CLL therapy in elderly versus younger patients?

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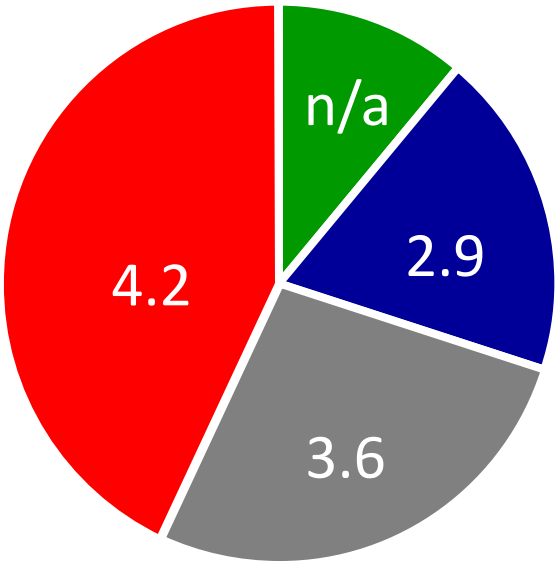
DEUTSCHE STUDIENGRUPPE

CIO Center for Integrated Oncology Köln Bonn

CLL patient characteristics at presentation

- Median age at diagnosis: 72 years[1]
- Many elderly patients are fit, but some have co-morbidities



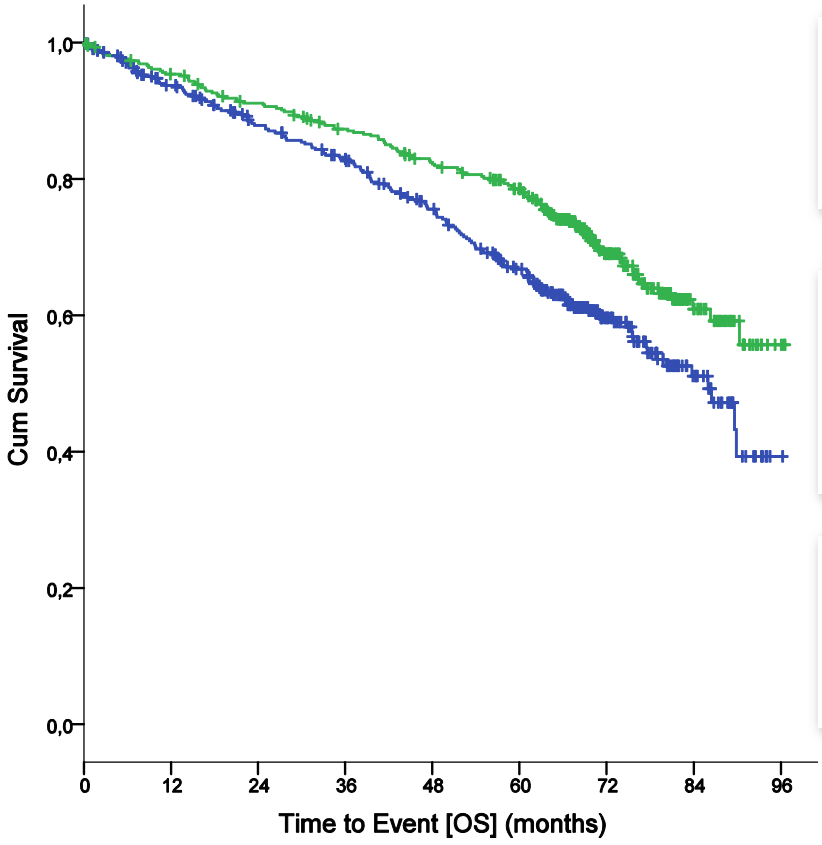
Age at CLL diagnosis (years)	Patients[1] (%)	Mean co-morbidities[2] (all cancer types, n)
≤ 54	11	n/a
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

1. Ries LAG, *et al.* SEER Cancer Statistics Review, 1975–2005.
2. Yancik R, *Cancer* 1997; 80:1273–1283.

Management of fit CLL patients

CLL8 trial: Overall survival, update 2012
FCR versus FC

Hallek et al. Lancet 2010; Fischer et al. ASH 2012

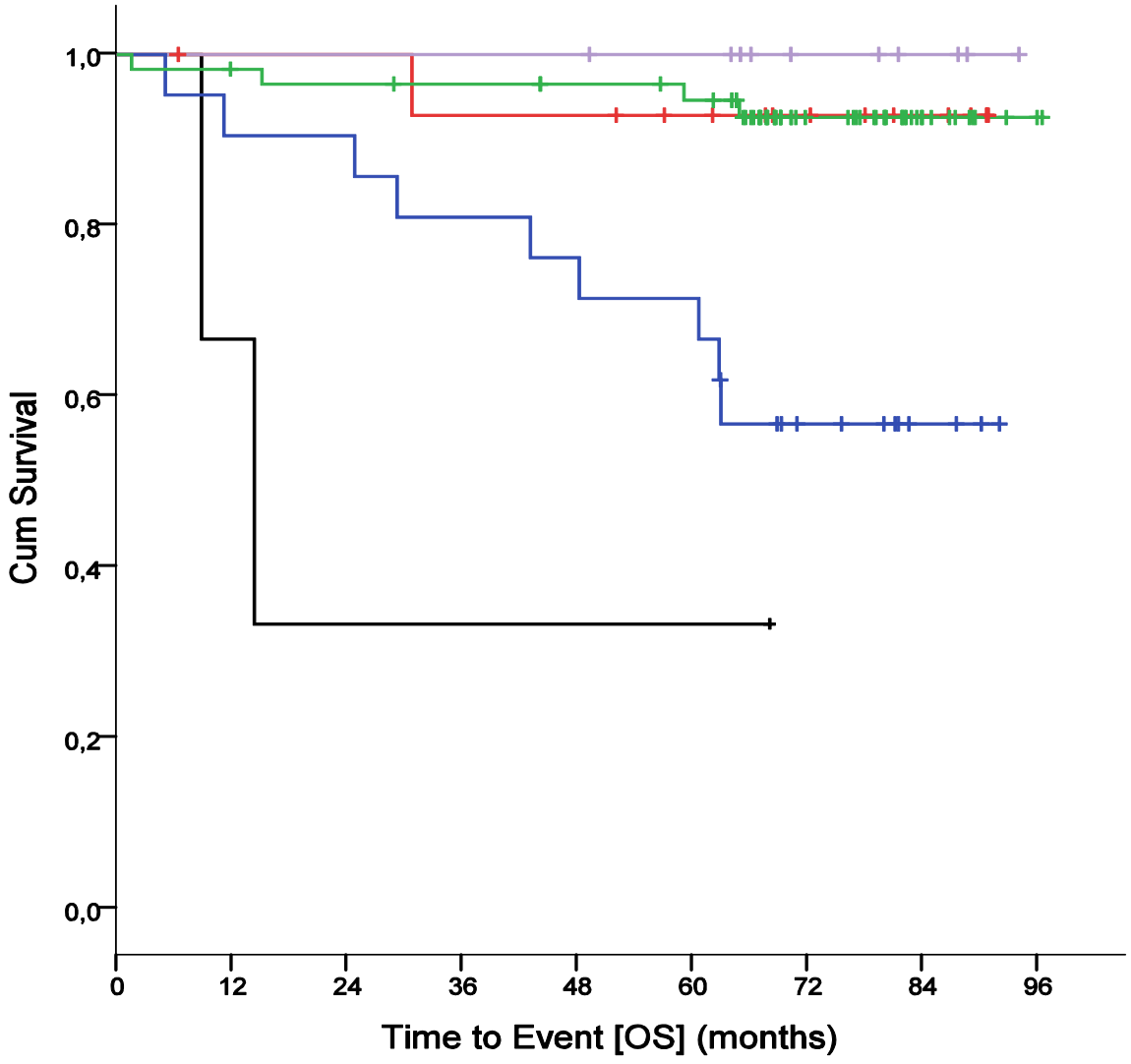


Median observation time 5.9 years

FCR 69.4% alive
Median not reached
FC 62.3% alive
Median 86 months

HR 0.68,
95% CI 0.535-0.858
p=0.001

Survival after FCR chemoimmunotherapy



	N (%)	Pts alive, %	5-year OS, %
IGHV mutated **patients***	107	85.0	66.6
+12q	10 (9.3)	100.0	100.0
13q-	58 (54.2)	93.1	94.6
11q-	15 (14.0)	93.3	92.9
Not**	21 (19.6)	57.1	71.4
17p-	3 (2.8)	33.3	33.3

* ***IGHV*** mutated **patients with FISH results**

**not 17p- / 11q- / +12q / 13q- acc. to Döhner H et al. NEJM 2000

CLL10 STUDY: FCR VS BR IN FRONT-LINE

DEUTSCHE STUDIENGRUPPE

Eichhorst B, *et al*. *Blood* 2013: Abstract 526

Patients with untreated, active CLL without del(17p) and good physical fitness
(CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Randomization

FCR

Fludarabine 25 mg/m² i.v., days 1-3
Cyclophosphamide 250 mg/m², days 1-3,
Rituximab 375 mg/ m² i.v. day 0, cycle 1
Rituximab 500 mg/m² i.v. day 1, cycle 2-6

BR

Bendamustine 90mg/m² day 1-2
Rituximab 375 mg/m² day 0, cycle 1
Rituximab 500 mg/m² day 1, cycle 2-6

Non-Inferiority of BR in comparison to FCR for PFS:

HR (λ BR/FCR) less than 1.388

CLL10 STUDY: FCR VS BR IN FRONTLINE

DEUTSCHE STUDIENGRUPPE

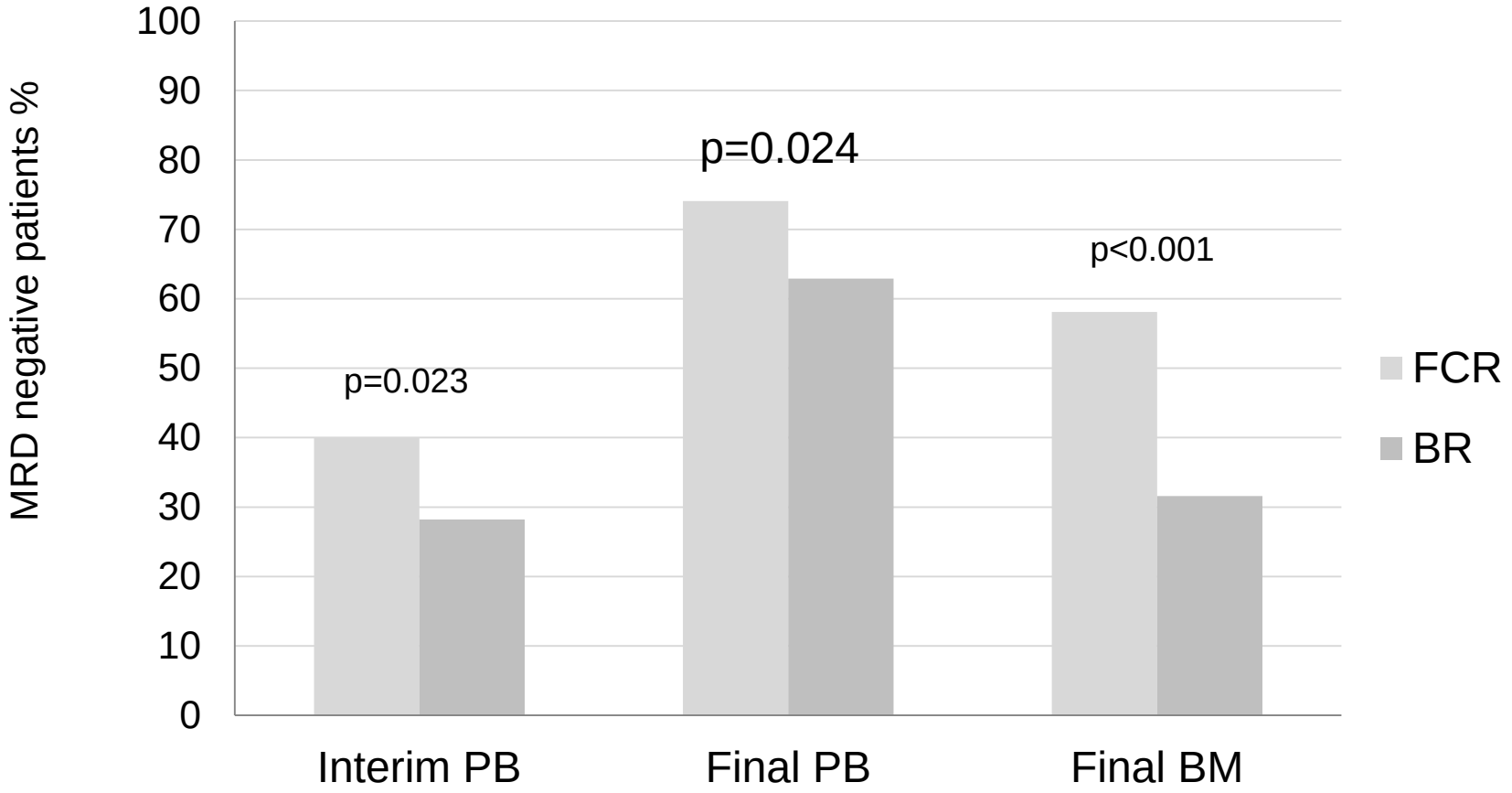
Response to therapy (Best response)

