On the architecture of translational research designed to control chronic lymphocytic leukemia

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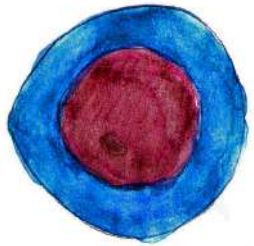


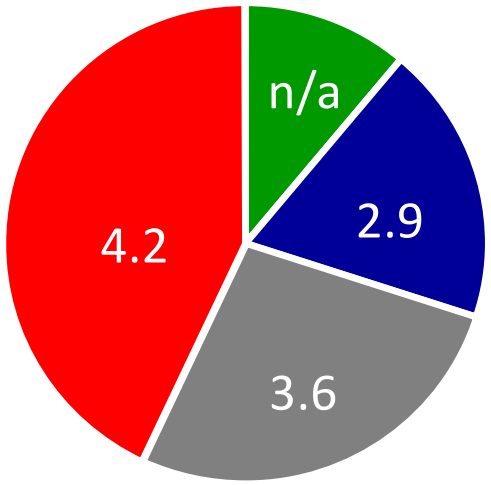
DEUTSCHE STUDIENGRUPPE

CECAD COLOGNE Excellent in Aging Research – Exzellent in Alternsforschung

CIO Center for Integrated Oncology Köln Bonn

Professional experience required to “tailor” CLL therapy: characteristics at presentation

- Median age at diagnosis: 72 years[1]
- Elderly patients may be fit or have comorbidities



Age at CLL diagnosis (years)	Patients [1] (%)	Mean comorbidities[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.


alamy

Treatment of CLL with chlorambucil

Dose

- Initial dose 0.4 mg/kg d1 q 14 days; increase to 0.8 mg/kg d 1 with increments of 0.1 mg/kg d1
- 0.07–0.1 mg/kg/d, d 1–14, repeat day 28

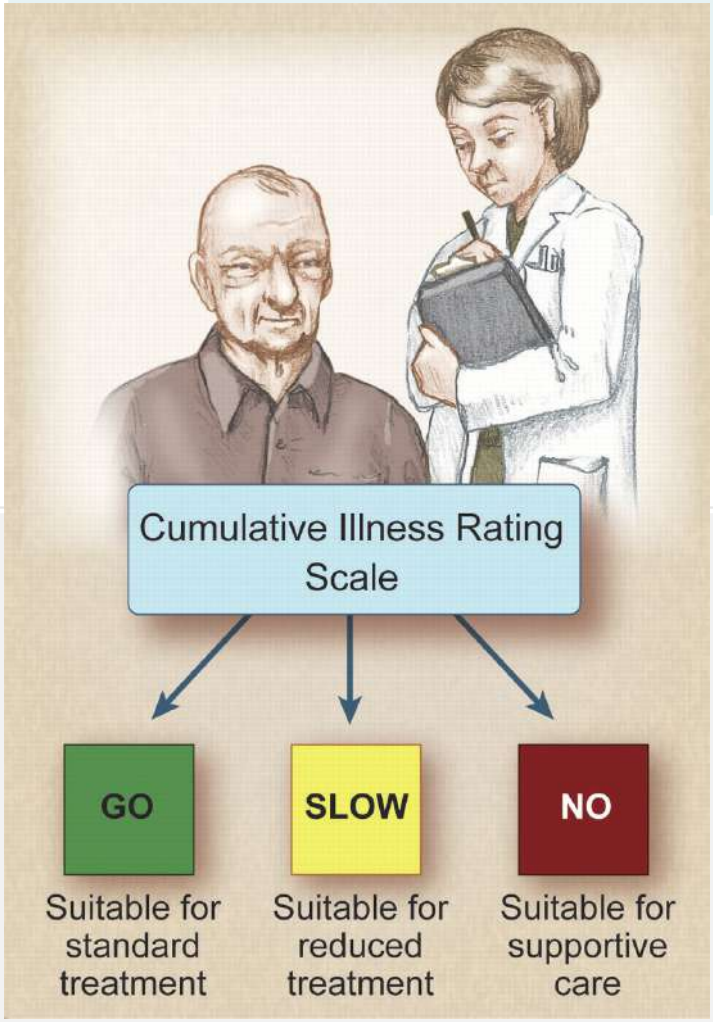
Duration

until maximal response (NCI criteria), usually 9 months

Chlorambucil versus CHOP, COP or CAP:
Metaanalysis of 2022 patients with advanced CLL

Therapy	*5-year survival*	*Significance*
CLB (± prednisone)	48%	n.s.
All combinations	48%	n.s.
Combinations with anthracyclins	52%	n.s.

CLL Trialists' Collaborative Group, *J Natl Cancer Inst* 91, 861-8 (1999).



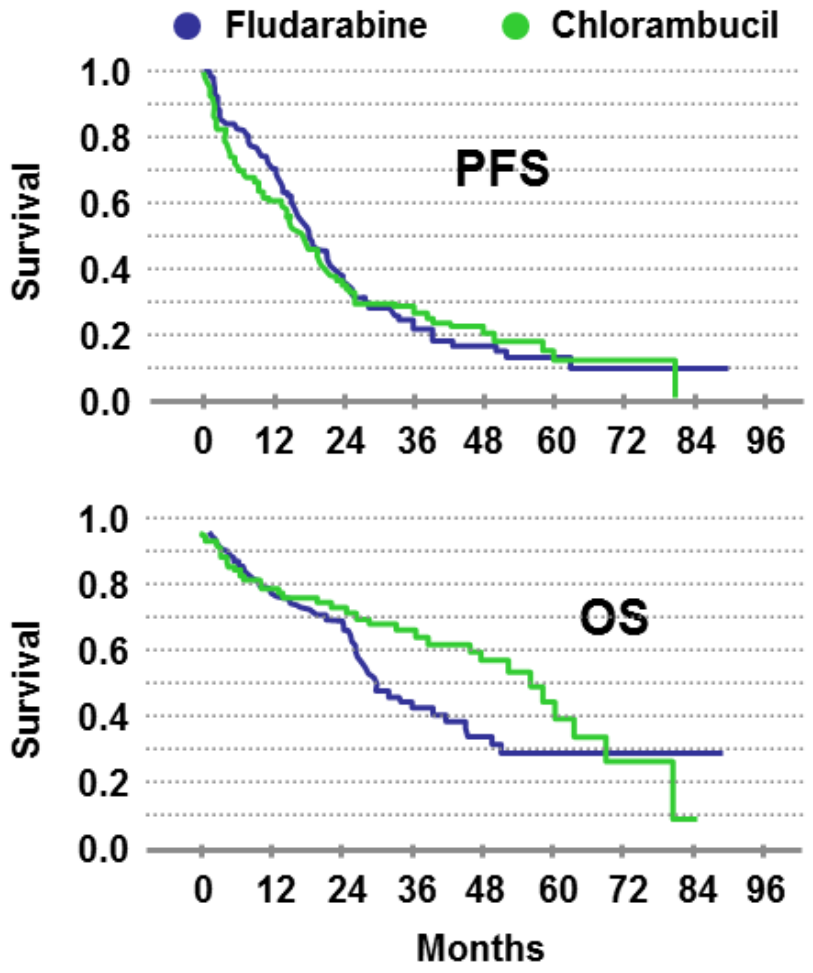
Unfit or older patients

- CLB
- F

CLL5 trial: Fludarabine offers no benefit compared to chlorambucil

Median age: 70 yrs

GCLLSG CLL5 Trial



Eichhorst et al., Blood 2009, 114: 3382-91

GCLLSG trial

(time of recruitment)

Unfit or older patients

CLL5

(1999-2004)

CLB

F

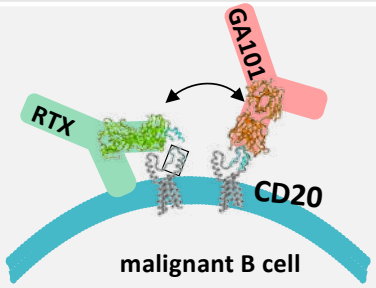
CLL11

(2010-2012)

