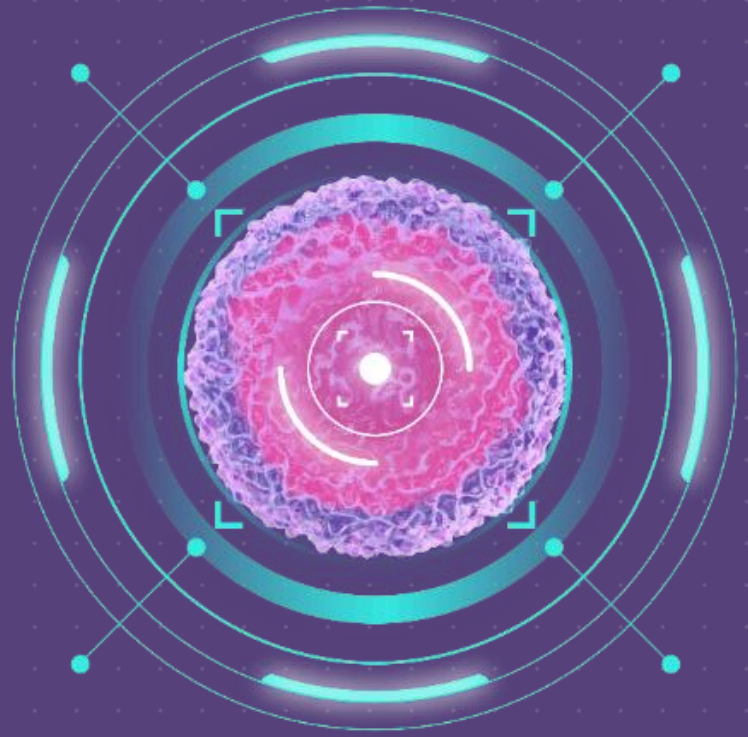
LymphomaHub

NEW CHEMOTHERAPY-FREE APPROACHES FOR THE TREATMENT OF LYMPHOID MALIGNANCIES



Scientific Education Support

Lymphoma Hub is delivered by Scientific Education Support (SES)

CLL – chemotherapy-free regimens: pros and cons

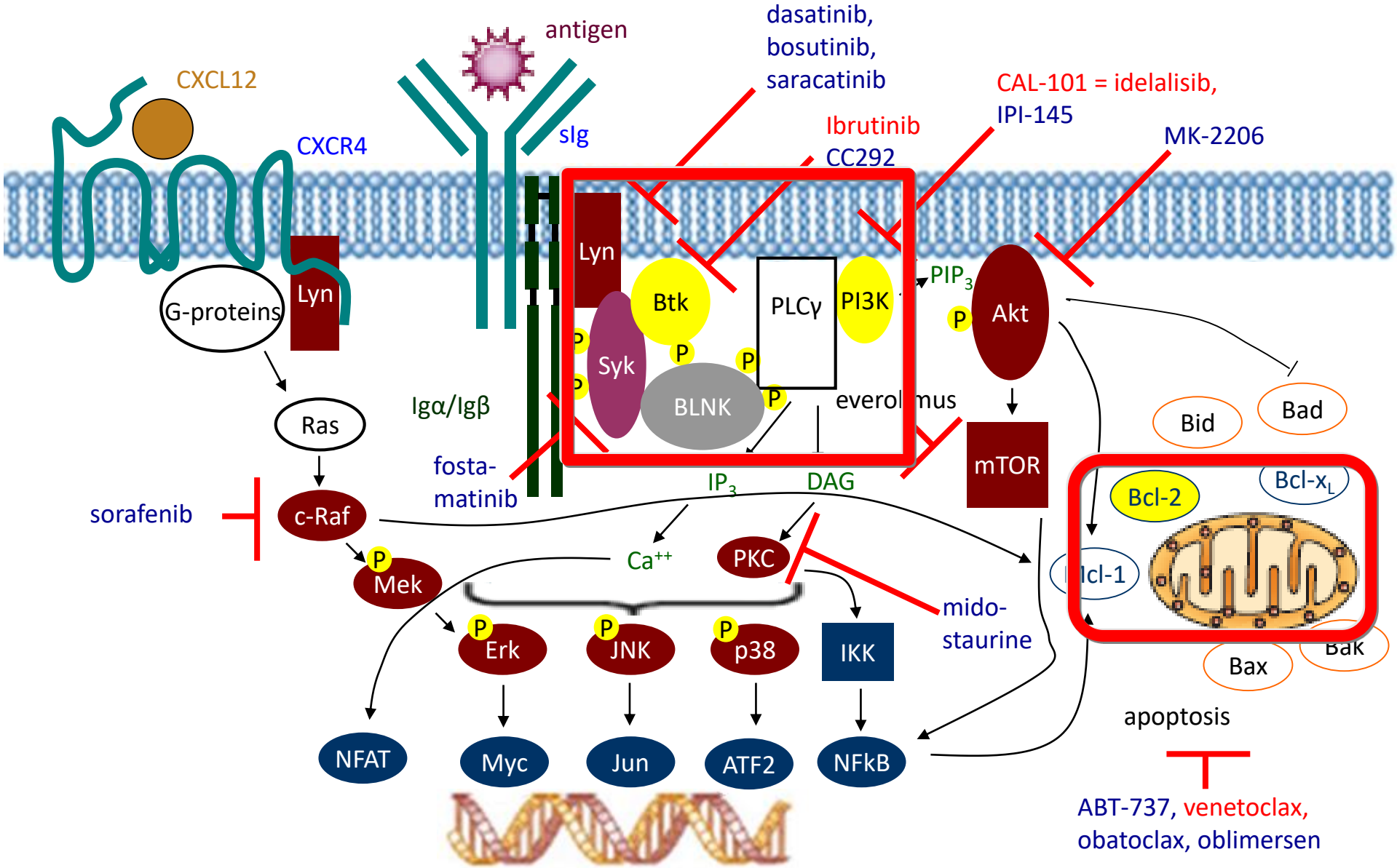
Michael Hallek
University Hospital of Cologne
Cologne, Germany

LymphomaHub

Disclosures

- Research support: Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Abbvie
- Honoraria (speaker’s bureau and/or advisory board): Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Abbvie

Novel agents target specific pathways in CLL



Type I CD20 antibodies

- CDC
- Low cell death
- Low aggregation
- ADCC
- Localize to lipid rafts
- FcgRIIB mediated internalization

