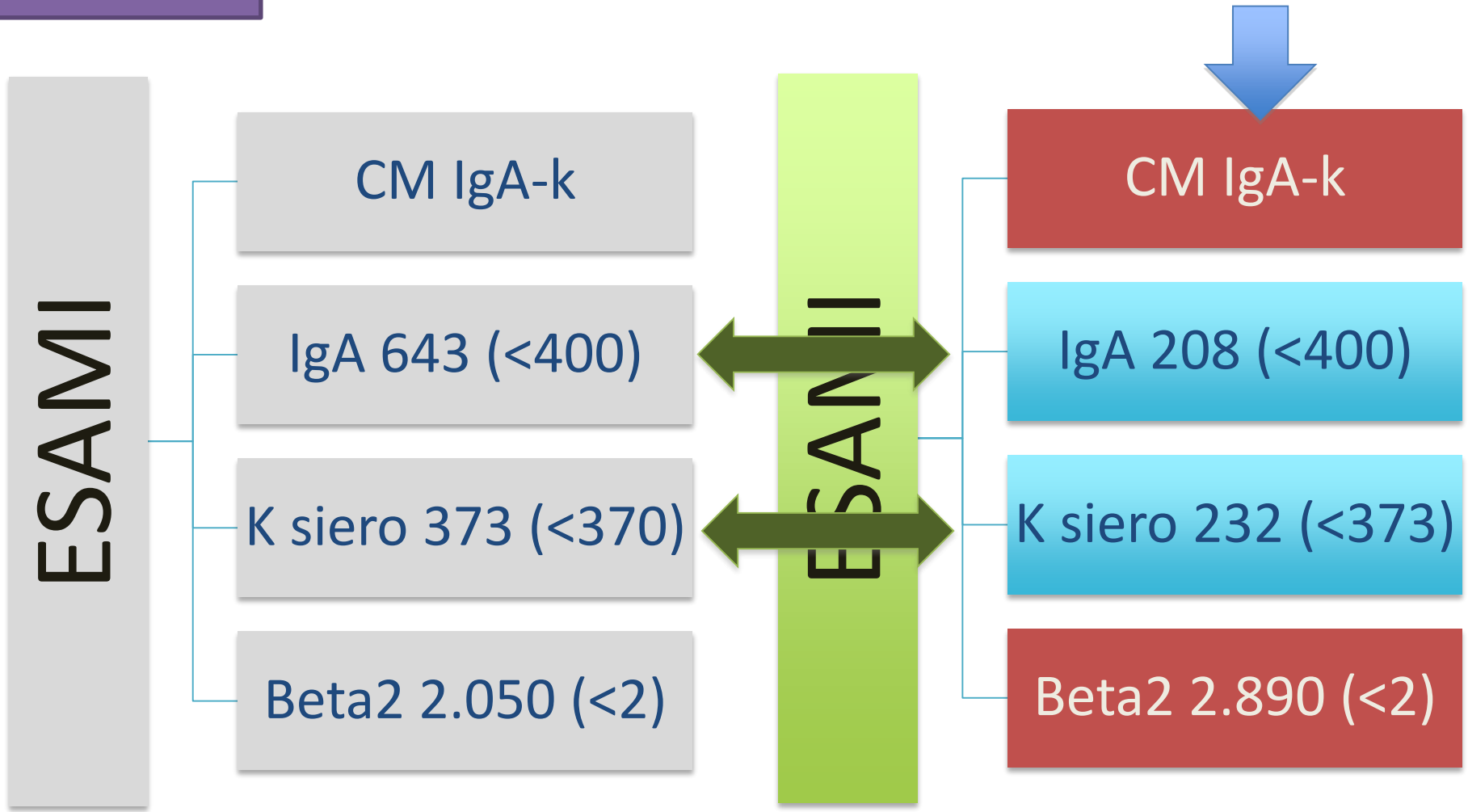
LA RISPOSTA a 4 cicli

Marzo 2013



LA RISPOSTA a 4 cicli

Marzo 2013



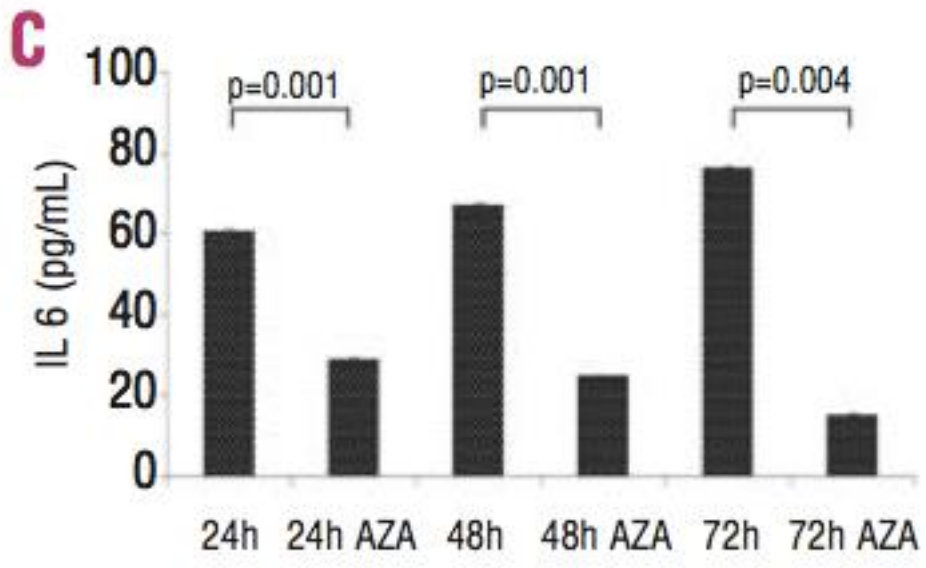
LA RISPOSTA - MDS

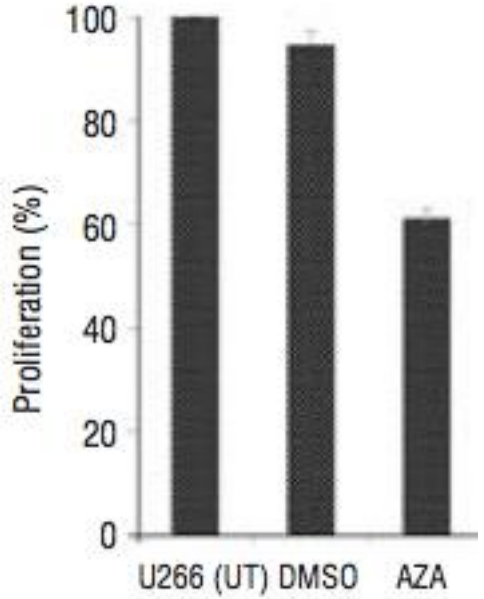
Category	Response Criteria (≥ 4 Wks)
CR	▪ Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines ▪ Persistent dysplasia will be noted ▪ Hb: ≥ 11 g/dL, platelets: ≥ 100 x 10^9/L, neutrophils: ≥ 1.0 x 10^9/L, blasts: 0%
PR	All CR criteria if abnormal before treatment except: ▪Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% ▪Cellularity and morphology not relevant
Marrow CR	▪ Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment ▪ Peripheral blood: if HI responses, they will be noted in addition to marrow CR
SD	▪ Failure to achieve at least PR, but no evidence of progression for > 8 wks

LA RISPOSTA - MM

Response	*IMWG criteria*
