

# CLL Patient Association September 2010

Daniel Catovsky



# CLL Treatment: Key Questions

1. Who to treat (stages)
2. When to treat (stage/progression)
3. How (treatment protocol)

# Treatment Decisions in CLL are Guided by the Clinical Stage

Stage (Binet)	Feature	Incidence
A	Nodes ( $\pm$ spleen) in $<3$ areas No anaemia or thrombocytopenia	50%
B	Nodes ( $\pm$ spleen/liver) in $\geq 3$ sites	30%
C	Anaemia (Hb $<10$ g/dl) Platelets ( $<100 \times 10^9/l$ )	20%

# Stage A CLL (50% of Cases)

There are 3 evolutionary forms:

stable/smouldering A 25%

(never requiring therapy)

slowly progressive A\* 15%

(may need treatment in 1-5 years)

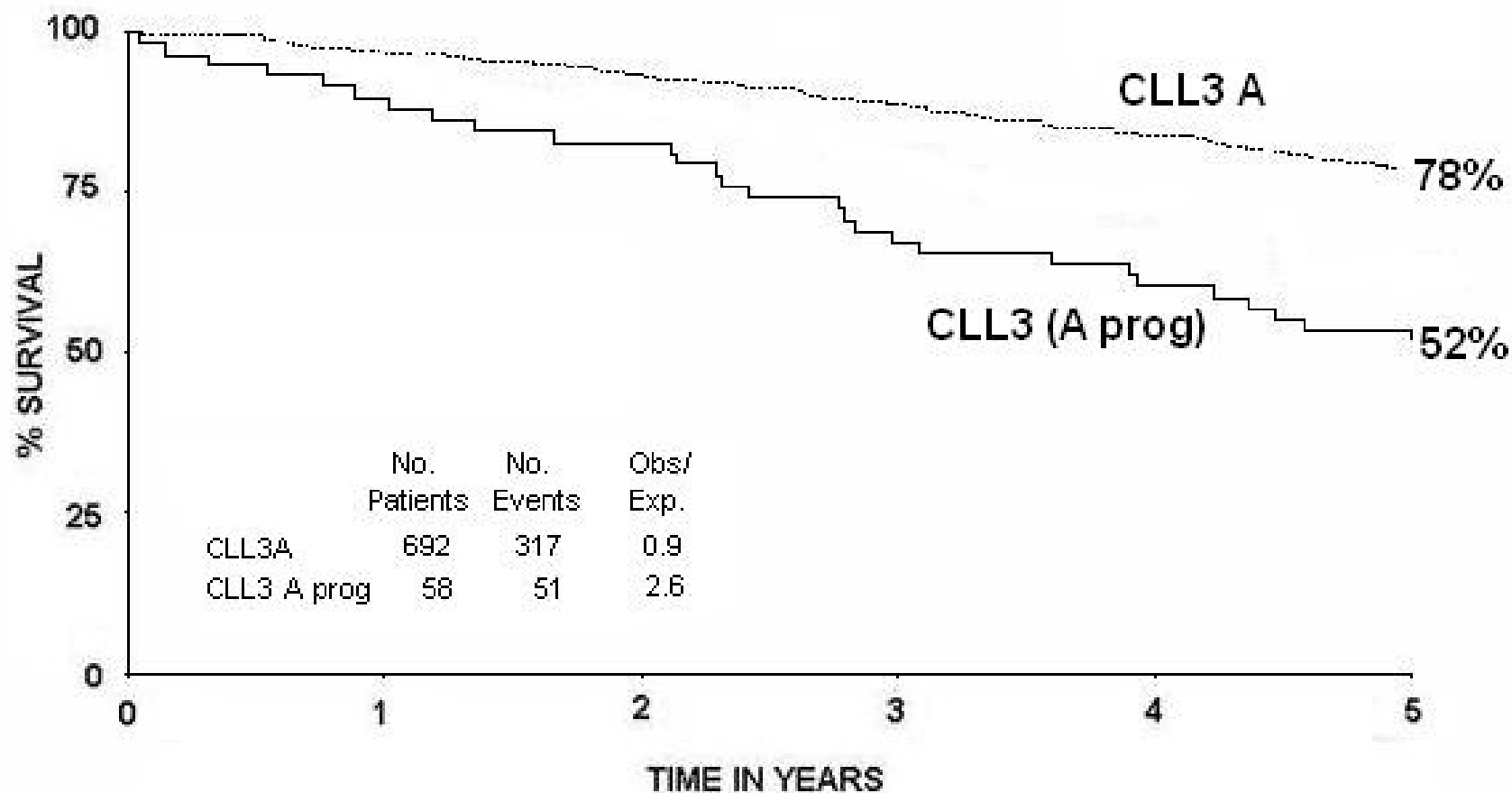
progressive A\* 10%

(apparent within 6 months of observation)

*\* Slowly progressive and progressive can be identified early by biological/genetic markers: mutation of Ig V<sub>H</sub> genes; expression of CD38 and ZAP-70.*

# MRC CLL3 Trial

## Survival in Stage A Patients



# Prognostic Biomarkers in CLL

- $\beta$ 2-microglobulin
- CD38, ZAP-70, CD49d
- IGHV mutational status & usage
- FISH analysis
- *TP53* mutations (and 17p del)
- Lipoprotein lipase
- Telomere length
- Soluble CD23
- Circulating VEGF

# Indications for Treatment in CLL

Binet stages:

A progressive, B & C (60% of cases)

