UNIKLINIK KÖLN

DEUTSCHE STUDIENGRUPPE

CLL – THERAPIE 2.0

CLEVER UND NEU KOMBINIERT

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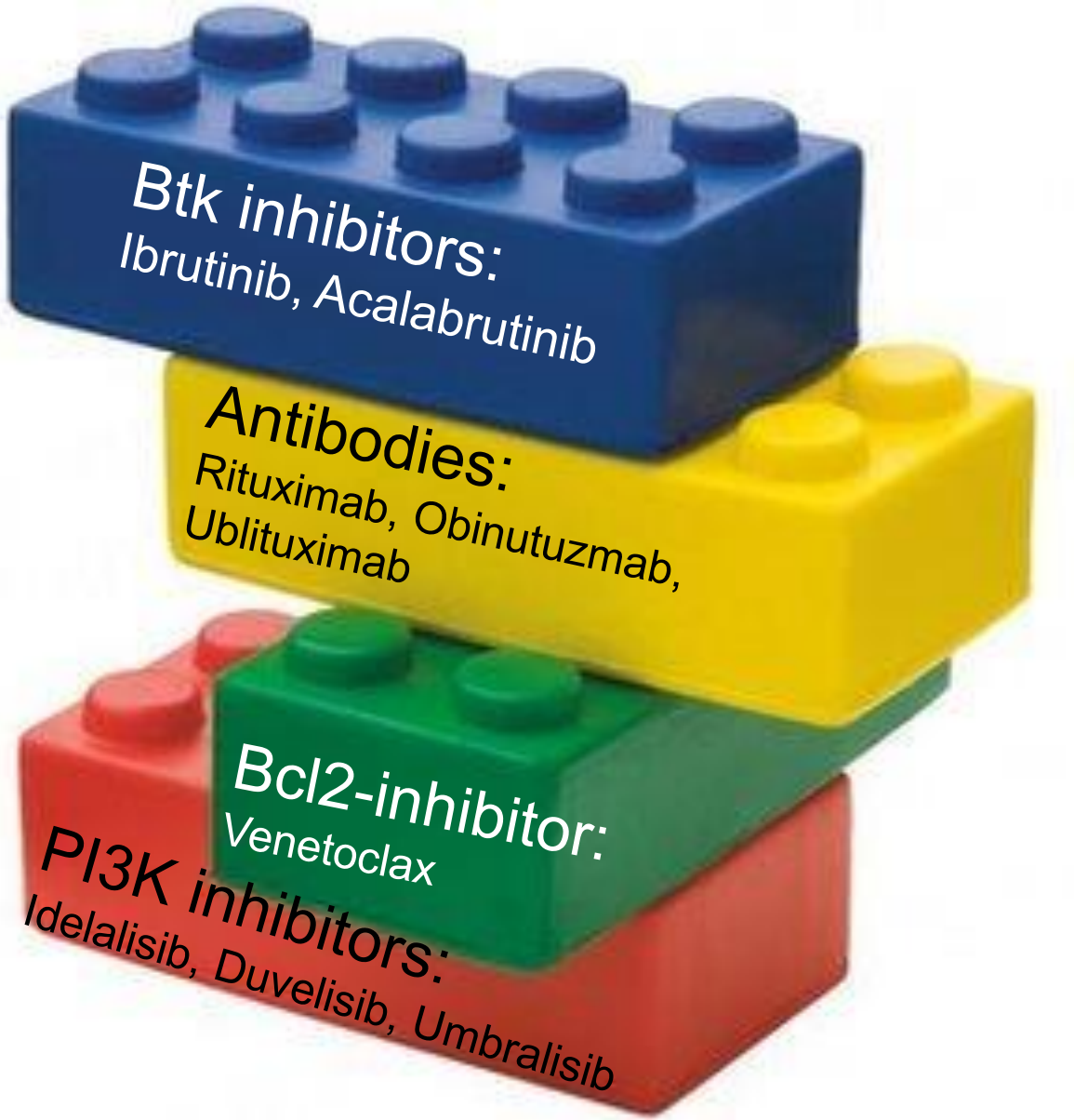
13. Oktober 2019

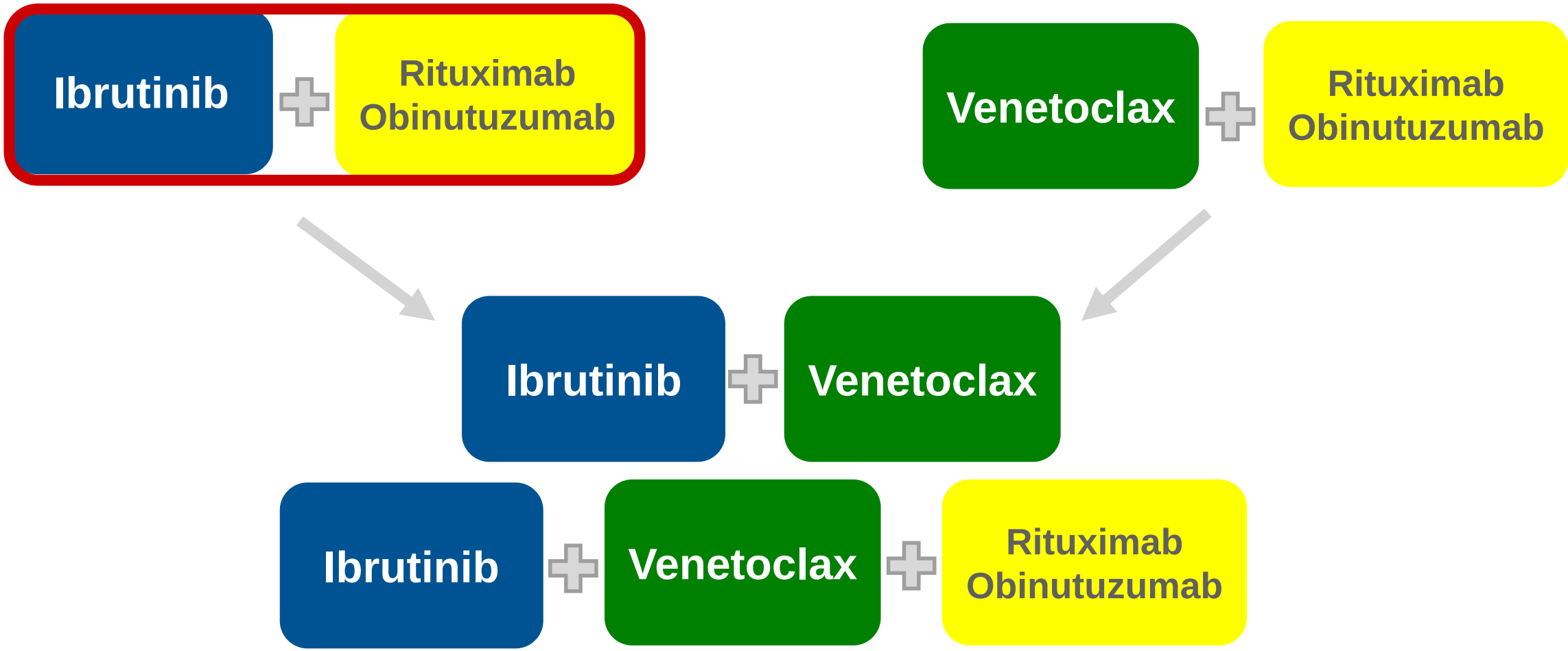
Jahrestreffen der DGHO/ÖGHO/SGHO in Berlin

DISCLOSURES

Name of Company	Research support	Employee	Consultant	Stock-holder	Speaker's Bureau	Advisory Board	Other
Roche	x	---	x	---	x	x	---
Janssen	x	---	x	---	x	x	---
AbbVie	x	---	x	---	x	x	---
Gilead	x	---	x	---	x	x	---
Novartis	--	--	x	--	x	x	--
Celgene	--	--	--	--	x	x	--
AstraZeneca	--	--	--	--	--	x	--
Arqule	--	--	--	--	-	x	


Btk inhibitors:
Ibrutinib, Acalabrutinib
Antibodies:
Rituximab, Obinutuzmab,
Ublituximab
Bcl2-inhibitor:
Venetoclax
PI3K inhibitors:
Idelalisib, Duvelisib, Umbralisib