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow[3] by immunohistochemistry or immunofluorescence[4]
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow[3]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable,[5] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA

NEL MM AZA riduce IL6 ed ha effetto antiproliferativo





Khong, Haematologica 2008

LA TERAPIA

NUMERO CICLI AZA E RISPOSTA

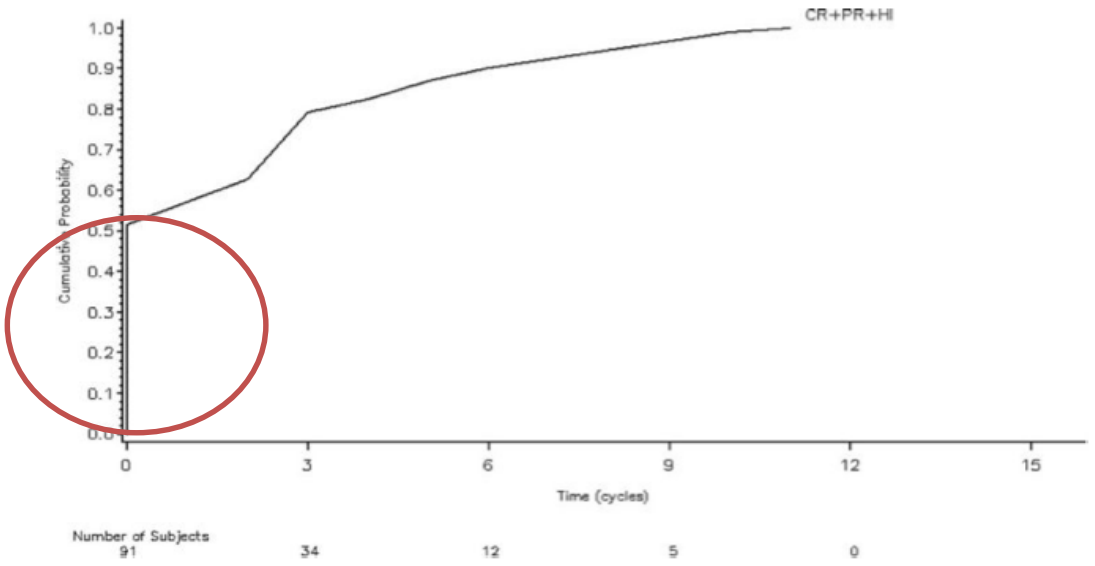


Figure 2.
Time to best response after first response in patients treated with azacitidine is shown. The vertical line on the y-axis represents the 52% of patients whose first response was their best response. The remaining 48% of patients had an improvement in their first response with continued azacitidine therapy; they all improved from a first response of hematological improvement (HI) to either partial response (PR) or complete response (CR).

