

Highlights from EHA

Report dei gruppi di lavoro >>
[Leucemia linfatica cronica]

Relatore: **A. CUNEO**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

Gruppo di lavoro

2

[Leucemia linfatica cronica]

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CUNEO A, LISO V: Report CLL Working group

1) Diagnostic Work-up for risk assessment

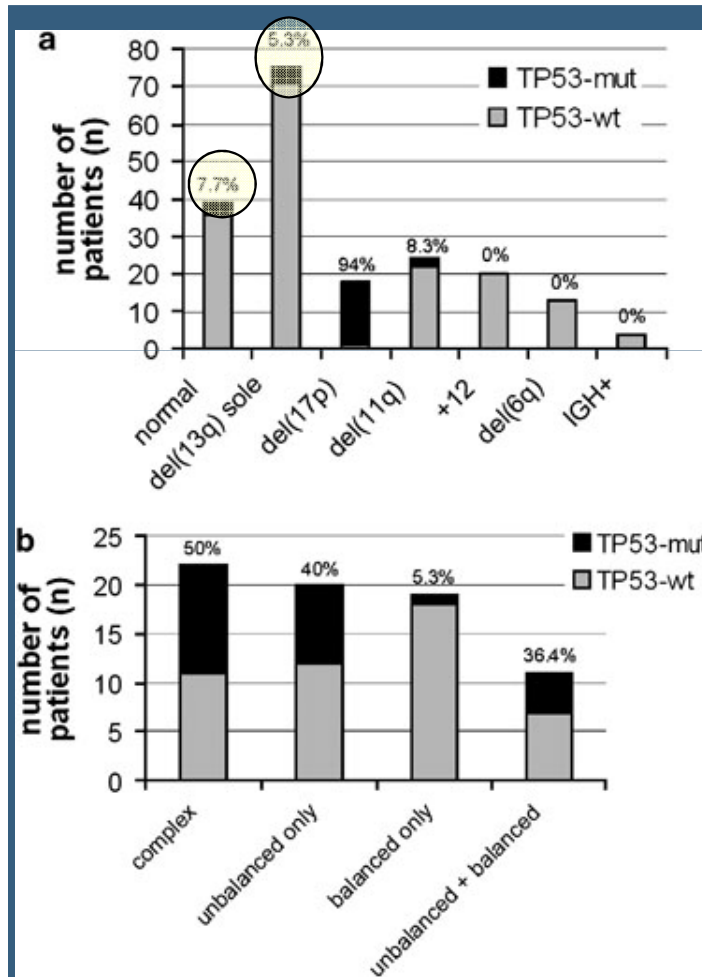
- immunophenotyping
- cytogenetics
- Molecular genetics (DHPLC and sequencing TP53 exons 4-9)
- Ig sequence (stereotyped receptors)

2) Therapy by risk groups

- high risk vs low risk
- specific cytogenetic subgroups
- consolidation

The detection of TP53 mutations in chronic lymphocytic leukemia independently predicts rapid disease progression and is highly correlated with a complex aberrant karyotype

