Purine analogs in Waldenström's Macroglobulinemia

Véronique Leblond

Hôpital Pitié Salpêtrière

Therapeutic options

- Alkylating agents
- Purine analogs
- Monoclonal antibodies
- Bortezomib

Alone or in combination

- No large randomized trials
- Elderly patients (median age: 70 years) with comorbidities
- Treatments must be tailored to patient status

Chemotherapy

	Overall response	CR	PFS	Randomized studies
Chlorambucil (Facon 1993, Kyle 2000 Dimopoulos 1994 Garcia- Sanz 2001)	40-80%	<5%	26m- 46m	Clb daily vs intermittent
Purine analogs (Foran 1999, Dhodapkar 2001)	38-79%	<5%	24- 40 m	F vs Clb WM1
Purine analogs + Cyclophosphamide (Tamburini 2006 Weber 2003)	70-90%	<5%	27-36m	

A randomized trial of chlorambucil vs. fludarabine as initial therapy in Waldenström's Macroglobulinemia (WM), non-MALT marginal zone lymphoma (MZL) and non-IgM lymphoplasmacytic lymphoma (LPL) (WM1 trial)

V Leblond, J Lejeune , O Tournilhac, P Morel , MS Dilhuydy, C Dartigeas, M Malphette, B Royer , M Ewings, S Chevret , S Johnson, R Owen

Hôpital Pitié Salpêtrière , Hôpital Saint Louis , CHU Clermont Ferrand, Hôpital Schaffner Lens, CHU Bordeaux , CHU Tours, CHU Amiens

Department of Haematology, Taunton and Somerset NHS Foundation Trust, Taunton, HMDS Laboratory, St James's Institute of Oncology, Leeds, UK.

NCRI Lymphoma Clinical Studies Group (UK)

Groupe coopérateur français LLC/MW (France)