Silverman, Cancer 2011

Marzo 2013

- Stop soldesam
- **Prosegue AZACITIDINA**

Gennaio 2014 (dopo 15 cicli)

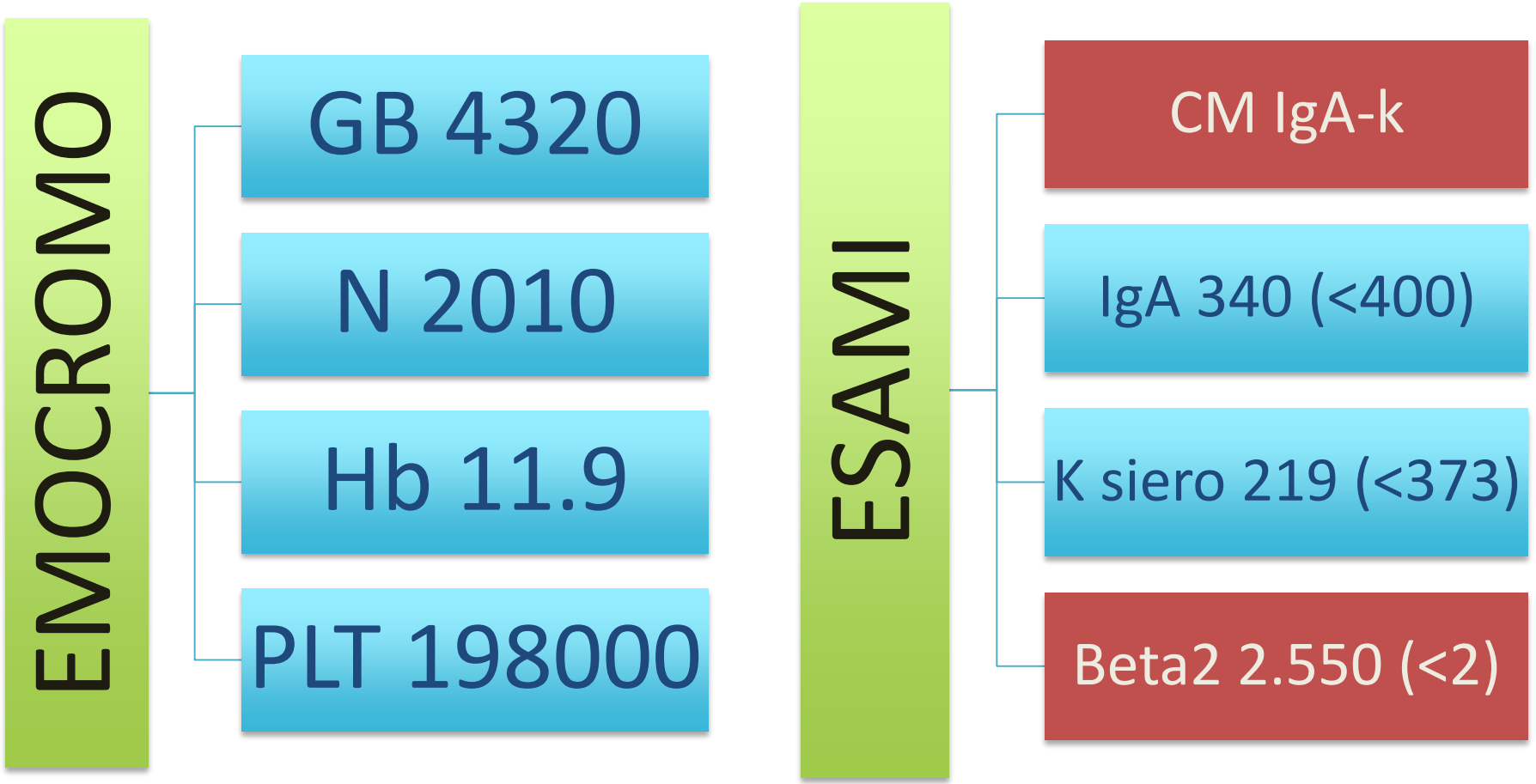
LA TERAPIA (15 cicli)