Response	FCR n=274	BR n=273	p value
CR (CR + CRi)	**47.4%**	**38.1%**	**0.031**
CR	40.1%	36.3%	
CRi	7.3%	1.8%	
PR	50.4%	59.7%	
ORR	**97.8%**	**97.8%**	**1.0**

CLL10 STUDY: FCR VS BR IN FRONTLINE

DEUTSCHE STUDIENGRUPPE

Minimal residual disease (MRD) negativity



No. of patients: 72/180 44/156 137/185 107/170 75/129 31/98

CLL10 STUDY: FCR VS BR IN FRONT-LINE

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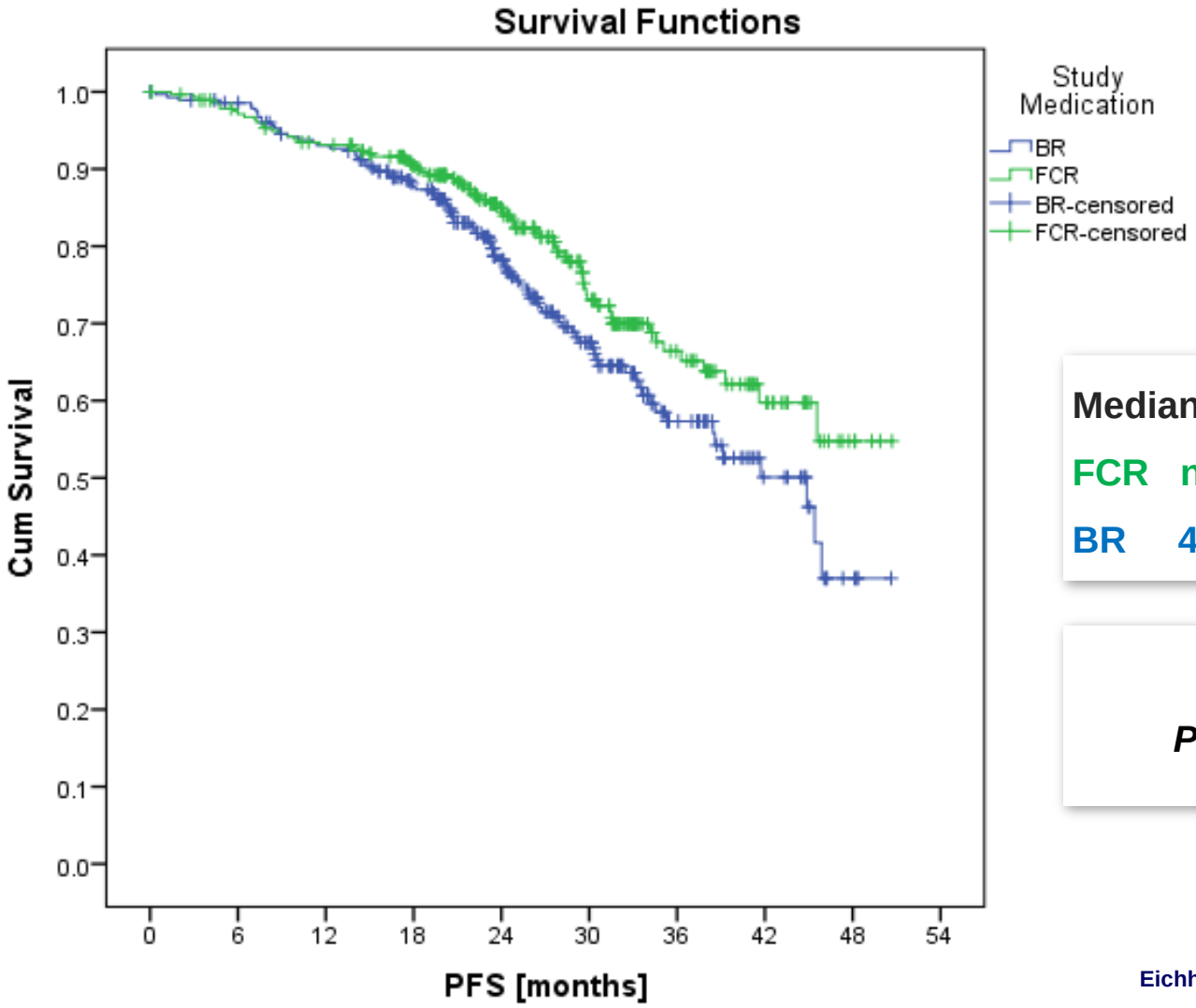
Progression-free survival = Primary endpoint



Median PFS

FCR not reached

BR 44.9 months

***P* = 0.041**

Eichhorst B, *et al*. *Blood* 2013: Abstract 526

CLL10 STUDY: FCR VS BR IN FRONTLINE

DEUTSCHE CLL STUDIENGRUPPE

Infections (FU period until 3 months after Final staging)

Adverse event	FCR (% of pt)	BR (% of pt)	p value
Infections CTC 1-5	74.1	66.7	0.064
Viral infections CTC 1-5	20.8	12.3	0.008
Infections CTC 3-5	39.0	25.4	0.001
Pneumonias	11.5	6.1	0.035
Infections CTC 3-5 in patients < 65years	34.8	24.7	0.048
Infections CTC 3-5 in patients ≥ 65years	47.4	26.5	0.002

Management of unfit CLL patients

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions

Valentin Goede, M.D., Kirsten Fischer, M.D., Raymonde Busch, M.S., Anja Engelke, M.D., Barbara Eichhorst, M.D., Clemens M. Wendtner, M.D., Tatiana Chagorova, M.D., Javier de la Serna, M.D., Marie-Sarah Dilhuydy, M.D., Thomas Illmer, M.D., Stephen Opat, M.D., Carolyn J. Owen, M.D., Olga Samoylova, M.D., Karl-Anton Kreuzer, M.D., Stephan Stilgenbauer, M.D., Hartmut Döhner, M.D., Anton W. Langerak, Ph.D., Matthias Ritgen, M.D., Michael Kneba, M.D., Elina Asikanius, M.Sc., Kathryn Humphrey, B.Sc., Michael Wenger, M.D., and Michael Hallek, M.D.