Dicker F et al, Leukemia, 2008

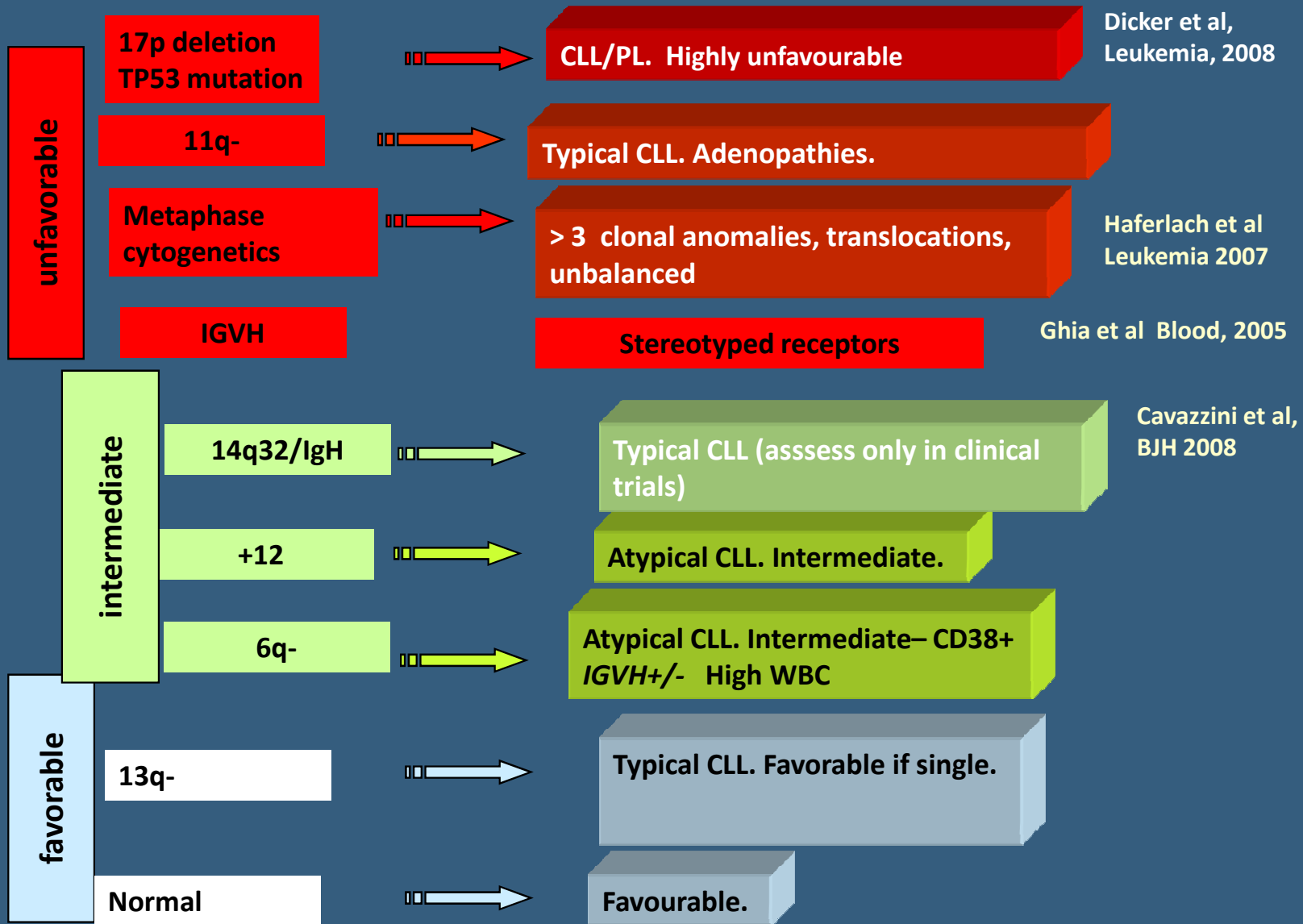


TP53 mutations: 26/193 pts = 13,5%
 17p13 deletion 18/193 pts = 9,3%

Median TFI (months)

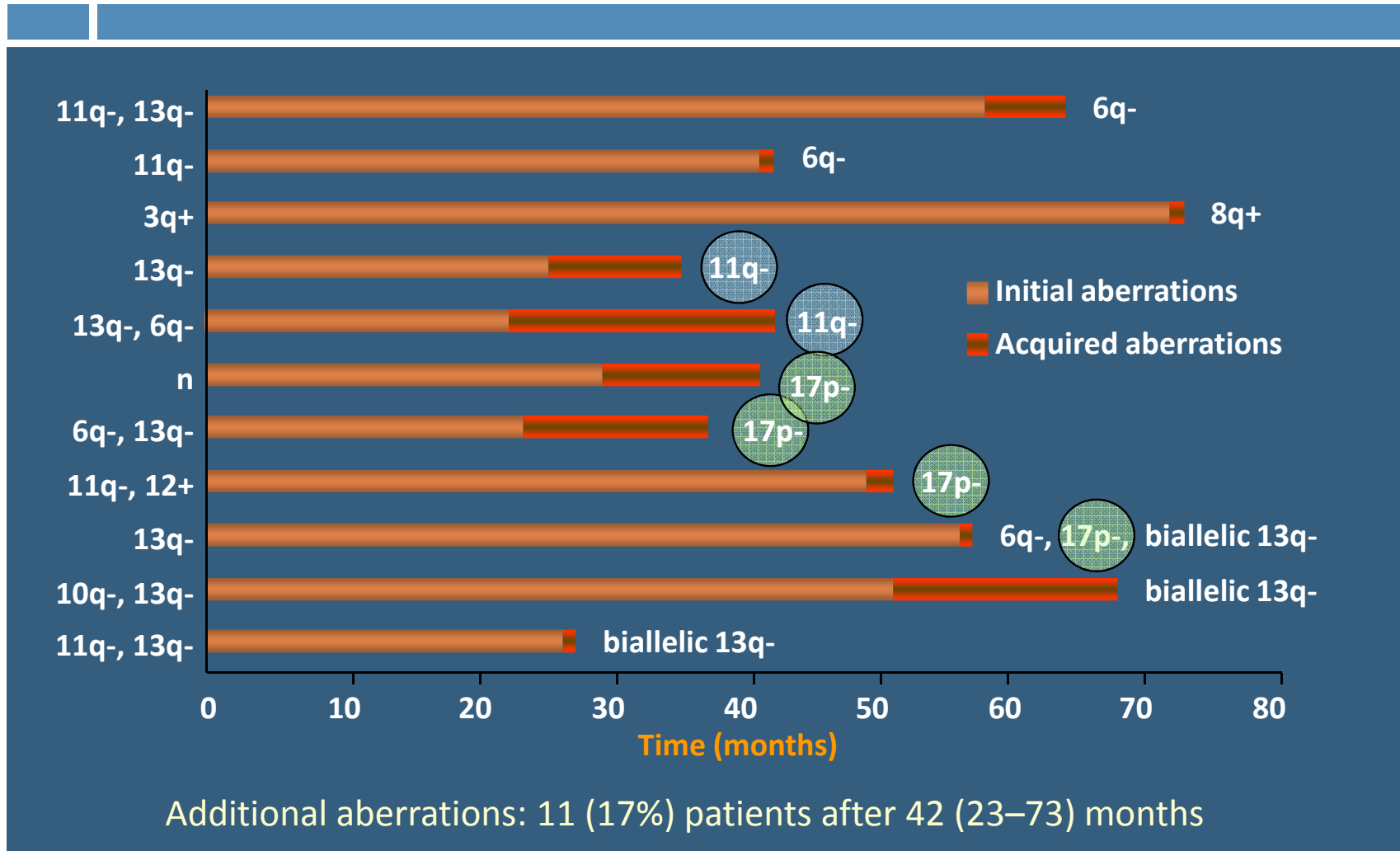
- 6 TP53 mutated pts without 17p- → 2
- 14 17p- pts → 21,3
- 127 pts without 17p- or TP53 mut → 64,9

