Chlorambucil plus anti-CD20 MoAb

Peter Hillmen

peter.hillmen@nhs.net

St James's University Hospital

Leeds

13th November 2017

Chlorambucil-based therapy

Questions to address:

1. Is there a role for chlorambucil-based therapy in 2017?

2. What is the best dose and schedule of chlorambucil?

3. Should chlorambucil be combined with anti-CD20 MoAb?

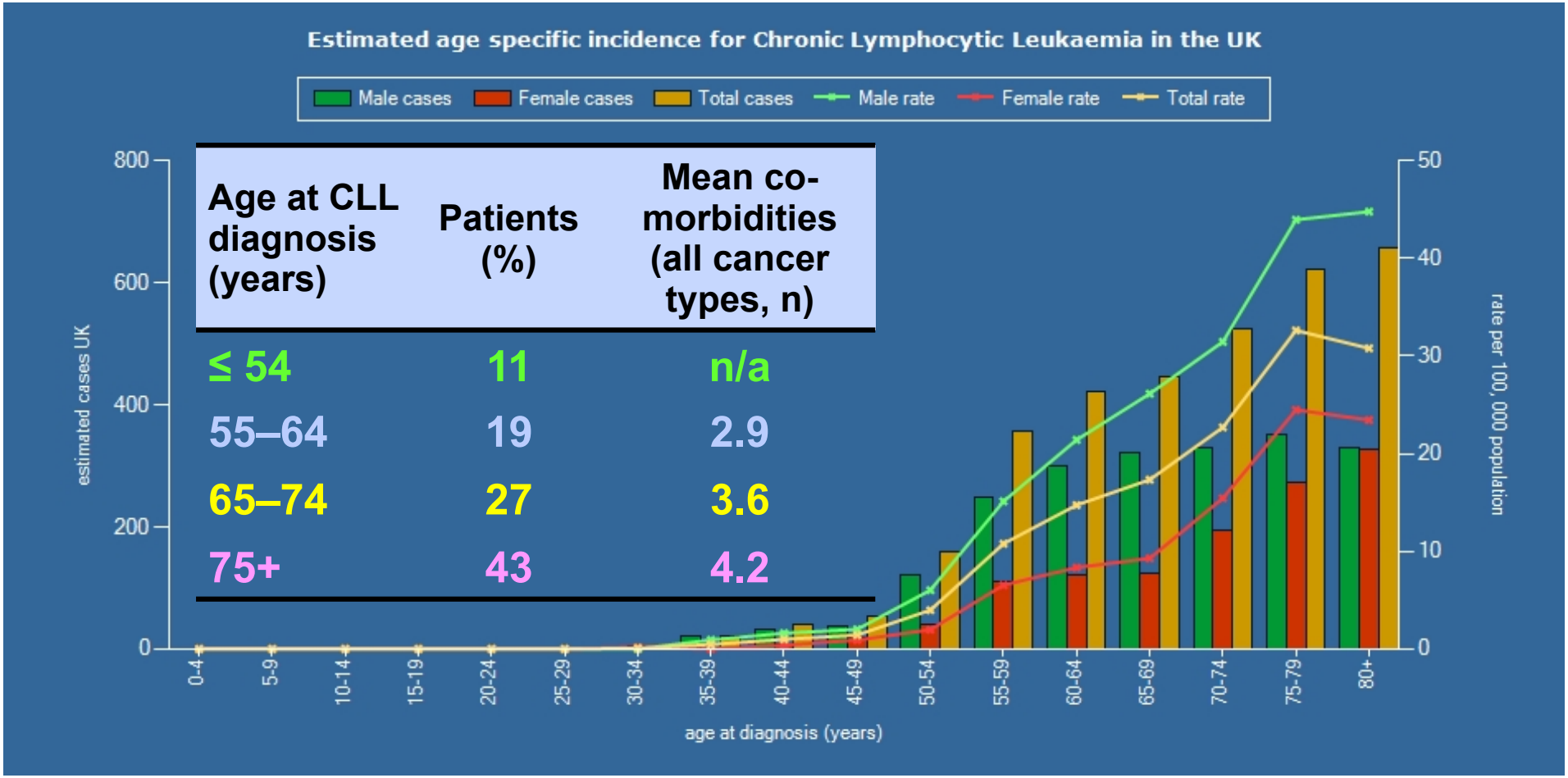
4. What is the best anti-CD20 to combine with chlorambucil?

CLL: incidence data (HMRN, Yorkshire, UK)

6.4 cases per 100,000; M:F 1.7

Median age at diagnosis 71yrs

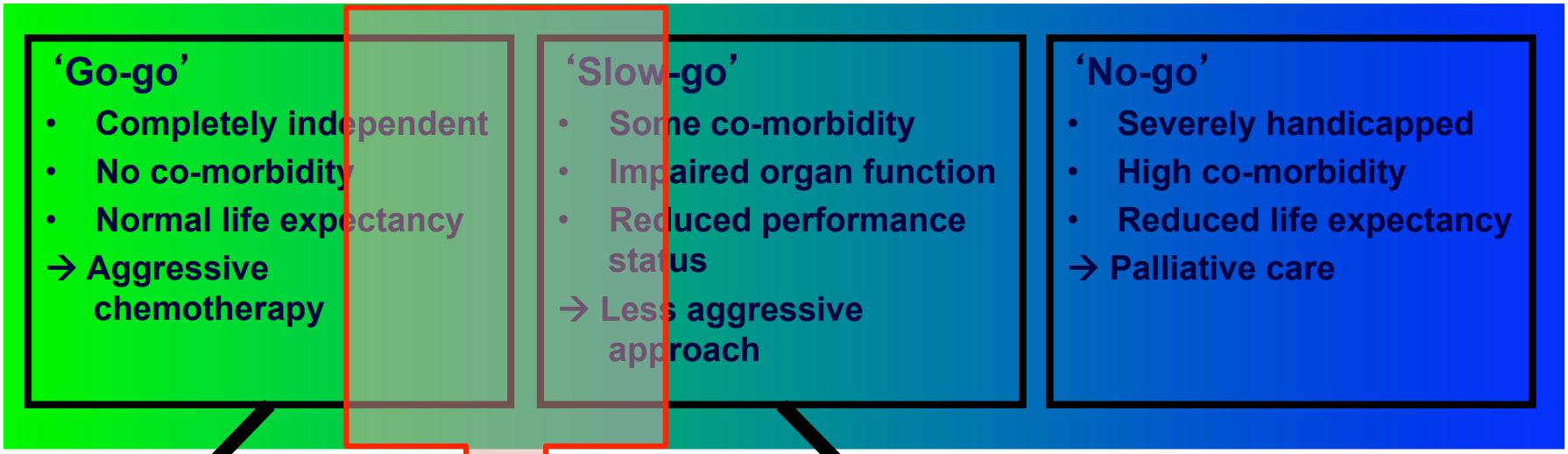
Estimated 3610 cases per annum in the UK



Age at CLL diagnosis (years)	Patients (%)	Mean co-morbidities (all cancer types, n)
≤ 54	11	n/a
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

Leeds data (www.hmrn.org.uk); Ries LAG, et al. SEER Cancer Statistics Review, 1975–2005. Available at: http://seer.cancer.gov/csr/1975_2005/ accessed February 2009., Yancik R, Cancer 1997; 80:1273–1283.

The boundaries between “Go-Go”, “Slow-Go” and “No-Go” depend on the therapy

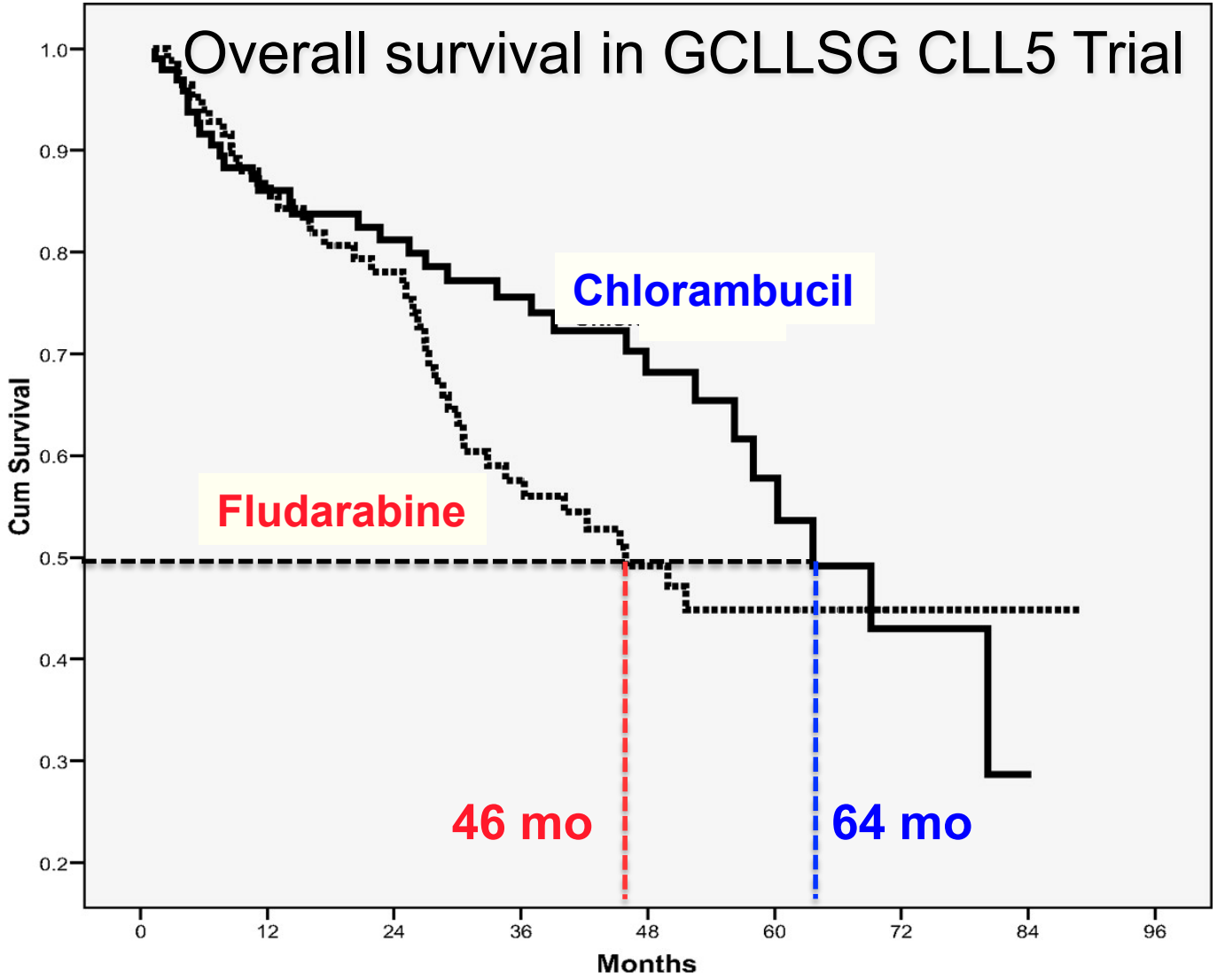


Rituximab-FC is the standard of care

Where to draw the line?