N Engl J Med 2014;370:1101-10.
DOI: 10.1056/NEJMoa1313984

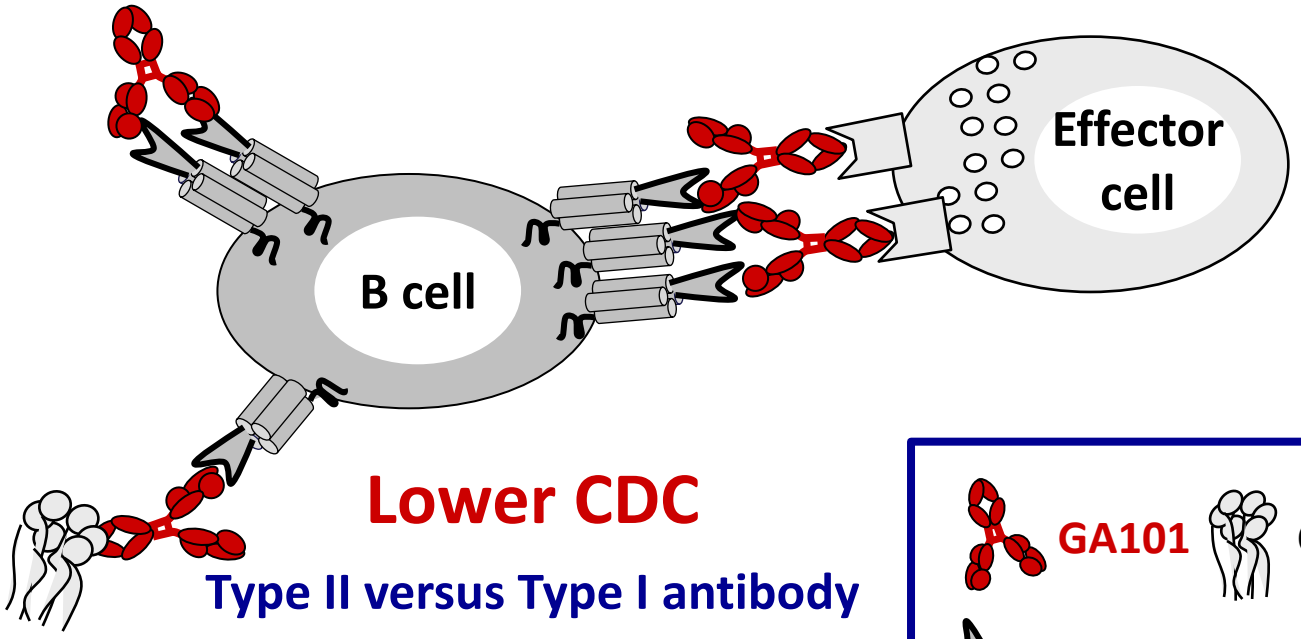
GA101: Mechanisms of action

Increased Direct Cell Death

Type II versus Type I antibody

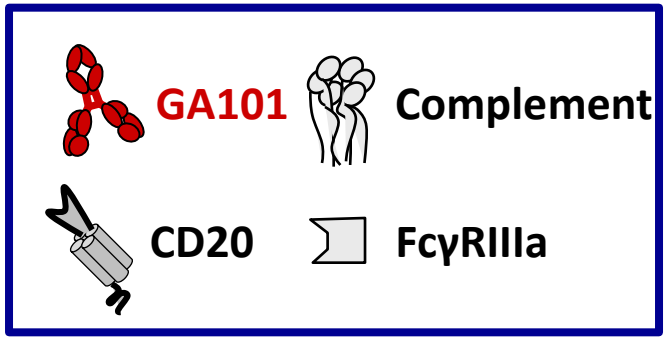
Enhanced ADCC

Glycoengineering for increased affinity to FcγRIIIa



Lower CDC

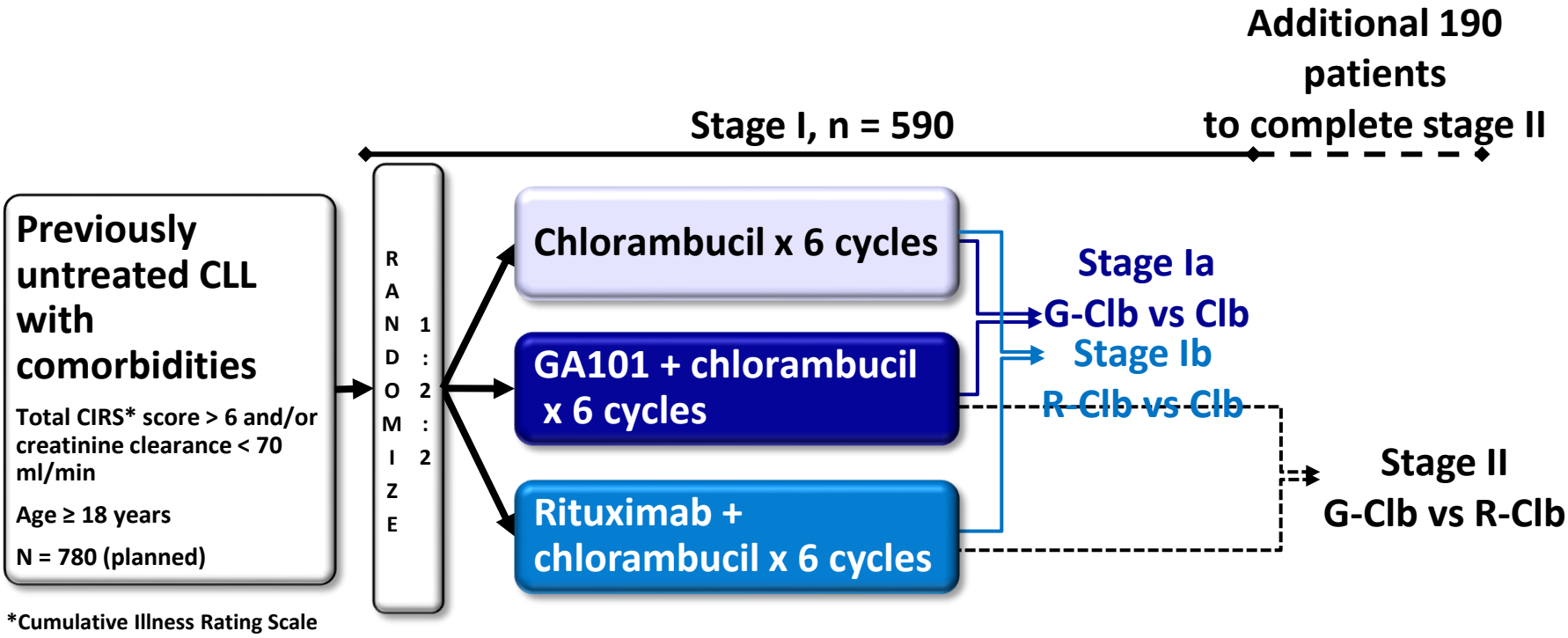
Type II versus Type I antibody



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

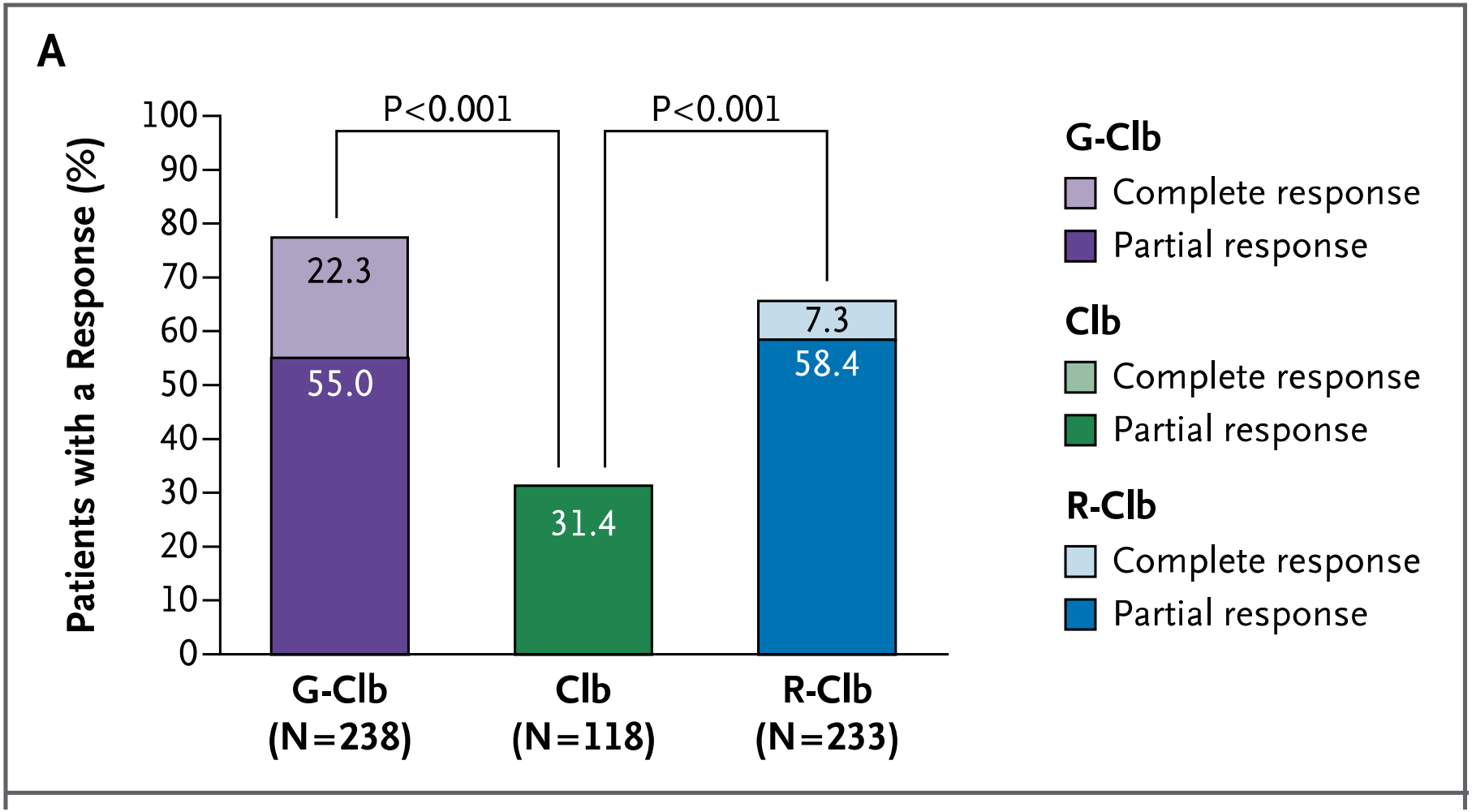
Mössner E, *et al*. *Blood* 2010; 115:4393–4402
Patz M, et al., *Br J Haematol* 2011; 152, 295-306.

CLL11: Study design

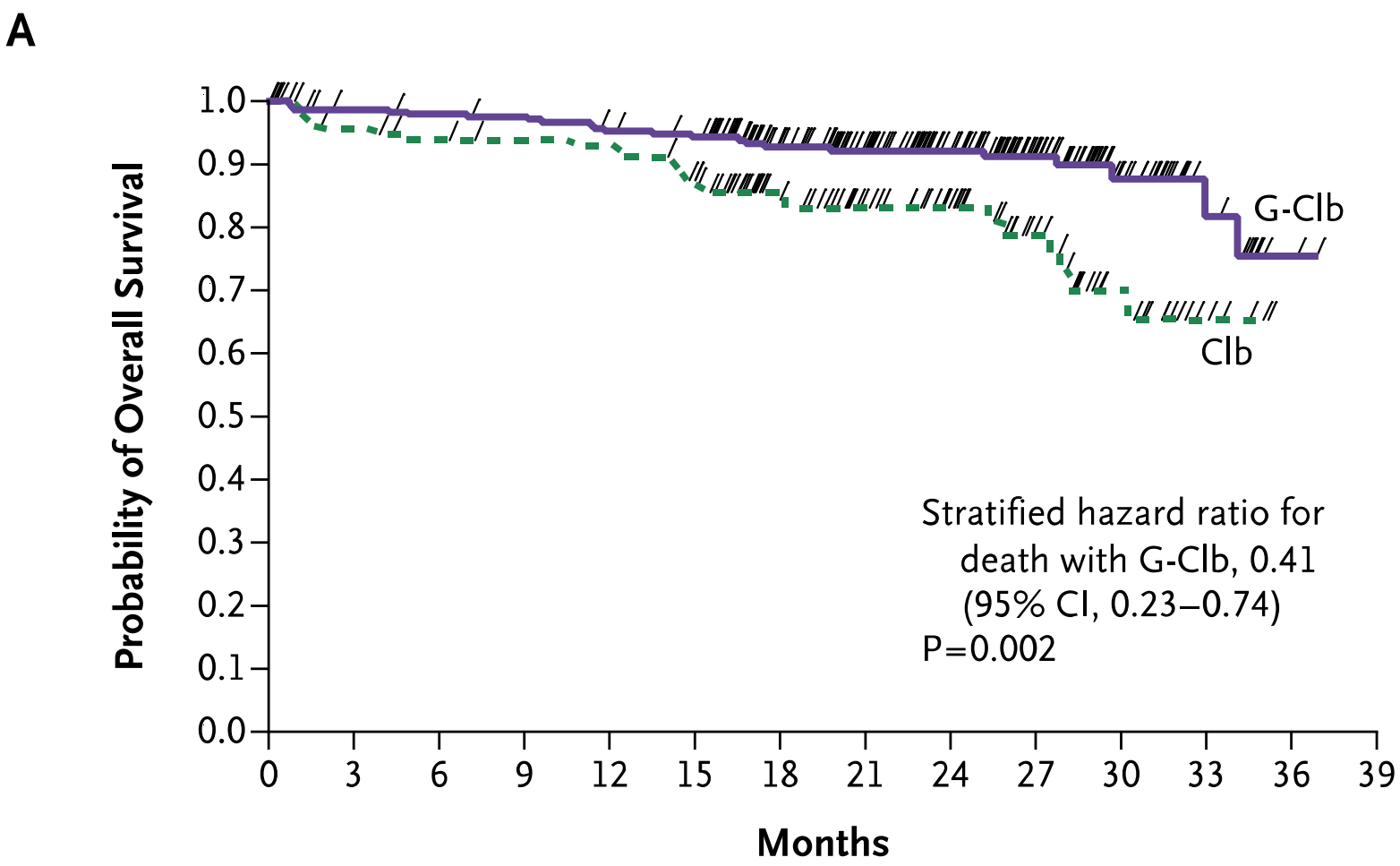


- GA101: 1,000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m^2 day 1 cycle 1, 500 mg/m^2 day 1 cycles 2–6, every 28 days
- Clb: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb

Response to treatment



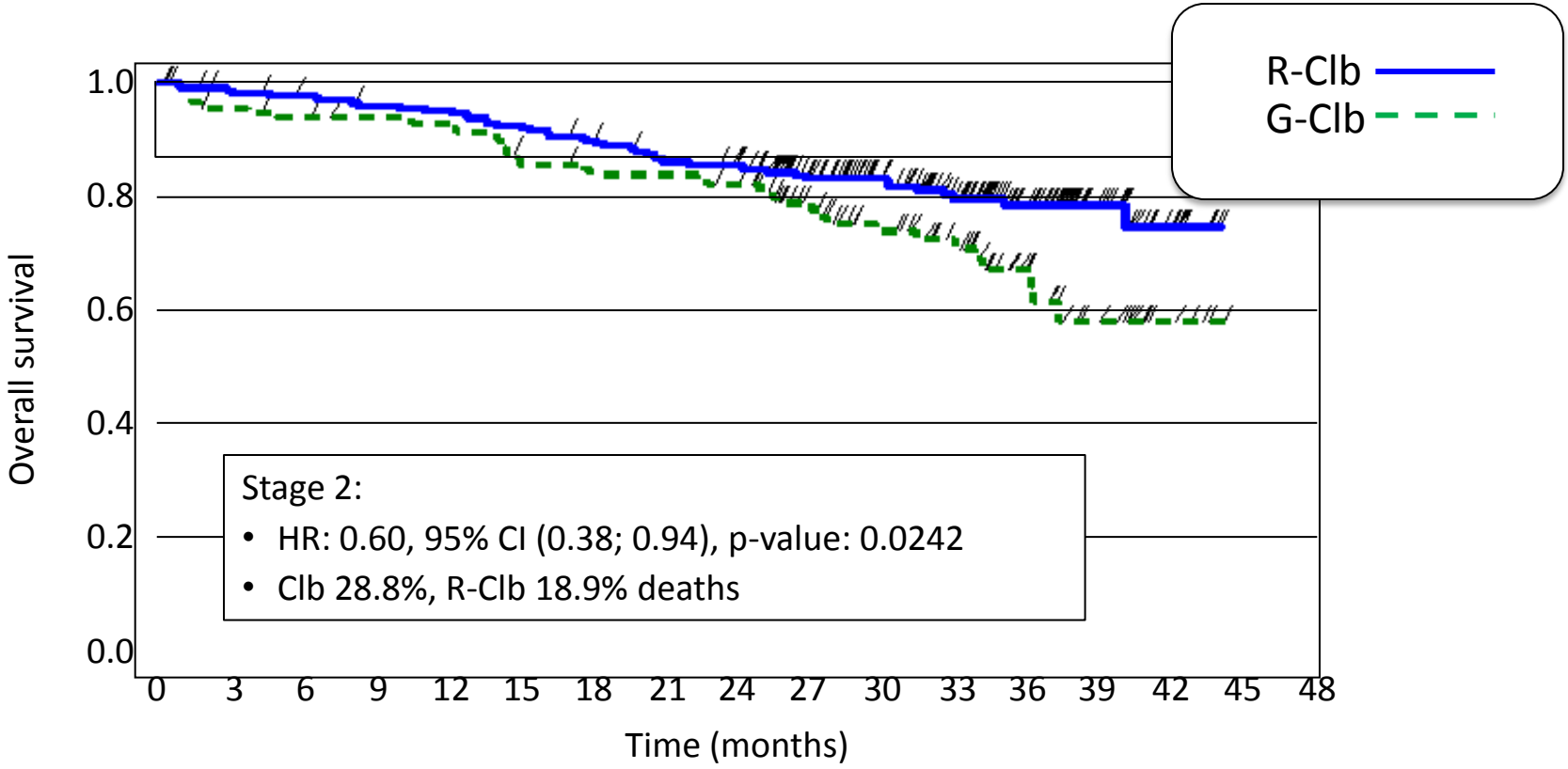
Overall survival following G-Clb vs Clb



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

Overall survival, R-Clb vs Clb



No. at risk

R-Clb:	238	227	223	218	216	210	204	193	190	161	134	105	65	29	12	0	0
Clb:	118	110	107	105	104	98	93	92	89	69	56	47	29	14	5	0	0

DEUTSCHE STUDIENGRUPPE

CLL11 stage II analysis: Baseline patient characteristics

Characteristic[2–3]	Patients, n (%)	
	R-Clb (n = 330)	G-Clb (n = 333)
Median age, years (range)	73 (40–90)	74 (39–89)
Median weight, kg (range)	71 (35–130)	73 (40–140)
Male	204 **(62)**	203 **(61)**
Aged ≥ 65 years	257 **(78)**	269 **(81)**
Aged ≥ 75 years	139 **(42)**	153 **(46)**
CIRS score > 6	246 **(75)**	259 **(78)**
Median CIRS score (range)	8.0 (0–18)	8.0 (0–22)
Calculated CrCl < 70 mL/min	212 **(64)**	222 **(67)**
Median calculated CrCl, mL/min (range)	62.6 (17–222)	62.5 (22–1,405)
Circulating lymphocyte count ≥ 25 x 10^9/L	235 **(72)***	248 **(75)**†

CrCl calculated by Cockroft–Gault formula.
* Circulating lymphocyte counts available for 328 patients.
† Circulating lymphocyte counts available for 332 patients.

1. Eichhorst B, *et al*. Ann Oncol 2011; 22(Suppl. 6):vi50–vi54.
2. Goede V, *et al*. N Engl J Med 2014; 370:1101–1110;
3. Goede V, *et al*. N Engl J Med 2014; 370:1101–1110; Supplemental appendix.

