CLL: Front line and Relapsed Refractory

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Head of Lymphoma section and
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Malignant Hematology Department

MOFFITT CANCER CENTER

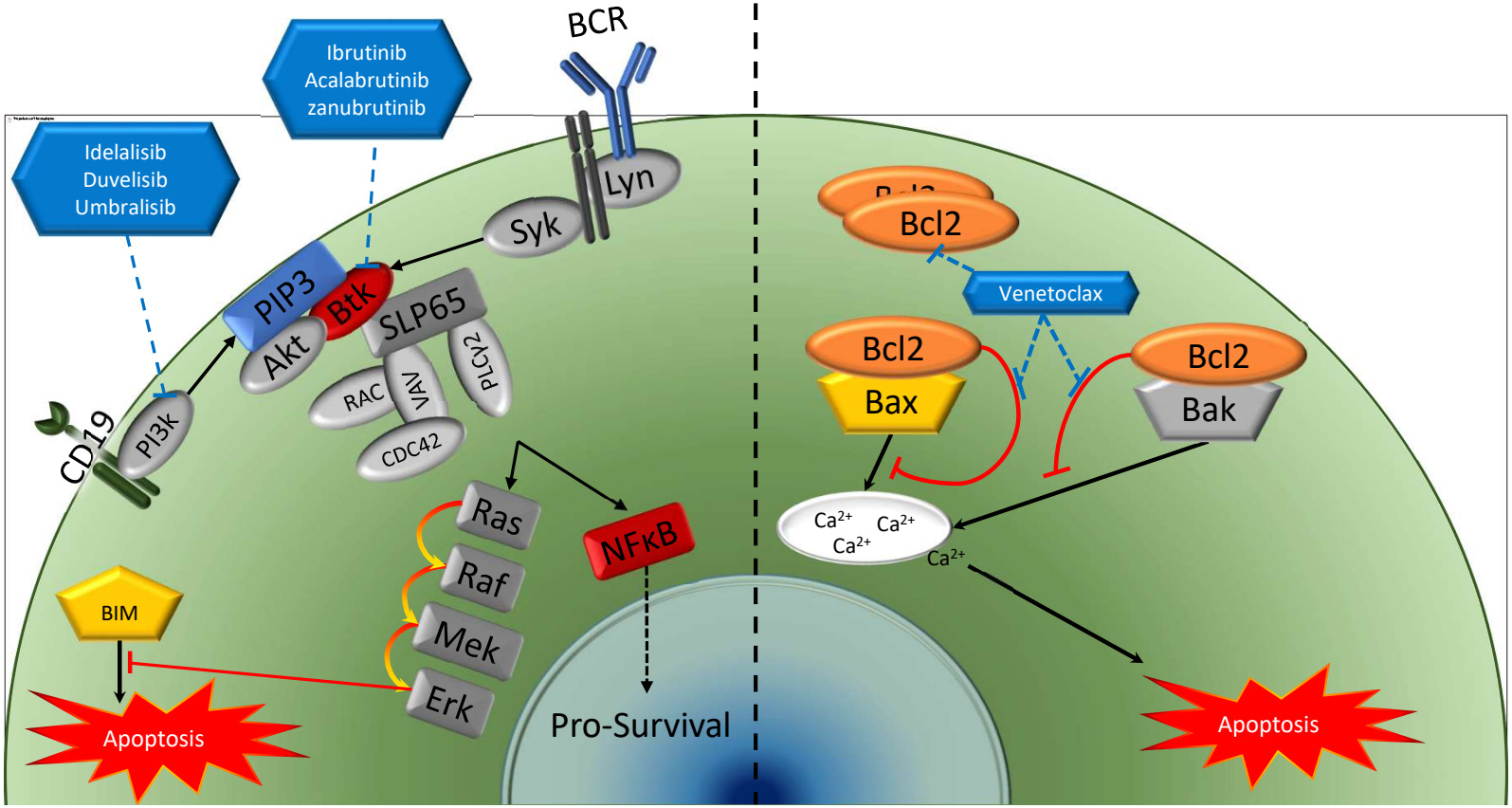
COI

- Janssen/Pharmacyclics: Consulting and speaker bureau.
- Abbvie: Consulting and speaker bureau
- TG Therapeutics: Consulting.
- AstraZeneca: Consulting and speaker bureau
- TEVA: Consulting

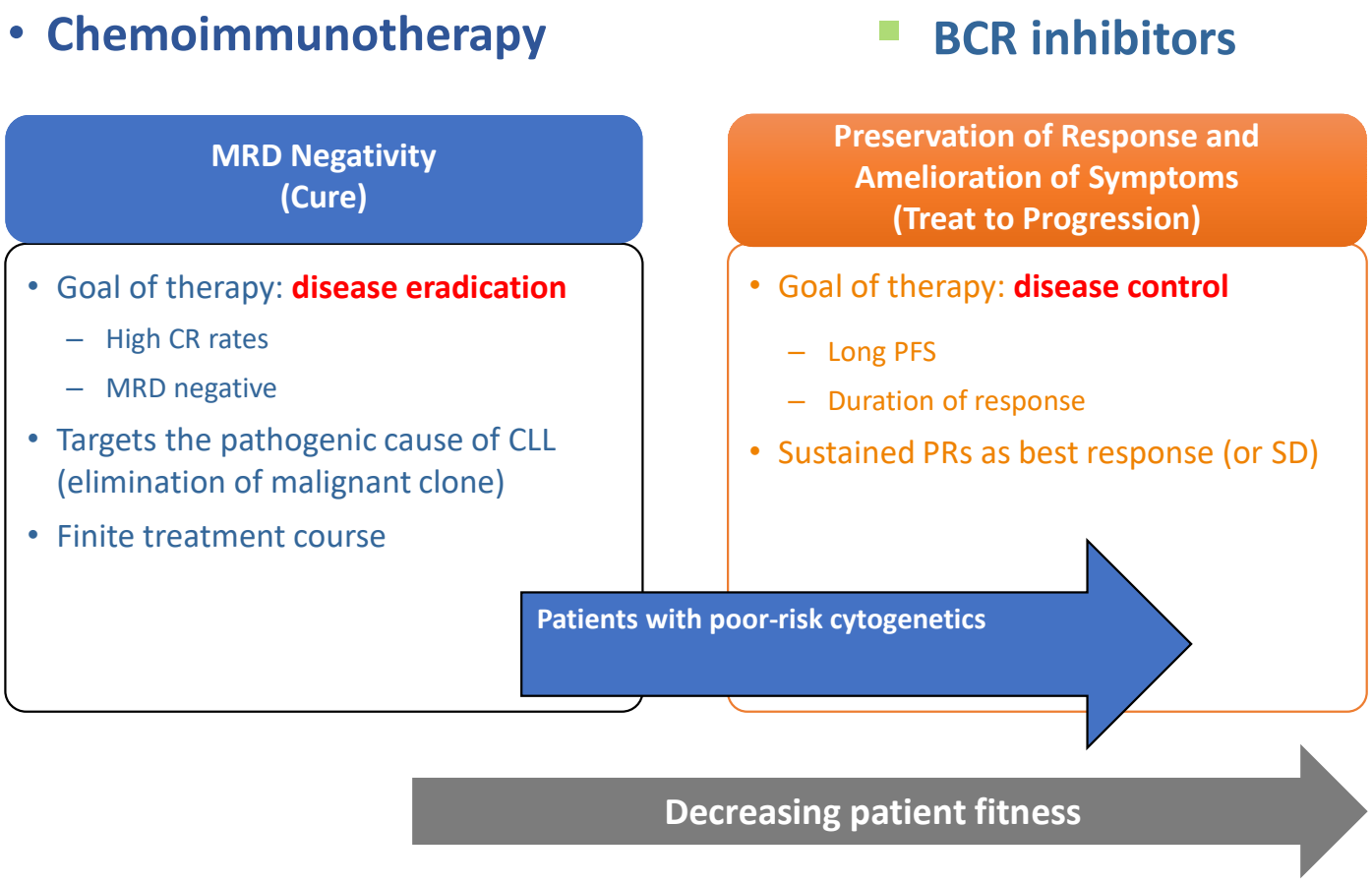
Blocking the two main mechanisms of survival in CLL

Blocking BCR signaling is a cytostatic mechanism

Blocking bcl2 pathways is a cytotoxic mechanism



The initial Changing Treatment Paradigm in CLL



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

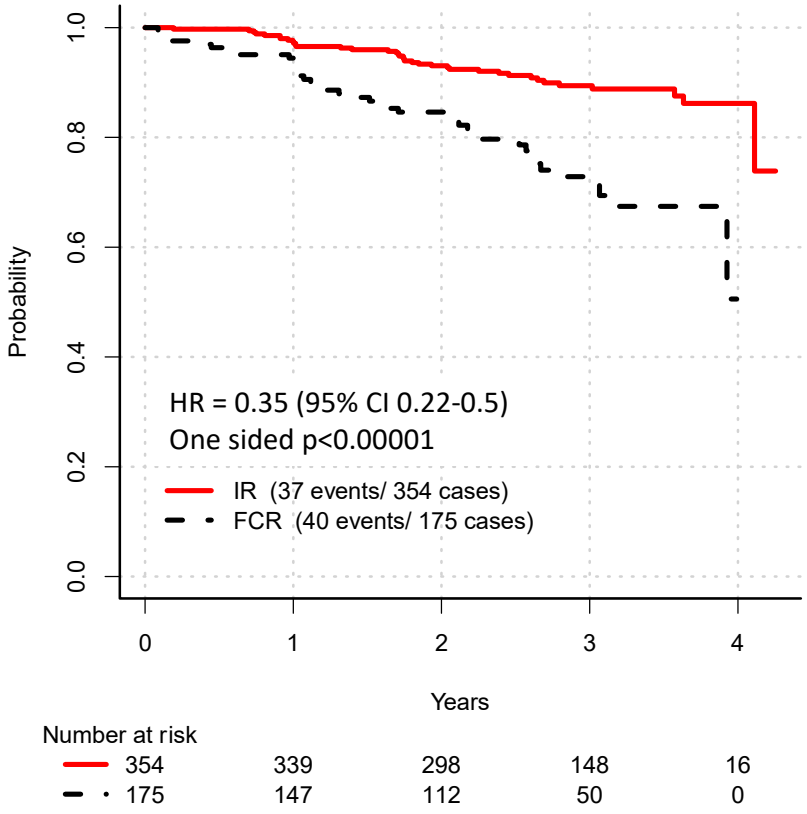
Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia

N ENGL J MED 381;5 NEJM.ORG AUGUST 1, 2019

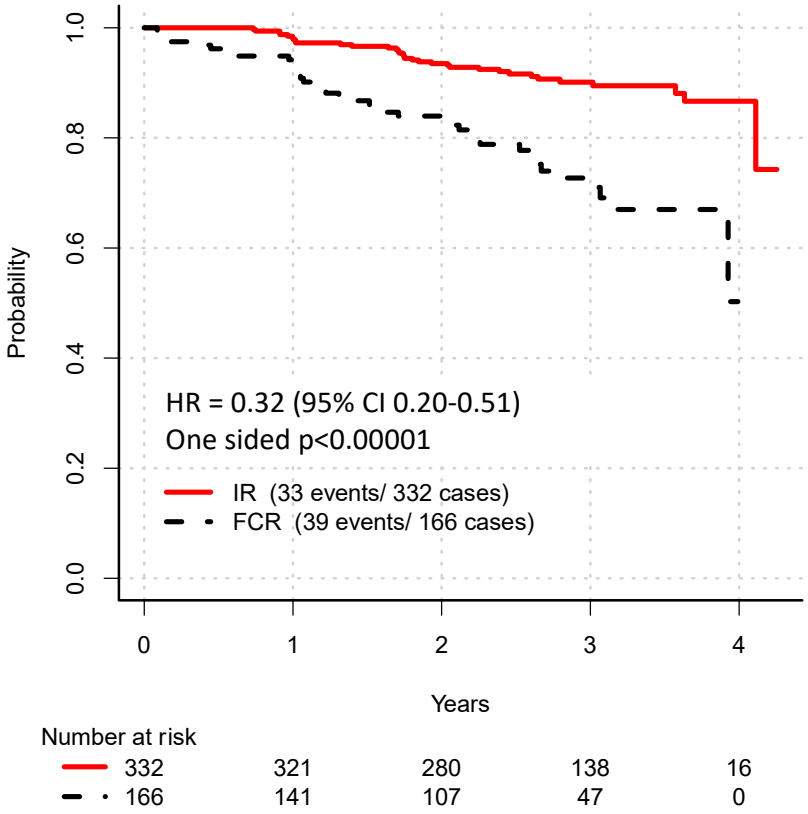
T.D. Shanafelt, X.V. Wang, N.E. Kay, C.A. Hanson, S. O'Brien, J. Barrientos, D.F. Jelinek, E. Braggio, J.F. Leis, C.C. Zhang, S.E. Coutre, P.M. Barr, A.F. Cashen, A.R. Mato, A.K. Singh, M.P. Mullane, R.F. Little, H. Erba, R.M. Stone, M. Litzow, and M. Tallman

Progression Free Survival

Intent to Treat



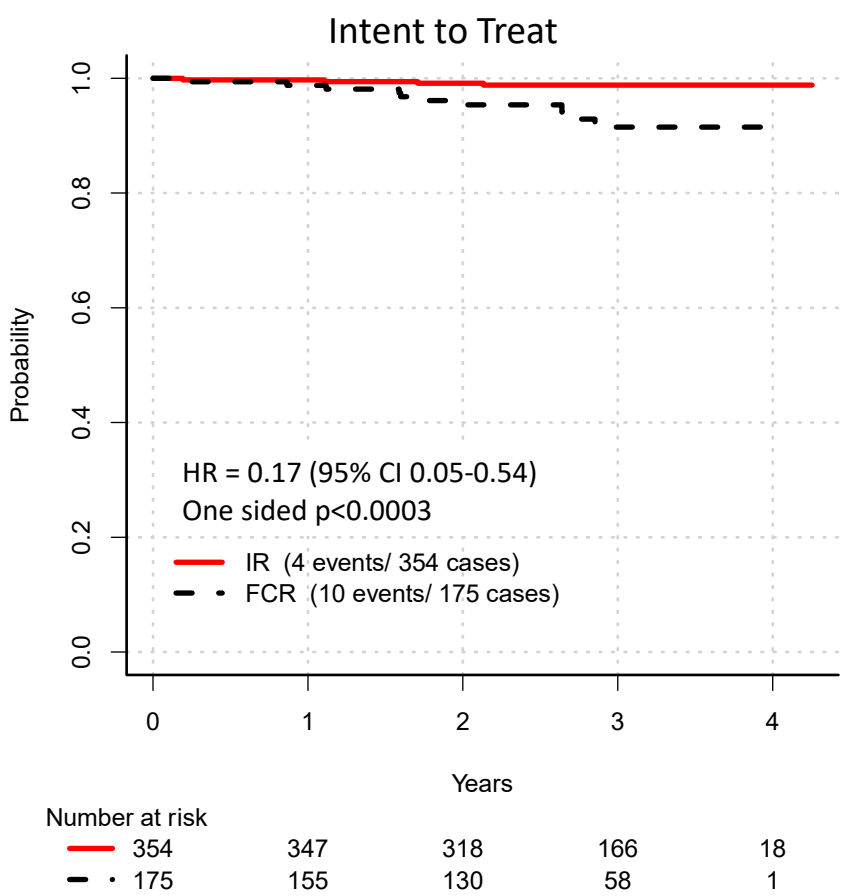
Eligible

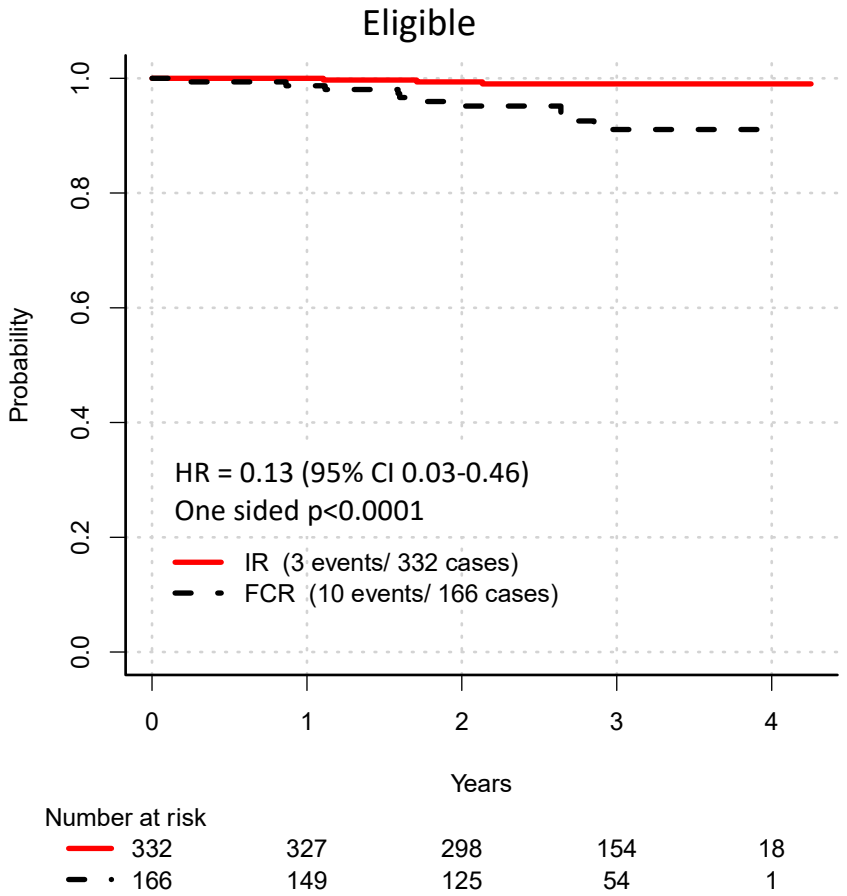


ECOG-ACRIN cancer research group | Reshaping the future of patient care

Shanafelt et al. ASH 2018. Abstract LBA-4. NCT02048813.

Overall Survival

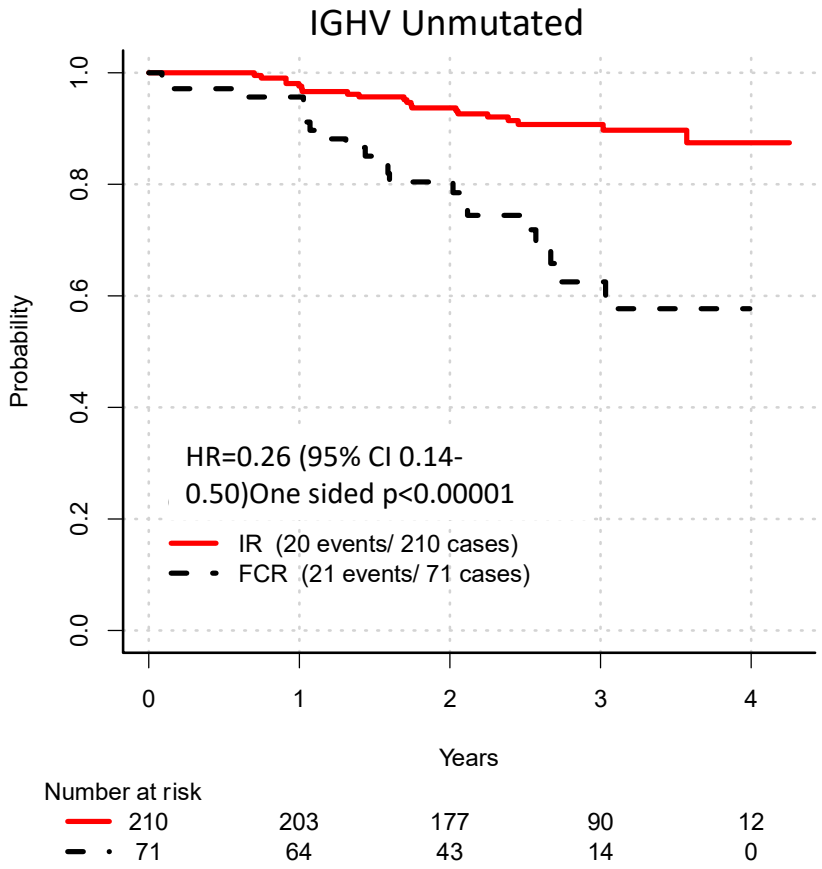


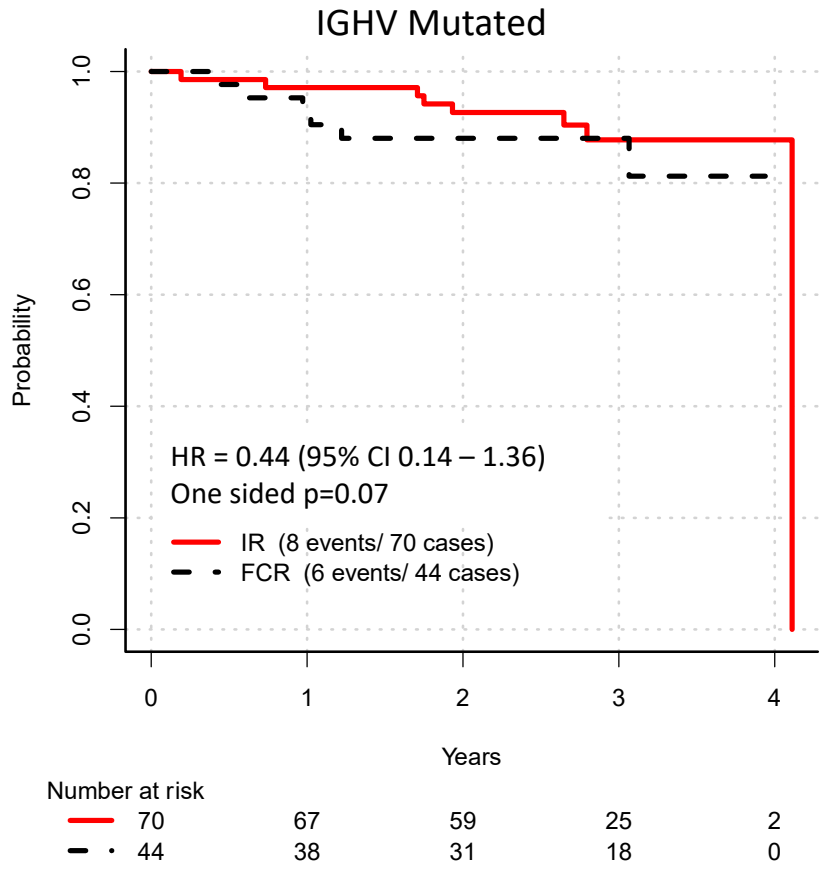


ECOG-ACRIN cancer research group | Reshaping the future of patient care

Shanafelt et al. ASH 2018. Abstract LBA-4. NCT02048813.

Progression Free Survival: IGHV Status





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

Shanafelt et al. ASH 2018. Abstract LBA-4. NCT02048813.

