

# **UK CLL Clinical Trials update**

**Peter Hillmen**

**On behalf of the CLL sub-group of the  
NCRI**

**29<sup>th</sup> April 2008**

# **UKCLL forum/NCRI CLL Trials**

- 1. Trials for patients without co-morbidity (“Go-Go”)**
- 2. Trials for patients with co-morbidity (“Slow-Go”)**
- 3. Consolidation/maintenance trials**
- 4. Trials for patients with p53 deletion or dysfunction**

# **UKCLL forum/NCRI CLL Trials**

- 1. Trials for patients without co-morbidity (“Go-Go”)**
- 2. Trials for patients with co-morbidity (“Slow-Go”)**
- 3. Consolidation/maintenance trials**
- 4. Trials for patients with p53 deletion or dysfunction**

# NCRI FCM+/-R (CLL201)

P.I. – Peter Hillmen, Mike Leach, Andy Pettitt

## Rationale:

- FC = LRF CLL4; FCR = MDACC; FCM = Barcelona

## Trial outline:

- Previously treated CLL (except FCM or rituximab)
- Flud + Cyclophos + Mitoxantrone +/- Rituximab
- Randomised Phase II, up to 28 patients in each arm
- Stratified by exposure/resistance to fludarabine

## Trial objectives:

- 1<sup>o</sup>: overall response rate to FCM and FCM-R
- 2<sup>o</sup>: assess eradication of MRD, safety, PFS, OS

# Responses in CLL201

	All patients	FCM	FCM-R
No: of patients	52	26	26
ORR	32 (62%)	15 (58%)	17 (65%)
CR	5 (10%)	1 (4%)	4 (15%)
CR(i)	9 (17%)	2 (8%)	7 (27%)
PR	18 (35%)	12 (46%)	6 (23%)
SD/PD	15 (29%)	8 (31%)	7 (27%)
Early Death (before assessment)	4 (8%)	2 (8%)	2 (8%)
Withdrew consent (before assessment)	1 (2%)	1 (4%)	0 (0%)
MRD negative	9 (17%)	3 (12%)	6 (23%)

} -12% (between FCM and FCM-R for CR and CR(i))  
} -42% (between FCM and FCM-R for CR and CR(i))

# Impact of age on outcome in CLL201

		FCM	FCM-R
Patients 68 and over	CR or CR(i)	2/14 (14%)	4/12 (33%)
	SAE (one or more)	9/14 (64%)	6/12 (50%)
Patients under 68	CR or CR(i)	1/12 (8%)	7/14 (50%)
	SAE (one or more)	3/12 (25%)	6/14 (43%)

# **CLL6: A randomised phase III three-arm trial in untreated patients with CLL to assess the addition of mitoxantrone and low dose rituximab to FC**

## **Eligibility:**

- Untreated patients with CLL requiring therapy
- Considered fit for fludarabine + cyclophosphamide