CLL11 stage II analysis: Baseline disease characteristics and prognostic factors

	Patients, n (%)	
Characteristic[1,2]	**R-Clb (n = 330)**	**G-Clb (n = 333)**
Binet stage		
A	74 **(22)**	74 **(22)**
B	135 **(41)**	142 **(43)**
C	121 **(37)**	117 **(35)**
IgHV unmutated*	182 **(61)**	188 **(62)**
Cytogenetics (hierarchical model)[1,2]	**n = 287**	**n = 295**
17p–	20 **(7)**	22 **(7)**
11q–	50 **(17)**	47 **(16)**
Tri12	47 **(16)**	46 **(16)**
13q–	85 **(30)**	85 **(29)**
Other abnormality	22 **(8)**	21 **(7)**
Normal karyotype	63 **(22)**	74 **(25)**

IgHV = immunoglobulin heavy chain variable region.
* Expressed as a percentage of patients tested (R-Clb, G-Clb): IgHV – 298, 305.

1. Goede V, *et al*. N Engl J Med 2014; 370:1101–1110;
2. Goede V, *et al*. N Engl J Med 2014; 370:1101–1110; Supplemental appendix.

CIRS comorbidities at baseline

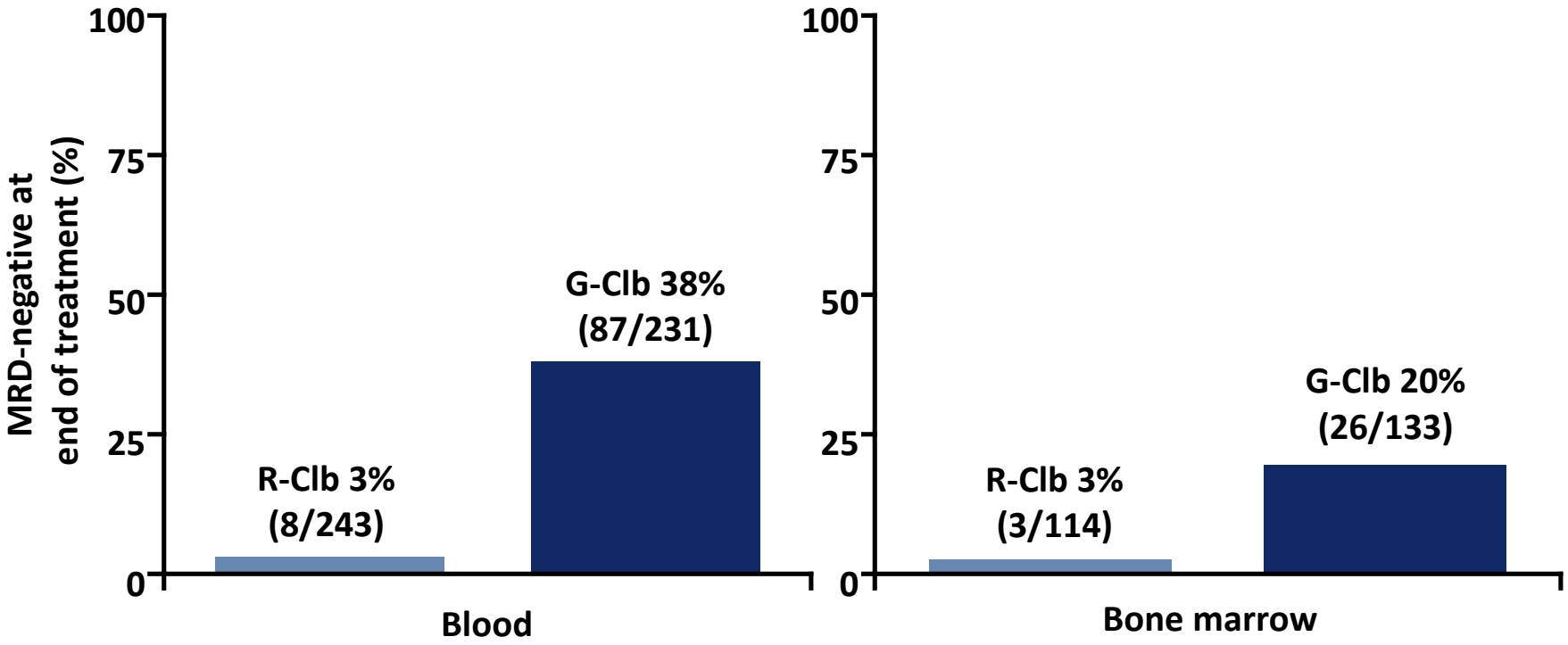
CIRS organ systems	Patients, n (%)	
	R-Clb (n = 330)	G-Clb (n = 333)
Cardiac	165 **(50)**	171 **(51)**
Hypertension	225 **(68)**	228 **(68)**
Vascular	95 **(29)**	114 **(34)**
Respiratory	127 **(38)**	121 **(36)**
Eye/ear/throat/larynx	141 **(43)**	131 **(39)**
Upper gastrointestinal	102 **(31)**	104 **(31)**
Lower gastrointestinal	55 **(17)**	68 **(20)**
Hepatic/biliary	66 **(20)**	56 **(17)**
Renal	145 **(44)**	137 **(41)**
Genitourinary	114 **(35)**	114 **(34)**
Musculoskeletal	135 **(41)**	148 **(44)**
Endocrine/metabolic	161 **(49)**	183 **(55)**
Neurological	72 **(22)**	72 **(22)**
Psychiatric	49 **(15)**	59 **(18)**

Comorbidity assessment using MedDRA coding.
Please note that since only the most severe conditions in each organ/system were collected in the comorbidity assessment, this list may under-represent the total burden of comorbidities in the patient population studied.

Goede V, *et al*. N Engl J Med 2014; 370:1101–1110; Supplemental appendix.

MRD at the end of treatment

MRD clearance was higher in the G-Clb arm[1]

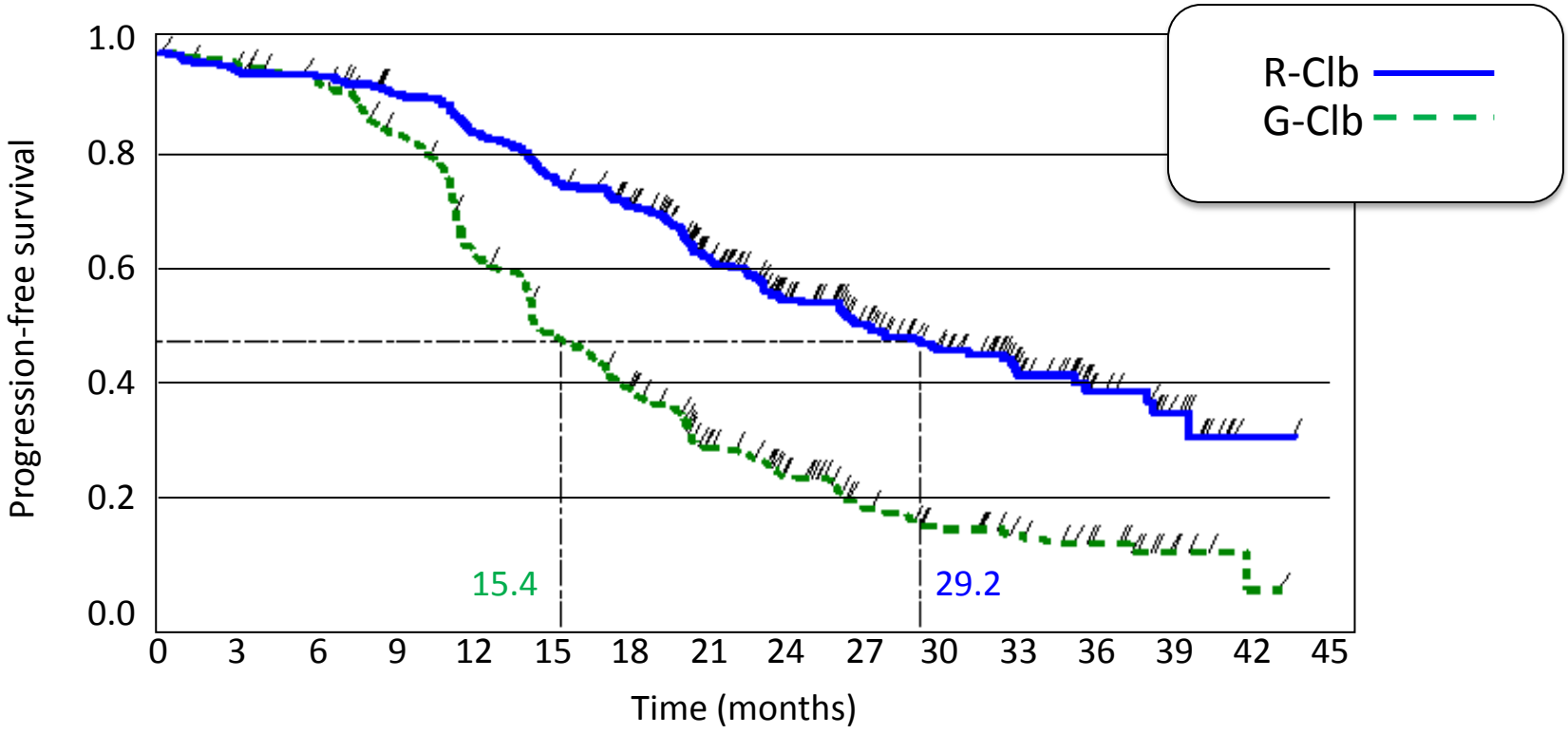


- MRD measured by central laboratory assessment (ASO-RQ-PCR) of blood and/or bone marrow samples taken at baseline and 3 months after last dose of study medication
- Patients are considered MRD-negative if they have fewer than one CLL cell in 10,000 cells (iwCLL guidelines[2])
- Bone marrow samples were usually only taken from patients thought to be in CR
- Patients who progressed or died prior to MRD measurement were counted as MRD-positive; patients without MRD results, and one in the R-Clb arm who had not reached their end-of-treatment analysis by the time of the data cut-off, were excluded

ASO-RQ-PCR = allele-specific oligonucleotide real-time quantitative polymerase chain reaction.

1. Goede V, *et al*. N Engl J Med 2014; 370:1101–1110;
2. Hallek M, *et al*. Blood 2008; 111:5446–5456.

Progression-free survival: R-Clb versus R-Clb

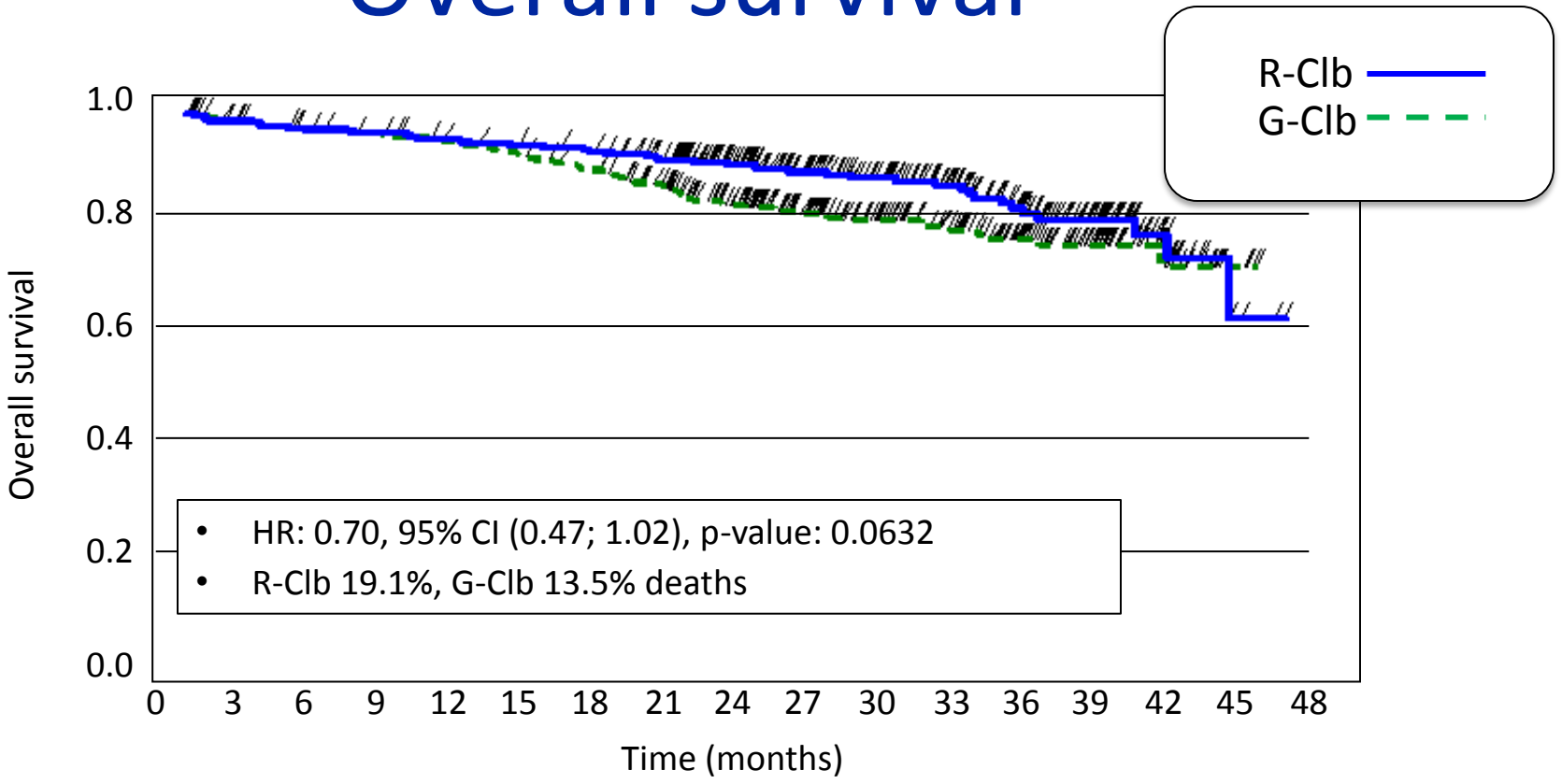


No. at risk

R-Clb:	330	317	309	273	204	160	128	82	59	38	26	20	13	4	1	0
G-Clb:	333	307	302	288	267	243	221	172	124	99	75	45	25	12	1	0