MIELOASPIRATO

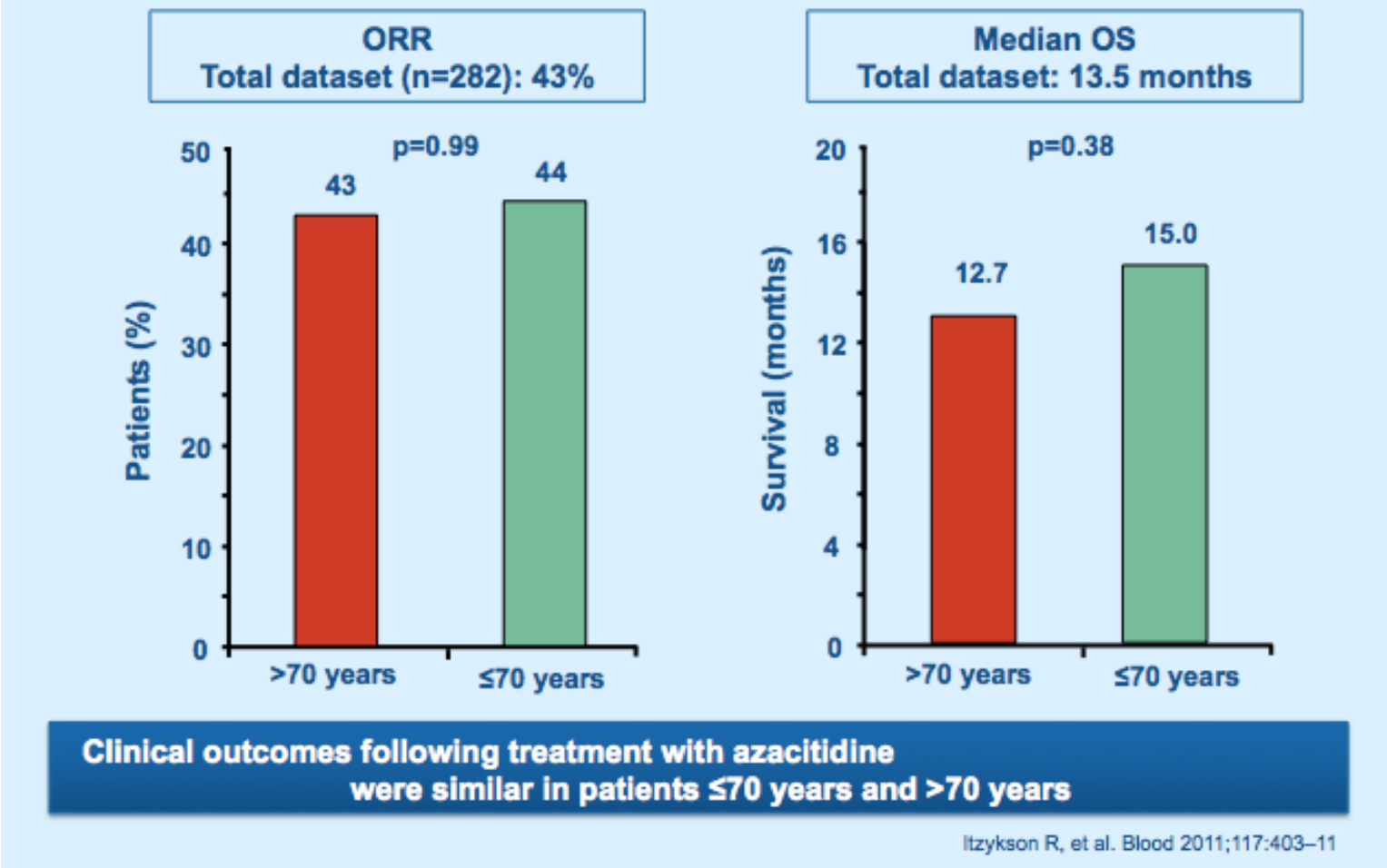
- Modica diseritropoiesi, **blasti 1% (FACS 0.3%)**
- Linfociti e **plasmacellule nei limiti**
- WT1 **2 (normale)**
- IgH **clonale**