ERGEBNISSE AUS STUDIEN ZU CHEMOTHERAPIE-FREIEN KOMBINATIONSTHERAPIEN

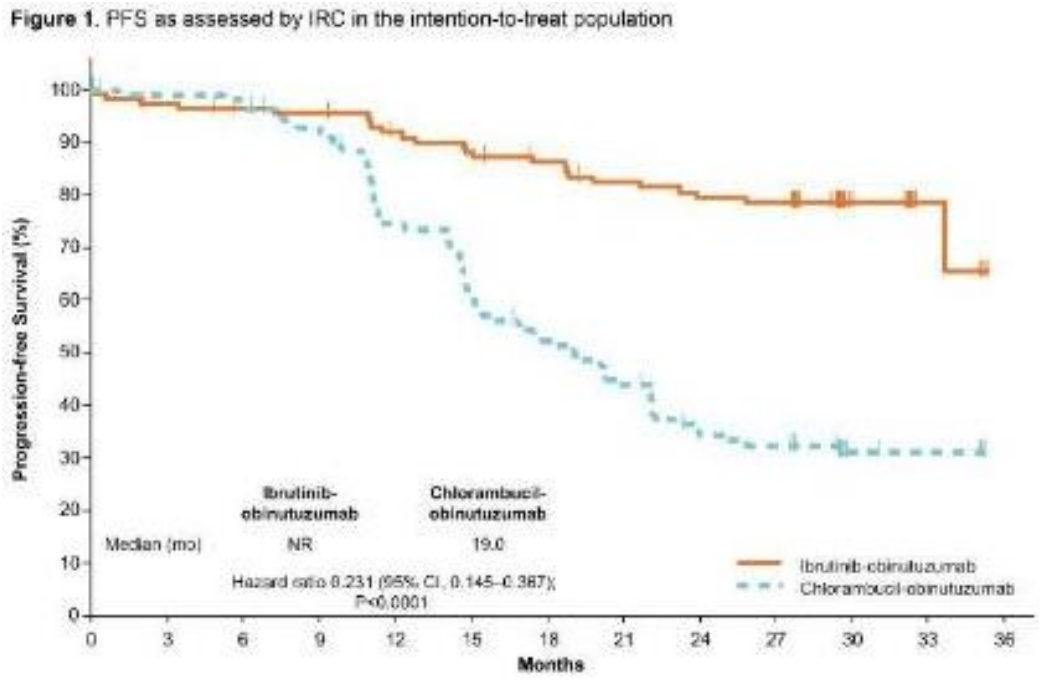


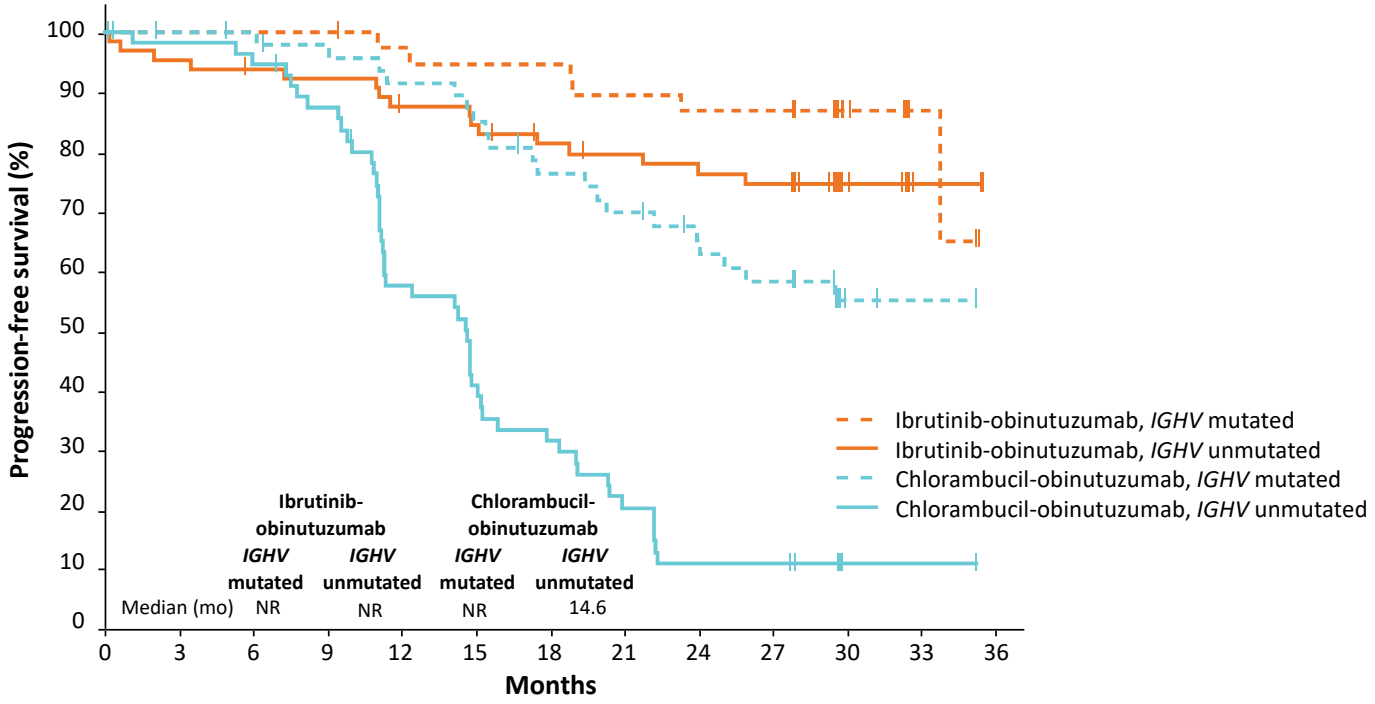
PHASE III STUDIEN: ERSTLINIE IBRUTINIB+CD20-ANTIKÖRPER VS CIT

Trial	Arms	N Pts	Median age	% TP53mut/del
iLLUMINATE	Clb + Obinutuzumab	116	72	20%
	Ibrutinib+Obinutuzumab	113	70	16%
Alliance	BR	183	70	9%
	Ibrutinib	182	71	12%
	Ibrutinib + Rituximab	182	71	12%
ECOG-ACRIN E1912	FCR	175	58	0%
	Ibrutinib + Rituximab	345	57	0%

C. Moreno et al., Lancet Oncol 2018
J. Woyach et al., NEJM 2018
T. Shanafelt et al., NEJM 2019

ILLUMINATE: PFS LÄNGER MIT IBRUTINIB + OBINUTUZUMAB

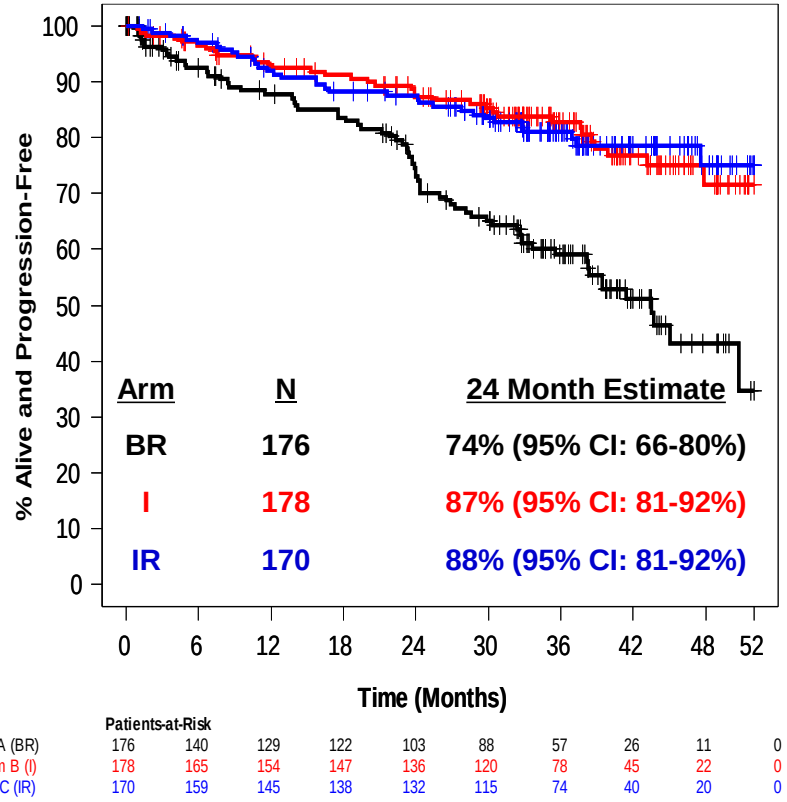




C. Moreno et al., Lancet Oncol 2018

ALLIANCE BR VS IBRUTINIB MONO VS IBRUTINIB + RITUXIMAB: PFS

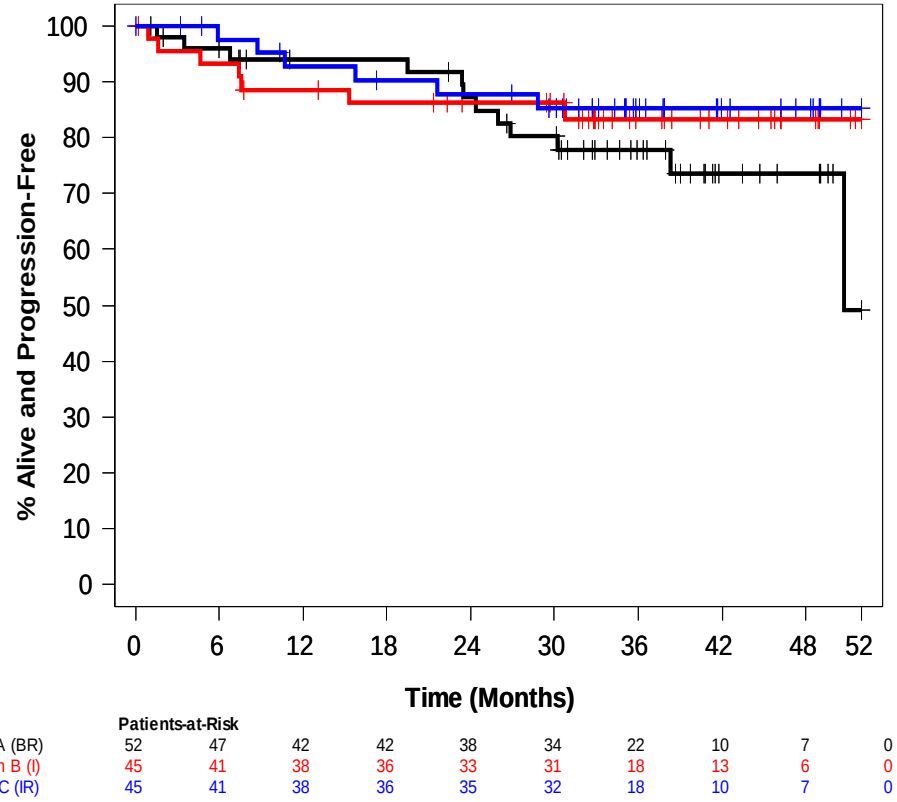
PFS alle Patienten



Patients-at-Risk

Arm A (BR)	176	140	129	122	103	88	57	26	11	0
Arm B (I)	178	165	154	147	136	120	78	45	22	0
Arm C (IR)	170	159	145	138	132	115	74	40	20	0