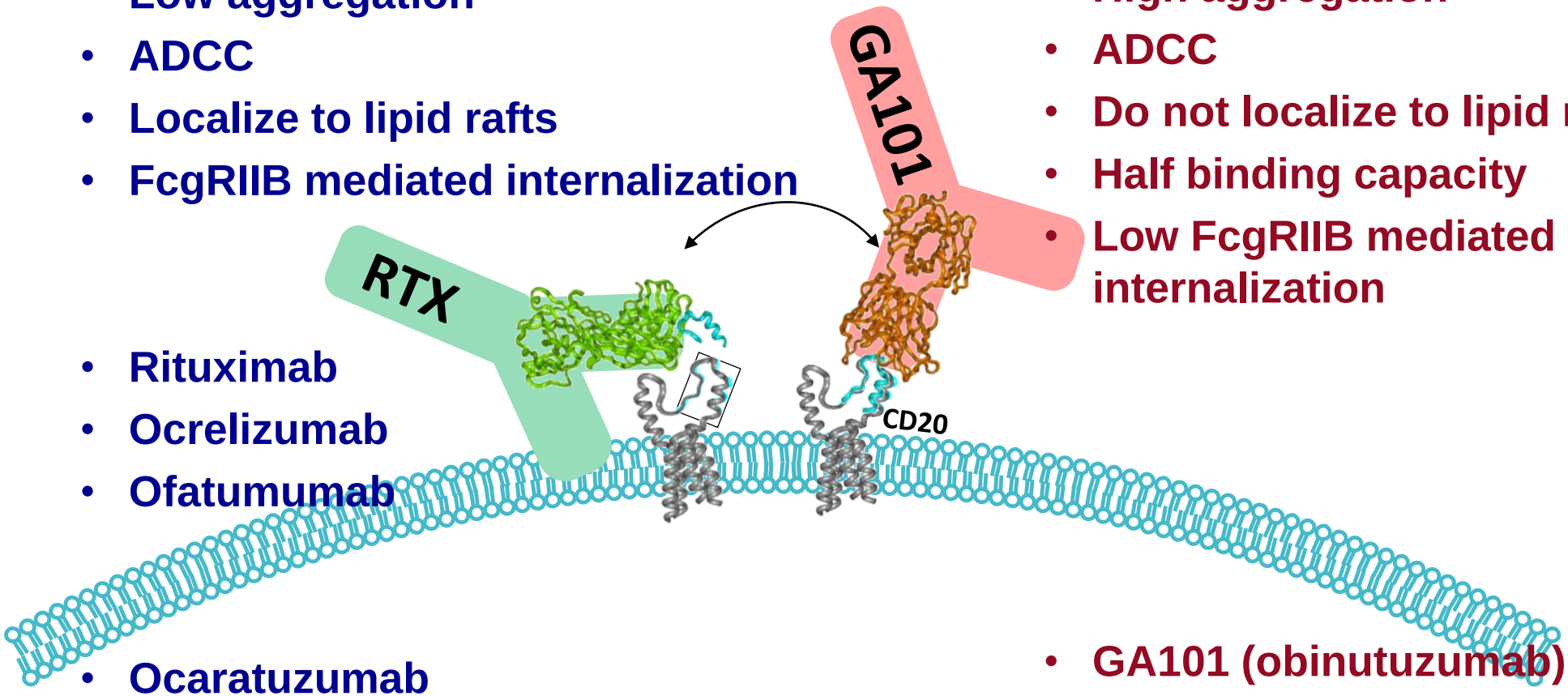
- Rituximab
- Ocrelizumab
- Ofatumumab

- Ocaratuzumab
- Veltuzumab
- Ublituximab

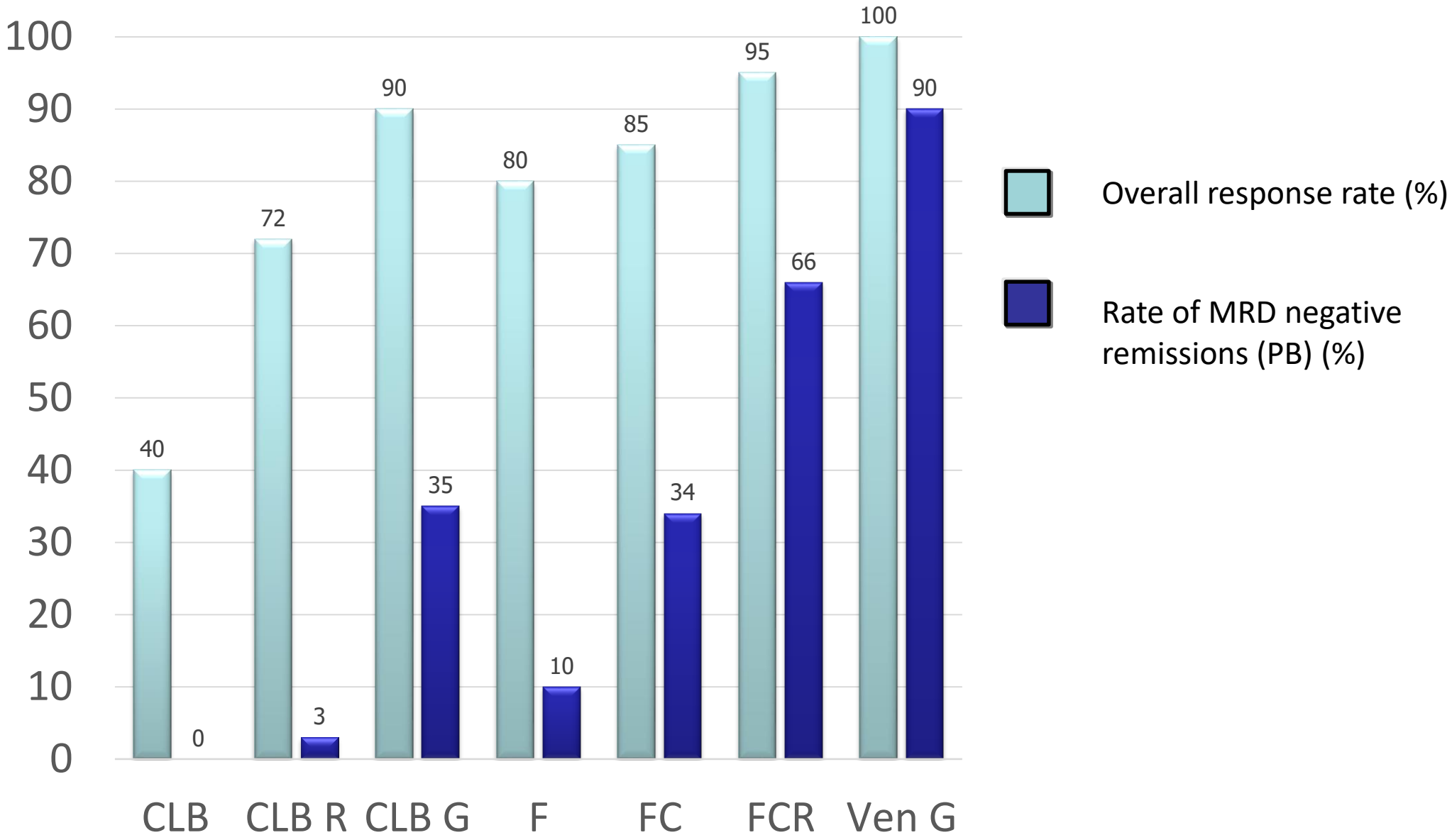
Type II antibodies

- Low CDC
- High cell death
- High aggregation
- ADCC
- Do not localize to lipid rafts
- Half binding capacity
- Low FcgRIIB mediated internalization

- GA101 (obinutuzumab)
- Tositumomab (B1)

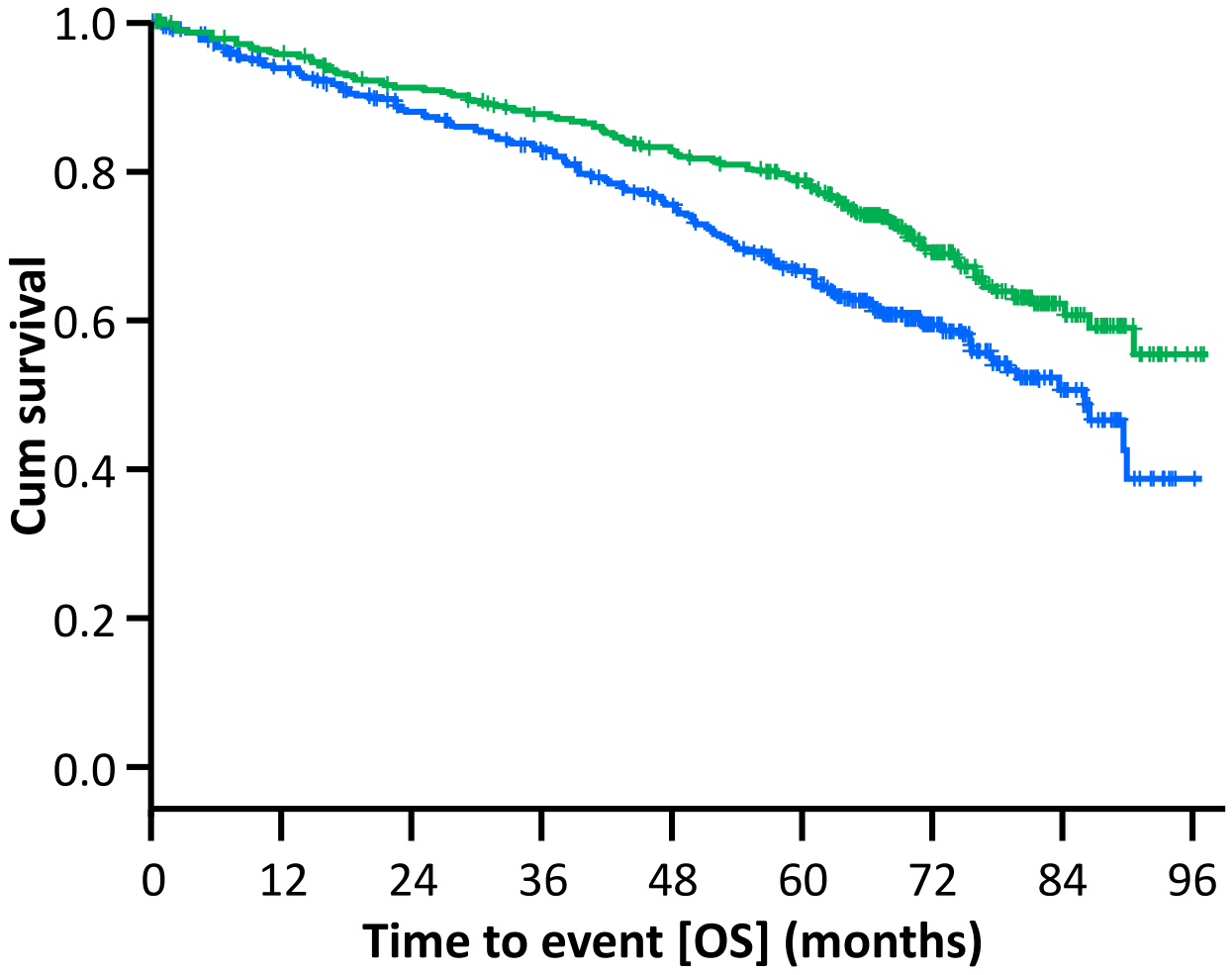


Increased efficacy of CLL therapies




alamy

CLL8 trial: Overall survival, update 2012
FCR versus FC



Median observation time 5.9 years

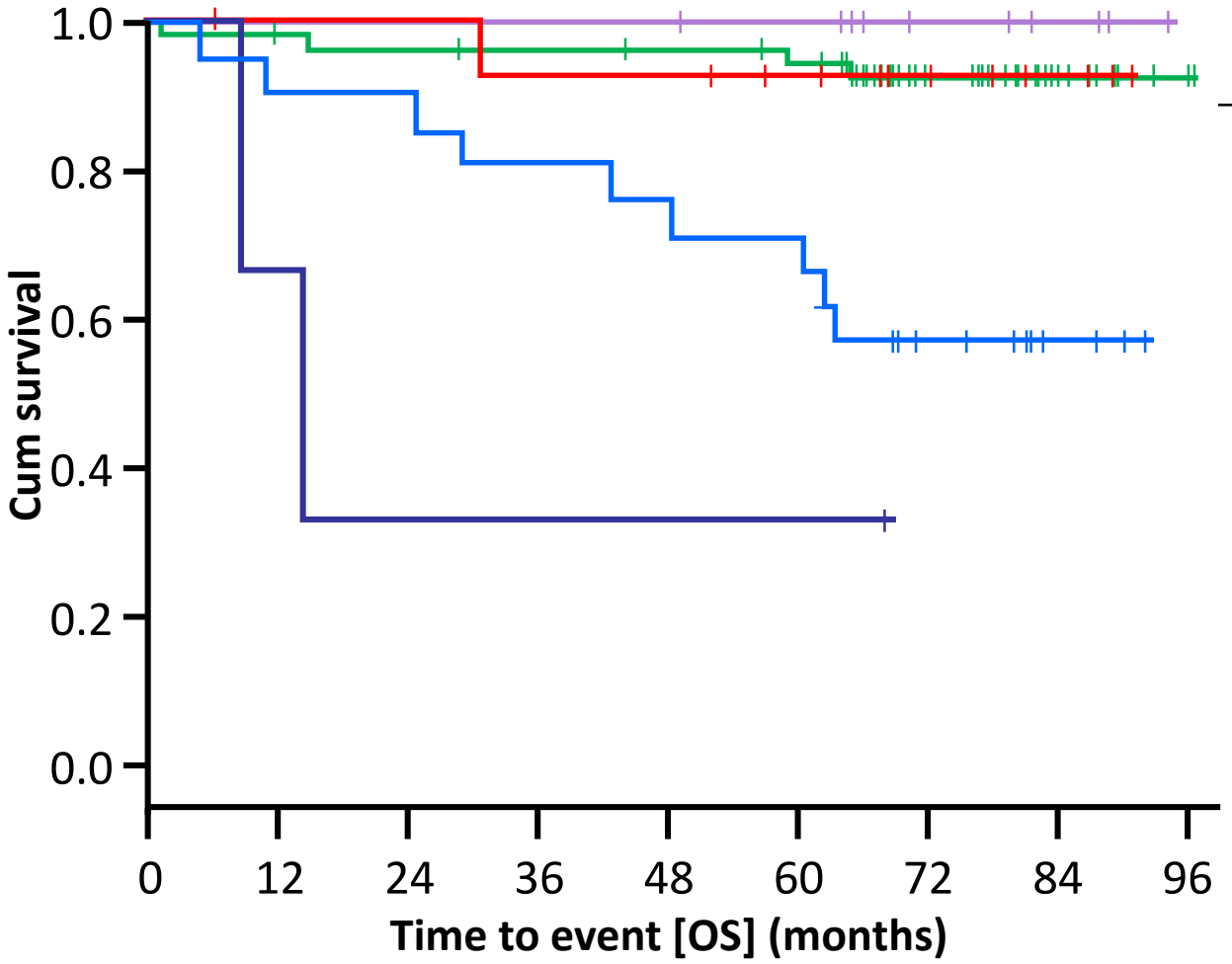
FCR 69.4% alive
Median not reached
FC 62.3% alive
Median 86 months