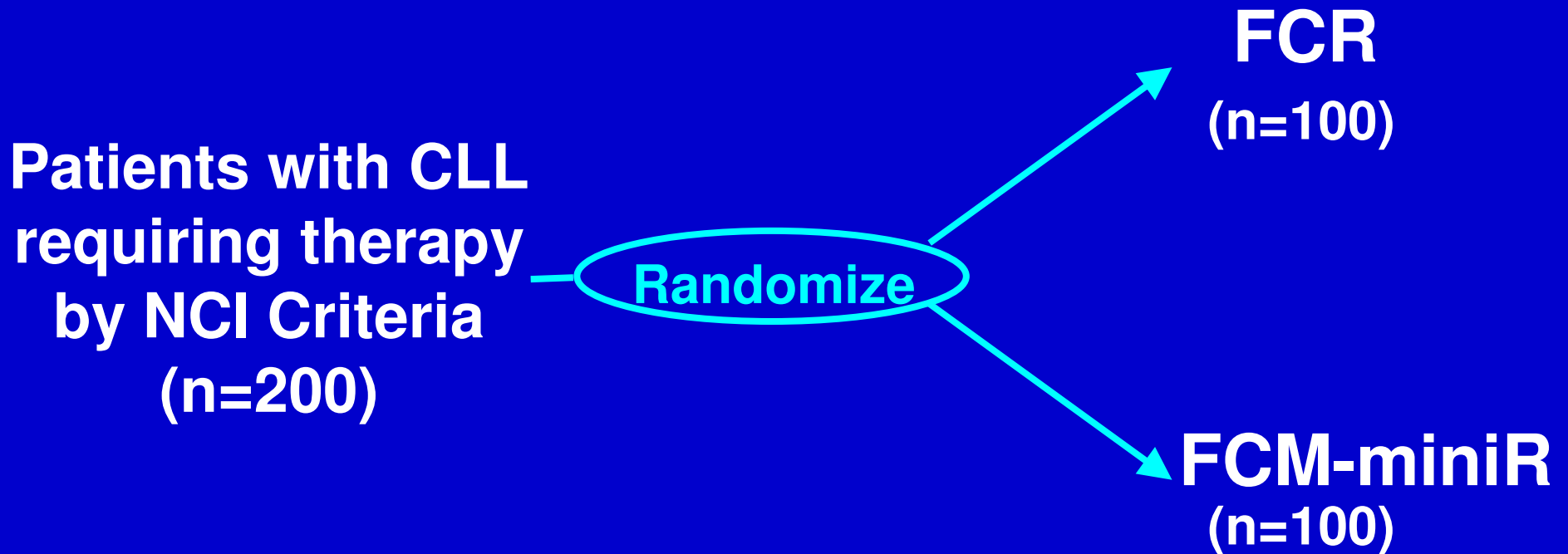
## **Design:**

- All patients receive FC
- Three-way randomisation to:
  - Oral Fludarabine+Cyclophosphamide (FC)
  - FC + mini-rituximab (FCminiR)
  - FC + Mitoxantrone + mini-rituximab (FCMminiR)