What is the standard of care?

GCLLSG CLL5 Trial: ?only study in elderly frail patients of chlorambucil monotherapy



Patients at risk									
Chlorambucil	98	75	63	47	33	14	7	1	0
Fludarabine	87	71	59	39	26	16	6	1	0

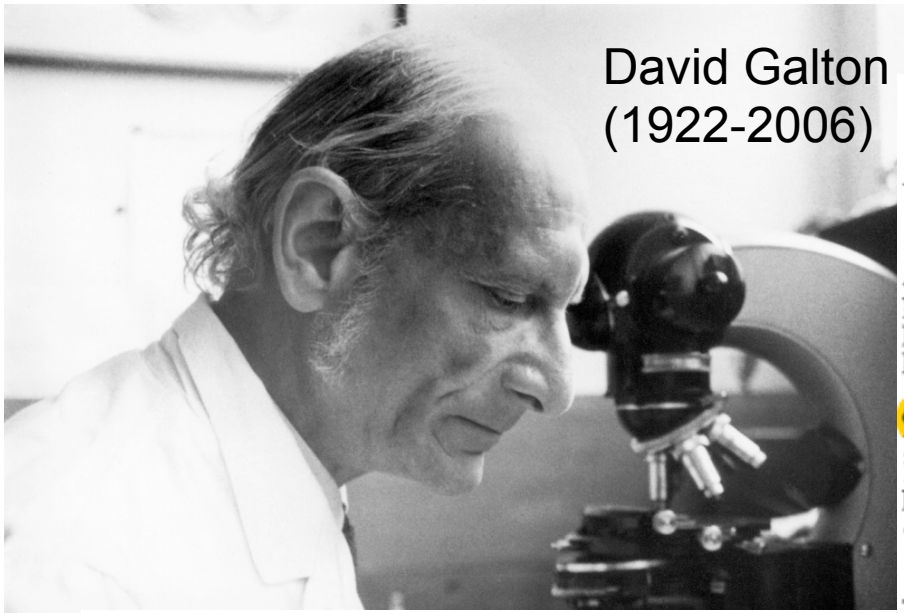
Eichhorst B F et al. Blood 2009;114:3382-3391

Chlorambucil-based therapy

Questions to address:

1. Is there a role for chlorambucil-based therapy in 2017?
   - ?probably
2. What is the best dose and schedule of chlorambucil?
3. Should chlorambucil be combined with anti-CD20 MoAb?
4. What is the best anti-CD20 to combine with chlorambucil?

First use of chlorambucil (Galton *et al.* 1955)



David Galton
(1922-2006)

TABLE I.—*Results of Treatment with CB 1348 in 62 Cases of Lymphoma*

Diagnosis	No. of Patients	Benefit	Some Effect	No Effect
Hodgkin's disease	23	4	14	5
Reticulum-cell sarcoma	11	0	6	5
Lymphocytic lymphoma, subleukaemic	12	7	3	2
Chronic lymphocytic leukaemia	8	4	1	3
Follicular lymphoma	6	5	1	0
Mycosis fungoides	1	0	0	1
Exfoliative erythrodermia	1	0	1	0
Total	62	20	26	16

CLINICAL TRIALS OF *p*-(DI-2-CHLOROETHYLAMINO)-PHENYLBUTYRIC ACID (CB 1348) IN MALIGNANT LYMPHOMA

BY

D. A. G. GALTON, M.B.
Chester Beatty Research Institute and Royal Marsden Hospital, London, S.W.3

LYONEL G. ISRAELS, F.R.C.P.(C.)
University of Manitoba, Winnipeg, Canada

J. D. N. NABARRO, M.D., M.R.C.P.
Middlesex Hospital, London, W.C.1

AND

MORWENNA TILL, M.B.
Chester Beatty Research Institute and Royal Marsden Hospital, London, S.W.3

Everett, Roberts, and Ross (1953) synthesized a series of water-soluble aromatic nitrogen mustards, one of which,

With few exceptions the oral dose ranged from 2 to 20 mg. a day (0.03–0.34 mg. per kg. of body weight). In most cases it was either 0.1 or 0.2 mg. per kg. daily (6 or 12 mg. for a patient weighing approximately 10 stone—63.5 kg.). A course of treatment usually lasted three to six weeks, but CB 1348 was given daily for 8 to 16 weeks on thirteen occasions and for 6 to 12 months on three. Eighteen patients had more than one course of treatment; 15 were given two courses at intervals of from 3 to 27 months; two had three courses; and one (Case 4) had six.

were usually followed 6–18 hours later by vomiting. Intraperitoneal injection was well tolerated.

Chlorambucil SmPC (Updated 03-Nov-2015)

CHRONIC LYMPHOCYTIC LEUKAEMIA

Adults

Initially Chlorambucil is given at a **dosage of 0.15 mg/kg/day until the total leucocyte count has fallen to 10,000 per µL**. Treatment may be resumed 4 weeks after the end of the first course and continued at a dosage of 0.1 mg/kg/day.

In a proportion of patients, usually after about 2 years of treatment, the blood leucocyte count is reduced to the normal range, enlarged spleen and lymph nodes become impalpable and the proportion of lymphocytes in the bone marrow is reduced to less than 20%.

Intermittent high dose therapy has been compared with daily Chlorambucil but no significant difference in therapeutic response or frequency of side effects was observed between the two treatment groups.

Chlorambucil in UK CLL Trials

Trial	Years	No. pts assessable	Dose x cycle	CR	ORR
CLL1	1978-84	62	60mg/m^2	15%	63%
CLL2	1984-90	94	60mg/m^2	21%	75%
CLL3	1990-98	190	60mg/m^2	17%	74%
CLL4	1999-2004	366	70mg/m^2	7% *	72% *

* 26% incl. NodPR; BM biopsies were not used in CLL1–3

Catovsky *et al.* Clinical Lymphoma, Myeloma & Leukemia, Vol. 11, No. S1, S2-6

Response Rates with Chlorambucil in Randomized Trials up to 2009

Study	Dose/m^2	Response rate	
		CR	ORR
Rai et al 2000	40mg	4%	37%
Eichhorst et al 2009	38mg	0%	51%
Hillmen et al 2007	40mg	2%	55%
Knauf et al 2009	60mg	2%	31%
Catovsky et al 2007	70mg	7%	72%

Other Examples of Importance of Dose Intensity of Alkylating Agents in CLL

	No. pts	ORR
CLL1 trial (1981)		
COP – Cyclo 625/m^2	34	53%
– Cyclo 1250/m^2	36	73%
French trial (2001)		
Binet CHOP – Cyclo 1500/m^2	351	71.5%
CAP – Cyclo 750/m^2	237	58.2%
Fludarabine – 25/m^2 x 5 days	336	71.1%
Jaksic trial (1997)		
HD Chlorambucil – 150-180/m^2	116	89.5%
Binet CHOP – Cyclo 1500/m^2	112	75%

Responses at 6 and 12 Months in CLL3

	Chlorambucil		Chlorambucil + Epirub	
	6 mths	12 mths	6 mths	12 mths
No. pts	187	154	192	158
CR	8.5% →	17%	14% →	24.5%
PR	61%	66%	60%	66%
NR	30.5%	12.5%	26%	9.5%
ORR	69.5% →	87.5%	74% →	90.5%

Catovsky *et al.* Clinical Lymphoma, Myeloma & Leukemia, Vol. 11, No. S1, S2-6

Chlorambucil ± anti-CD20 MoAb (1997-2017)