PFS Patienten mit mutiertem IGHV

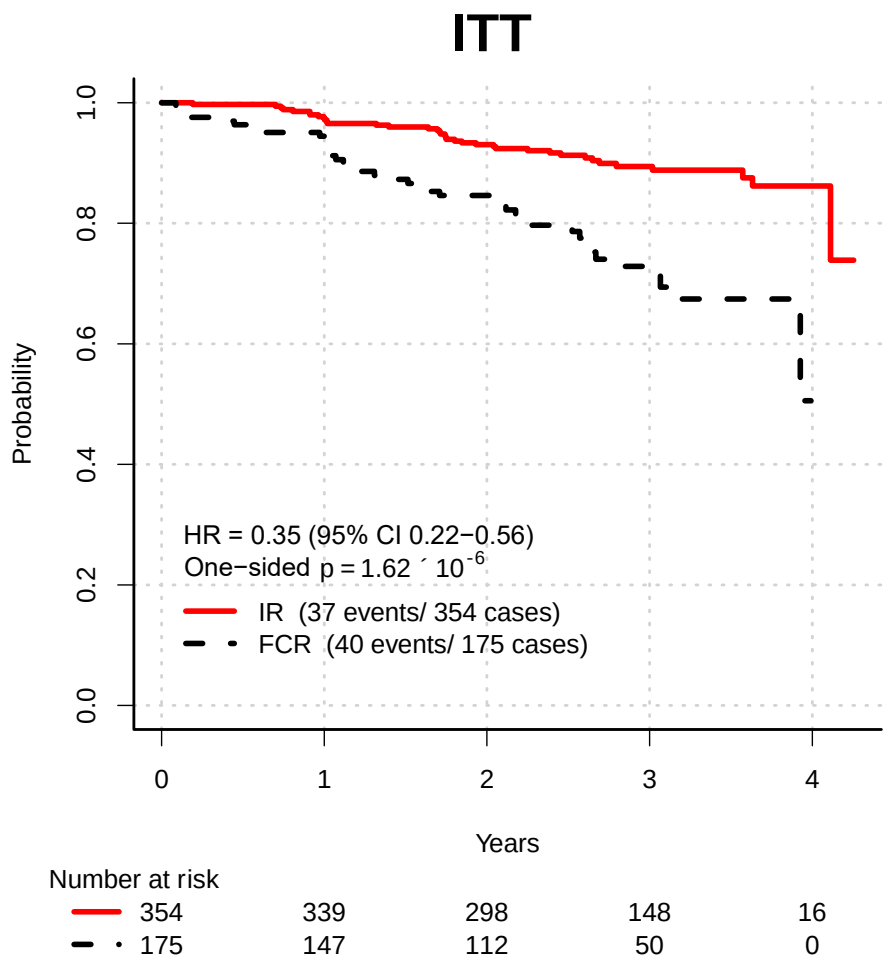


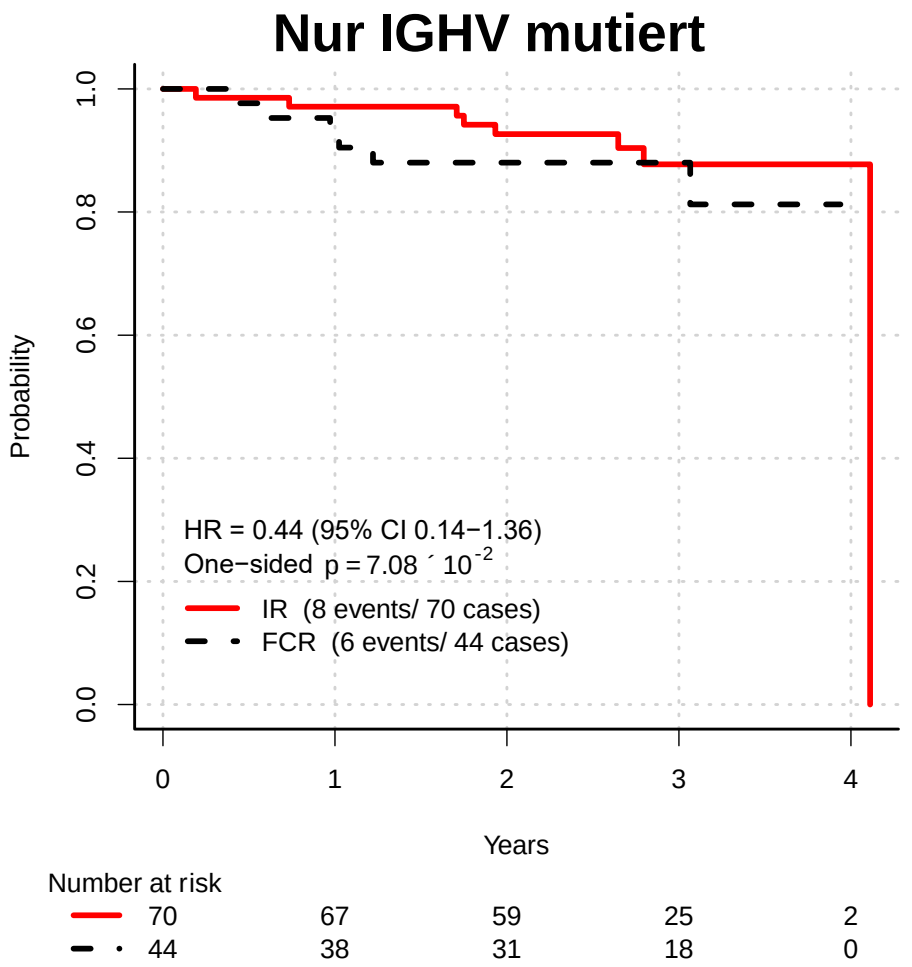
Patients-at-Risk

Arm A (BR)	52	47	42	42	38	34	22	10	7	0
Arm B (I)	45	41	38	36	33	31	18	13	6	0
Arm C (IR)	45	41	38	36	35	32	18	10	7	0