## **HTA outcome:- resubmission requested**

- ?standard arm FC when should be FCR

**CLL6a: A randomised phase II trial**  
**HTA Application submitted March '08 (June '08)**



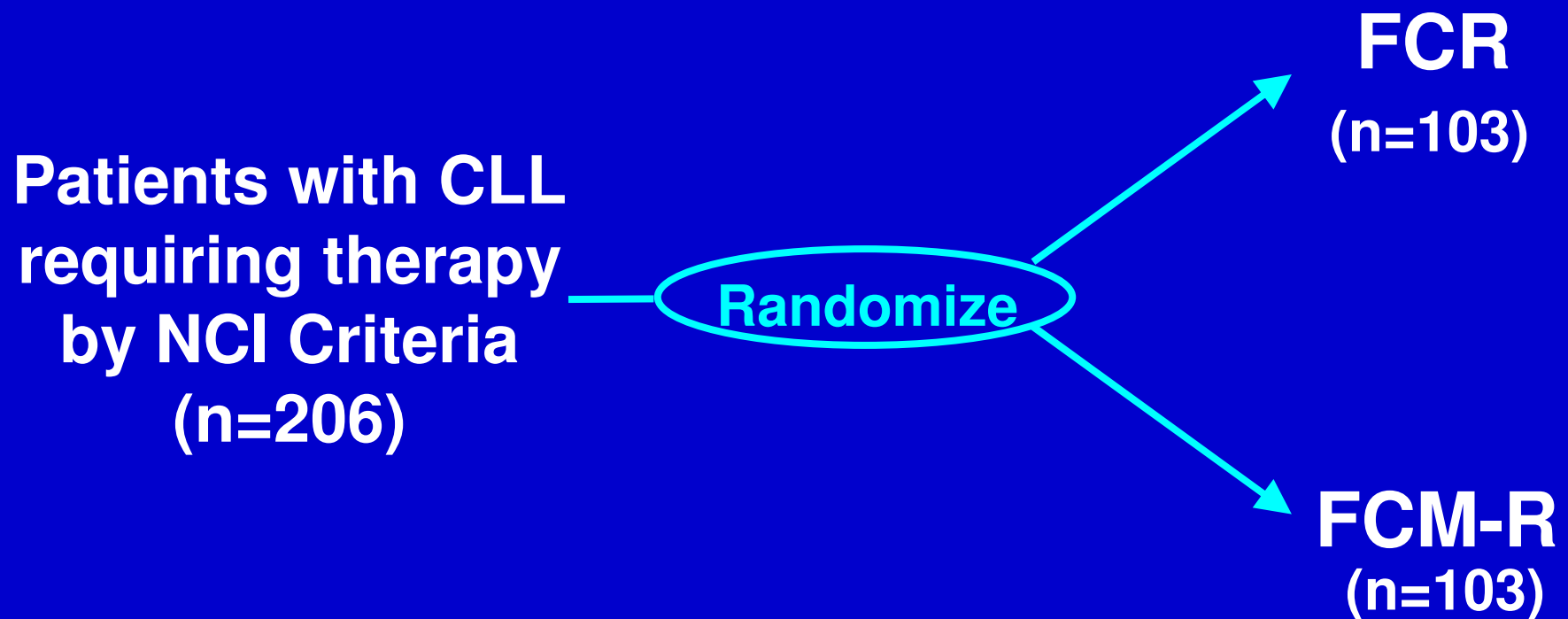
**Trial end-points: CR rate and ORR**

**If successful then FCR probably NICE approved**

**Then apply for 3 arm trial: FCR vs FCM-R vs FCM-miniR**

# CLL6b: A randomised phase II trial

- ?Roche to support rituximab and trial



**Trial end-points:**

**Primary end-point = Complete remission rate**

**If encouraging to power Phase III on PFS**

# UKCLL forum/NCRI CLL Trials

1. Trials for patients without co-morbidity (“Go-Go”)
2. Trials for patients with co-morbidity (“Slow-Go”)
3. Consolidation/maintenance trials
4. Trials for patients with p53 deletion or dysfunction

# Chlorambucil + rituximab for patients with co-morbidity (CLL208)

P.I. – Peter Hillmen, Andy Pettitt

Roche – Delphine Moreau, Colin Haywood

## Trial outline:

- Untreated CLL unfit for fludarabine-based therapy
- Chlorambucil (10mg/m<sup>2</sup>/d x7) + Rituximab (6 doses)
- Single arm, Phase II, 50 patients in total

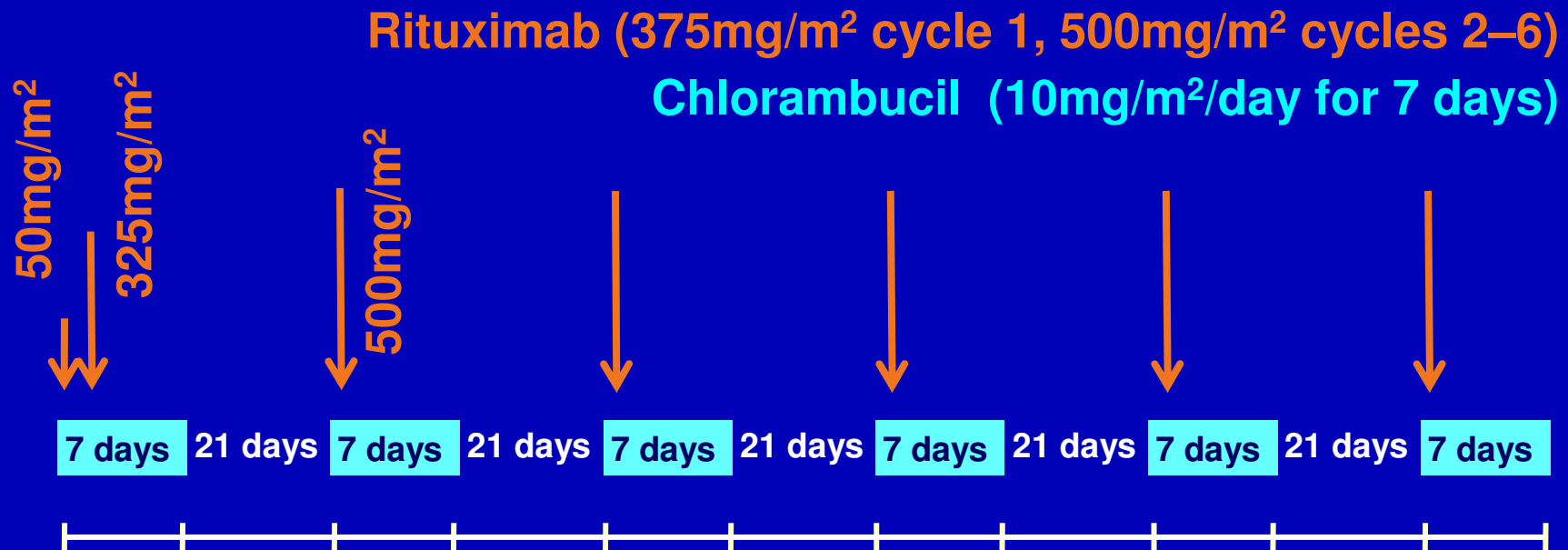
## Trial objectives:

- 1<sup>o</sup>: Safety analysis
- 2<sup>o</sup>: assess eradication of response rate, MRD, PFS, OS