CLB

CLB+R

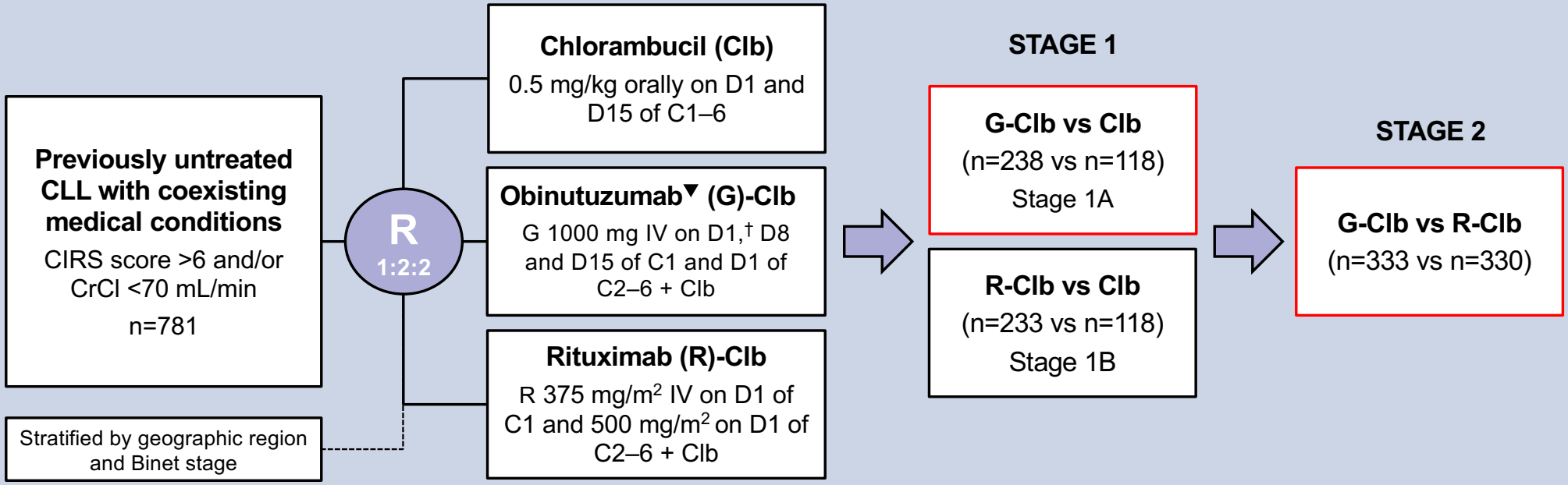
CLB+G



▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the Regulatory authorities in your country according to your national requirements.

CLL11: Study design

*Open-label, randomised Phase III study in previously untreated CLL patients with coexisting medical conditions**



Primary endpoint
- PFS (INV-assessed)

Secondary endpoints
- OS
- TTNT
- MRD
- Safety

*NCT01010061; †dose split over two days; CIRS, Cumulative Illness Rating Scale; CrCl; creatinine clearance; C, cycle; D, day; INV, investigator; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; TTNT, time to new treatment

Goede V, et al. N Engl J Med 2014

CLL11: Final analysis

- Data cut-off: 10th October 2017
  - Median observation time, G-Clb vs Clb: 62.5 months
  - Median observation time, G-Clb vs R-Clb: 59.4 months

Baseline characteristics

	G-Clb vs Clb		G-Clb vs R-Clb	
	G-Clb n=238	Clb n=118	G-Clb n=333	R-Clb n=330
Median age, years (range)	74 (39–88)	72 (43–87)	74 (39–89)	73 (40–90)
Median CIRS score (range)	8 (1–20)	8 (0–18)	8 (0–22)	8 (0–18)
Median CrCl, mL/min (range)	61.4 (22.4–1404.6)	63.8 (30.4–208.8)	62.5 (22.4–1404.6)	62.6 (17.4–221.6)
Median ECOG ps (range)	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)
Binet stage, n (%)				
A	55 (23)	24 (20)	74 (22)	74 (22)
B	98 (41)	50 (42)	142 (43)	135 (41)
C	85 (36)	44 (37)	117 (35)	121 (37)
Unmutated IGHV, n/N (%)	129/210 (61)	58/99 (59)	188/305 (62)	182/298 (61)
Del(17p) on FISH, n/N (%)	16/203 (8)	10/96 (10)	22/295 (7)	20/287 (7)

ECOG ps, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridisation; IGHV, immunoglobulin heavy chain variable region

AEs: Overview

N (%)	G-Clb vs Clb		G-Clb vs R-Clb	
	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
≥1 AEs (any grade)	228 (95)	96 (83)	316 (94)	290 (90)
Grade 3–5 AEs	179 (74)	59 (51)	241 (72)	191 (60)
Serious AEs	113 (47)	45 (39)	150 (45)	124 (39)
Grade 5 (fatal) AEs	19 (8)	13 (11)	23 (7)	31 (10)
2nd malignancies*	11 (5)	1 (<1)	12 (4)	13 (4)
Infections†	1 (<1)	7 (6)	2 (<1)	2 (<1)

No new safety signals detected

*Neoplasms benign, malignant and unspecified (MedDRA SOC), occurring 6 months after first study drug intake; †all AEs classified as infections and infestations (MedDRA SOC)

AEs: Late onset

N (%)	G-Clb vs Clb		G-Clb vs R-Clb	
	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
Prolonged neutropenia,*† n/N	5/184 (3)	8/86 (9)	5/256 (2)	10/268 (4)
Late onset neutropenia,‡§ n/N	37/213 (17)	10/90 (11)	45/297 (15)	36/304 (12)
Second malignancies¶	33 (14)	8 (7)	37 (11)	33 (10)
Squamous cell carcinoma	6 (2)	0 (0)	6 (2)	5 (2)
Basal cell carcinoma	5 (2)	1 (<1)	6 (2)	4 (1)

No new late-onset toxicity detected

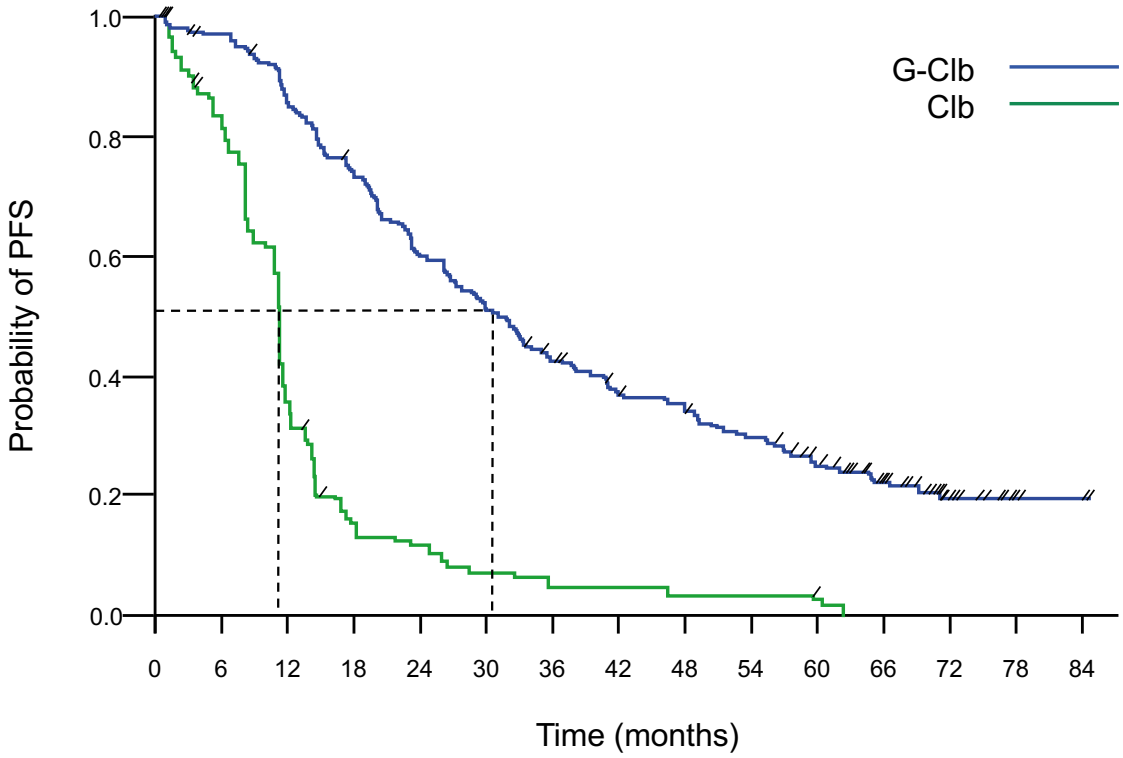
*Neutropenia not resolved within 28 days of treatment completion; †includes patients who completed treatment with a neutrophil assessment available 24–41 days after EOT; ‡neutropenia (<1000 cells/mm^3) occurring ≥28 days after treatment completion or discontinuation; §includes patients who completed treatment with a neutrophil assessment available 24–200 days after EOT; ¶second malignancies starting 6 months after initiation of study treatment

MRD negative response at EOT*

	G-Clb vs Clb		G-Clb vs R-Clb†	
	G-Clb n=238	Clb n=118	G-Clb n=333	R-Clb n=330
Patients included in analysis (peripheral blood and bone marrow combined)	166	90	237	246
MRD-negative response,‡ n (%)	42 (25%)	0 (0%)	57 (24%)	6 (2%)
Difference in MRD negativity rates	25%		22%	

*Includes all patients with an evaluable MRD result in peripheral blood and/or bone marrow at EOT; †minor changes to MRD results due to a re-run in sequencing of samples for some patients, triggered by receipt of additional follow-up samples after cut-off for primary analysis; ‡defined as <1 CLL cell per 10,000 leukocytes