E1912 Update: PFS and OS

- Median follow-up 48 mos

Outcome	Ibrutinib + Rituximab	FCR	HR (95% CI)	*P* Value
PFS (all patients)				
▪ Events/cases, n	58/354	52/175	0.39 (0.26-0.57)	< .0001
▪ 3-yr PFS, %	89	71		
PFS (*IGHV* mutated)				
▪ Events/cases, n	10/70	8/44	0.42 (0.16-1.16)	.086
▪ 3-yr PFS, %	88	82		
PFS (*IGHV* unmutated)				
▪ Events/cases, n	36/210	29/71	0.28 (0.17-0.48)	< .0001
▪ 3-yr PFS, %	89	65		
OS (all patients)				
▪ Events/cases, n	11/354	12/175	0.34 (0.15-0.79)	.009
▪ 3-yr OS, %	99	93		

Shanafelt. ASH 2019. Abstr 33.

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (iFCG) for Firstline Treatment of Patients with CLL with Mutated *IGHV* and without *TP53* Aberrations

Nitin Jain, Philip Thompson, Jan Burger, Alessandra Ferrajoli, Gautam Borthakur, Prithviraj Bose, Zeev Estrov, Tapan Kadia, Koichi Takahashi, Naveen Garg, Xuemei Wang, Rashmi Kanagal-Shamanna, Keyur Patel, Wanda Lopez, Ana Ayala, William Plunkett, Varsha Gandhi, Hagop Kantarjian, Susan O'Brien, Michael Keating, William Wierda

Department of Leukemia, MDACC

ASH 2018, Abstract 185

iFCG: Study Design

iFCG 3 courses

↓

Ibrutinib 9 courses (all pts)

+

Obinutuzumab 3 courses (CR/CRi with BM U-MRD4)

or

Obinutuzumab 9 courses (PR or BM MRD^{pos})

↓

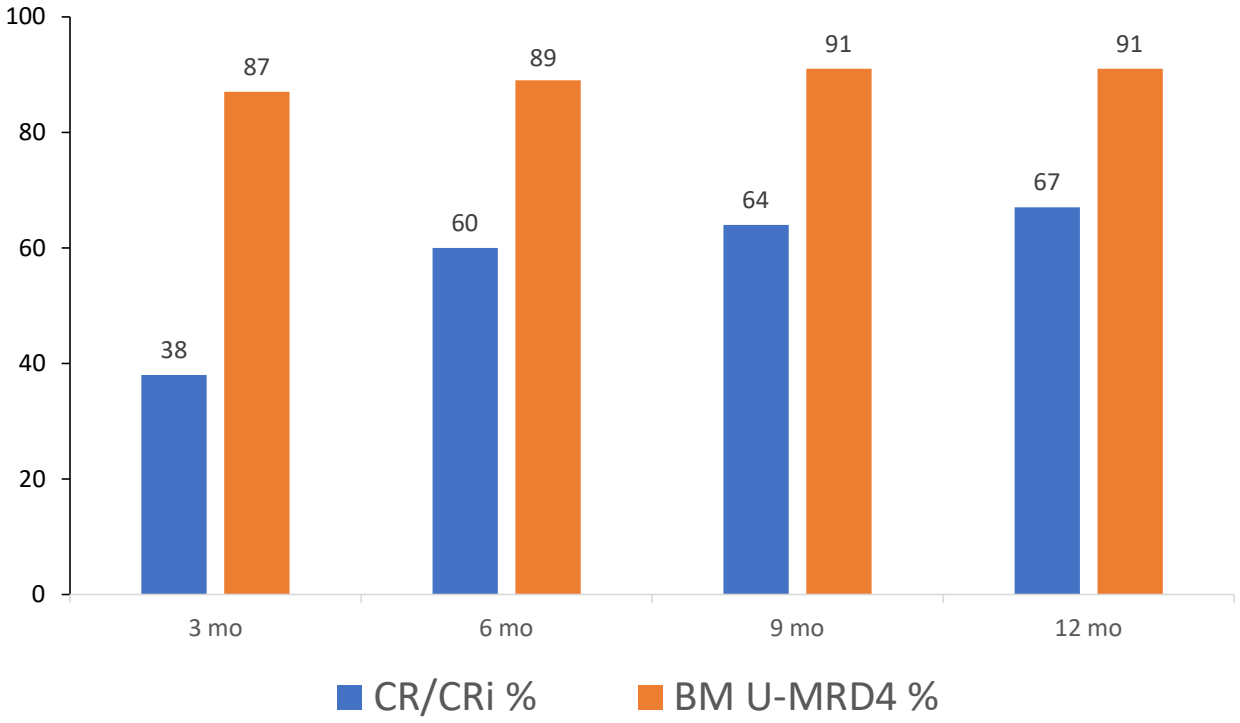
After 12 courses

BM U-MRD4 → stop ibrutinib

BM MRD^{pos} → continue ibrutinib

Responses Improve with Time Intent to Treat (N=45)

iFCG ➡ Ibrutinib + obinutuzumab ➡ Ibrutinib +/- obinutuzumab

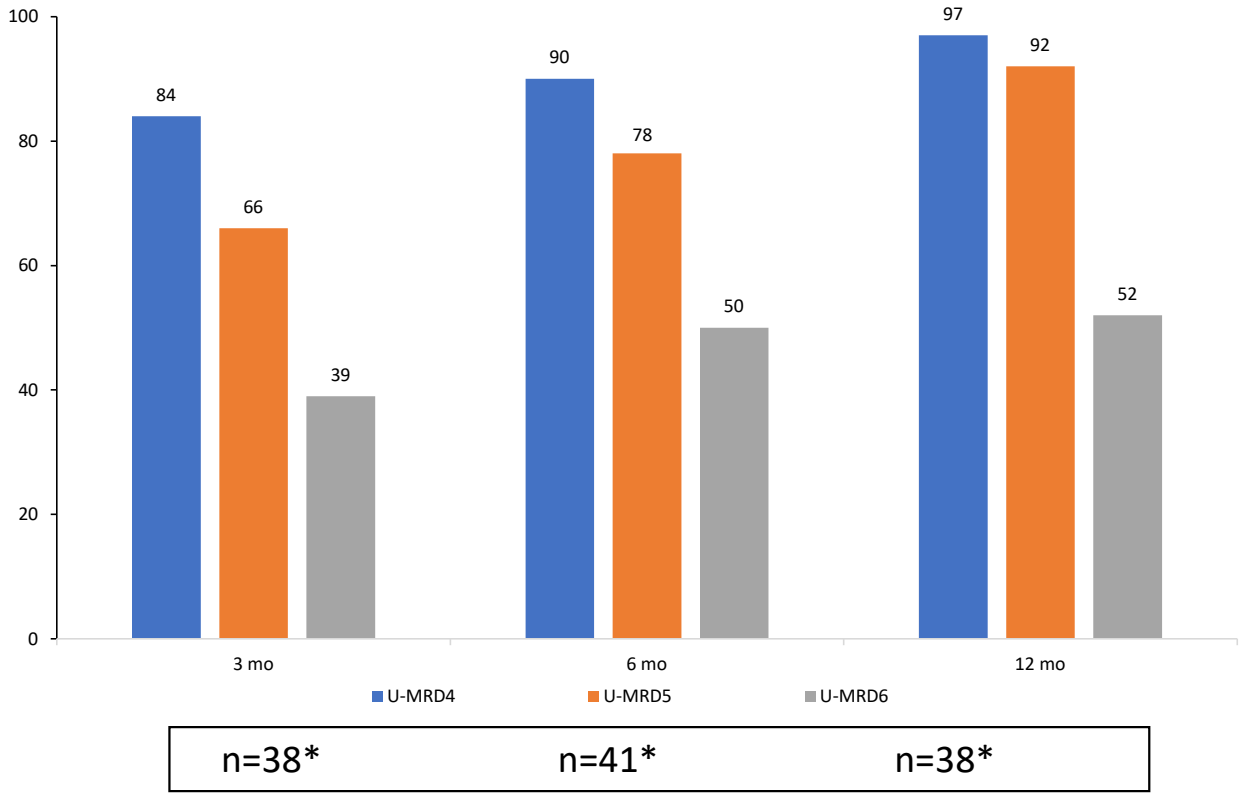


BM-UMRD4 in *IGHV*-M after C6

Trial	Regimen	N	BM U-MRD4 %	
			Evaluable	ITT
MDACC[1]	FCR x6	88	51	40
MDACC[2]	FCR x6	82	56	34
CLL8[3]	FCR x6	113	50	13
CLL10[4]	FCR x6	123	62	28
GREEN[5]	FCG x6	37	67	38
DFCI[6]	iFCR x6	33	79	79
MDACC	iFCG x3 → iG x3	45	95	89

[1]Keating, JCO 2005; [1]Tam, Blood 2008; [1]Thompson, Blood 2016; [2]Strati, Blood 2014; [3]Hallek, Lancet 2010; [3]Bottcher, JCO 2012, [4]Eichhorst, Lancet Onc 2016; [4]Personal communication Barbara Eichhorst, GCLLSG; [5]Bosch, Leukemia 2019; [6]Davids, Lancet Haematol 2019.

Serial BM MRD by NGS-MRD Assay



* for MRD6 sensitivity (cycle 3, n=28; cycle 6, n=28, cycle 12, n=23)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

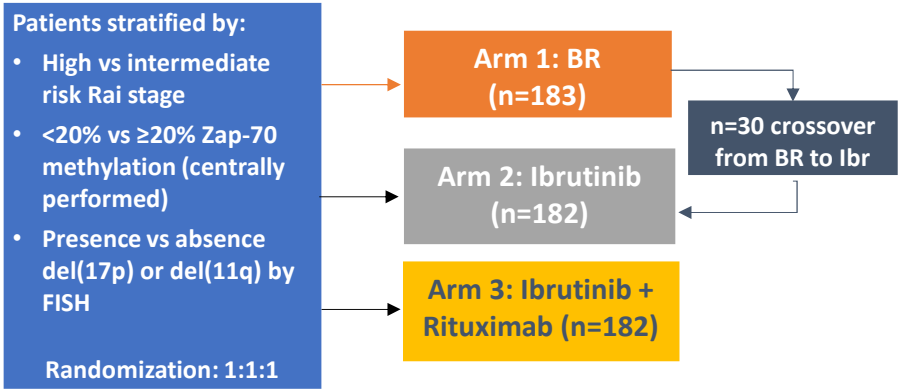
Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL

J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria,* J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, and J.C. Byrd

Phase 3 Study of Ibrutinib ± Rituximab vs BR in TN CLL (ALLIANCE A041202)

Key eligibility criteria

- Age ≥ 65 y and ECOG PS 0-2
- Treatment naive, symptomatic CLL
- CrCl ≥ 40 mL/min; AST/ALT ≤2.5xULN
- Include 17p/TP53

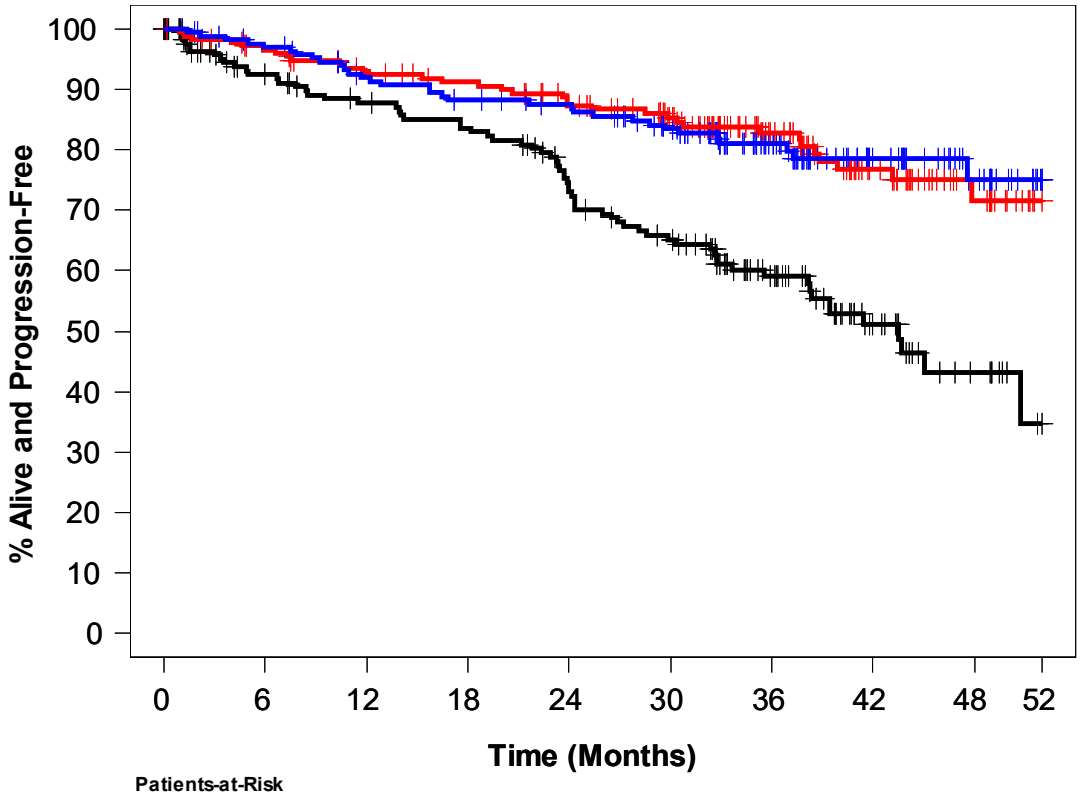


Primary endpoints: PFS
Secondary endpoints: OS, TTP, DOR. Proportion achieving MRD negativity, Biopsy proven CR, Toxicity

Patient Characteristics	All Patients (N = 547)
Median age, y (range)	71 (65-89)
ECOG PS 0-1	97%
FISH characteristics	
del(17p)	6%
del(11q)[a]	19%
TP53 mutation	10%
Complex karyotype	29%
Zap-70 unmethylated	53%
IGVH unmutated (n=360)	61%

Data cutoff: October 4, 2018.
Woyach (Coutre) et al. ASH 2018. Abstract 6.
https://clinicaltrials.gov/ct2/show/NCT01886872.

Phase 3 Study of Ibrutinib ± Rituximab vs BR in TN CLL (ALLIANCE A041202); PFS



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

Pairwise comparisons

I vs BR
HR: 0.39 (95% CI: 0.26-0.58)
(1-sided p value <0.001)

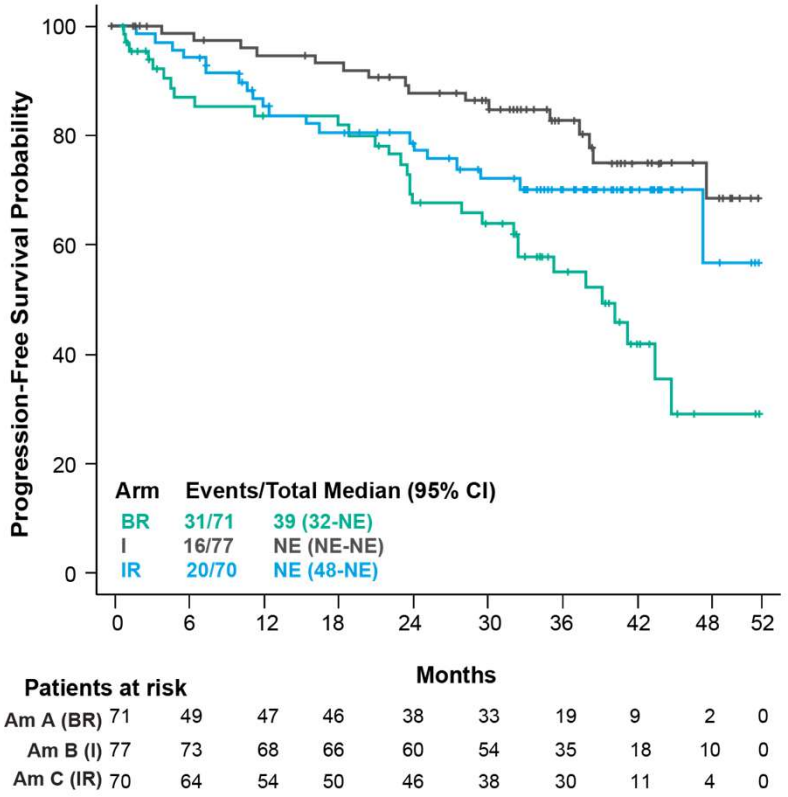
IR vs BR
HR: 0.38 (95% CI: 0.25-0.59)
(1-sided p value <0.001)

IR vs I
HR: 1.00 (95% CI: 0.62-1.62)
(1-sided p value 0.49)

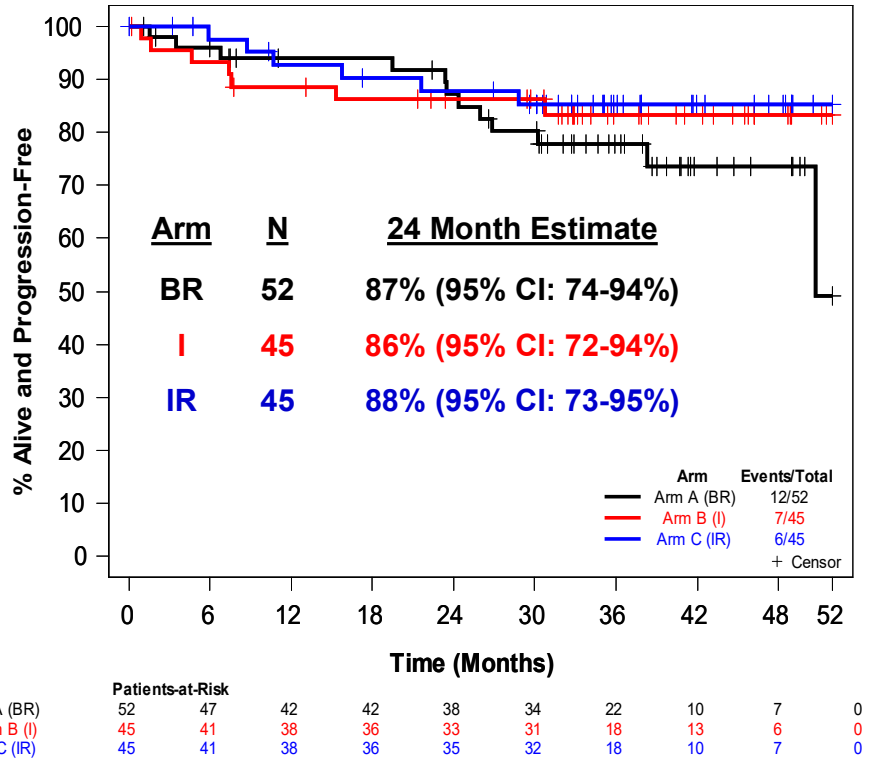
Woyach et al., ASH 2018,

IGVH mutated & unmutated Subgroups PFS
Intention-to-Treat Patient Population

IGVH unmutated



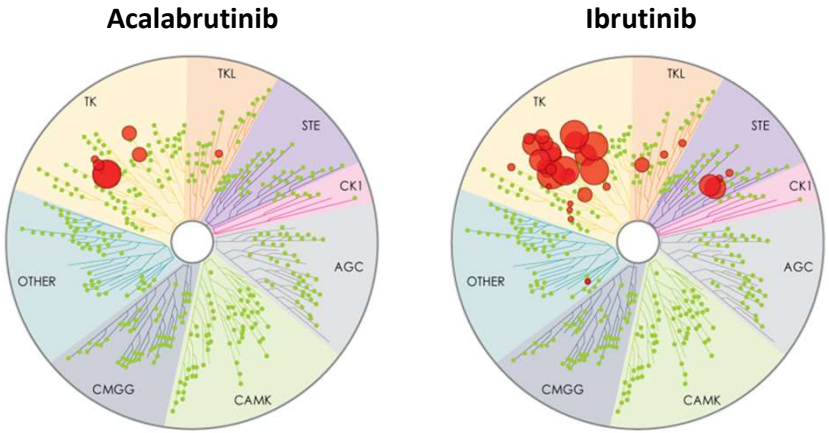
IGVH Mutated



Acalabrutinib

- Highly-selective, potent kinase inhibitor
- Designed to minimize off-target activity with minimal effects on TEC, EGFR, or ITK signaling

Kinase selectivity profiling at 1 μM



The size of the red circle is proportional to the degree of inhibition.

