

Highlights from EHA

Novità dall'EHA >> [Leucemia linfatica cronica]

Relatore: **P. GHIA**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

Number and type of abstracts

2

Number of abstracts

CLL and related disorders - Biology

60

36

CLL and related disorders - Clinical

58

9

Prognostic markers

Prognosis on the stage

3

	Oral	poster
<u>Poster Sessions</u>		
CLL – Biology and Clinical Prognosis		20
CLL – Prognostic Factors		15
CLL – Clinical		15
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CLL - Biology and clinical	5	

Simultaneous Session

4

CLL – Biology and Clinical

- Short telomere length is an independent predictor of survival, progression, Richter's Syndrome transformation and recurrent infections: an analysis on 421 CLL patients including blinded validation in 230 cases (Rossi D., et al – Novara)
- The most frequent t(14;19)(q32;q13)-positive B cell malignancy corresponds to an aggressive subgroup of atypical CLL (Nguyen-Khac F. et al – Paris)
- CD49d expression is an independent risk factor of progressive disease in early stage CLL (Rossi D., et al – Novara)
- TP53 mutations and del17p13 predict similar outcome and chemorefractoriness in CLL (Cerri M., et al – Novara)
- Clinical and biological characterization of circulating endothelial cells in CLL (Rigolin G.M. et al, Ferrara)

Simultaneous Session

5

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6

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TP53 mutations and del 17p

7

Oral poster

TP53 mutations and del17p

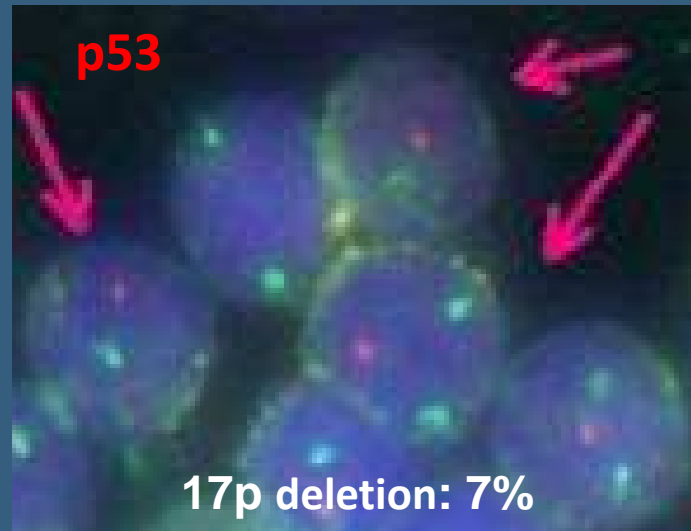
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8

- TP53 mutations and del17p13 predict similar outcome and chemorefractorines in CLL (Cerri M., et al – Novara)
- Analysis of TP53 mutations in a large cohort of CLL patients before first-line treatment: analysis of the genetic profile within the CLL4 trial (F vs FC) of the GCLLSG (Zenz T., et al – Ulm, Cologne)
- P53 mutations in a large cohort of CLL patients with 17p deletion: detailed analysis of mutation profile, alternative mechanisms of inactivation, clone size and clonal evolution (Zenz T., et al – Ulm)
- Inferior overall survival in CLL patients with TP53 mutations and MDM2 SNP309 polymorphism (Linderholm R.H., et al – Lund)