Treatment for stage A with unmutated Ig V<sub>H</sub> genes, CD38+/Zap70+ is not indicated unless clinical progression but currently this issue is addressed in randomised clinical trials in Germany, USA and UK

# Treatment Modalities in CLL (1)

## Chemotherapy

- single agent
  - chlorambucil (Chl)
  - cyclophosphamide (C)
  - fludarabine (F)
  - cladribine (Clad)
  - corticosteroids (Pred)
  - high dose methylpred (HDMP)
  - lenalidomide
- combinations
  - FC; Clad/C; COP;
  - CHOP (conventional or 'french')
  - FCM (FC+M=mitoxantrone)

# Treatment Modalities in CLL (2)

## Monoclonal Antibodies

- Rituximab (anti-CD20)
- Ofatumumab (anti-CD20)
- GA101 (anti-CD20)
- Luminiximab (anti-CD23)
- Alemtuzumab (anti-CD52)
- HA22 [HA22-LR] (anti-CD22 immunotoxin)

# Treatment Modalities in CLL (3)

## Combinations of Chemo and Antibodies

FR; FCR; FCMR; FluCam; CamFlu;  
CFAR; Ritux/Campath; HDMP/Ritux  
Chl/Ritux; Chl/Ofat; Chl/GA101

## Stem-Cell Transplantation

autologous

allogeneic (low intensity)

# Improved Survival in CLL in the Last 3-4 Decades (I)

- Evidence from several historical series
- Data from MRC CLL trials 1-4
- Single centre studies (Barcelona)

# Improved Survival in CLL in the Last 3-4 Decades (II)

Period	5 year	10 year
1980's	54%	28%
2001	60%	35%

*Brenner et al 2008*

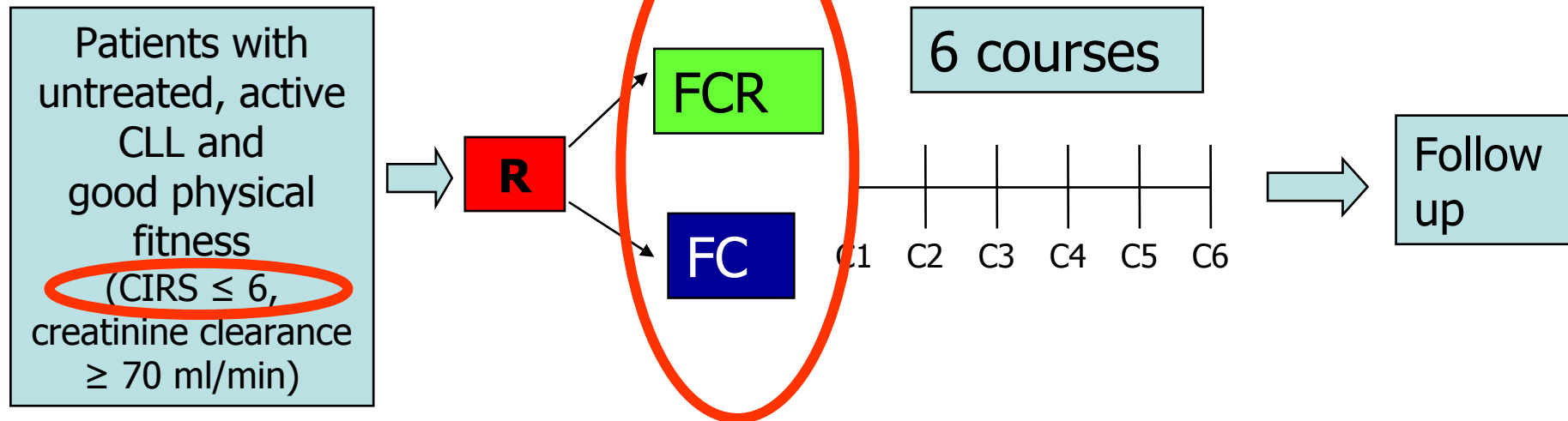
# UK CLL Trials: Survival from Randomisation

	5 Years	10 Years
CLL1	43.4%	17.5%
CLL2	52.8%	24.7%
CLL3	46.7%	10.5%
CLL4	57.1%	32.0%

# Increase in the Rate of CR in CLL in the Last 4 Decades

Decade	Drug/Combination	CR (%)
1970s	Chlorambucil/COP	5-10
1980s	CHOP, CAP, Chl + Epir	15-20
1990s	Fludarabine (F)	10-30
2000	F + Cyclo (FC)	20-40
	F + Rituximab (R)	30-40
2005-8	FCR	52-72
2007-8	FC + Mitox (FCM)	64
	FCMR	74

## CLL8 Study Design



### Primary endpoint

- Progression-free survival (PFS)

### Secondary endpoints

- Overall survival
- Rates of molecular, complete and partial remission
- Rates of treatment-related adverse effects

## FCR First-Line Treatment in CLL

- **FCR is superior to FC in most cytogenetic subgroups with regard to:**
    - **Response rates (CR, ORR, MRD).**
    - **Progression-free and overall survival.**
  - **FCR and FC inefficient in del(17p)**
  - **Low MRD level associated with improved PFS**
  - **FCR is safe:**
    - **FCR causes more neutropenias**
    - **FCR does not cause more infections or other severe side.**
    - **FCR is well tolerated in physically fit patients**
- **FCR is the new standard treatment for physically fit CLL patients**

\* Hallek et al, Lancet 2010 (in press)