DEUTSCHE STUDIENGRUPPE

Overall survival



No. at risk

R-Clb:	330	320	314	309	302	293	279	238	198	161	134	105	65	29	12	0	0
G-Clb:	333	317	311	306	300	296	289	257	205	169	141	105	72	38	9	2	0

DEUTSCHE STUDIENGRUPPE

Grade ≥ 3 Adverse Events

Incidence of grade ≥ 3 AEs with G-Clb vs R-Clb was higher owing to increased grade ≥ 3 IRRs

Patients, n (%)	R-Clb (n = 321)	G-Clb (n = 336)
Any grade ≥ 3 AE	177 **(55)**	235 **(70)**
IRRs	12 **(4)**	67 **(20)**
Neutropenia	91 **(28)**	111 **(33)**
Infections	44 **(14)**	40 **(12)**
Thrombocytopenia	10 **(3)**	35 **(10)**

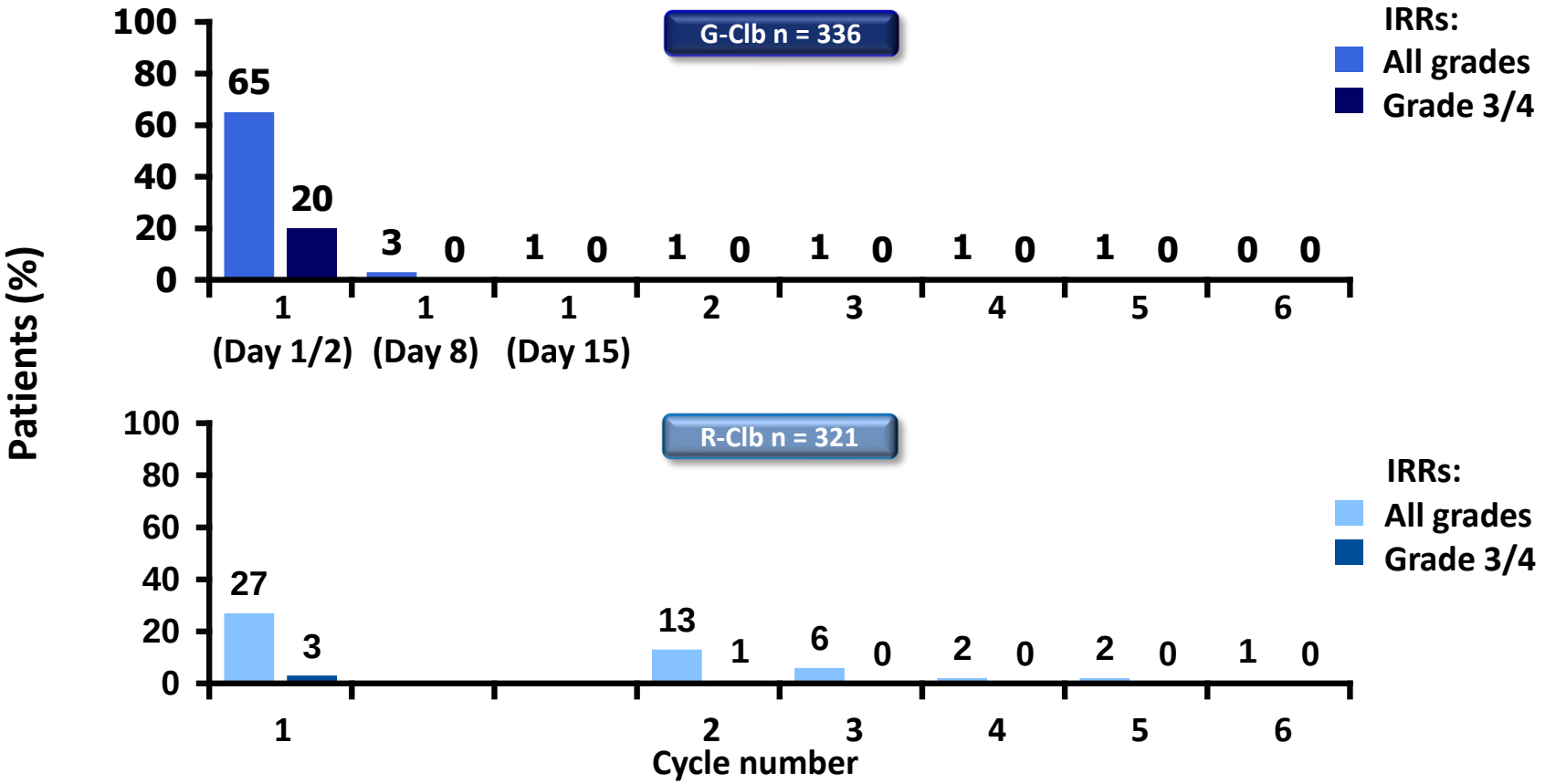
- All grade ≥ 3 AEs occurring until the May 2013 clinical cut-off in ≥ 5% of patients are shown
- There were no deaths attributed to IRRs, neutropenia, or thrombocytopenia. There were two deaths from infection in the R-Clb arm (both pneumonia) and two in the G-Clb arm (septic shock, pulmonary sepsis)

Five patients who were randomized to R-Clb received one infusion of GAZYVA in error and are included in the safety population for G-Clb and not R-Clb.
Patients who received no treatment are excluded from the safety population (G-Clb = 2; R-Clb = 4).

Goede V, *et al*. N Engl J Med 2014; 370:1101–1110.

IRRs by treatment cycle

IRRs occurred primarily during the first infusion and were infrequent after the first 1,000 mg dose of GAZYVA



Patients with grade 4 or recurring grade 3 IRRs were discontinued (per protocol); in the G-Clb arm, 7% of patients discontinued due to IRRs, 6% due to other AEs, 1.5% due to death, 1% due to progressive disease or insufficient response, and 4% for other reasons. 81% of patients received the 6 cycles of GAZYVA.

Goede V, *et al*. N Engl J Med 2014; 370:1101–1110; Supplemental appendix.

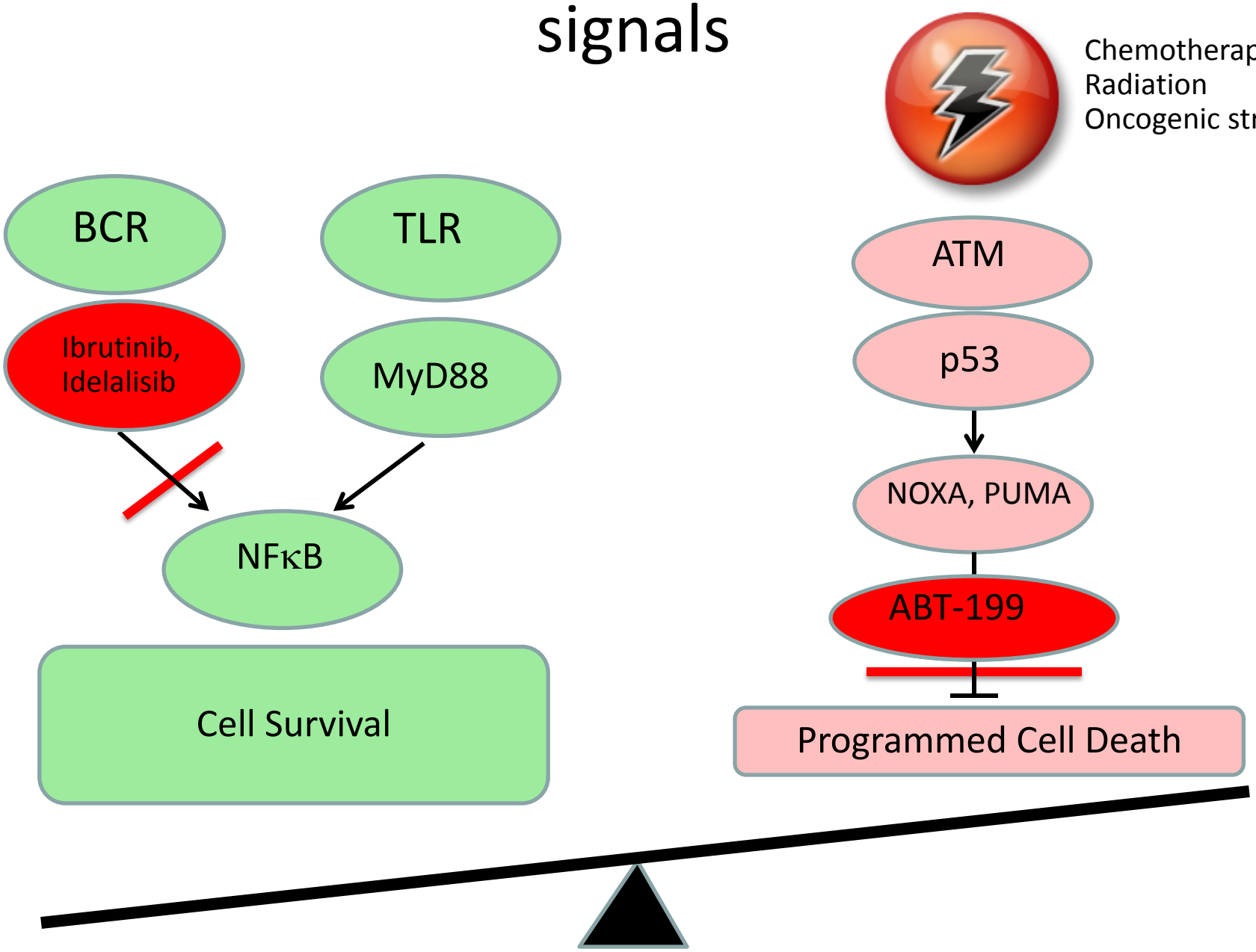
Ofatumumab + Chlorambucil Versus Chlorambucil Alone In Untreated CLL

(*Hillmen et al, ASH 2013, abst. 528*)

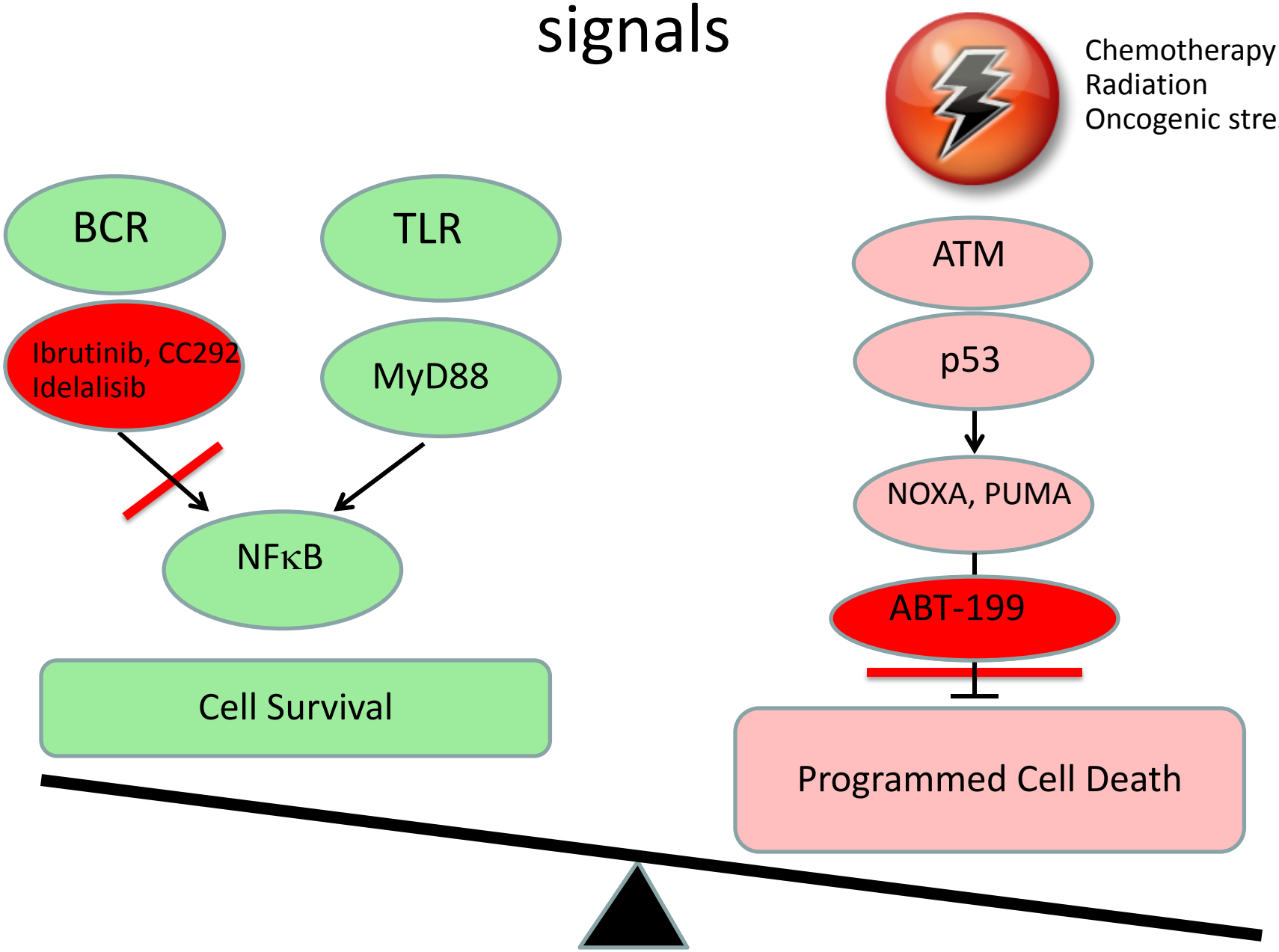
	CHL	O+CHL
Efficacy	**(n=226)**	**(n=221)**
mPFS, IRC-assessed [m]	13.1	22.4
Hazard Ratio (95% CI), p-value	0.57 (0.45-0.73), p<0.001	
ORR [%]	69	82
Odds Ratio	2.16, p<0.001	
CR [%]	1	12
MRD negative, all subjects [%]	4	12
MRD negative, CR subjects [%]	0	37

