

Oxford Biomedical Research Centre

Post-ASH 2010 up-date:

B-cell chronic lymphocytic leukaemia (and others?)

Dr Anna Schuh

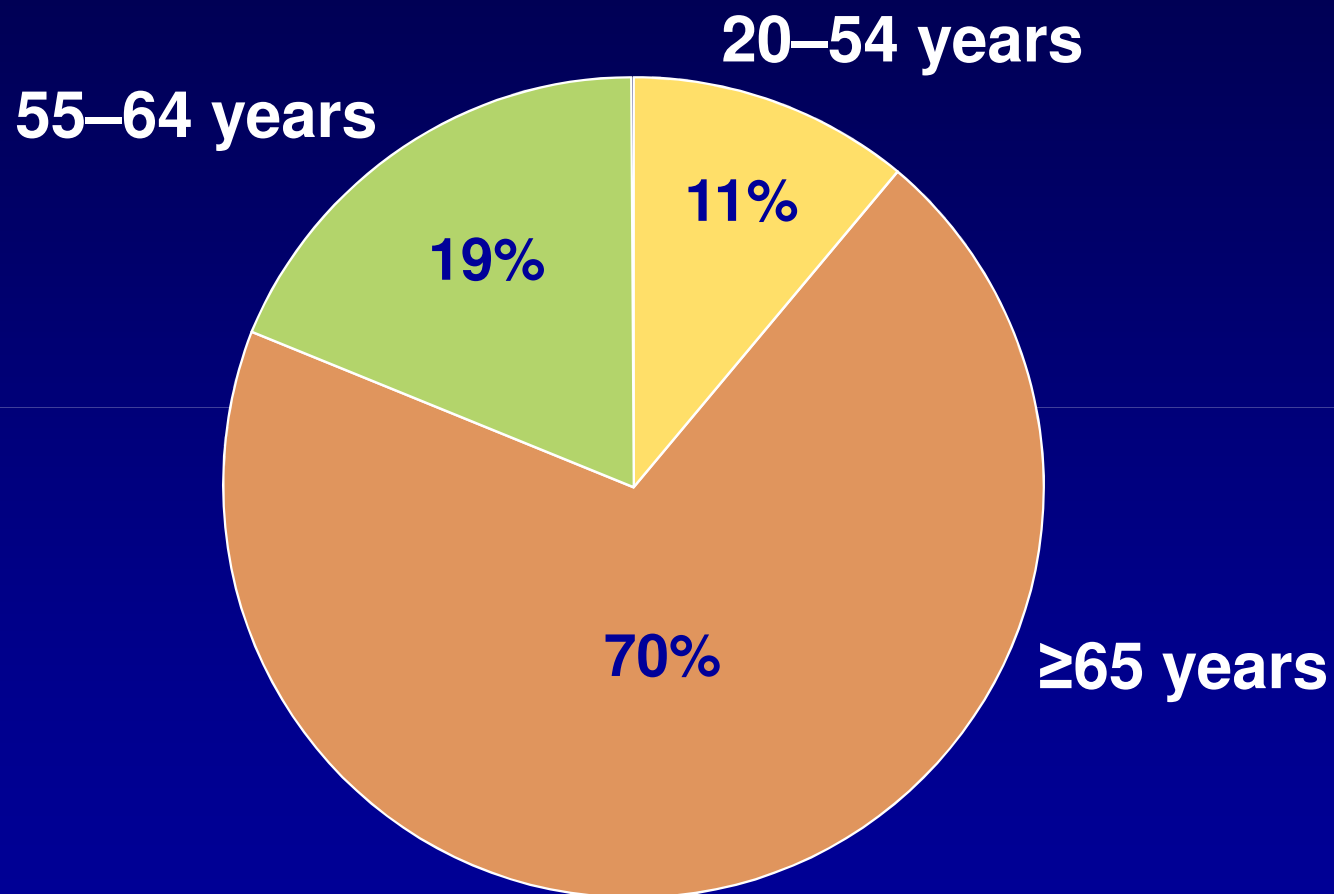
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NICE 23.12.2010