## Timelines:

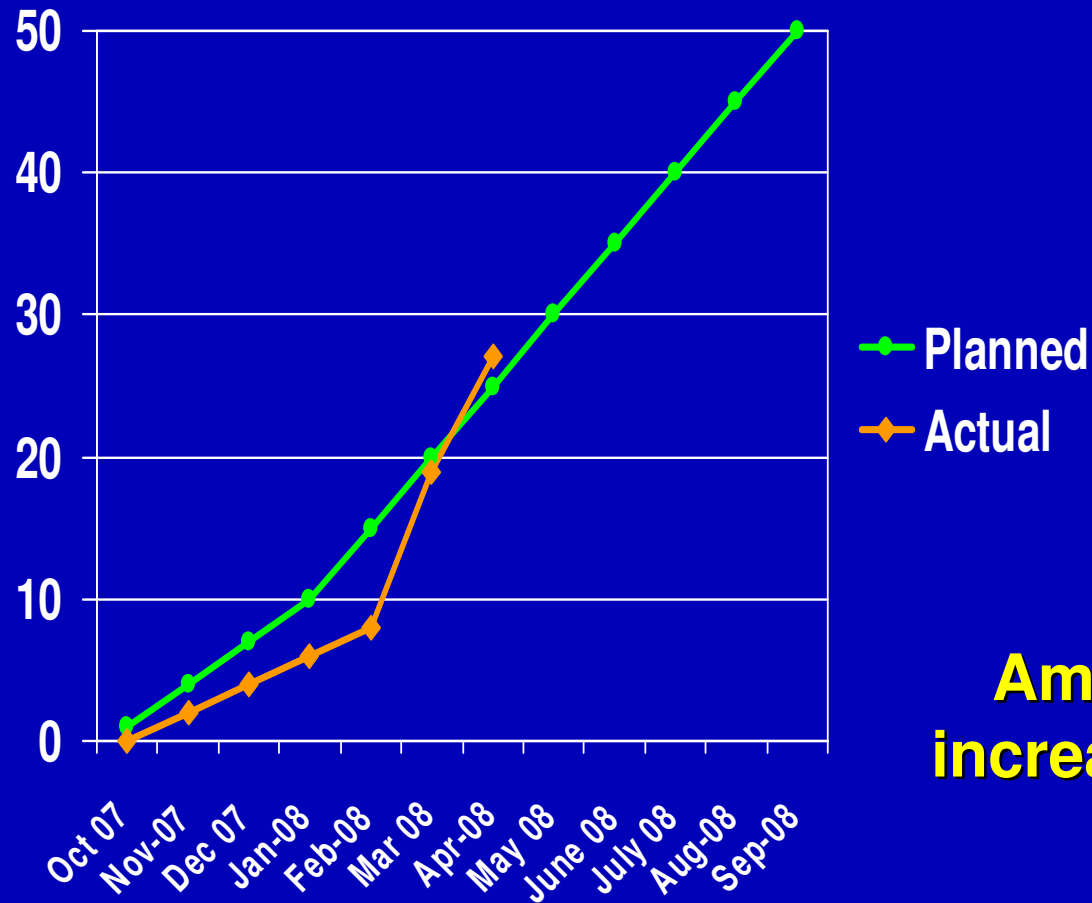
- Investigator Meeting Nov 2007 – first patient recruited

# R-chlorambucil - the CLL208 study design: Phase II trial in 50 previously untreated patients



- Formal assessment after 6 cycles of therapy → CT scan and BM A&T for MRD if in clinical remission
- Option for further 6 cycles chlorambucil monotherapy if continuing to respond

# R+Chlorambucil trial recruitment status (CLL208)



**Proposed Trial  
Amendment Possibly  
increasing from 50 to 100  
patients**

**11 centres currently recruiting in the UK**

# **CLL7: A Phase III randomized trial for patients with co-morbidity**

## **Ofatumumab:**

- Human anti-CD20 antibody
- Phase II single agent data in relapsed and/or refractory CLL presented 2006
- Large non-randomised single agent Phase II registration study in refractory CLL in progress