Molecular cytogenetic aberrations in CLL



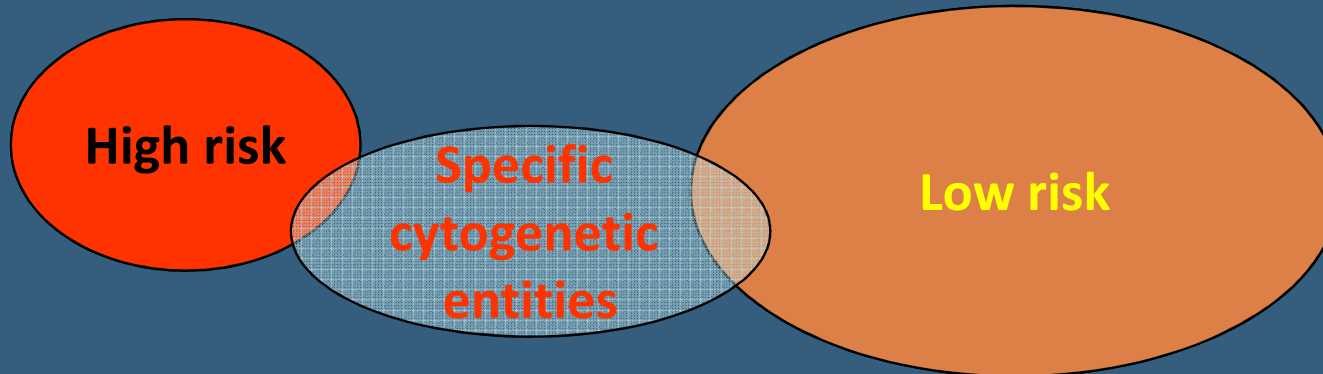
Clonal evolution in CLL

Stilgenbauer et al. Haematologica 2007;92:1242–5



Cytogenetic risk in CLL

- **TP53 mutations** by DHPLC + I-FISH) –
- Conventional karyotyping with odn + IL2
- **Evaluate before therapy and at relapse**



- **Feasibility – diagnostic networks –**
- **Research in clinical trials**

Discussione - I

Discussione - II

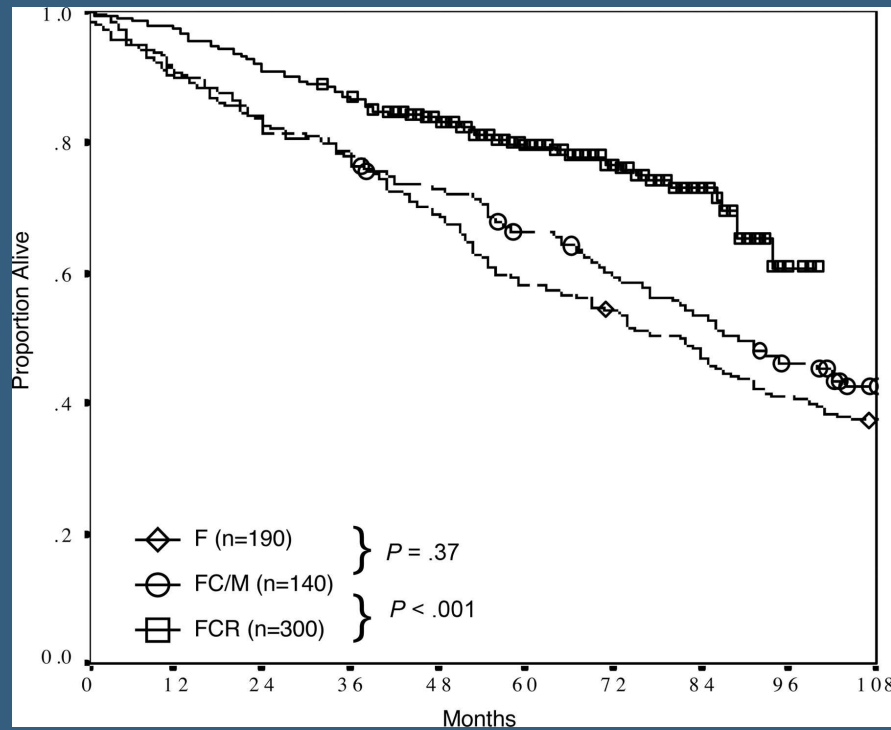
CUNEO: Report CLL Working group

- 1) Diagnostic Work-up for risk assessment
 - immunophenotyping
 - molecular cytogenetics

- 2) Therapy by risk groups**
 - high risk vs low risk**
 - specific cytogenetic subgroups**
 - consolidation**

FCR: the best available regimen?

Tam, C. S. et al. Blood 2008;112:975-980



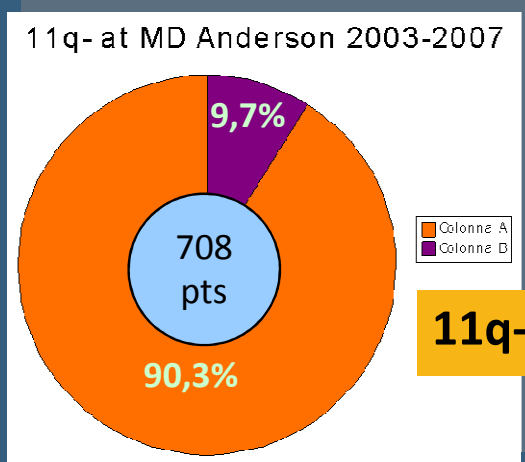
No cytogenetics
No FISH
No CD38
No mutational status
No ZAP70

Historical control!