Study	Treatment	Patients		Dose (m^2) /per 4 week cycle	7/28 days or 1/14 days	Number of cycles delivered	Total dose of clb	Anti-CD20 antibody	Response rate		
		No	Med age						CR/CRi	ORR	PFS
Jaksic et al 1997	Clb mono	228	??	150–180/ m2	Continuous	??	??	None	??	89.5%	68 (OS)
Rai et al 2000	Clb mono	193	62	40mg/m^2	1/28	Up to 12	??	None	4%	37%	14
Eichhorst et al 2009	Clb mono	100	70	38mg/m^2	1/14	6.5	0.5mg/kg	None	0%	51%	18
Hillmen et al 2007	Clb mono	148	60	40mg/m^2	1/28	7	515mg	None	2%	55%	11.7
Knauf et al 2009	Clb mono	156	66	60mg/m^2	1/14	6	522mg	None	2%	31%	8.3
Catovsky et al 2007	Clb mono	387	65	70mg/m^2	7/28	??	??	None	7%	72%	20
Hillmen et al CLL208	Clb + ritux	100	70	70mg/m^2	7/28	6	??	Ritux	10%	84%	23.5
Foa et al (Clb+rit)	Clb + ritux	85	70	56mg/m^2	7/28	8	~700mg	Ritux	18.9%	82.4%	34.7**
Hillmen et al (Compl	Clb	226	70	70mg/m^2	7/28	6 (12)	728mg	None	1%*	69%*	13.1
	Clb + Ofa	221	69	70mg/m^2	7/28	6 (12)	763mg	Ofatum	14%*	82%*	22.4
Goede et al (CLL11	Clb	118	72	38mg/m^2	1/14	6 (6)	384mg	None	0	31.4%	11.1
	Clb + ritux	330	73	38mg/m^2	1/14	6 (6)	396mg	Rituximab	7%	65.1%	15.2
	Clb + Obin	333	74	38mg/m^2	1/14	6 (6)	366mg	Obinutuz	20.7%	78.4%	26.7

Chlorambucil monotherapy

Study	Patients		Dose (m^2) /per 4 week cycle	7/28 or 1/14 days	No. of cycles	Total dose of chloram bucil	Response rate		
	No	Med age					CR/CRi	ORR	PFS
Goede *et al* CLL11 (2014)	118	72	38mg/m^2	1/14	6 (6)	384mg	0	31.4%	11.1
Eichhorst *et al* GM CLL5 (2009)	100	70	38mg/m^2	1/14	6.5	0.5mg/ kg	0%	51%	18
Rai *et al* ECOG (2000)	193	62	40mg/m^2	1/28	(12)	??	4%	37%	14
Hillmen *et al* CAM307 (2007)	148	60	40mg					5%	11.7
Knauf *et al* Chl v Bend (2009)	156	66	60mg/m^2	1/14	6	522mg	2%	31%	8.3
Catovsky *et al* UK CLL4 (2007)	387	65	70mg/m^2	7/28	(12)	>700mg	7%	72%	20
Hillmen *et al* Compl-1 (2015)	226	70	70mg/m^2	7/28	6 (12)	728mg	1%*	69%*	13.1
Jaksic *et al* HD Chl (1997)	228	??	150–180/ m2	Continu ous	??	??	??	89.5%	68 (OS)

Mean number courses = 4.9
31% patients had a dose reduction

N = 1,556 patients

* IRC

Chlorambucil + anti-CD20 MoAb

Study	Patients		Dose (m^2) /per 4 week cycle	7/28 days or 1/14 days	No: of cycles	Total dose of clb	Anti-CD20 antibody	Response rate		
	No	Med age						CR/ CRi	ORR	PFS
Goede et al CLL11	330	73	38mg/m^2	1/14	6 (6)	396mg	Rituximab	7%	65.1%	15.2
Goede et al CLL11	333	74	38mg/m^2	1/14	6 (6)	366mg	Obinutuzumab	20.7%	78.4%	26.7
Hillmen et al CLL208	100	70	70mg/m^2	7/28	6	~700mg	Rituximab	10%	84%	23.5
Foa et al Clb +rit	85	70	56mg/m^2	7/28	8	~700mg	Rituximab	18.9%	82.4%	34.7**
Hillmen et al Complement	221	69	70mg/m^2	7/28	6 (12)	763mg	Ofatumumab	14%*	82%*	22.4

N = 1,069 patients

* IRC; **included rituximab maintenance

Chlorambucil-based therapy

Questions to address:

1.Is there a role for chlorambucil-based therapy in 2017?

- ?probably

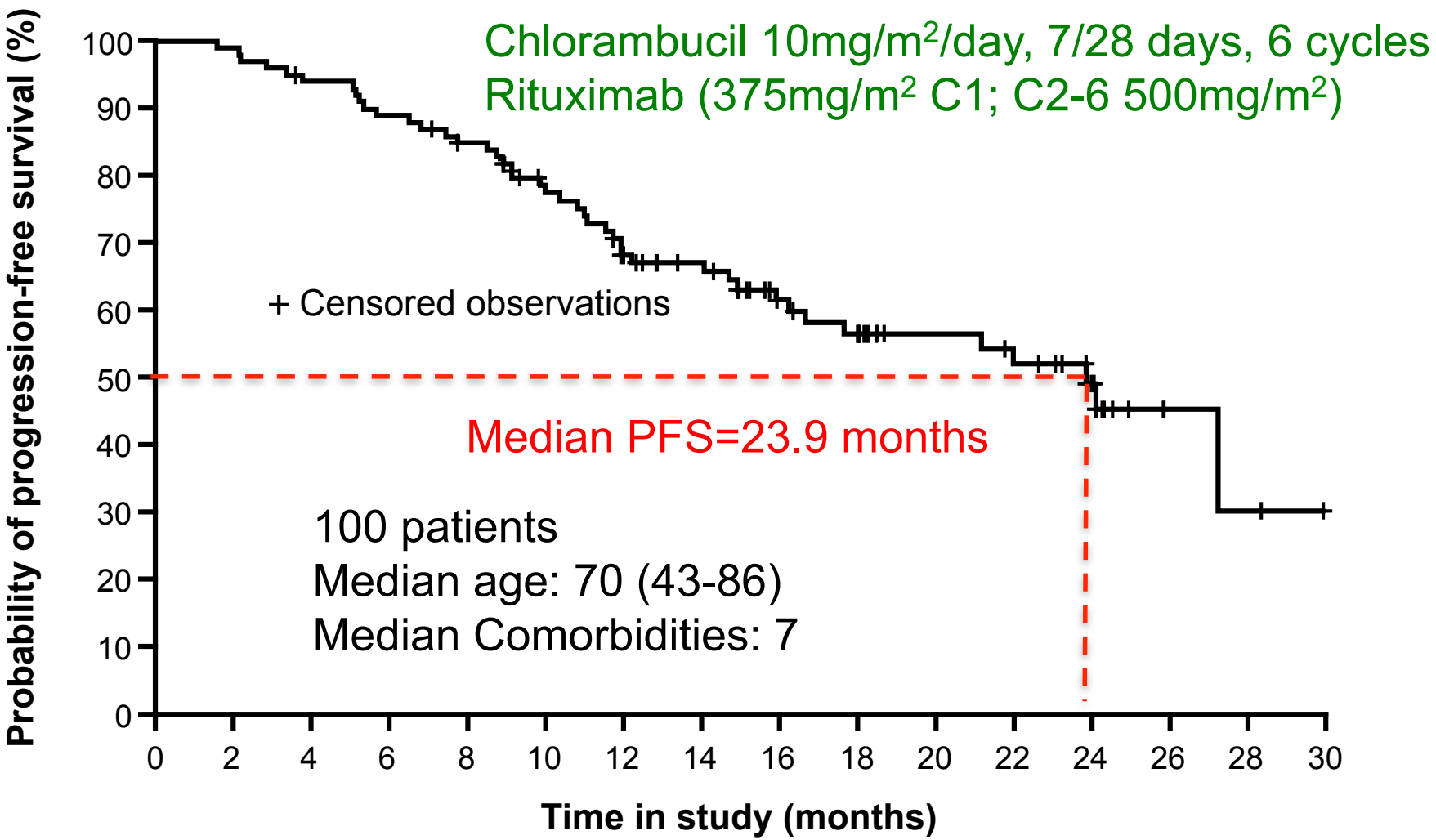
2.What is the best dose and schedule of chlorambucil?

- ≥70mg/m^2/cycle; 7/28 day cycles; 6-12 cycles

3.Should chlorambucil be combined with anti-CD20 MoAb?

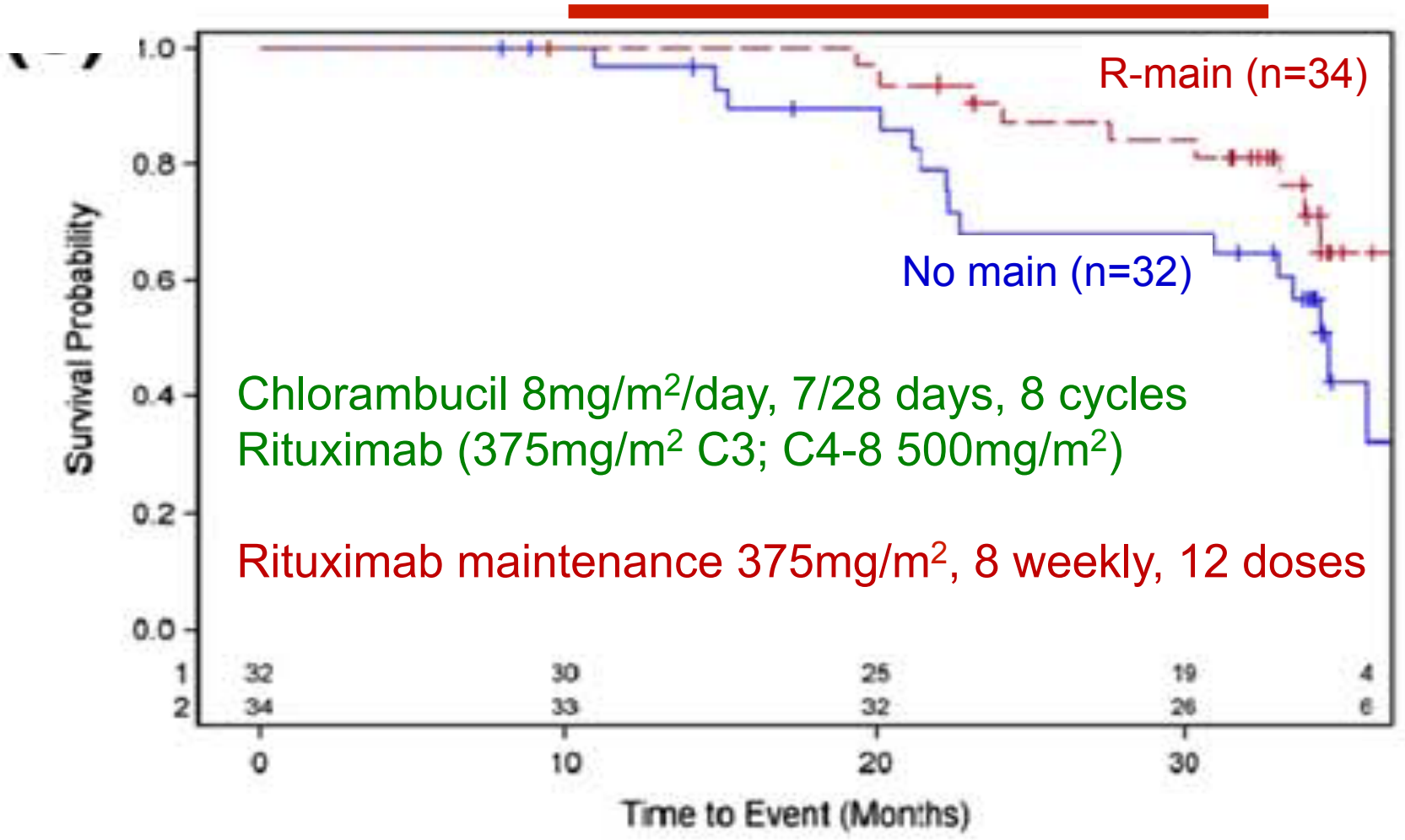
4.What is the best anti-CD20 to combine with chlorambucil?