HR 0.68,
95% CI 0.535–0.858
p=0.001

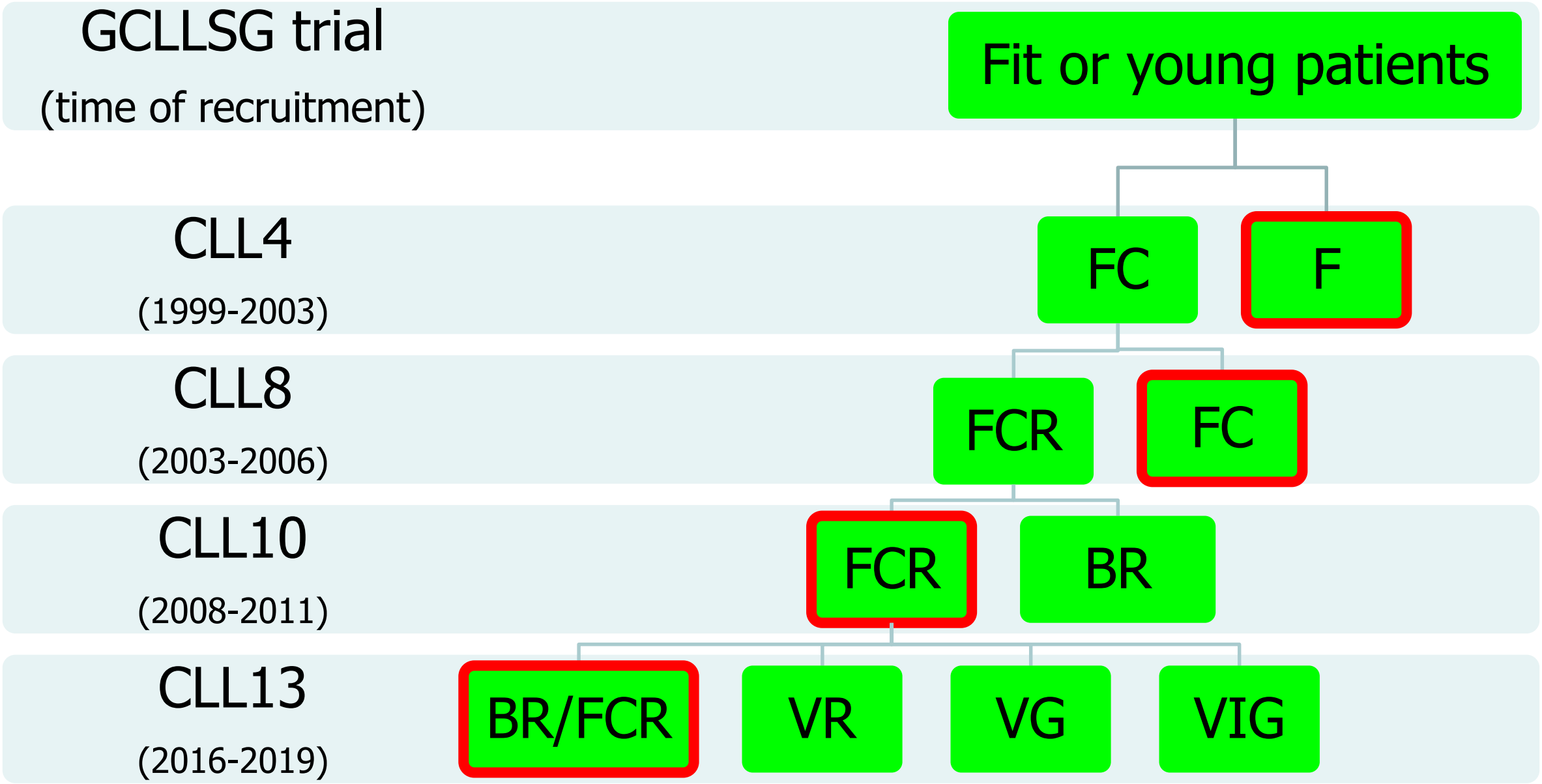
Fischer K, *et al. Blood* 2012; 120:Abstract 435 (Oral presentation).
Hallek M, *et al. Lancet* 2010; 376:1164–1174.

Survival after FCR chemoimmunotherapy

(Fischer et al., Blood 2016)



	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


GCLLSG trial
(time of recruitment)
Fit or young patients
CLL4
(1999-2003)
FC
F
CLL8
(2003-2006)
FCR
FC
CLL10
(2008-2011)
FCR
BR
CLL13
(2016-2019)
BR/FCR
VR
VG
VIG

ECOG-ACRIN trial

Shanefelt et al., ASH 2018

E1912

Eligibility:
-Previously untreated CLL
-Requires treatment (IWCLL 2008)
-Age ≤ 70
-ECOG 0-2
-CrCL>40
-Able to tolerate FCR
-No deletion 17p by FISH

Planned Accrual: 519

Randomization

Arm A – Ibrutinib + Rituximab

Cycles 1:
Ibrutinib 420 mg PO daily, days 1-28

Cycle 2:
Ibrutinib 420 mg PO daily, days 1-28
Rituximab 50 mg/m^2 IV, day 1
Rituximab 325 mg/m^2 IV, day 2

Cycles 3-7:
Ibrutinib 420 mg PO daily, days 1-28
Rituximab 500 mg/m^2 IV, day 1

Cycle 8 until progression:
Ibrutinib 420 mg PO daily, days 1-28

Arm B - FCR

Cycles 1-6:
Fludarabine 25 mg/m^2 IV, days 1-3
Cyclophosphamide 250 mg/m^2 IV, days 1-3

Cycle 1:
Rituximab 50 mg/m^2 IV, day 1, cycle 1
Rituximab 325 mg/m^2 IV, day 2, cycle 1

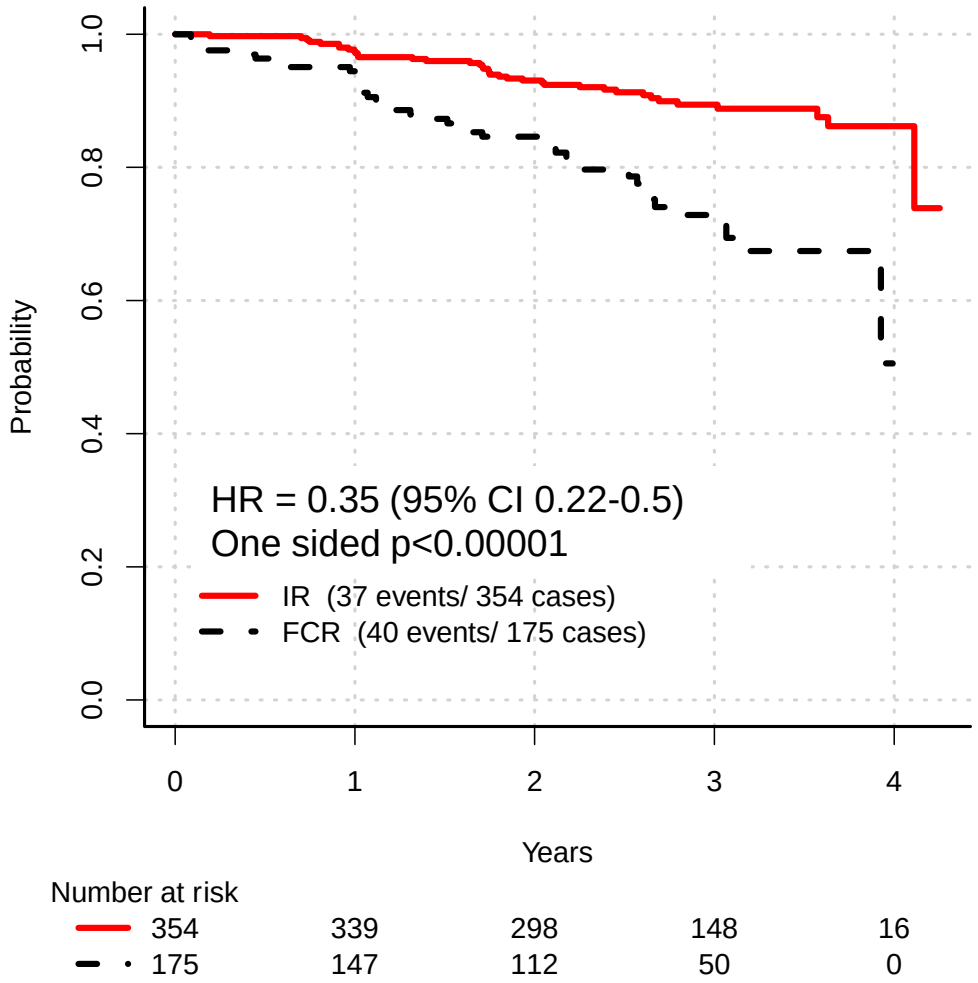
Cycle 2-6:
Rituximab 500 mg/m^2 IV, day 1, cycles 2-6