FCR was the strongest determinant of survival in patients treated by fludarabine-based regimens at MD Anderson

Features of CLL with 11q- at MDACC

Tsimberidou A et al, ASH 2007



11q- in 9-98% of the cells, median 53%

- Rai 3-4 in 13%
- lymphadenopathy 96% (> 5 cm 11%)
- splenomegaly 19%
- ZAP70+ 74% - CD38+ 61% - IGVH unmutated 89%
- median ALC doubling time 237 days

Outcome of CLL with 11q- treated at MD Anderson years 2003-2008

40 CLL requiring
1st line treatment

FCR 29 Pts; FCR+anti CD52 (CFAR) 4 pts; other
treatment 7

median FU 13 months – 3 deaths (1 sepsis in RS; 2nd cancers)

ORR response rate for FCR and CFAR: 100%

CR rate 88% and 100% for FCR and CFAR respectively

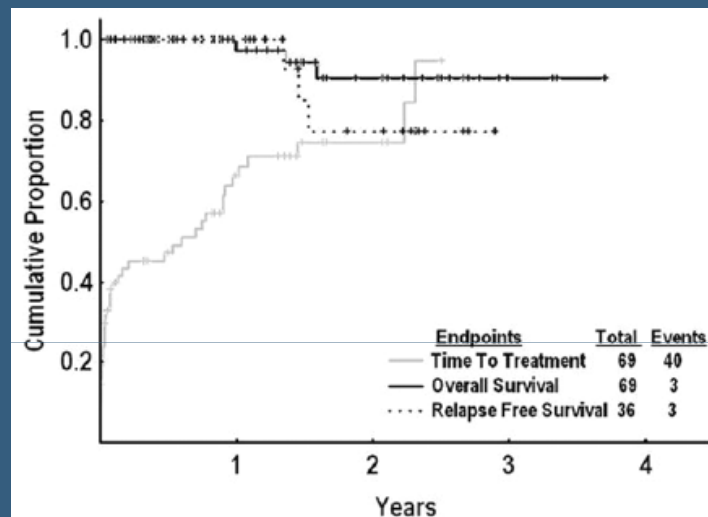
97% OS at 1 yr – 91% OS at 3 yrs

3 relapses at 16-18 months

Tsimberidou et al, ASH 2007

The Prognostic Significance of 11q Deletion Detected by Fluorescence In Situ Hybridization (FISH) in Untreated CLL: The MDACC Experience

Tsimberidou A et al, ASH 2007



**Chemioimmunotherapy (FCR+/- anti CD52)
in CLL 11q-**

**High proportion of CR
Very good RFS
Good survival**

FCR: the best available regimen for patients with progressive disease?

FCR 1st line regimen (224 pts)

Median age 58

13% were > 70 y.o.

26% did not complete 6 courses

16% required dose reduction

Keating et al. JCO 2005; 23: 4079-88

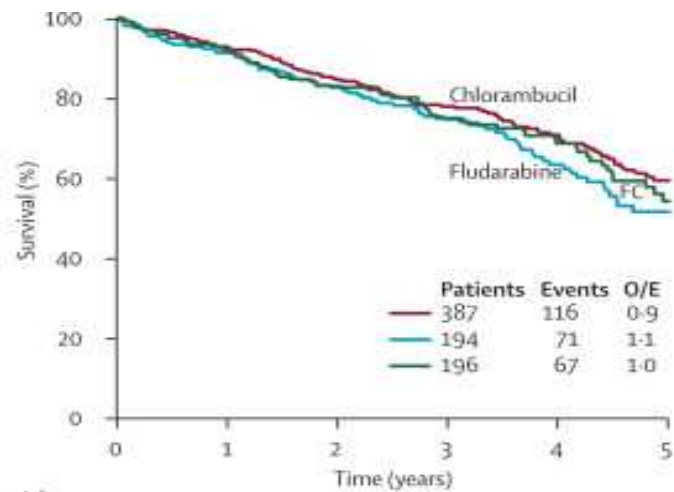
FCR 2nd line regimen (177 pts)

Median age 59

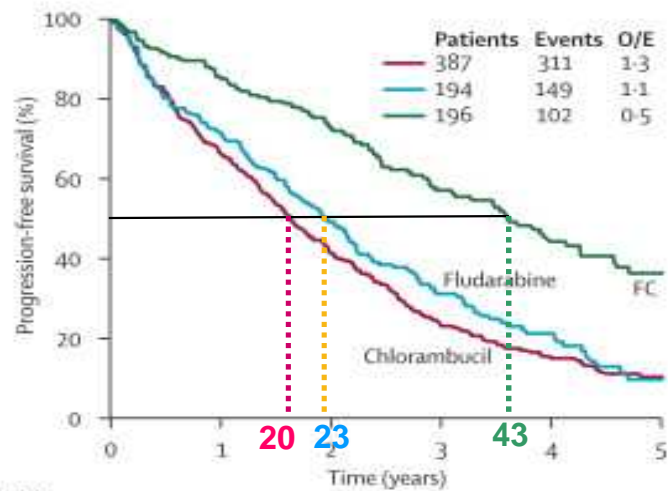
54% did not complete 6 courses

38,4% received the planned dose

Wierda et al. JCO 2005; 23:4070-8



Patients at risk	0	1	2	3	4	5
Chlorambucil	387	359	302	201	132	60
Fludarabine	194	177	150	100	62	29
FC	196	181	149	97	70	30



