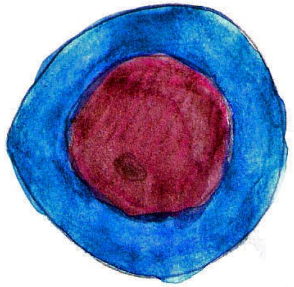
CLL

Michael Hallek
Universität zu Köln



DEUTSCHE STUDIENGRUPPE

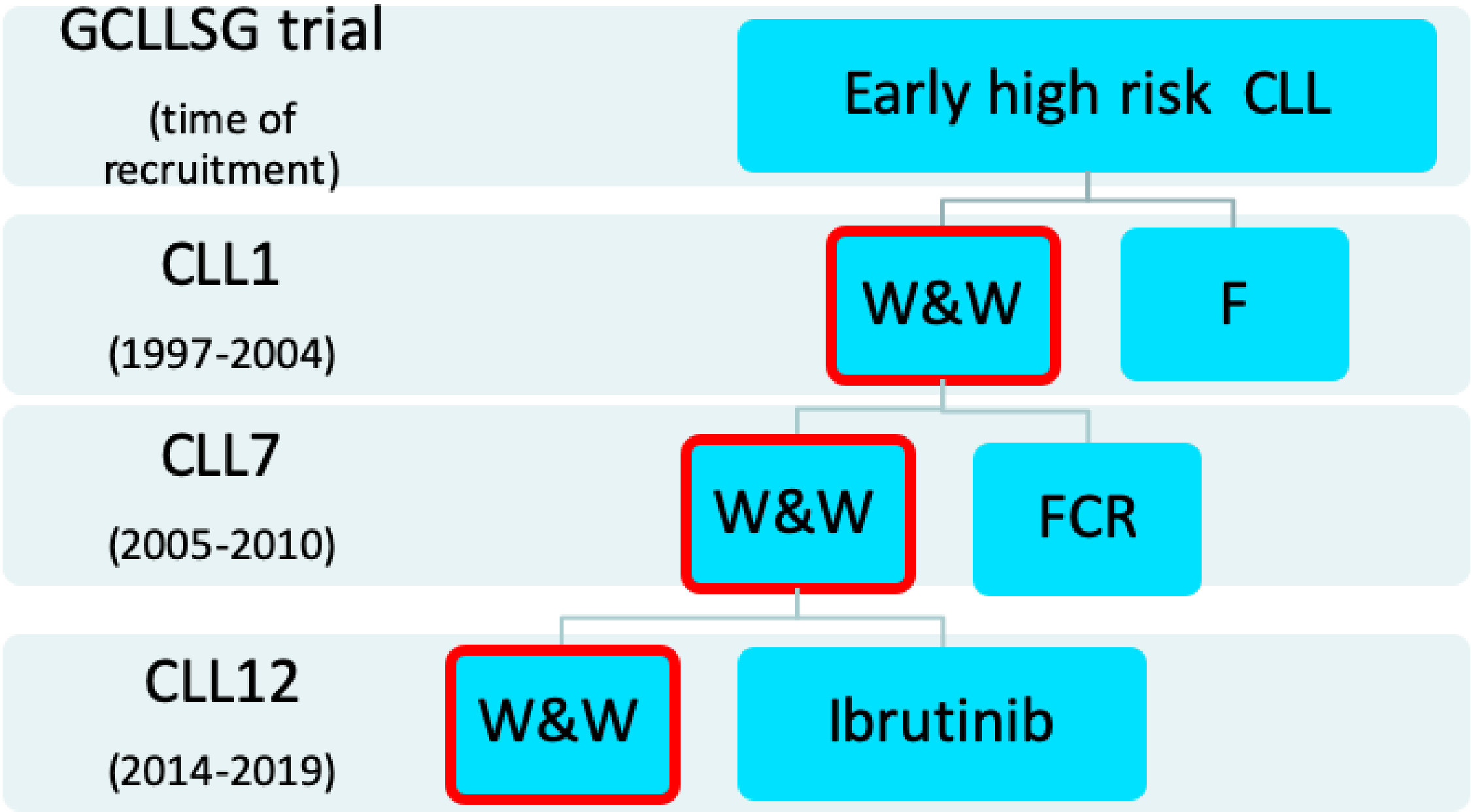
CECAD COLOGNE Excellent in Aging Research – Exzellent in Alternsforschung