J. Woyach et al., NEJM 2018

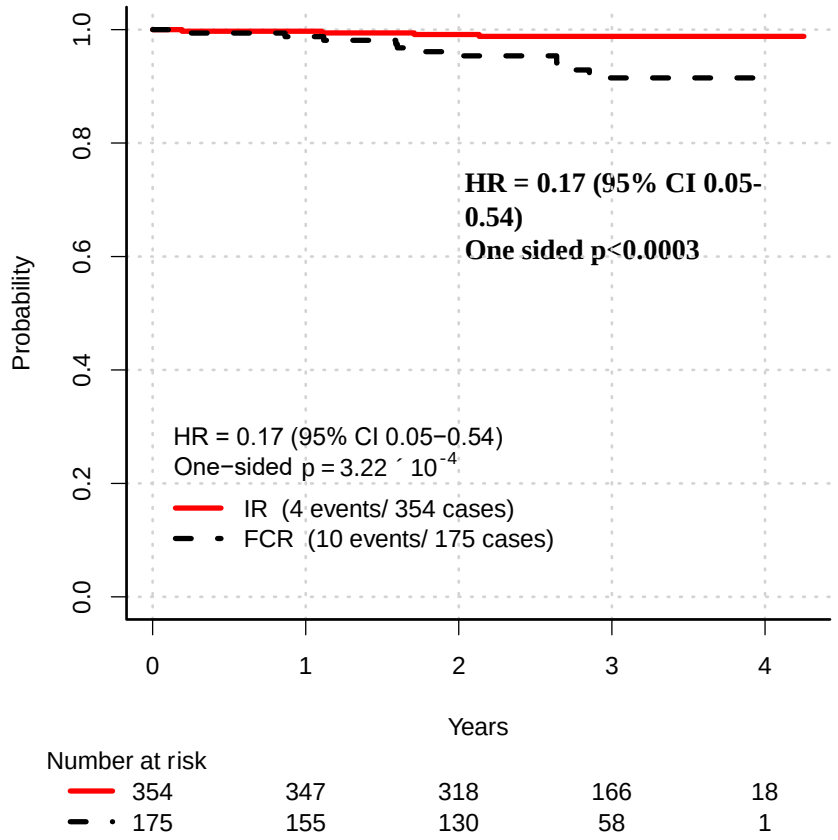
ECOG/ACRIN E1912: IBRUTINIB+RITUXIMAB VS FCR PROGRESSION-FREE SURVIVAL





T. Shanafelt et al., NEJM 2019

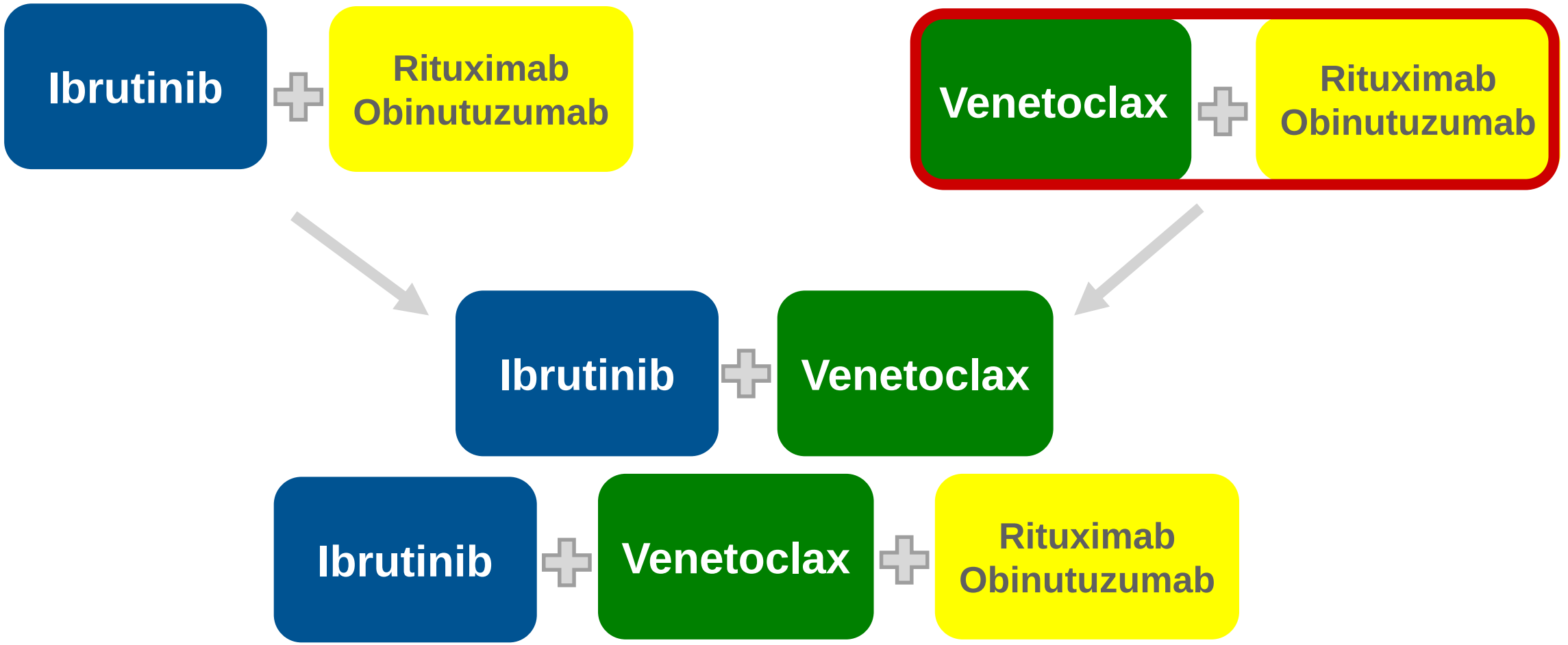
ECOG/ACRIN E1912
OVERALL SURVIVAL



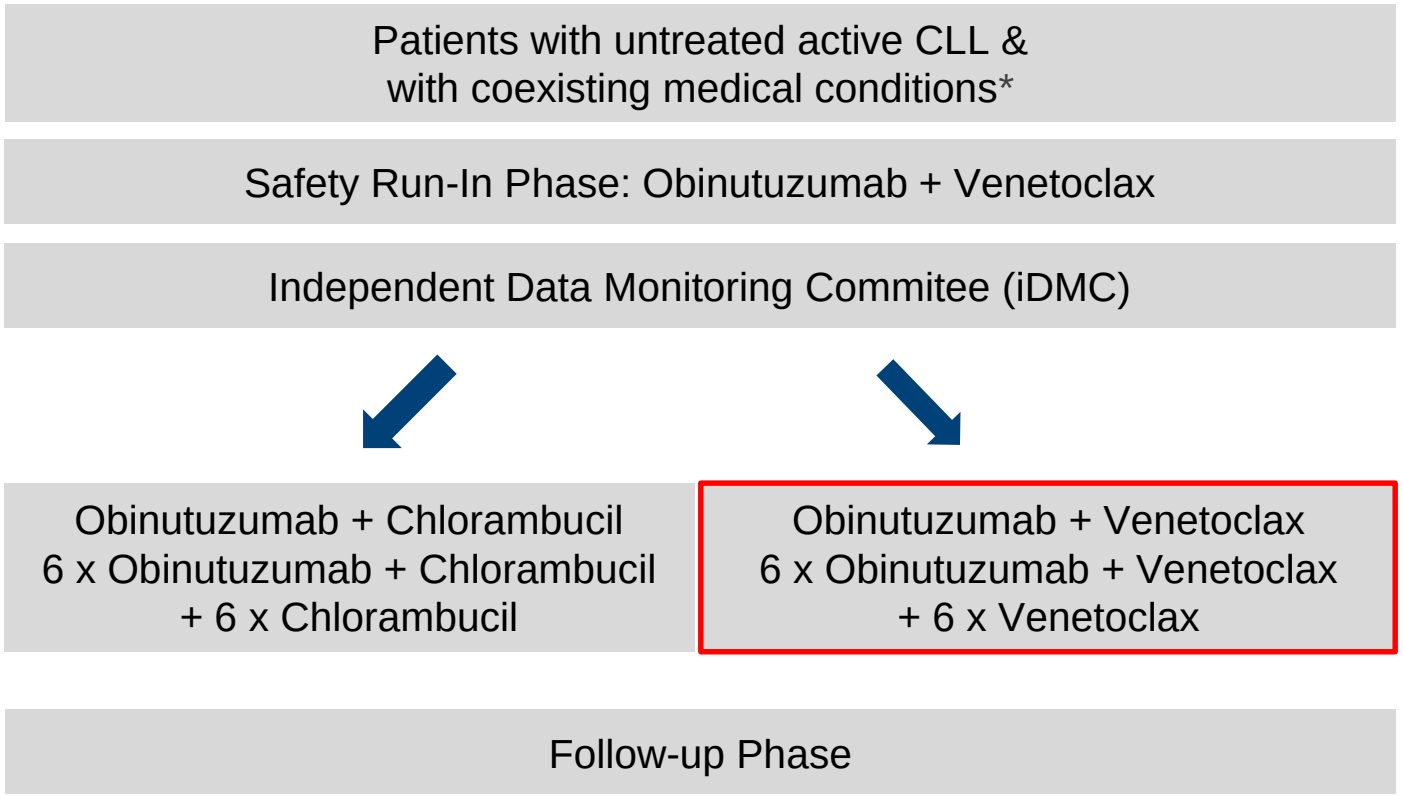
Cause of Death	IR n=354	FCR n=175
CLL	1	4
Unexplained/unwitnessed	1	-
Secondary cancer	1	4 (2 AML)
Infection	1	1
Drug overdose	0	1
TOTAL	4	10