PFS: G-Clb vs Clb



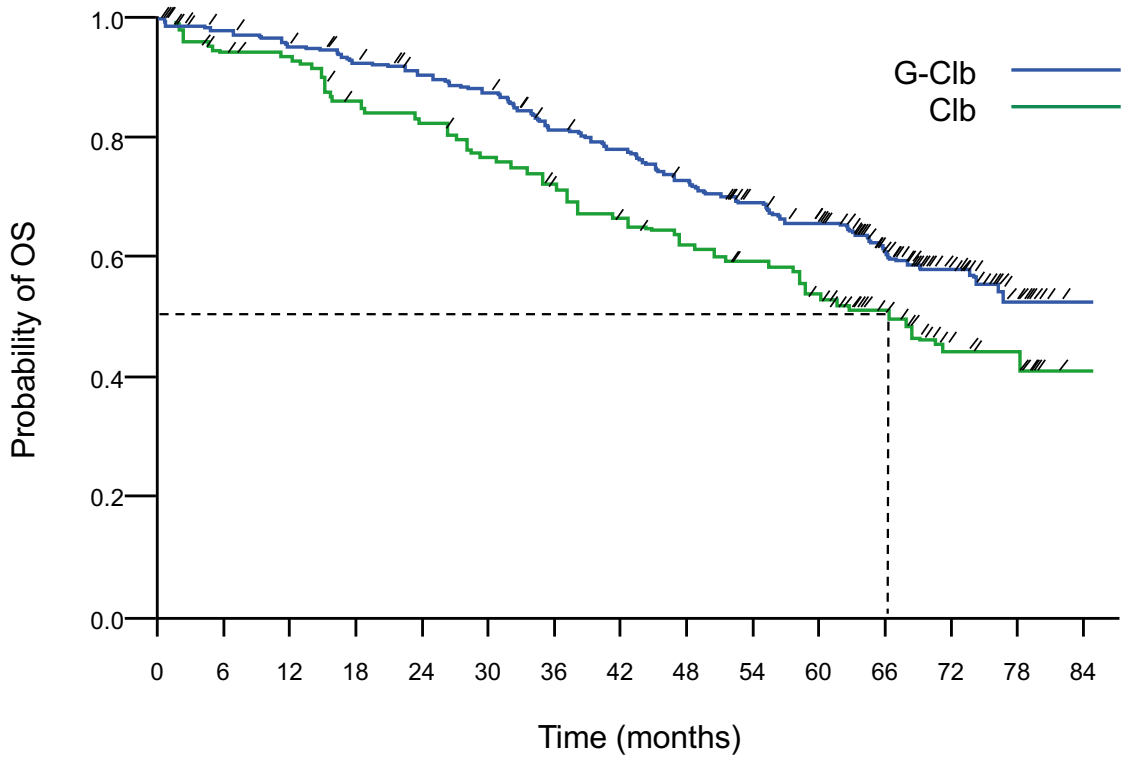
No. of pts at risk

G-Clb	238	218	190	162	133	114	92	78	73	60	48	33	14	4	2
Clb	118	90	37	14	11	7	5	5	3	3	1	0	0	0	0

	G-Clb n=238	Clb n=118
Patients with events, n (%)	173 (72.7)	107 (90.7)
5-year PFS, % (95% CI)	25 (19–31)	2 (0–4)
Median PFS, months	31.1	11.1
HR (95% CI), p-value	0.21 (0.16–0.28), p<0.0001	

Median observation time: 62.5 months

OS: G-Clb vs Clb



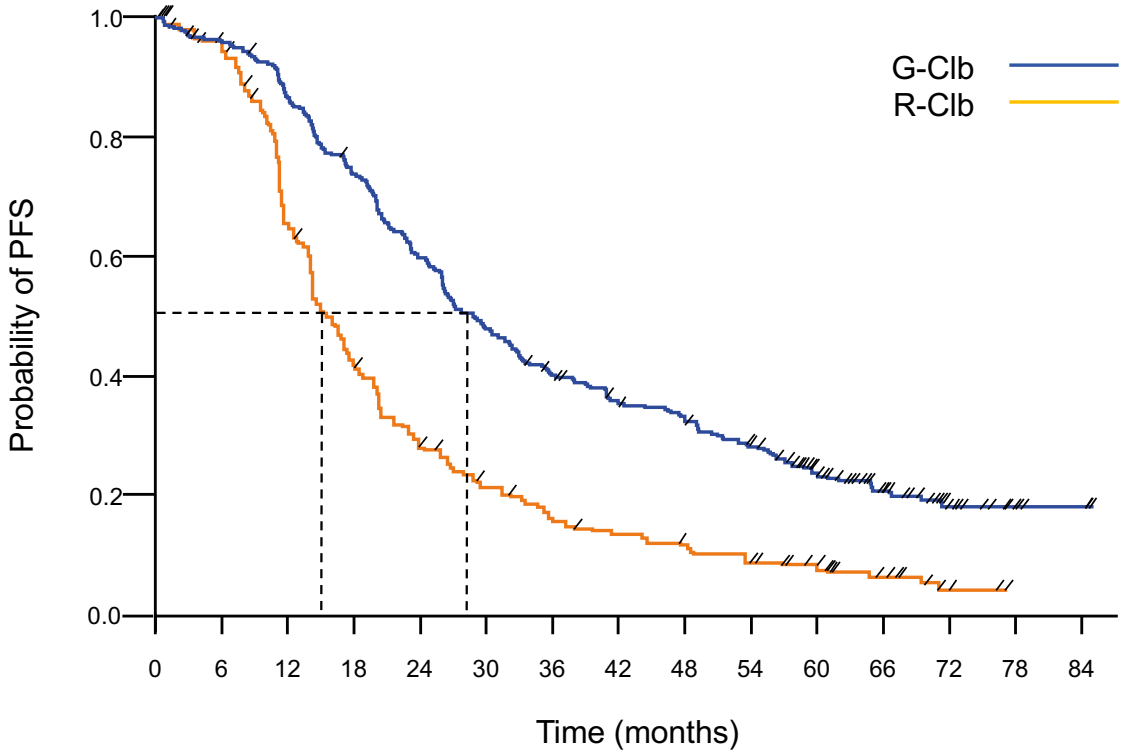
No. of pts at risk

G-Clb	238	223	216	208	200	194	177	169	158	147	134	107	69	28	2
Clb	118	105	102	91	88	81	74	68	61	57	51	37	20	14	1

	G-Clb n=238	Clb n=118
Patients with events, n (%)	93 (39.1)	57 (48.3)
5-year OS, % (95% CI)	66 (60–72)	53 (43–62)
Median OS, months	NR	66.7
HR (95% CI), p-value	0.68 (0.49–0.94), p=0.0196	

Median observation time: 62.5 months

PFS: G-Clb vs R-Clb



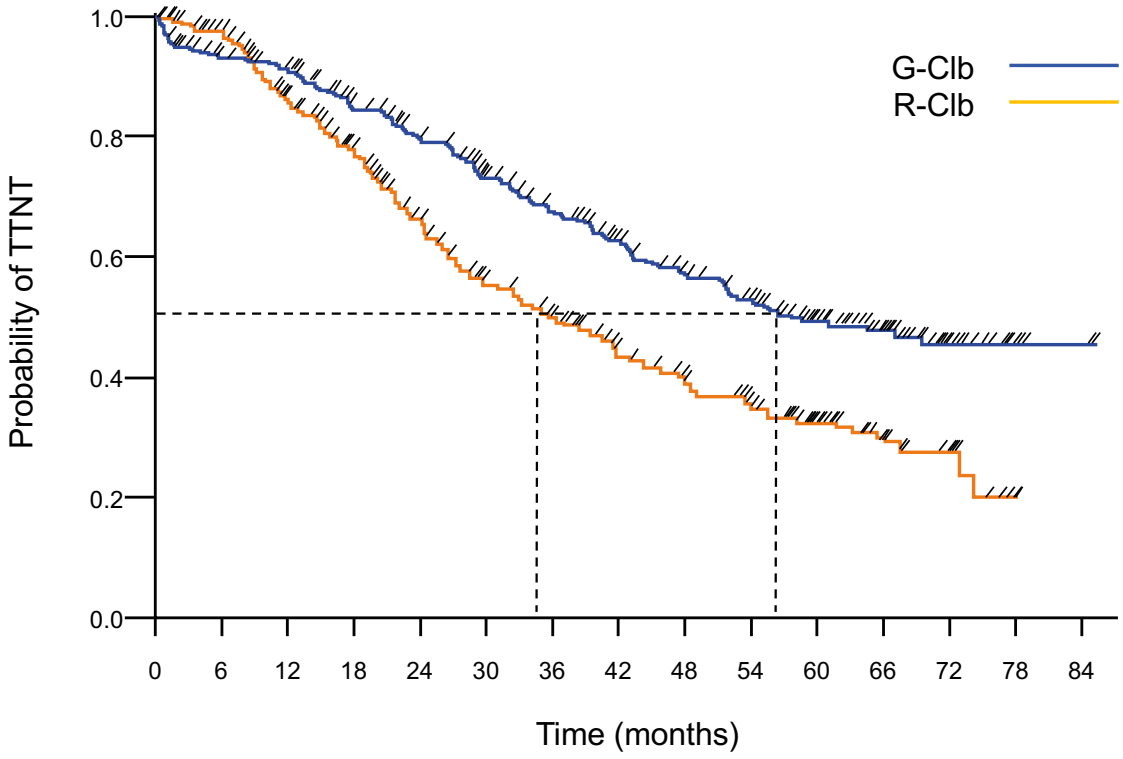
No. of pts at risk

G-Clb	333	302	270	229	185	149	123	106	98	80	54	33	14	4	2
R-Clb	330	310	209	136	89	67	51	41	35	27	20	10	3	0	0