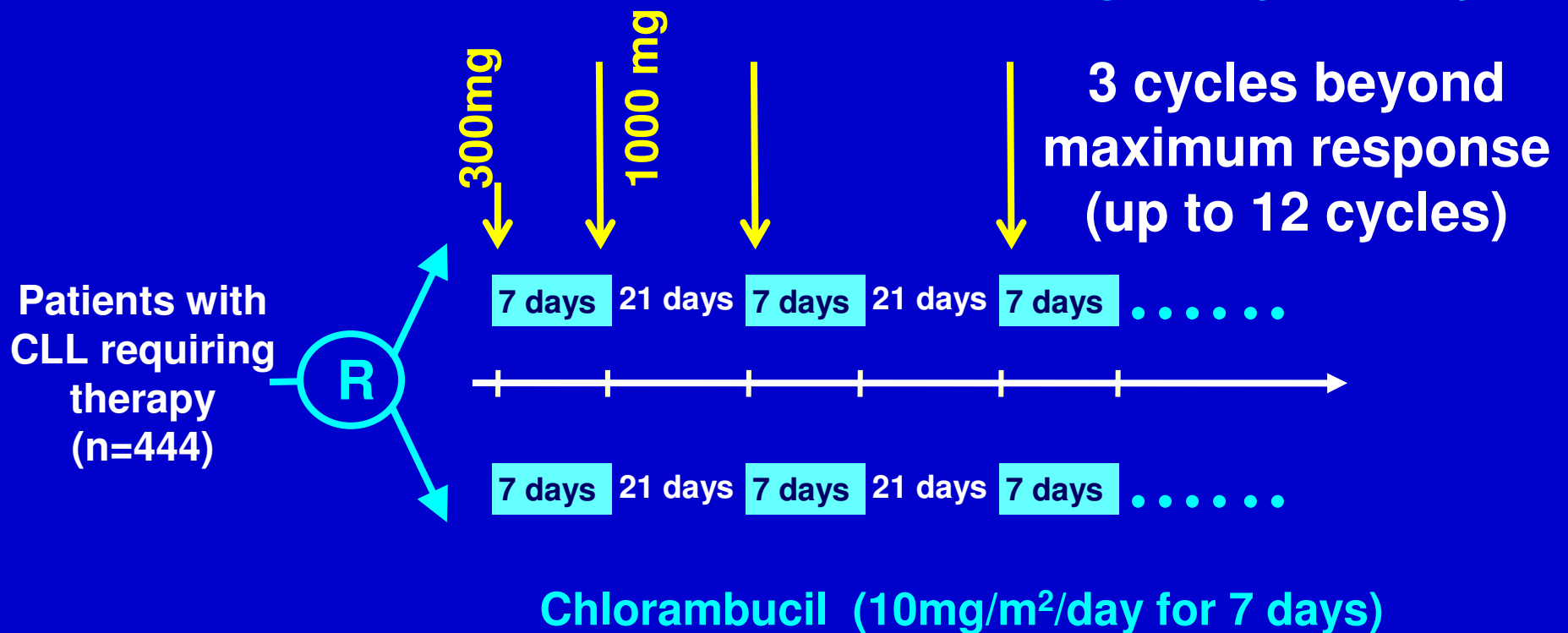
## **OMB110911 Trial (NCRI CLL7 Trial):**

- Registration study for front-line CLL
- NCRI-badged and UK leading the study
- 25-40 UK sites depending on feasibility

# CLL7: GSK Registration Study for ofatumumab (OMB110911 Trial)

Ofatumumab (300mg + 1000mg cycle 1, 1000mg cycles 2–12)

Chlorambucil (10mg/m<sup>2</sup>/day for 7 days)



**Primary end-point = Progression Free Survival**

# UKCLL forum/NCRI CLL Trials

1. Trials for patients without co-morbidity (“Go-Go”)
2. Trials for patients with co-morbidity (“Slow-Go”)
3. Consolidation/maintenance trials
4. Trials for patients with p53 deletion or dysfunction