Disease Progression

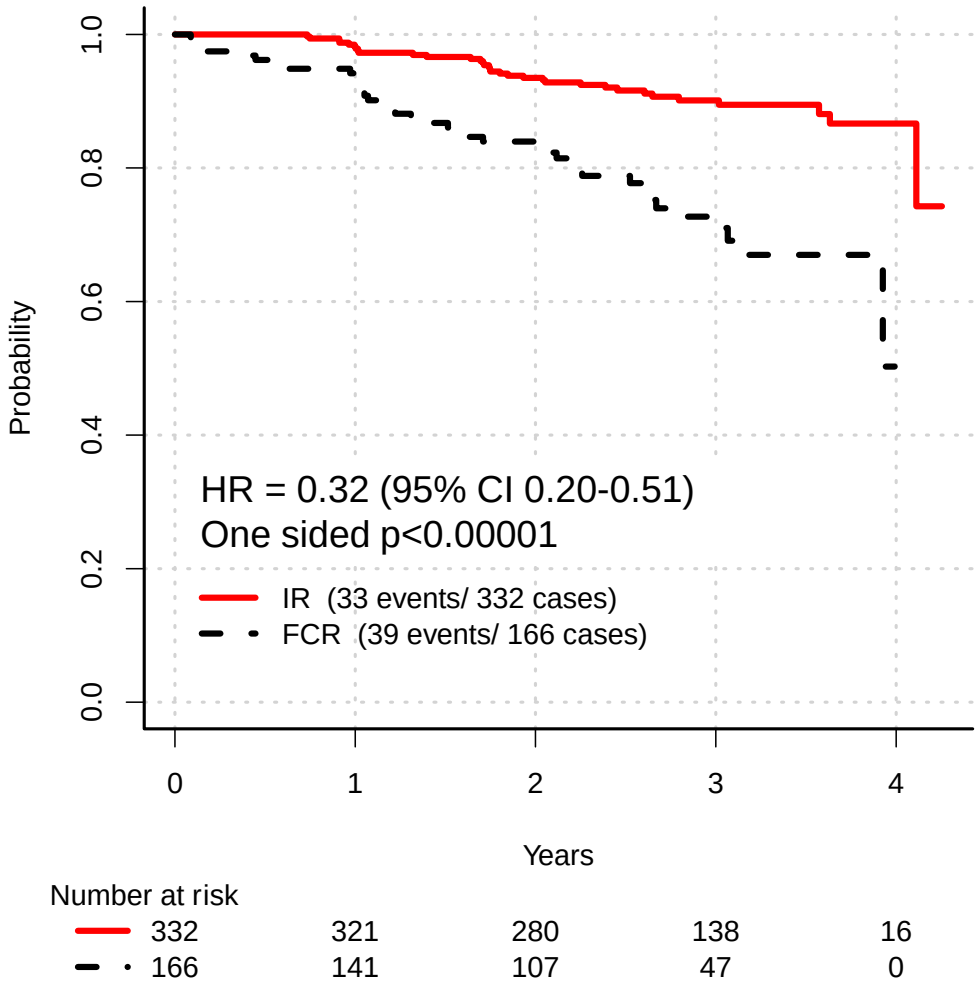
ECOG-ACRIN cancer research group | Reshaping the future of patient care