	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	244 (73.3)	292 (88.5)
5-year PFS, % (95% CI)	23 (19–28)	9 (6–12)
Median PFS, months	28.9	15.7
HR (95% CI), p-value	0.49 (0.41–0.58), p<0.0001	

Median observation time: 59.4 months

TTNT: G-Clb vs R-Clb



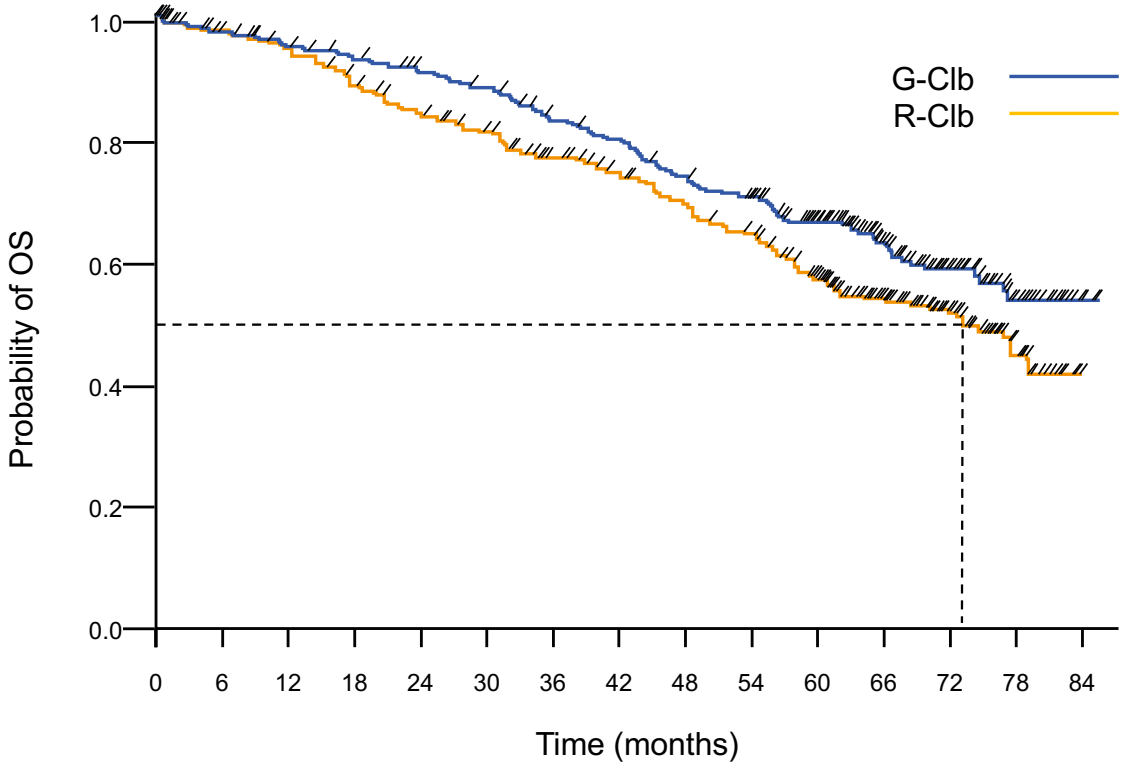
No. of pts at risk

G-Clb	333	281	266	237	217	189	167	139	122	102	73	48	20	5	2
R-Clb	330	303	244	207	160	126	109	84	70	58	38	19	10	1	0

	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	136 (40.8)	174 (52.7)
5-year TTNT, % (95% CI)	49 (42–55)	32 (25–38)
Median TTNT, months	56.4	34.9
HR (95% CI), p-value	0.58 (0.46–0.73), p<0.0001	

Median observation time: 59.4 months

OS: G-Clb vs R-Clb



No. of pts at risk

G-Clb	333	310	299	290	279	270	250	239	220	206	171	108	69	28	2
R-Clb	330	314	303	283	263	248	227	212	197	178	147	96	64	22	0

	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	121 (36.3)	147 (44.5)
5-year OS, % (95% CI)	66 (61–72)	57 (51–62)
Median OS, months	NR	73.1
HR (95% CI), p-value	0.76 (0.60–0.97), p=0.0245	

Median observation time: 59.4 months

Common AEs (any grade)*

N (%)	G-Clb vs Clb		G-Clb vs R-Clb	
	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
Infusion-related reactions	167 (69)	0 (0)	222 (66)	121 (38)
Neutropenia	99 (41)	21 (18)	129 (38)	104 (32)
Nausea	32 (13)	29 (25)	40 (12)	42 (13)
Thrombocytopenia	37 (15)	9 (8)	48 (14)	21 (7)
Anaemia	30 (12)	12 (10)	36 (11)	36 (11)
Vomiting	13 (5)	14 (12)	19 (6)	22 (7)
Diarrhoea	25 (10)	13 (11)	34 (10)	24 (8)
Pyrexia	26 (11)	8 (7)	30 (9)	24 (7)
Fatigue	17 (7)	12 (10)	27 (8)	30 (9)
Constipation	17 (7)	12 (10)	28 (8)	16 (5)

*Incidence ≥10% in any arm

Common Grade 3–5 AEs*

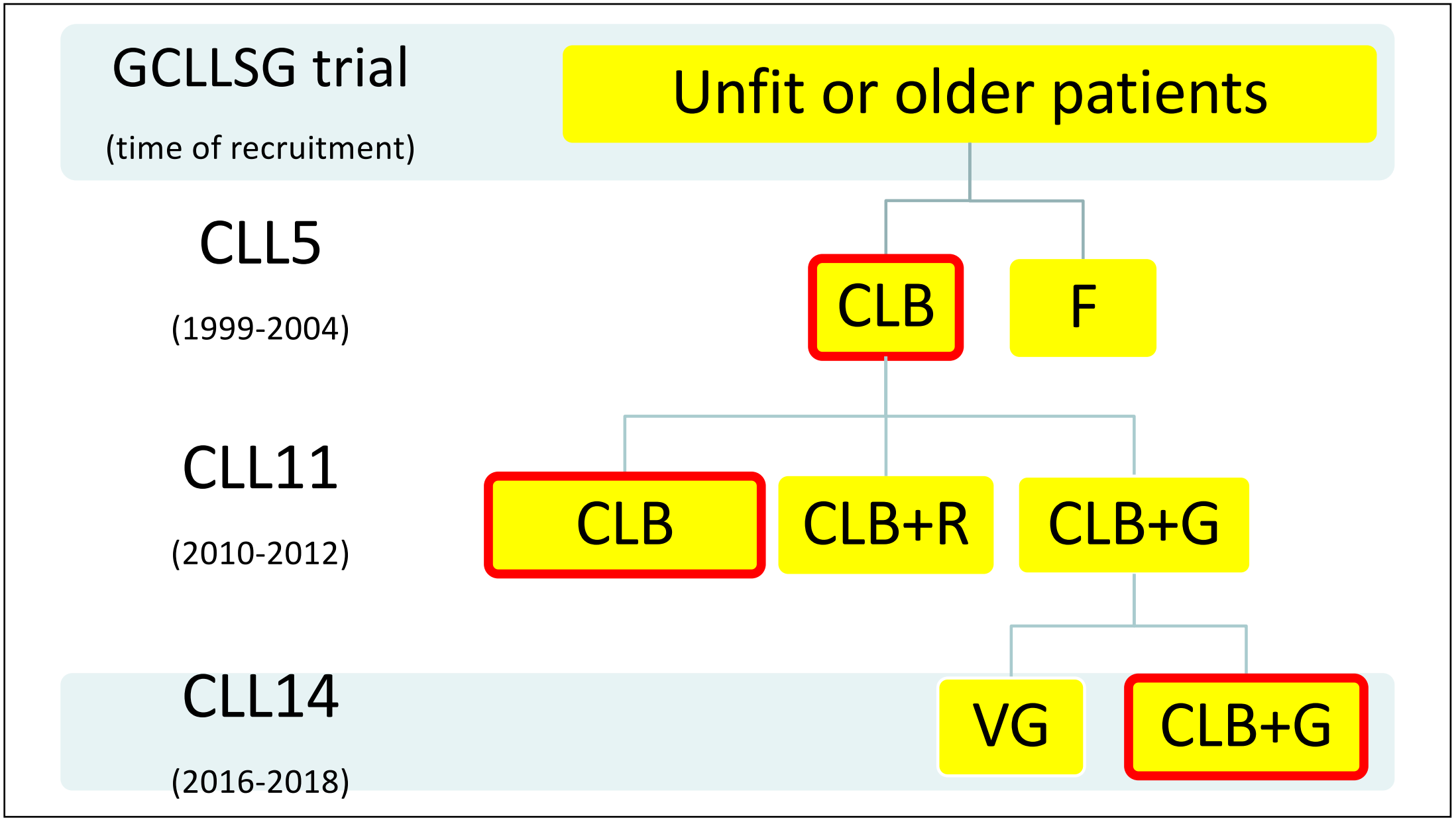
N (%)	G-Clb vs Clb		G-Clb vs R-Clb	
	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
Infusion-related reactions	52 (22)	0 (0)	68 (20)	13 (4)
Neutropenia	84 (35)	18 (16)	111 (33)	92 (29)
Thrombocytopenia	27 (11)	5 (4)	35 (10)	11 (3)
Anaemia	11 (5)	5 (4)	13 (4)	14 (4)
Febrile neutropenia	4 (2)	5 (4)	8 (2)	4 (1)
Leukopenia	13 (5)	0 (0)	16 (5)	4 (1)
Infections	28 (12)	16 (14)	41 (12)	46 (14)
Pneumonia	8 (3)	4 (3)	13 (4)	19 (6)
Sepsis	2 (<1)	4 (3)	2 (<1)	2 (<1)
Respiratory tract infection	1 (<1)	3 (3)	2 (<1)	0 (0)