GOELAMS

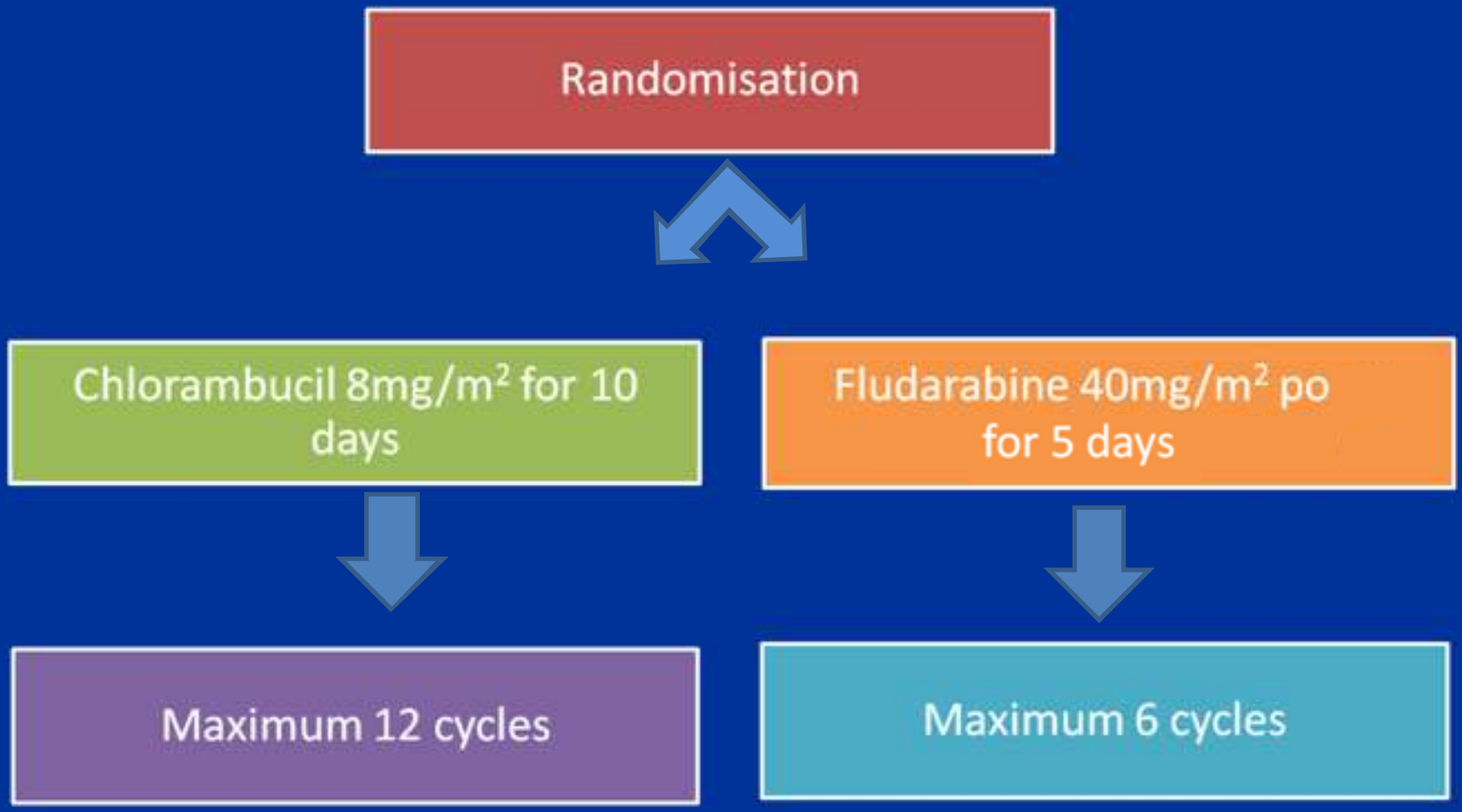
GELA

Inclusion criteria and end points

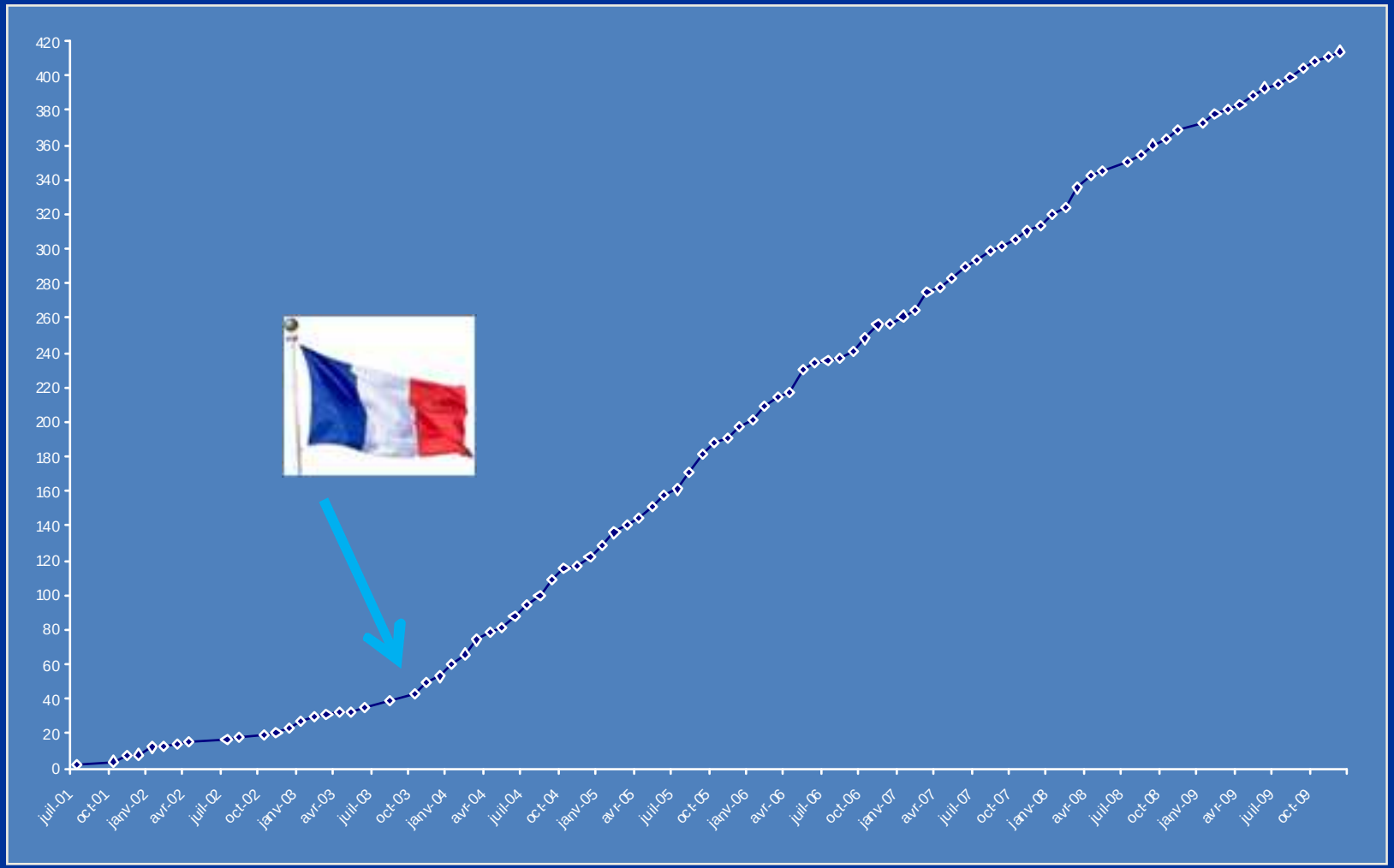
- WM, non- MALT MZL, LPL in untreated symtomatic patients (except splenectomy in splenic MZL)
- Tumor population B CD5-CD23- (mandatory immunophenotyping)
- PS<3