Improved PFS with the addition of rituximab to chlorambucil (R-chlorambucil; NCRI CLL208)



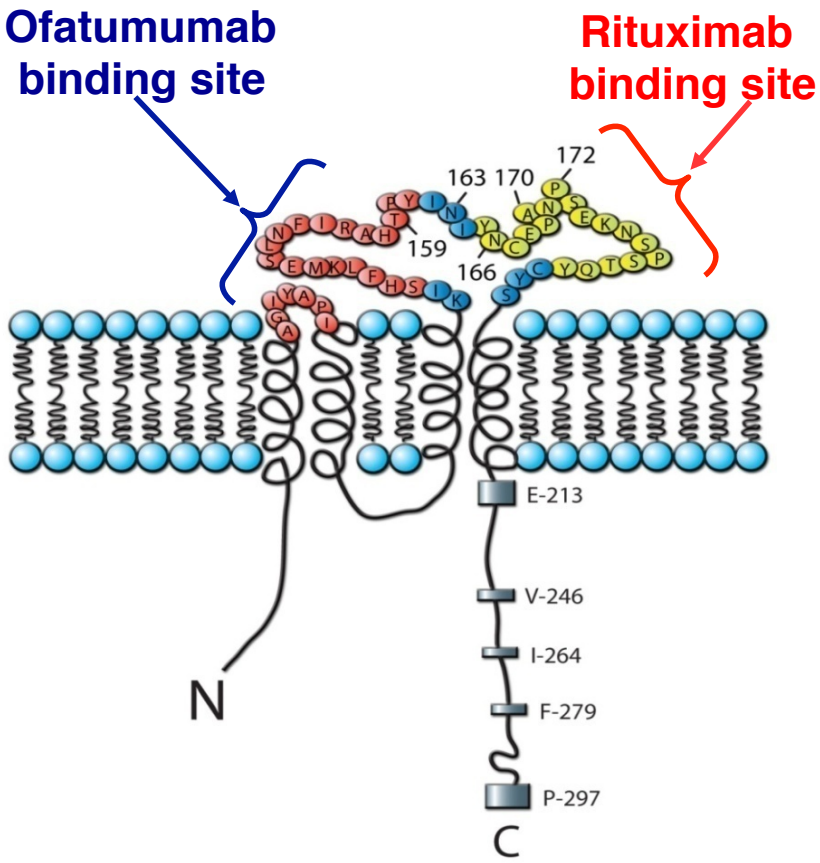
Hillmen *et al.*, *JCO*, 2014; 32: 1236-41.

PFS with the addition of rituximab to chlorambucil followed by R-maintenance



Foa *et al.*, *Am. J. Hematol.* 2014; 89:480–486.

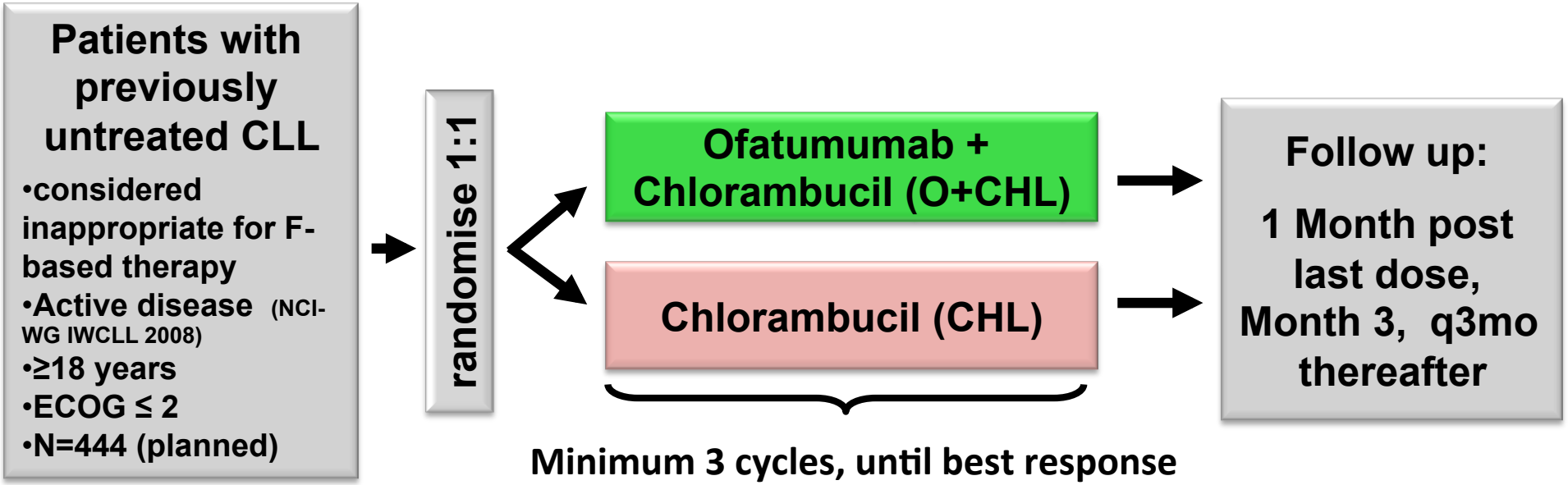
Can we improve on rituximab? Ofatumumab?



- Different Epitope to rituximab
- Induces potent in vitro lysis by CDC of B cells with low CD20 expression, including CLL
- Pivotal trial demonstrated activity in 206 patients with refractory CLL[3]
  - ORR 47% in 206 F-refractory pts
  - ORR 43% in 117 patients previously treated with rituximab
- No comparative studies versus rituximab

Wierda et al. Blood 2012

COMPLEMENT 1: Ofatumumab in CLL



Minimum 3 cycles, until best response or PD , maximum 12 cycles

- No cross over allowed -

O: cycle 1 d1 300 mg, d8 1000 mg, Cycle 2-12 d1 1000 mg every 28 days

CHL: 10 mg/m^2 d1-7 every 28 days

Dose rationale: evidence of highest ORR and longest PFS with low toxicity compared to any other CHL monotherapy regimen

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

Complement-1: Patient Characteristics

	CHL (n=226)	O+CHL (n=221)
Age, Years, median (range)	**70 (36-91)**	**69 (35-92)**
≥ 65, %	**69**	**69**
≥ 75, %	**28**	**25**
Male, %	**62**	**64**
ECOG - 0,1, %	**91**	**91**
Comorbidities, median (range)	**3 (0-10)**	**3 (0-10)**
≥2, %	**70**	**73**
CrCl mL/min, median (min-max)	**69 (21-209)**	**72 (26-172)**
<70 mL/min, %	**51**	**45**
≥65 yrs or ≥2 comorbidities or CrCl <70 ml/min, %	**87**	**87**
CIRS, median (range)	**8 (4-19)**	**9 (4-21)**

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

Complement-1: End-of-treatment Response

as assessed by an Independent Review Committee

	CHL (n=226)	O+CHL (n=221)
Overall Response Rate*, %	**69**	**82**
p-value	<0.001	
CR, %	**1**	**14**
PR, %	**67**	**68**
SD, %	**23**	**12**
PD, %	**4**	**2**
NE, %	**3**	**3**
Missing, %	<1	<1
MRD negative		**8**