LA RISPOSTA a 15 cicli

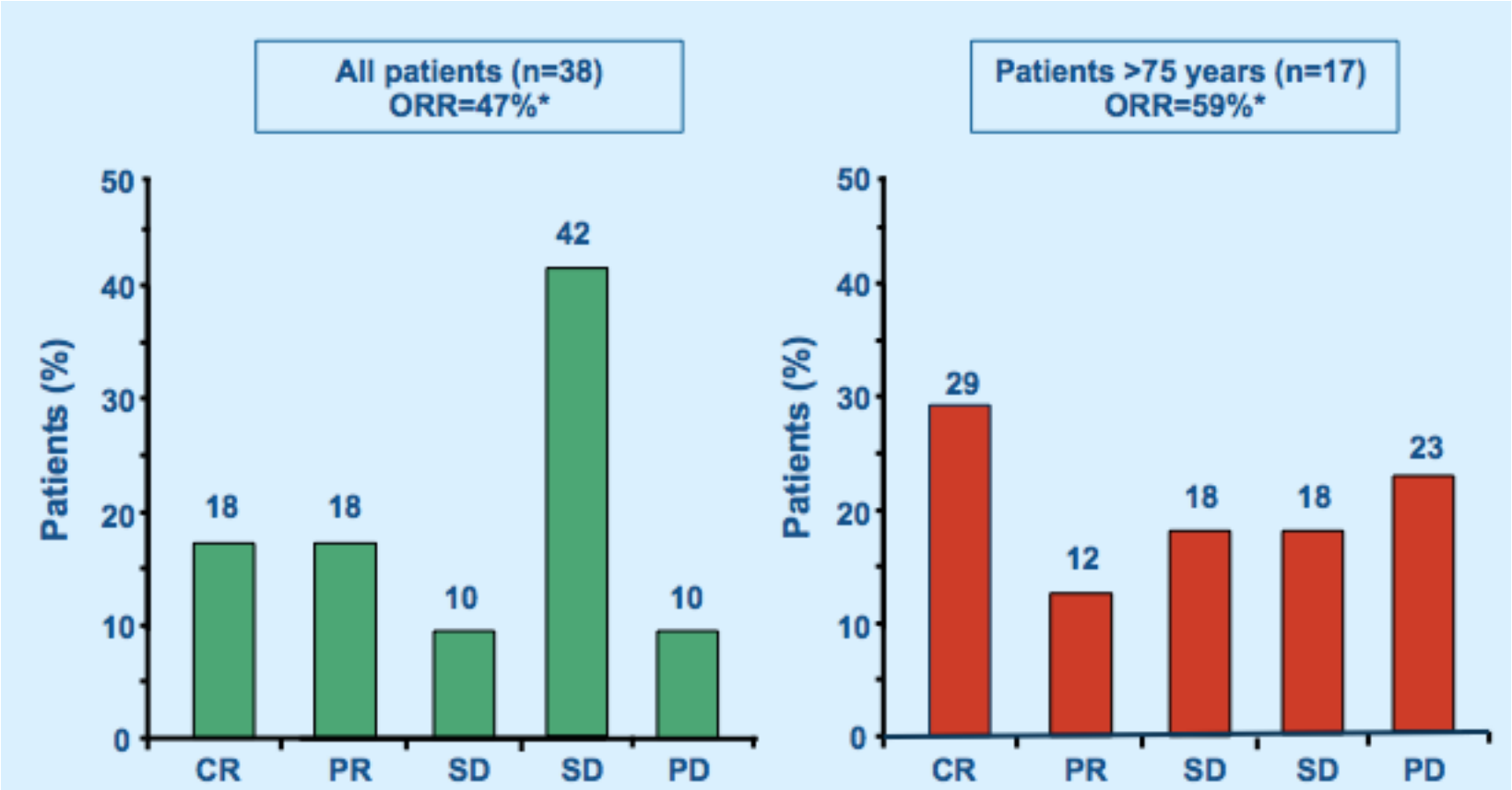
Gennaio 2014



EFFICACIA


ORR
Total dataset (n=282): 43%
p=0.99
43
44
Patients (%)
50
40
30
20
10
0
>70 years
≤70 years
Median OS
Total dataset: 13.5 months
p=0.38
12.7
15.0
Survival (months)
20
16
12
8
4
0
>70 years
≤70 years
Clinical outcomes following treatment with azacitidine
were similar in patients ≤70 years and >70 years
Itzykson R, et al. Blood 2011;117:403–11

EFFICACIA


All patients (n=38)
ORR=47%*
Patients (%)
50
40
30
20
10
0
18
18
10
42
10
CR
PR
SD
SD
PD
Patients >75 years (n=17)
ORR=59%*
Patients (%)
50
40
30
20
10
0
29
12
18
18
23
CR
PR
SD
SD
PD

LA TOSSICITA'

- **Neutropenia grado 3**, supportata con G-CSF
- **Neutropenia febbrile** (1 evento, 2 giorni)
- **Anemia grado 2,** responsiva ad eritropoietina 40000

D3 . “pensate che questa tossicità sia accettabile”?

1. Si
2. No
3. Non so

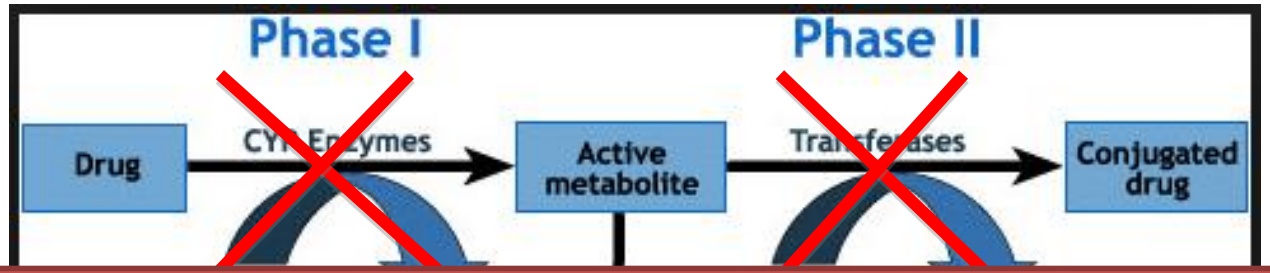
AEs in AZA-001 >75y

	Safety population	
Event, %	Azacitidine (n=38)	CCR (n=47)
≥1 TEAE	82	72
Anaemia	13	4
Thrombocytopenia	50	30
Neutropenia	61	17
Infection	39	26
Diarrhoea	0	4
Pyrexia	8	2
Fatigue	3	2