CIO Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf

Disclosure

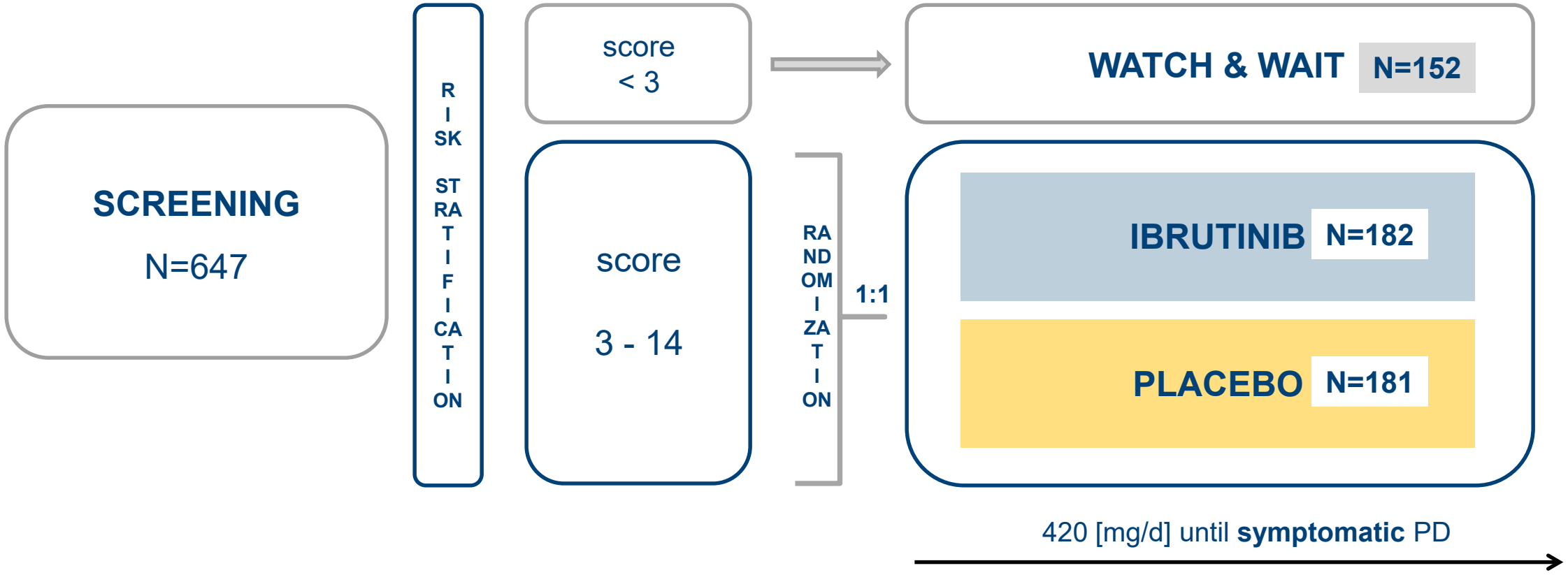
- Research support: Roche, Gilead, Mundipharma, Janssen, Celgene, Pharmacyclics, Abbvie

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


GCLLSG trial
(time of recruitment)
Early high risk CLL
CLL1
(1997-2004)
W&W
F
CLL7
(2005-2010)
W&W
FCR
CLL12
(2014-2019)
W&W
Ibrutinib