Kinase Inhibition IC_{50} (nM)		
Kinase	**Acalabrutinib**	**Ibrutinib**
BTK	5.1	1.5
TEC	126	10
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

Abstract 31

Phase 3 Study of Acalabrutinib Combined With Obinutuzumab or Alone vs Obinutuzumab Plus Chlorambucil in Patients With Treatment-Naive Chronic Lymphocytic Leukemia: Results From ELEVATE TN

Jeff P. Sharman, Versha Banerji, Laura Maria Fogliatto, Yair Herishanu, Talha Munir, Renata Walewska, George Follows, Karin Karlsson, Paolo Ghia, Gillian Corbett, Patricia Walker, Miklos Egyed, Wojciech Jurczak, Gilles Salles, Ann Janssens, Florence Cymbalista, William Wierda, Steven Coutre, John M. Pagel, Alan P. Skarbnik, Manali Kamdar, Jennifer A. Woyach, Raquel Izumi, Veerendra Munugalavadla, Priti Patel, Min Hui Wang, Sofia Wong, and John C. Byrd

ClinicalTrials.gov identifier: NCT02475681. This study was sponsored by Acerta Pharma, a member of the AstraZeneca group

ELEVATE TN Study Design (ACE-CL-007)

Treatment-naive CLL (N=535)

Age ≥65 or

<65 years with coexisting conditions:

- CIRS score >6, or
- creatinine clearance <70 mL/min

Stratification

- del(17p), y vs n
- ECOG PS 0-1 vs 2
- Geographic region (N America, W Europe, or other)

RANDOMIZE 1:1:1

Acalabrutinib[a] + Obinutuzumab (G)[b]

[a]100 mg PO BID

[b]1000 mg IV on D1, 2, 8, and 15 of Cycle 2, + D1 of subsequent 28-day cycles for a total of 6 cycles

Acalabrutinib

100 mg PO BID

Obinutuzumab (G)[c] + Chlorambucil[d]

[c]1000 mg IV on D1, 2, 8, and 15 of Cycle 1, + D1 of subsequent 28-day cycles for a total of 6 cycles

[d]0.5 mg/kg PO on D1 + 15 of each 28-day cycle for 6 cycles

Primary endpoint

- PFS (assessed by IRC) Acala-G vs G-Clb

Key secondary endpoints

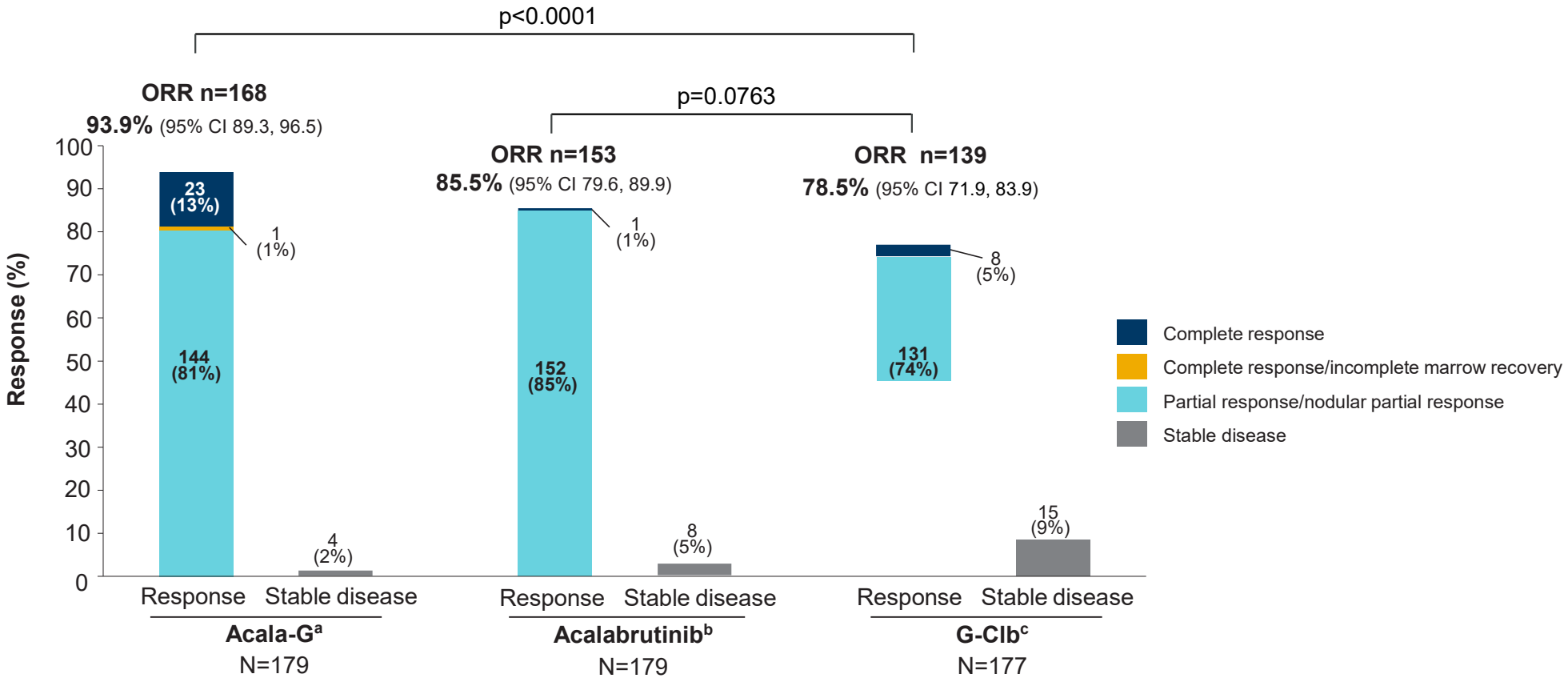
- PFS acalabrutinib vs G-Clb
- ORR (assessed by IRC and investigator)
- Time to next treatment
- OS
- Safety

***Crossover** from G-Clb to acalabrutinib was allowed after IRC-confirmed progression*

- Interim analysis was planned based on events (after occurrence of ~111 IRC-assessed PFS events in the combination therapy arms) or after 24 months if the required number of events was not met by this time

Acala, acalabrutinib; CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenously; OS, overall survival; PO, orally

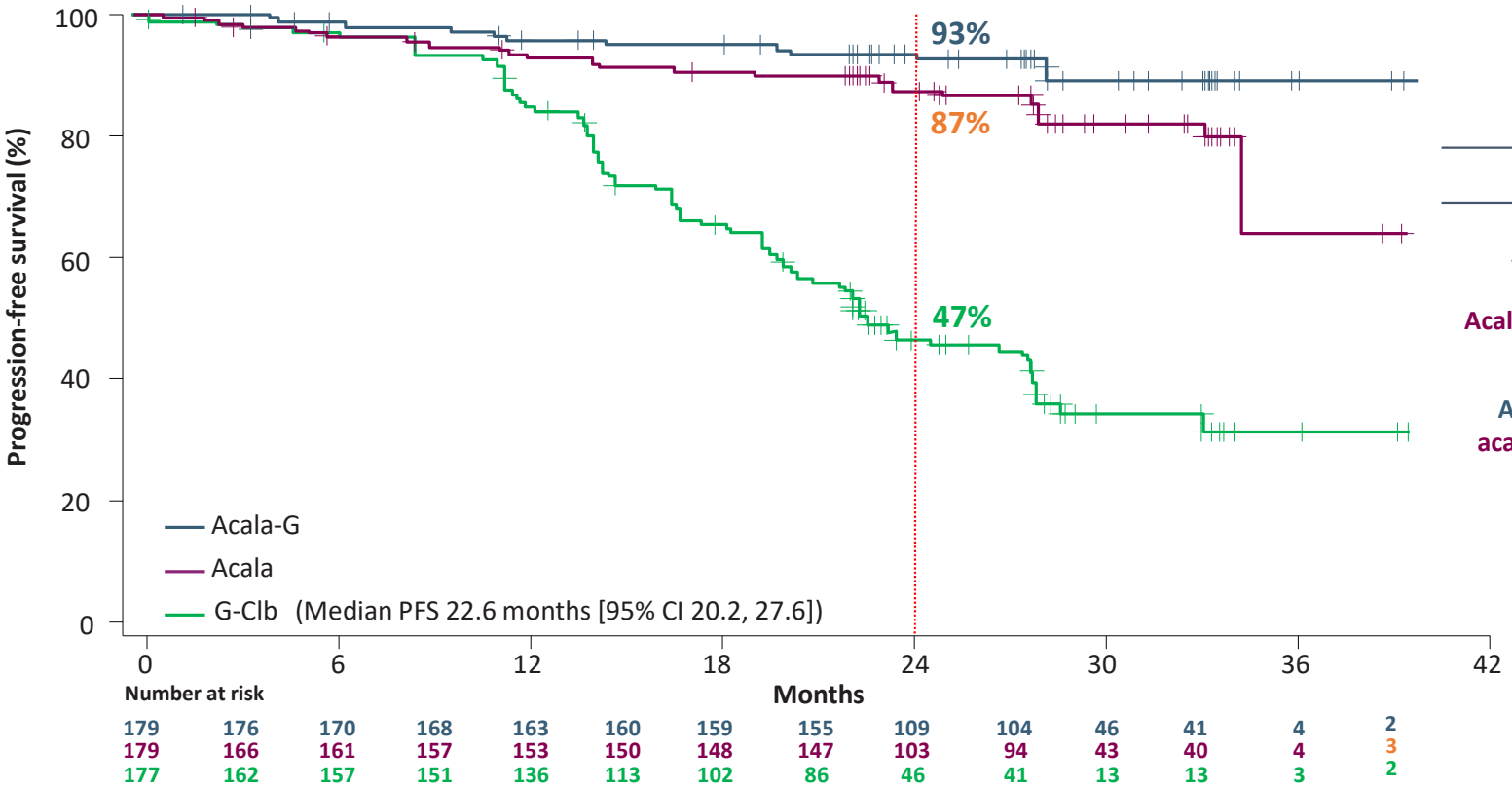
IRC-Assessed Response Rates



[a]Six patients (3%) had unknown response, and one patient (1%) had a response of non-PD, defined as not having adequate CT or MRI data and not meeting criteria for PD by physical examination. [b]Two patients (1%) had PR-L, three patients (2%) had PD, 12 patients (7%) had unknown response, and one patient's (1%) response was not evaluable. [c]Two patients (1%) had non-PD, 12 patients (7%) had an unknown response, one patient (1%) had no evaluable disease, and eight patients' (5%) responses were not evaluable
PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis

IRC-Assessed Progression-Free Survival

Median follow-up 28.3 months



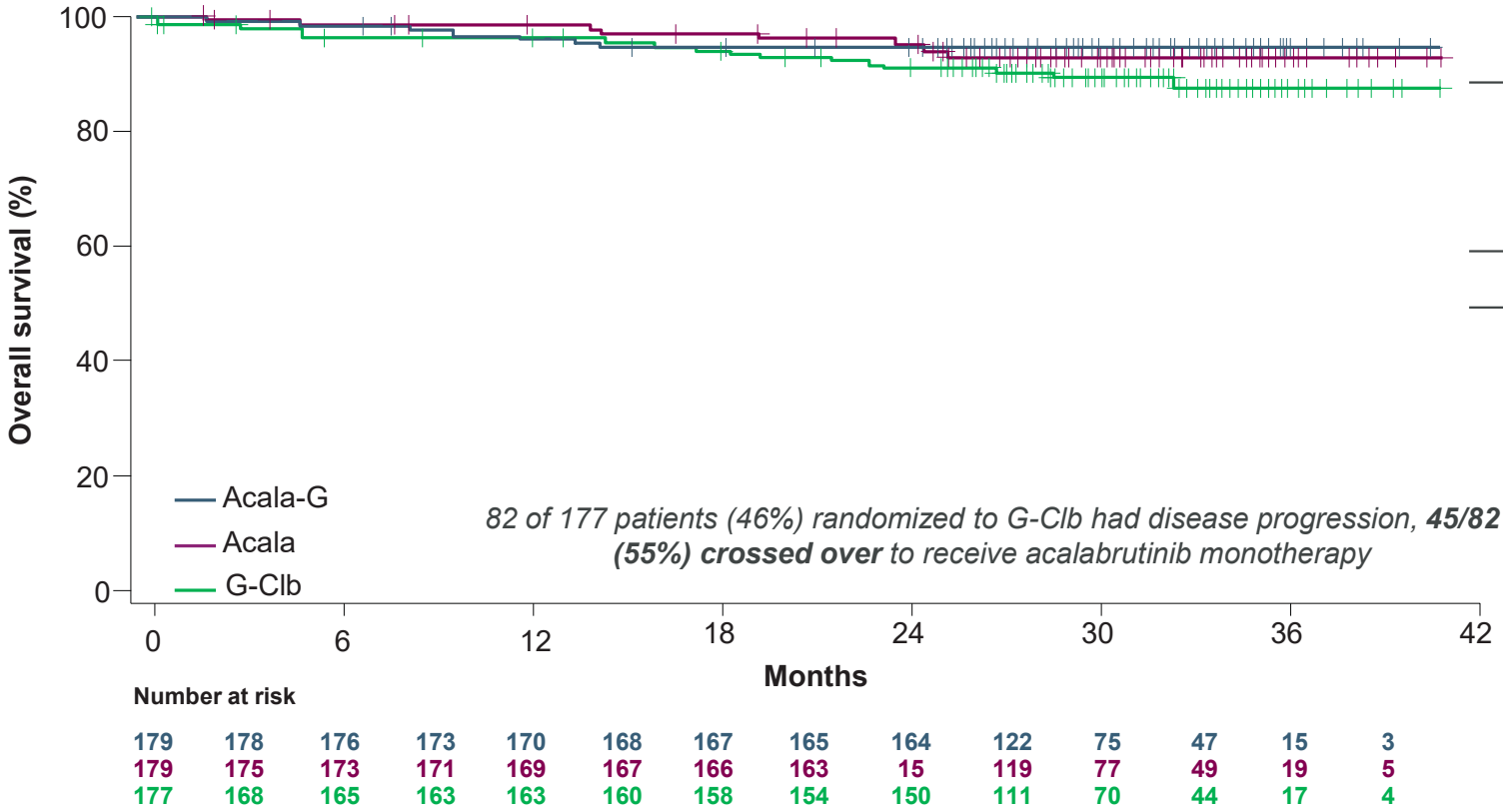
Hazard ratio (95% CI)	
Acala-G vs G-Clb	**0.10** (0.06, 0.17) p<0.0001
Acalabrutinib vs G-Clb	**0.20** (0.13, 0.30) p<0.0001
Acala-G vs acalabrutinib[a]	**0.49** (0.26, 0.95)

Kaplan-Meier estimates performed by IRC and all analyses for the intention-to-treat population. No. of events: Acala-G, 14 (7.8%); Acala, 26 (14.5%); G-Clb, 93 (52.5%)

[a]*Post hoc* analysis.

Richter's transformation occurred in: Acala-G n=1, Acala n=5, G-Clb n=1

Overall Survival
(Median follow-up 28.3 months)



*82 of 177 patients (46%) randomized to G-Clb had disease progression, **45/82 (55%) crossed over** to receive acalabrutinib monotherapy*

Deaths	N (%)
Acala-G	9 (5.0)
Acala	11 (6.1)
G-Clb	17 (9.6)
Hazard ratio (95% CI)	
Acala-G vs G-Clb	**0.47** (0.21, 1.06) p=0.0577
Acalabrutinib vs G-Clb	**0.60** (0.28, 1.27) p=0.1556

The New Changing Treatment Paradigm in CLL

- **Bcl2 inhibitors**

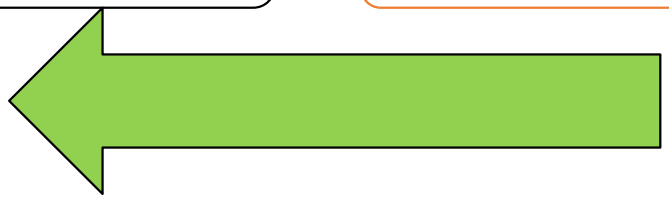
MRD Negativity (Cure)

- Goal of therapy: **disease eradication**
  - High CR rates
  - MRD negative
  - Long PFS
- Targets the pathogenic cause of CLL (elimination of malignant clone)
- Finite treatment course

- **BCR inhibitors**

Preservation of Response and Amelioration of Symptoms (Treat to Progression)

- Goal of therapy: **disease control**
  - Long PFS
  - Duration of response
- Sustained PRs as best response (or SD)