IL GERIATRIA CHIAMA L'EMATOLOGO…

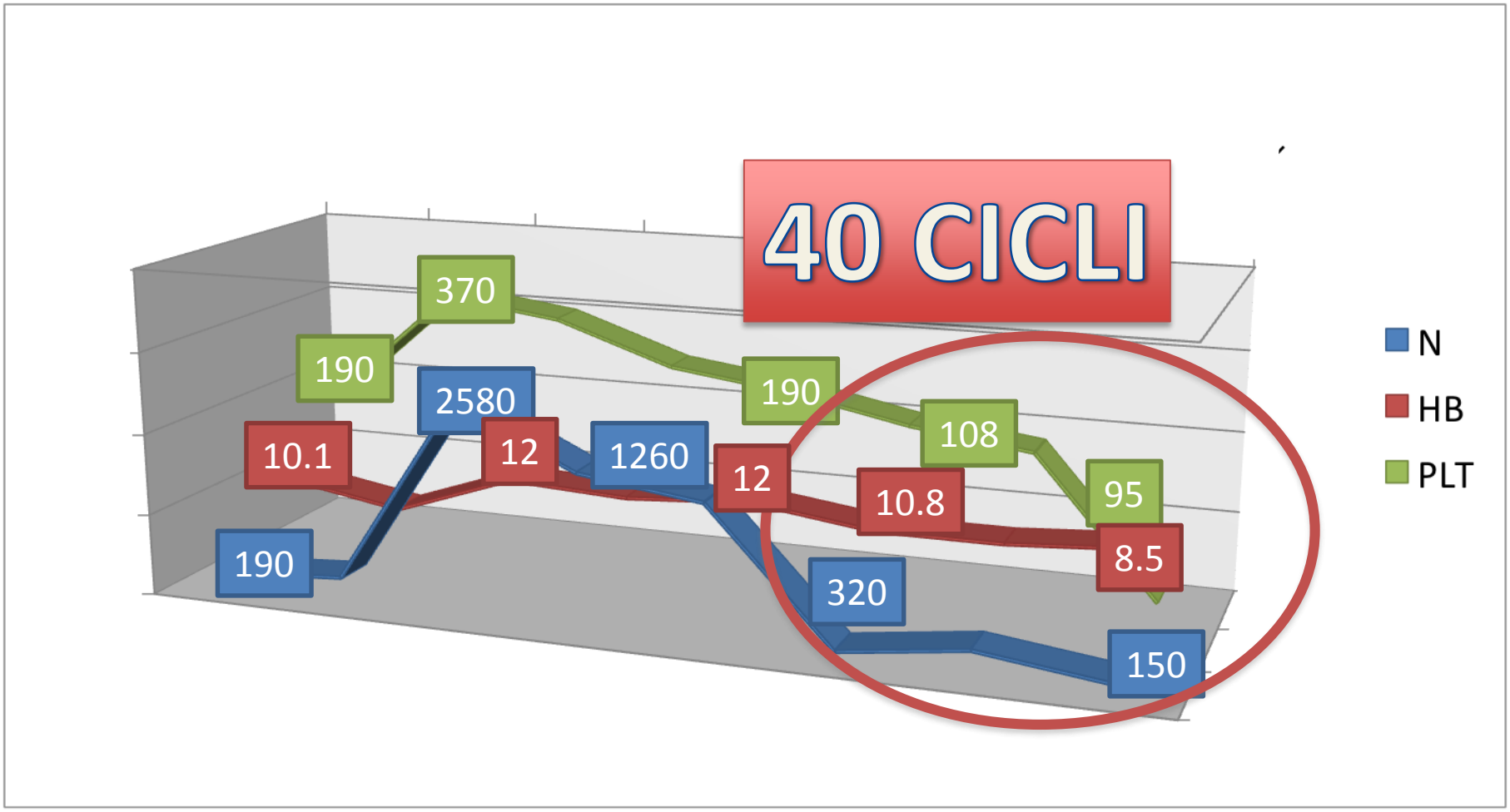
AZA & INTERAZIONI

Anticoagulanti orali di