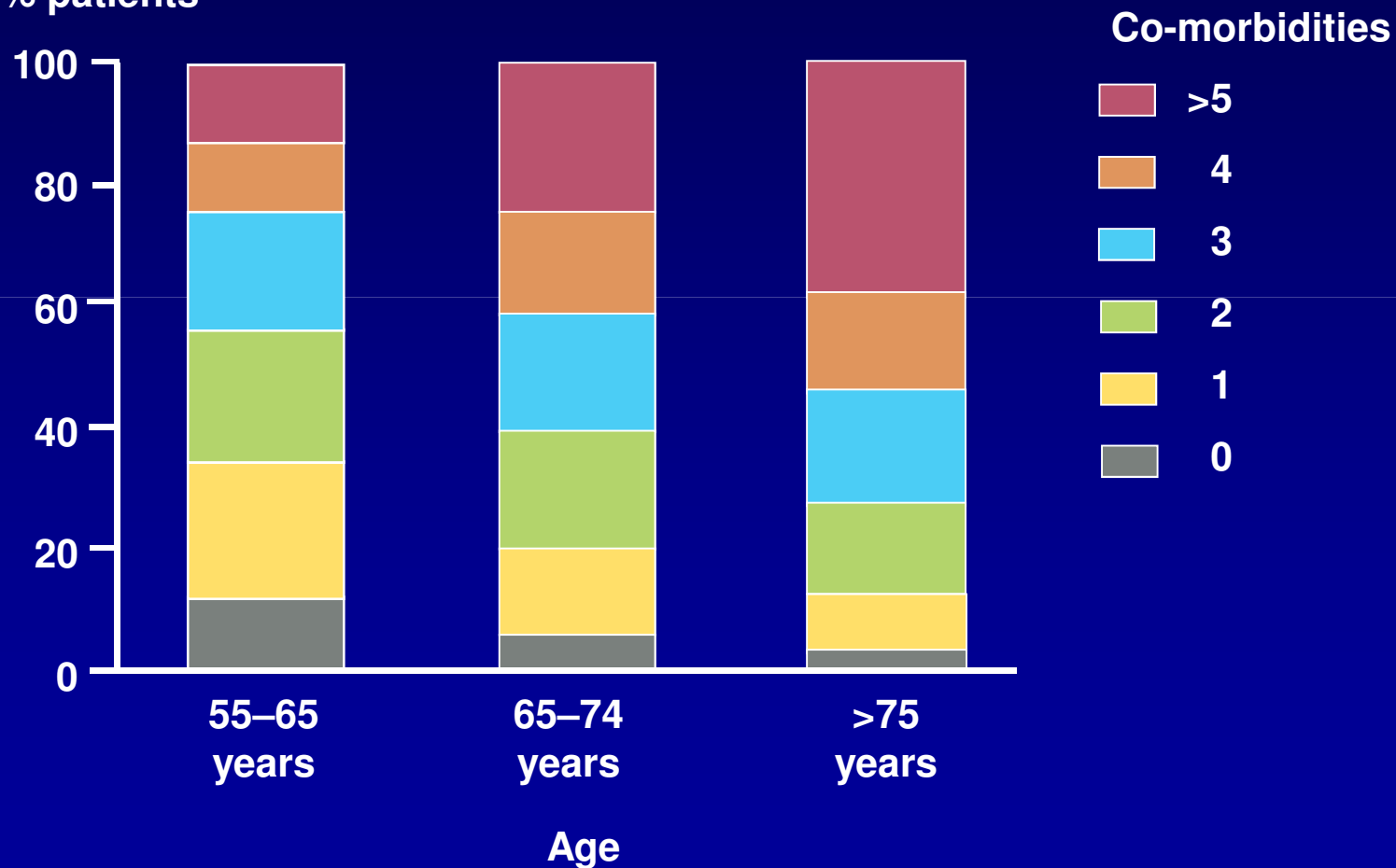
- Final appraisal determination: “Bendamustine is recommended as an option for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate”
- £4741.54, assuming a body surface area of 1.72 m² and an average treatment course of 4.9 cycles (including product wastage).
- Final issue date: April 2011