Primary end-point: response rate and duration of the response

Trial design.

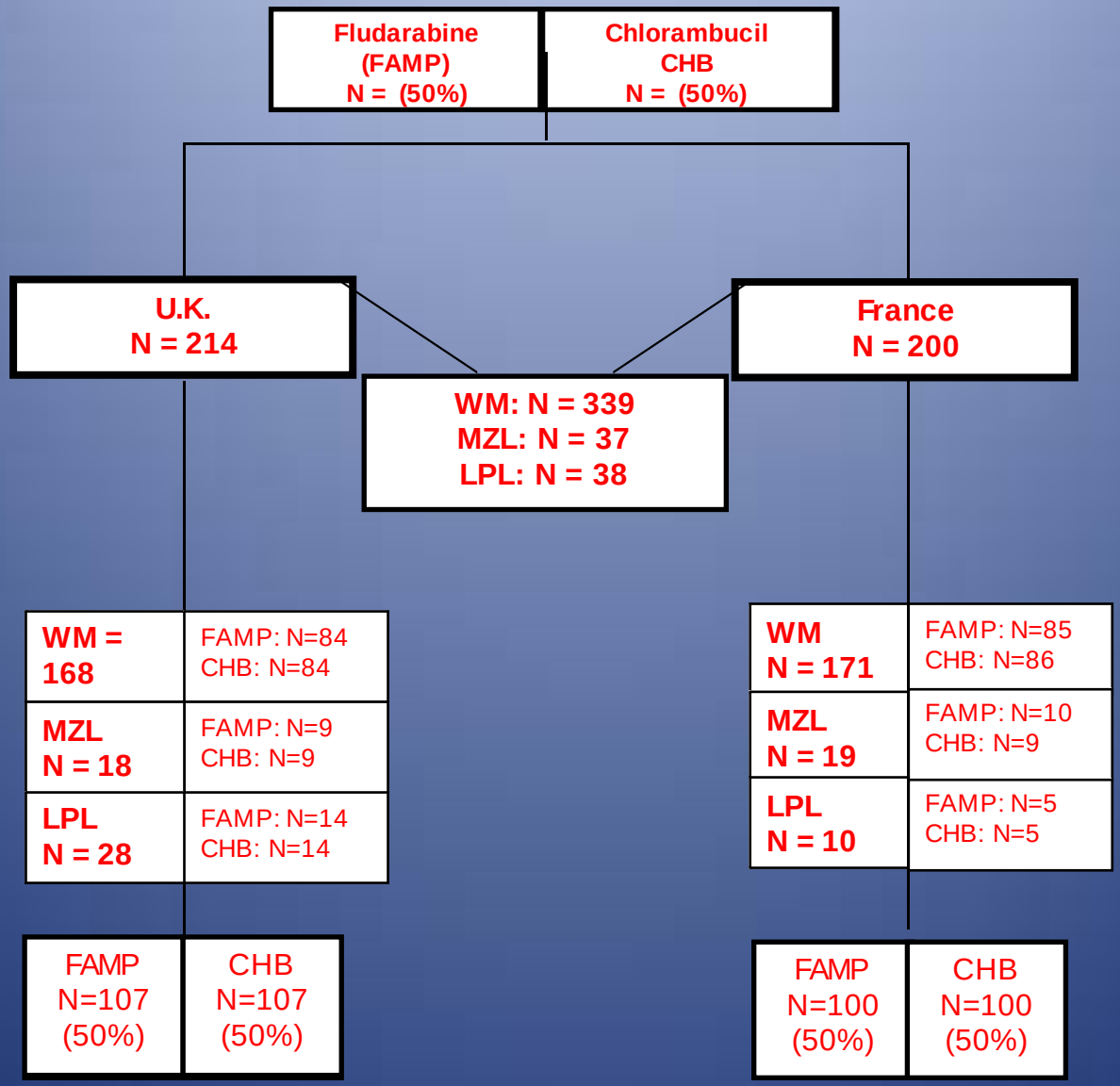


Rate of accrual 7/01 – 12/09 (n=418).



Inclusion N = 418

4 exclusions (2 errors of randomisation, 2 wrong diagnoses)



Clinical and biological parameters

	Fludarabine	Chlorambucil	P-value
Age (ans)	67.1 ± 9.6	67.3 ± 9.4	0.8
Sex (male. %)	67.1	66.7±	0.9
Hb (g/dl)	10.1 ± 2.1	10.2 ± 2.1	0.9
WBC (G/l)	9.2 ± 13.8	9.3 ± 14.8	0.3
Neutrophil (G/l)	3.6 ± 1.9	3.4 ± 1.9	0.9
Lymphocytes (G/l)	4.7 ± 13.3	4.9 ± 13.3	0.8
Platelets (G/l)	228 ± 128	220 ± 123	0.5
Creatinine (µmoles/l)	88 ± 23	93 ± 25	0.08
Albumin (g/l)	38 ± 8	37 ± 37	0.4
β2M (mg/l)	3.7 ± 1.7	4 ± 2	0.08
IgM	30 ± 21	30 ± 20	1

Response criteria

WM+ LPL

- **PR : > 50% of tumor masses and monoclonal component: 2nd international workshop (Weber 2003)**

Marginal Zone Lymphoma

Cheson's criteria (1999)

Response Evaluation

	Fludarabine (N=207)	Chlorambucil (N=207)	P
PR	88 (42.5%)	76 (36.7%)	P=0.06
CR	11 (5%)	4 (2%)	
PR+CR	99 (47.8%)	80 (38.6%)	P=0.03
Stable	66 (32%)	68 (33%)	
Failure	22 (10.5%)	37 (18 %)	
Not evaluable	20 (9.7 %)	22 (10.7%)	
Median duration of response	42.1months	22.9 months	P=0.001
response rate at 5 y	30%	15%	

Response Evaluation

Entities	Fludarabine	Chlorambucil
WM (N=339)	N=168	N= 171
Response	77 (45.8%)	61 (35.7%)
Failure	76 (45.2%)	89 (52%)
NE	15(9%)	21 (12.2%)
MZL+LPL (N= 75)	N=38	N= 37
Response	22 (58%)	19 (51%)
Failure	12 (31.5%)	16 (43.2%)
NE	4 (10.5%)	2 (5.4%)