Deletion 17p

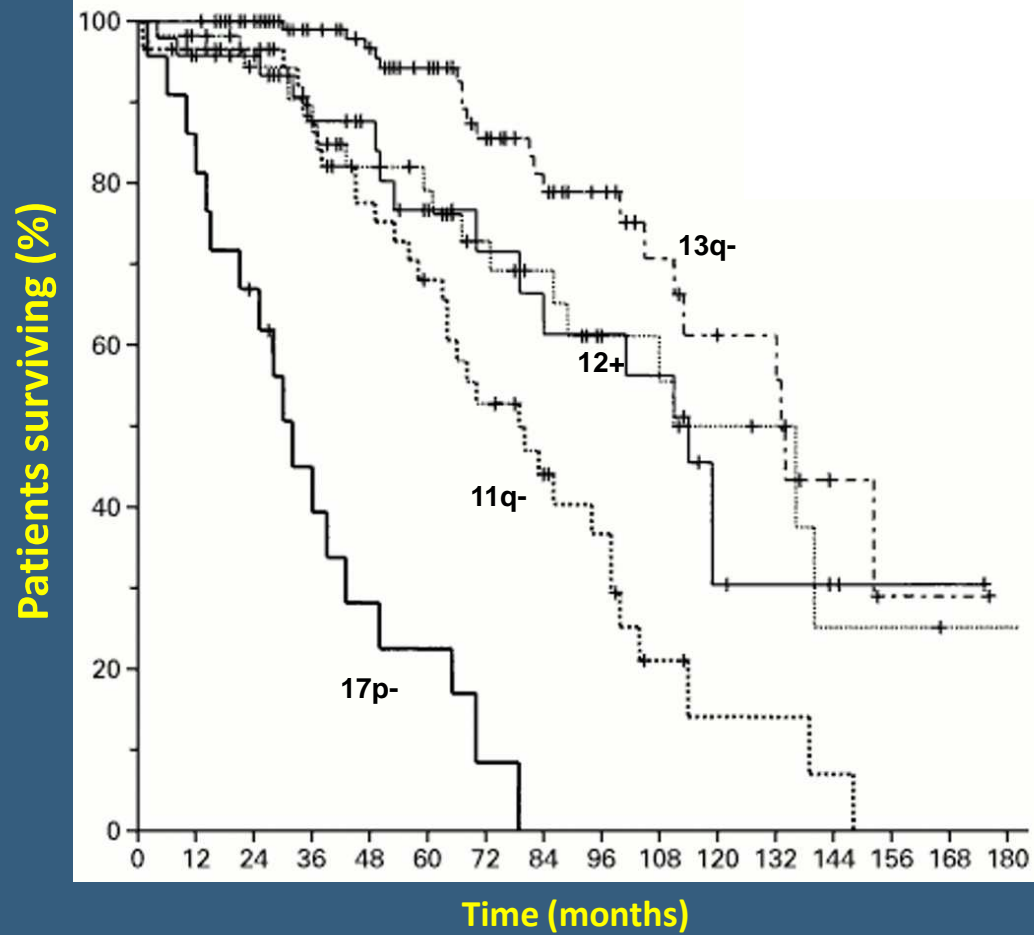
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Dohner et al. 2000