Novel agents

CLL results from an imbalance of life and death signals



CLL results from an imbalance of life and death signals



Comparison of new drugs in *advanced* clinical development

Class	Agent	Reference	Target	Response rate in relapsed, refractory CLL as a single agent			
				N	CR (%)	PR (%)	ORR (%)
Bcl-2 antagonist	ABT-199	Seymour ASCO 2013	Bcl-2	56	13	72	85
Tyrosine kinase inhibitors	Idelalisib (CAL-101)	Brown ASCO 2013	PI3 kinase p110δ	54	4	52	56
	Ibrutinib	Byrd NEJM 2013	Bruton tyrosine kinase	85	2	68	71

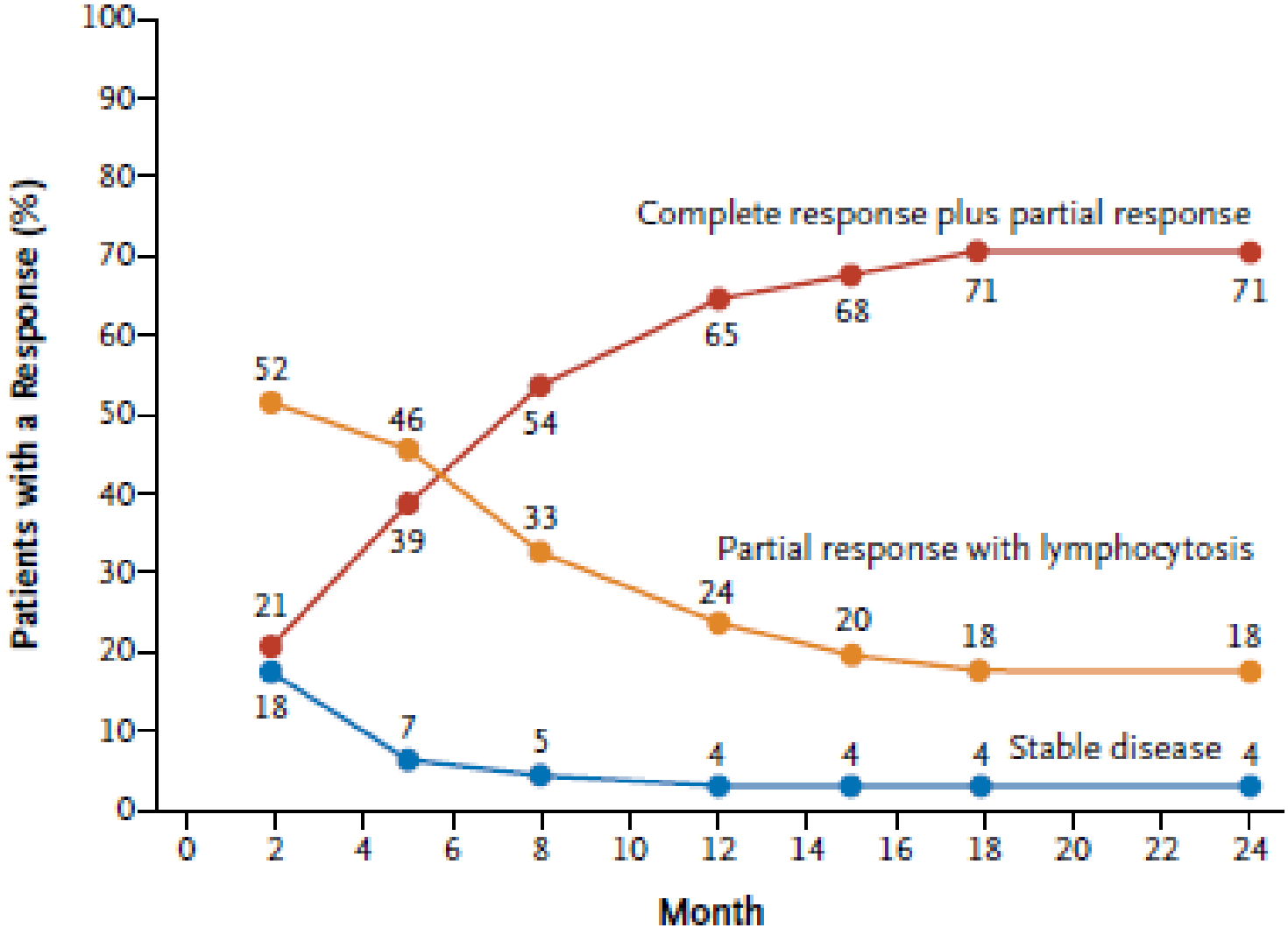
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

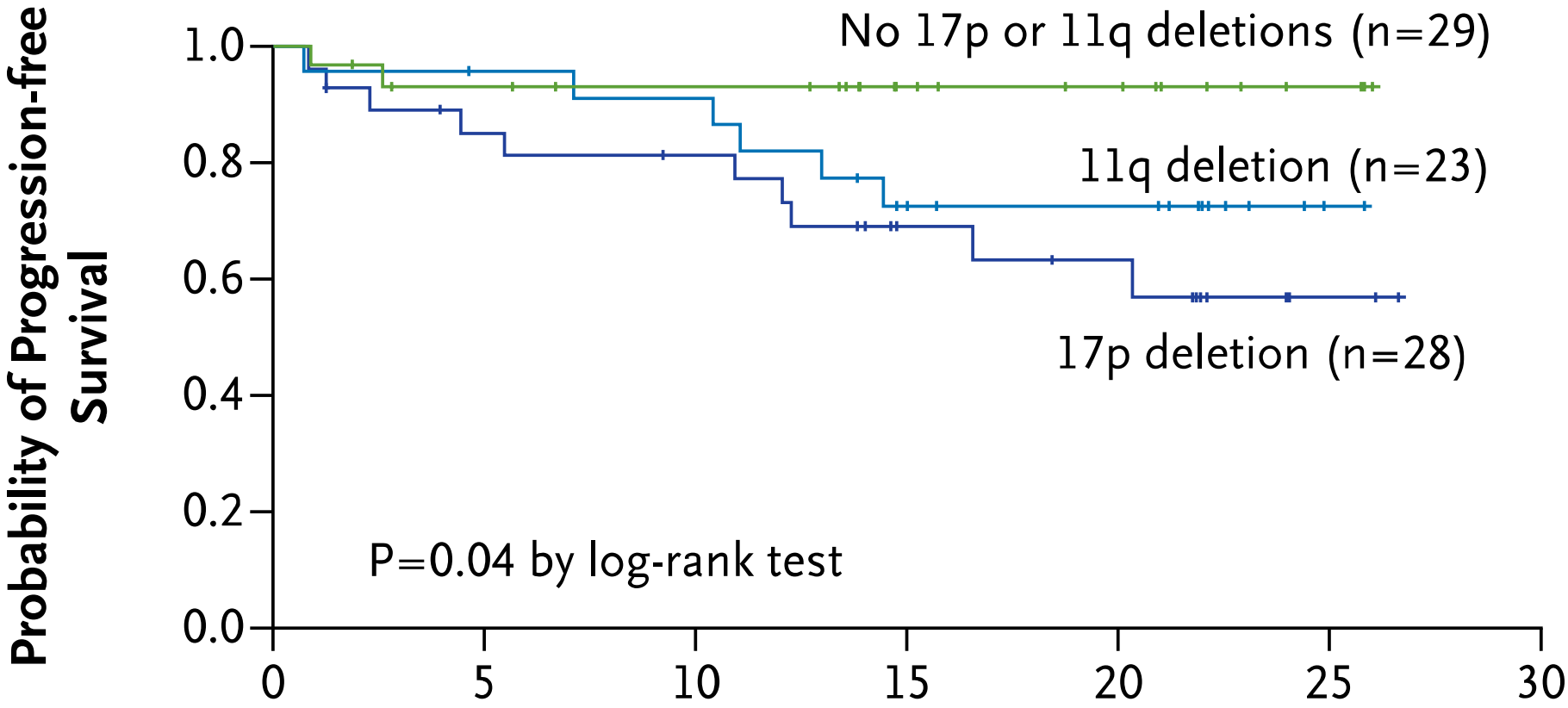
John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.

Ibrutinib in relapsed/refractory CLL



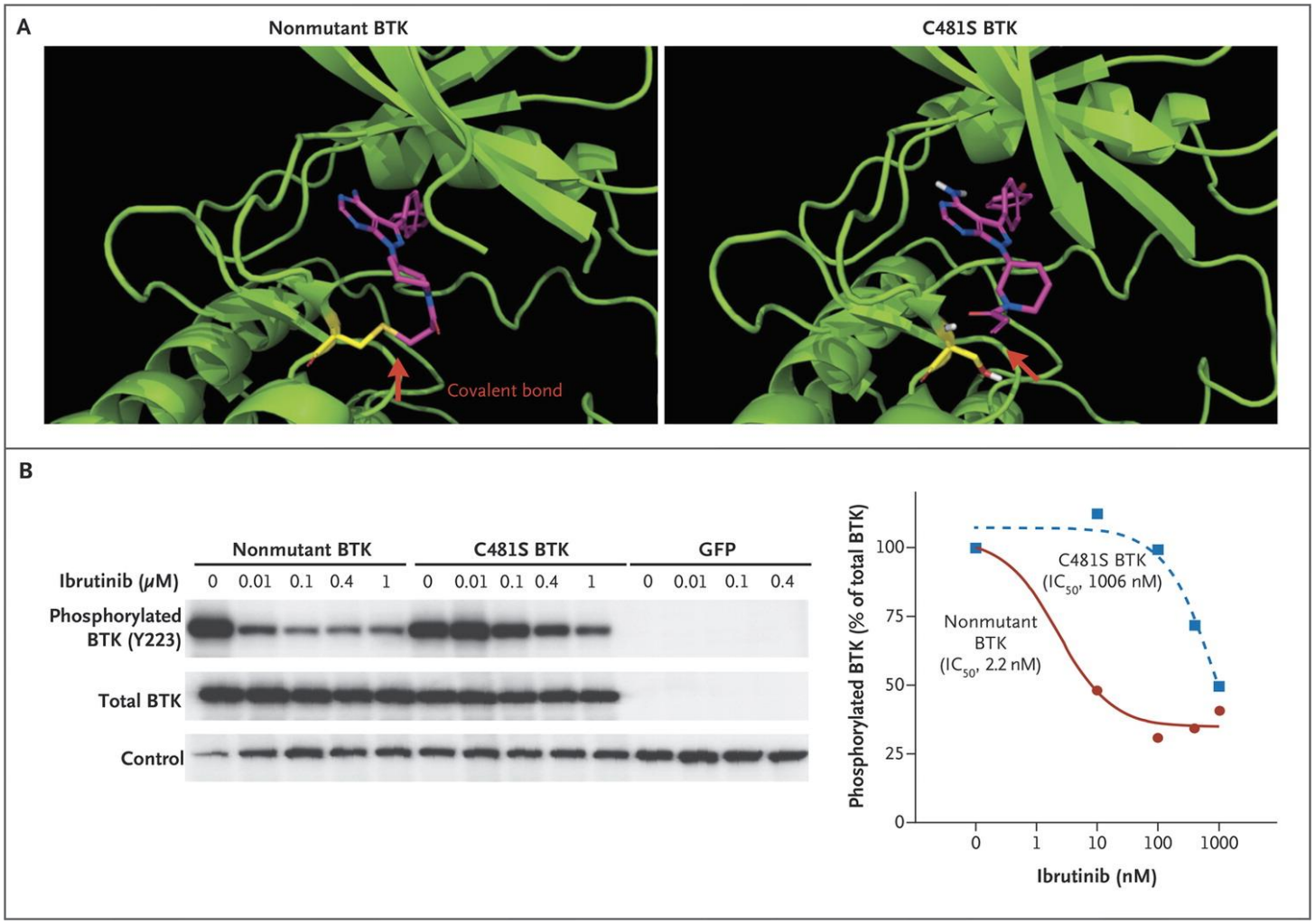
Byrd et al., NEJM July 2013

Ibrutinib in genetically defined CLL subgroups: PFS



Byrd et al., NEJM July 2013

Effect of C481S Mutation of Bruton's Tyrosine Kinase (BTK) on Ibrutinib Binding and the Ability of Ibrutinib to Inhibit BTK Phosphorylation.