CLL-14

The NEW ENGLAND JOURNAL of MEDICINE

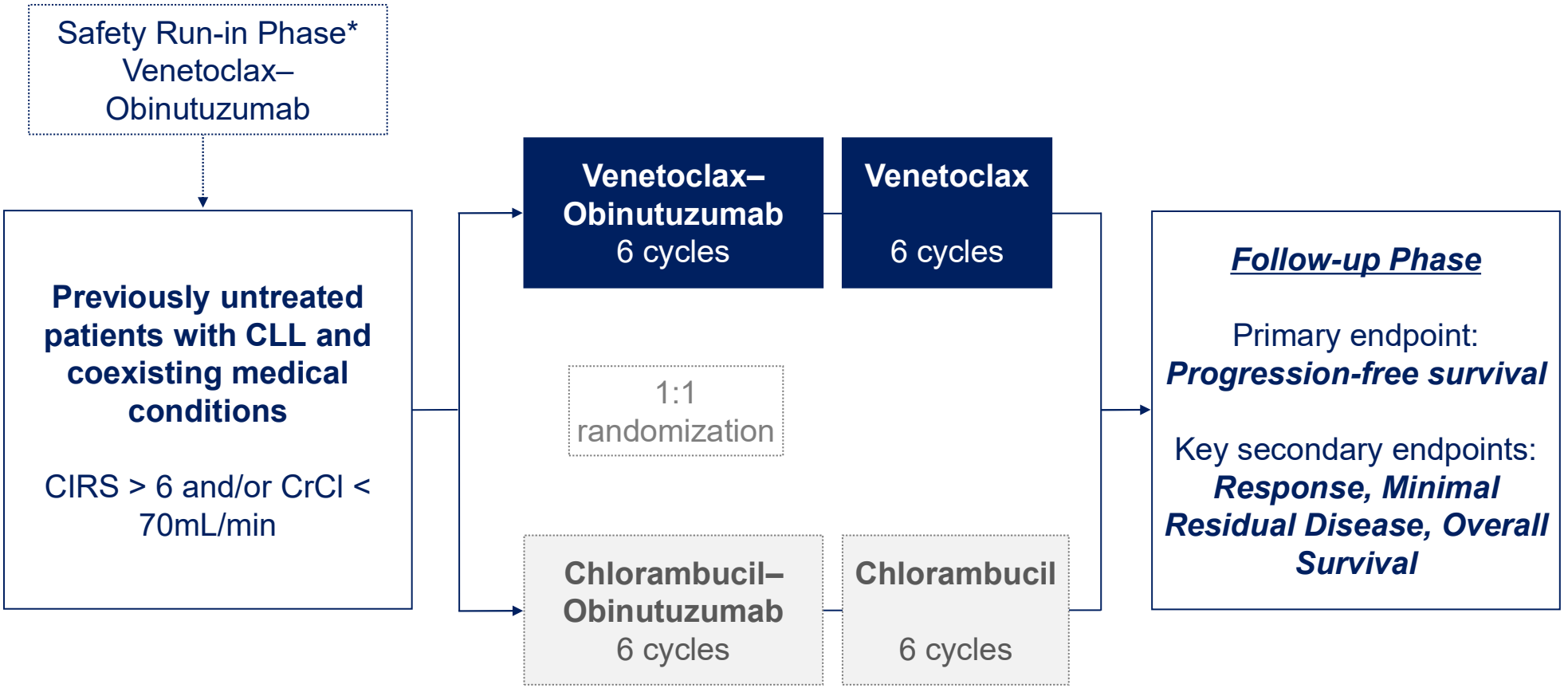
ORIGINAL ARTICLE

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

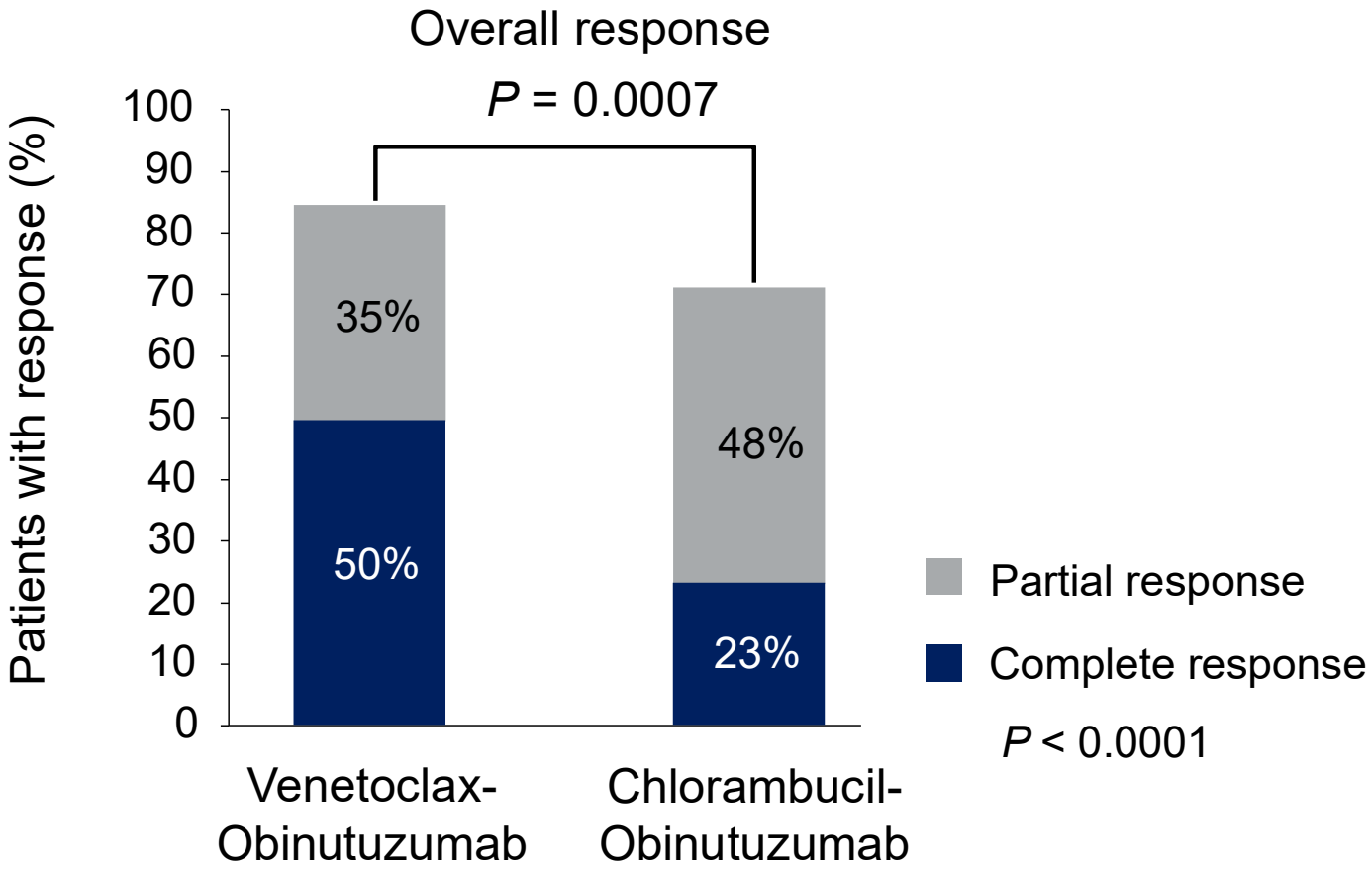
Fisher et al. New Eng J Med, June 2019

TRIAL DESIGN

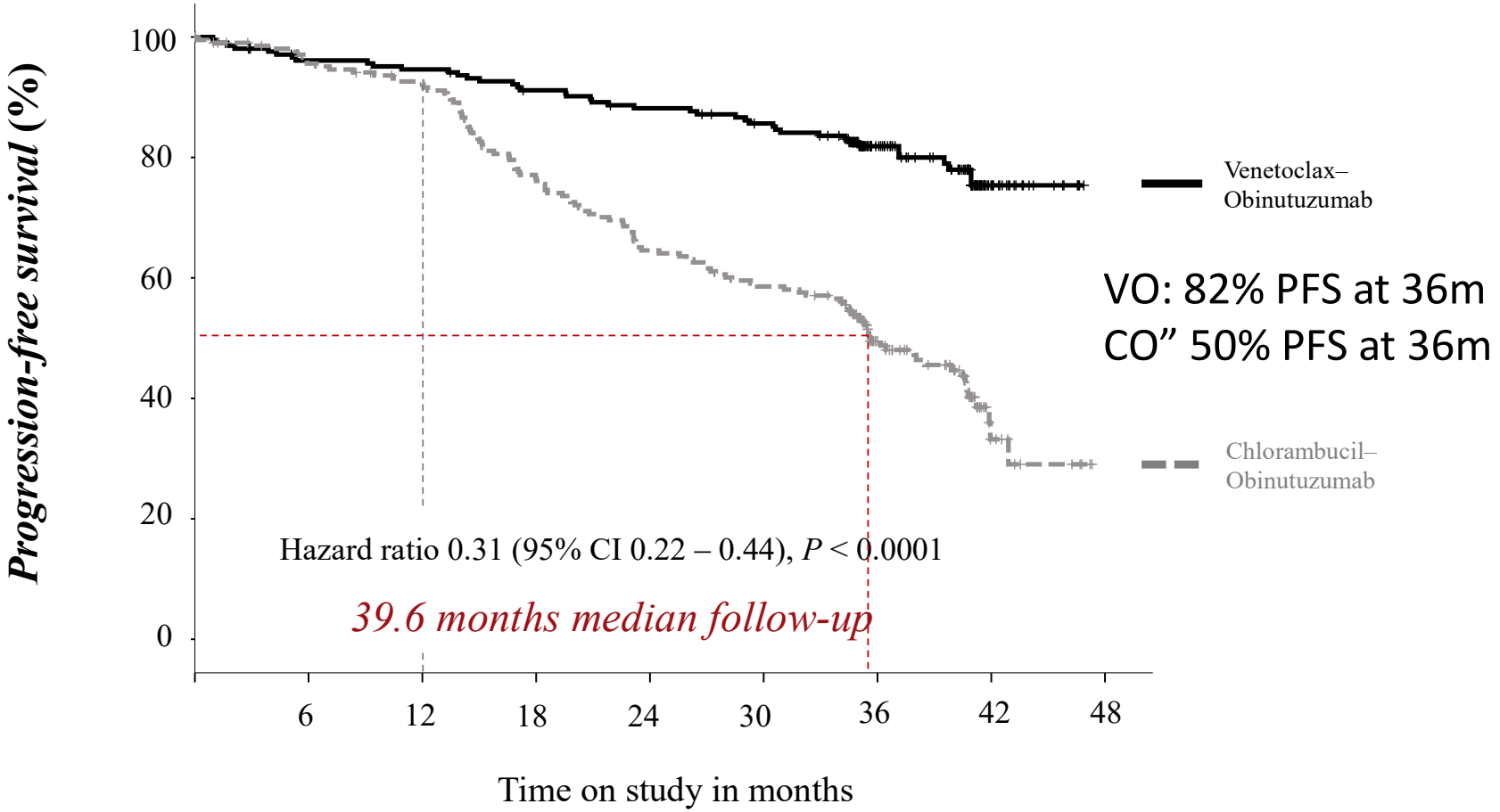


CLL-14

RESPONSE TO TREATMENT



Progression Free Survival

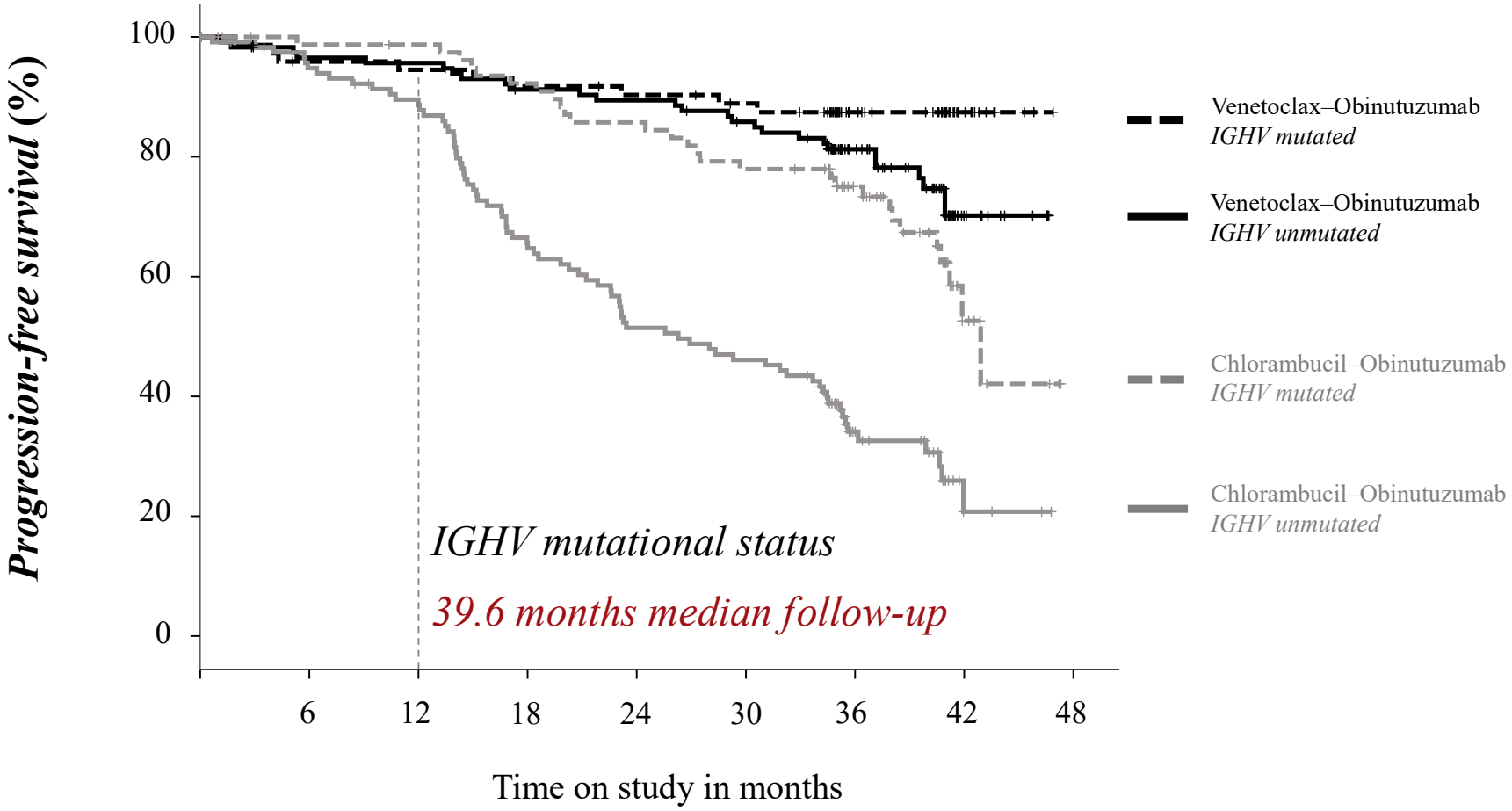


VO: 82% PFS at 36m

CO" 50% PFS at 36m

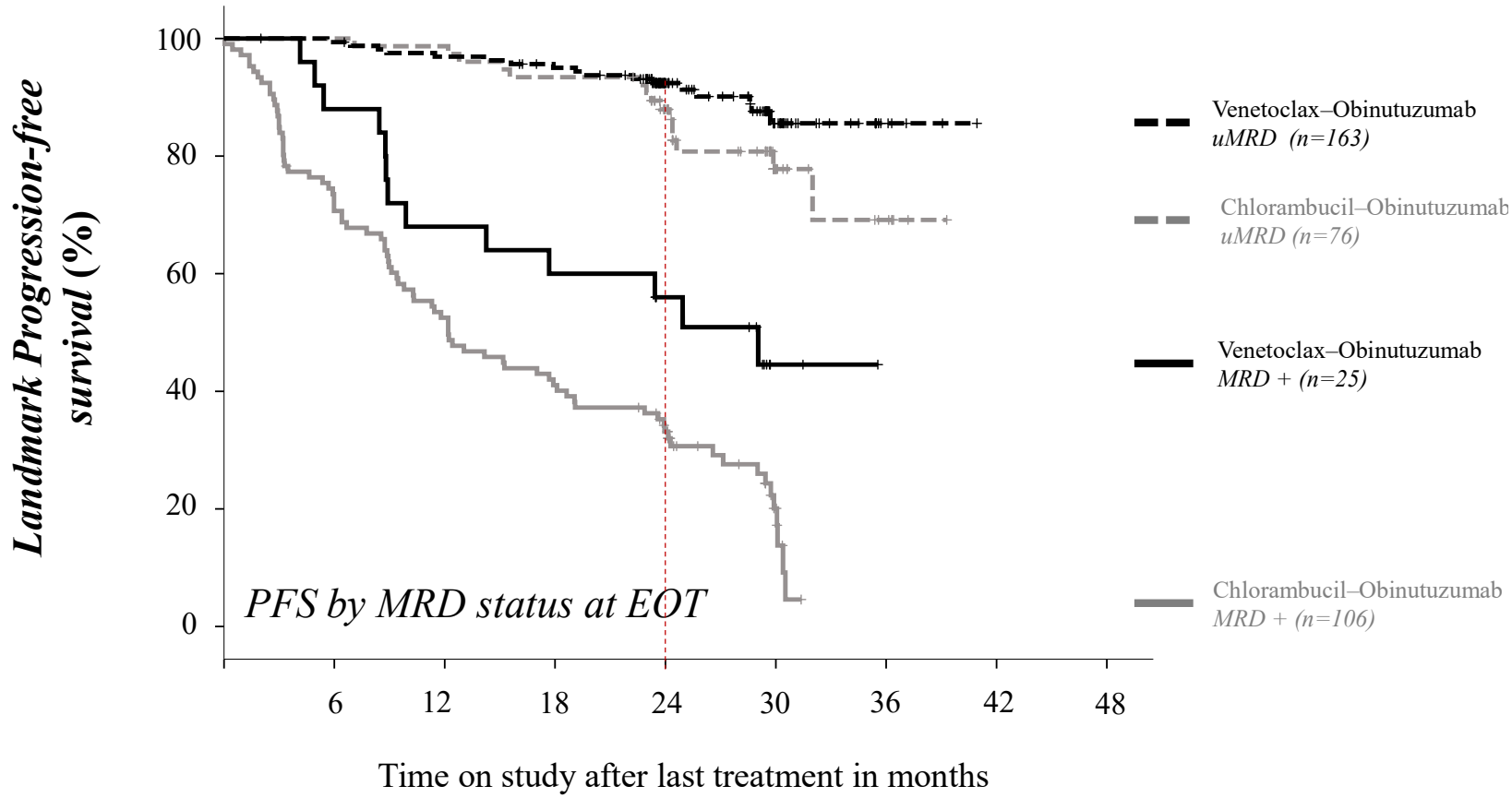
● CLL*14*

PFS by IGHV mutational status



● CLL *14*

PFS by MRD status at EOT



MRD status as per ITT

Undetectable MRD by ASO-PCR	**Venetoclax-Obinutuzumab**	**Chlorambucil-Obinutuzumab**	*P* value
Number of patients, N	**216**	**216**	
Peripheral blood			
Undetectable (<10-4)	**76 %**	**35 %**	**< 0.001**
Undetectable ($<10^{-4}$) in complete response	42 %	14 %	< 0.001
Bone marrow			
Undetectable ($<10^{-4}$)	**57 %**	**17 %**	**< 0.001**
Undetectable ($<10^{-4}$) in complete response	34 %	11 %	< 0.001

By ASO-PCR 3 months after completion of treatment
Concordance BM vs. Blood: 86.8% for both treatment groups

MRD status as per NGS testing

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

By NGS in peripheral blood 3 months after completion of treatment
Adaptive Clonoseq assay, cut-off: 10^{-4}, 10^{-5} and 10^{-6}

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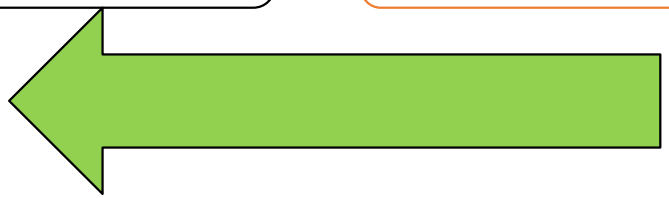
  - Duration of response
- Sustained PRs as best response (or SD)



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Ibrutinib and Venetoclax for First-Line Treatment of CLL

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Phase 2 Firstline Ibrutinib and Venetoclax in High-Risk CLL

Key eligibility criteria

- Treatment-naïve CLL meeting 2008 iwCLL criteria
- ≥ 1 high-risk feature: del(17p), mutated TP53, del(11q), *IGHV* unmutated, and/or age ≥ 65 y

Part 1
Ibr 420 mg/d for 3 cycles (continued c4-27) +
Cycle 4-27 added Ven weekly ramp-up to 400 mg/d

Combo administered for 24 cycles

Patients with BM U-MRD4 (10^{-4}) at 24 cycles of combined therapy stop Ibr

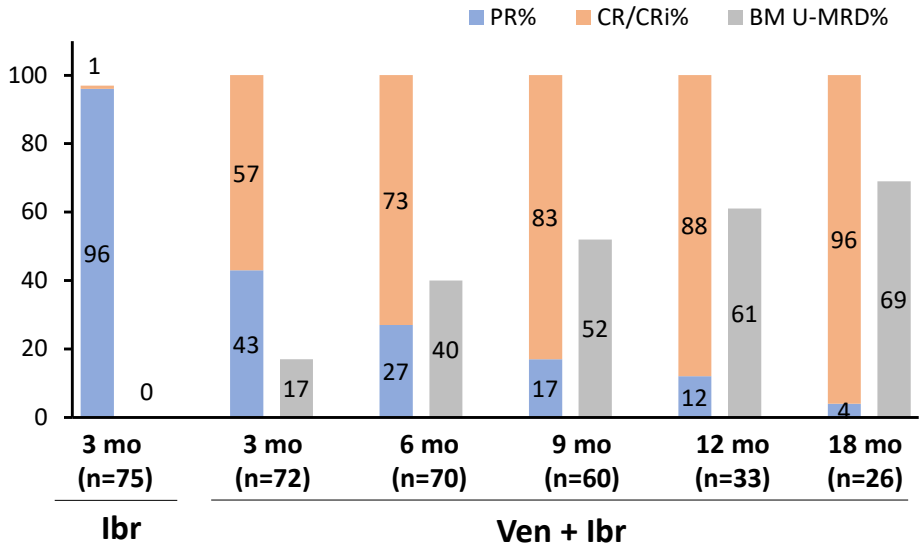
Patients with MRD-positive CLL continued Ibr

Response assessed PB, BM and CT (2008 iwCLL) after cycle 3 of Ibr, and q6mo during year 2 of Ibr + Ven

Primary endpoint: CR/CRi

Jain et al. ASH 2018. Abstract 186.
https://clinicaltrials.gov/ct2/show/NCT02756897.

- 92% of patients had *IGHV* unmutated, TP53, or del(11q)
- n=75 initiated Ven; median follow-up was 14.8 mo (range, 5.6-27.5)



- 76% of patients ≥65 y (n=17) achieved UMRD4 at 12 mo of Ibr+Ven
- U-MRD4 responses were seen across subgroups, including *IGHV* unmutated, del(17p), and *TP53*, *NOTCH1*, and *SF3B1* mutations

Ibrutinib Plus Venetoclax for First-Line Treatment of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Results From the MRD Cohort of the Phase 2 CAPTIVATE Study

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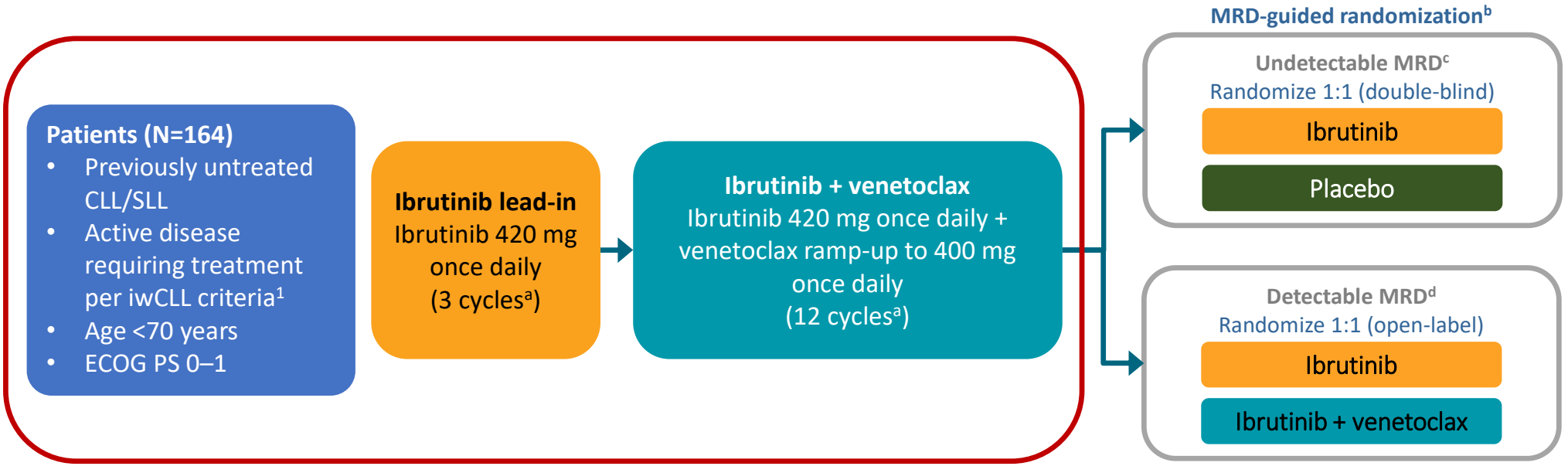
CAPTIVATE-MRD Cohort: Study Design



- Results presented for prerandomization phase of the CAPTIVATE-MRD cohort (N=164) with 12 cycles of ibrutinib + venetoclax prior to MRD-guided randomization
- Time-limited therapy with 12 cycles of ibrutinib + venetoclax to be evaluated in separate fixed-duration cohort (N=159)

ECOG PS, Eastern Cooperative Oncology Group performance status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia.
[a]1 cycle = 28 days; patients may have received 1 additional cycle while awaiting confirmation of undetectable MRD for randomization. [b]Stratified by *IGHV* mutation status. [c]Confirmed as having undetectable MRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles in PB, and undetectable MRD in both PB and BM. [d]Defined as having detectable MRD or undetectable MRD not confirmed serially or not confirmed in both PB and BM.
1. Hallek M et al. *Blood*. 2008;111:5446-5456.

High Rates of Undetectable MRD Achieved in PB and BM With Up to 12 Cycles of Combination

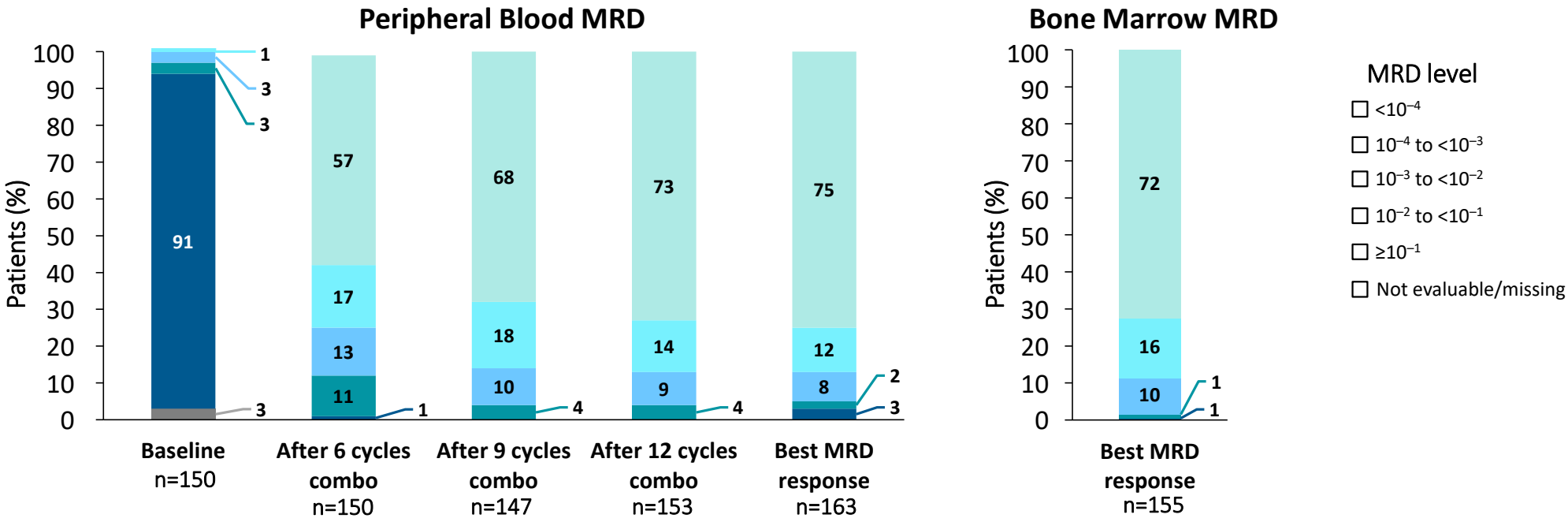
	Peripheral Blood n=163	Bone Marrow[a] n=155
Undetectable MRD in evaluable patients[b] (95% CI)	75% (67-81)	72% (64-79)

- In patients with undetectable MRD at cycle 16 in peripheral blood with matched bone marrow samples, 93% had undetectable MRD in both peripheral blood and bone marrow
- In the intention-to-treat population (N=164), undetectable MRD was achieved in 74% of patients in peripheral blood and in 68% of patients in bone marrow with up to 12 cycles of combination

[a]BM MRD assessment was scheduled after completion of 12 cycles of combination treatment.
[b]Patients with undetectable MRD at any postbaseline assessment; evaluable patients are those who had at least 1 MRD sample taken postbaseline.

ASH 2019, CAPTIVATE-MRD; Tam et al.

High Rates of Undetectable MRD Sustained Over Time in MRD-Evaluable Patients



- Proportion of patients with undetectable MRD in peripheral blood increased over the 12 cycles of combination therapy

[a]BM MRD assessment was scheduled after completion of 12 cycles of combination treatment.