Progression Free Survival

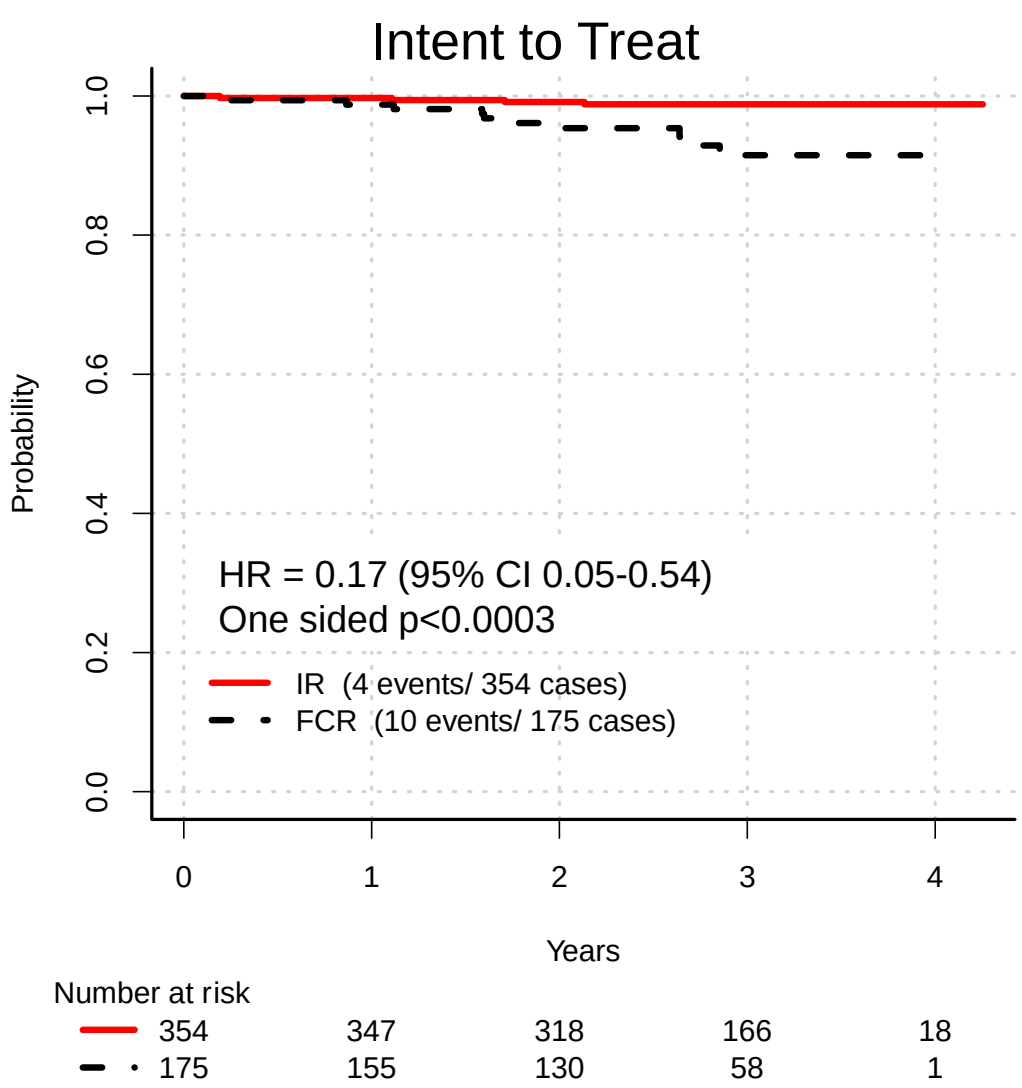
Intent to Treat

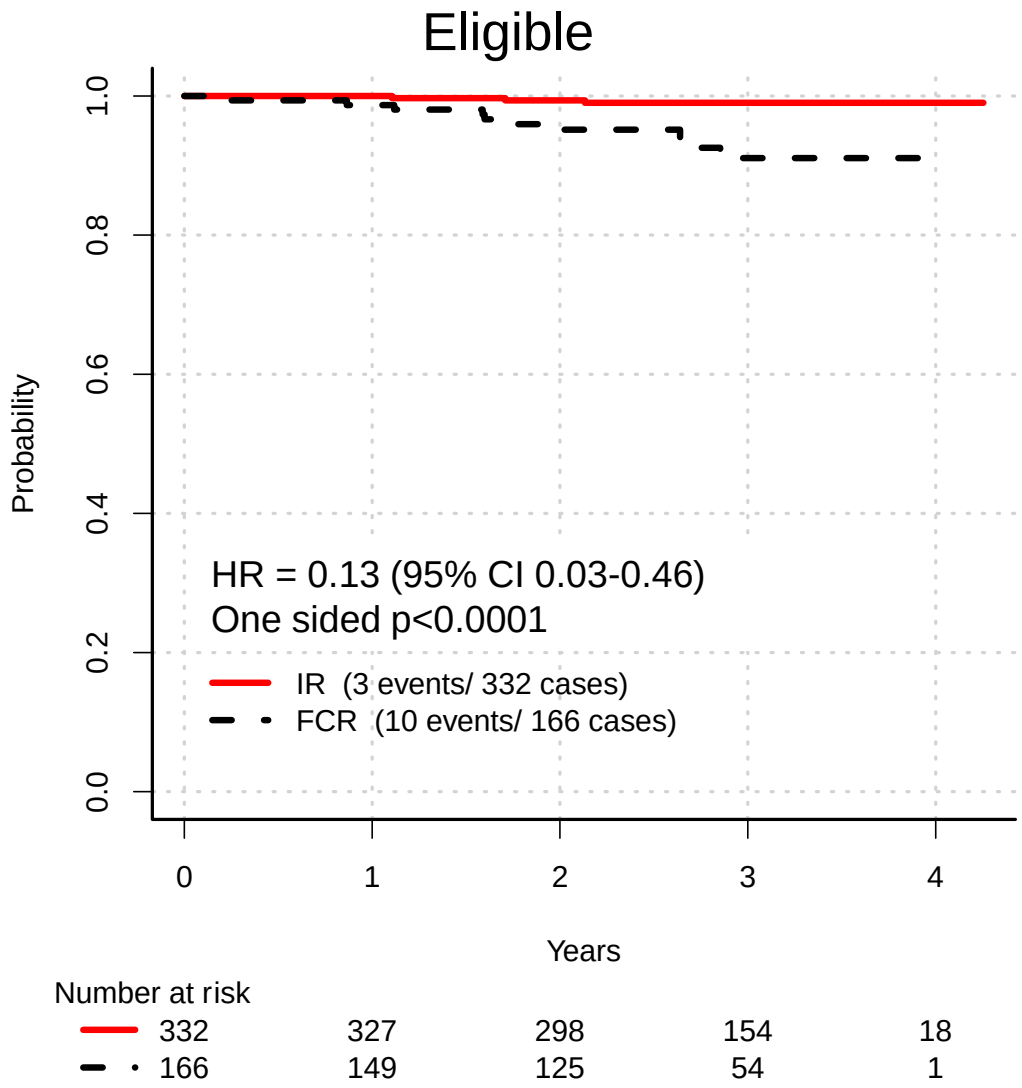


Eligible



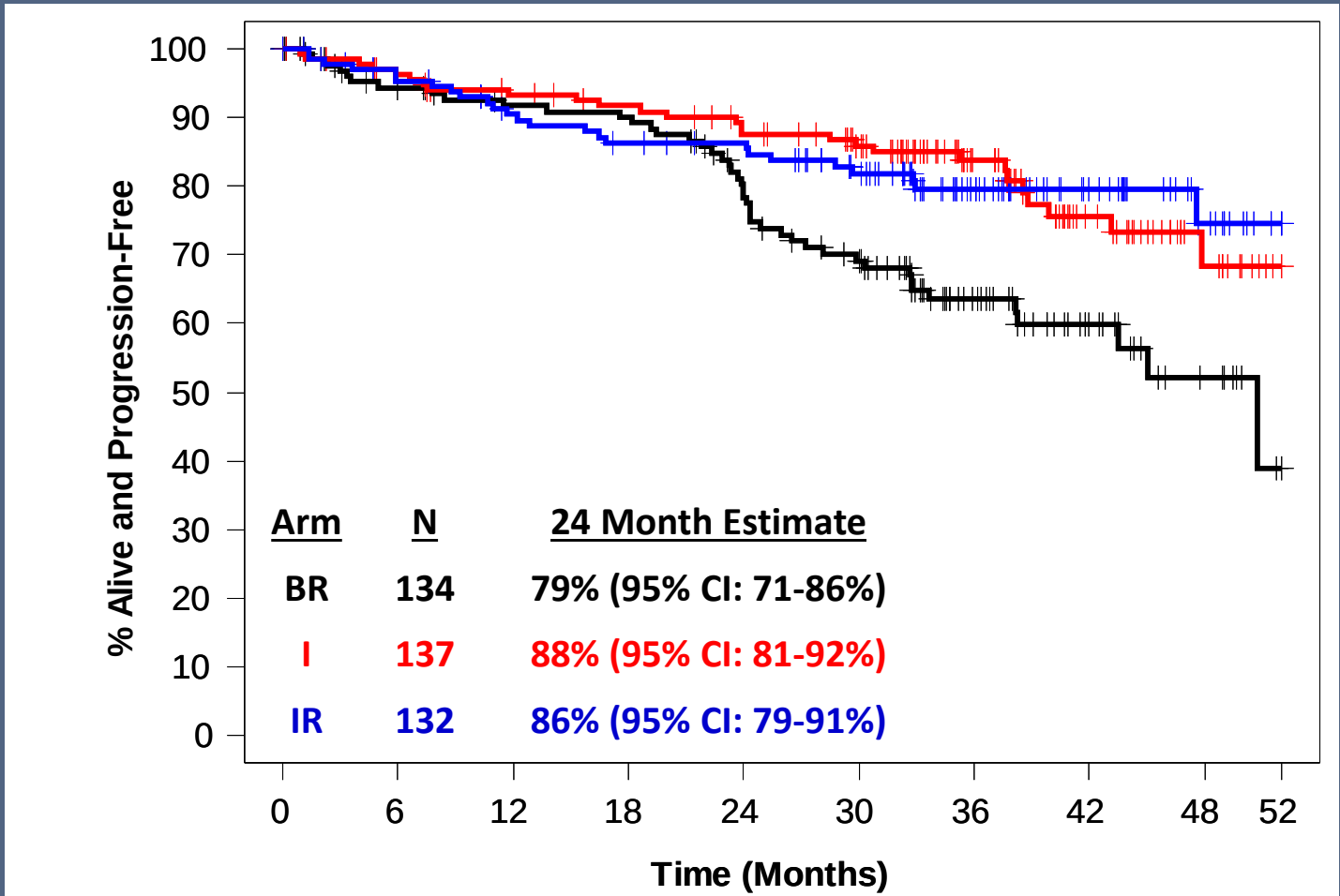
Overall Survival





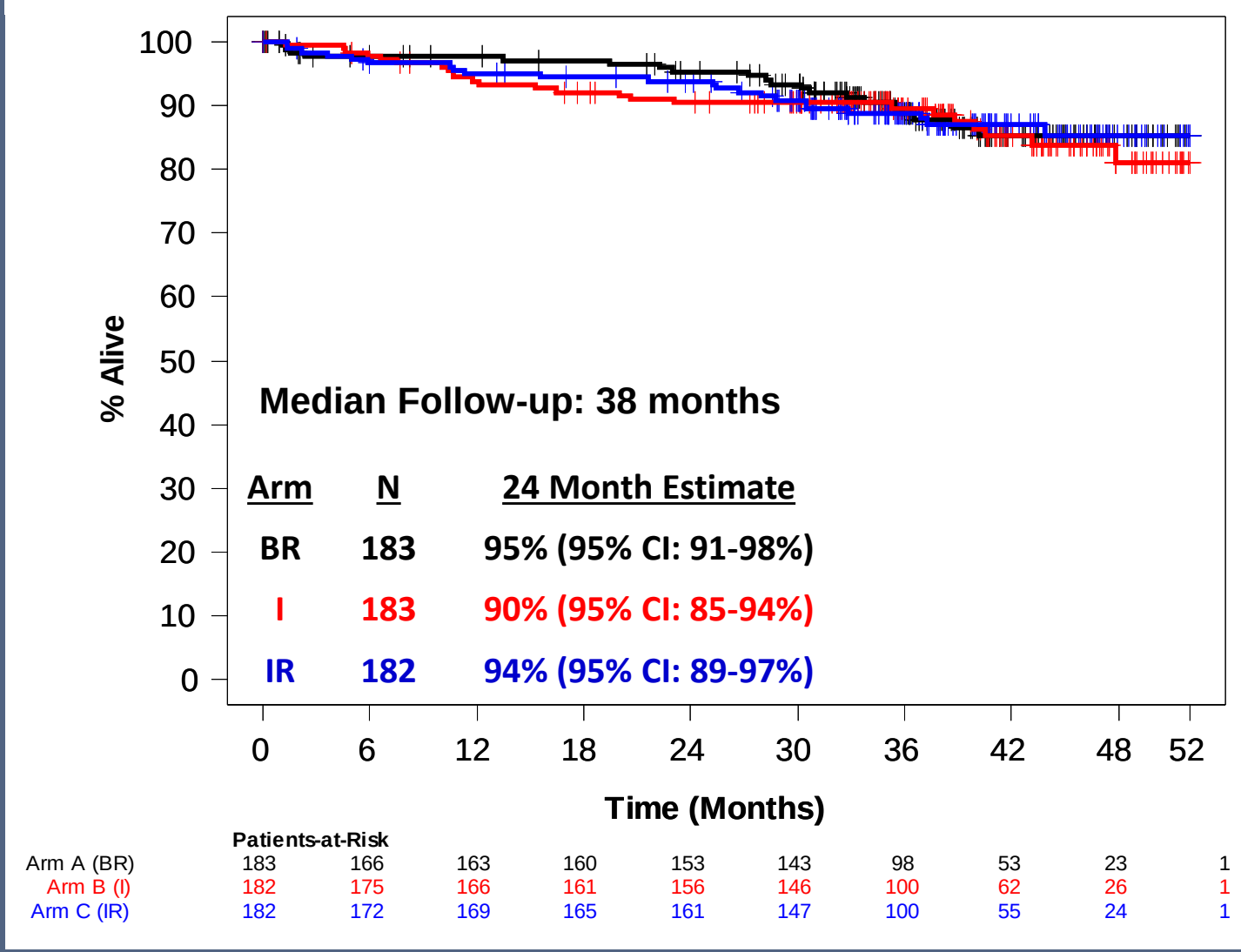
Alliance North American Intergroup Study A041202,

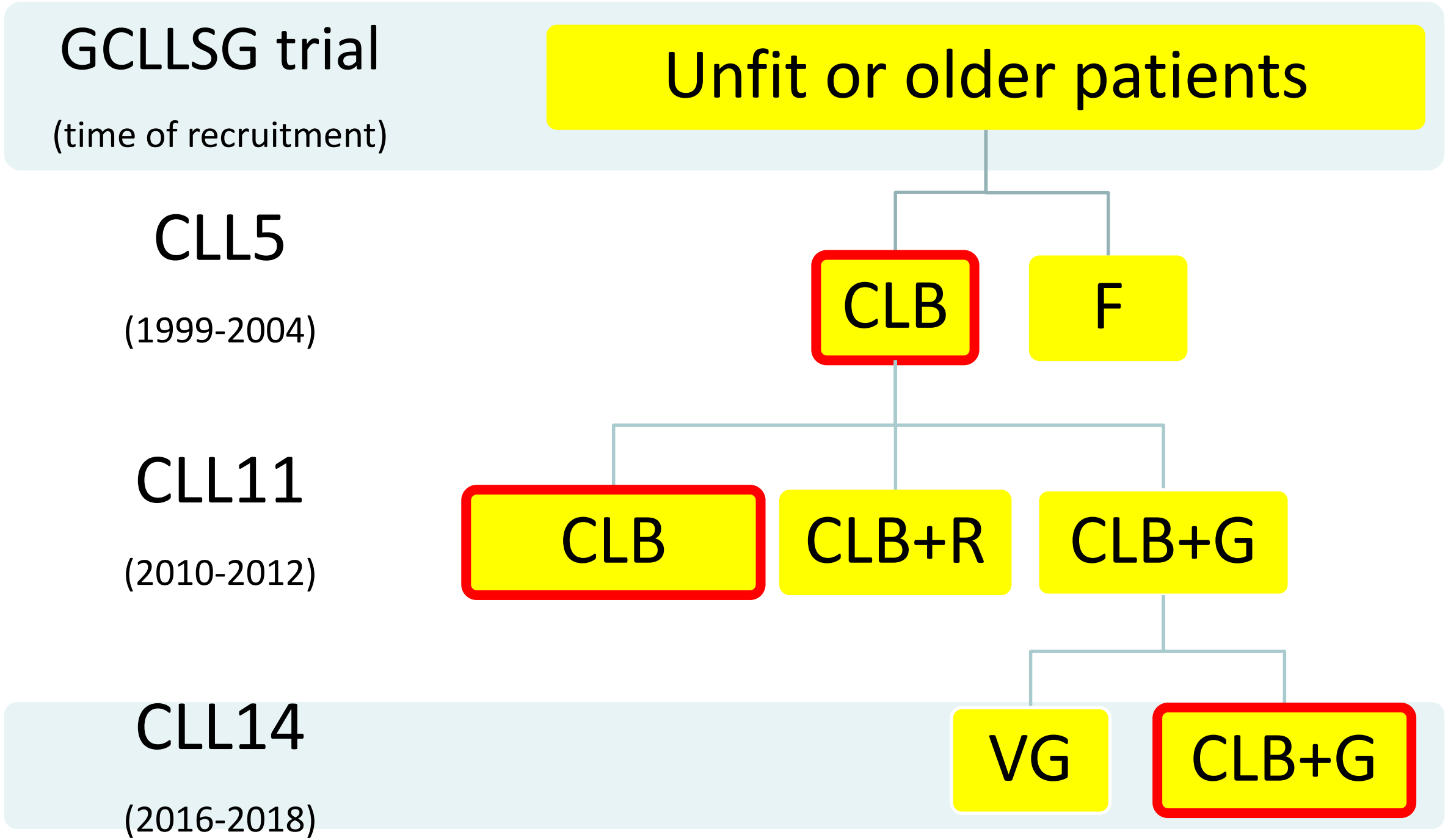
Woyach et al., 2018 (ASH and NEJM)