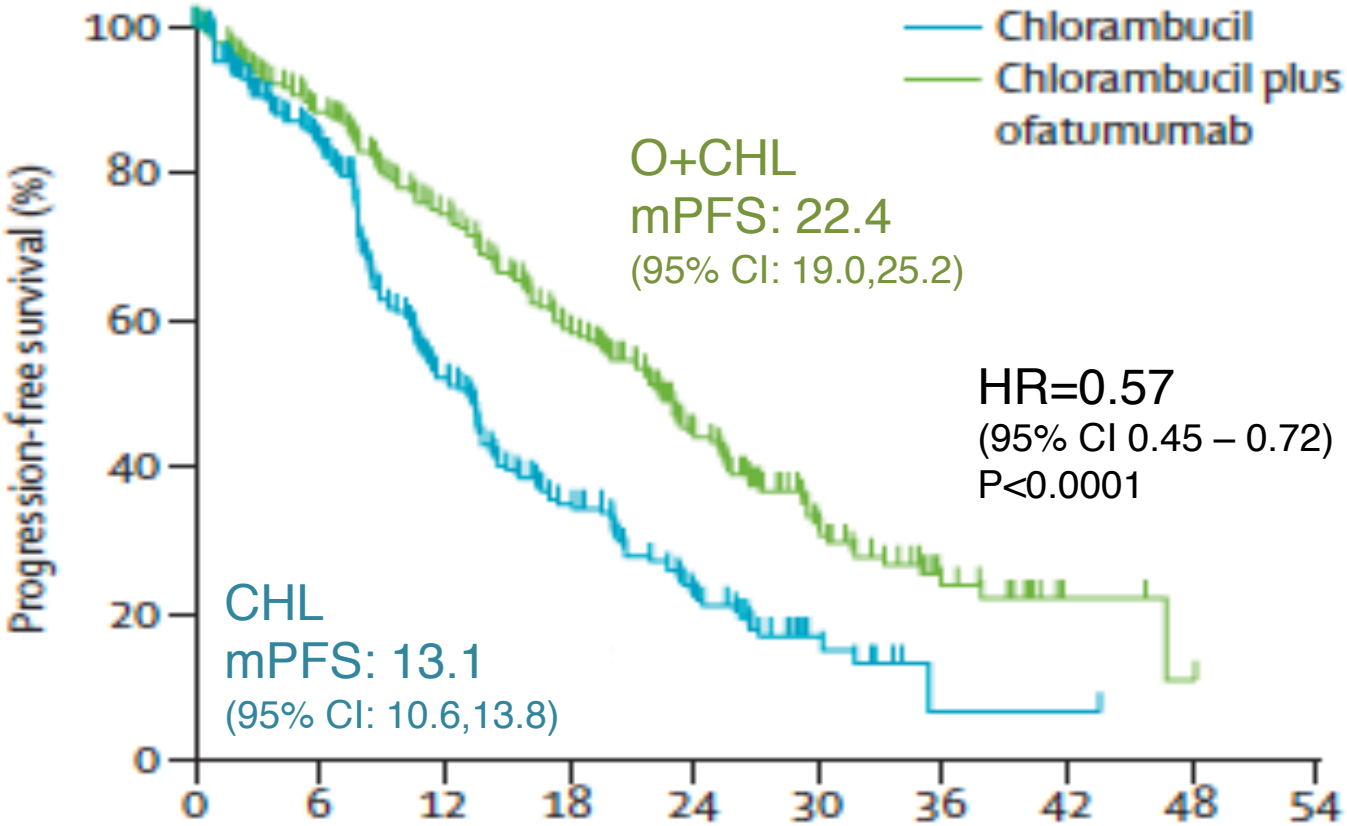
*As per IWCLL 2008 criteria, CR includes CRi, PR includes nPR

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

Complement-1: Median PFS (months)

as assessed by an Independent Review Committee

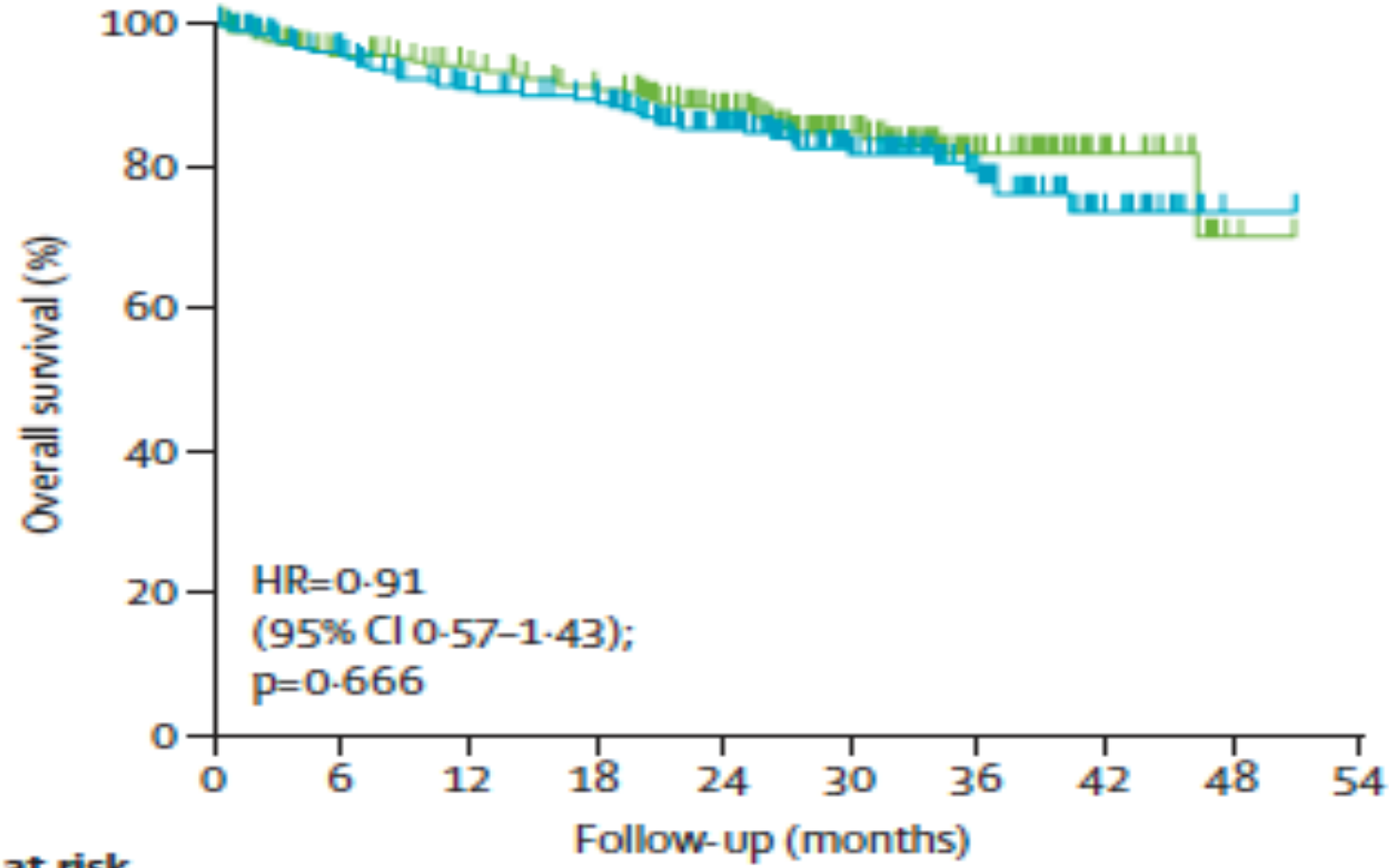


Number at risk					
Chlorambucil	226	92	33	1	0
Chlorambucil plus ofatumumab	221	149	70	15	1

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

Complement-1: Overall Survival



Number at risk					
Chlorambucil	226	191	148	53	1
Chlorambucil plus ofatumumab	221	193	153	57	2

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

Complement-1: Incidence of Adverse Events

	Chlorambucil (n=227)		Chlorambucil + ofatumumab (n = 217)	
	All grades	≥ grade 3	All grades	≥ grade 3
AE, any	197 (87%)	98 (43%)	204 (94%)	109 (50%)
AE, related to study treatment	148 (65%)	-	182 (84%)	-
AE, leading to WD of treatment	29 (13%)	-	28 (13%)	-
Neutropenia	40 (18%)	32 (14%)	59 (27%)	56 (26%)
Thrombocytopenia	58 (26%)	22 (10%)	30 (14%)	10 (7%)
Anaemia	30 (13%)	12 (5%)	19 (9%)	10 (5%)
Infections	104 (46%)	27 (12%)	91 (42%)	20 (9%)
Infusion reactions	n/a	n/a	146 (67%)	22 (10%)

Hillmen *et al.*, Lancet. 2015;385:1873-83.