T. Shanafelt et al., NEJM 2019

ERGEBNISSE AUS STUDIEN ZU CHEMOTHERAPIE-FREIEN KOMBINATIONSTHERAPIEN

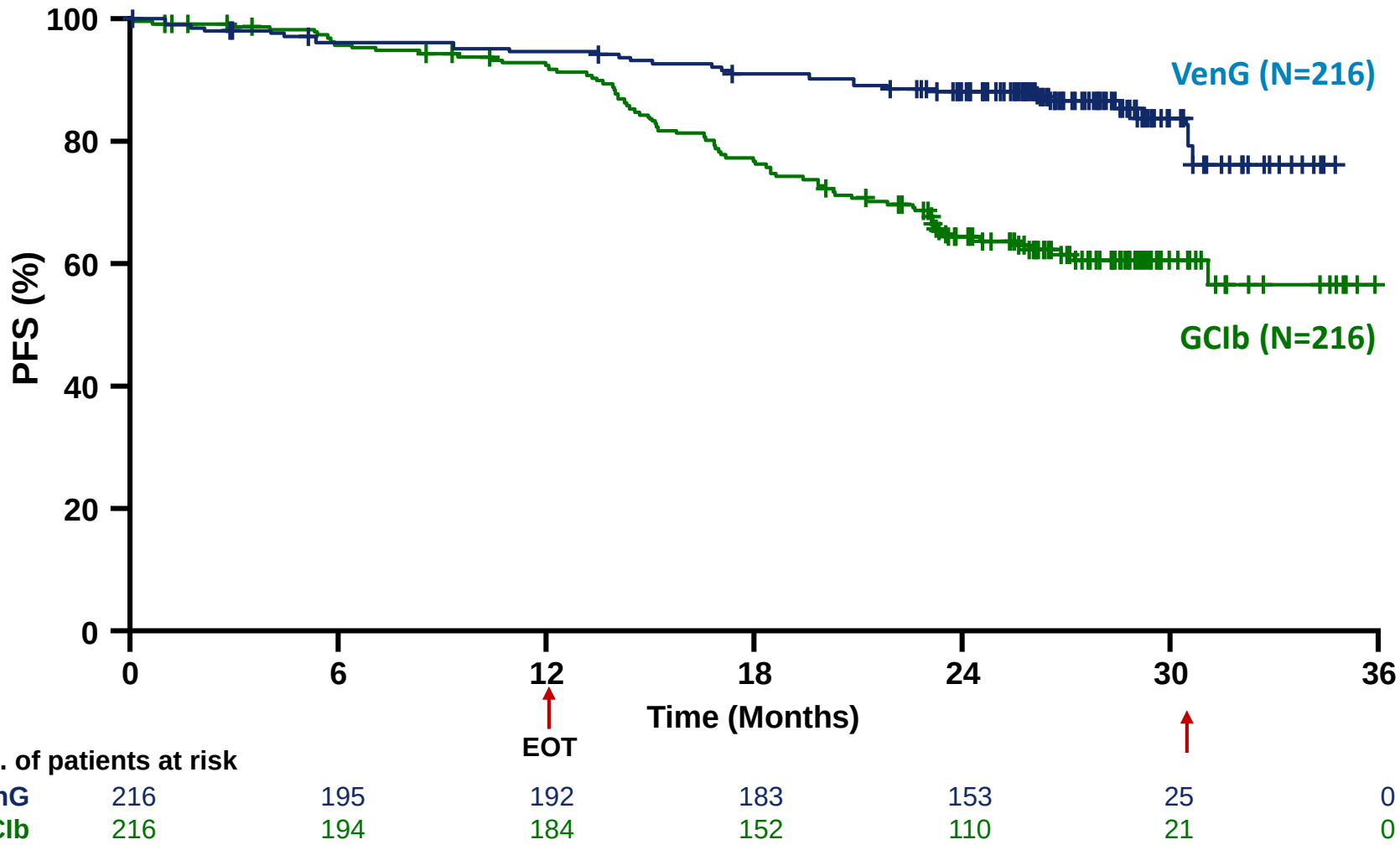


CLL 14 DESIGN



K. Fischer et al., NEJM 2019

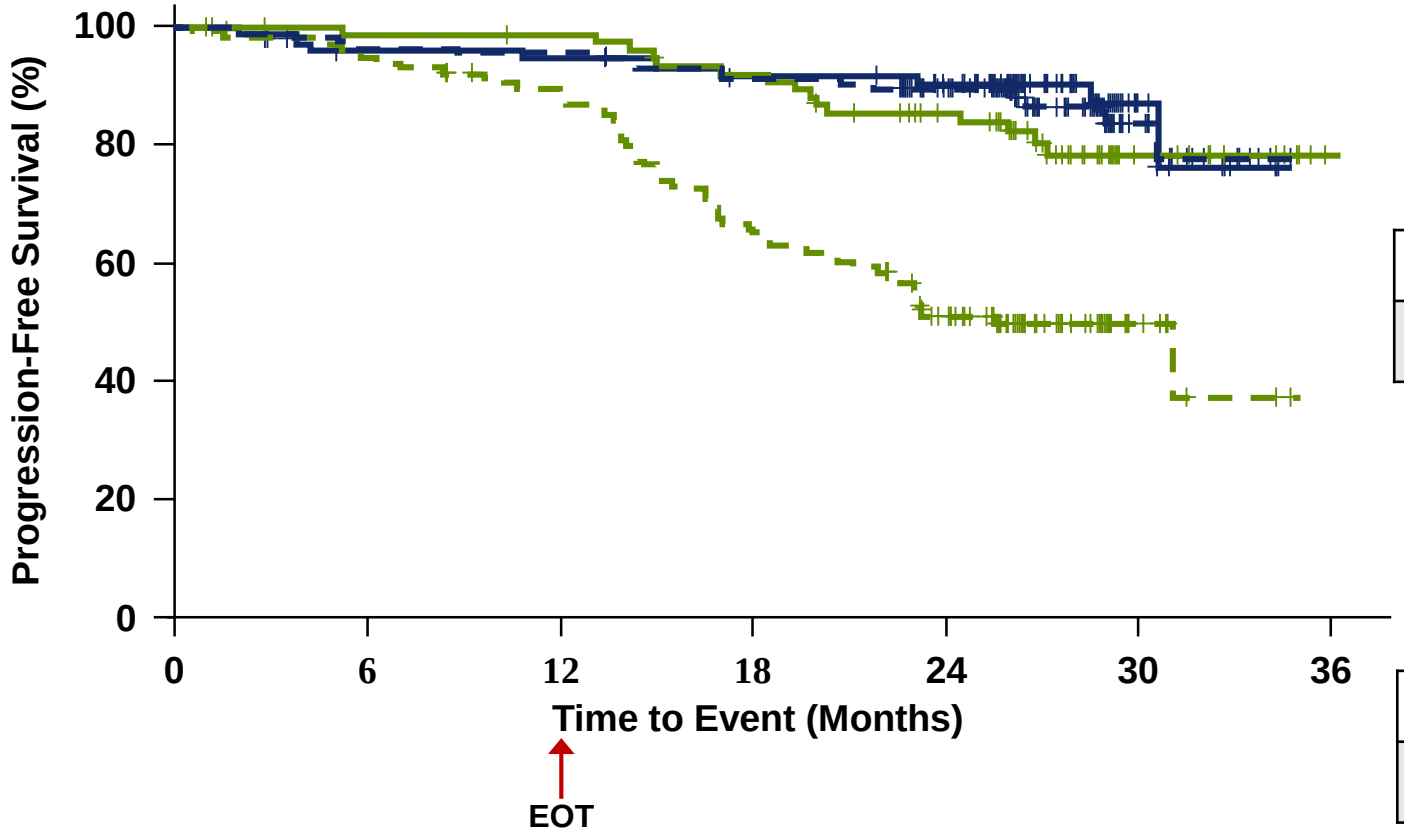
CLL14: PFS



	VenG (N=216)	GClb (N=216)
Events, n (%)	30† (13.9)	77‡ (35.6)
HR (95% CI)	0.35 (0.23–0.53)	
Stratified p-value	**P<0.0001**	
Pre-specified IA boundary	**P=0.0009**	
PFS 1 Year (%)	94.62	92.11
PFS 2 Year (%)	88.15	64.10

K. Fischer et al., NEJM 2019

CLL14: PFS NACH IGHV MUTATIONS-STATUS



Patients at risk

VenG *IGHV* mutated	76	69	68	66	62	9	0
VenG *IGHV* unmutated	121	110	109	102	87	16	0
GClb *IGHV* mutated	83	77	76	70	56	12	0
GClb *IGHV* unmutated	123	109	100	74	50	8	0

***IGHV* mutated**

VenG — GClb

	VenG (n=76)	GClb (n=83)
Events, n (%)	9 (11.8)	15 (18.1)
HR (95% CI)	0.64 (0.28–1.46)	

***IGHV* unmutated**

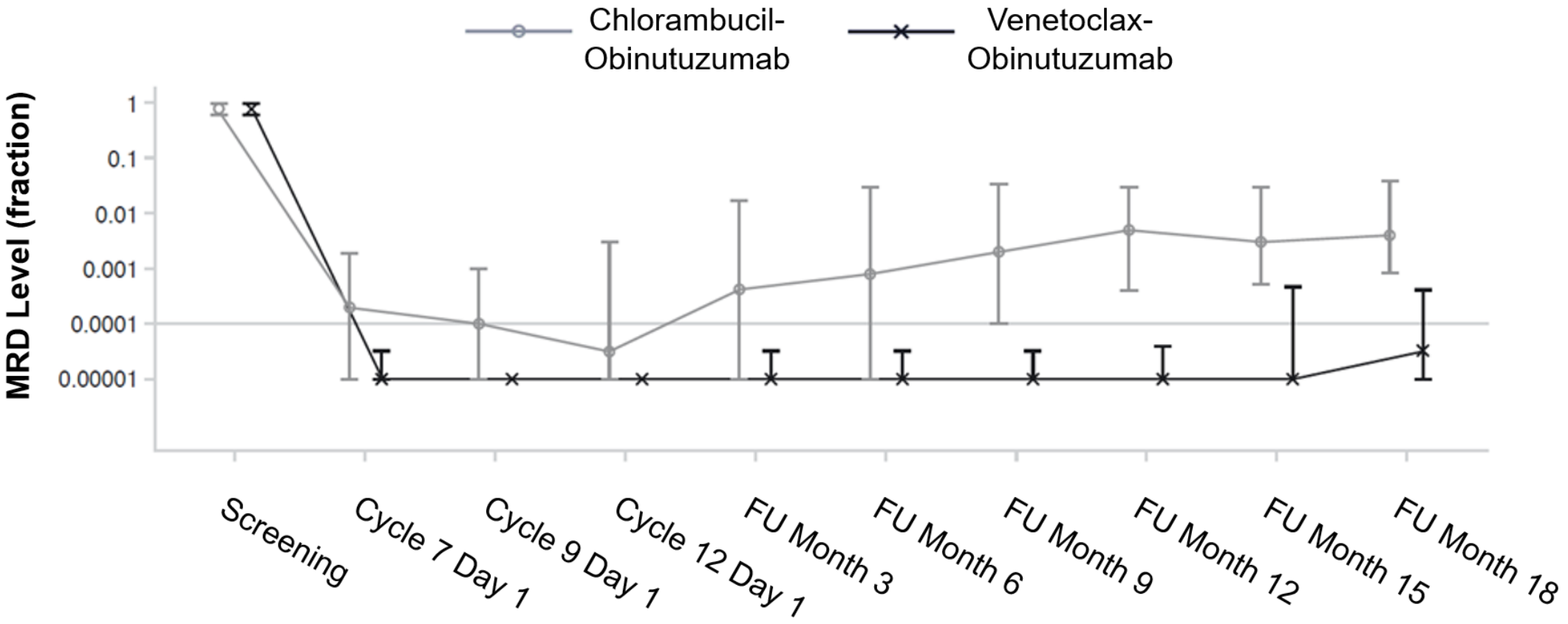
VenG - - - GClb

	VenG (n=121)	GClb (n=123)
Events, n (%)	16 (13.2)	57 (46.3)
HR (95% CI)	0.22 (0.12–0.38)	