*Incidence ≥3% in any arm

Deaths

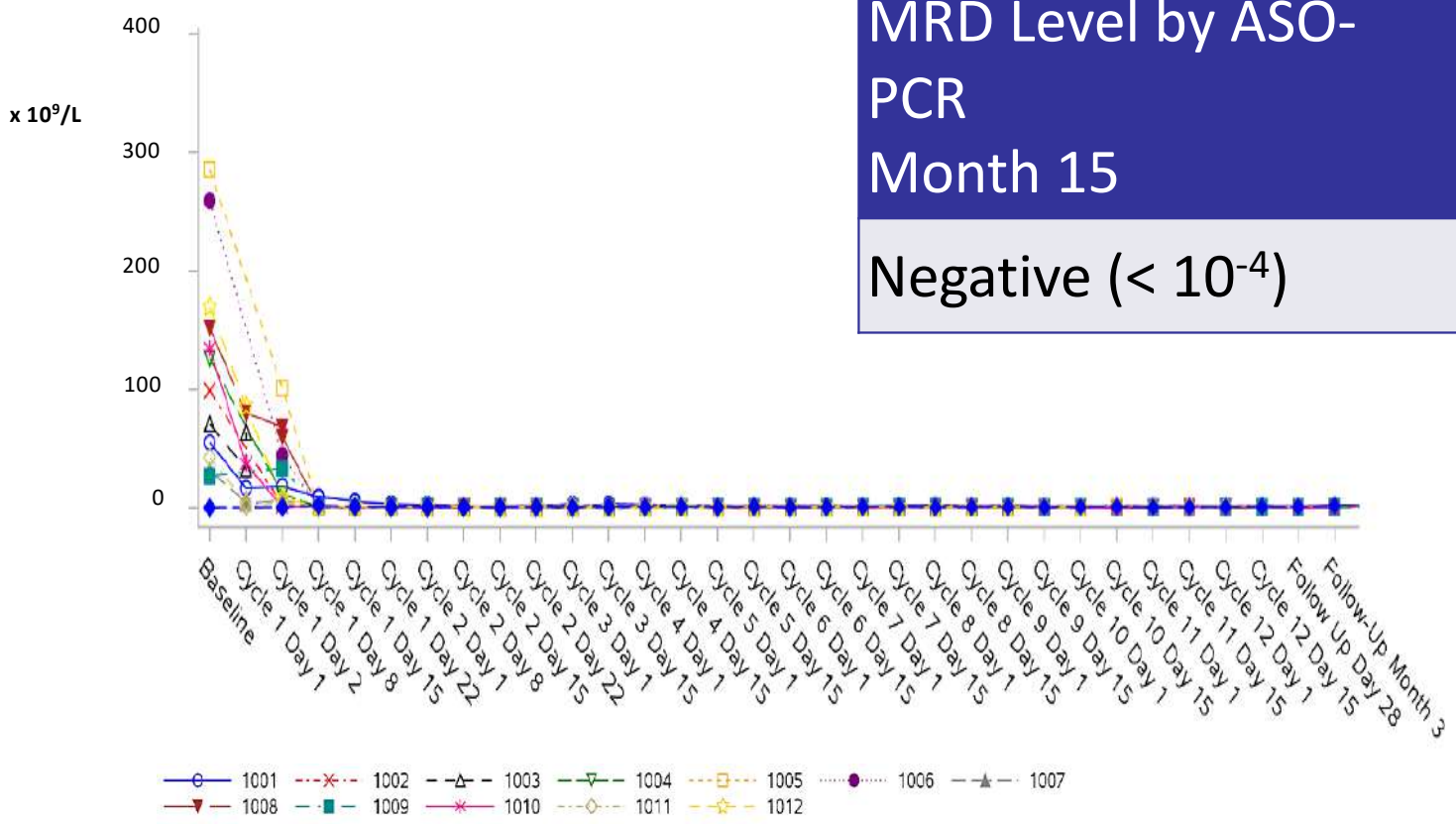
N (%)	G-Clb vs Clb		G-Clb vs R-Clb	
	G-Clb n=241	Clb n=116	G-Clb n=336	R-Clb n=321
All deaths	95 (39)	57 (49)	123 (37)	144 (45)
Treatment period/follow-up*	35 (15)	19 (16)	43 (13)	45 (14)
Main causes of death				
AEs	23 (10)	17 (15)	29 (9)	36 (11)
Disease progression	12 (5)	2 (2)	14 (4)	9 (3)
Survival follow-up period†	60 (25)	38 (33)	80 (24)	99 (31)
Main cause of death				
Disease progression	24 (10)	22 (19)	34 (10)	48 (15)

*Time from D1C1 until last day of treatment, and from last day of treatment until disease progression or next therapy; †time from disease progression or next therapy until last visit or death


GCLLSG trial
(time of recruitment)
Unfit or older patients
CLL5
(1999-2004)
CLB
F
CLL11
(2010-2012)
CLB
CLB+R
CLB+G
CLL14
(2016-2018)
VG
CLB+G

CLL14 protocol: Response to therapy with Venetoclax and Obinutuzumab – Peripheral blood leukocytes