CLL 12 PROTOCOL

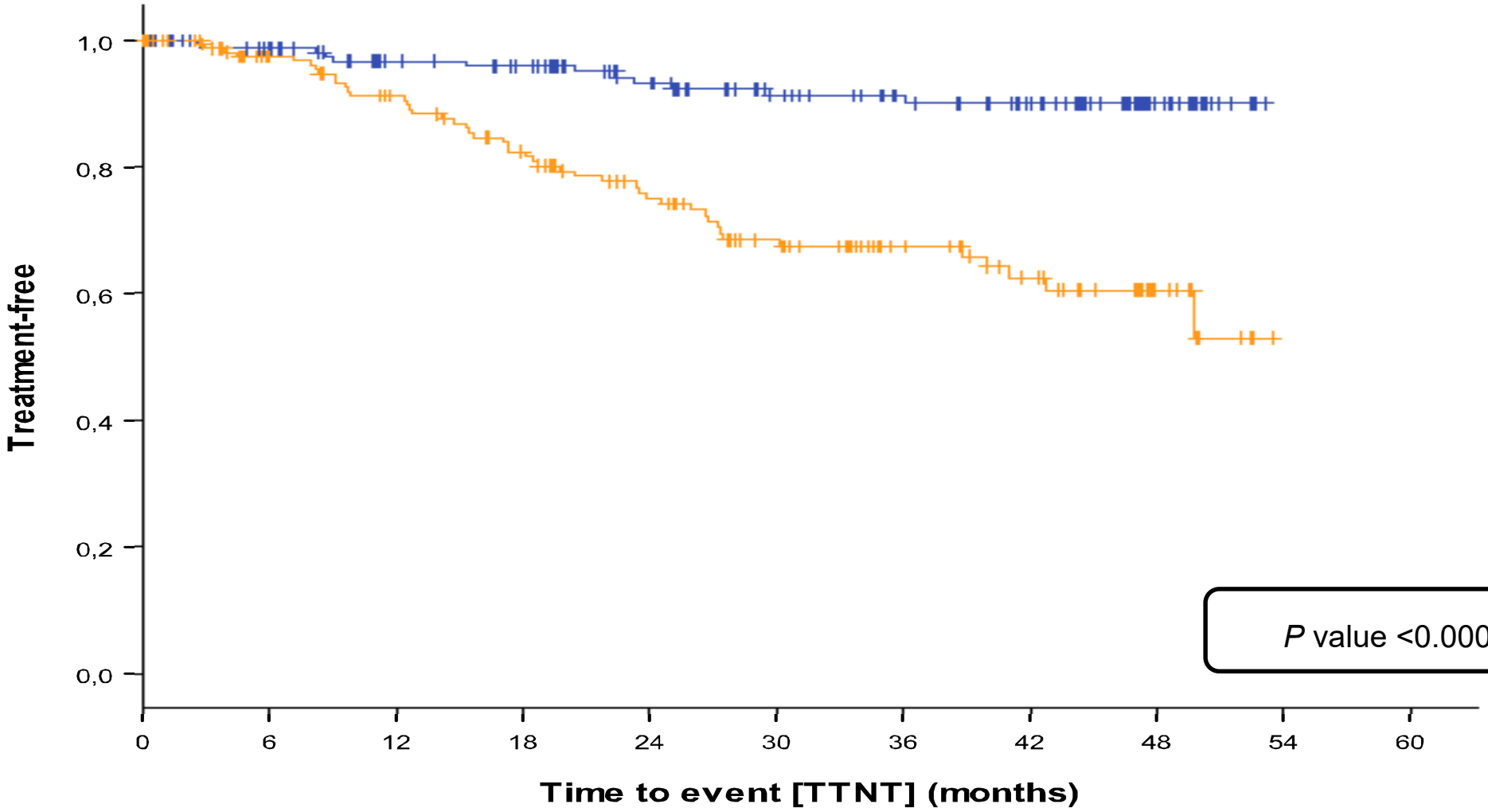
DEUTSCHE STUDIENGRUPPE



Langerbeins et al.
Date: Sunday, June 16, 11:30 - 11:45
Location: Hall 5
Final Abstract Code: LB2602

TIME TO NEXT TREATMENT

DEUTSCHE STUDIENGRUPPE



P value <0.0001, HR 0.205

GCLLSG trial

(time of recruitment)

Unfit or older patients

CLL5

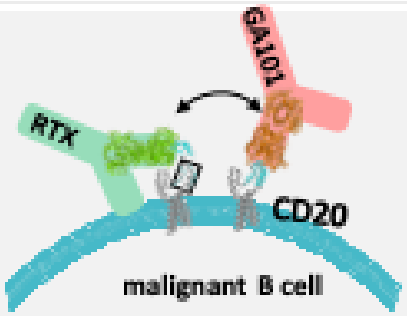
(1999-2004)

- **CLB**
- **F**

CLL11

(2010-2012)