CLL is a disease of the elderly



Co-morbidities in elderly patients

SEER Cancer Registry
% patients



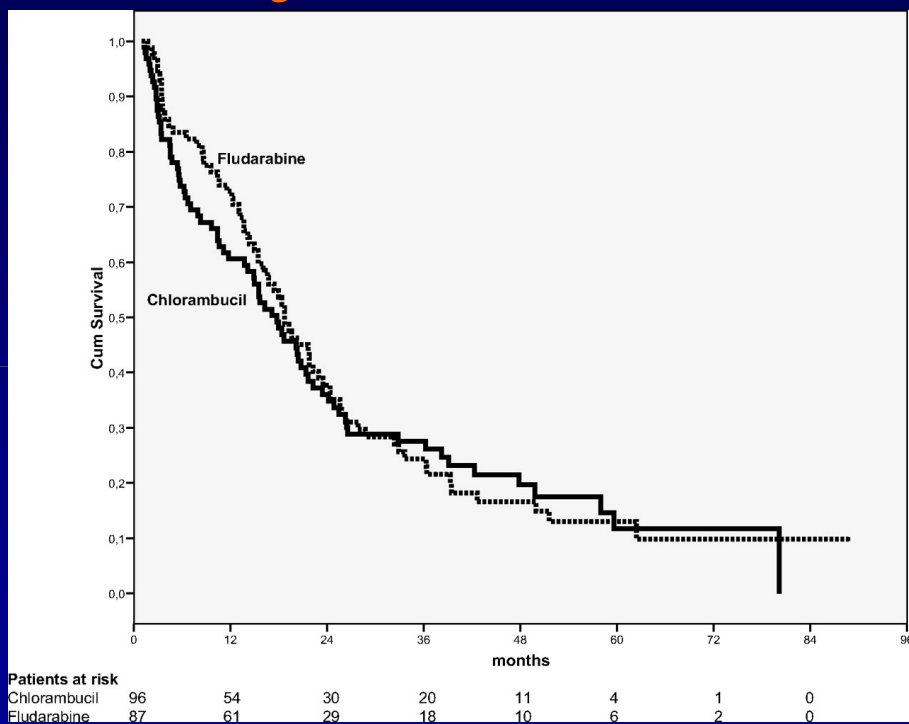
Limitations of current cytotoxic agents in CLL

Chlorambucil and fludarabine are well established agents used in CLL, with extensive clinical data. However, when used as single agents:

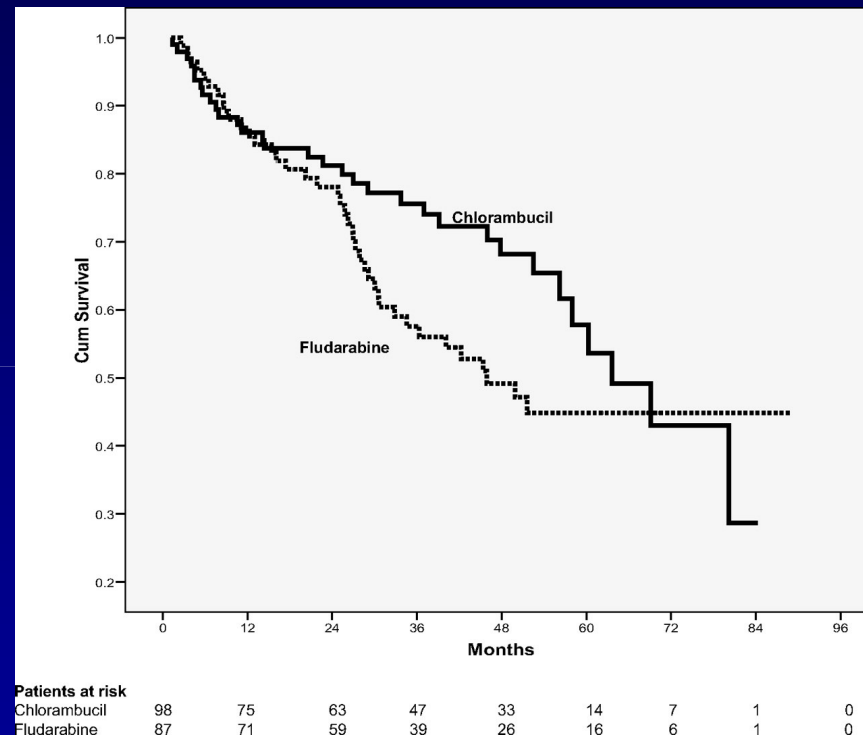
- Chlorambucil achieves low CR rates (<10%)
- Fludarabine achieves a higher CR rate and longer duration of remission than chlorambucil but is associated with:
 - Moderate/severe myelosuppression and immunosuppression
 - Creatinine clearance
 - risk of opportunistic infections