Overall Survival

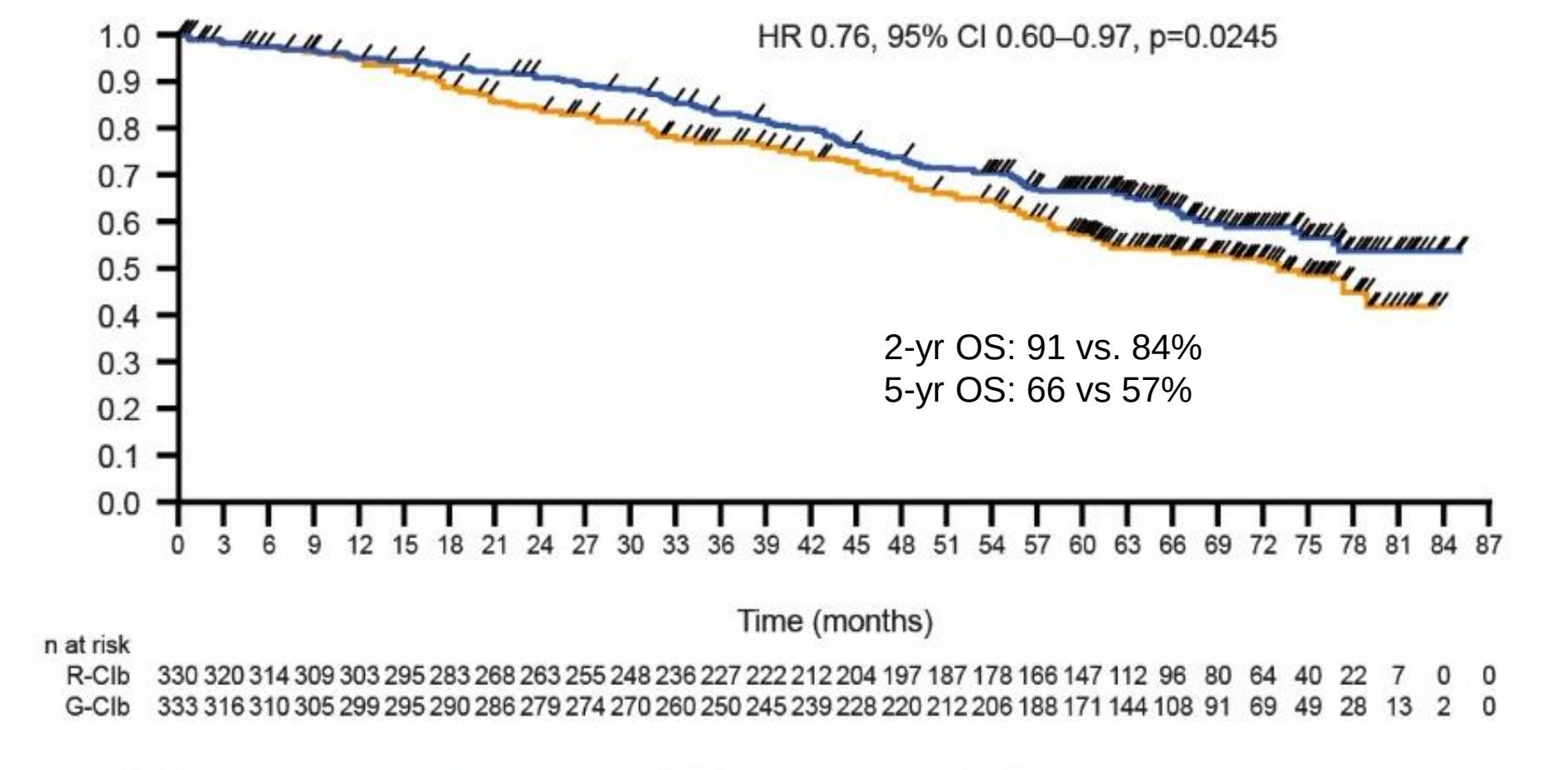
Intention-to-Treat Patient Population



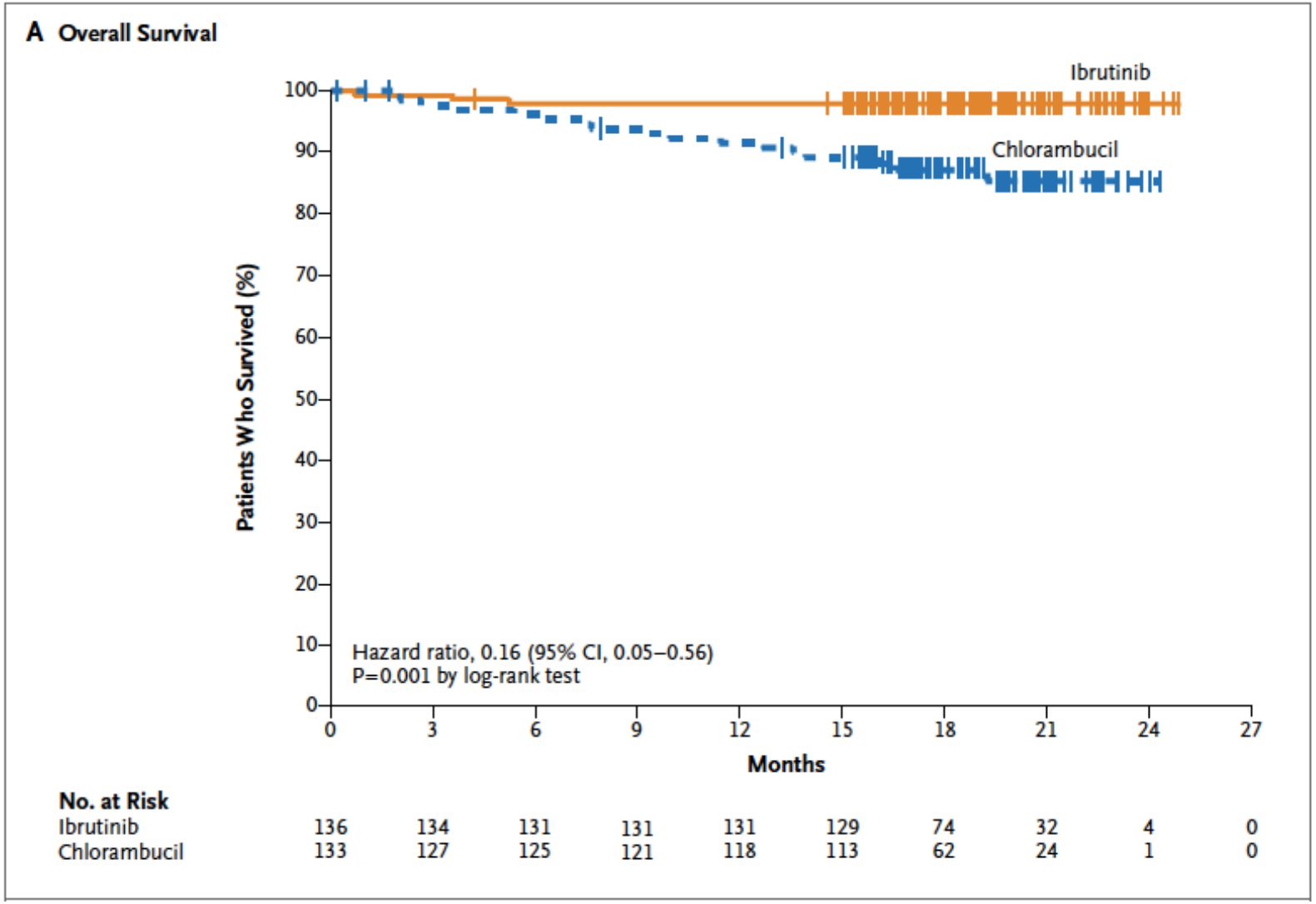

GCLLSG trial
(time of recruitment)
Unfit or older patients
CLL5
(1999-2004)
CLB
F
CLL11
(2010-2012)
CLB
CLB+R
CLB+G
CLL14
(2016-2018)
VG
CLB+G

CLL11: Obinutuzumab improves overall survival compared with rituximab

(Goede et al., update 2018)