K. Fischer et al., NEJM 2019

CLL14-STUDIE: MRD

MRD mit ASO-PCR gemessen



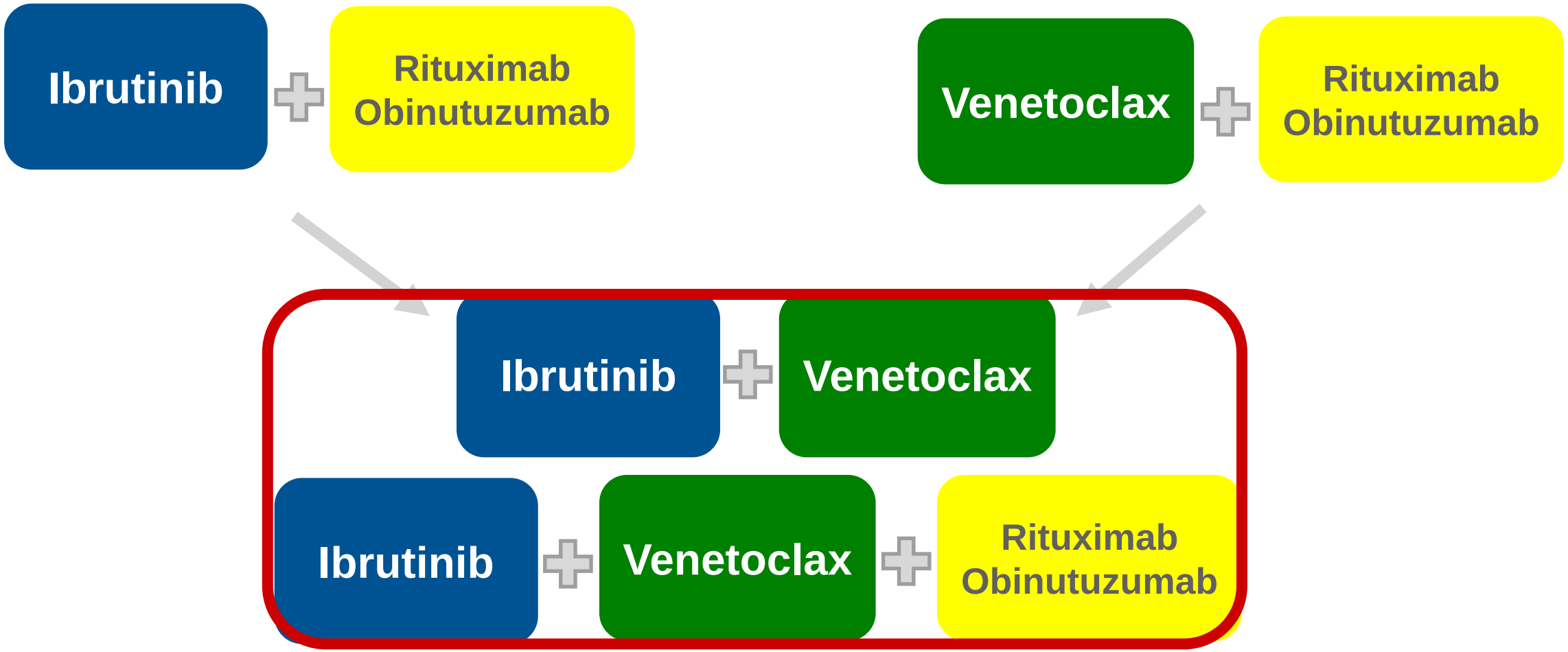
K. Fischer et al., NEJM 2019

CLL14-STUDIE: GRAD 3&4 AES

n, (%)	VenG (N=212)	GClb (N=214)
Blood and lymphatic system disorders		
Neutropenia†‡	112 (52.8)	103 (48.1)
Thrombocytopenia	29 (13.7)	32 (15.0)
Anemia	17 (8.0)	14 (6.5)
Febrile neutropenia†	11 (5.2)	8 (3.7)
Leukopenia	5 (2.4)	10 (4.7)
Infections and infestations†		
Pneumonia	9 (4.2)	8 (3.7)
Injury, poisoning and procedural complications		
Infusion-related reaction	19 (9.0)	22 (10.3)
Investigations		
Neutrophil count decreased	9 (4.2)	10 (4.7)
Aspartate aminotransferase increased	5 (2.4)	7 (3.3)
Alanine aminotransferase increased	4 (1.9)	7 (3.3)
Metabolism and nutritional disorders		
Hyperglycemia	8 (3.8)	3 (1.4)
Gastrointestinal disorders		
Diarrhea	9 (4.2)	1 (0.5)