- **CLB**
- **CLB+R**
- **CLB+G**



The NEW ENGLAND JOURNAL of MEDICINE

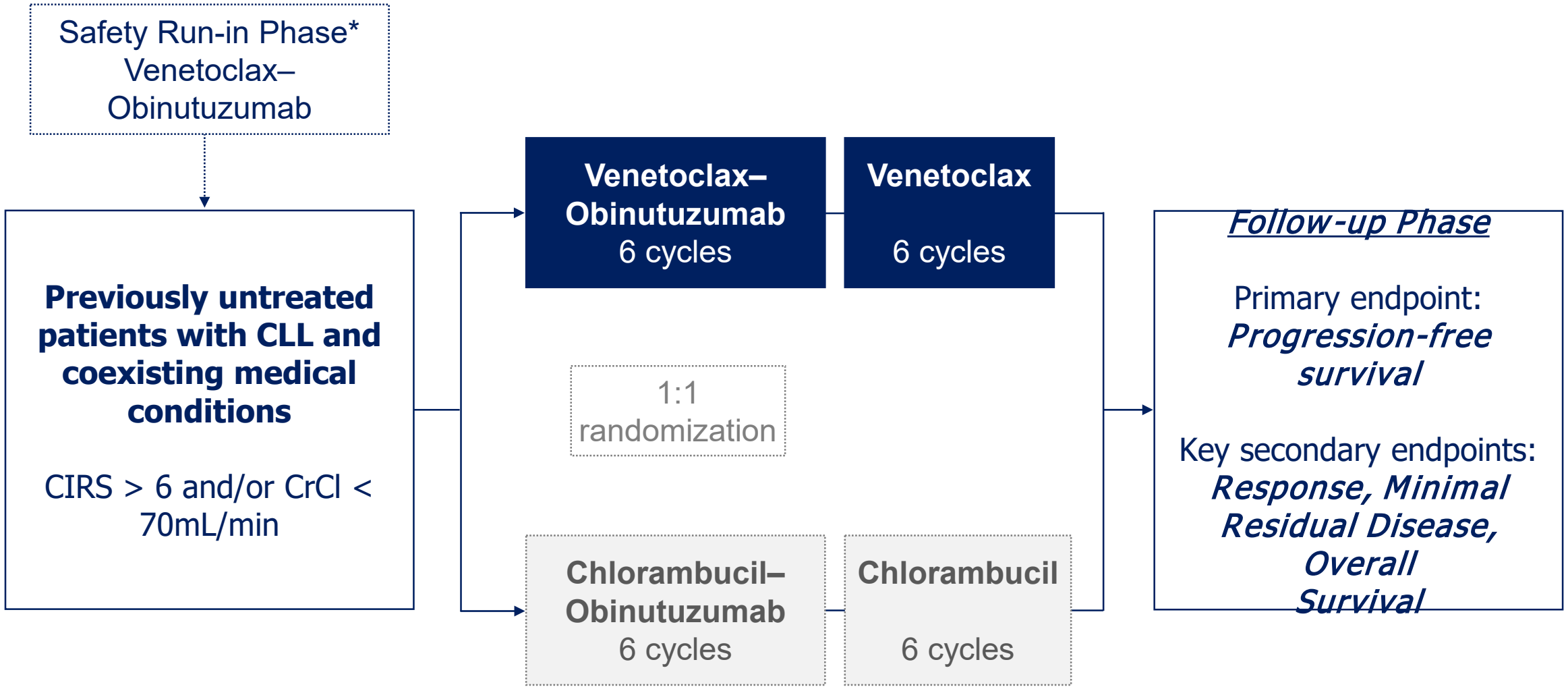
ORIGINAL ARTICLE

Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions

K. Fischer, O. Al-Sawaf, J. Bahlo, A.-M. Fink, M. Tandon, M. Dixon, S. Robrecht, S. Warburton, K. Humphrey, O. Samoylova, A.M. Liberati, J. Pinilla-Ibarz, S. Opat, L. Sivcheva, K. Le Dû, L.M. Fogliatto, C.U. Niemann, R. Weinkove, S. Robinson, T.J. Kipps, S. Boettcher, E. Tausch, R. Humerickhouse, B. Eichhorst, C.-M. Wendtner, A.W. Langerak, K.-A. Kreuzer, M. Ritgen, V. Goede, S. Stilgenbauer, M. Mobasher, and M. Hallek

This article was published on June 4, 2019, at NEJM.org.