Benefits of fludarabine unclear in elderly patients

Progression free survival



Overall survival



Age: 70 (65-78)

Bendamustine versus chlorambucil: the European Phase III 'Intergroup' CLL Study

B-CLL

Binet stage B/C
No pretreatment
Age ≤ 75 years

→ **Randomization 1:1 (open label)**

Bendamustine

100 mg/m² days 1+2, every 4 weeks
for a maximum of 6 cycles

Chlorambucil

0.8 mg/kg (Broca's normal weight)
days 1+15, for a maximum of 6 cycles

Mean age: 63 years

Responses were assessed in a blinded fashion by an
Independent Committee for Response Assessment (ICRA)

European Phase III 'Intergroup' CLL Study: response rates

	Bendamustine (n=162)	Chlorambucil (n=157)	BR (n=117)	FCR (n=408)
Overall response, n (%)	110 (68)	48 (31)	100 (90.9)	(95.1)
Complete response, n (%)	50 (31)	3 (2)	36 (32.7)	(44.1)
Nodular partial response, n (%)	17 (11)	4 (3)	61 (55.5)	(51)
Partial response, n (%)	43 (27)	41 (26)	3 (2.7)	(3.4)

Difference in overall response rate: 37%, 95% CI (27%, 47%), $p < 0.0001$

*German CLL Study Group Phase II trial with bendamustine + rituximab (BR) Fischer K et al. Blood 2009;114:Abs 205
Knauf W et al. J Clin Oncol 2009;27:4378–84*

European Phase III 'Intergroup' CLL Study: response by Binet stage

	Binet B		Binet C	
ICRA	Bendamustine	Chlorambucil	Bendamustine	Chlorambucil
No. of patients overall	116	111	46	46
Complete response	41 (35%)	3 (3%)	9 (20%)	0 (0%)
Nodular partial response	14 (12%)	4 (4%)	3 (7%)	0 (0%)
Partial response	27 (23%)	31 (28%)	16 (35%)	10 (22%)
Overall response rate	82 (71%)	38 (34%)	28 (61%)	10 (22%)

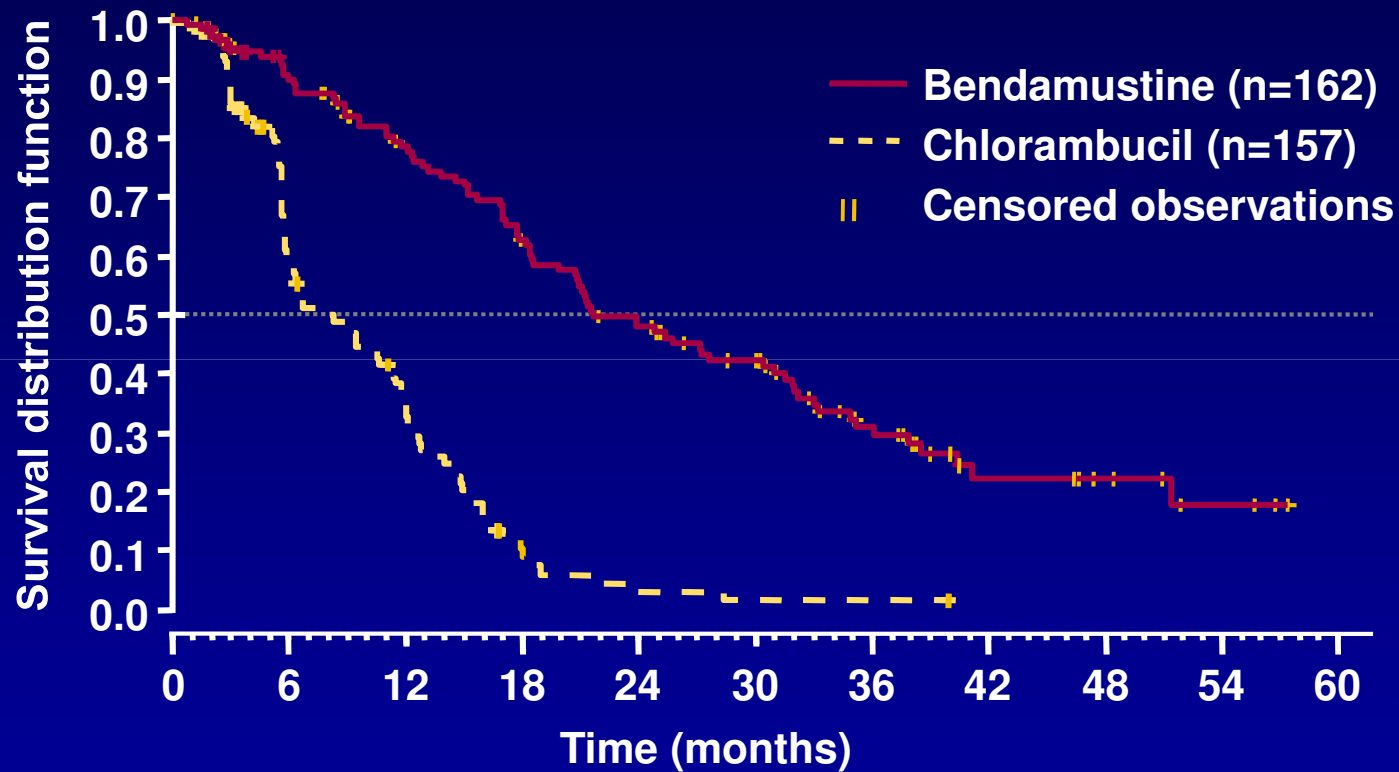
German CLL Study Group Phase II trial with bendamustine + rituximab (BR): response rates by genetic subgroup

