CLL Patient Association
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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 (± spleen) in <3 areas No anaemia or thrombocytopenia	50%
B	Nodes (± spleen/liver) in ≥3 sites	30%
C	Anaemia (Hb<10g/dl) Platelets (<100×10^9/l)	20%

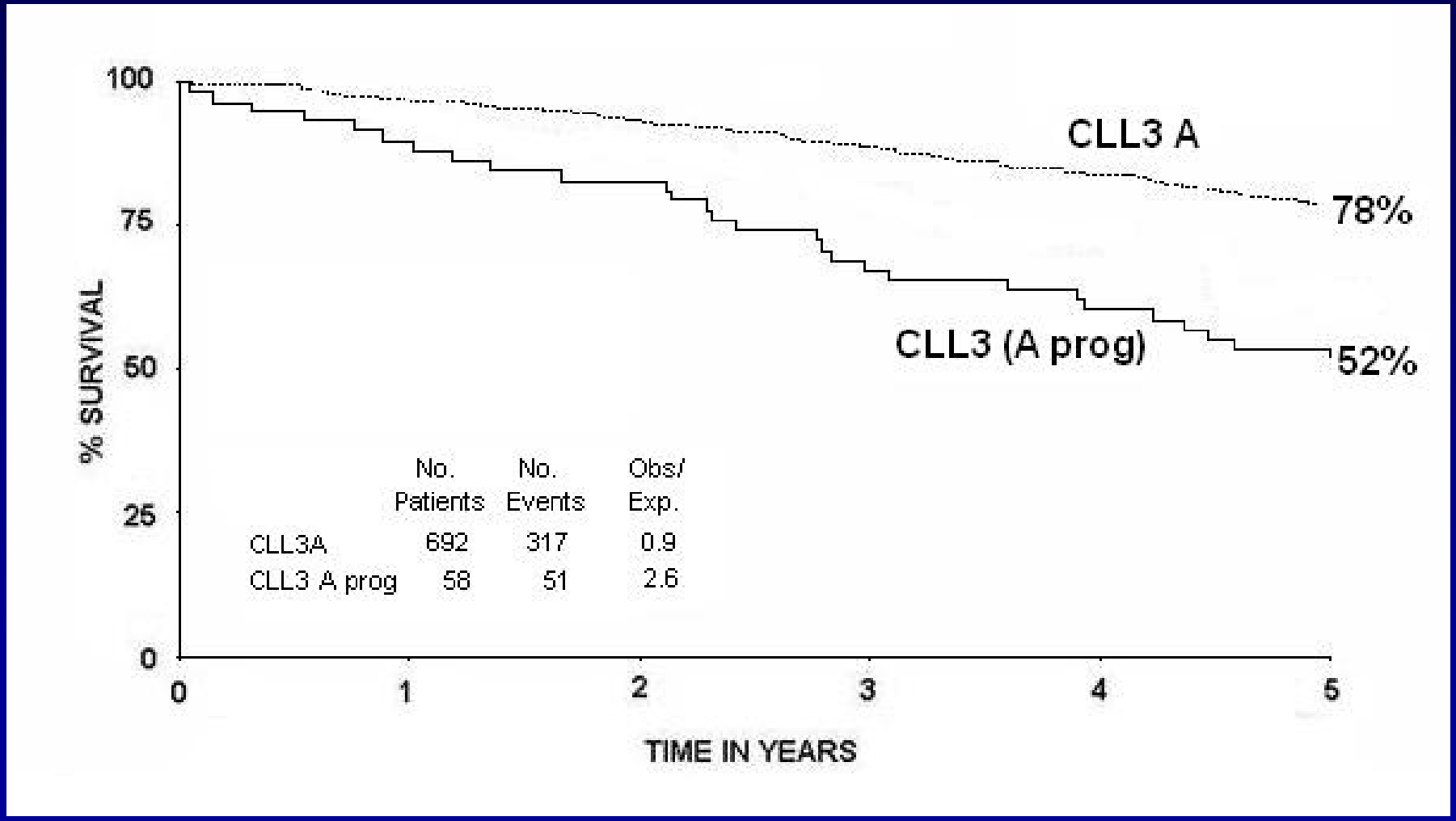
Stage A CLL (50% of Cases)

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_H genes; expression of CD38 and ZAP-70.*

MRC CLL3 Trial
Survival in Stage A Patients



Prognostic Biomarkers in CLL

- β2-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_H 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
- Date 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

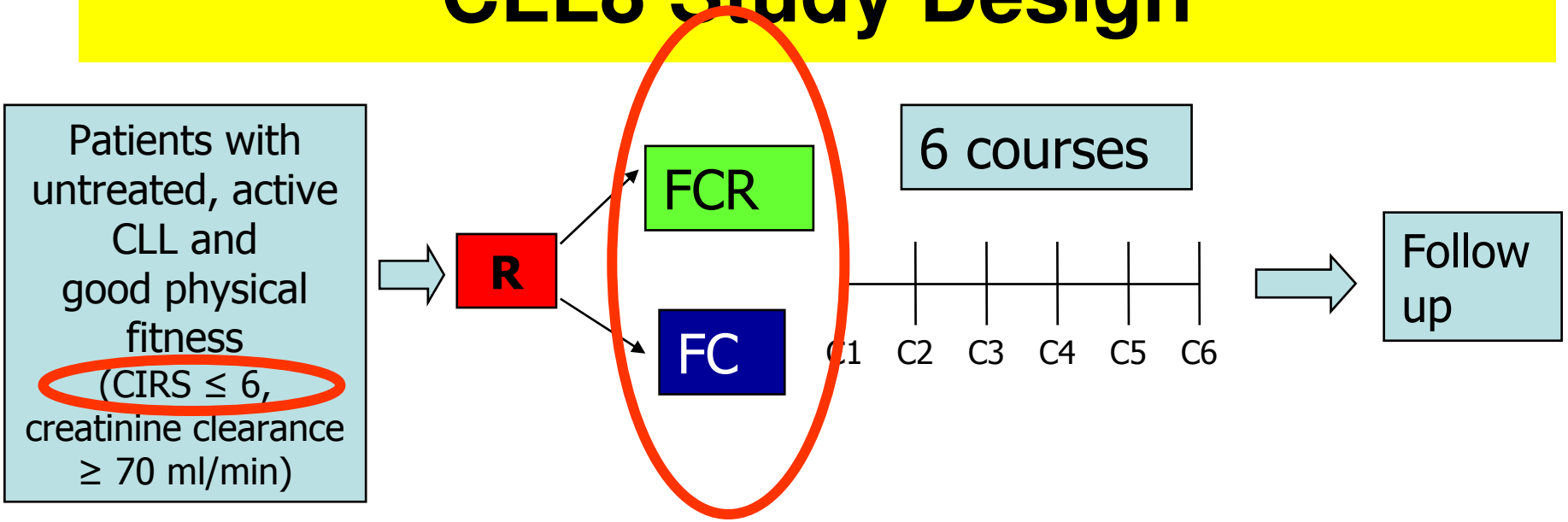
	5 Years	10 Years
CLL1	43.4%	17.5%
CLL2	52.8%	24.7%
CLL3	46.7%	10.5%
CLL4	57.1%	32.0%

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

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

CLL8 *

DEUTSCHE CLL STUDIENGRUPPE

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)