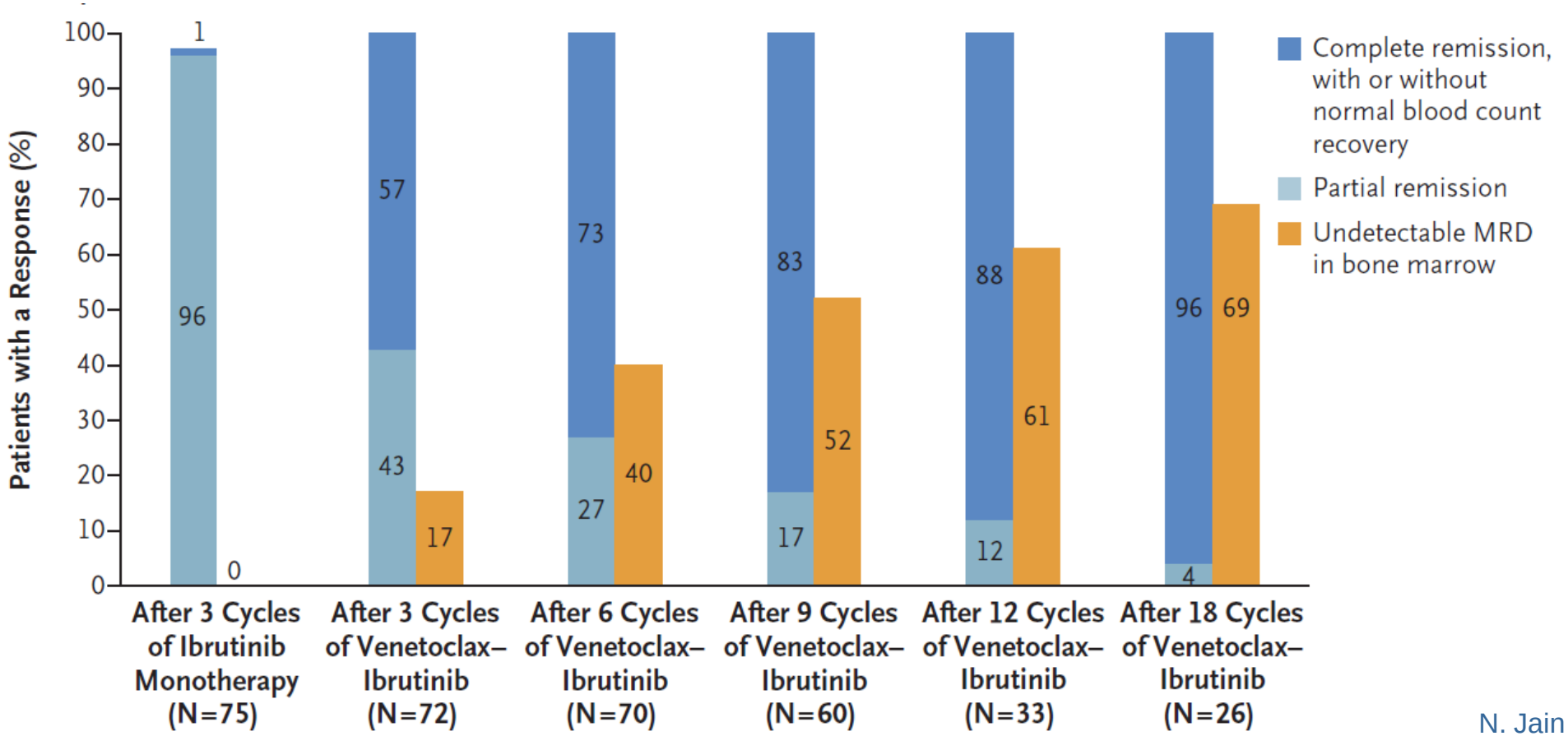
K. Fischer et al., NEJM 2019

ERGEBNISSE AUS STUDIEN ZU CHEMOTHERAPIE-FREIEN KOMBINATIONSTHERAPIEN



IBRUTINIB PLUS VENETOCLAX: HOHE RATEN NICHT-NACHWEISBARER MRD

Phase II-Studie: Erstlinie



N. Jain et al., NEJM 2019

CLL2-GIVE – STUDY DESIGN

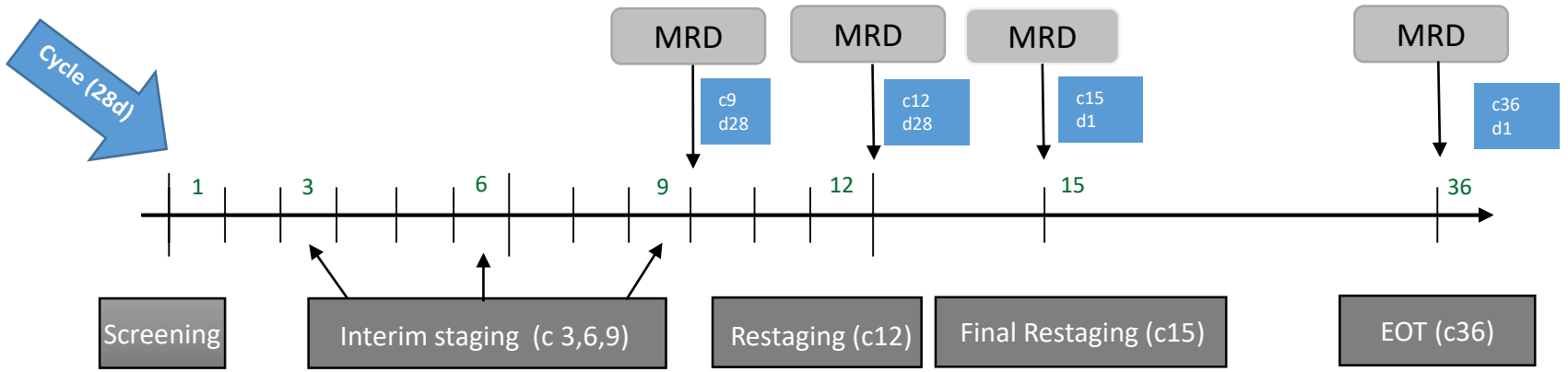
DEUTSCHE STUDIENGRUPPE

Induction therapy → **Consolidation** → **Maintenance therapy**

Obinutuzumab (C 1-6)

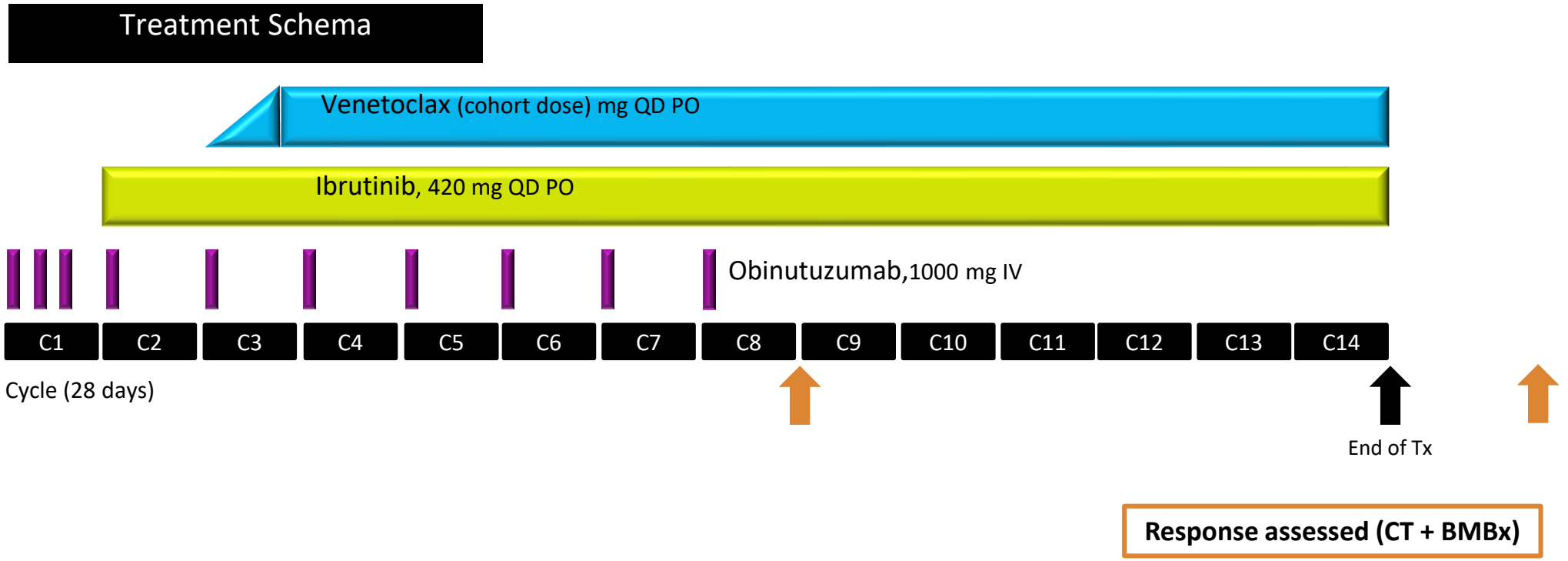
Venetoclax (Cycle 1 (d22) / 2-12)

Ibrutinib (Cycle 1-36)
[stop at cycle 15, in case of CR / CRi (iwCLL criteria) **and** MRD negativity after cycle 9 and 12]



DREIFACHKOMBINATION: OBINUTUZUMAB+IBRUTINIB+VENETOCLAX IN DER R/R CLL

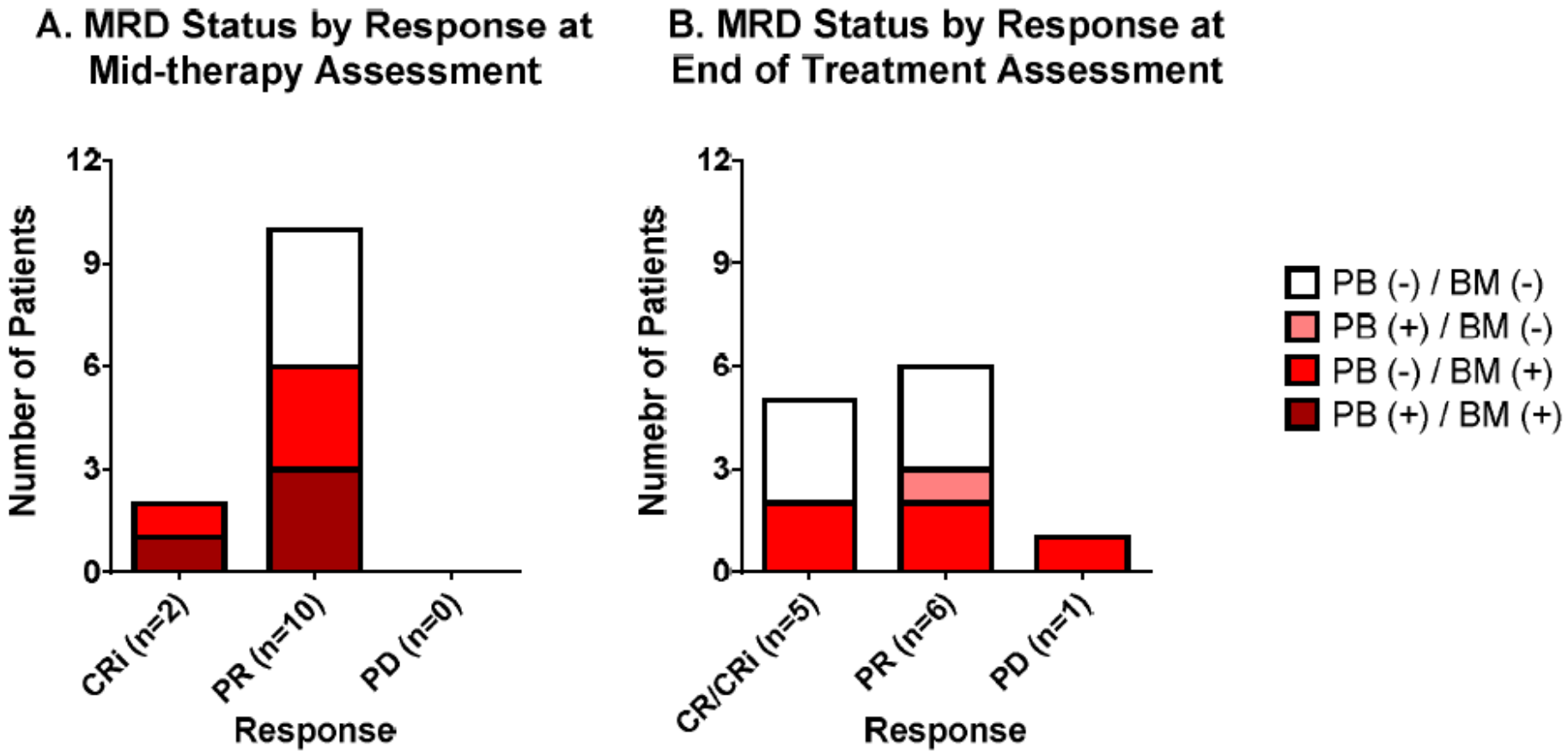
Phase Ib Studie bei der R/R CLL in 12 Patienten