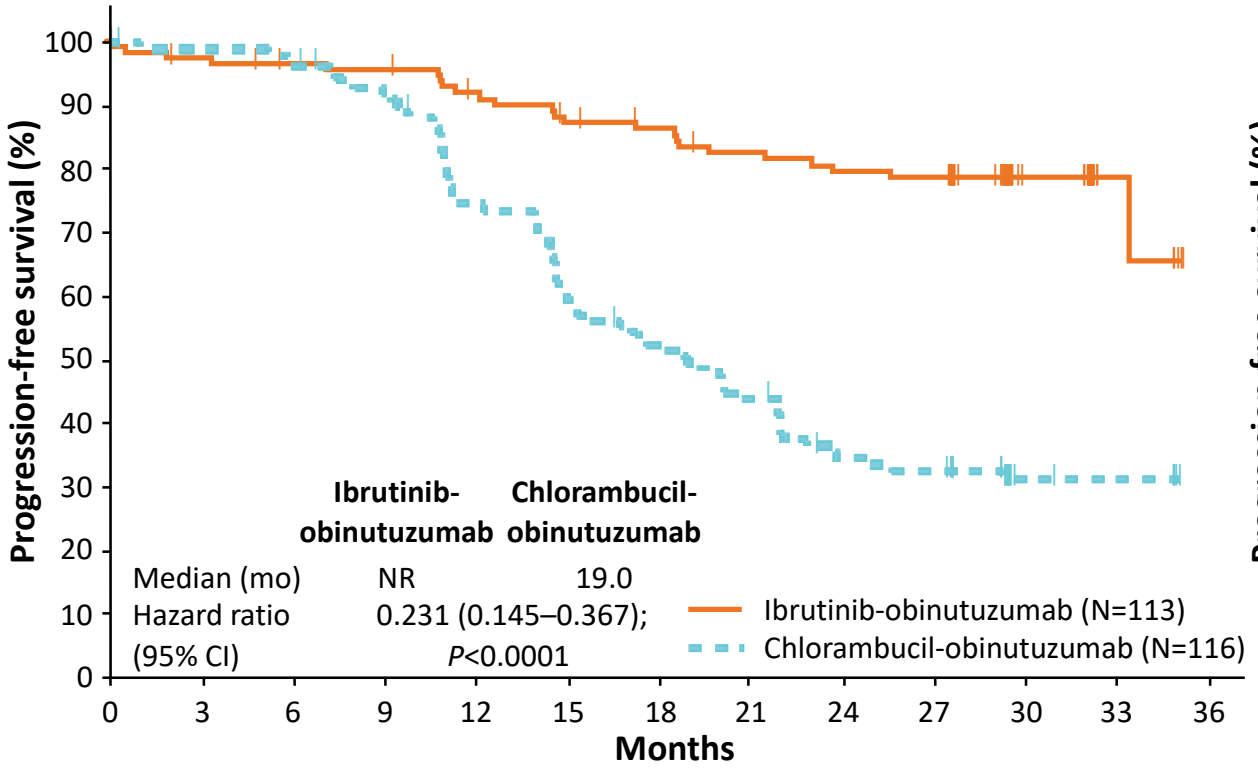
Resonate Trial, Overall Survival



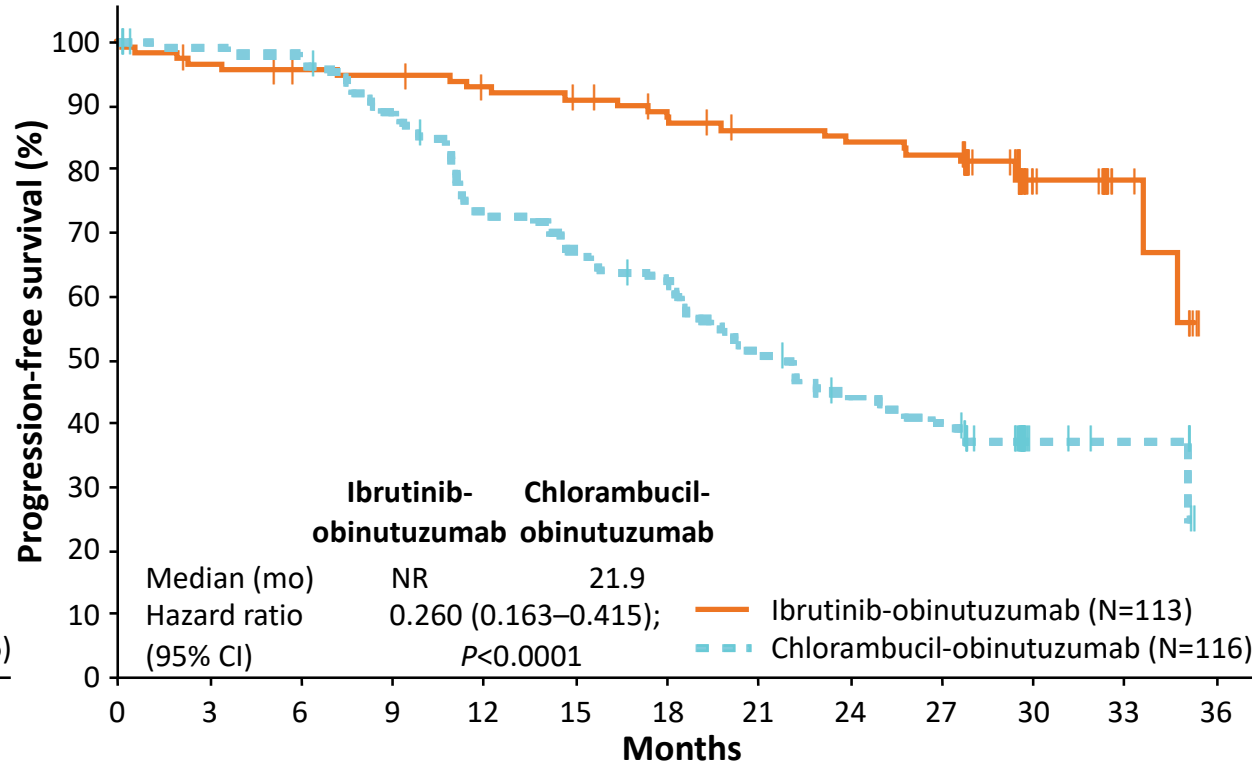
Burger et al., NEJM 273 (25): 2425-37, 2016

iLLUMINATE (PCYC-1130)
Superior Progression-Free Survival with Ibrutinib-Obinutuzumab

IRC Assessment



INV Assessment

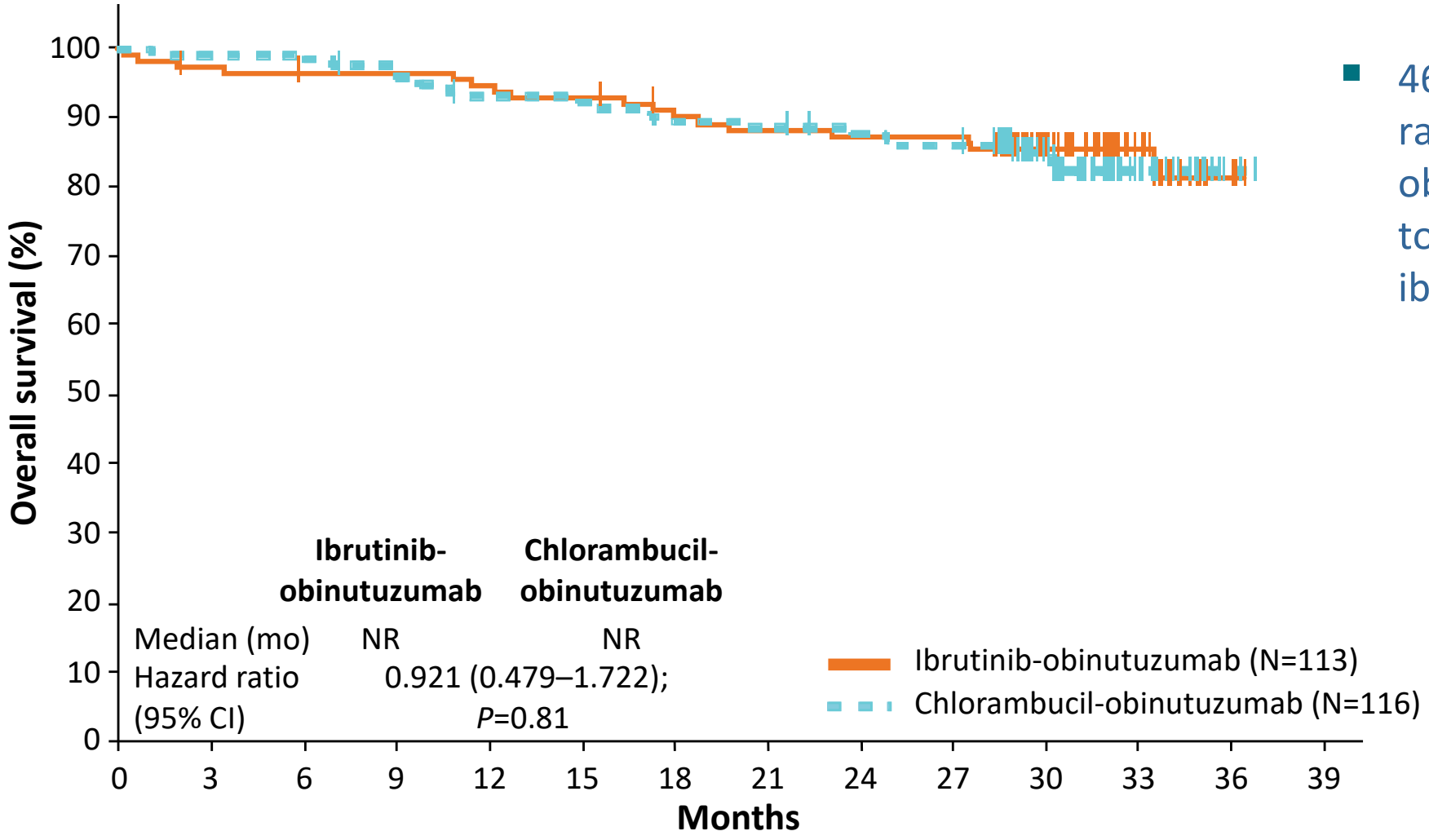


- Median follow-up, 31.3 months (range, 0.2–36.9)
- Estimated PFS at 30 months: 79% with ibrutinib-obinutuzumab vs. 31% with chlorambucil-obinutuzumab
- Even after excluding patients with del(17p): 74% reduction in risk of progression or death with ibrutinib-obinutuzumab

INV, investigator; NR, not reached.

ASH 2018, PCYC-1130; Moreno et al.