COMPLEMENT 1

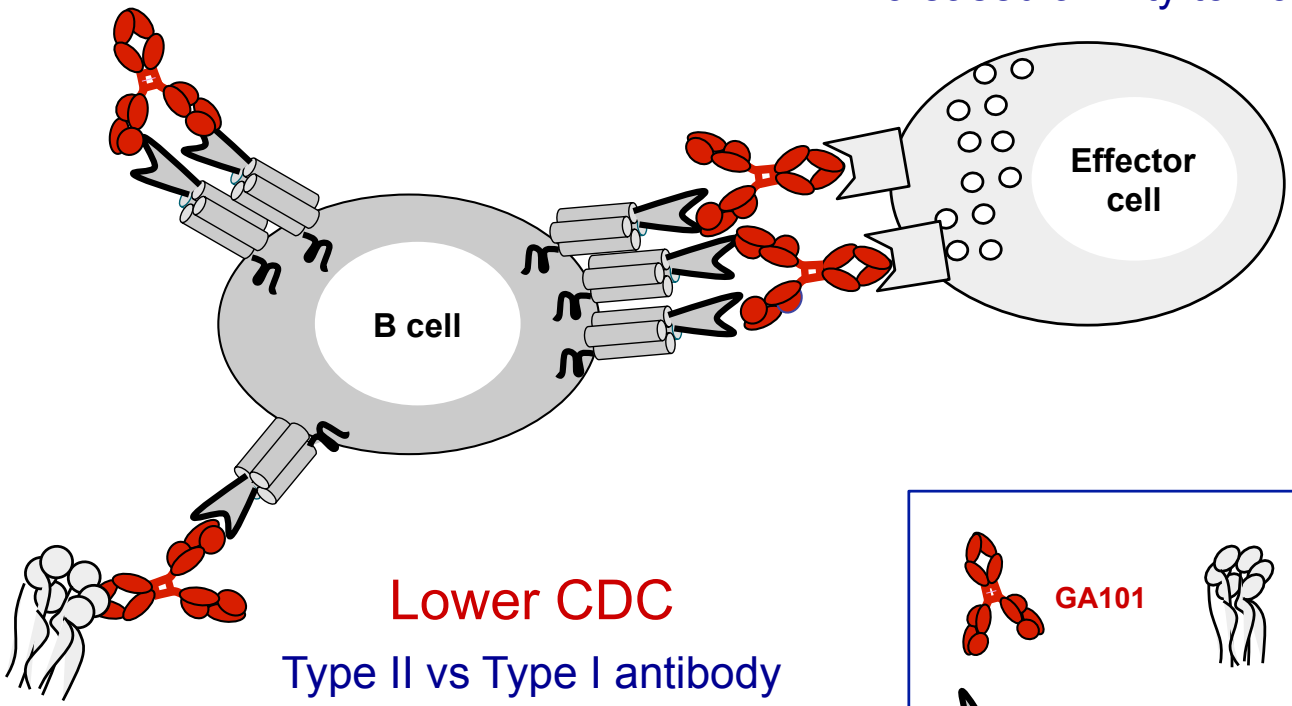
GA101: Mechanisms of action

Increased Direct Cell Death

Type II vs Type I antibody

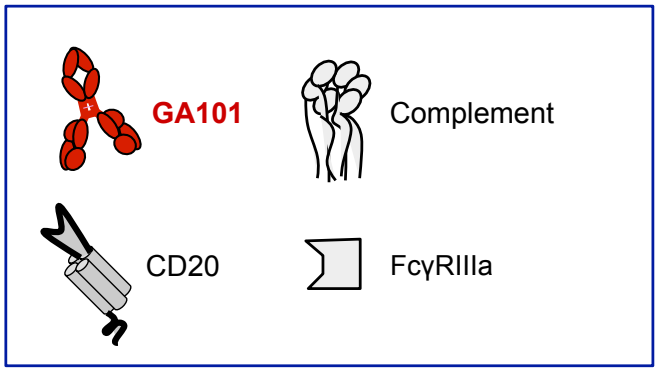
Enhanced ADCC

Glycoengineering for
increased affinity to FcγRIIIa



Lower CDC

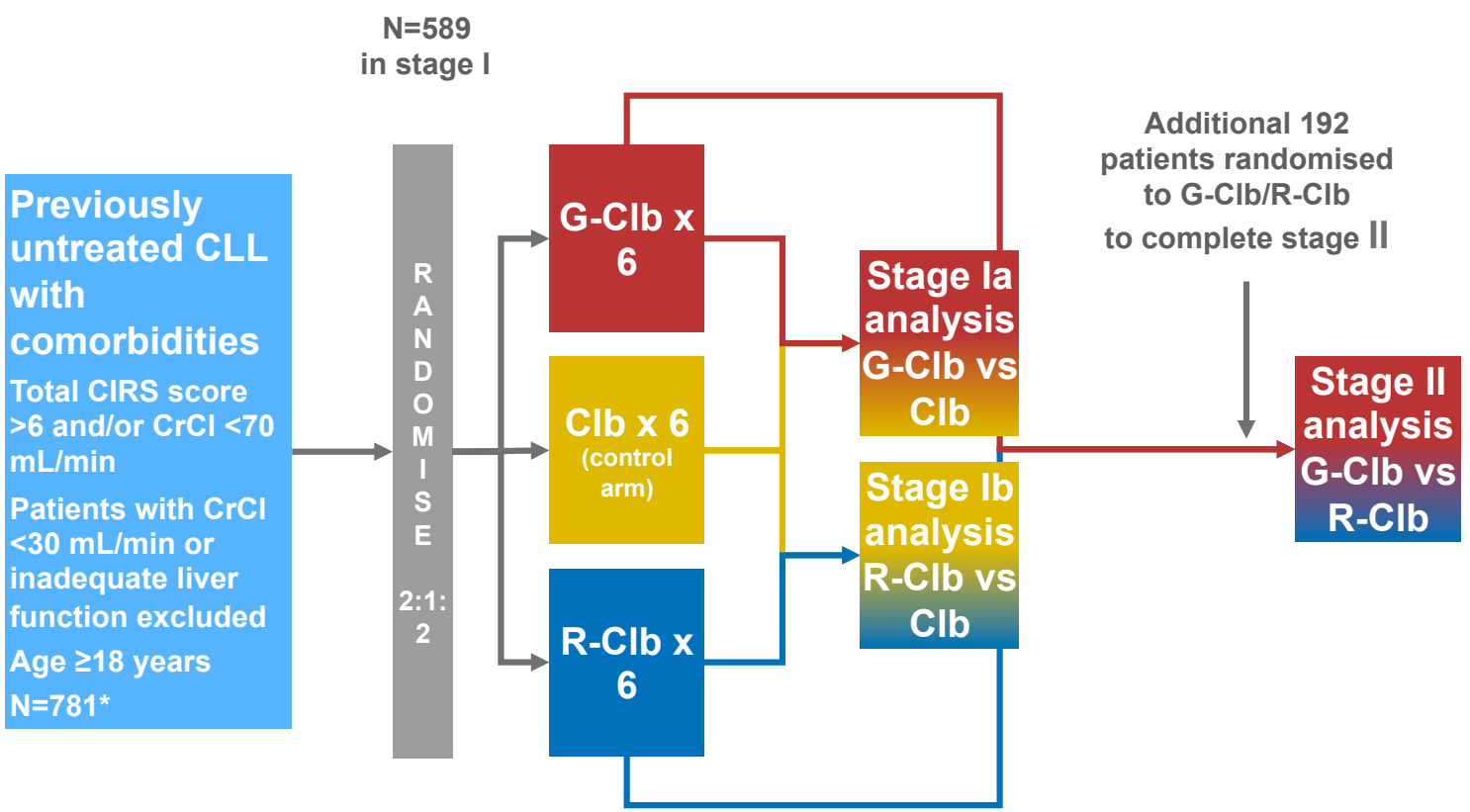
Type II vs Type I antibody



ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity

Mössner et al. *Blood* 2010;115:4393-4402

GCLLSG CLL11 Trial – Study Design



obinutuzumab: 1,000 mg days 1, 8 and 15 cycle 1; day 1 cycles 2–6, every 28 days

rituximab: 375 mg/m^2 day 1 cycle 1; 500 mg/m^2 day 1 cycles 2–6, every 28 days

Clb: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days

Patients with PD in the Clb arm were allowed to crossover to the G-Clb arm

Primary endpoint	**Investigator-assessed PFS**
Secondary endpoints	ORR, CR rate, PR rate, IRC-assessed PFS, OS, EFS, time to next treatment, MRD, safety, patient-reported outcomes and symptom burden by EORTC questionnaire

References: 1. Goede V, et al. N Engl J Med 2014;370:1101–1110; 2. Goede V, et al. Leukemia 2013;27:1172–1174.

GCLLSG CLL11: Baseline patient characteristics

	G-Clb (n=333) %	R-Clb (n=330) %
Male	61	62
Median age, years (range)	74 (39–89)	73 (40–90)
Aged ≥65 years	81	78
Aged ≥75 years	46	42
Median ECOG PS (range)	1 (0-3)	1 (0-3)
Median CIRS score	8.0	8.0
CIRS score >6	78	75
Median CrCl	62.5	62.6
CrCl <70 mL/min	65	64
CrCl <50 mL/min	27	25

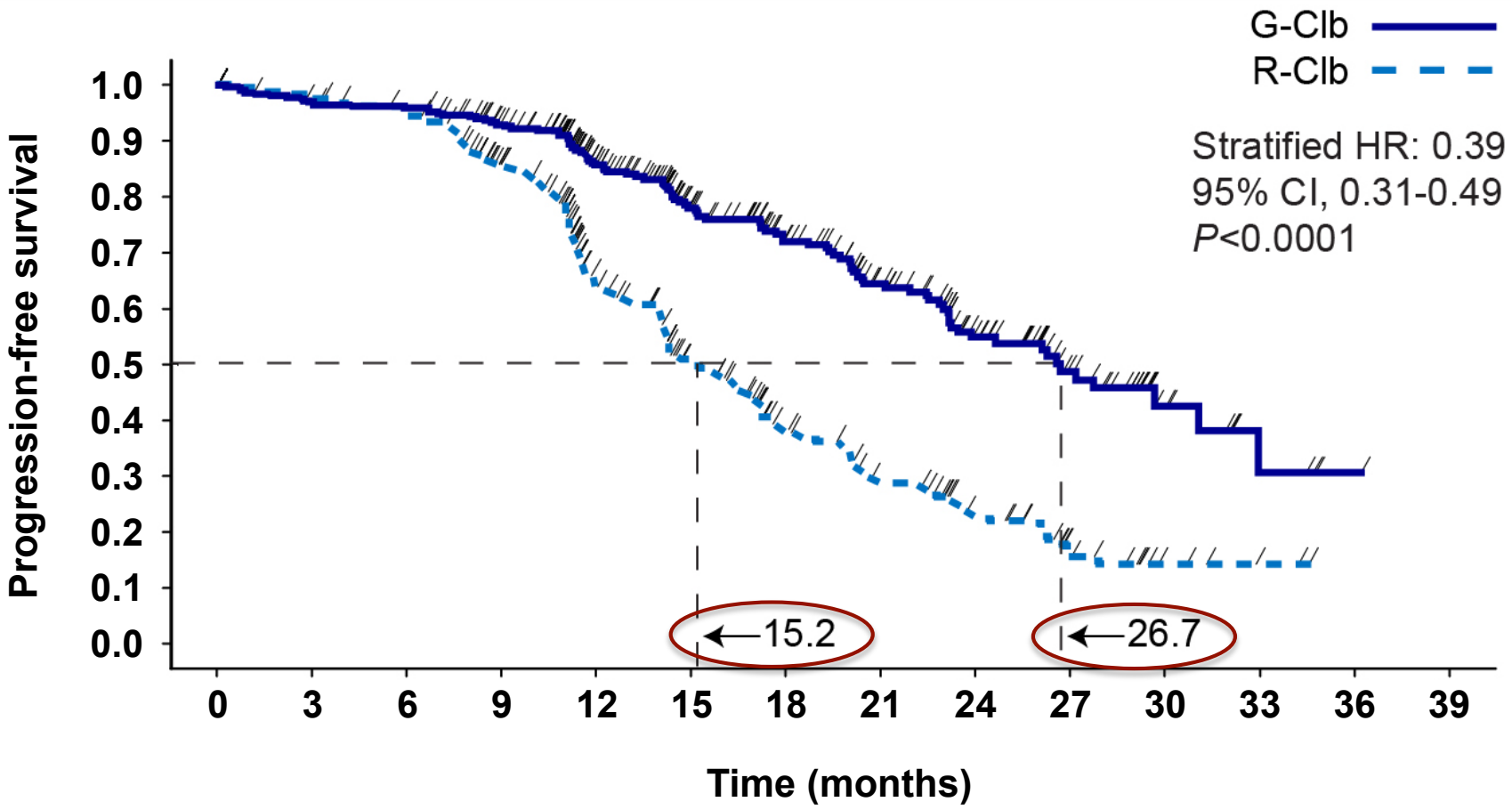
ECOG PS, Eastern Cooperative Oncology Group performance status;
CIRS, cumulative illness rating scale; CrCl, creatinine clearance