# NCRI CLL207 MRD Eradication Trial

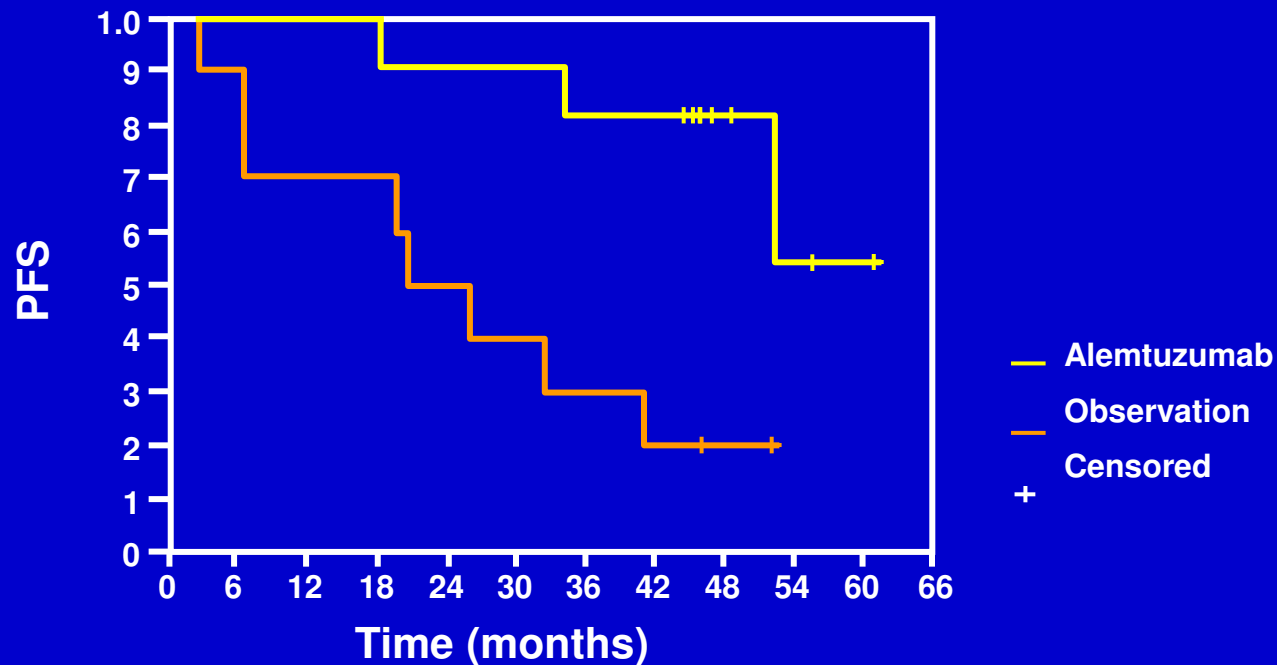
## Rationale:

MRD negative patients have better survival

GMCLLSG CLL4B trial – impressive PFS but toxicity

Interval of 6 months from completing chemotherapy  
to commencing alemtuzumab consolidation

# Update on CLL4B Study (06/2006): Progression-free Survival



**Median follow-up since randomization to CLL4B = 48 months**

Events (progressive disease)

- Alemtuzumab = 3
- Observation = 8

Progression-free survival ( $P = 0.0035$ )

- Alemtuzumab = not reached
- Observation = 20.6 months

**Schweighofer C et al. Blood 2006; 108: abstract 33**

# Overview on Published Consolidation Studies

Group and Lead Author	Induction	Interval from Induction to Campath	Dose, Route and Duration	Improvement in response after consolidation	N	Deaths
CALGB (Rai '02)	4 X Flu	2 months	30 IV tiw, 6 wks	23%	36	1
CALGB (Rai '03)	4 x Flu	2 months	30 SQ tiw, 6 wks	10%	18	0
Hainsworth '05	FR	4 weeks or 8 weeks	30 IV tiw, 4 wks	17%	37	0
GMCLLSG (Wendtner '03)	6 x F or 6 x FC	10 weeks	30 IV tiw, 12 wks	18% PFS longer	21	0
Montillo '04	F or FC	16 weeks	10 SQ tiw, 6 wks	44%	34	0
MDACC (O'Brien '03)	N/A	5 months	10 SQ tiw, 4 wks 30 SQ tiw, 4 wks	39% 65%	24 34	0 0
Delmer, '06	3 x FC	2 months	10 SQ tiw, 8 wks	27%	33	0
CALGB (Lin, 07)	6 x FR	3 months	30 SQ, 6 wks	??	51	6

**Total = 288 7**

# NCRI CLL207 MRD Eradication Trial

## Rationale:

MRD negative patients have better survival  
GMCLLSG CLL4B trial – impressive PFS but toxicity  
Interval of 6 months from completing chemotherapy  
to commencing alemtuzumab consolidation

## Aims:

1. Effectiveness and safety of SC alemtuzumab in eradicating MRD in consolidation
2. Effectiveness and safety of “MRD-guided” maintenance with SC alemtuzumab

# NCRI CLL207 MRD Eradication Trial

## Details of trial design

- Will recruit up to 54 patients – 24 interim analysis
- CR or good PR, 6 to 24 months post-therapy (1-3 prior)
- SC alemtuzumab
  - 30mg, 3x a week, no escalation
  - self-administration permissible after week 2
  - 6 to 12 weeks depending on MRD response in marrow
- Pharmacokinetic study in a proportion of patients

## Progress to date

- 16 patients have completed or on consolidation
- Safety enhanced due to CALGB results
- Results to assist design of Phase III NCRI CLL8 trial

# CLL8: A Phase III randomized trial of alemtuzumab consolidation

## Eligibility:

Patients in CR or good PR 6 to 12 months post-treatment  
Patients from CLL6 or 7 or out-with trials

## Objectives:

Primary: effect on PFS of alemtuzumab consolidation in patients who responded to previous therapy.