Overall Survival with Median 31 Months of Follow-Up

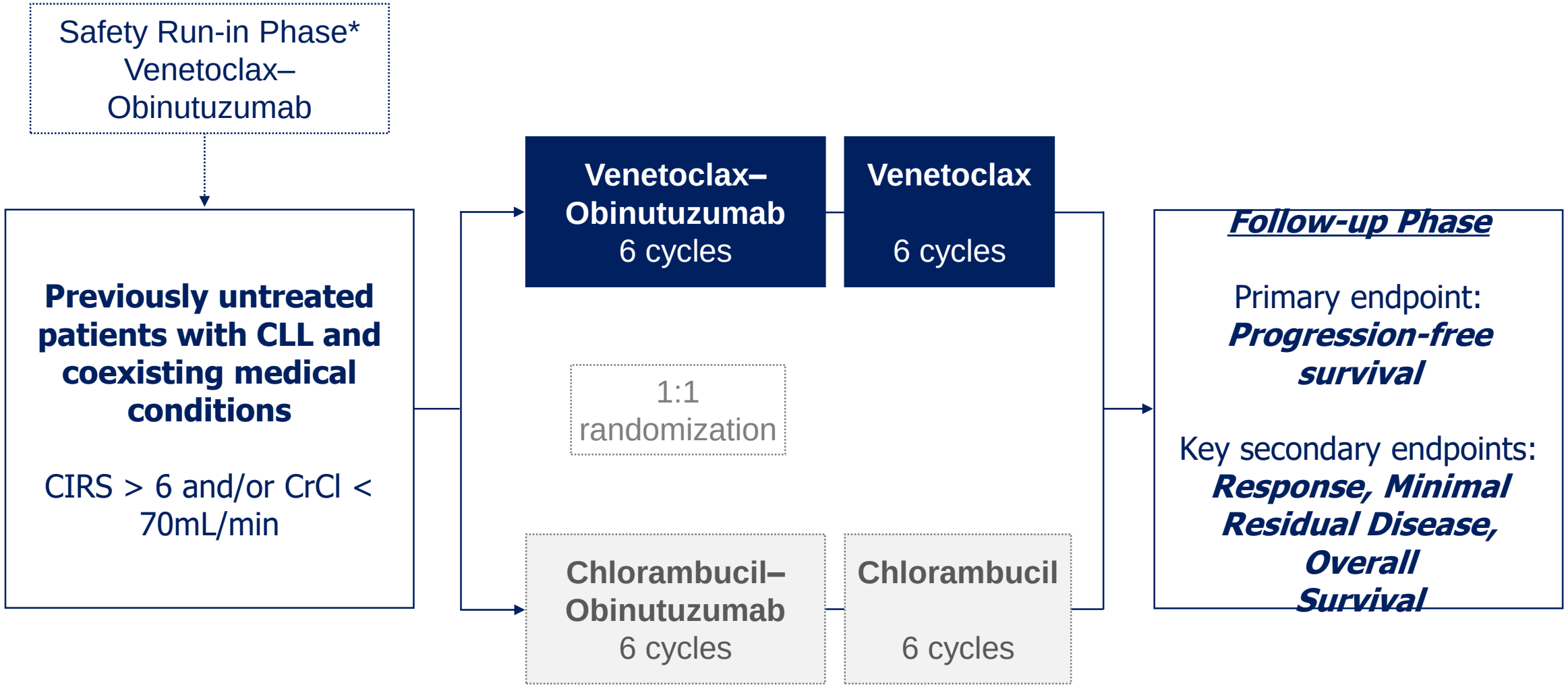


- 46 of 116 patients (40%) randomized to chlorambucil-obinutuzumab crossed over to receive single-agent ibrutinib

ASH 2018, PCYC-1130; Moreno et al.

CLL14 trial: Design

Fischer et al., N Engl J Med 2019; 380:2225-2236

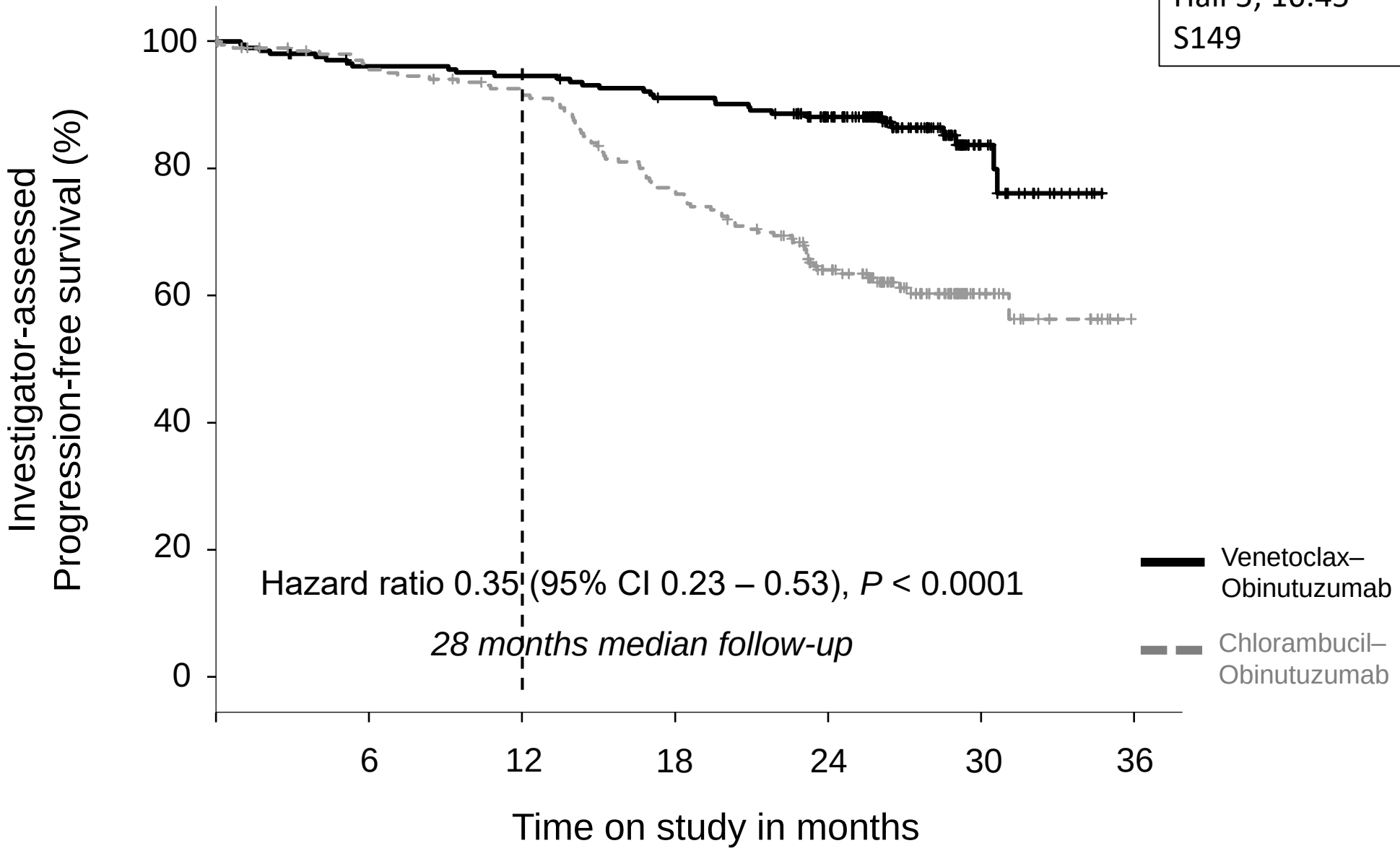


CLL-14

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

Progression-free survival

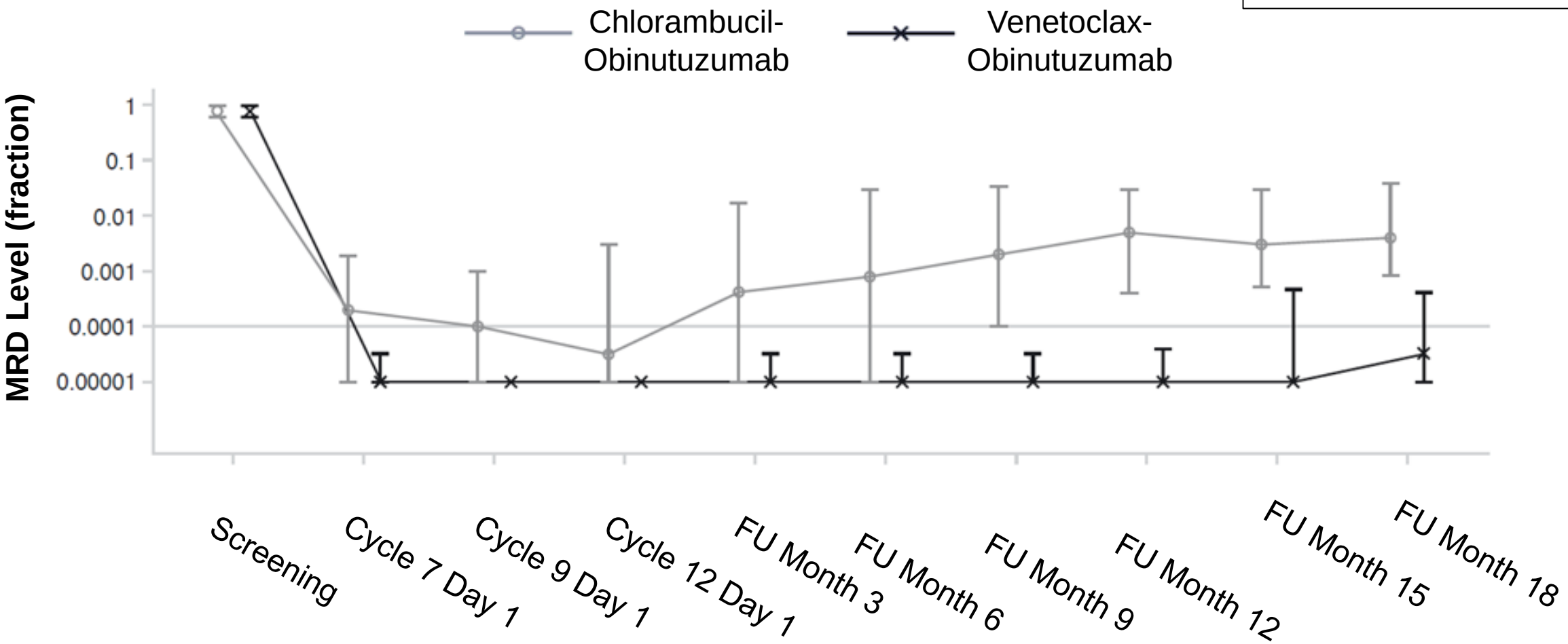
Fischer et al.
Presidential Symposium
Hall 5; 16:45
S149



CLL·14

MRD levels Over time

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



By ASO-PCR in peripheral blood

CLL-14

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).


Round table
discussion

Thank you