GCLLSG CLL11 Trial: End-of-treatment response

	G-Clb (n=333) %	R-Clb (n=329)[a] %
Response rate		
ORR	78	65
	p <0.0001	
CR[b]	21	7
PR[c]	58	58
SD	5	15
PD	4	11
Not evaluable[d]	13	9

[a] Assessment not reached by data cut-off in 1 patient in R-Clb arm; as assessed by iwCLL criteria 3 months after end of treatment
[b] Confirmed by imaging and bone marrow, and includes incomplete CR
[c] Includes nodular PR
[d] Due to missing data or withdrawal from study treatment prior to response assessment
ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

GCLLSG CLL11 Trial: PFS for G-Clb vs R-Clb



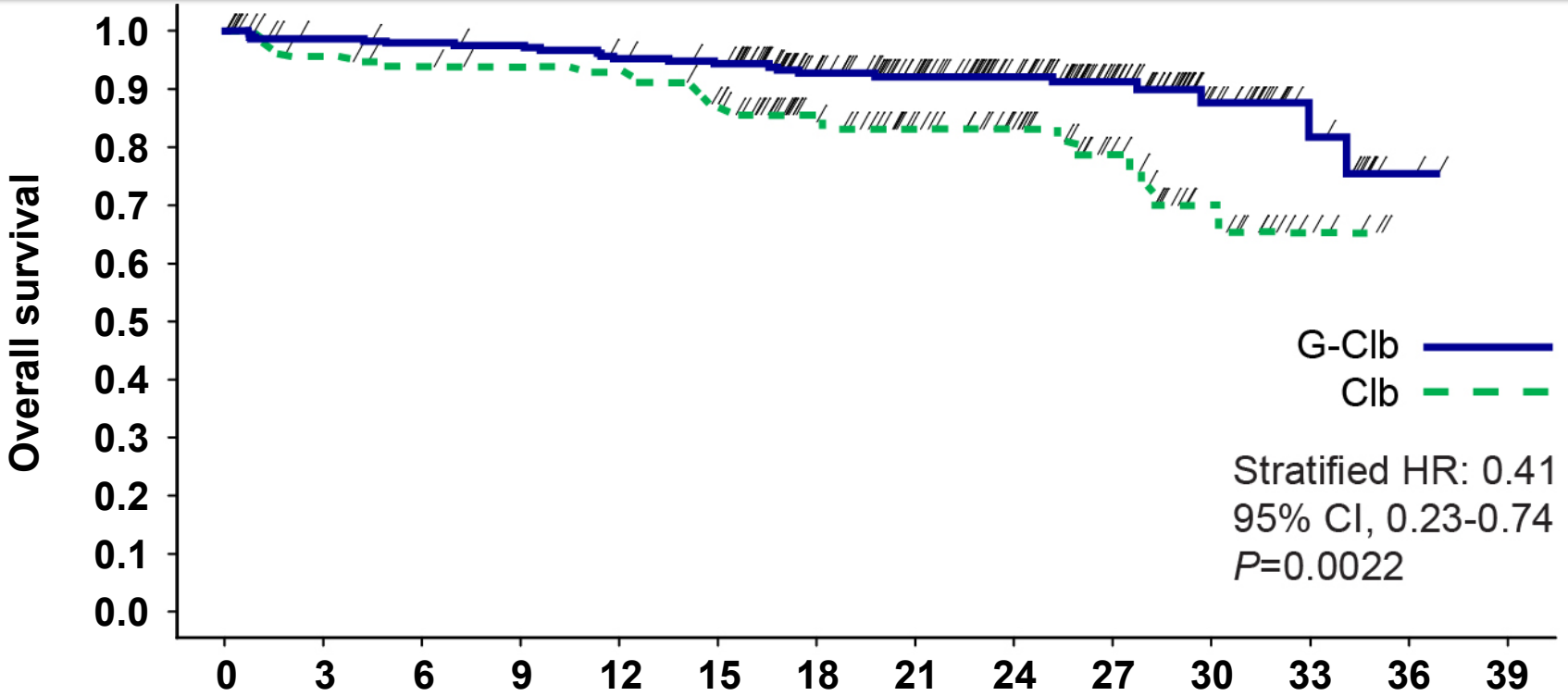
No. at risk

G-Clb:	**330**	**307**	**302**	**278**	**213**	**156**	**122**	**93**	**60**	**34**	**12**	**4**	**1**	**0**
R-Clb:	**330**	**317**	**309**	**259**	**163**	**114**	**72**	**49**	**31**	**14**	**5**	**2**	**0**	**0**

Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months
Type 1 error controlled through closed test procedure; *P* value of the global test was <0.0001
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS

Goede *et al.*, N Engl J Med, 2014; 370: 1101-10.

GCLLSG CLL11 Trial: Overall survival G-Clb vs Clb



No. at risk

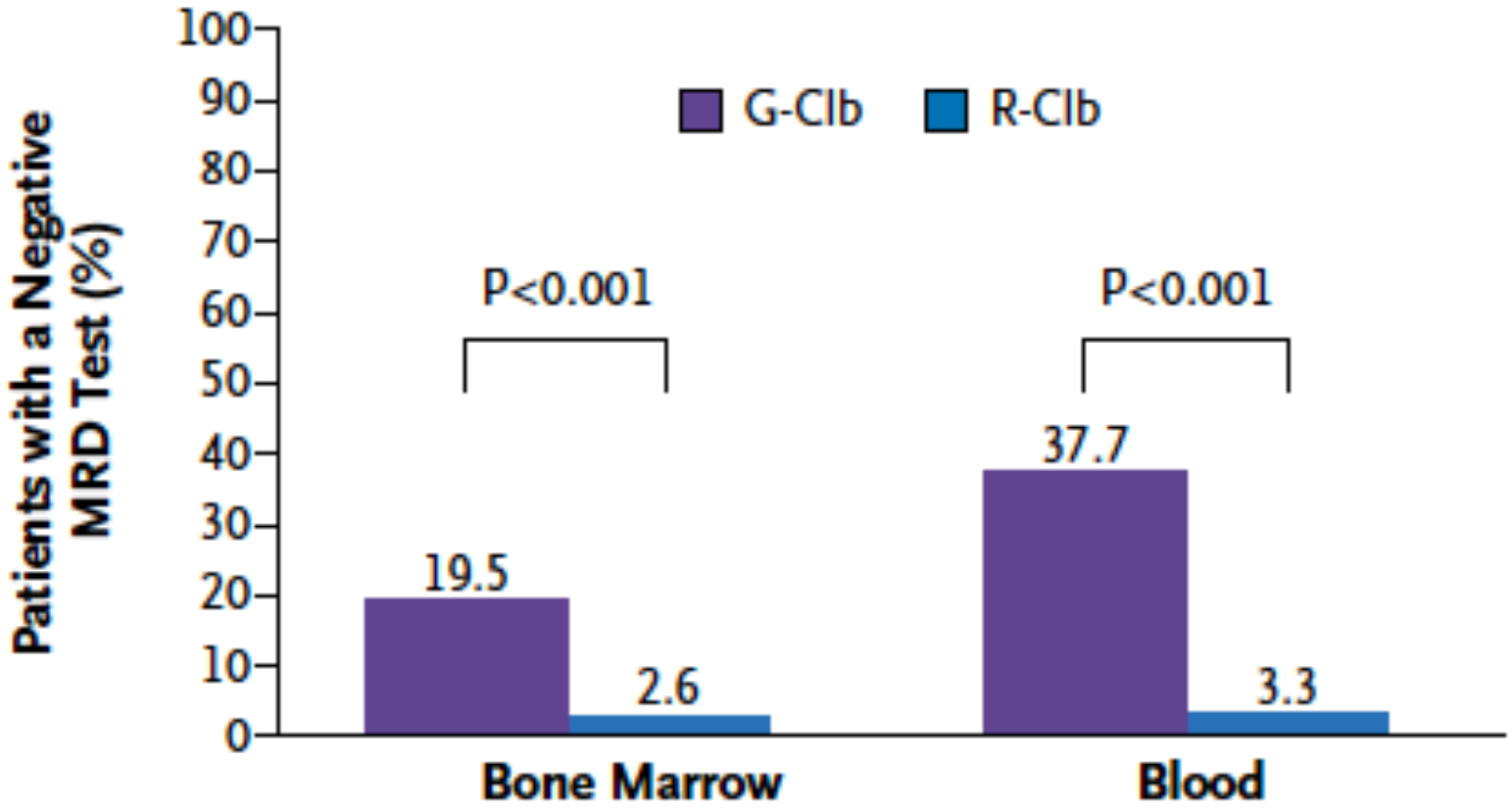
G-Clb:	**238**	**226**	**223**	**221**	**215**	**211**	**170**	**144**	**115**	**71**	**34**	**14**	**2**	**0**
Clb:	**118**	**109**	**105**	**103**	**102**	**94**	**70**	**56**	**44**	**29**	**15**	**5**	**0**	**0**

Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

Median observation time: G-Clb, 23.2 months; Clb, 20.4 months
No multiplicity adjustment was done for secondary endpoints

Goede *et al.*, N Engl J Med, 2014; 370: 1101-10.