After a mean of 5.0 treatment cycles

Genetic subgroup	n	ORR, n (%)	CR, n (%)	PR, n (%)
11q-	21	19 (90.5)	9 (42.9)	10 (47.6)
+12	19	17 (89.5)	3 (15.8)	14 (73.7)
17p-	7	3 (42.9)	0	3 (42.9)
Unmutated IgV _H status	63	56 (88.9)	NR	NR

ORR, overall response rate; CR, complete response;
PR, partial response.

European Phase III 'Intergroup' CLL Study: progression-free survival



	CHL	Benda	BR	FCR
PFS (months)	8.3	21.6	??	51.8

European Phase III 'Intergroup' CLL Study: grade 3 or 4 toxicities

	Bendamustine	Chlorambucil
Neutropenia/granulocytopenia, %	23	11
Leukopenia, %	14	1
Thrombocytopenia, %	12	8
Infections, %	8	3
Skin, %	2.5	2
Gastrointestinal disorders, %	3	1
Anemia, %	3	0
Tumour lysis syndrome, %	1	0

ASH 2010 update

- Median time to next treatment (ITT): 31.5 months with BEN and 10.1 months with CLB ($P < 0.0001$)
- ORR after second line therapy of any type was 35.4% in the BEN first line arm and 45.9% in the CLB first line arm ($P = 0.131$)
- OS all ($P = 0.24$; hazard ratio = 1.3 in favour of BEN) in the ITT population
- OS in CR (almost exclusively after BEN): median not reached versus 76.2 months; $P = 0.002$)
- OS (CR + PR) either after BEN or CLB: median not reached versus 68.3 months; $P < 0.0001$).

First-line therapy with bendamustine in CLL: summary

- Most patients with CLL are aged over 65 years and have at least 2 co-morbidities^{1,2}
- A large proportion of such patients may therefore not be suitable for fludarabine based combination chemotherapy
- Bendamustine +/- R is an option in first-line therapy for these patients³
- The clinical benefit of bendamustine over chlorambucil is maintained in patients ≥ 65 and across clinically defined major risk groups⁴
- A Phase III study with BR versus FCR in treatment-naïve patients with CLL is on-going

1. SEER Report 2009

2. Yancik R. Cancer 1997;80:1273–83

3. Knauf W *et al.* J Clin Oncol 2009;27:4378–84

4. Knauf W *et al.* Blood 2009;114: Abs 2367

697 Rituximab Plus Chlorambucil In Patients with CD20-Positive B-Cell Chronic Lymphocytic Leukemia (CLL): Final Response Analysis of An Open-Label Phase II Study

1st line Phase II: Chlorambucil +R in patients with co-morbidities
Final response analysis of 100 patients
Comparison with CLL4 chlorambucil arm
Median age 70.5 years, 52% Stage C
Grade 3-4 neutropenia: 40%