Preliminary Safety and Efficacy Results from a Phase 2 Study of Acalabrutinib, Venetoclax, and Obinutuzumab in Patients with Previously Untreated Chronic Lymphocytic Leukemia

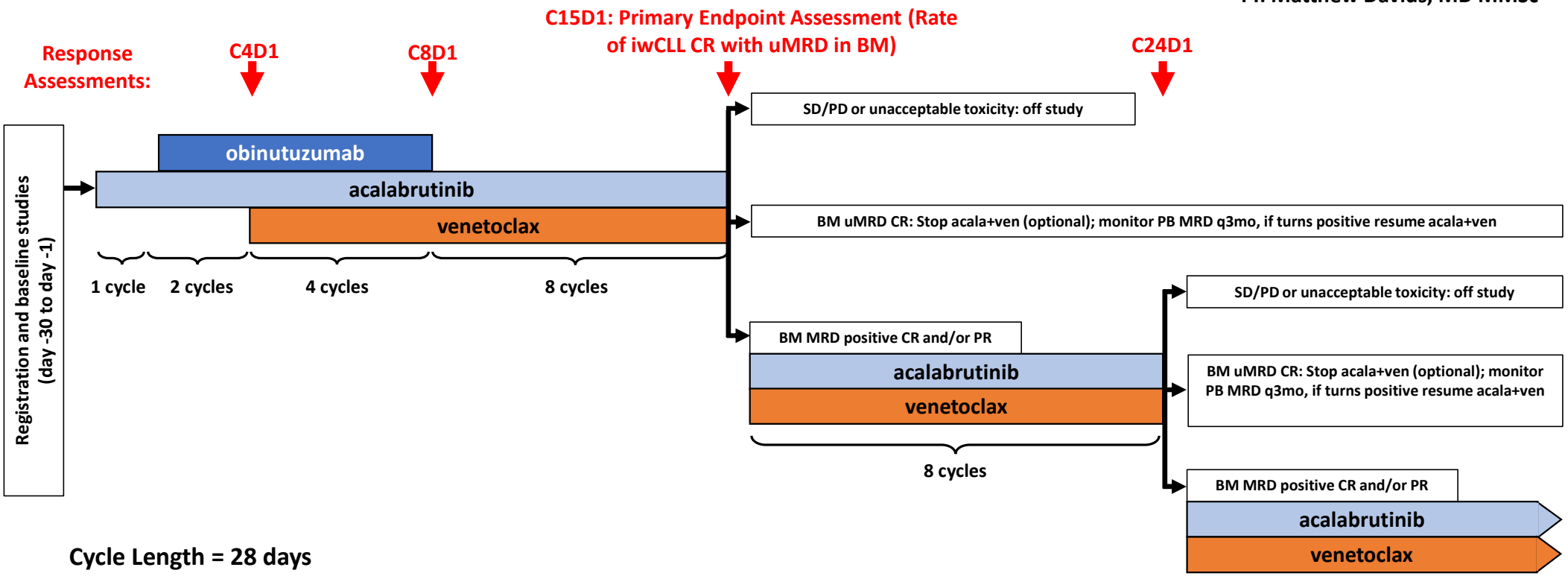
Benjamin L. Lampson, MD, PhD[1], Svitlana Tyekucheva, PhD[2], Jennifer L. Crombie, MD[1], Austin I. Kim, MD[1], Reid W. Merryman, MD[1], Jessica C. Lowney,[1] Josie Montegaard, NP[1], Victoria Patterson, RN[1], Caron A. Jacobson, MD[1], Eric D. Jacobsen, MD[1], Ann S. LaCasce, MD, MMSc[1], Jon E. Arnason, MD[3], Philippe Armand, MD, PhD[1], David C. Fisher, MD[1], Jennifer R. Brown, MD, PhD[1], and Matthew S. Davids, MD, MMSc[1]

[1]Dept. of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; [2]Dept. of Biostatistics, Dana-Farber Cancer Institute, Boston, MA; [3]Beth Israel Deaconess Medical Center, Boston, MA

2019 ASH Annual Meeting – Orlando, Florida – December 7, 2019

Study Schema

PI: Matthew Davids, MD MMSc



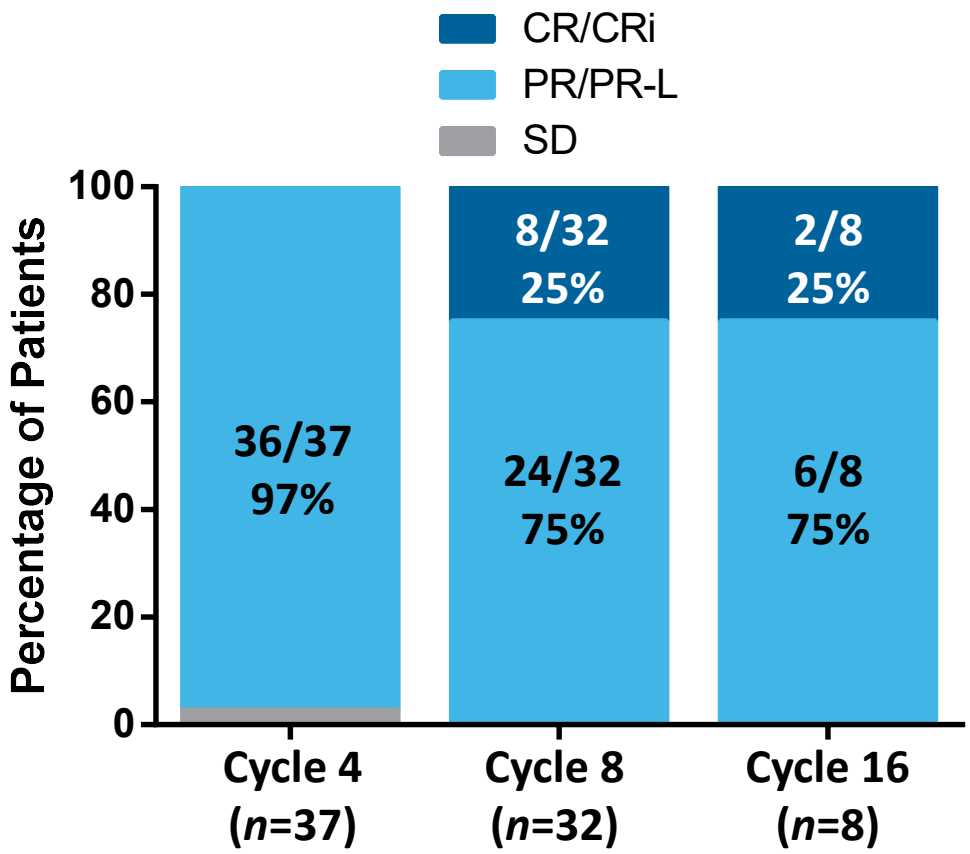
Cycle Length = 28 days
Acalabrutinib and obinutuzumab at standard doses
Venetoclax 20mg C4D1, 50mg C4D2, then standard ramp-up to 400mg dose
PJP and HSV/VZV PPX mandatory

Median Follow-up:
11 cycles (range, 6-16)

Efficacy Analysis: Response

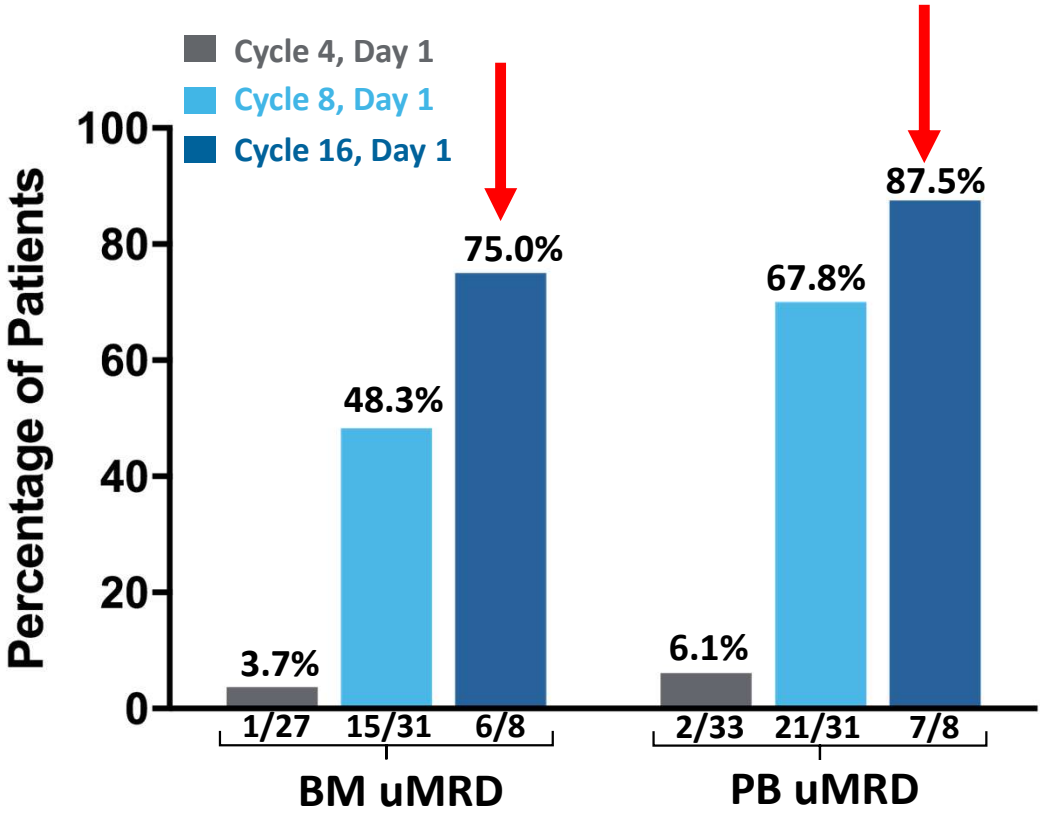
Response Category	N	%
Cycle 4 ORR	37	97.3%
CR/CRi	0	
PR/PR-L	36	
SD	1	
Cycle 8 ORR	32	100%
CR/CRi	8	25.0%
PR/PR-L	24	75.0%
SD	0	0%
Cycle 16 ORR	8	100%
CR/CRi	2	25.0%
PR/PR-L	6	75.0%
SD	0	0%

Median Follow-up:
11 cycles (range, 6-16)



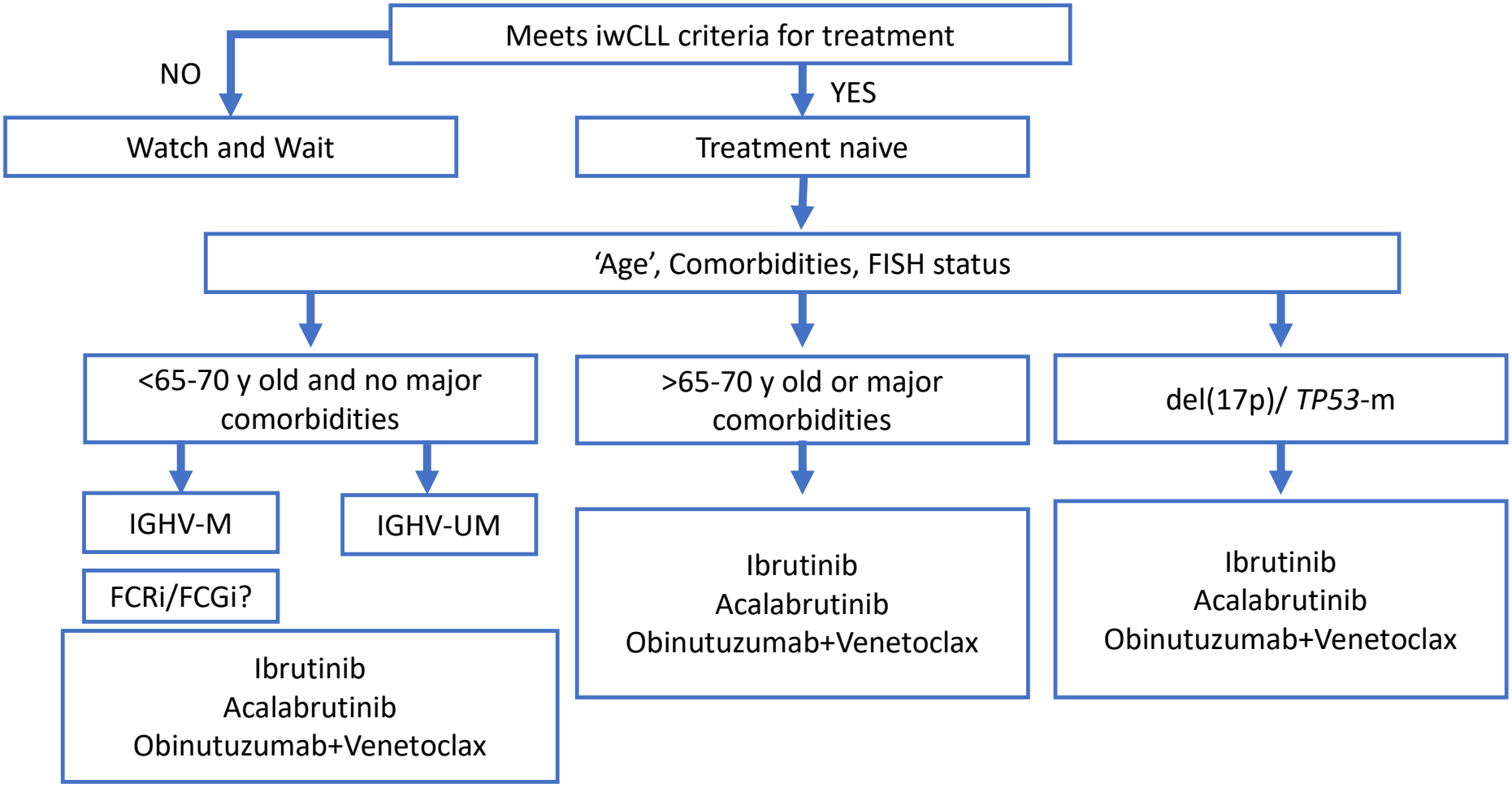
Efficacy Analysis: MRD

Response Category	N	%
Cycle 4		
uMRD Bone Marrow (BM)	1/27	3.7%
uMRD Blood	2/33	6.1%
CR with uMRD BM	0	0%
Cycle 8		
uMRD BM	15/31	48.3%
uMRD Blood	21/31	67.8%
CR with uMRD BM	5/31	16.7%
Cycle 16		
uMRD BM	6/8	75.0%
uMRD Blood	7/8	87.5%
CR with uMRD BM	1/8	12.5%

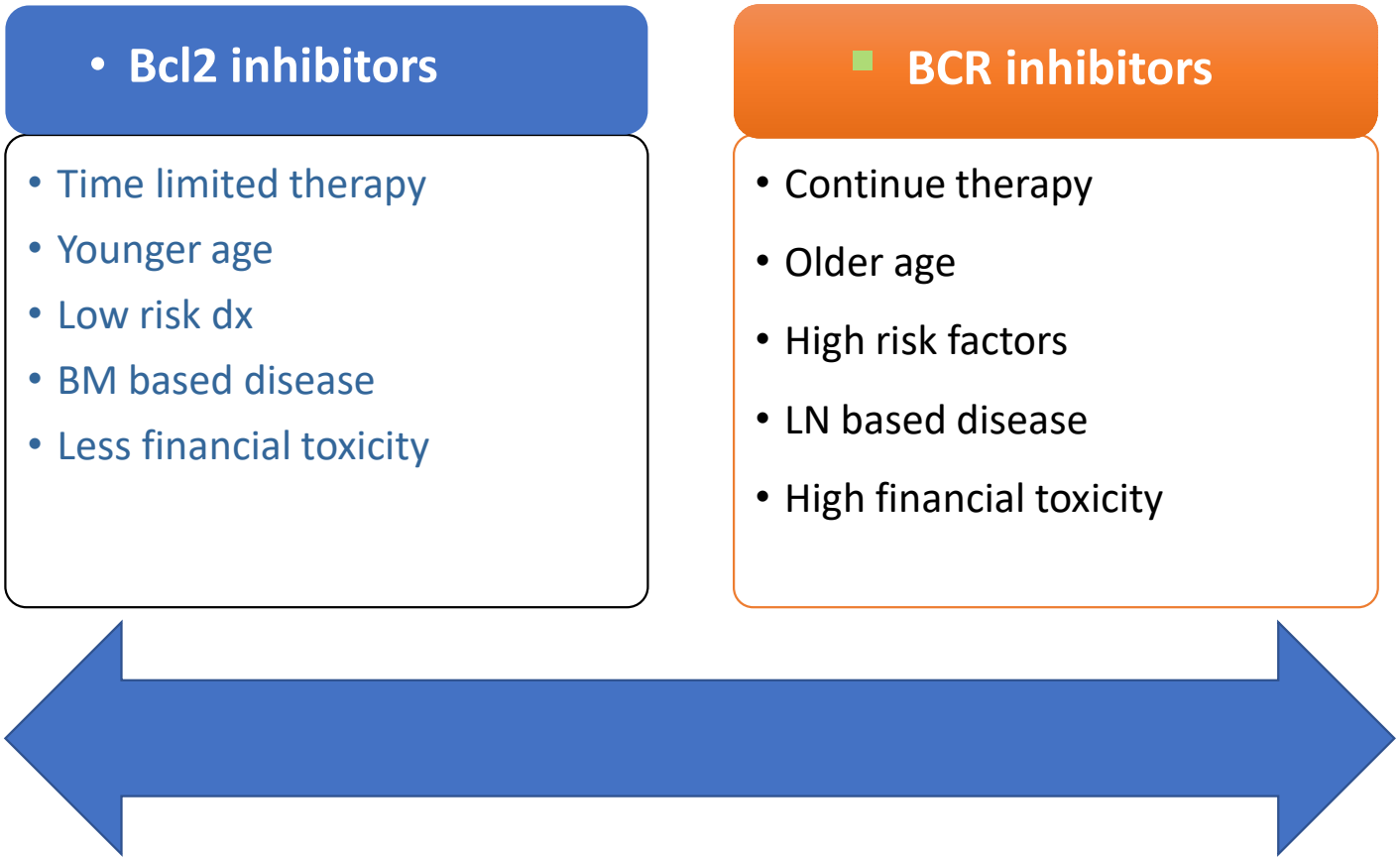


No significant difference in response rate or uMRD between *IGHV* subgroups

CLL Front Line Treatment Algorithm 2020

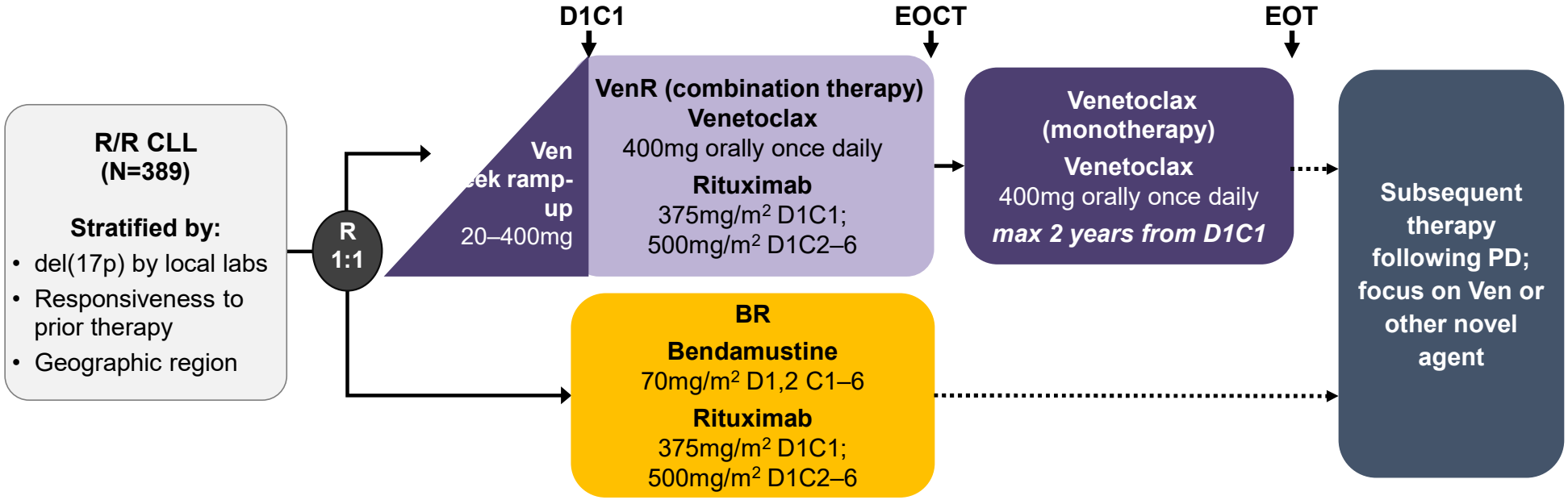


The alternatives Treatment Paradigm in CLL



Treatment for Relapsed/Refractory CLL

MURANO study design

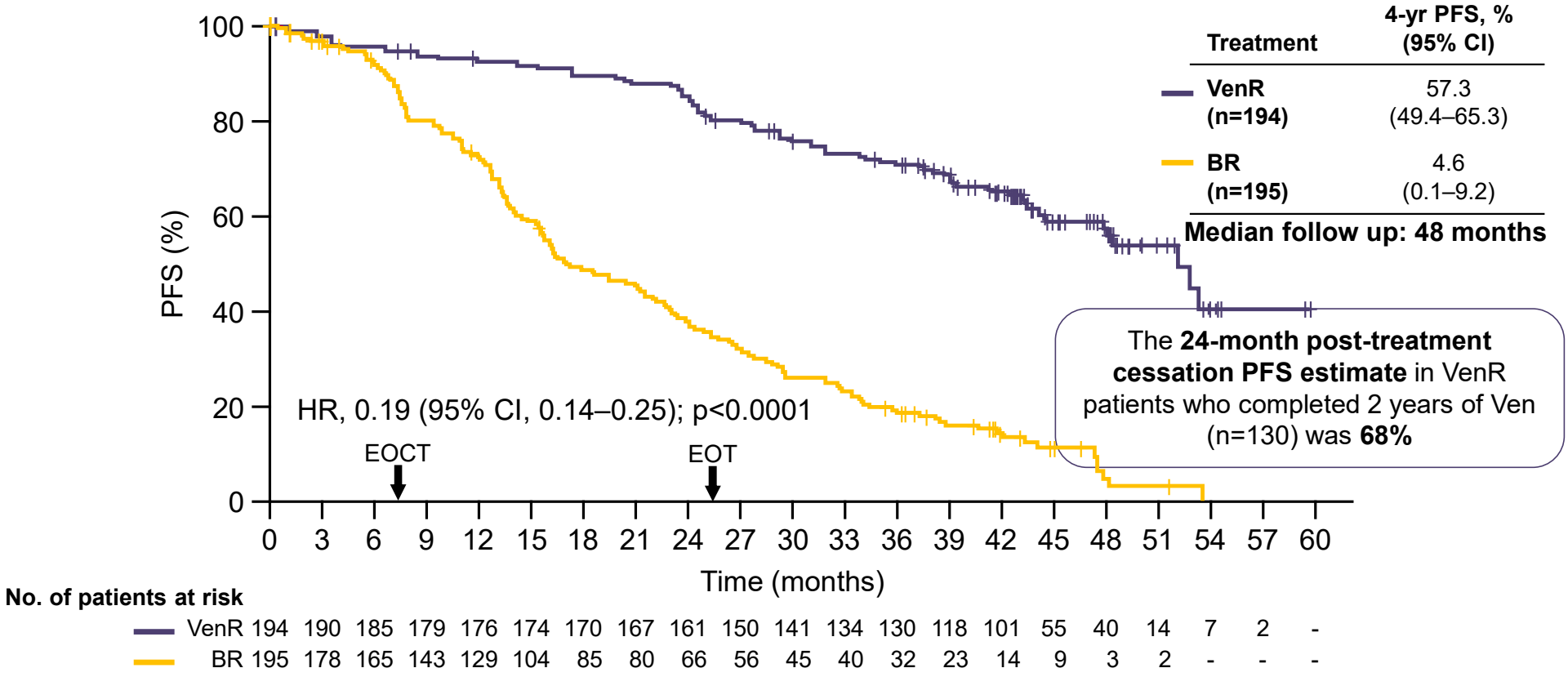


- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoint:** rates of clearance of MRD
- Clinical response and MRD* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

*Undetectable MRD defined as <1 CLL cell/10,000 leukocytes, determined by ASO-PCR or flow cytometry per iwCLL recommendations for reporting of MRD.
BR, bendamustine–rituximab; D1C1, day 1, cycle 1; D1C2-6, day 1, cycles 2-6; EOCT, end of combination treatment; EOT, end of treatment; MRD, minimal residual disease; PB, peripheral blood; PD, progressive disease/disease progression; R, randomization; R/R, relapsed/refractory VenR, venetoclax–rituximab

PFS benefit with VenR vs BR sustained 2 years post-EOT

Investigator-assessed PFS

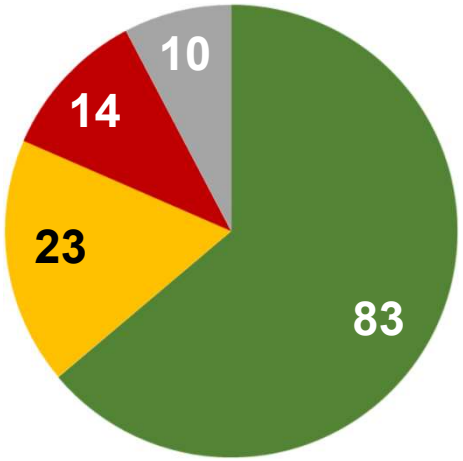


BR, bendamustine–rituximab; CI, confidence interval; EOCT, end of combination treatment; EOT, end of treatment; HR, hazard ratio; PFS, progression-free survival; VenR, venetoclax–rituximab