Patients at risk	0	1	2	3	4	5
Chlorambucil	387	258	151	61	30	11
Fludarabine	194	139	91	40	21	5
FC	196	168	131	74	43	19

Severe adverse events (% of the cases)

Chlor	Fluda	FC
4%	7%	11%

Neutropenia < 1X10⁹/L (% of the cases)

Chlor	Fluda	FC
28%	41%	56%

Febrile episodes (% of the cases)

Chlor	Fluda	FC
25%	27%	35%

Catovsky et al, Lancet 2007

Rituximab as consolidation in CLL after chlorambucil

Mauro et al. EHA, 2007, abstract 124

19 CLL who had required treatment (NCI)

61-81 years (median 65)
PR following treatment by Chlor + Pred
26% IGVH unmutated

RITUXIMAB 375 MG/SQM WEEKLY FOR 4 wks

68% responders

13/19 PR → CR

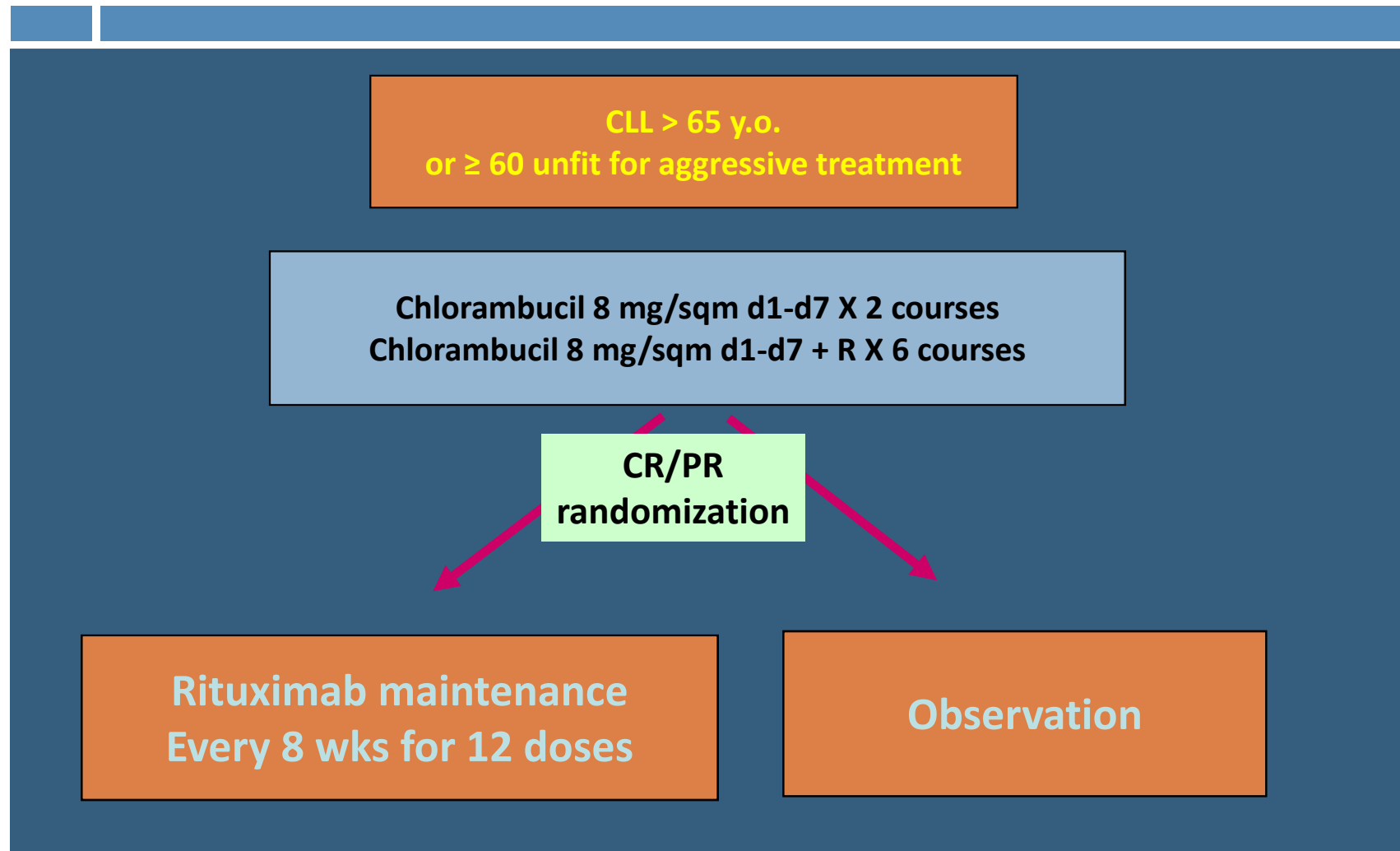
2/13 CR with < 1% CD5/CD19+ cells PB and BM

2/5 PR → CR among unmutated

Median time to loss of response: 16 months (range 3-46)

Median time to next treatment 29,5 months (range 15-68 months)