Trial Design

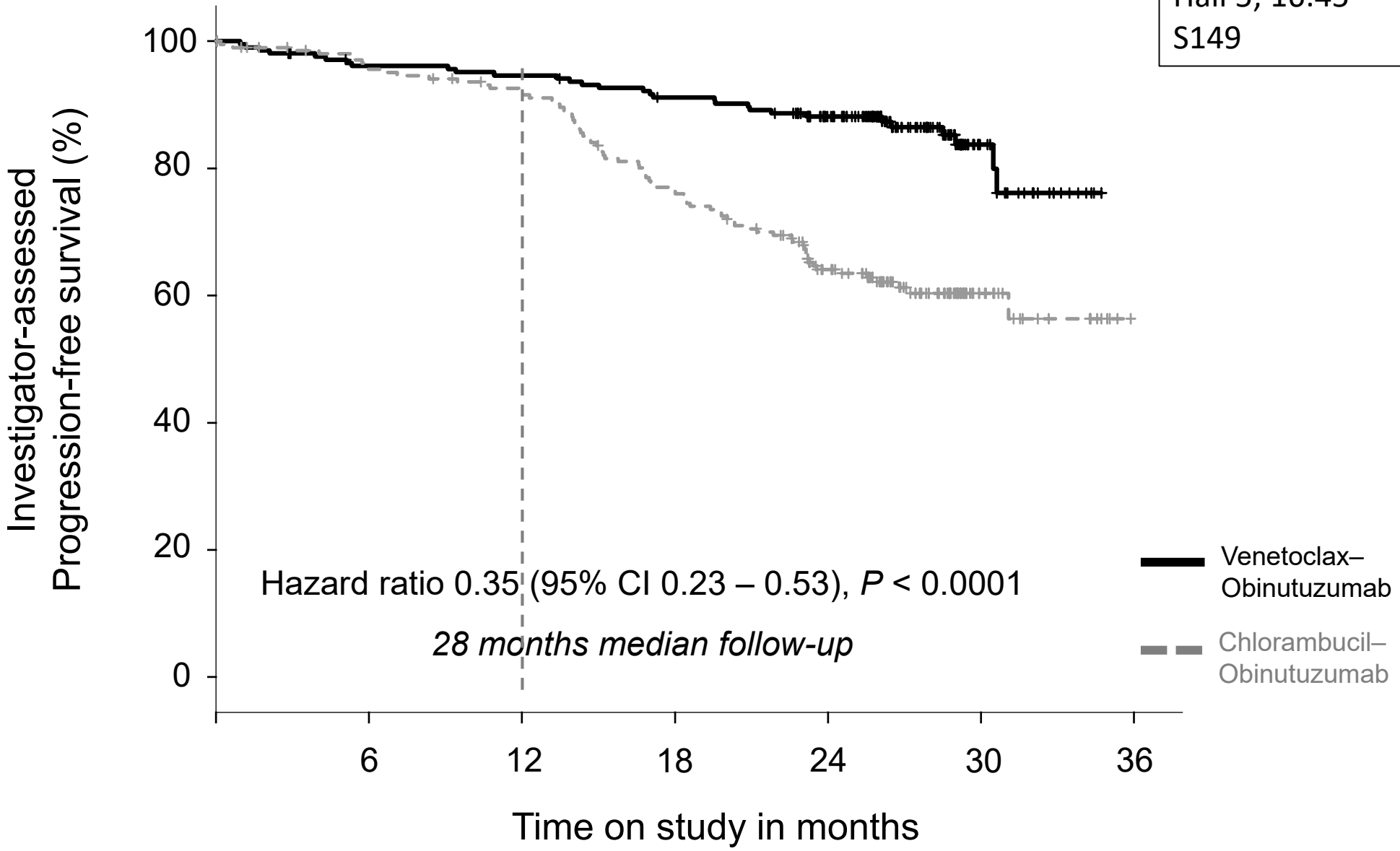


CLL-14

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

PROGRESSION-FREE SURVIVAL

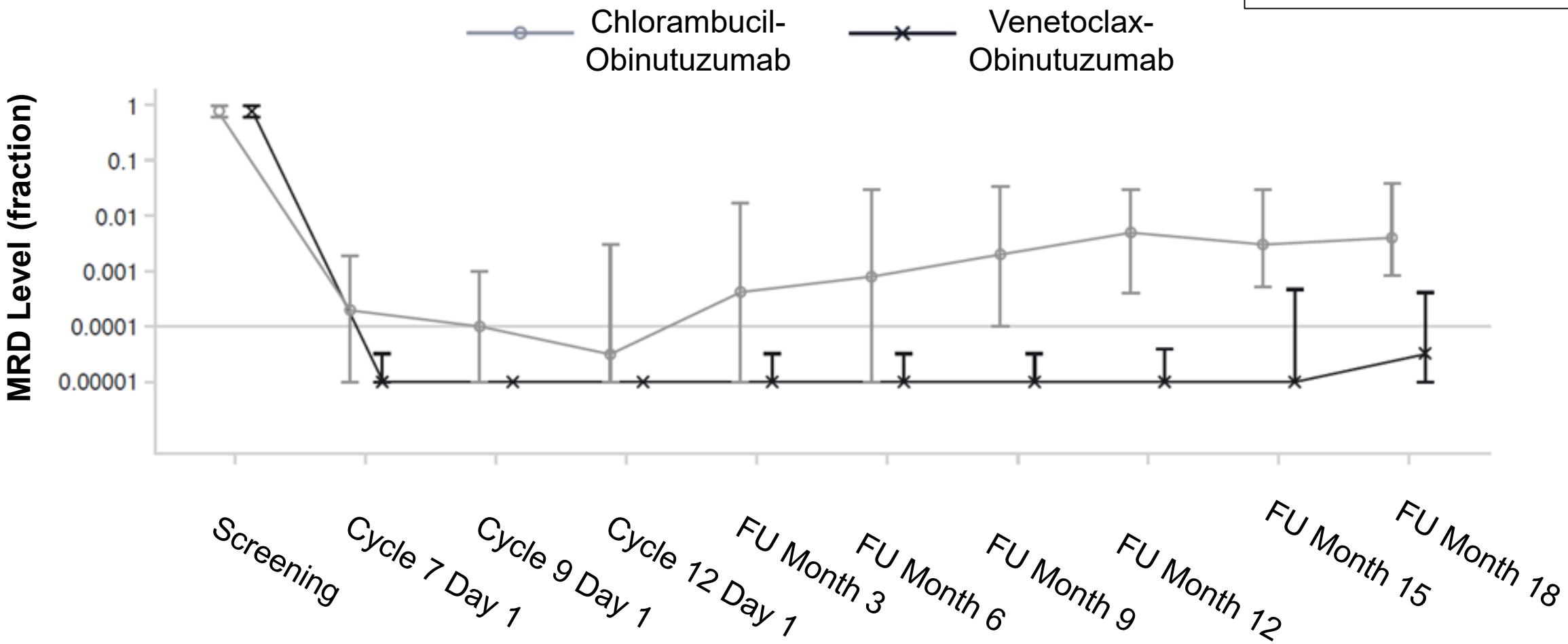
Fischer et al.
Presidential Symposium
Hall 5; 16:45
S149