Deletion 17p

9

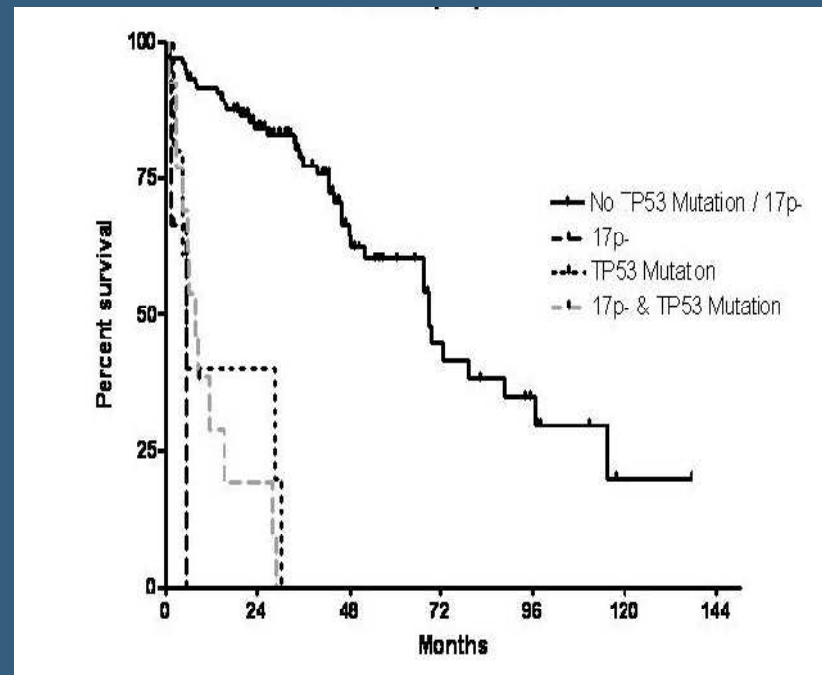


Dohner et al. 2000

TP53 mutation

10

- >80% del17 carry TP53 mutations
- TP53 mutations as sole mutation in 4.5% CLL



- TP53 mutations are an independent prognostic factor

TP53 mutation

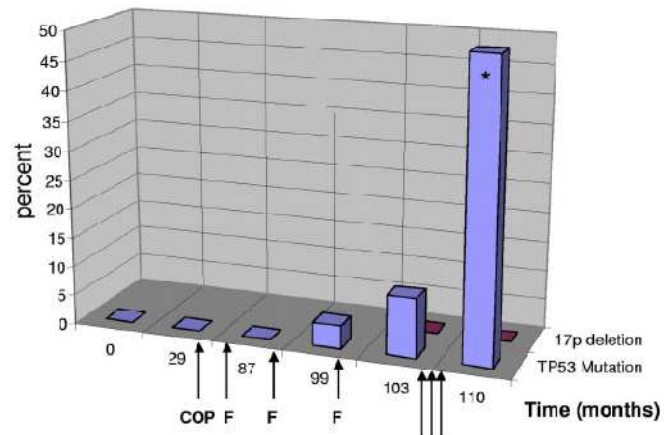
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- TP53 mutations as sole mutation in 4.5% CLL
- >80% del17 carry TP53 mutations
- TP53 mutations are an independent prognostic factor
 - Inferior overall survival in CLL patients with TP53 mutations and MDM2 SNP309 polymorphism (Linderholm R.H., et al – Lund)
- **Detection by HPLC exons 4-9 and sequencing**
 - P53 evaluation in CLL by p53 array: a simple, sensitive and specific method that unravels a high percentage of polymorphisms and mutations (Chiaretti S., et al – Roma)

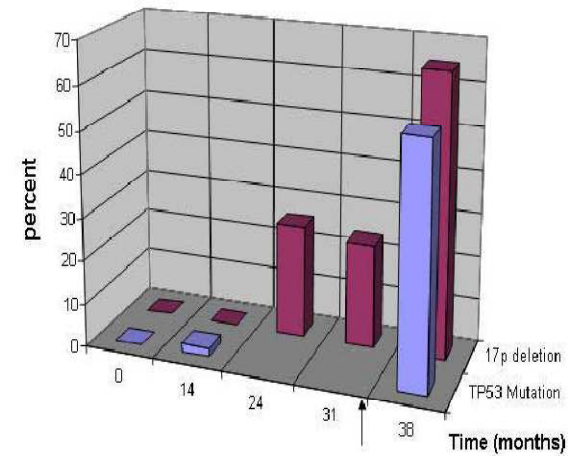
TP53 mutations and del17

➤ Abnormalities may be acquired with time

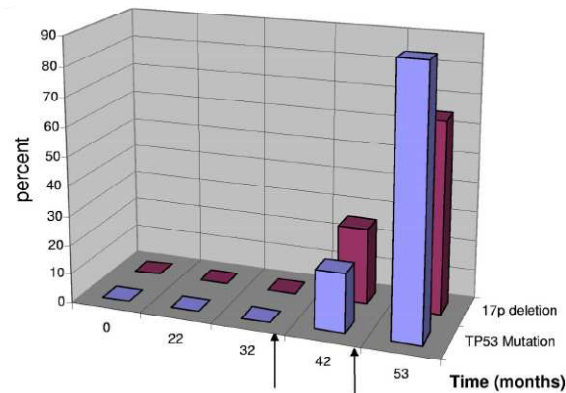
A



MULTIPLE REGIMENS
(CHOP, COP, Bendamustine, Dauno)