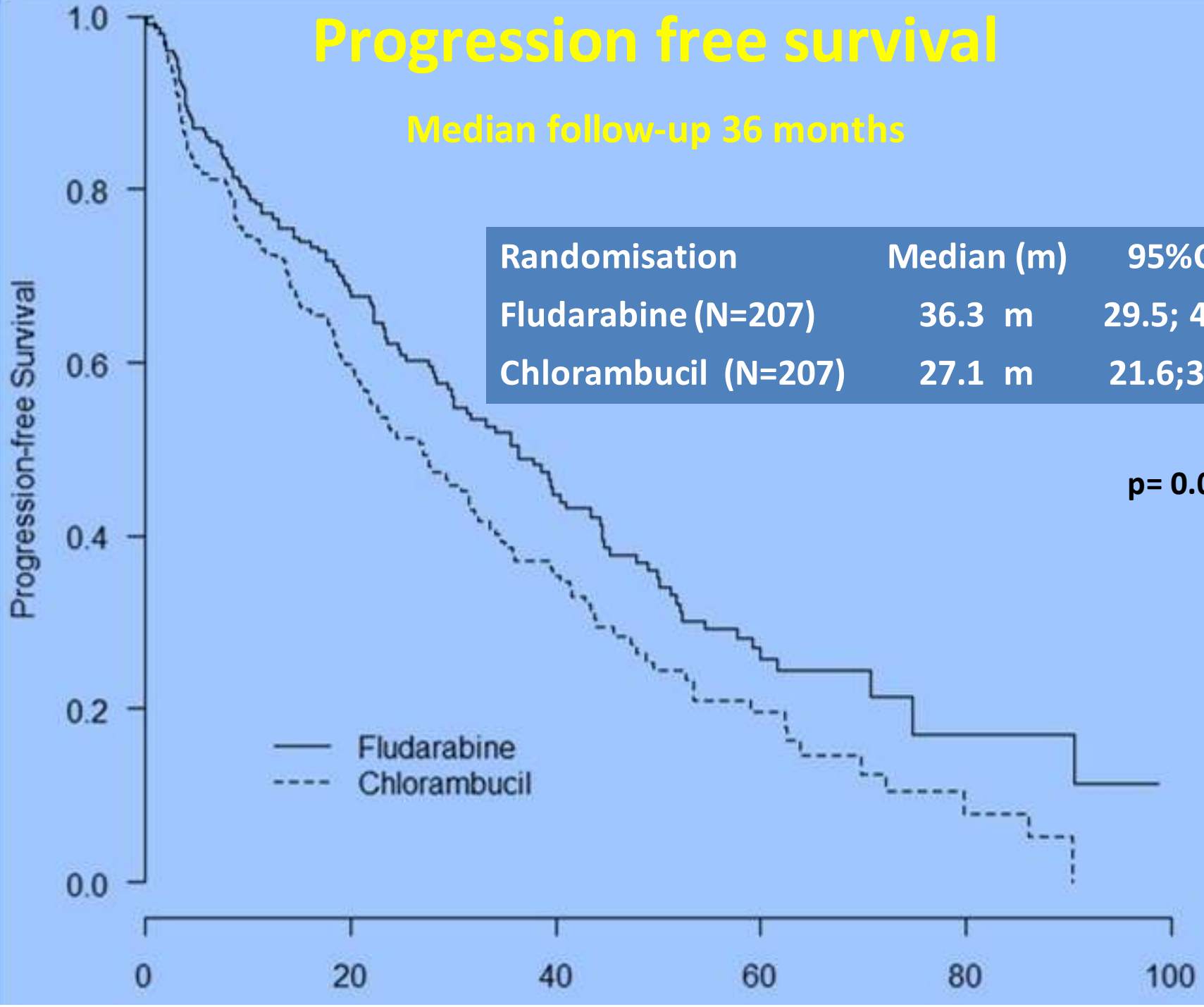
Age, hemoglobin , albumin and β2Microglobulin levels had no impact on the response rate

Progression free survival

Median follow-up 36 months

Randomisation	Median (m)	95%C I
Fludarabine (N=207)	36.3 m	29.5; 44.5
Chlorambucil (N=207)	27.1 m	21.6;32.5