CLL·14

MRD LEVELS OVER TIME

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



By ASO-PCR in peripheral blood

CLL-14

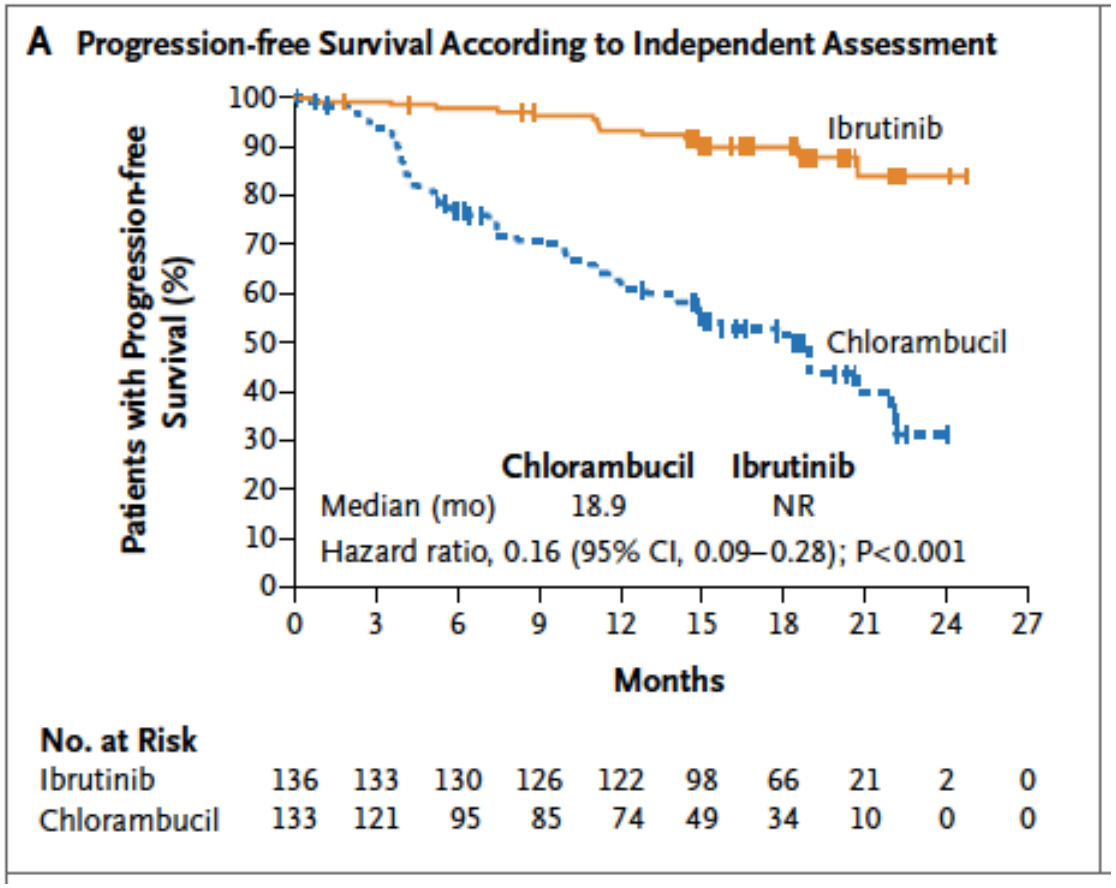
MRD NEGATIVITY BY NGS

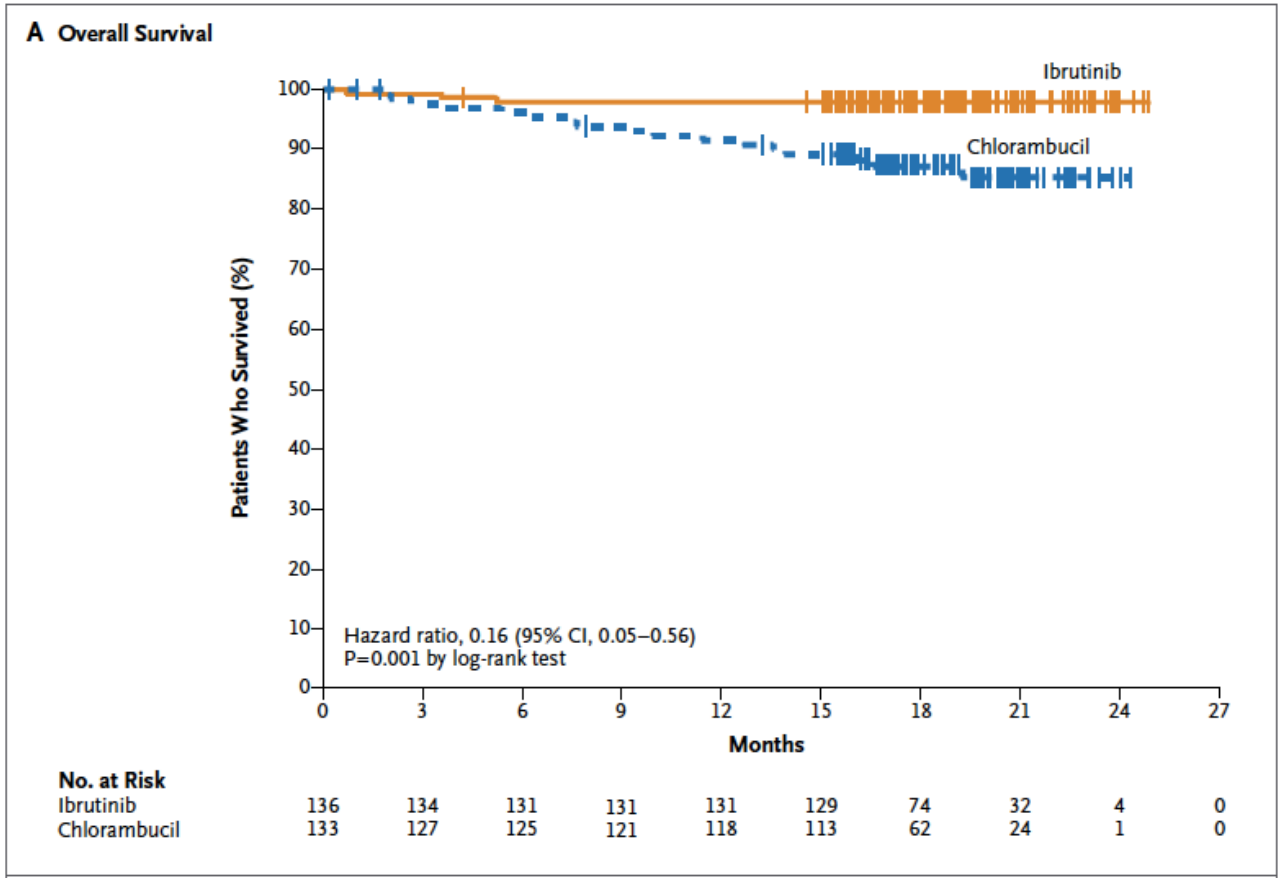
	Venetoclax-Obinutuzumab	Chlorambucil-Obinutuzumab
Number of patients, N	216	216
Minimal residual disease level		
$< 10^{-6}$	42 %	7 %
$\geq 10^{-6}$ and $<10^{-5}$	26 %	13 %
$\geq 10^{-5}$ and $<10^{-4}$	11 %	14 %
$\geq 10^{-4}$ and $<10^{-2}$	6 %	23 %
$\geq 10^{-2}$	5 %	29 %
No sample / not evaluable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

rapid communication

Ibrutinib Plus Venetoclax in Relapsed/Refractory Chronic Lymphocytic Leukemia: The CLARITY Study

Peter Hillmen, MBChB, PhD[1,2]; Andy C. Rawstron, PhD[2]; Kristian Brock, MSc[3]; Samuel Muñoz-Vicente, MSc[3]; Francesca J. Yates, PhD[3]; Rebecca Bishop[3]; Rebecca Boucher, MSc[3]; Donald MacDonald, PhD[4]; Christopher Fegan, MD[5,6]; Alison McCaig, PhD[7]; Anna Schuh, MD, PhD[8]; Andrew Pettitt, MA, MB BChir, PhD[9]; John G. Gribben, MD, DSc[10]; Piers E.M. Patten, MBChB, PhD[11,15]; Stephen Devereux, PhD[11]; Adrian Bloor, MA, MB BChir, PhD[12]; Christopher P. Fox, MBChB, PhD[13]; Francesco Forconi, MD, DM, PhD[14,16]; and Talha Munir, MBBS[2]

J Clin Oncol 37.