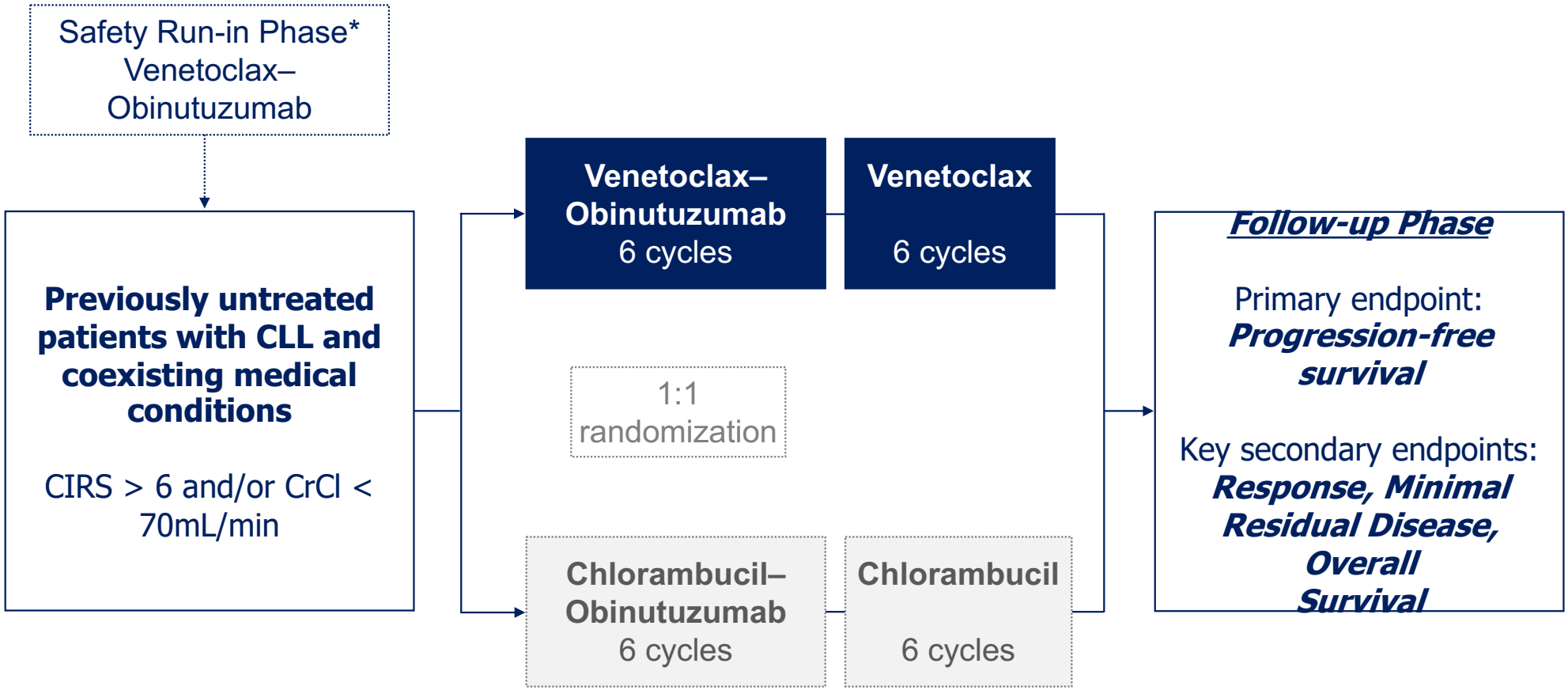
N=12



MRD Level by ASO-PCR Month 15	
Negative (< 10^{-4})	91%

Fischer et al. Blood 2017

Trial Design

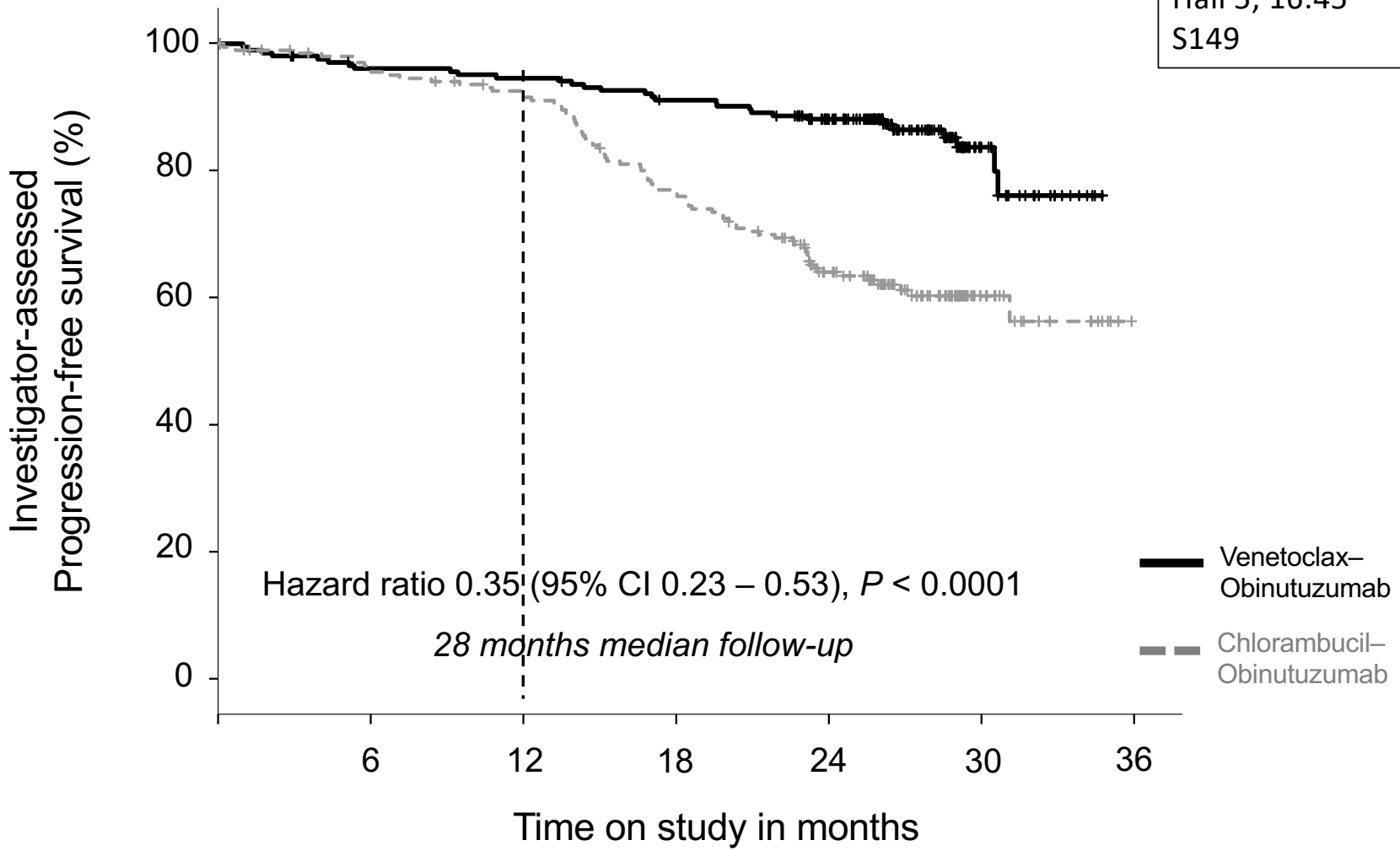


CLL-14

* Fischer K et al. Venetoclax and Obinutuzumab in chronic lymphocytic leukemia, Blood 11 May 2017

Progression-free survival

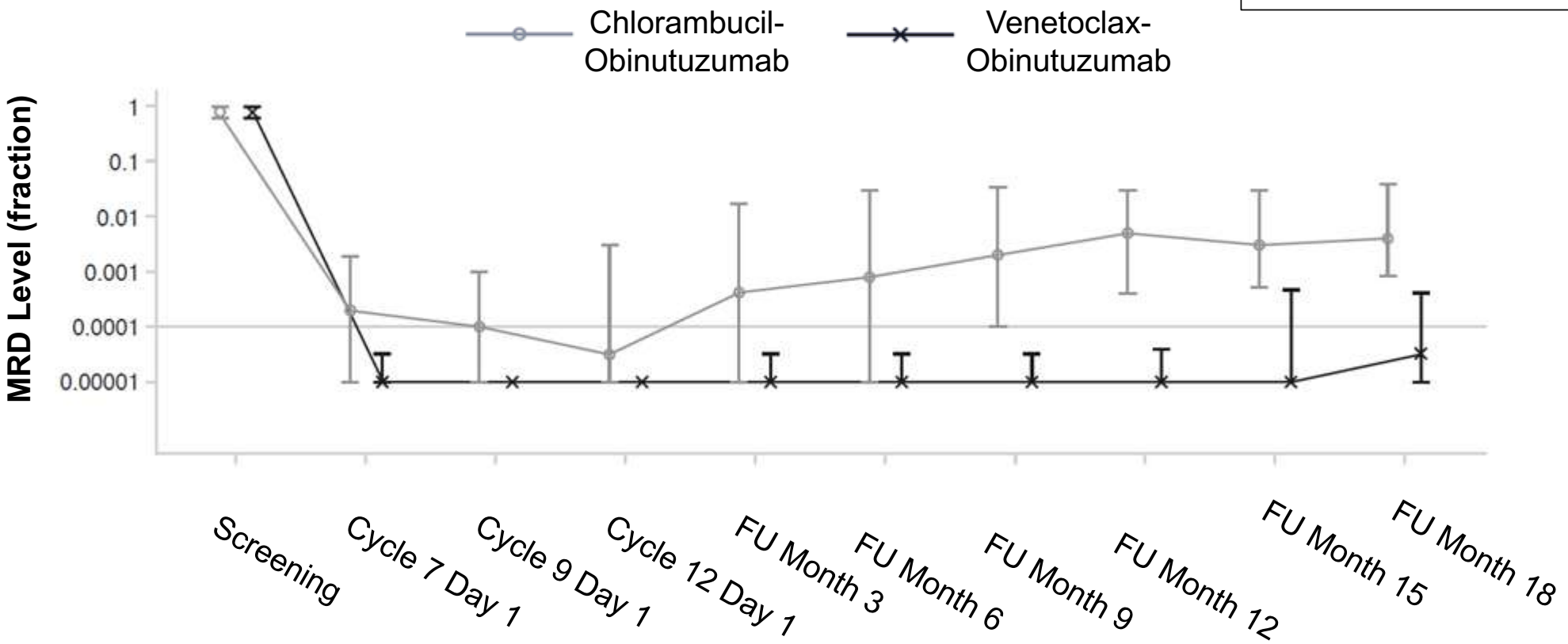
Fischer et al.
Presidential Symposium
Hall 5; 16:45
S149