Most patients had uMRD in PB upon completion of Ven monotherapy (EOT)

- In total, 130/194 patients completed 2 years of Ven therapy
- With a median 22 months off therapy (range 1–25 months), **35 progression events had occurred in 130 patients who completed 2 years of Ven**

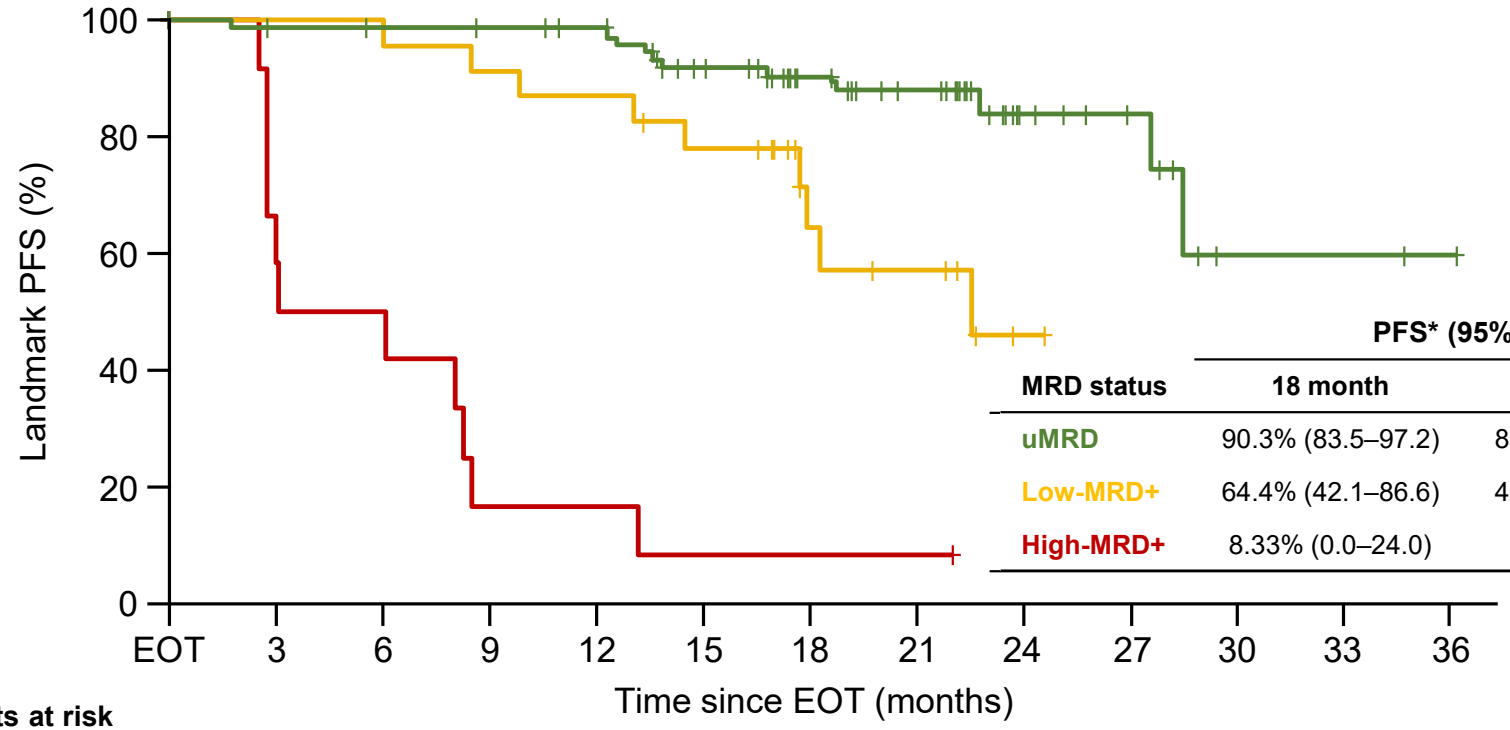
MRD status at EOT (month 24; n=130)



Status off-therapy, n (%)	uMRD ($<10^{-4}$) n=83	Low-MRD+ (10^{-4}–10^{-2}) n=23	High-MRD+ ($>10^{-2}$) n=14	Unknown n=10
Progression-free	72 (86.7)	14 (60.9)	1 (7.1)	8 (80.0)
PD	11 (13.3)	9 (39.1)	13 (92.9)	2 (20.0)

EOT, end of treatment; PB, peripheral blood; PD, progressive disease/disease progression; (u)MRD, (undetectable) minimal residual disease; Ven, venetoclax; VenR, venetoclax–rituximab

PFS was longest in patients in the VenR arm with uMRD at EOT



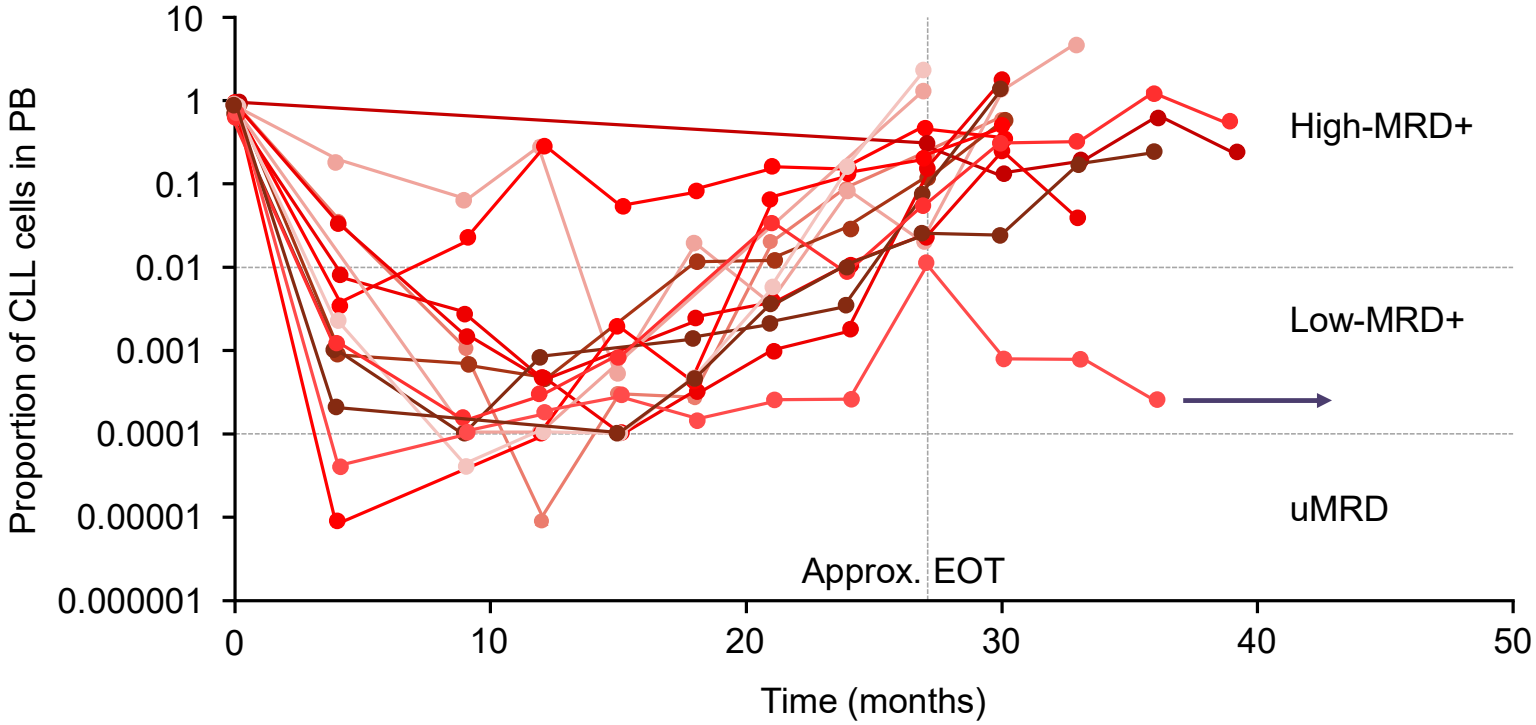
MRD status	PFS* (95% CI) 18 month	24 month
uMRD	90.3% (83.5–97.2)	83.9% (72.9–94.9)
Low-MRD+	64.4% (42.1–86.6)	45.7% (18.1–73.4)
High-MRD+	8.33% (0.0–24.0)	NE

No. of patients at risk

VenR uMRD	83	78	77	76	74	63	42	33	13	9	2	2	1
VenR low-MRD+	23	23	23	21	20	17	9	7	1	-	-	-	-
VenR high-MRD+	12	8	6	2	2	1	1	1	-	-	-	-	-

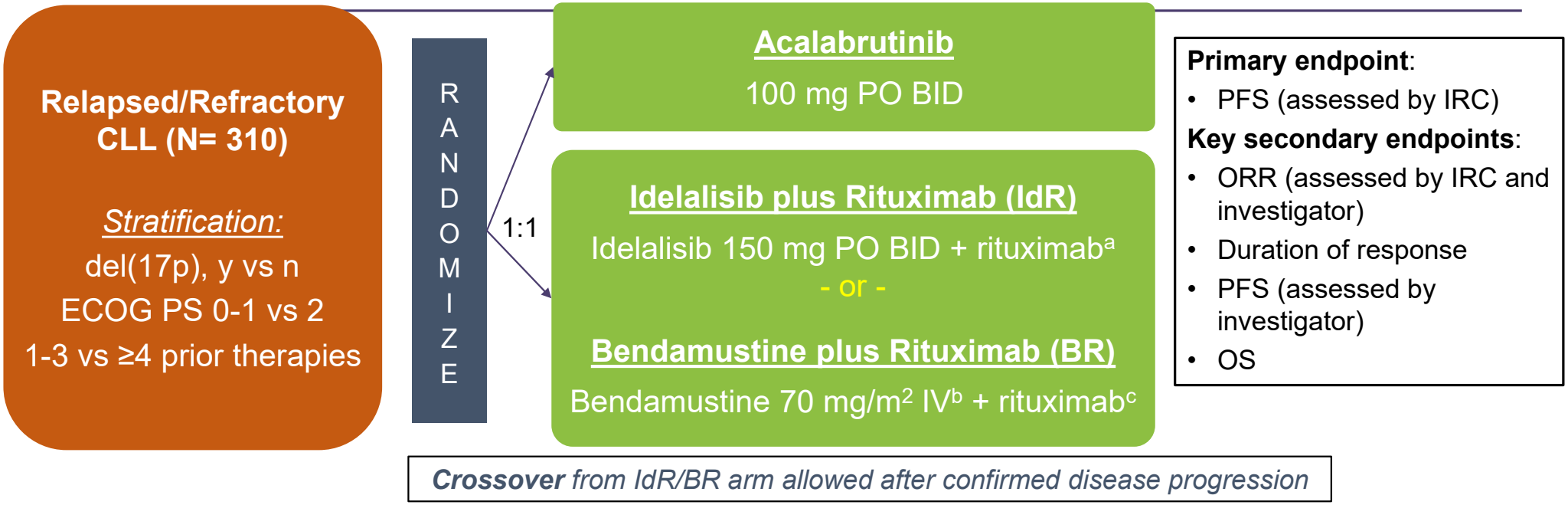
*PFS rates shown refer to time since EOT. 2/14 VenR patients with high-MRD+ status had PD before EOT landmark visit and as such were not included in this analysis. CI, confidence interval; EOT, end of treatment; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; (u)MRD, (undetectable) minimal residual disease; NE, not evaluable; VenR, venetoclax–rituximab

Patients with high-MRD+ status at EOT had rising MRD levels in PB on treatment prior to Ven cessation



EOT; end of treatment; PB, peripheral blood; (u)MRD, (undetectable) minimal residual disease

ASCEND Study Design (ACE-CL-309)



- Interim analysis was planned after occurrence of ~79 PFS events (2/3 of primary event goal)

[a]First dose at 375 mg/m^2, subsequent doses (up to 8) at 500 mg/m^2 every 2 wk for 4 infusions, then every 4 wk for 3 infusions.

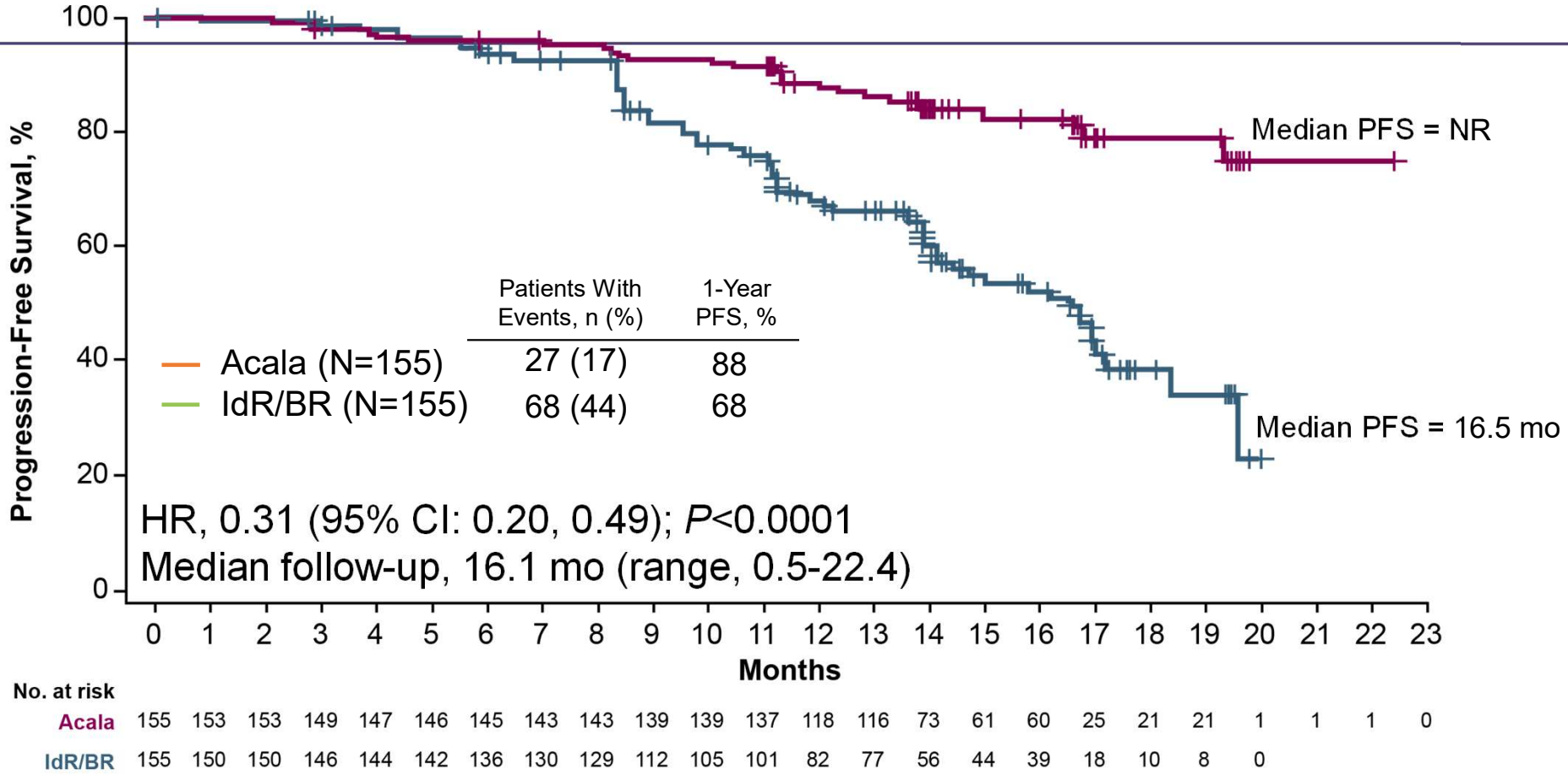
[b]On day 1 and day 2 of each cycle.

[c]First dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 on day 1 of each cycle for up to 6 cycles.

BID = twice daily; CLL = chronic lymphocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; IRC = independent review committee; IV = intravenous; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PO = orally.

Ghia, EHA 2019

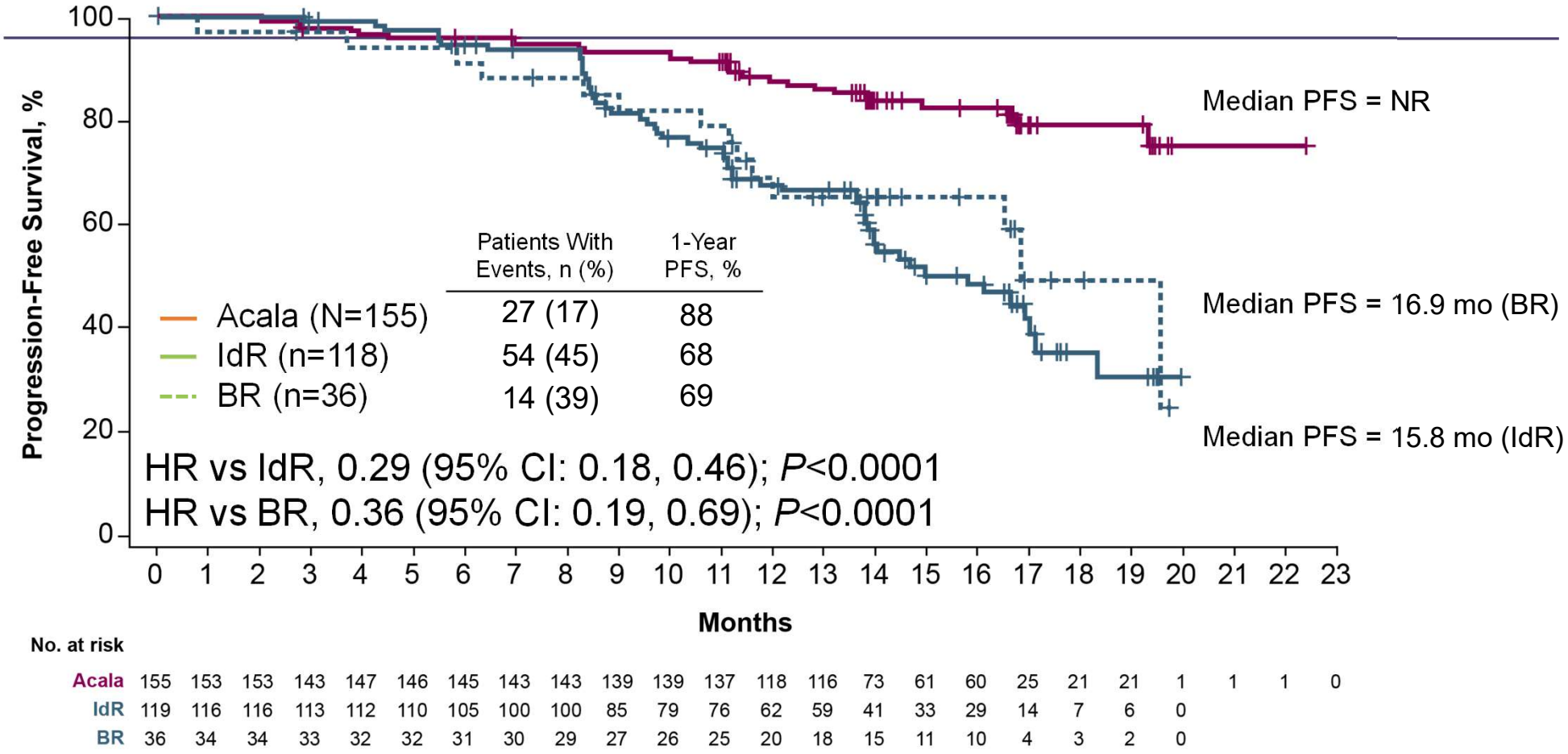
IRC-Assessed PFS Superior for Acalabrutinib vs IdR/BR



Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; NR = not reached; PFS = progression-free survival.

Ghia, EHA 2019

IRC-Assessed PFS Superior for Acalabrutinib vs IdR or BR

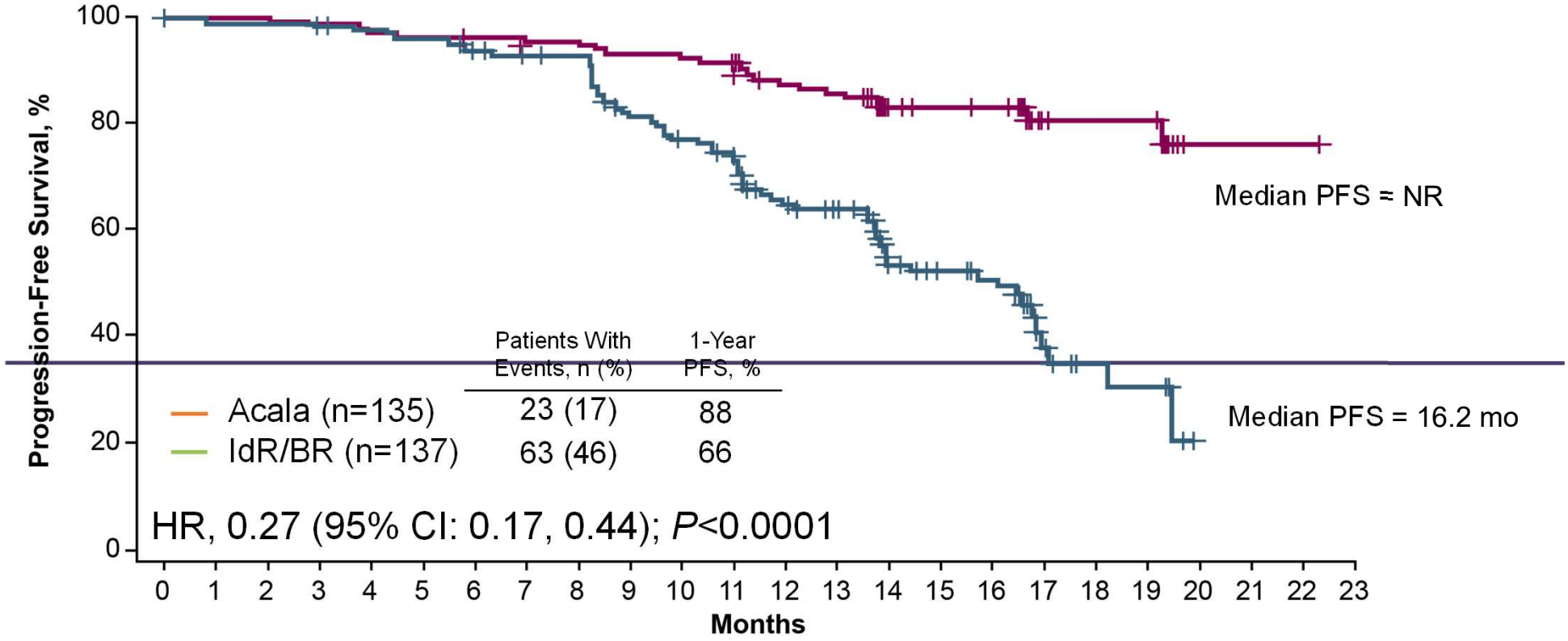


No. at risk

Acala	155	153	153	143	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
IdR	119	116	116	113	112	110	105	100	100	85	79	76	62	59	41	33	29	14	7	6	0			
BR	36	34	34	33	32	32	31	30	29	27	26	25	20	18	15	11	10	4	3	2	0			

Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; NR = not reached; PFS = progression-free survival.