Cbl



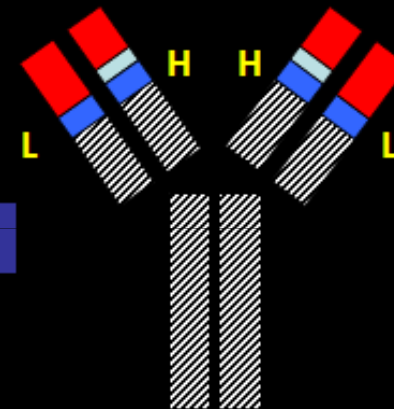
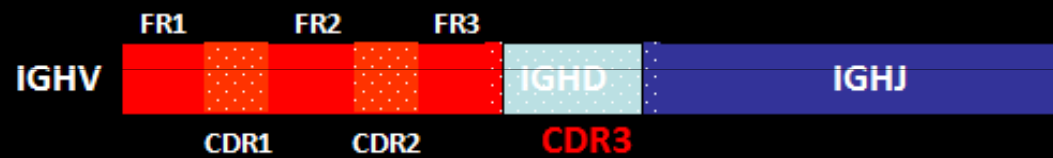
Cbl

F

Zenz et al. Blood 2008

Stereotyped Receptors

13



- **113** stereotyped antigen receptors (subsets)
- **26.9%** of all CLL cases (530/1967)

Stamatopoulos et al, 2007

Stereotyped Receptors

14

- Common herpesviruses and CLL: molecular evidence for a potential link with a subset of patients expressing stereotyped IGHV4-34 B cell receptors (Kostareli E., et al – Thessaloniki)
- CLL transforming to Richter's syndrome carry stereotyped HCDR3s at very high frequency (>50%) and display biased use of IGHV4-39 genes (Valeria S. et al – Novara)
- Novel molecular and clinical features of CLL expressing or not expressing stereotyped B cell receptors: results of an Italian multicentric study (Bomben R., et al – Aviano)
- Analysis of Chronic Lymphocytic Leukemias cases with stereotypic immunoglobulin's receptors in Ukrainian cohort (Bilous N., et al – Kiev)

- Common herpesviruses and CLL: molecular evidence for a potential link with a subset of patients expressing stereotyped IGHV4-34 B cell receptors (Kostareli E., et al – Thessaloniki)