CLL·14

MRD levels Over time

Fischer et al.
Presidential Symposium
Hall 5; 16:45
S149



By ASO-PCR in peripheral blood

CLL-14

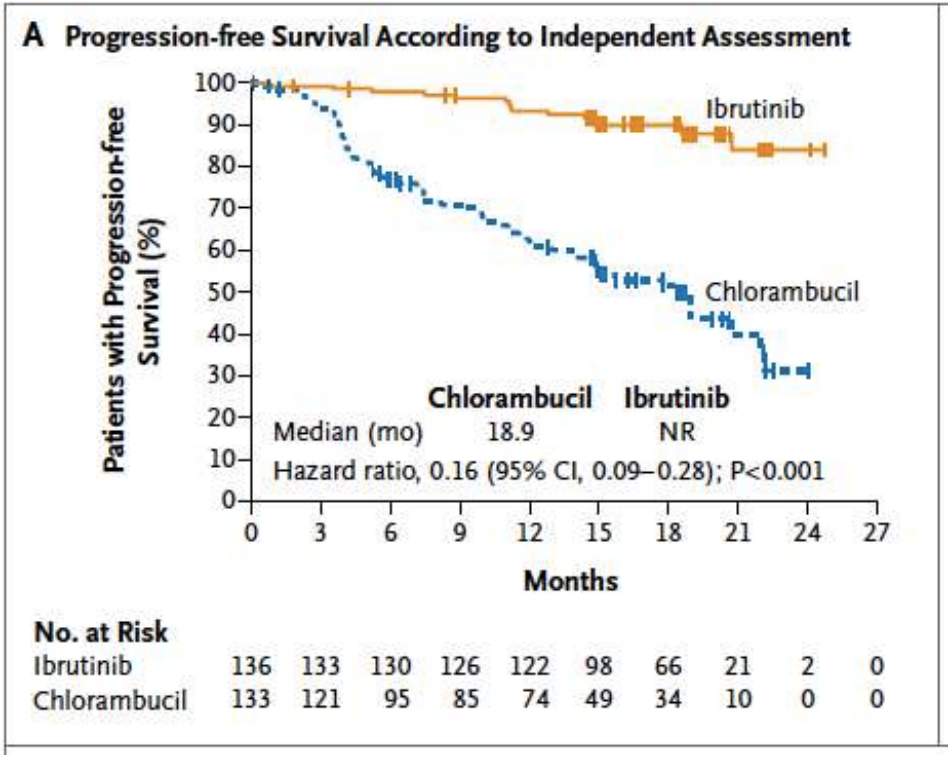
MRD negativity by NGS

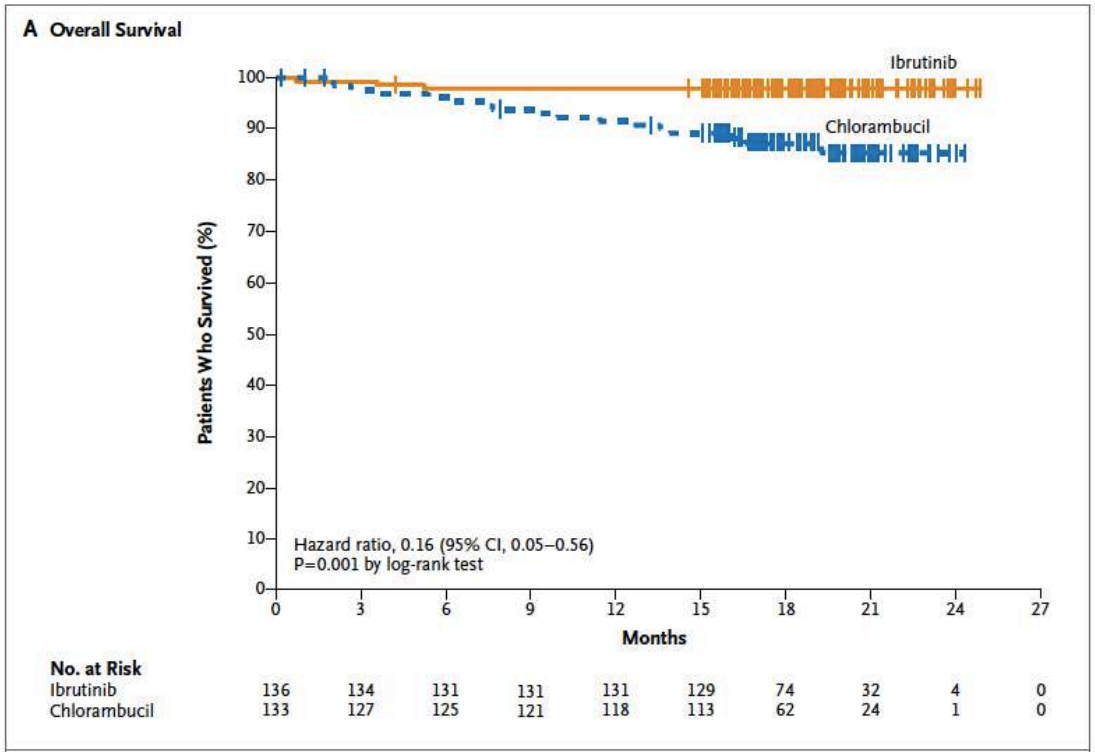
	Venetoclax-Obinutuzumab	Chlorambucil-Obinutuzumab
Number of patients, N	216	216
Minimal residual disease level		
$< 10^{-6}$	42 %	7 %
$\geq 10^{-6}$ and $<10^{-5}$	26 %	13 %
$\geq 10^{-5}$ and $<10^{-4}$	11 %	14 %
$\geq 10^{-4}$ and $<10^{-2}$	6 %	23 %
$\geq 10^{-2}$	5 %	29 %
No sample / not evaluable	12 %	14 %

By NGS in peripheral blood 3 months after completion of treatment

CLL-14

Resonate-2 Trial: Ibrutinib vs. Chlorambucil





Burger et al., NEJM 273 (25): 2425-37, 2016

iLLUMINATE (PCYC-1130) Study Design

Patients (N=229)
- Previously untreated CLL/SLL
- Requiring treatment per iwCLL criteria
- Age ≥65 years or <65 years old with ≥1 coexisting condition:
  - CIRS >6
  - CrCl <70 mL/min
  - del(17p) or *TP53* mutation

RANDOMIZE 1:1

Ibrutinib-obinutuzumab
Ibrutinib 420 mg once daily until PD or unacceptable toxicity + obinutuzumab 1000 mg split on days 1-2, and on day 8 and 15 (cycle 1) then day 1 (total 6 cycles)

Chlorambucil-obinutuzumab
Chlorambucil 0.5 mg/kg on days 1 and 15 (6 cycles) + obinutuzumab 1000 mg split on days 1-2 and on day 8 and 15 (cycle 1) then day 1 (total 6 cycles)

After IRC-confirmed PD, patients were allowed to receive single-agent ibrutinib[a]

Stratification: del(17p) vs. del(11q) vs. neither del(17p) or del(11q); ECOG 2 vs 0-1

Primary end point
- PFS by IRC assessment

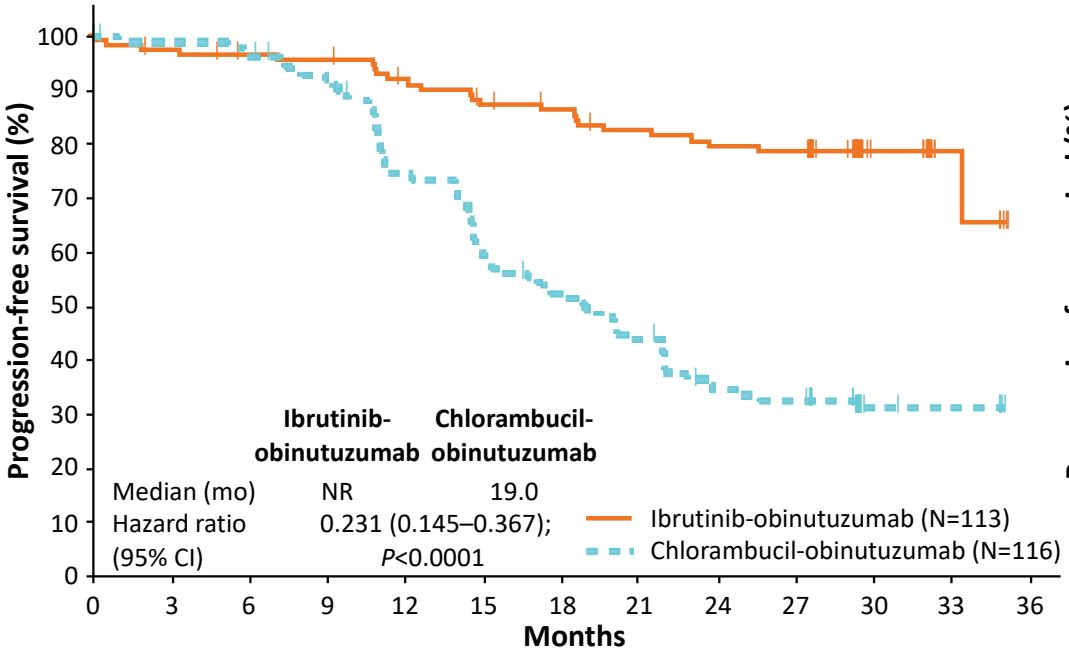
Secondary end points include
- PFS by IRC in high-risk population
- Rate of undetectable MRD
- ORR
- Infusion-related reactions
- Safety

CIRS, Cumulative Illness Rating Scale; IRC, independent review committee; iwCLL, International Working Group on CLL; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
[a]Patients in the chlorambucil-obinutuzumab arm could receive next-line single-agent ibrutinib in crossover following IRC-confirmed PD.