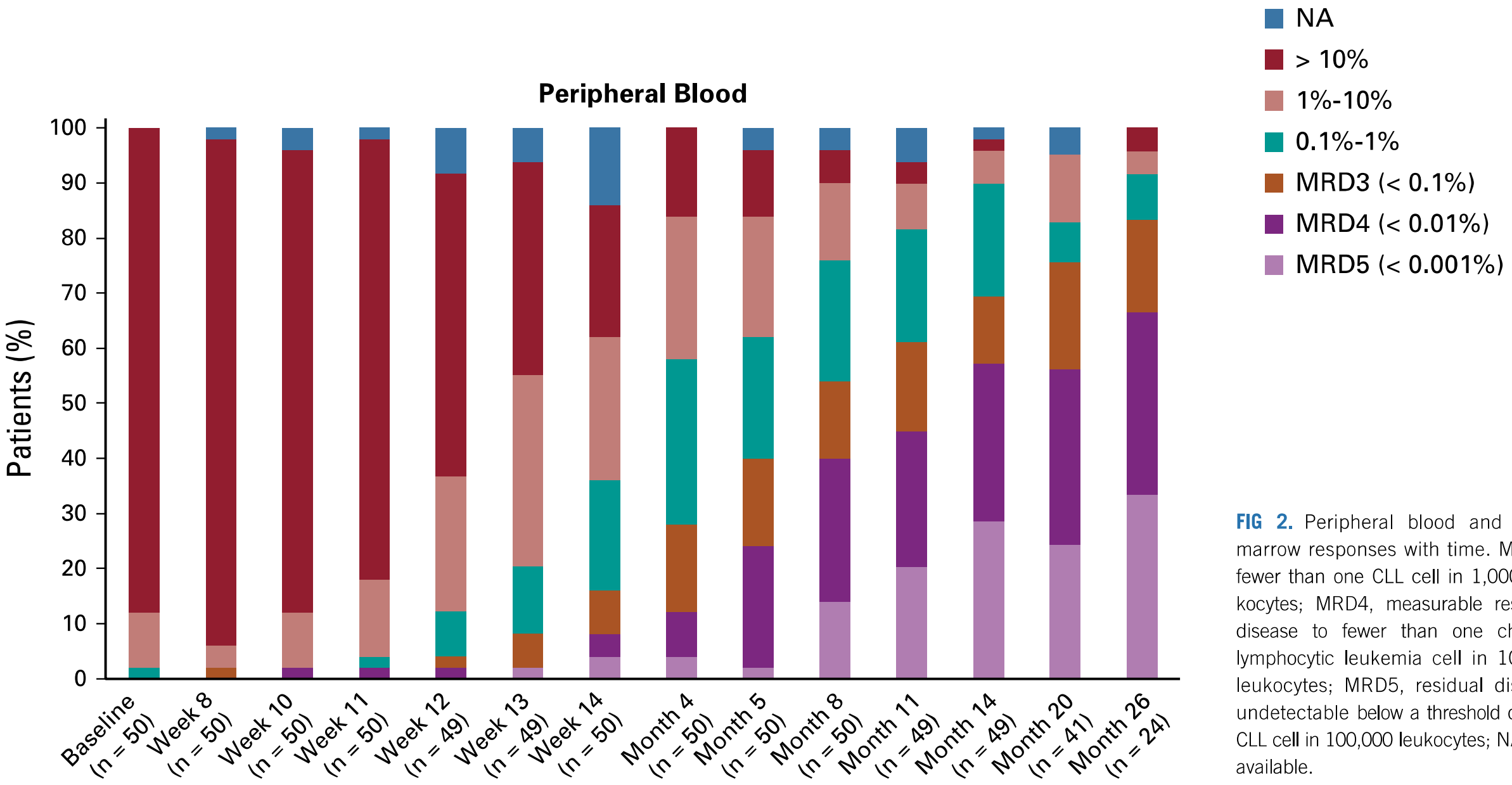


FIG 2. Peripheral blood and bone marrow responses with time. MRD3, fewer than one CLL cell in 1,000 leukocytes; MRD4, measurable residual disease to fewer than one chronic lymphocytic leukemia cell in 10,000 leukocytes; MRD5, residual disease undetectable below a threshold of one CLL cell in 100,000 leukocytes; NA, not available.