K. Rogers et al., Blood 2018

DREIFACHKOMBINATION: OBINUTUZUMAB+IBRUTINIB+VENETOCLAX IN DER R/R CLL

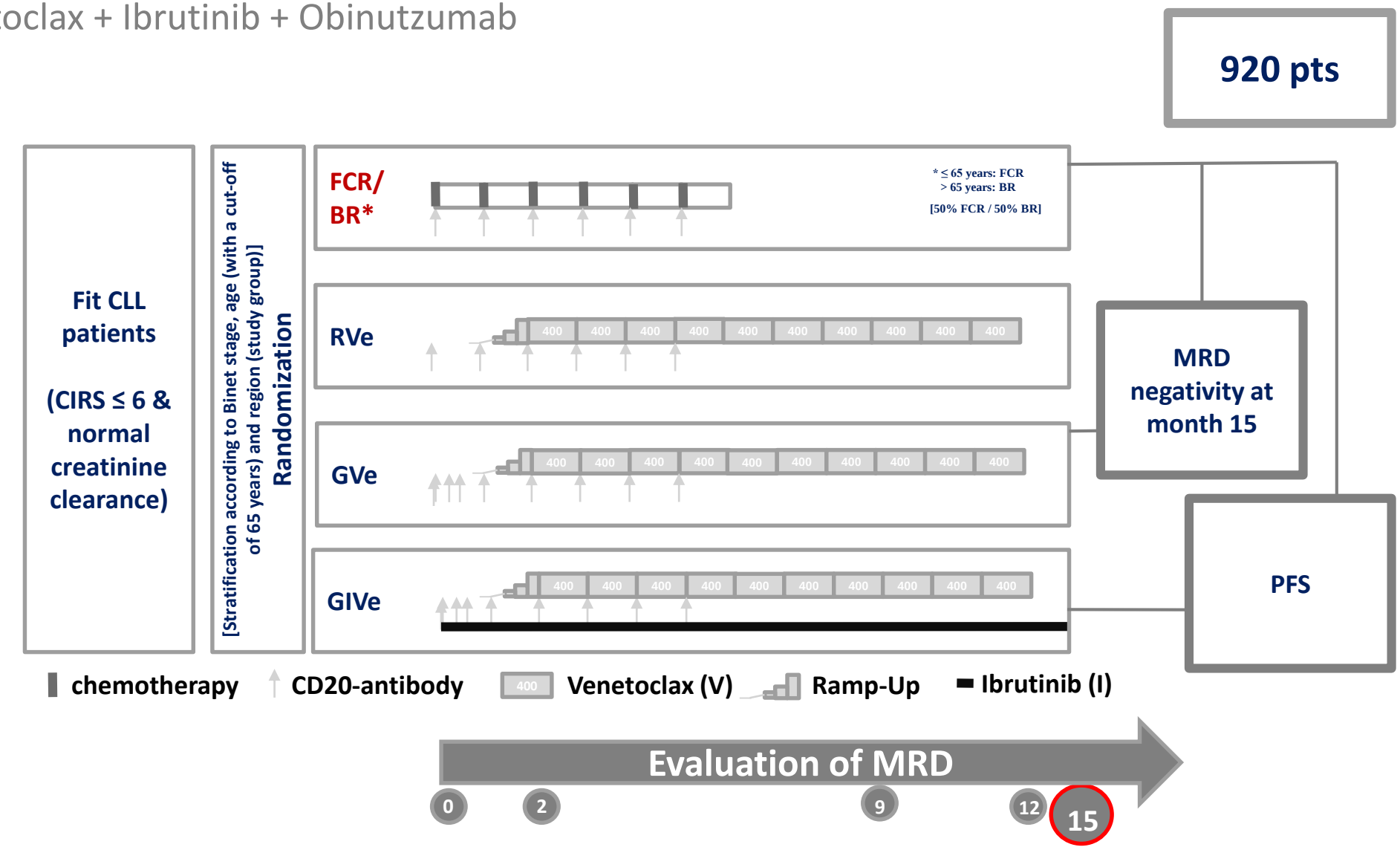
Phase Ib Studie bei der R/R CLL in 12 Patienten



K. Rogers et al., Blood 2018

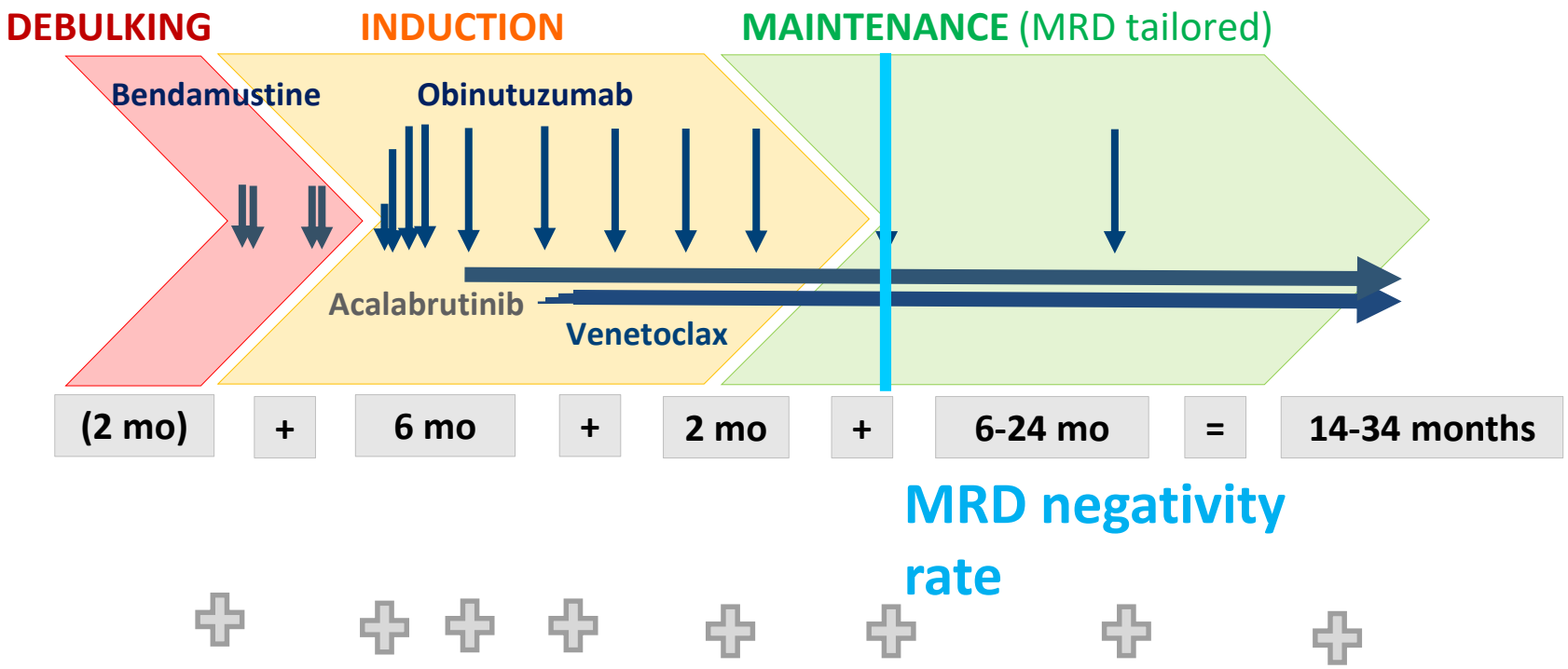
CLL13-GAIA-TRIAL

Standard chemoimmunotherapy vs. Venetoclax + Rituximab vs. Venetoclax + Obinutuzumab (GA101) vs. Venetoclax + Ibrutinib + Obinutzumab



CLL2-BAAG

Bendamustine, followed by
ACP-196 (Acalabrutinib), ABT-199 (venetoclax) and, GA101 (obinutuzumab)



✚ Clonal assessment

Relapsed/refractory patients irrespective of type of prior therapy, fitness and high risk genetic features.

ZUSAMMENFASSUNG

- Venetoclax+ Rituximab bisher einzige zugelassen Chemotherapie-freie, zeitlich begrenzte Kombinationstherapie (Rezidiv)
- Ibrutinib+Obinutuzumab zugelassen in der Erstlinie (zeitlich unbegrenzt)
- Zulassung für Venetoclax+Obinutuzumab (zeitlich begrenzte Therapie) für 2020 erwartet (Erstlinie)
- Kombination Venetoclax+BTK Inhibitor oder Dreifach-Kombination +Obinutuzumab vorerst nur in Studien (Erstlinie und Rezidiv)