nuova generazione: nessun problema



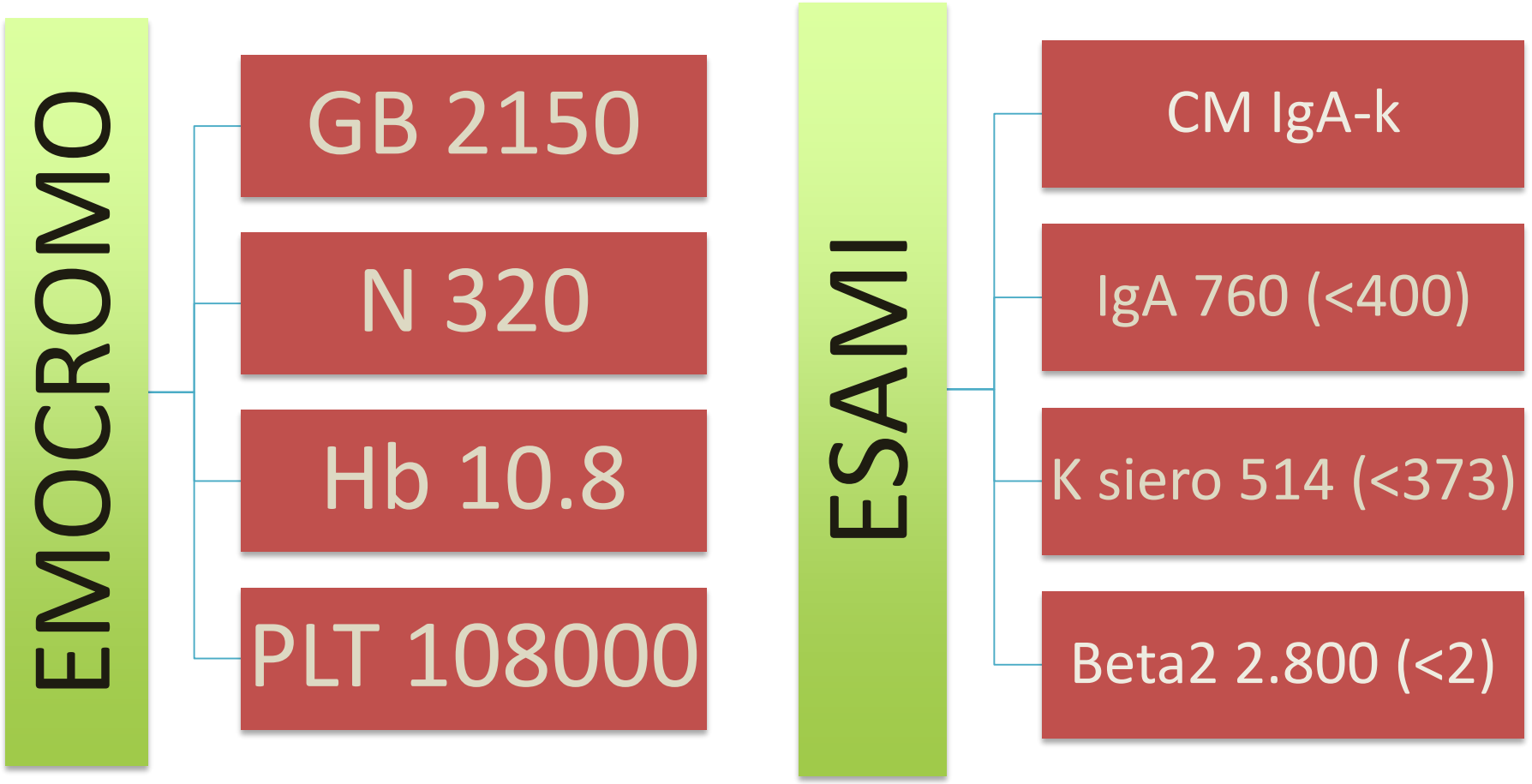
32 interazioni "maggiori"
80 "modeste"