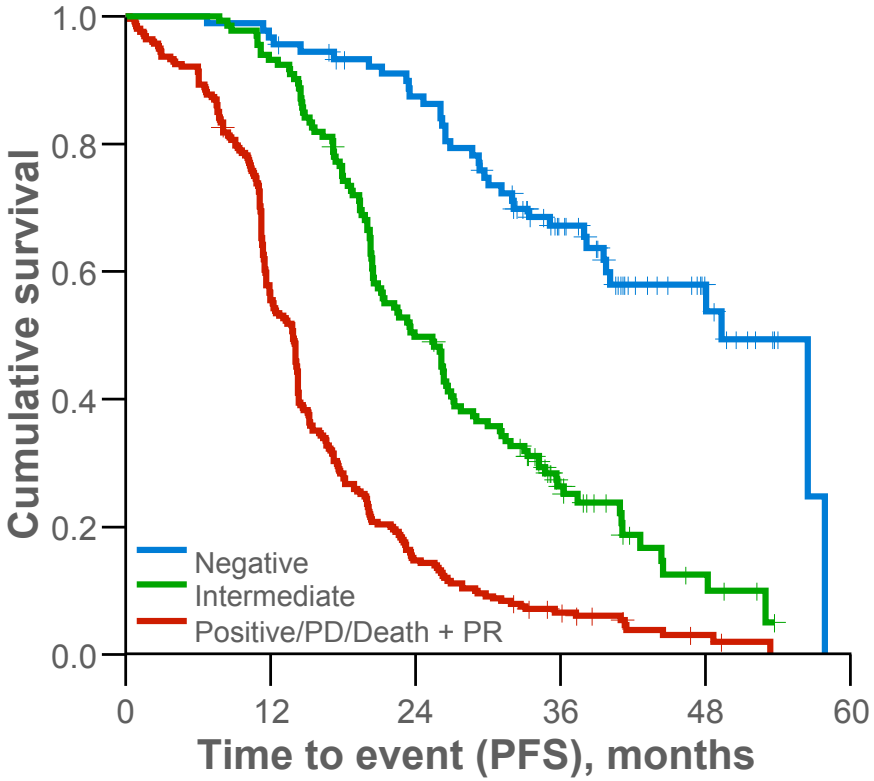
GCLLSG CLL11 Trial: MRD blood and marrow

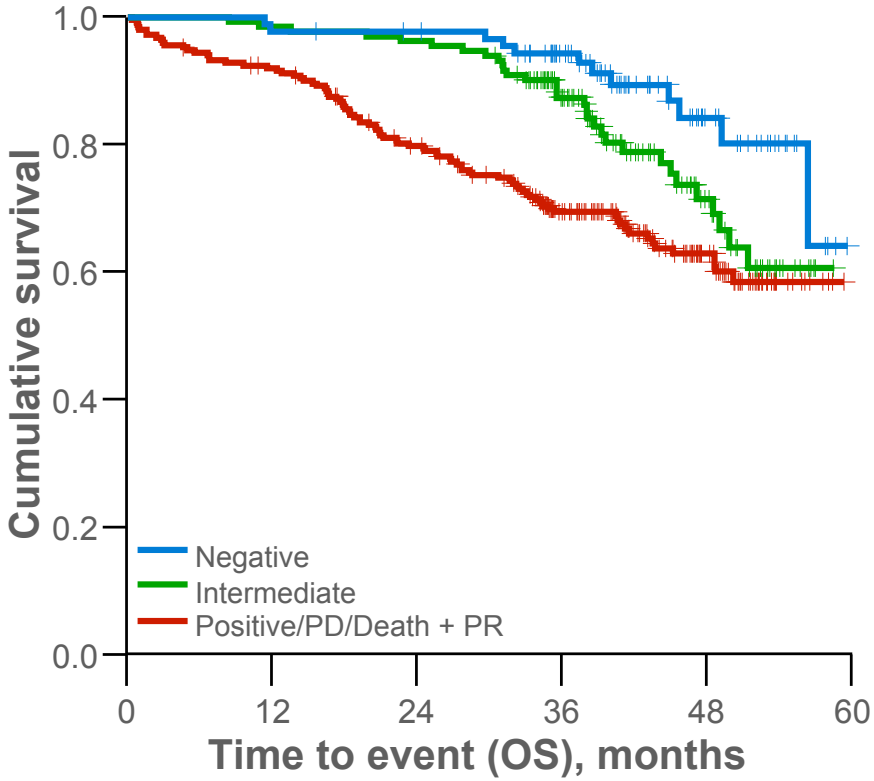


No. of Patients			
26/133	3/114	87/231	8/243

Goede *et al.*, N Engl J Med, 2014; 370: 1101-10.

GCLLSG CLL11 Trial: MRD negativity in the blood





At EOT, G-Clb had higher MRD negativity than R-Clb
MRD negativity in peripheral blood was significantly correlated with, and a strong prognostic factor for, PFS and OS

References: 1. Ritgen et al, EHA 2016 abstract.

GCLLSG CLL11 Trial: Adverse events of interest

	G-Clb (n=336)[a] %	R-Clb (n=321)[a] %
Any AE grade ≥ 3[b]	70	55
Infusion-related reaction	20	4
Neutropenia	33	28
Anemia	4	4
Thrombocytopenia	10	3
Infection	12	14
Pneumonia	4	5

[a] Safety population for G-Clb includes 5 patients randomized to R-Clb who received one infusion of GA101 in error
[b] Incidence rate of ≥3% in any treatment arm

Chlorambucil-based therapy

Questions to address:

1. Is there a role for chlorambucil-based therapy in 2017?
   - ?probably
2. What is the best dose and schedule of chlorambucil?
   - ≥70mg/m^2/cycle; 7/28 day cycles; 6-12 cycles
3. Should chlorambucil be combined with anti-CD20 MoAb?
   - Yes a second generation anti-CD20 antibody
4. What is the best anti-CD20 to combine with chlorambucil?

	GCLLSG CLL11 (Chlorambucil + obinutuzumab)
Strengths	• Compared to Chlorambucil + rituximab and chlorambucil • Median age (74yo) appropriate • “Objective” assessment of fitness (CIRS)
Weakness	• Dose of obinutuzumab not equivalent to rituximab • Dose/schedule of chlorambucil ineffective therefore accentuates anti-CD20 effect • Investigator decision to switch from chlorambucil arm • Investigator-assessment of PFS (primary end-point)

	GCLLSG CLL11 (Chlorambucil + obinutuzumab)	Complement-1 (Chlorambucil + ofatumumab
Strengths	• Compared to Chlorambucil + rituximab and chlorambucil • Median age (74yo) appropriate • "Objective" assessment of fitness (CIRS)	• Most effective dose/schedule of chlorambucil as comparator • No cross-over within the trial • IRC assessment of PFS (primary end-point)
Weakness	• Dose of obinutuzumab not equivalent to rituximab • Dose/schedule of chlorambucil ineffective therefore accentuates anti-CD20 effect • Investigator decision to switch from chlorambucil arm • Investigator-assessment of PFS (primary end-point)	• Only chlorambucil monotherapy comparison • Median age (69yo) low for chlorambucil-based therapy

Chlorambucil-based therapy

Questions to address:

1. Is there a role for chlorambucil-based therapy in 2017?
   - ?probably
2. What is the best dose and schedule of chlorambucil?
   - ≥70mg/m^2/cycle; 7/28 day cycles; 6-12 cycles
3. Should chlorambucil be combined with anti-CD20 MoAb?
   - Yes a second generation anti-CD20 antibody
4. What is the best anti-CD20 to combine with chlorambucil?
   - Not known – probably obinutuzumab

Front-line Phase III CLL Trials involving chlorambucil

Trial	Sponsor	Arms	Dose chlorambucil	Number	Status
Illuminate (PCYC1130)	Pharmacyclics	Ibrutinib+Obin vs Cbl+Obin	0.5mg/kg 1/14, 6 cycles	212 (1:1)	Completed recruitment
GCLLSG CLL14	GCLLSG/ Abbvie	Venetoclax+Obin vs Cbl+Obi	0.5mg/kg 1/14, 12 cycles	432 (1:1)	Completed recruitment
ACE-007	Acerta	ACP-196+obin vs Cbl+Obin	0.5mg/kg 1/14, 6 cycles	510 (1:1:1)	Completed recruitment
RIAltO	NCRI	Cbl+Ofat vs Benda+Ofat	10mg/m^2 7/28, 12 cycles	670 (1:1)	Closes 2018

Why the low dose of chlorambucil?

Conclusion

- Chlorambucil → use adequate dose (70mg/m^2/day; 7 in 28 day cycle; up to 12 cycles)
- Better responses with either ofatumumab or obinutuzumab
  - No direct comparison but obinutuzumab as given seems to result in deeper remissions
- What do I use out of trials?
  - Chlorambucil 10mg/m^2/day; 7/28 day cycle + obinutuzumab
- Should we really be allowing inadequate chlorambucil dosing in Phase III trials??