Furman RR et al. N Engl J Med 2014;370:2352-2354.

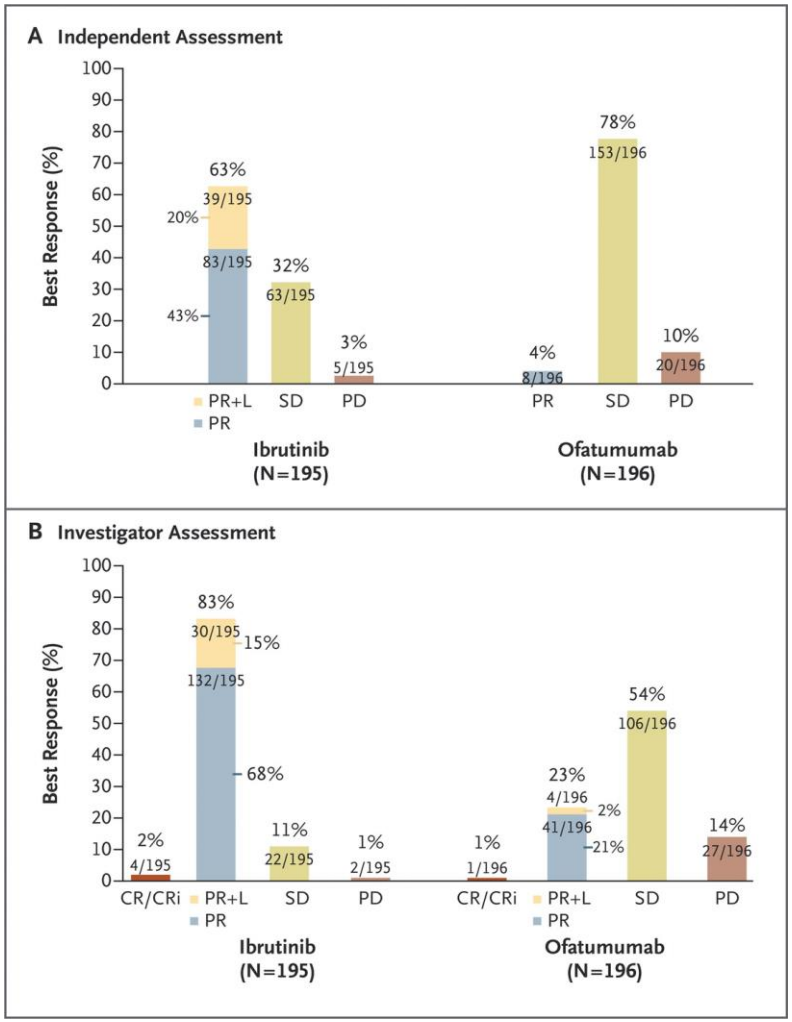
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

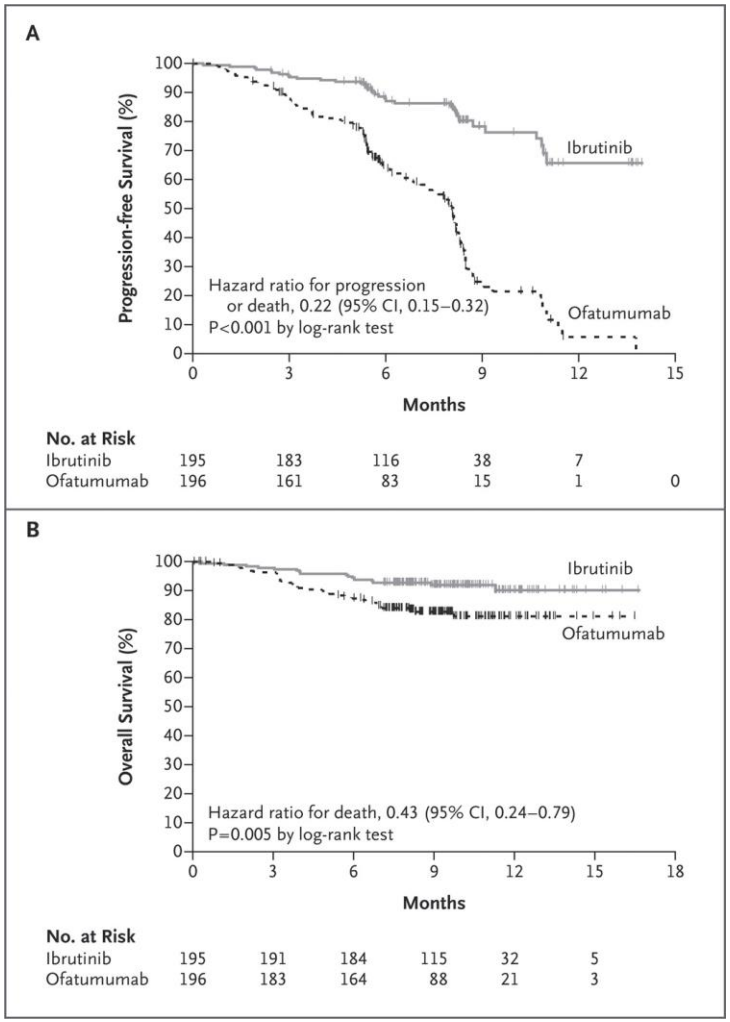
J.C. Byrd, J.R. Brown, S. O'Brien, J.C. Barrientos, N.E. Kay, N.M. Reddy, S. Coutre, C.S. Tam, S.P. Mulligan, U. Jaeger, S. Devereux, P.M. Barr, R.R. Furman, T.J. Kipps, F. Cymbalista, C. Pocock, P. Thornton, F. Caligaris-Cappio, T. Robak, J. Delgado, S.J. Schuster, M. Montillo, A. Schuh, S. de Vos, D. Gill, A. Bloor, C. Dearden, C. Moreno, J.J. Jones, A.D. Chu, M. Fardis, J. McGreivy, F. Clow, D.F. James, and P. Hillmen, for the RESONATE Investigators*

Best Response to Therapy, as Assessed by Independent Reviewers and by Investigators.



Byrd JC et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1400376

Progression-free and Overall Survival.



Byrd JC et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1400376

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

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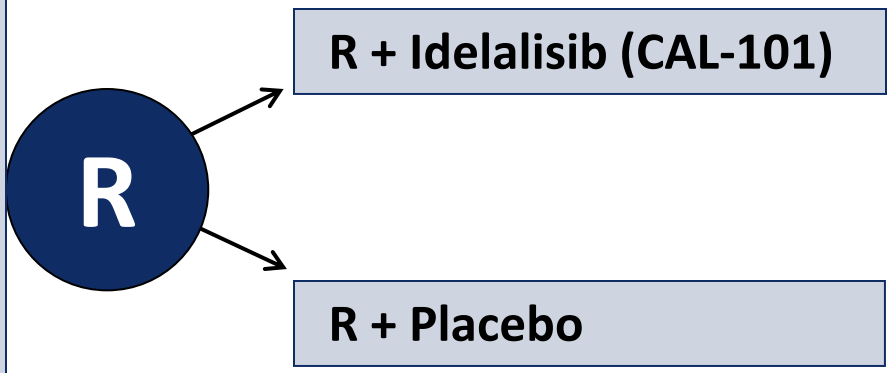
Rituximab plus Idelalisib

Furman et al. NEJM 2014

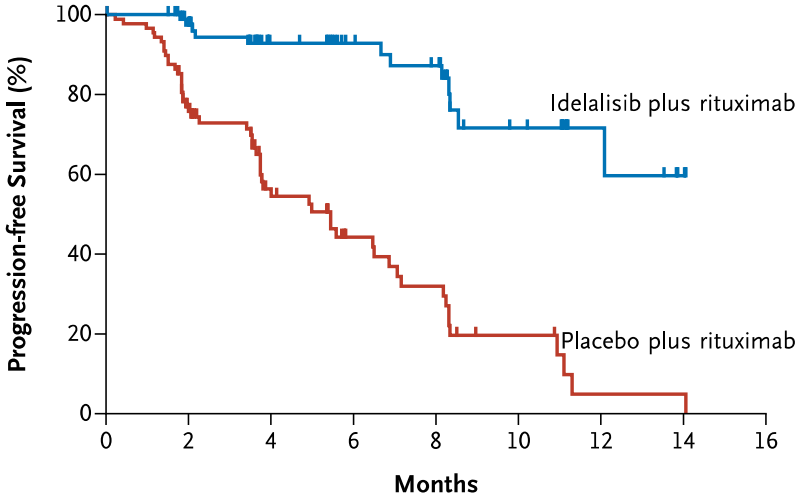
Relapsed CLL patients not eligible for chemo-immunotherapy due to

- comorbidity (CIRS-Score > 6 and/or creatinine-clearance <60ml/Min) or
- cytopenias CTC°III-IV due to cumulative myelotoxicity (bone marrow biopsy required)



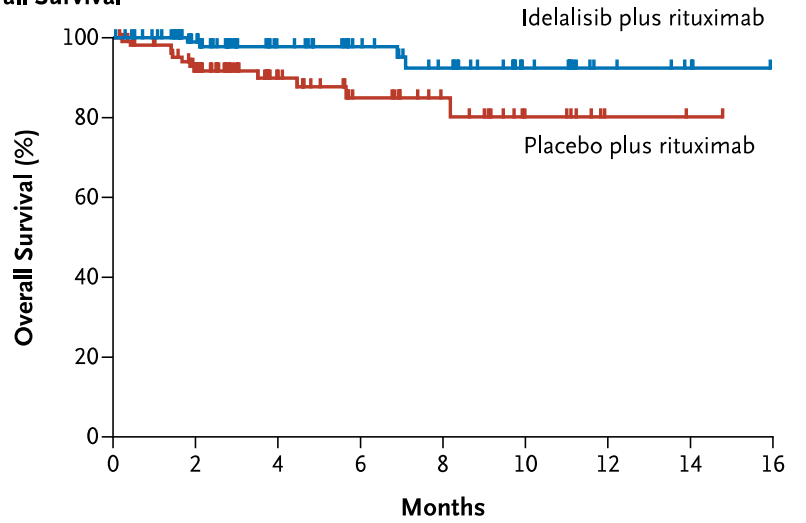
R: Rituximab: 375mg/m² week 0, 500mg/m² 7x, weeks 2-20
+/- Idelalisib (CAL-101):
150 mg p.o. BID until PD/unacceptable toxicity

A **Progression-free Survival**



No. at Risk (events)									
Idelalisib	110 (0)	69 (2)	44 (5)	34 (5)	30 (7)	14 (11)	6 (11)	2 (12)	0 (12)
Placebo	110 (0)	62 (20)	30 (33)	18 (39)	13 (44)	6 (49)	1 (52)	1 (52)	0 (53)

B **Overall Survival**

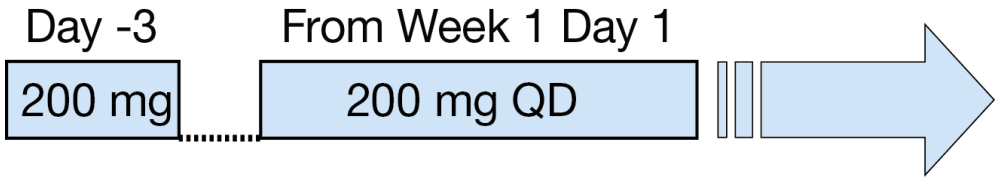


No. at Risk (events)									
Idelalisib	110 (0)	88 (1)	55 (2)	40 (2)	31 (4)	16 (4)	7 (4)	4 (4)	0 (4)
Placebo	110 (0)	76 (8)	43 (9)	25 (11)	18 (11)	8 (12)	2 (12)	1 (12)	0 (12)

ABT-199, a Bcl-2 inhibitor

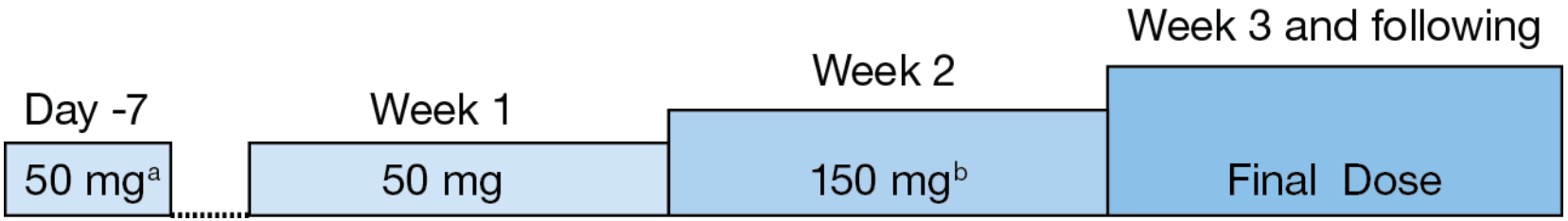
(*J. Seymour et al., ASCO and iwCLL 2013*)

Dose Escalation Schematic of Cohort 1



- **>95% reduction in lymphocytosis within 24h in two patients**
- **Rapid reduction in palpable lymphadenopathy**
- **3 out of 3 patients enrolled in Cohort 1 experienced dose-limiting laboratory tumor lysis syndrome (TLS): No clinical sequelae, no organ dysfunction**