93 patients



EBV-	EBV-	CMV-	EBV+
CMV-	CMV+	EBV+	CMV+
58	4	21	9

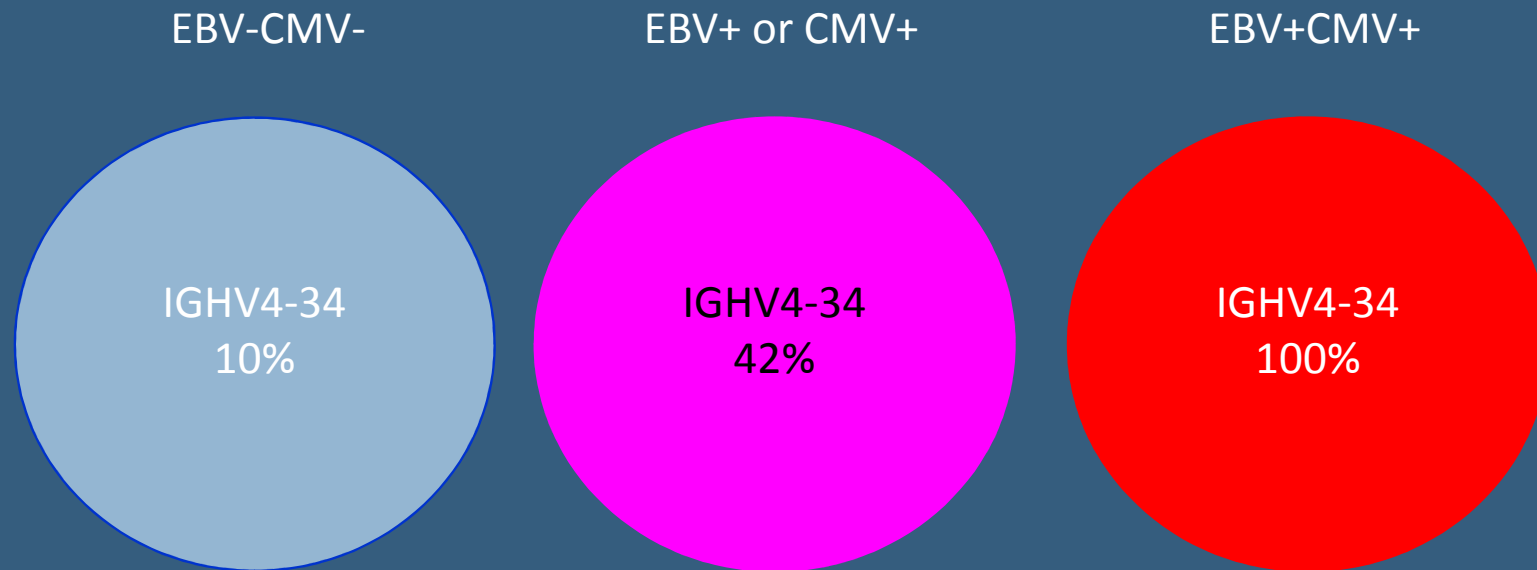
Group A

Group B

Group C

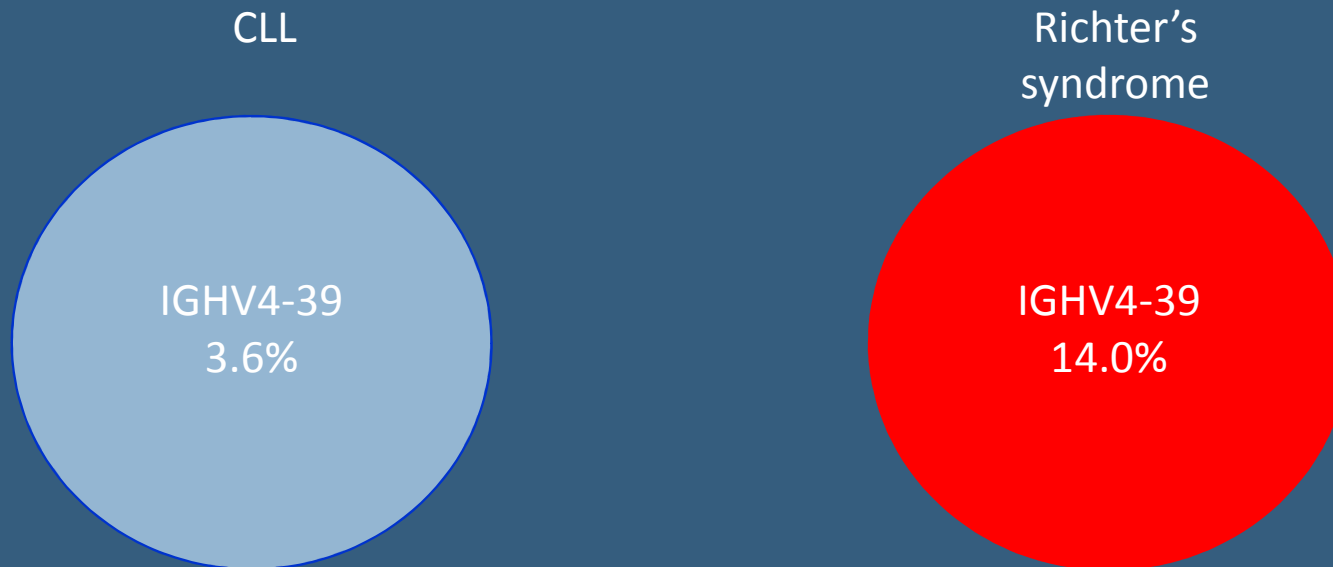
Kostareli et al. submitted

- **Common herpesviruses and CLL: molecular evidence for a potential link with a subset of patients expressing stereotyped IGHV4-34 B cell receptors (Kostareli E., et al – Thessaloniki)**