Toxicity

- The most common AEs were gastrointestinal disorders
- 25 serious AEs (SAEs) reported in 17 patients
- Most common SAEs were infections (10 SAEs, in 6 patients)
- Grade 3 or 4 neutropenia was reported in 40% of patients
- Additionally there were 3 cases (in 3 patients) of febrile neutropenia

Courtesy Peter Hillmen

R-chlorambucil - CLL208 vs LRF CLL4

Overall response rate

Overall Response Rate and 95% Confidence Interval

Trial	ORR	SD/PD	Missing	95% CI achieving at least a PR*	PFS	Total number of patients
CLL208	82.0% (CR: 9%)	15.0%	3.0%	[73.1- 89%]	23.5 months	100
CLL4 (Chlor)	66.0% (CR: 6%)	30.0%	4.0%	[59.0-72.5%]	18 months	200

**920 Subcutaneous Alemtuzumab Combined with Oral Dexamethasone,
Followed by Alemtuzumab Maintenance or Allo-SCT In CLL with 17p- or
Refractory to Fludarabine – Interim Analysis of the CLL20 Trial of the
GCLLSG and FCGCLL/MW (S Stilgenbauer)**

*Active CLL
Purine analogue resistant
TP53 deleted 1st line and relapse*

*30mgs Alemtuzumab sc
3x/week +Dexamethazone PO 40mgs D1-4 and 15-18
G-CSF*

*30mgs Alemtuzumab sc
maintenance*

Allo-BMT

Subcutaneous Alemtuzumab Combined with Oral Dexamethasone, Followed by Alemtuzumab Maintenance or Allo-SCT In CLL with 17p- or Refractory to Fludarabine

	FR (n=19)	17p- 1 st line (n=22)	17p- relapse (n=9)
Full treatment duration achieved	47%	82%	67%
ORR/CR	56%/4%	96%/24% (71.4%/4.7% for FCR in CLL8)	75%/0
Grade 3/4 non CMV infection	35%	16%	12%
CMV infection	32%	16%	18%
Estimated OS at 12 months	54%	100%	66%

923 Results of a Phase I-II Clinical Trial of Oxaliplatin, Fludarabine, Cytarabine, and Rituximab (OFAR) Combination Therapy In Patients with Aggressive, Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) and Richter Syndrome (RS)

OFAR2 consisted of oxaliplatin 30mg/m² D1-4; fludarabine 30mg/m²; Ara-C 0.5g/m²; rituximab 375mg/m² D3; and pelfigrastim 6mg D6. Fludarabine and Ara-C were given on D2-3 (level 1) D2-4 (level 2) or D2-5 (level 3) every 4 weeks.

	RS, N=27		Refractory CLL, N=53	
	No. of patients	%	No. of patients	%
CR	2	7	2	4
nPR	0	0	8	15
PR	9	33	19	36
Fail	14	52	19	36
Early death	2	7	5	9
Overall response	11	41	29	55

Oxford Lymphoma Clinical Trial Group CLL trial portfolio

Indication	Name	IMP	Phase	Recruitment	end of recruitment	Sponsor	Oxford contribution
relapsed/refractory B-cell malignancy	HGS 1029	IAP inhibitor	Phase I First into man	2	1-Dec-2011	commercial	CI
1st line GO-GO patients	ARCTIC	FCR vs FCM miniR	Phase IIb	12	1-Dec-2011	NCRN	PI
DLBCL RICHTER's transformation	CHOP-OR	CHOP-Ofatumumab followed by O maintenance	Phase IIa	Due to open in Jan 2011	1-Dec-2013	NCRN	CI
1st line SLOW-GO patients	911	Chlorambucil +/- Ofatumumab	Phase III	4	1-Dec-2011	commercial/NCRN	PI
1st and 2nd line SLOW-GO patients	Mable	CR vs BR	Phase III	8	1-Jun-2012	commercial	CI
maintenance after 2nd line treatment	Continuum	Lenalidomide vs Placebo 2:1	Phase III	3	1-Dec-2012	commercial	PI
fludarabine-refractory bulky B-CLL SLOW-GO	NCRN 042	Ofatumumab single agent	Phase IIb	Due to open in Spring 2011	1-Dec-2012	commercial/NCRN	CI
fludarabine-refractory/TP53 deleted B-CLL GO-GO	NCRN 210	Camp + Dex + Lenalidomide followed by Lenalidomide maintenance or RIC BMT	Phase II	Due to open in Spring 2011	1-Dec-2014	NCRN	PI