p= 0.015



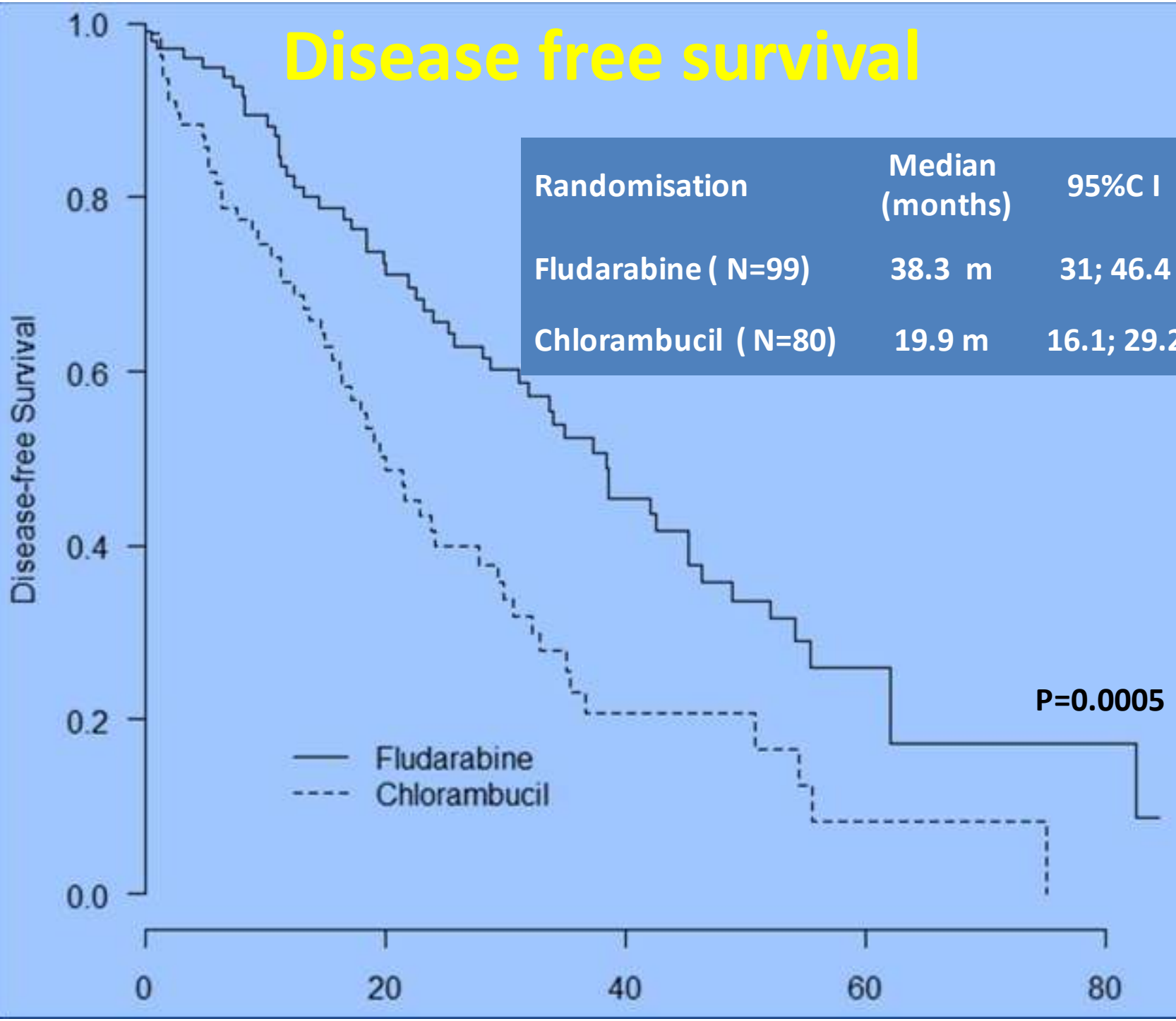
Progression free survival

(Multivariate analysis)