Secondary: MRD, survival, safety, toxicity and QoL

## Statistical plan:

288 patients (144 alemtuzumab, 144 placebo) to detect an increase in PFS from 2 years to 3 years

# **CLL8: A Phase III randomized trial of alemtuzumab consolidation**

## **Funding:**

Full costing and drug costs agreed by Bayer  
Schering Pharma

## **Start date:**

Awaiting results of CLL207 – safety and efficacy  
Already approved by CTAAC for NCRN-badging  
Aim to commence recruitment end 2008 or 2009

# UKCLL forum/NCRI CLL Trials

1. Trials for patients without co-morbidity (“Go-Go”)
2. Trials for patients with co-morbidity (“Slow-Go”)
3. Consolidation/maintenance trials
4. Trials for patients with p53 deletion or dysfunction

# NCRI CLL with p53 deletion (CLL206)

Chief Investigator:

Andy Pettitt

Co-investigators:

Estella Matutes

Peter Hillmen

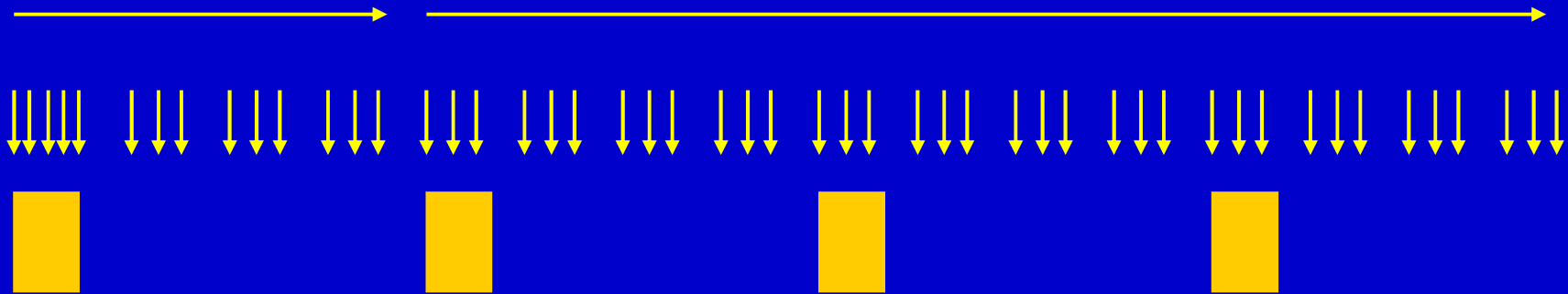
David Oscier

Liverpool Trials Unit

# CLL206: CAM-PRED regimen

**IV alemtuzumab**  
30 mg thrice  
weekly after  
dose escalation

**SC alemtuzumab**  
30 mg thrice  
weekly from  
week 5



**IV methylprednisolone**  
1.0 g/m<sup>2</sup> day 1–5  
repeated every 28 days

**Infection surveillance and  
prophylaxis!!!**

# UKCLL206 trial: Update

Completed recruitment of 41 patients Jan. 2008

Preliminary results presented at IWCLL Sept. '07:

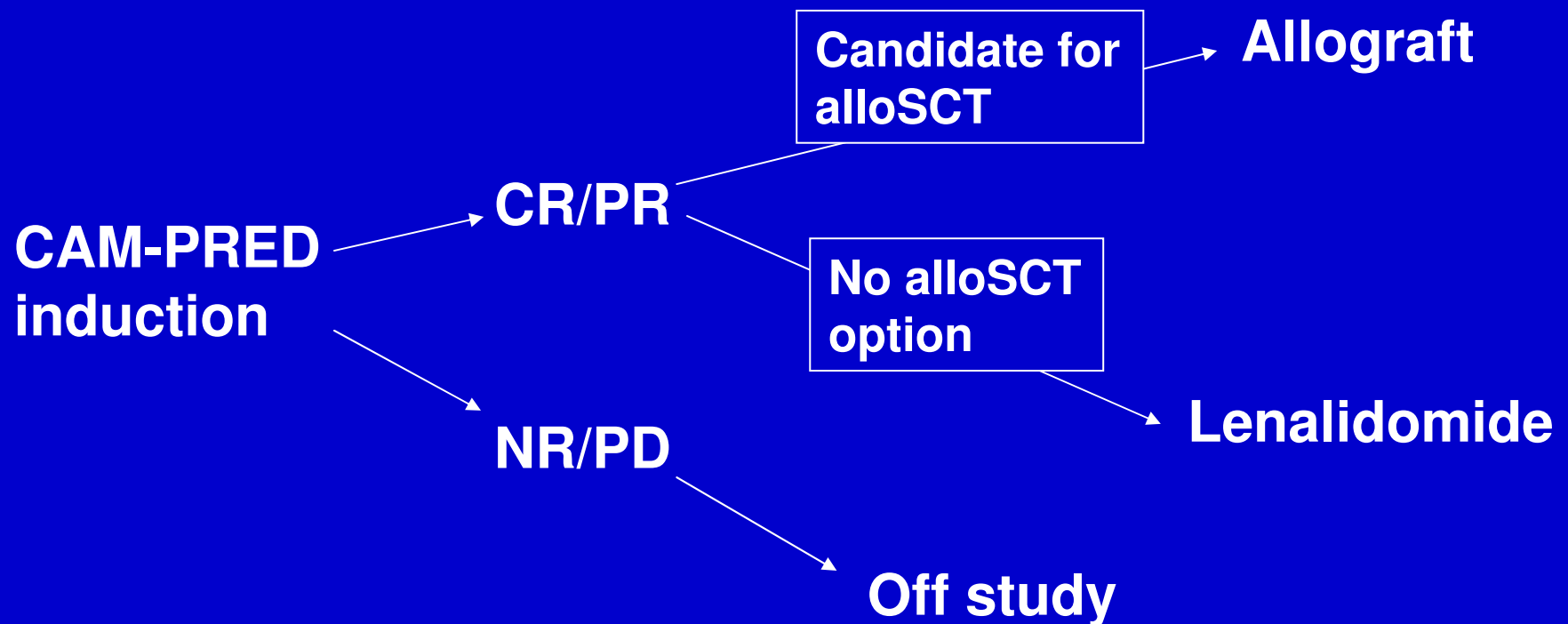
- BM MRD negativity rates in first 19 patients:
  - 50% overall
  - 30% in previously treated patients
  - 70% in previously untreated patients

Full results expected for ASH 2008

Relapse remains a problem:

- CLL210 trial

# UKCLL210 trial for p53 deleted and fludarabine refractory CLL



## Phase II NCRI CLL Trials (Since 2002)

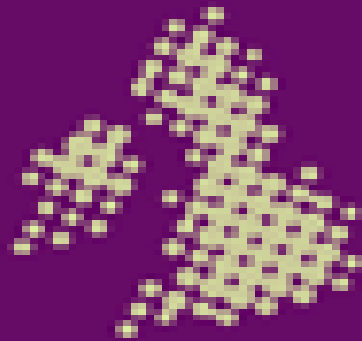
<b>Trial</b>	<b>Summary</b>	<b>Status</b>
CLL201	FCM-R	Closed January 2007
CLL202	CamFlud	Closed January 2006
CLL203	Stage A Poor Risk	In planning
CLL204	Allogeneic SCT	Closed August 2007
CLL205	T-PLL	Closed Nov 2007
CLL206	CamPred	Closed January 2008
CLL207	MRD Eradication	Open
CLL208	Chorambucil + rituximab	Open
CLL209	Rituximab dose finding	In development
CLL210	CamPred + Revlimid	In planning

## Phase III NCRI CLL Trials (April 2008)

Trial	Summary	Status
CLL6	Addition of mitoxantrone to FCR Dose of rituximab	Discussion with Roche Application to HTA
CLL7	Patients with co-morbidity	Chlorambucil +/- ofatumumab
CLL8	Alemtuzumab consolidation	Funding Bayer Schering; Awaiting CLL207

# Acknowledgements

## NCRI CLL Trials Sub-group



**NCRI**

National  
Cancer  
Research  
Institute

Peter Hillmen (Chair)  
Samir Agrawal  
Andrew Bosanquet  
Adrian Bloor  
Daniel Catovsky  
Kim Cocks  
Claire Dearden  
Steve Devereux  
Monica Else  
Chris Fegan  
John Gribben

Terry Hamblin  
Ben Kennedy  
Estella Matutes  
Don Milligan  
David Oscier  
Chris Pepper  
Andy Pettitt  
Chris Pocock  
Sue Richards  
Alistair Smith  
Elisabeth van der Bergh



Alex Smith  
Kim Cocks  
Emma Lindop  
Julia Brown

Dena Cohen  
Gill Eddison  
Walter Gregory

**Trial Support: Roche Pharmaceuticals, Bayer SP**