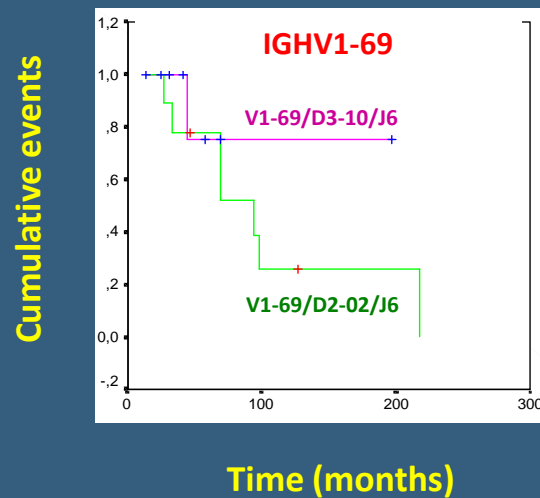
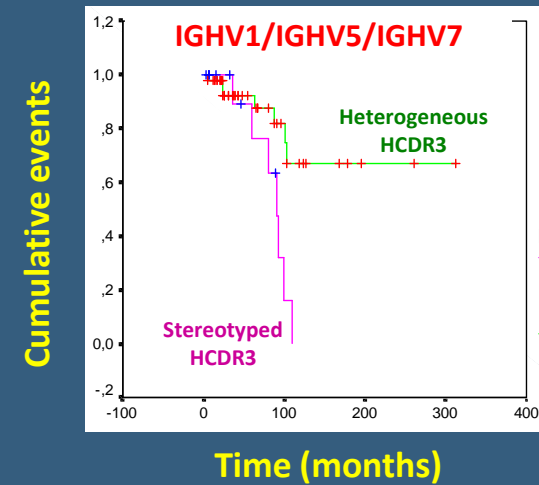
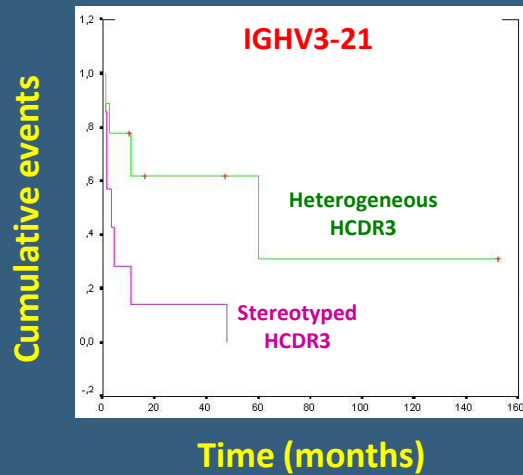
7/9 cases expressed stereotyped IGHV4-34/IGKV2-30 BCRs

- CLL transforming to Richter's syndrome carry stereotyped HCDR3s at very high frequency (>50%) and display biased use of IGHV4-39 genes (Valeria S. et al – Novara)



7/8 cases expressed stereotyped IGHV4-39 BCRs

- Novel molecular and clinical features of CLL expressing or not expressing stereotyped B cell receptors: results of an Italian multicentric study (Bomben R., et al – Aviano)



Stamatopoulos et al, 2007

Clinical - Thalidomide

19

CLL - Biology

Clinical and biological characterization of circulating **endothelial cells** in CLL (Rigolin G.M. et al, Ferrara)

Aberrant gene expression pattern of **angiogenesis-related** factors characterizes B cell chronic lymphocytic leukemia (Maffei R. et al, Modena)

CLL - Clinical

Combined **thalidomide** and **fludarabine** therapy in chronic lymphocytic leukemia results in distinct molecular and antileukemic effects (Giannopoulos K. et al, Lublin - Ulm)