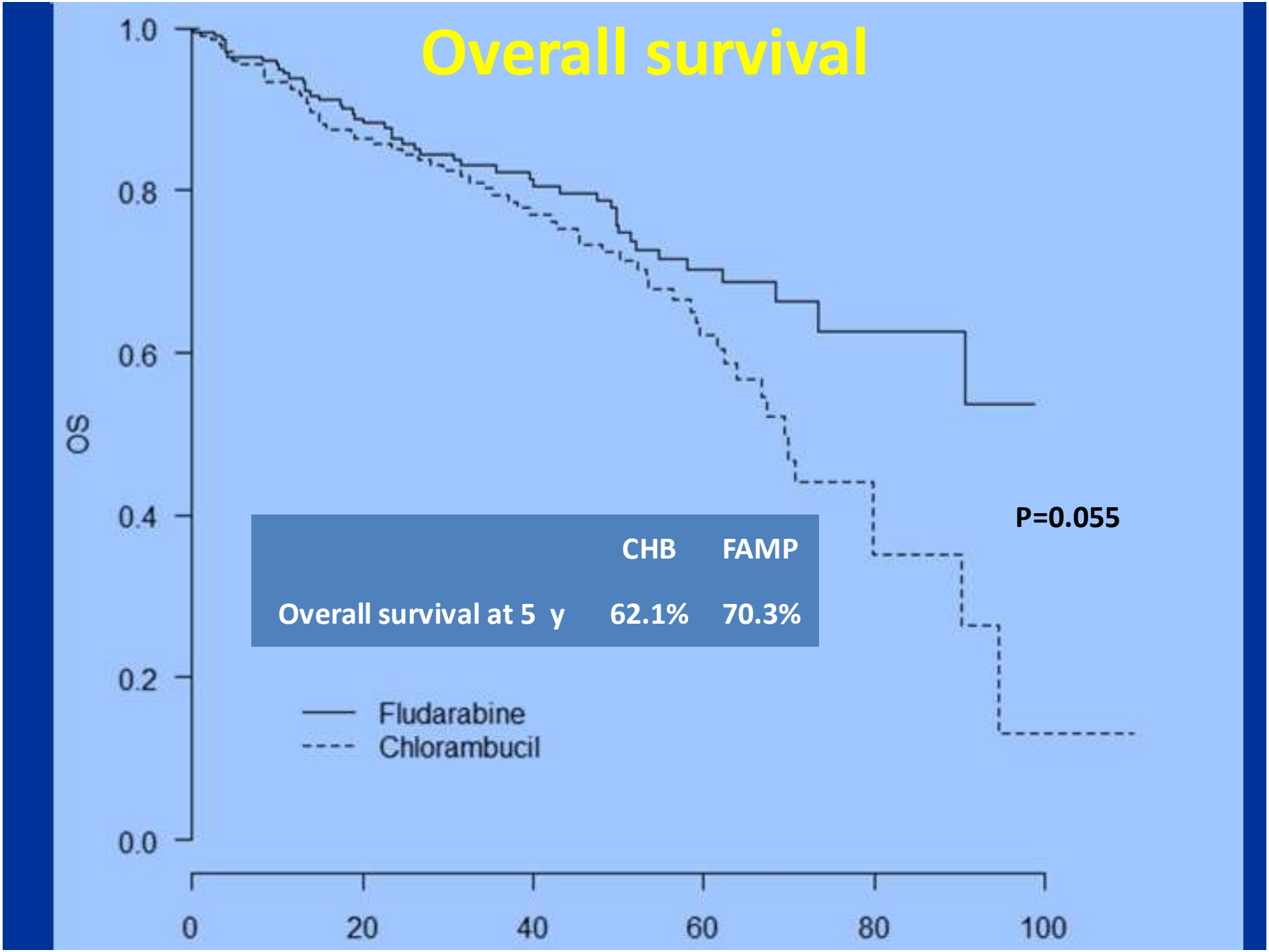
Parameter	Hazard Ratio [95%IC]	p
Fludarabine	1	
Chlorambucil	1.3 [1.0 ; 1.7]	0.03
Albumin ≥ 40 g/l	0.7 [0.5 ; 0,9]	0.03
Beta 2 microglobulin >3 mg/l	1.3 [0.5 ; 0.9]	0.04

Disease free survival

Randomisation	Median (months)	95%C I
Fludarabine (N=99)	38.3 m	31; 46.4
Chlorambucil (N=80)	19.9 m	16.1; 29.2