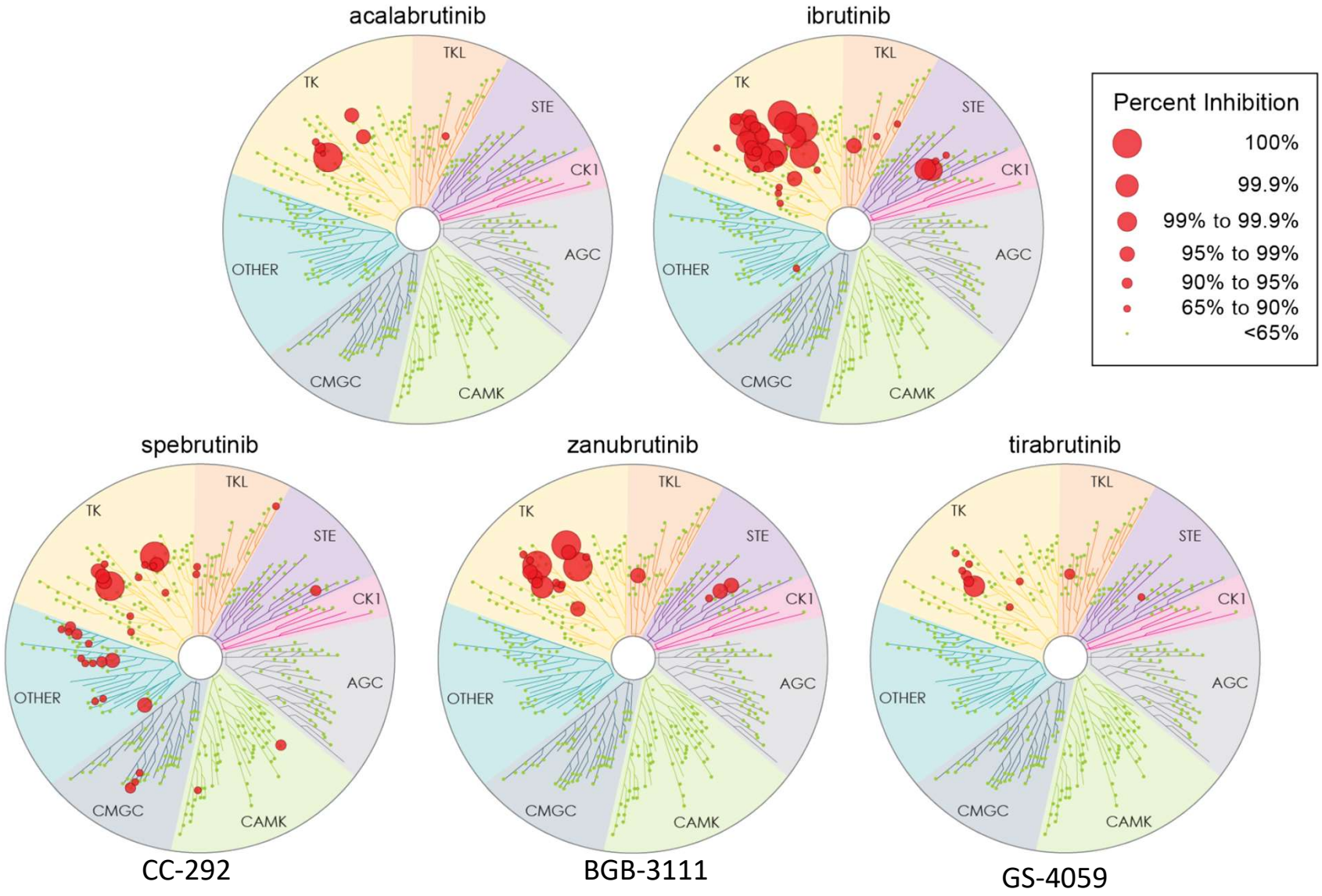
IRC-Assessed PFS in Patients With High-Risk Cytogenetic Features[a]



No. at risk

Acala	135	133	133	130	128	127	126	125	125	122	122	120	102	100	62	54	53	23	19	19	1	1	1	0
IdR/BR	137	132	132	128	126	124	119	114	113	98	91	87	70	65	46	38	34	14	8	7	0			

[a]Including del(17p), *TP53* mutation, del(11q), or unmutated IGHV.
Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IGHV = immunoglobulin heavy-chain variable region gene; IRC = independent review committee; NR = not reached; PFS = progression-free survival.



CC-292 BGB-3111 GS-4059

Treatment With the Bruton Tyrosine Kinase Inhibitor Zanubrutinib (BGB-3111) Demonstrates High Overall Response Rate and Durable Responses in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Updated Results From a Phase 1/2 Trial

Gavin Cull, MBBS, DM, FRACP, FRCPA[1,2]; David Simpson, MBChB, FRACP, FRCPA[3]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[4,5]; Jan A. Burger, MD, PhD[6]; Judith Trotman, MBChB, FRACP, FRCPA[7,8]; Paula Marlton, MBBS (Hons), FRACP, FRCPA[9,10]; David Gottlieb, MBBS, MD, FRACP, FRCPA[11]; Javier Munoz, MD, MS, FACP[12]; John F. Seymour, MBBS, FRACP, PhD[13-15]; Andrew W. Roberts, MBBS, PhD, FRACP, FRCPA[13-15]; Ken Wu, PhD[16]; Siminder Atwal, PhD[16]; William Novotny, MD[16]; Jane Huang, MD[16]; and **Constantine S. Tam, MBBS, MD**[13-15,17]

[1]Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; [2]University of Western Australia, Perth, Western Australia, Australia; [3]North Shore Hospital, Auckland, New Zealand; [4]Monash Health, Clayton, Victoria, Australia; [5]Monash University, Clayton, Victoria, Australia; [6]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Concord Repatriation General Hospital, Concord, New South Wales, Australia; [8]University of Sydney, Concord, New South Wales Australia; [9]Princess Alexandra Hospital, Brisbane, Queensland, Australia; [10]University of Queensland, Brisbane, Queensland, Australia; [11]Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Sydney, New South Wales, Australia; [12]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [13]Peter MacCallum Cancer Center, Melbourne, Victoria, Australia; [14]University of Melbourne, Parkville, Victoria, Australia; [15]Royal Melbourne Hospital, Parkville, Victoria, Australia; [16]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; and [17]St Vincent's Hospital, Fitzroy, Victoria, Australia

AU-003 Study Schema
Indication-Specific Expansion Cohorts

DOSE ESCALATION

Dose		All Dosed (CLL/SLL)
40 mg	qd	3 (0)
80 mg	qd	4 (0)
160 mg	qd	5 (2)
320 mg	qd	1 (0)
160 mg	bid	4 (2)

RP2D[a]
320 mg qd
or
160 mg bid

DOSE EXPANSION

Pop	RP2D Dose	Disease	All Dosed (CLL/SLL)
R/R	qd	All B-cell	18 (2)
R/R	bid	All B-cell	21 (4)
R/R	bid	Non-GCB DLBCL	37
R/R	bid	CLL/SLL	71 (71)
R/R	bid	WM	20
R/R	qd	CLL/SLL	20 (20)
Any	Any	WM	50
R/R	Any	MCL	20
TN	Any	CLL/SLL	21 (21)
TN	Any	MCL	20
R/R	Any	HCL	11
R/R	bid	iNHL	40
R/R	bid	Richter Transformation	15
R/R	bid	All B-cell (prior BTKi)	3 (1)

Eligibility:

- WHO-defined B-cell malignancy
- >1 Prior therapy (relapsed cohorts only)
- No available higher priority treatment
- ECOG PS 0-2
- ANC >1000/μL, platelets >100000/μL[b]
- Adequate renal and hepatic function; no significant cardiac disease[c]

ANC, absolute neutrophil count; bid, twice daily; BTKi, Bruton tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB-DLBCL, germinal center B-cell–like diffuse large B-cell lymphoma; HCL, hairy cell leukemia; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; qd, every day; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; TN, treatment naïve; WM, Waldenström macroglobulinemia.

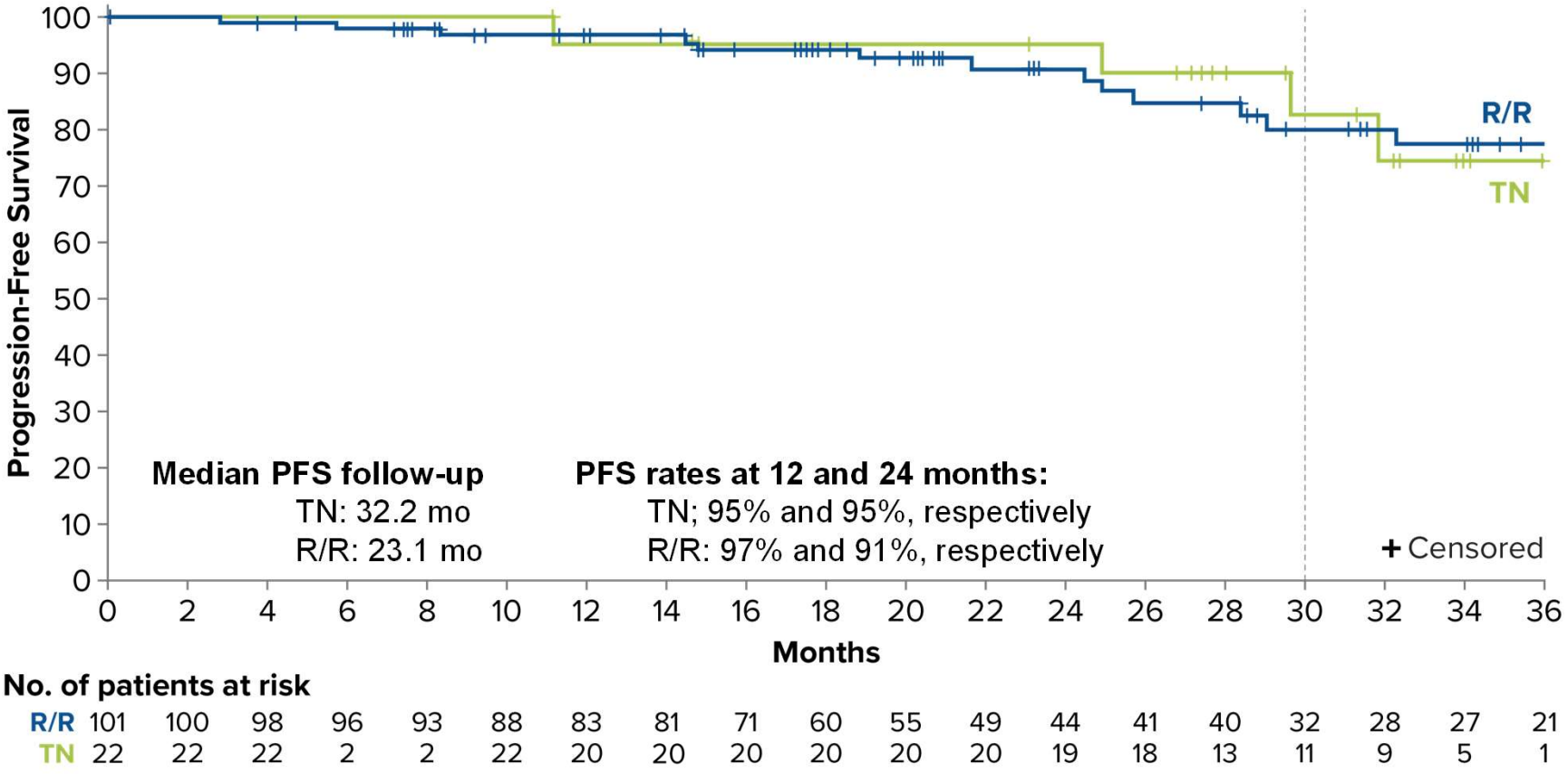
[a]Both doses RP2D but as of protocol v.6, all patients were encouraged to switch to 160 mg bid. [b]Growth factor/transfusion allowed. [c]Anticoagulation allowed.

Disease Response by Investigator Assessment

	TN (n=22)	R/R (n=101)	Overall (N=123)
Follow-up, median (range), mo	31.7 (11.1-47.6)	24.3 (3.7-52.0)	29.5 (3.7-52.0)
Best response, n (%)			
ORR	22 (100.0)	96 (95.0)	118 (95.9)
CR	5 (22.7)	14 (13.9)	19 (15.4)
CRi	0	1 (1.0)	1 (0.8)
PR	17 (77.3)	73 (72.3)	90 (73.2)[a]
PR-L	0	8 (7.9)	8 (6.5)
SD	0	4 (4.0)	4 (3.3)
Discontinued before first assessment, n (%)	0	1 (1.0)	1 (0.8)
Event rate remaining in response at 12 mo, % (95% CI)[b]	95.2 (70.7-99.3)	97.6 (90.8-99.4)	97.2 (91.5-99.1)

Data cutoff: May 8, 2019.
CR, complete response; CRi, complete response with incomplete bone marrow recovery; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.
[a]As of data cutoff (May 8, 2019), 4 patients met criteria for CR except required bone marrow to confirm; of these, 2 submitted bone marrow after data cutoff and confirmed CR. [B] Duration of response is summarized only for responders. Estimated using Kaplan-Meier method.

Progression-Free Survival



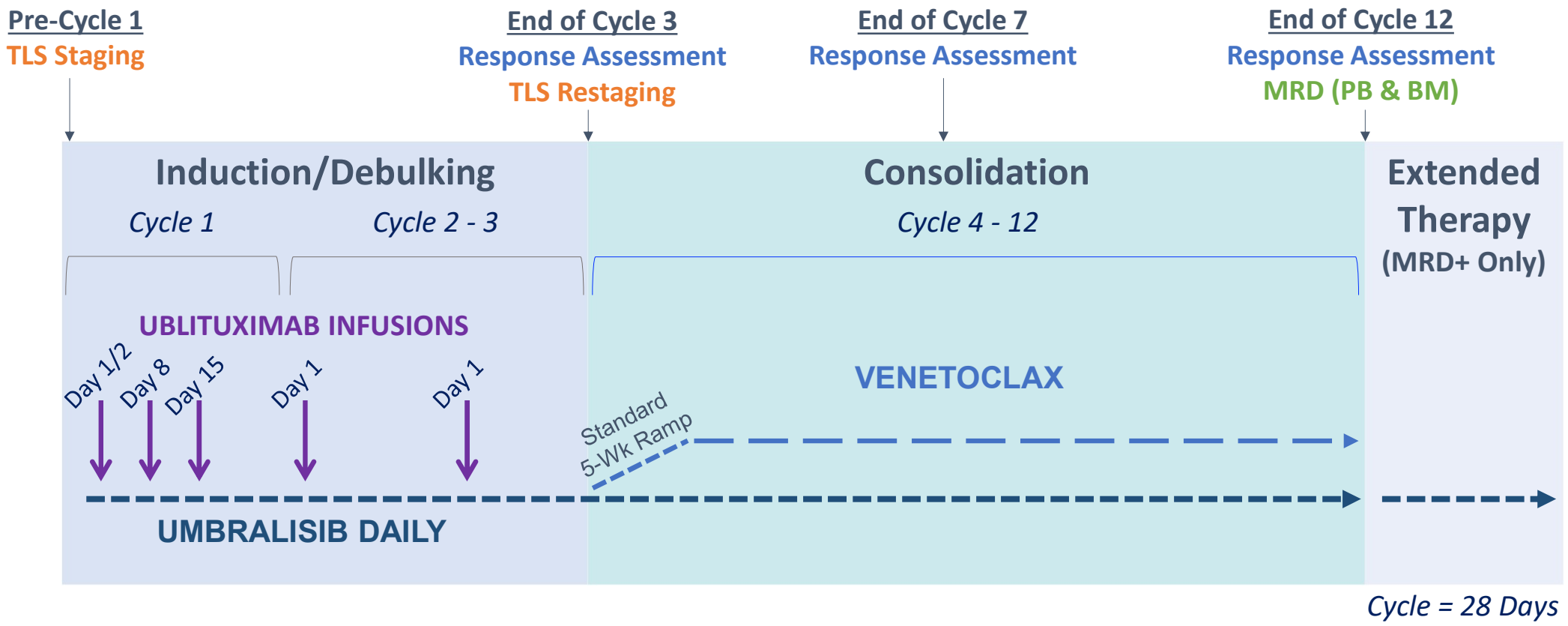
Data cutoff: May 8, 2019.
PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naïve.

Phase I/II Study of Umbralisib in Combination with Ublituximab and Venetoclax (U2-Ven) in Patients with Relapsed/Refractory CLL

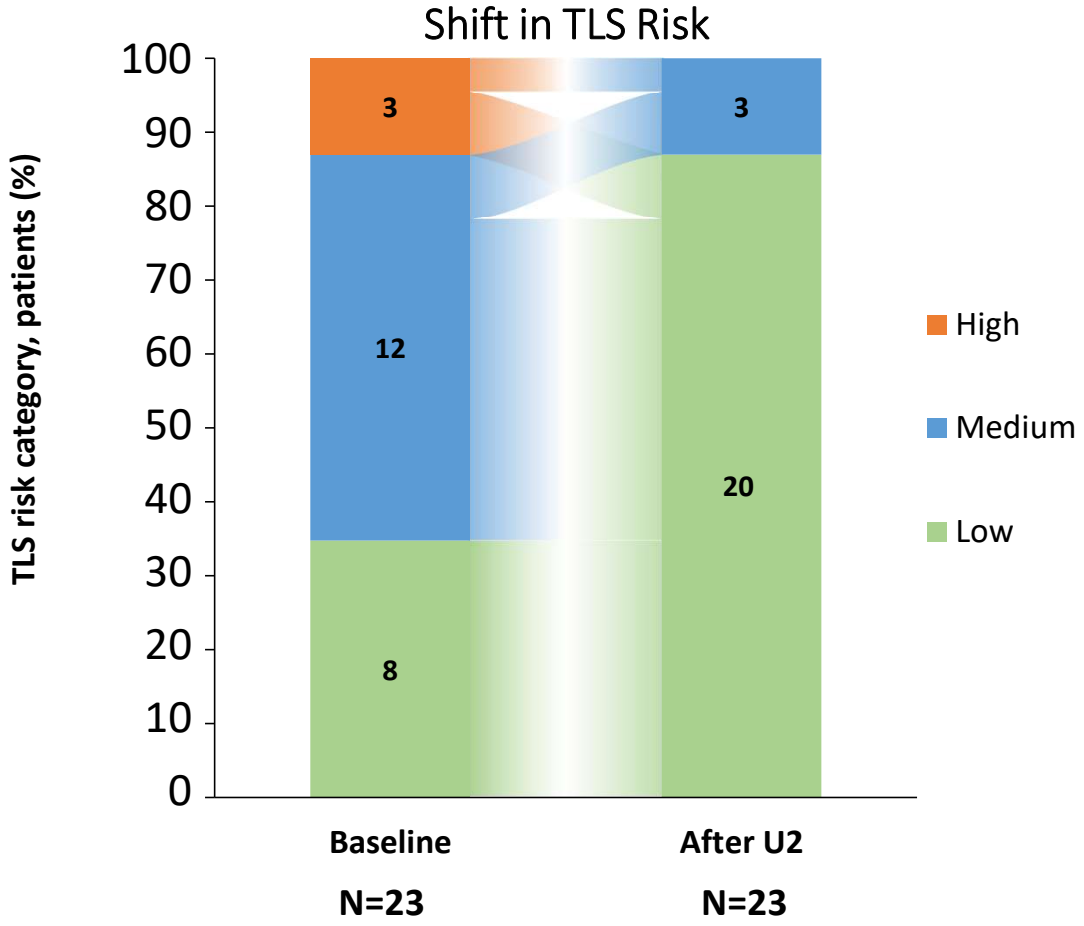
Paul M. Barr, MD[1], Brian T. Hill, MD, PhD[2], Shuo Ma MD, PhD[3], Andrea M. Baran, MS[1], Andrew Bui, MS [1], Phil Meacham, MS[1], Ashley Ochaba[2], Jane L. Liesveld MD[1], Deborah A. Mulford, MD[1], Peter Sportelli, BS[4], Hari P. Miskin, MS[4], Michael S. Weiss[4], Jonathan W. Friedberg, MD[1], Clive S. Zent, MD[1]

[1]Wilmot Cancer Institute, University of Rochester, Rochester, NY; [2]Cleveland Clinic, Cleveland, OH; [3]Northwestern University, Chicago, IL; [4]TG Therapeutics, Inc., New York, NY