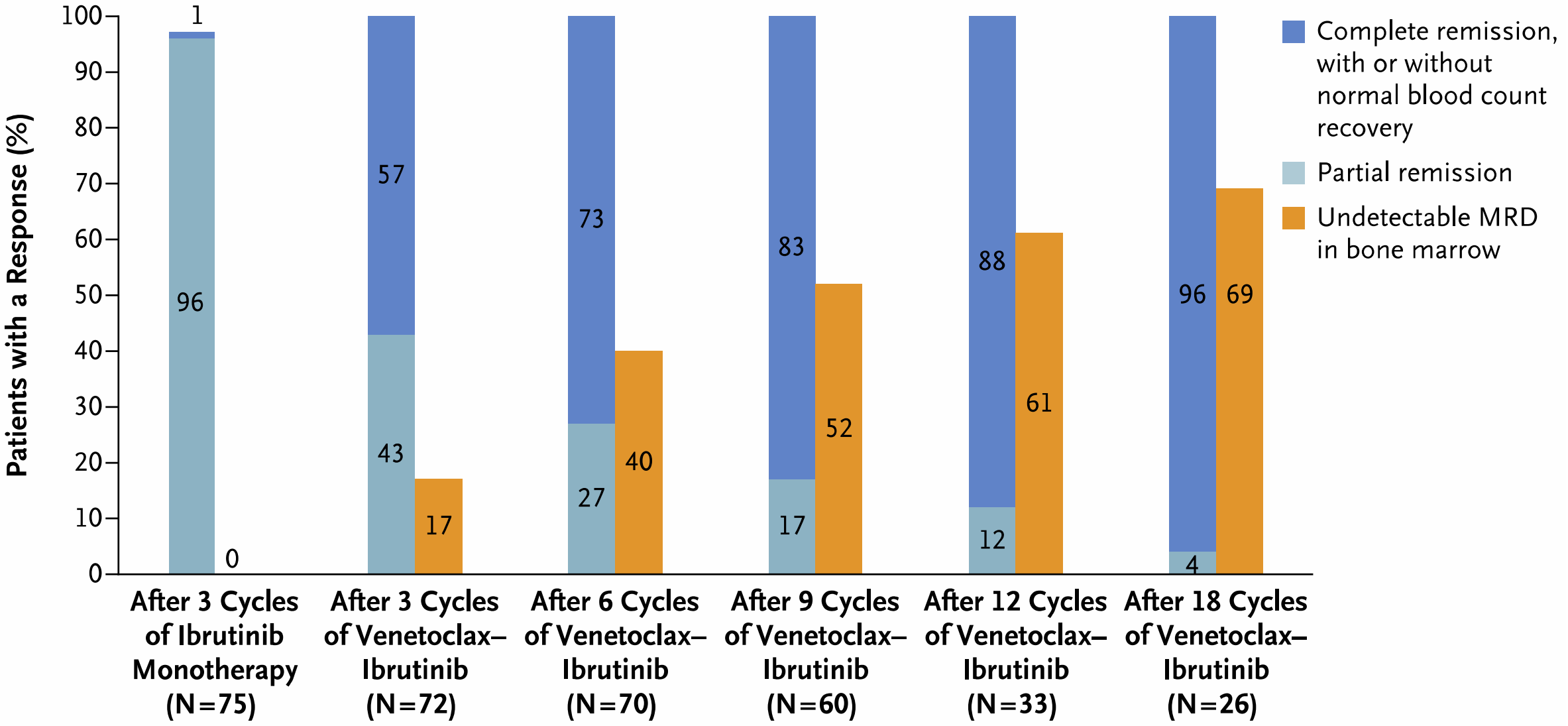
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 30, 2019 VOL. 380 NO. 22

Ibrutinib and Venetoclax for First-Line Treatment of CLL

Nitin Jain, M.D., Michael Keating, M.D., Philip Thompson, M.D., Alessandra Ferrajoli, M.D., Jan Burger, M.D., Ph.D., Gautam Borthakur, M.D., Koichi Takahashi, M.D., Zeev Estrov, M.D., Nathan Fowler, M.D., Tapan Kadia, M.D., Marina Konopleva, M.D., Ph.D., Yesid Alvarado, M.D., Musa Yilmaz, M.D., Courtney DiNardo, M.D., Prithviraj Bose, M.D., Maro Ohanian, D.O., Naveen Pemmaraju, M.D., Elias Jabbour, M.D., Koji Sasaki, M.D., Rashmi Kanagal-Shamanna, M.D., Keyur Patel, M.D., Ph.D., Jeffrey Jorgensen, M.D., Ph.D., Naveen Garg, M.D., Xuemei Wang, M.S., Katrina Sondermann, B.A., Nichole Cruz, R.N., Chongjuan Wei, Ph.D., Ana Ayala, R.N., William Plunkett, Ph.D., Hagop Kantarjian, M.D., Varsha Gandhi, Ph.D., and William Wierda, M.D., Ph.D.

B Response to Treatment over Time



Comparison of MRD results of 4 recent trials using venetoclax combinations in CLL

First Author	Journal Year	Name of Trial	Therapeutic intervention		MRD, PB 10^{-4} ITT-based N/N	MRD, PB 10^{-4} ITT-based %	Time point of MRD assessment
Fischer	NEJM 2019	CLL14	Venetoclax + Obinutuzumab	1L	165/216	76	@15 months
Cramer	Lancet Oncol 2018	CLL2-BAG	(Benda)→ Venetoclax + Obinutuzumab	1L	31/34	91	@15 months
				RR	24/29	83	@15 months
Jain	NEJM 2019	CAPTIVATE	Ibrutinib + Venetoclax	1L	29/80	36	@12 months
Hillmen	JCO 2019	CLARTIY	Ibrutinib + Venetoclax	RR	28/53	53	@14 months

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).