Overall survival



	CHB	FAMP
Overall survival at 5 y	62.1%	70.3%

P=0.055

Toxicity > grade II

(p=0.03)

symptoms	Fludarabine Number of cycles: 1017		Chlorambucil Number of cycles: 1618	
	Grade III N = 50	Grade IV N = 45	Grade III N = 47	Grade IV N = 25
Hemoglobin	24 (11.8)	25 (12.3)	25 (12.4)	14 (6.9)
Neutrophils	30 (14.8)	28 (13.8)	27 (13.4)	7 (3.5)
Platelets	6 (3.0)	11 (5.4)	10 (5.0)	8 (4.0)
Urea	1 (0.5)	5 (2.5)	3 (1.5)	4 (2.0)
Creatinine	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)
ALT / AST	0 (0.0)	1 (0.5)	0 (0,0)	0 (0.0)
Infection	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Lung toxicity	1 (0.5)	2 (0.9)	0 (0.0)	2 (1.0)
Neuropathy	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Cardiac toxicity	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)

Causes of death

65 UK, 46 France : 111 patients

- Progression: 35
- Infection: 18
- Large- cell non Hodgkin lymphoma: 9 (7 B-cell and 2 T-cell)
- Solid tumors : 8 (1 mesothelioma, 2 lung K, 1 glioblastoma, 1 liver K, 1 epidermoid carcinoma, 1 rectal carcinoma, 1 unknown)
- ALL: 1
- AML: 1
- Hemorrhage: 4
- Others: 13
- Unknown : 22

Immunochemotherapy

	Overall response	CR	PFS
Rituximab + fludarabine Treon Blood 2009 43 patients Treated: 20 Untreated: 23	95%	5%	Response duration 52 m Median treated :38m Median untreated: 77 m
Rituximab + purine analogs (Treon 2004)	82%	7%	80% at 17m
Rituxumab + fludarabine+ cyclo (Leblond 2011) 62 patients Treated: 46 Untreated: 16	84%	VGPR/RC 30%	Median not reached at 45 months Response duration 41 months
R- 2CDA (Lazlo 2008) (29 pts)	89.6%	28%	NA

Incidences of MDS/AML and Richter syndrome following Fludarabine, alone or combined with Cyclophosphamide in 4 studies of the French Cooperative group on CLL/WM.

N	Study	Status	TTT	Previous treatment	Study treatment	S (month)	F-U (month)	MDS AML	RS
71	Retrospective Study 1 Leblond (J Clin oncol 1998)	Relapse refractory	5.9 yrs	Alkylating-based regimen	Fluda IV x 6	23	34	1/71 (1.4 %)	5/71 (7 %)
46	Randomized prospective Study 2 Leblond (Blood 2001)	First relapse Primary refractory	3.9 yrs	Alkylating-based regimen	Fluda IV x 6	41	34	4/45 (8.9 %)	3/45 (6.6 %)
46	Randomized prospective Study 2 Leblond (Blood 2001)	First relapse Primary refractory	3.9 yrs	Alkylating-based regimen	CAP x 6	45	34	2/45 (4.5 %)	2/45 (4.5%)
49	Retrospective Study 3 (Tamburini Leukemia 2005)	Untreated:14 Relapse: 35	2.1 yrs	Alkylating-based regimen, fludarabine	Fluda + Cy IV x 6	NR	42	2/49 (4 %)	5/49 (10 %)
62	Retrospective study 4 (Leblond 2011)	Untreated:16 Relapse: 46	4 yrs	Alkylating-based regimen, fludarabine Rituximab	Rituximab + fluda+ Cyx6	NR	45	2/62 (3.2 %)	3/62 (4.8 %)

N: number of patients; TTT: Time To Treatment from diagnosis to study; Fluda IV: Fludarabine 40mg/m2 J1-J3 IV; CAP: Doxorubicine 25mg/m2 IV D1, Cyclophophamide 750mg/m2 IV D1, Prednisone 40mg/m2 D1-5; Fluda + Cy PO: Fludarabine 30mg/M2 D1-3 plus Cyclophosphamide 300mg/m2 D1-3; S: Survival; F-U: Follow-Up; MDS: myelodysplasic Syndrome; AML: Acute Myeloid Leukemia; RS: Richter's Syndrome.Rituximab

Conclusions.

- Fludarabine is more effective than chlorambucil, with acceptable toxicity
- Purine analogs are highly efficacious in WM – learn from CLL
- The impact of highly active regimens on the incidence of therapy related complications (MDS/AML, RS, long- lasting cytopenia) must be assessed in prospective trials
- Randomized phase III trials are possible in WM but international collaboration (and patience!) is essential