CLL protocol for elderly patients



Discussione

CR rate with FCR in 17p-

Tam CS, et al, Blood 2008

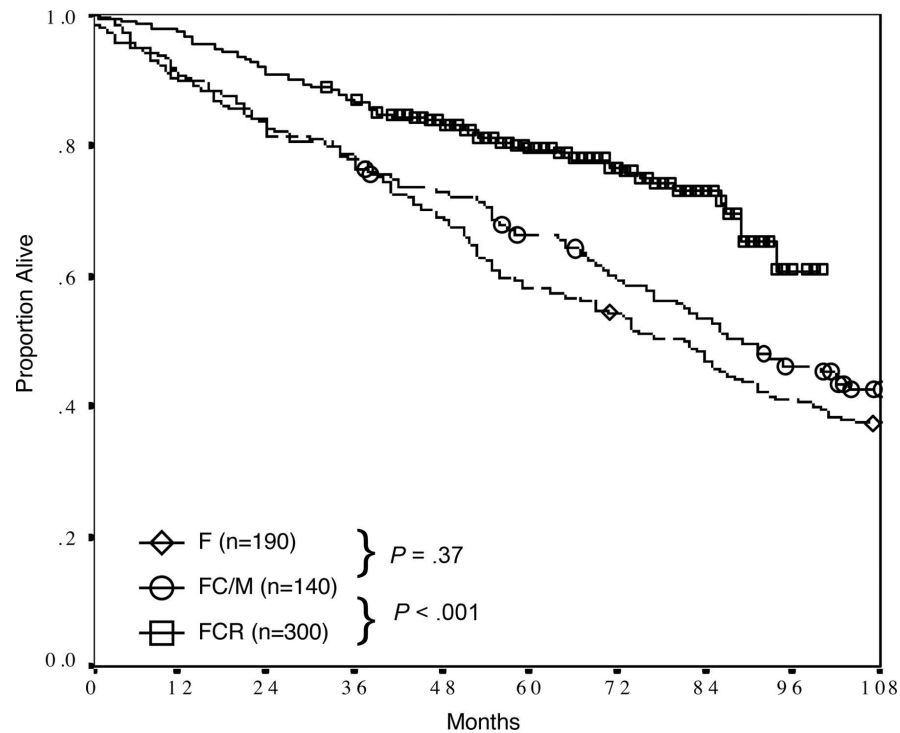


Table 1. Pretreatment characteristics

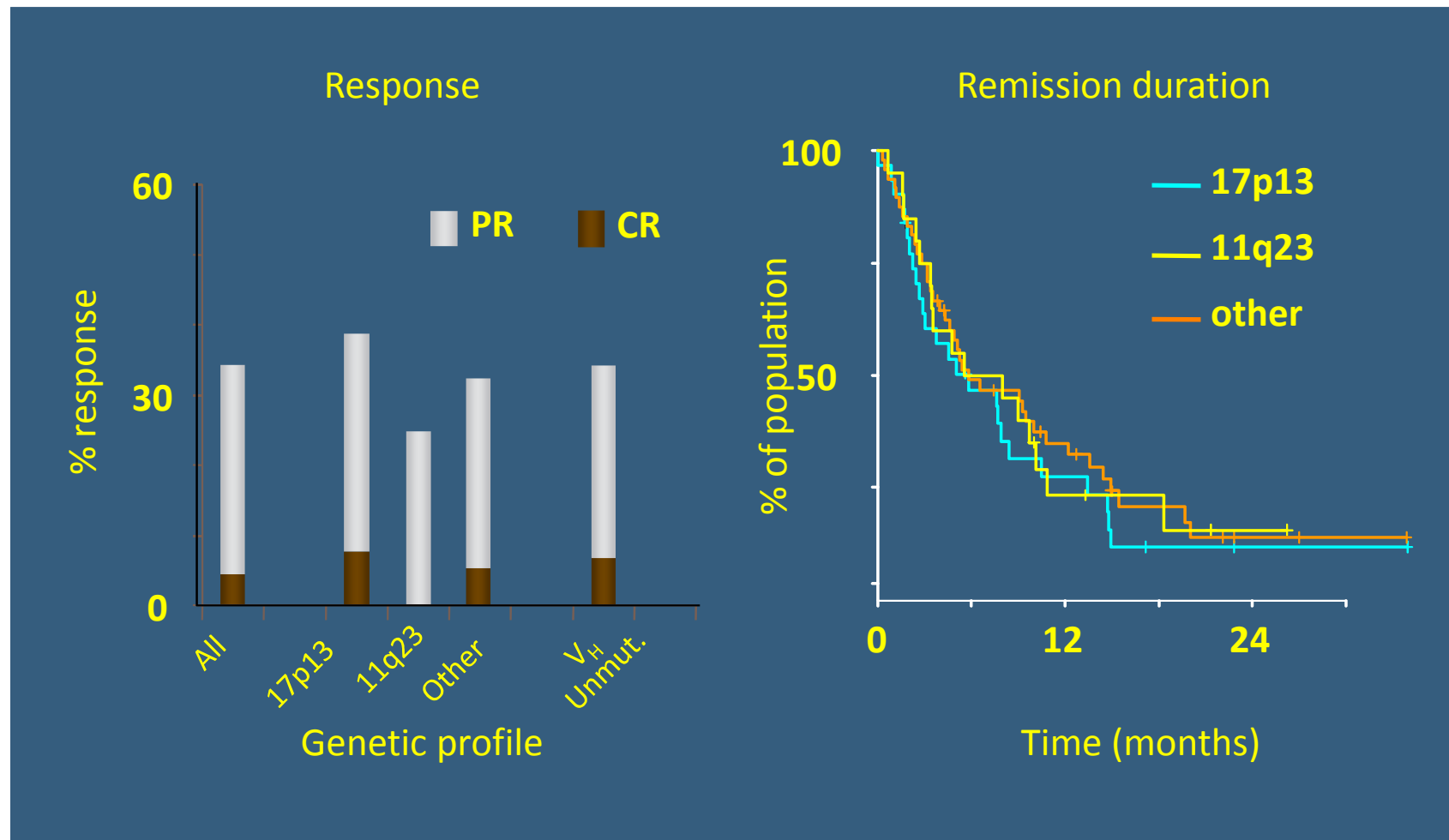
Pretreatment characteristic	Value	Complete response (%)
Median age, y (range)	57 (17-86)	—
Younger than 60 y	186 (62)	140 (75)
60 to 69 y	73 (24)	56 (77)
70 y or older	41 (14)	21 (51)
Male	211 (70)	154 (73)
Female	89 (30)	63 (71)
Median time from diagnosis, mo (range)	24 (0-155)	—
Rai stage 0	11 (4)	10 (91)
Rai stages I to II	182 (61)	136 (75)
Rai stages III to IV	107 (36)	71 (66)
Zubrod performance status 0	119 (40)	96 (81)
Zubrod performance status 1	171 (57)	116 (68)
Zubrod performance status 2	10 (3)	5 (50)
Median white cell count $\times 10^9/L$ (range)	76 (2-620)	—
Less than $50 \times 10^9/L$	110 (37)	82 (75)
50 to $149 \times 10^9/L$	139 (46)	107 (77)
$150 \times 10^9/L$ or more	51 (17)	28 (55)
Median serum $\beta 2$-microglobulin, mg/L (range)	3.7 (1.6-16.4)	—
Less than $2 \times$ upper limit normal	168 (57)	141 (84)
$2 \times$ or more upper limit normal	127 (43)	73 (58)
Median serum lactate dehydrogenase, IU/L (range)	548 (100-1828)	—
Less than $2 \times$ upper limit normal (%)	293 (98)	72 (71)
$2 \times$ or more upper limit normal (%)	6 (2)	2 (33)
Diploid cytogenetics	156 (70)	118 (76)
Abnormal cytogenetics, not chromosome 17	58 (26)	42 (72)
Abnormality of chromosome 17	8 (4)	2 (25)
Bone marrow lymphocyte CD19/38 less than 30%	201 (79)	156 (78)
Bone marrow lymphocyte CD19/38 30% or more	52 (21)	34 (66)