Fludarabine plus **thalidomide** as frontline therapy for newly diagnosed patients with chronic lymphocytic leukemia (Ailawadhi S. et al, Buffalo)

Clinical - Thalidomide

20

- Combined **thalidomide** and **fludarabine** therapy in chronic lymphocytic leukemia results in distinct molecular and antileukemic effects (Giannopoulos K. et al, Lublin - Ulm)

d1:THAL 200mg/day
d7-11 FLU 25mg/sqm/day
Every 28 days for 6 cycles

20 patients first line: ORR 80%; 25% CR
20 patients second or third line: ORR 25%; 0% CR

- **Fludarabine** plus **thalidomide** as frontline therapy for newly diagnosed patients with chronic lymphocytic leukemia (Ailawadhi S. et al, Buffalo)

d1:THAL 200mg/day
d8-12 FLU 25mg/sqm/day
Every 28 days for 6 cycles

35 patients front line: ORR 97%; 52% CR
> grade 3: Neutropenia and thrombocytopenia; non-hematological: nausea and constipation

Clinical – F based regimen

21

- **Oral fludarabine plus rituximab result in high complete emission rate in CLL (Del Poeta G. et al, Rome)**

D1-5: FLU 35mg/sqm/day po 6 cy → (after 40 days) → Rituximab 375mg/sqm/w 4w

46 patients first line: ORR 100%; 80% CR (80% <1% MRD)

Myelotoxicity and infections: 5 pts grade $\frac{3}{4}$ infective lung toxicity and 5 herpes zoster

- **Oral fludarabine plus rituximab result in high complete emission rate in CLL (Del Poeta G. et al, Rome)**

D1-5: FLU 25mg/sqm/day iv 6 cy → (after 40 days) → Rituximab 375mg/sqm/w 4w

96 patients first line: ORR 96%; 79% CR (80% <1% MRD)

Myelotoxicity and infections: 3 pts grade $\frac{3}{4}$ infective lung toxicity and 1 hepatitis

CR (MRD +/- and PR) → Rituximab 375mg/sqm/mo 4mo → 150mg/sqm/mo 12mo

(75% vs 9% at 6 years)

Clinical – FC

22

- **Comparison of Cladribine plus Cyclophosphamide or Fludarabine plus Cyclophosphamide in different age groups in previously untreated patients with CLL (Robak T. et al, Lodz)**
- **Low dose oral fludarabine plus cyclophosphamide in elderly patients with untreated and refractory CLL (Forconi F. et al, Siena)**

d1-4 FLU 25mg/sqm/day

d1-4 Cy 120mg/sqm/day

Every 28 days for 4 cycles (received median 3)

Median age 70 years

25 patients untreated (13) or refractory (12): ORR 92%; 44% CR

untreated : ORR 100%; 61.5% CR

refractory : ORR 83.5%; 25% CR

Clinical – FCR and beyond

23

- **Retrospective comparison of efficacy and toxicity of FC and FCR regimens in untreated patients with CLL (Nikitin A. et al, St. Petersburg)**

D1-3:F 25mg/sqm/day Cy 250mg/sqm/day
D1 Rituximab 375mg/sqm/day
Every 28 days for 6 cycles

102 patients front line: FC: ORR 87%; 39% CR
FCR: ORR 95%; 60% CR

- **Lumiliximab in combination with FCR for the treatment of relapsed CLL: results from a phase I/II multicenter study (Byrd J. et al, Columbus)**

Lumiliximab: 375 or 500 mg/sqm/day

31 patients - relapsed: ORR 65%; 52% CR

- **Chemoimmunotherapy regimen of fludarabine, cyclophosphamide and rituximab followed by alemtuzumab as initial therapy for CLL: a valid approach for eradication of minimal residual disease (Galimberti S A. et al, Pisa)**

Alemtuzumab sc 10mg 3 times/week for 12 weeks (MRD+ and PR)

16 patients front line: ORR 87%; 74% CR