Dose Escalation Schematic of Cohorts 2 – 8



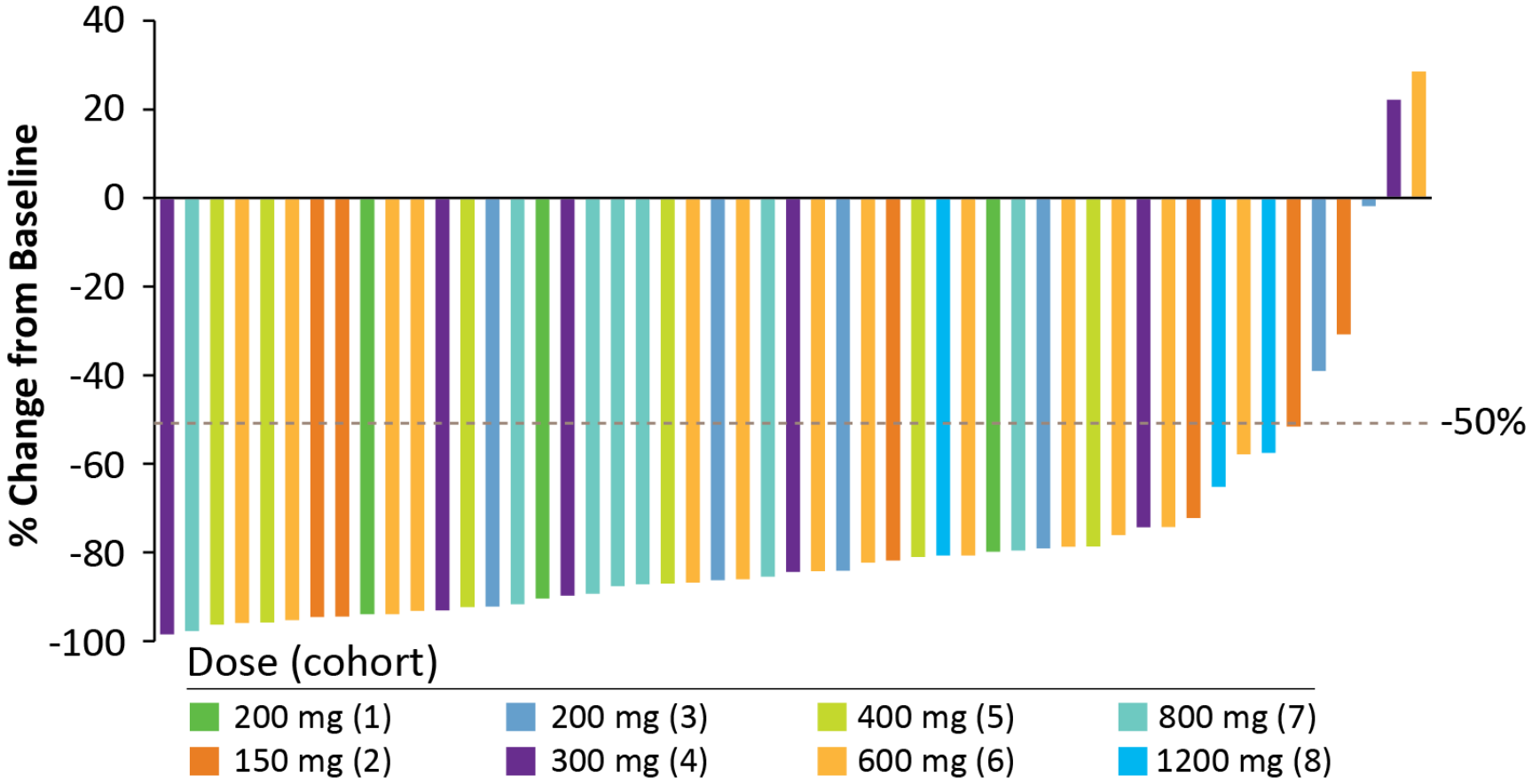
•3 of 53 patients experienced an event of tumor lysis with modified schedule

[a]**3 patients (1 each in cohort 2 and 3, and 1 in cohort 5) received ABT-199 20 mg as the initial dose.**
[b]**Week 2 dose in cohorts 2 - 5 = 100 mg.**

ABT-199: Lymph node response by CAT scan

N = 51 evaluable (at minimum, 6 weeks assessment)

Median Time to 50% Reduction = 1.4 months (range 0.7 to 13.7)



Translation into current practice

CLL first line treatment 2014

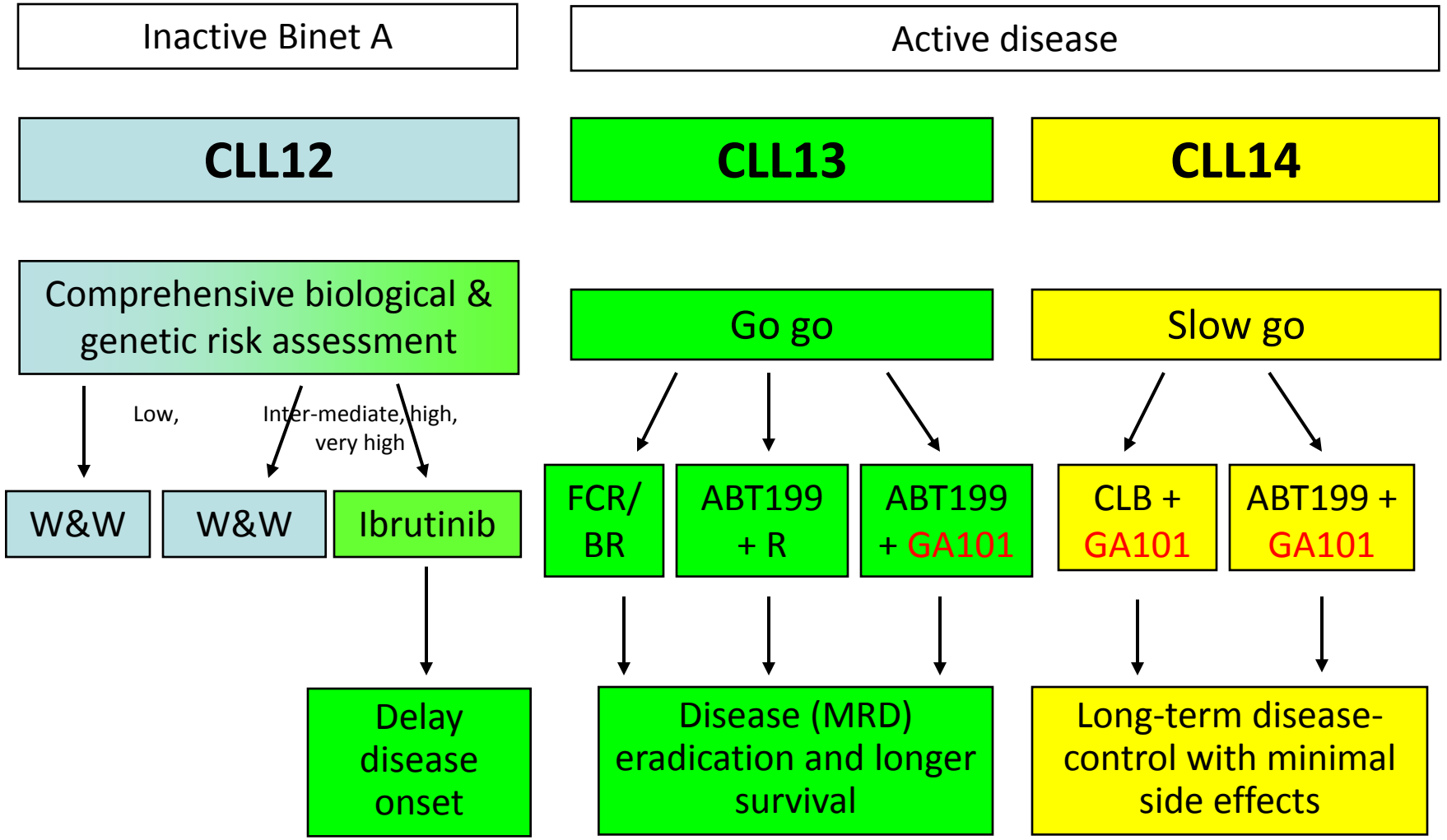
Stage	Fitness	del(17p) p53mut	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Go go	No	FCR (BR above 65 years?)
		Yes	Allogeneic SCT (?)
	Slow go	No	Chlorambucil + Obinutuzumab (GA-101, Gazyvaro) or Rituximab
		Yes	Ibrutinib, Alemtuzumab, HD Rituximab or Ofatumumab

CLL second line treatment 2014

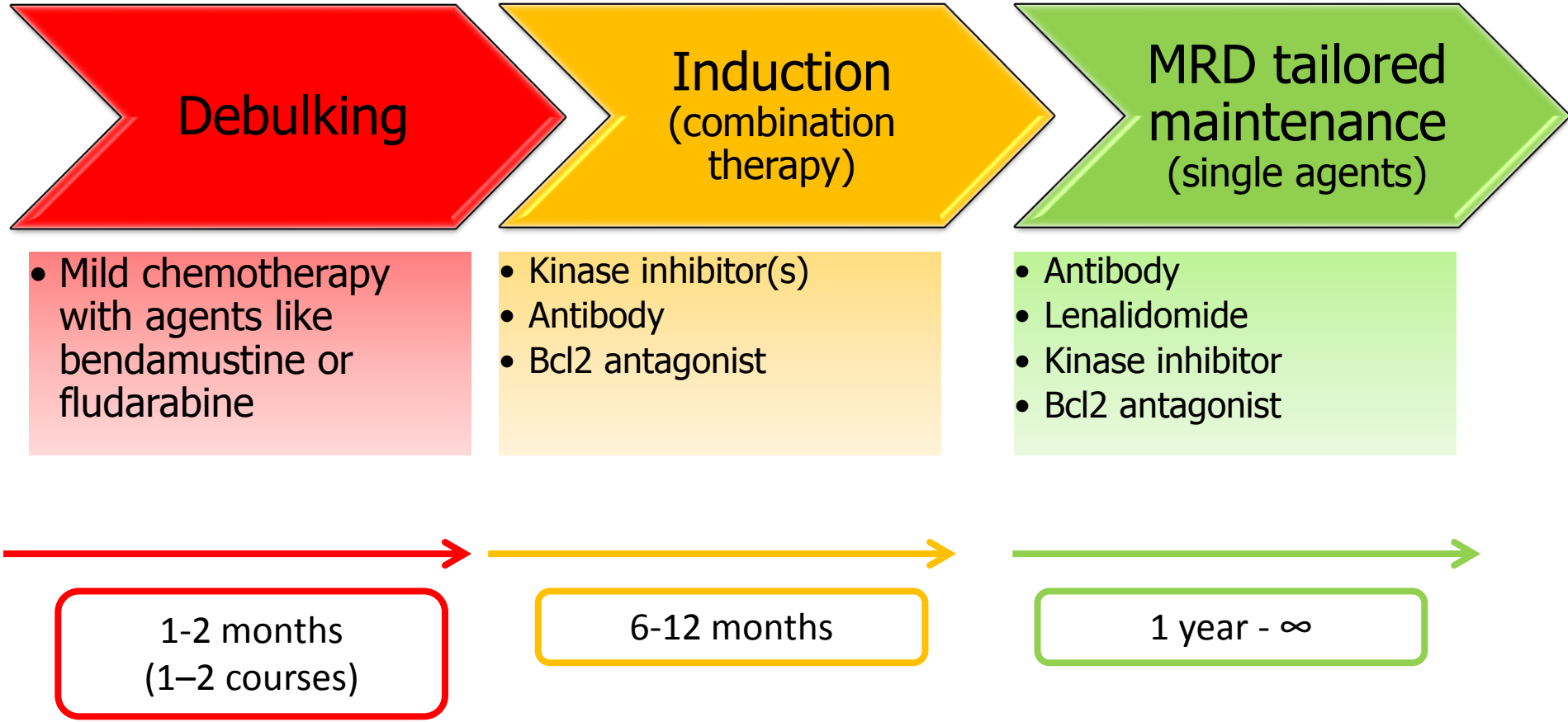
Response to First-Line Therapy	Fitness	Therapy	
		Standard	Alternatives (trials)
Refractory or progress within 2 years	Go go	Ibrutinib, A-Dex, FA, FCR, → Allogeneic SCT (?)	Lenalidomide, BR, (other kinase inhibitors, ABT-199)
	Slow go	Change therapy (include in trial)	Ibrutinib, Idelalisib + Rituximab, Alemtuzumab for del(17p), ABT-199, FCR-lite, BR, lenalidomide, ofatumumab, HD rituximab
Progress after 2 years	All	Repeat first-line therapy	

Fourth Generation of GCLLSG Trials

Risk, Stage and Fitness Adapted, Using Targeted Agents



Potential future strategies to achieve long-term control of CLL: **"sequential triple T": tailored, targeted, total** eradication of MRD



Summary

- With the arrival of very potent antibodies and kinase inhibitors it seems justified to plan a long-term control (cure?) of CLL.
- Potential conversion of treatment algorithms for „go go“ and „slow go“ CLL with less toxic novel agents.
- Need for systematic evaluation of novel treatments compared to previous standard in clinical trials.
- Decreased use of allogeneic SCT in CLL.