Data are numbers (%) except where specified.

CLL2H trial for fludarabine-refractory CLL: Subcutaneous alemtuzumab

21

Stilgenbauer et al. ASH 2007; abstr 3120



Lenalidomide: Response in poor risk CLL

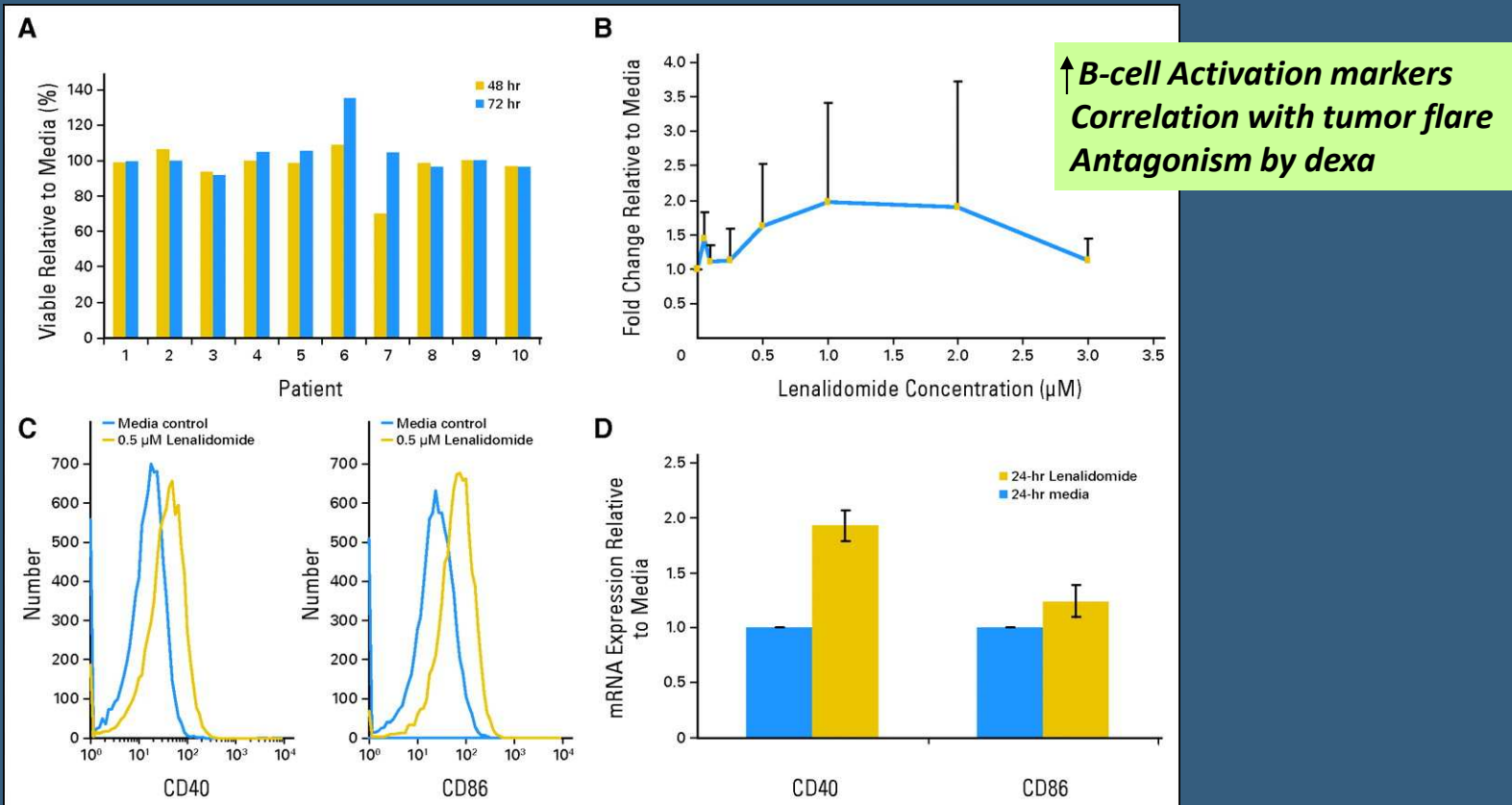
22

Subgroup	Number	Response	
17p-	6	3 PR, 1 SD, 2 NE	} 44%
11q-	10	1 CR, 3 PR*, 4 SD, 2 NE	
F-refractory	23	1 CR, 6 PR, 3 SD	30%
ZAP-70+	10	4 CR, 2 PR, 2 SD, 2 NE	60%

Chanan-Khan et al. ASH 2007; abstr 3108; Similar data: Ferrajoli et al. ASH 2007; abstr 754

Mechanism of tumor flare reaction following high doses lenalidomide in CLL which induced unacceptable toxicity in 4 patients

Andritsos, L. A. et al. J Clin Oncol; 26:2519-2525 2008

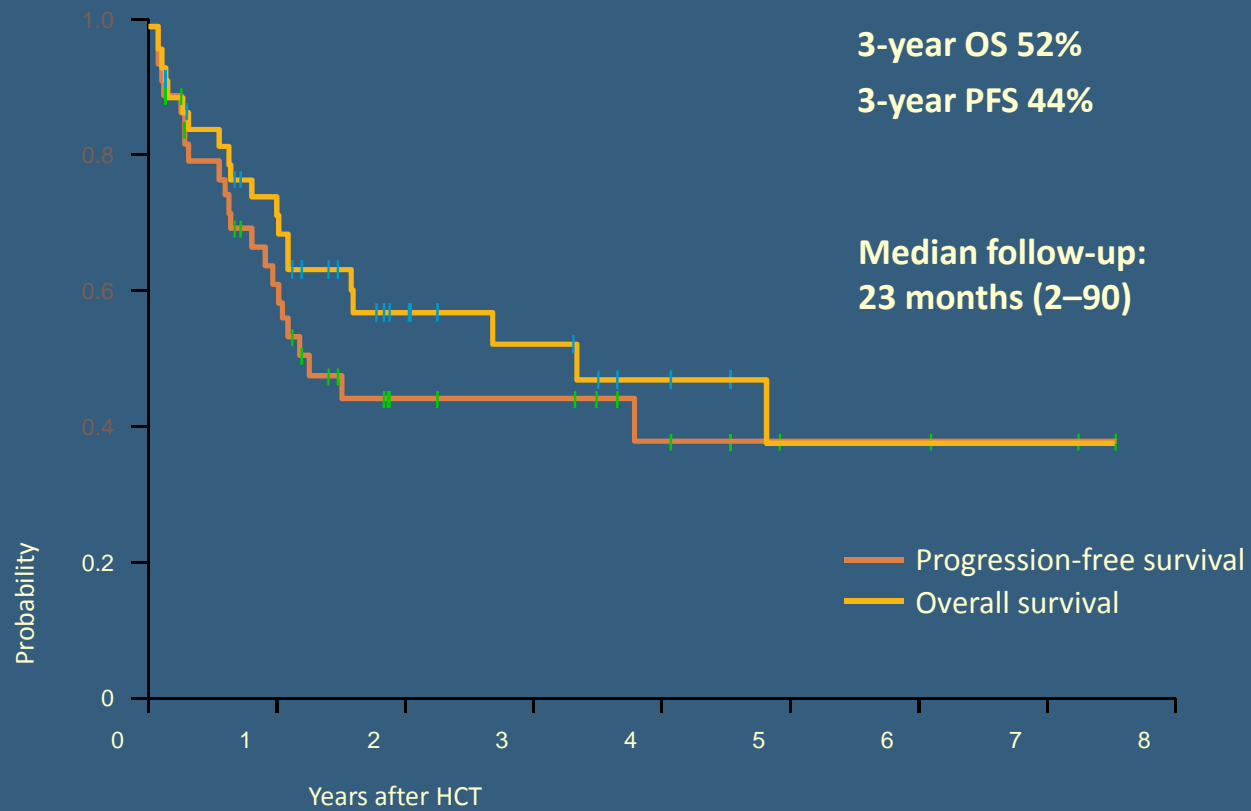


↑ *B-cell Activation markers*
Correlation with tumor flare
Antagonism by dexa

Fig 3. Treatment of CLL cells ex vivo with lenalidomide (0.5 μmol/L) for 48 and 72 hours does not promote loss of viability in vitro and upregulates CD40 and CD86 expression

Allo-SCT for 17p- CLL: EBMT survey

Schetelig et al. ASH 2007; abstr 47



Approccio terapeutico alla LLC con 17p-/TP53 mutato

- Problema sentito molto non solo per 17p- ma anche per giovane NR a terapia
- Problema di valutazione della risposta (TAC?)
- Prima linea FCR se “fit”, valutazione precoce della risposta (2 cicli) e switch terapia se NR (?)
- Alternativa prima linea: Alemtuzumab +/- HD metil predisolone e/o allo BMT (?)

Discussione