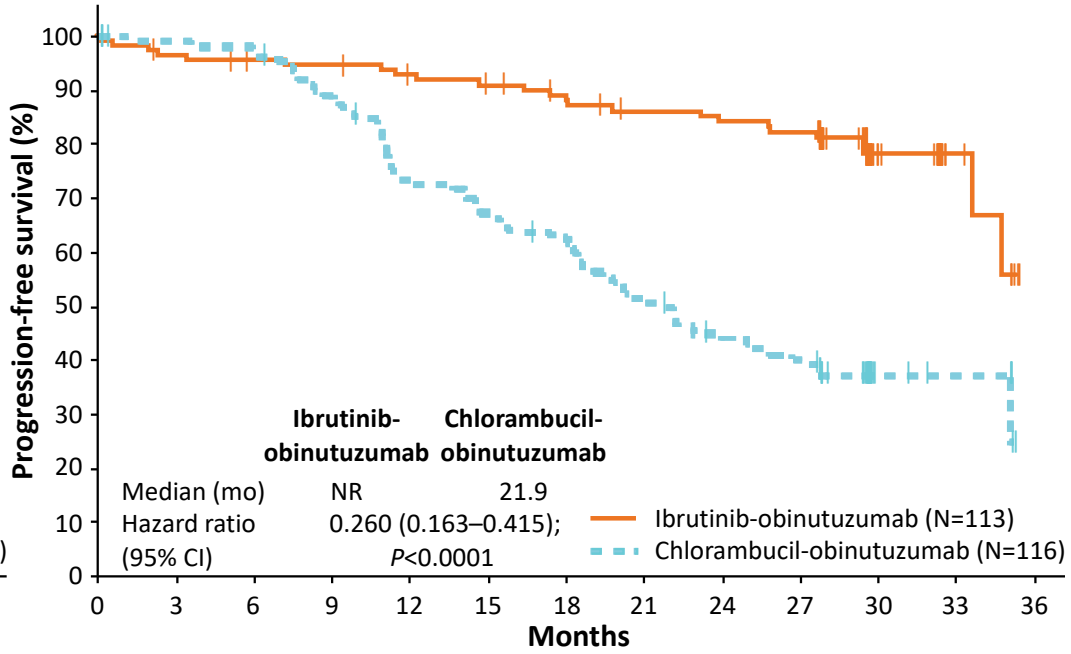
ASH 2018, PCYC-1130; Moreno et al.

Superior Progression-Free Survival with Ibrutinib-Obinutuzumab

IRC Assessment



INV Assessment

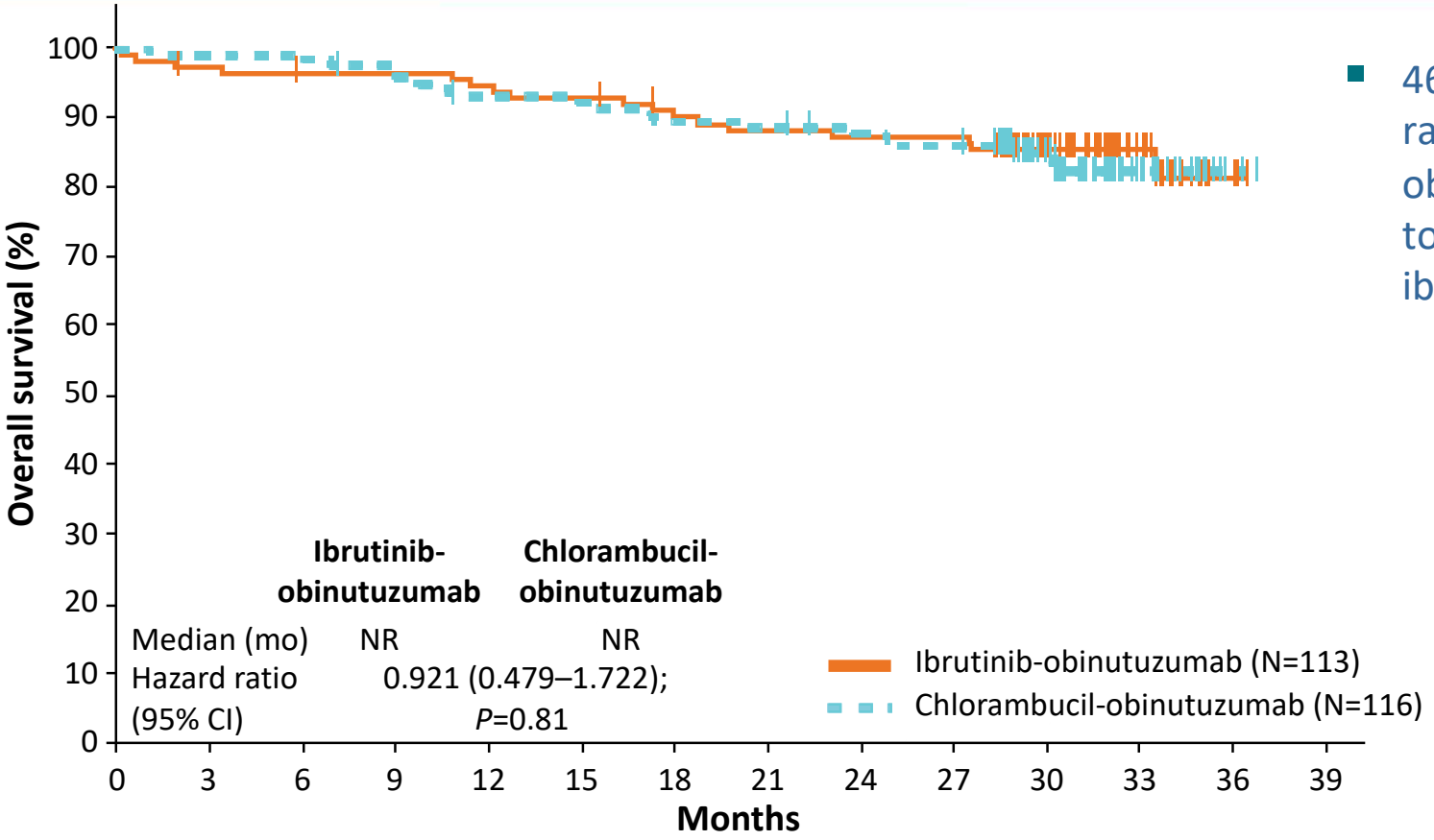


- Median follow-up, 31.3 months (range, 0.2–36.9)
- Estimated PFS at 30 months: 79% with ibrutinib-obinutuzumab vs. 31% with chlorambucil-obinutuzumab
- Even after excluding patients with del(17p): 74% reduction in risk of progression or death with ibrutinib-obinutuzumab

INV, investigator; NR, not reached.

ASH 2018, PCYC-1130; Moreno et al.

Overall Survival with Median 31 Months of Follow-Up



- 46 of 116 patients (40%) randomized to chlorambucil-obinutuzumab crossed over to receive single-agent ibrutinib

ASH 2018, PCYC-1130; Moreno et al.

CLL first line treatment (updated June 2019)

Stage	del(17p) or p53mut	Fitness	IGVH	Therapy
Binet A-B, Rai 0-II, inactive disease	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib or Venetoclax + Obinutuzumab or Idelalisib + Rituximab (if contraindications for ibrutinib)*
	No	Go go	M	FCR (BR above 65 years) or ibrutinib*
			U	Ibrutinib or FCR (BR above 65 years)*
		Slow go	M	Venetoclax + Obinutuzumab or Chlorambucil + Obinutuzumab or Ibrutinib*
			U	Venetoclax + Obinutuzumab or Ibrutinib or Chlorambucil + Obinutuzumab*

* Consider and discuss with patient: long-term vs fixed (6-12 m) duration therapy, lack of convincing evidence of overall survival differences, specific side effects of each therapeutic option (myelosuppression, infections, secondary malignancies for CIT; cardiac toxicity, bleeding and autoimmune disease for Ibru; TLS and infections for Ven-Obi; autoimmune disease (diarrhea) and opportunistic infections for Idelalisib).


We thank our patients.