LA TERAPIA

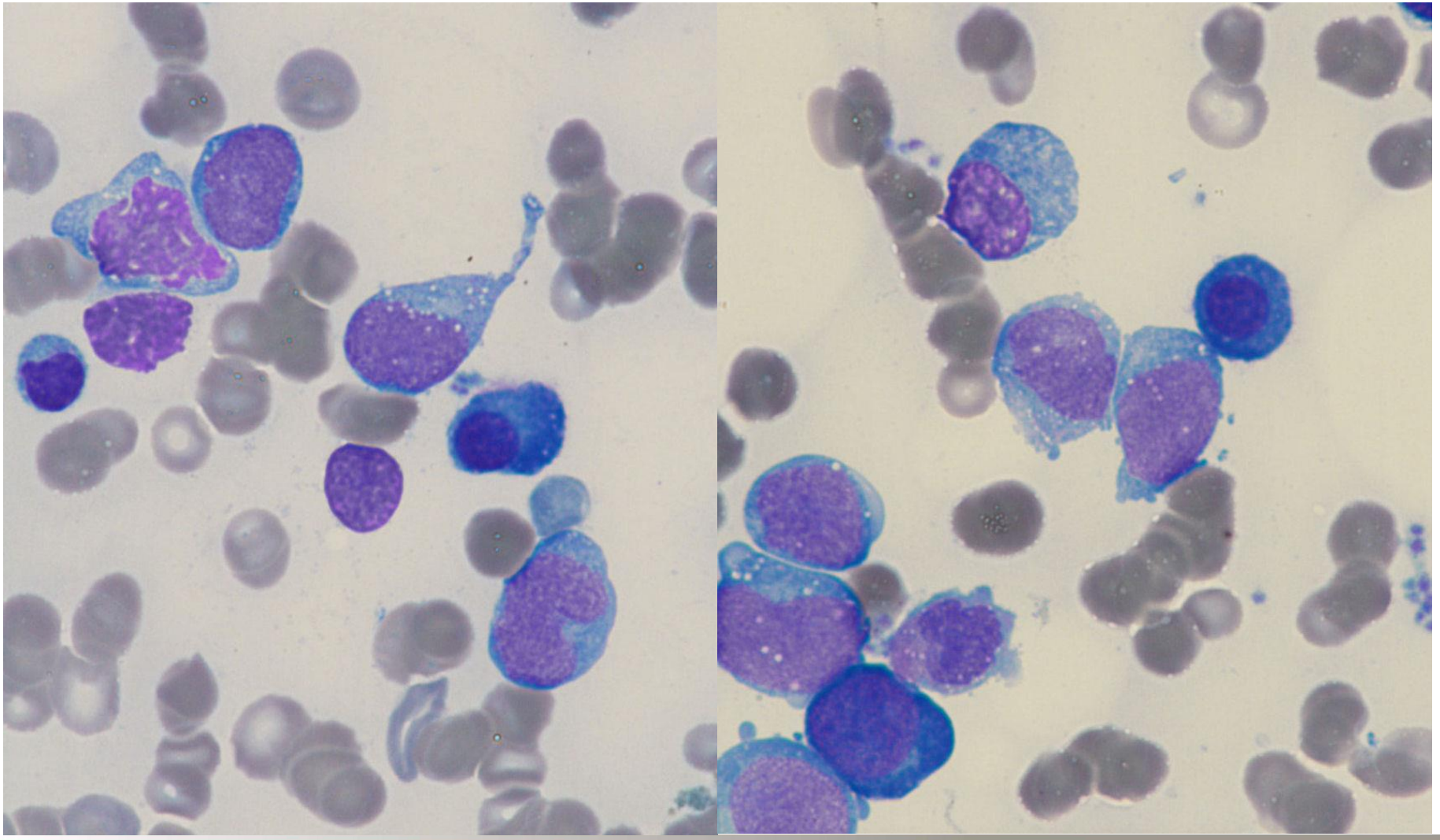

40 CICLI
370
190
190
108
95
2580
10.1
12
1260
12
10.8
8.5
190
320
150
N
HB
PLT

Marzo 2016

LA RISPOSTA a 40 cicli



MIELOASPIRATO alla PROGRESSIONE



Marzo 2016 (dopo 40 cicli)

LA PROGRESSIONE

MIELOASPIRATO

- **blasti mieloidi 35% (FACS 25%)**
- Linfociti nei limiti
- **Plasmacellule: 10%**

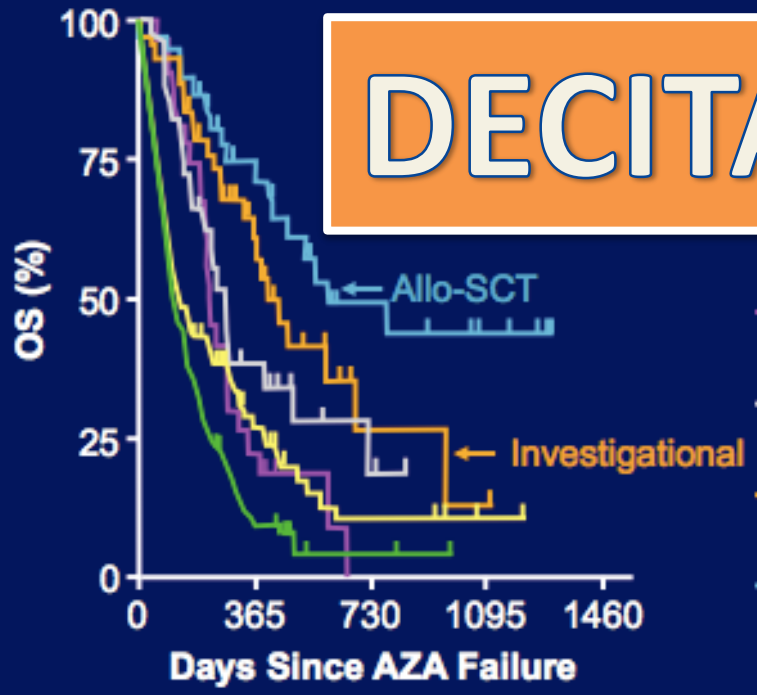
WT1 **229 -** NPM1 wild-type, FLT3 wild-type
CARIOTIPO: 46, XY

D4 . “pensate valga la pena di ritrattare il nostro professore”?

1. Assolutamente no
2. Certamente Sì
3. Probabilmente sì

OS dopo fallimento AZA

Salvage Therapy After Azacitidine Failure: GFM and AZA-001 Studies



DECITABINA

		ORR	Median OS, Mos
		NA	3.6
		NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

Prebert, JCO 2011

IL NOSTRO CASO…

- ✓ AZA si è dimostrata efficace …sia sulla MDS che sul MM
- ✓ Scarsa tossicità
- ✓ La durata della risposta ed il tempo alla progressione è risultato superiore alle attese…

IL NOSTRO CASO…

- ✓ Paziente anagraficamente anziano, privo di sindromi geriatriche, ha ben tollerato un trattamento “aggressivo”
- ✓ Fondamentale valutare il soggetto “a tutto tondo”