Study Design: Treatment Schedule

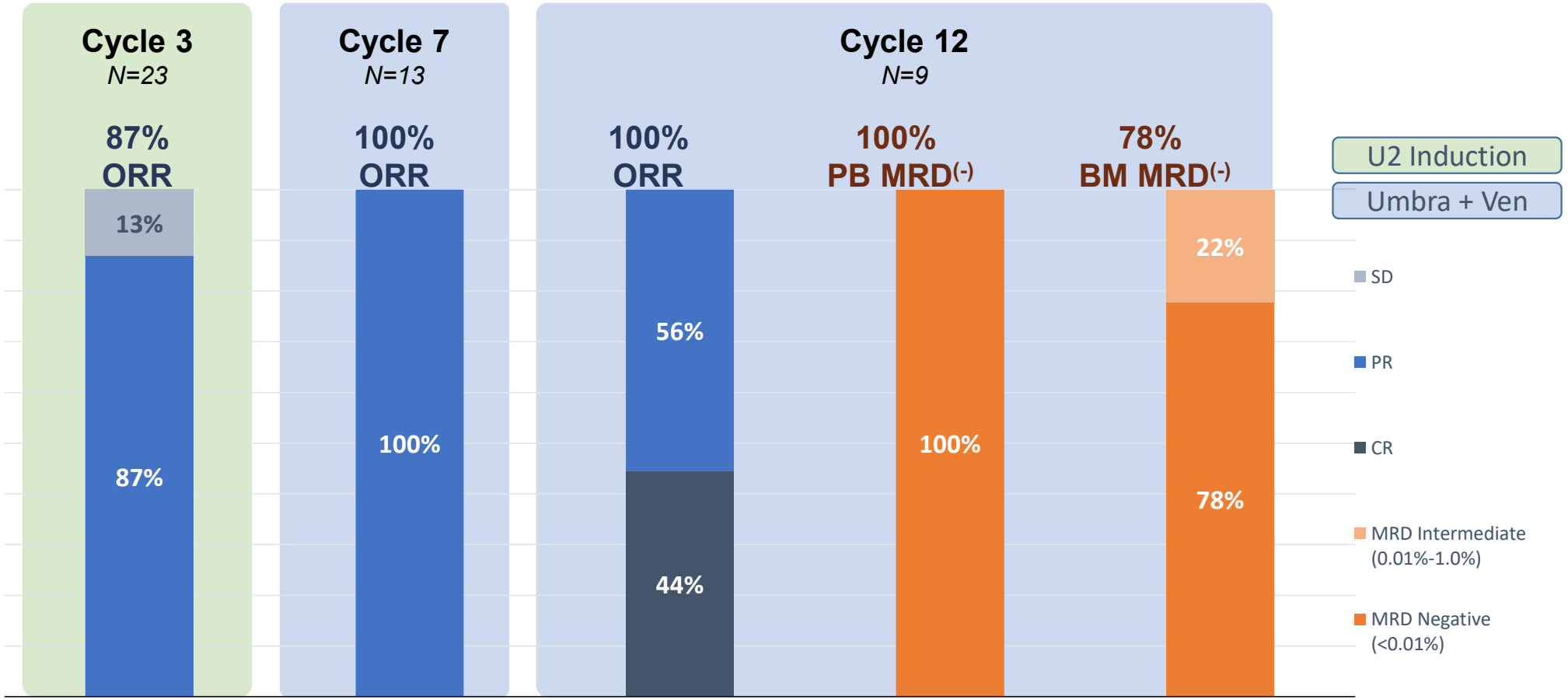


3 Cycles of U2 Induction Reduces Venetoclax TLS risk



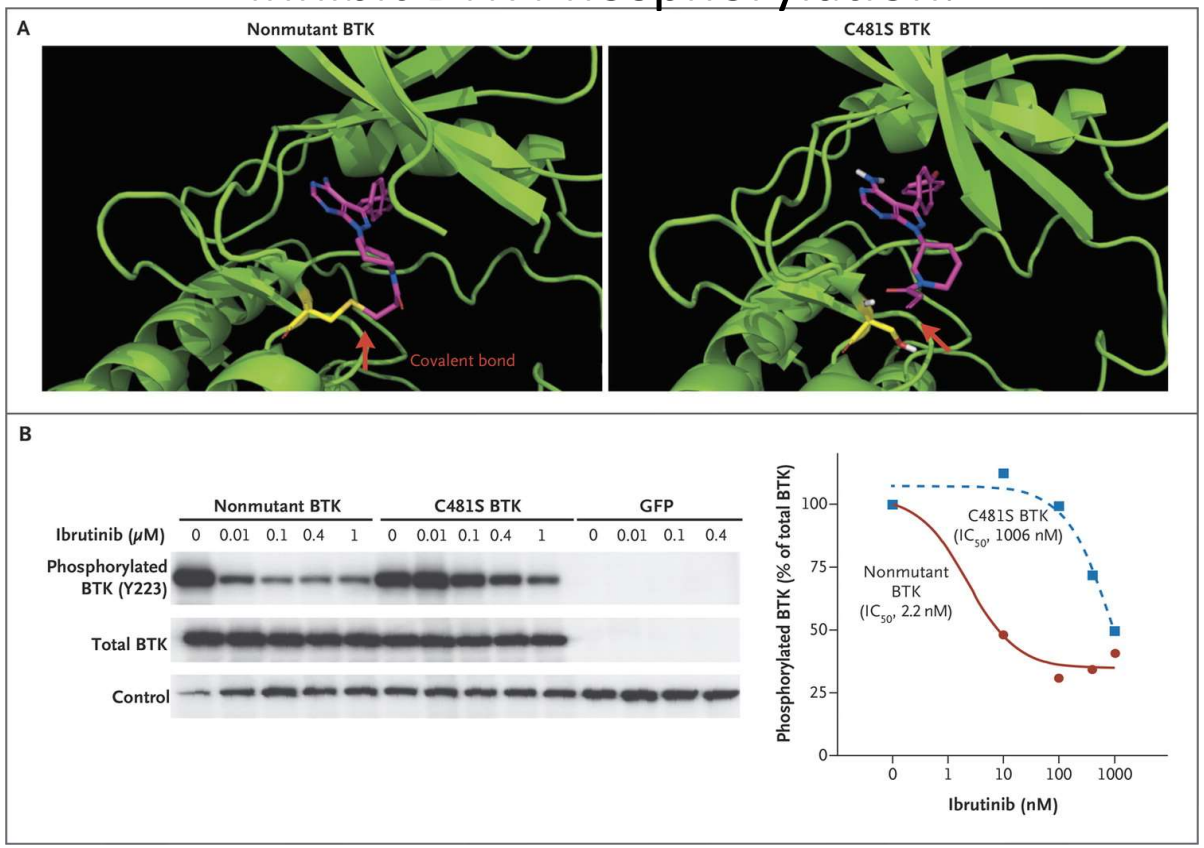
- After 3 cycles of ublituximab and umbralisib debulking:
  - No TLS High-Risk patients remaining
  - No patients developed clinical or laboratory TLS during venetoclax ramp up

Efficacy: Response and MRD



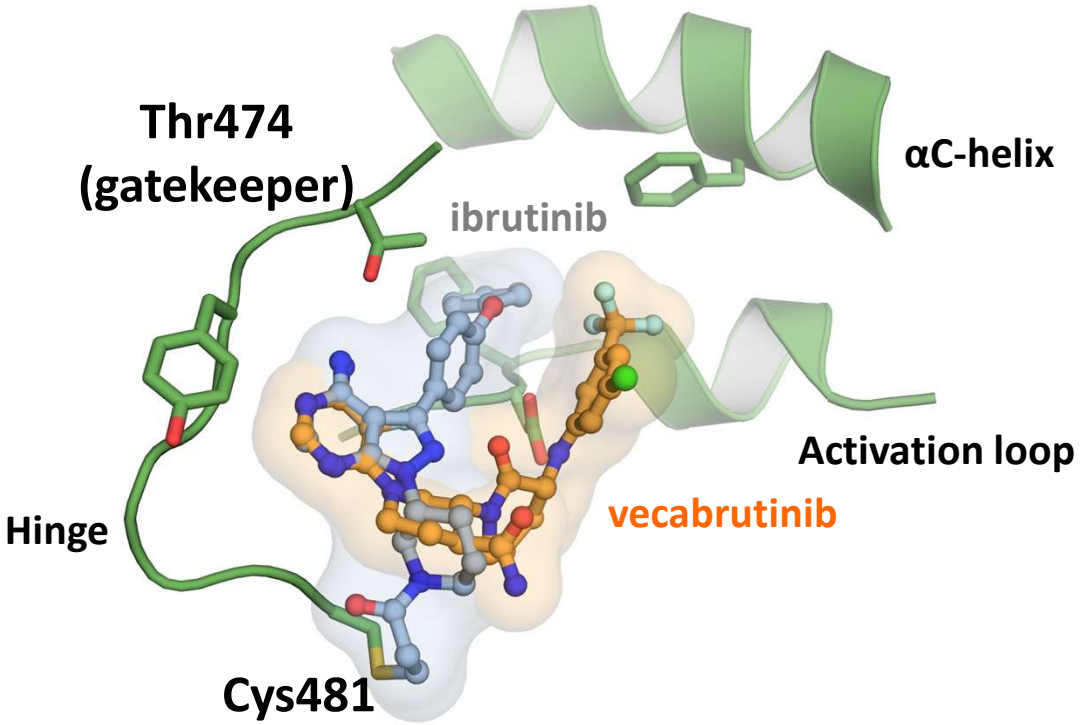
Cycle 3 & 7 Assessments were by CT only without BM, therefore CR could not be assessed

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



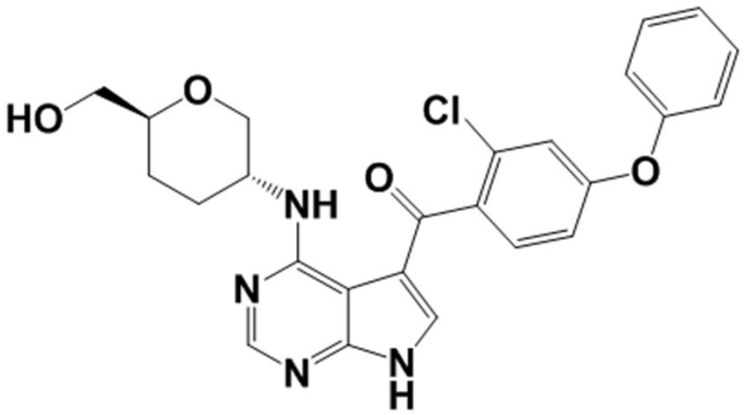
Furman RR et al. N Engl J Med 2014;370:2352-2354.

Vecabrutinib

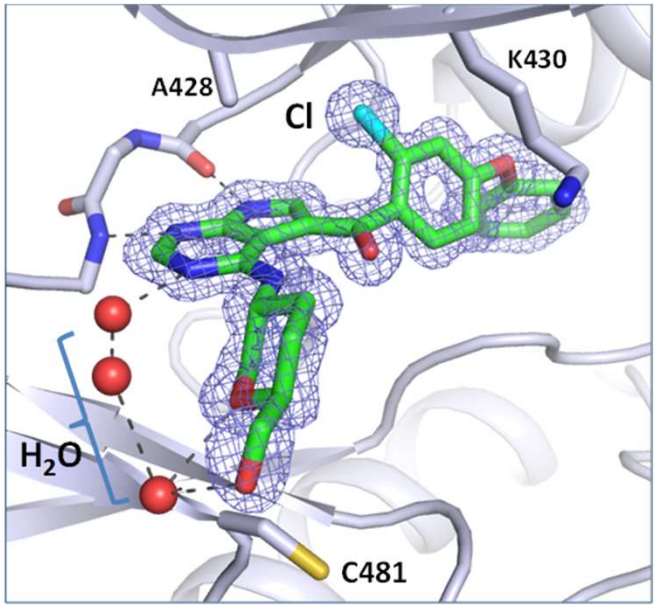


- Vecabrutinib interacts with a distinct set of residues in the αC-helix

ARQ 531



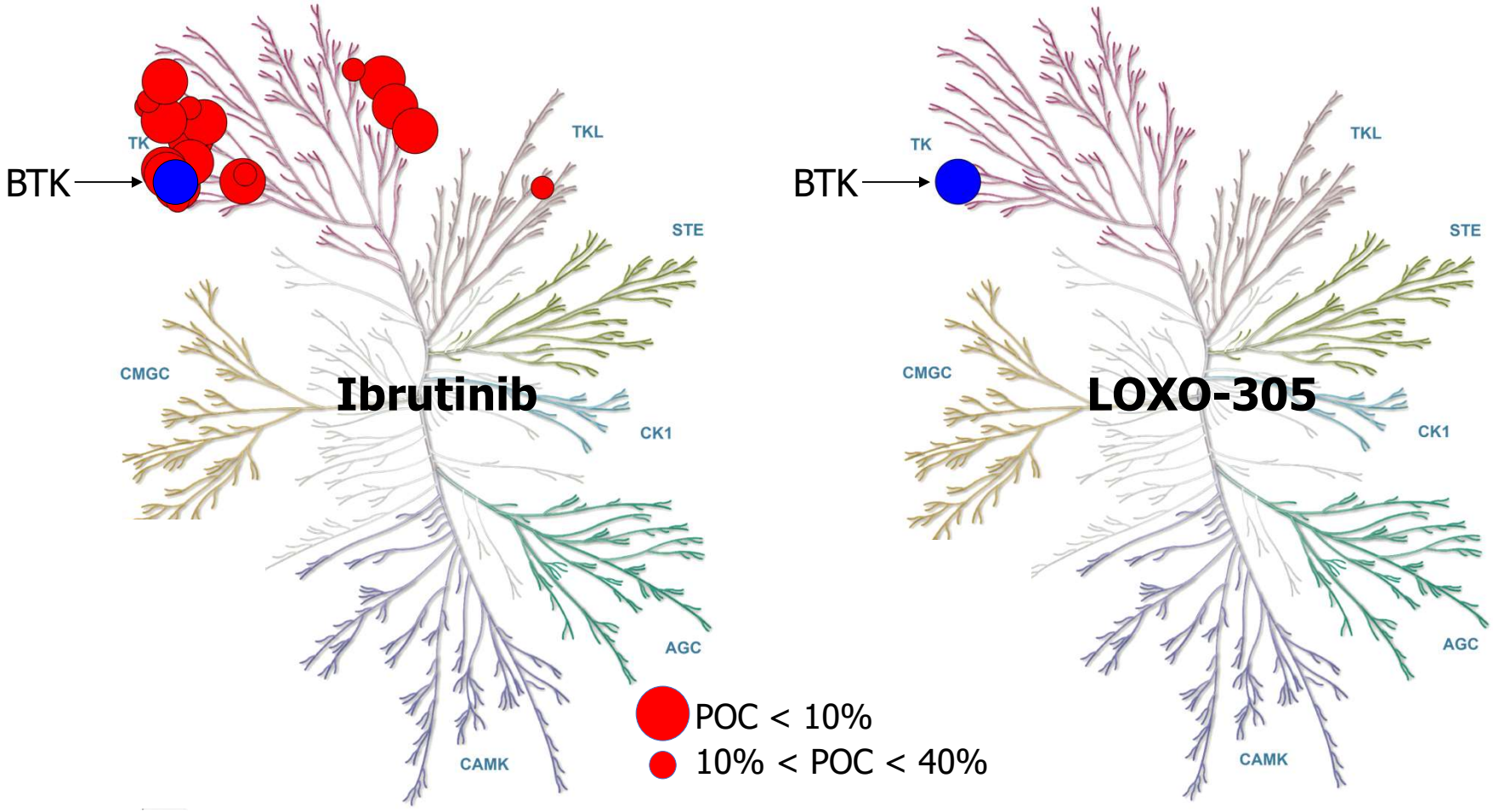
ARQ 531



- Reversible inhibition of BTK
- Occupies the ATP binding pocket – non C481
- Orally bioavailable

Reiff et al, Cancer Discovery, in press

LOXO-305



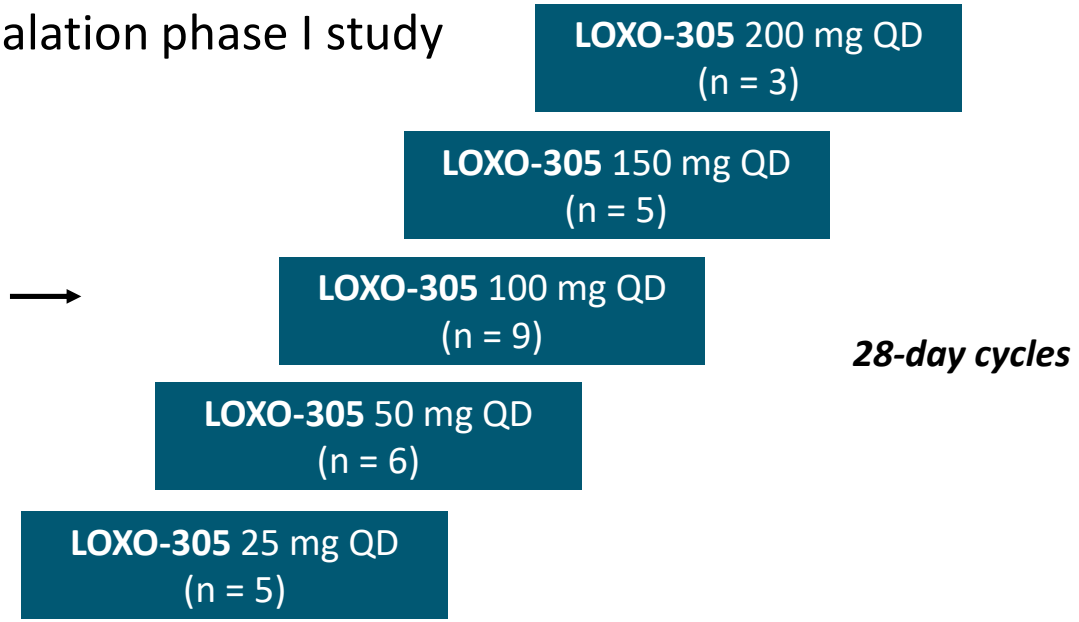
Each agent tested at 100 nM, n=369 kinases, kinases with % control < 40 shown

BRUIN: First-in-Human Phase I Trial Investigating Non-Covalent BTK Inhibitor LOXO-305 in Pretreated B-Cell Malignancies

BRUIN: Study Design

- 3 + 3 design, dose-escalation phase I study

Patients ≥ 18 yrs of age with CLL or B-cell non-Hodgkin lymphoma; ECOG PS 0-2; ≥ 2 prior therapies including BTK intolerance (N = 28)



28-day cycles

- Primary endpoints: MTD and recommended phase II dose
- Secondary endpoints: safety, PK, ORR

Mato. ASH 2019. Abstr 501. NCT03740529.

BRUIN: Prior Therapy

Characteristic	All Patients (N = 28)	CLL (n = 16)	MCL (n = 8)	Other (n = 4)
Median prior therapies, n (range)	3 (2-8)	4 (2-5)	3 (2-6)	4 (3-8)
Prior therapy, n (%)				
▪ Venetoclax	3 (11)	3 (19)	0	0
▪ Anti-CD20 antibody	26 (93)	15 (94)	8 (100)	3 (75)
▪ Chemotherapy	26 (93)	14 (88)	8 (100)	4 (100)
▪ PI3K agent	7 (25)	5 (31)	1 (13)	1 (25)
▪ Lenalidomide	3 (11)	2 (13)	0	1 (25)
▪ Stem cell transplant	3 (11)	0	3 (38)	0
▪ Other therapy	6 (21)	2 (13)	2 (25)	2 (50)
Prior BTK inhibitor, n (%)	22 (79)	12 (75)	7 (88)	3 (75)
▪ Discontinued due to disease progression	14 (64)	6 (50)	6 (86)	2 (67)
▪ Discontinued due to intolerance	4 (18)	3 (25)	1 (14)	0
▪ Discontinued for other reason	4 (18)	3 (25)	0	1 (33)

Mato. ASH 2019. Abstr 501.

BRUIN: Response

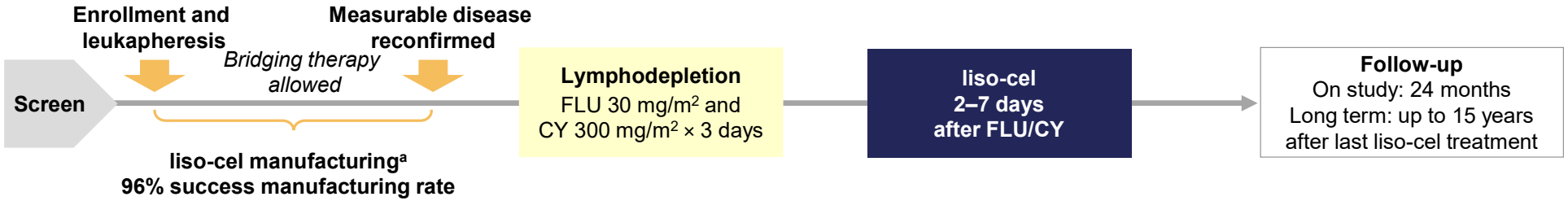
Best Response, n (%)	CLL (n = 13)	MCL (n = 6)	Other* (n = 2)
ORR†	10 (77)	3 (50)	1 (50)
CR	0	1 (17)	0
PR	8 (62)	2 (33)	0
PR-L	2 (15)	NA	0
MR	NA	NA	1 (50)
SD	3 (23)	0	1 (50)
PD	0	2 (33)	0
Not evaluable‡	0	1 (17)	0

*Includes WM. †Includes patients with best response of CR, PR, PR-L for CLL; CR or PR for MCL and other NHL; and CR, VGPR, PR, or MR for WM. ‡Patients that discontinued treatment prior to first response assessment.

- Median duration of treatment: 2.7 mos (range: 0.2-7.6); all responding patients remain on therapy
- Responses deepen over time in CLL patients
  - PR/PR-L 50% at cycle 3, 88% at cycle 5
  - All CLL patients had tumor shrinkage
- Responses observed at all dose levels and in BTKi-resistant CLL and MCL, regardless of C481S status
- Plasma exposure of LOXO-305 dose-dependent and linear

Mato. ASH 2019. Abstr 501.

TRANSCEND CLL 004 Study Design



Key Eligibility

- Relapsed/refractory CLL/SLL
- Failed or ineligible for BTKi[b]
- High-risk disease[c]: failed ≥2 prior therapies
- Standard-risk disease: failed ≥3 prior therapies
- ECOG PS of 0–1

Dose Escalation: mTPI-2 Design[d]

28-day DLT period

Primary Objectives

- Safety
- Determine recommended dose

Exploratory Objectives

- Antitumor activity
- Pharmacokinetic profile

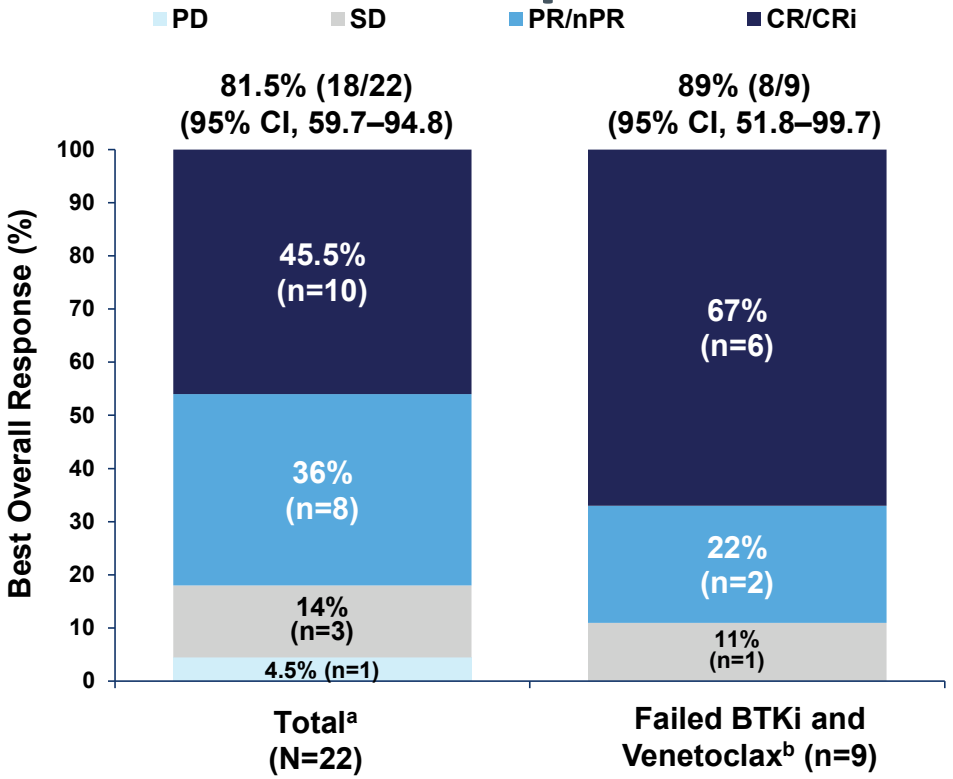
Dose Level	Dose	Evaluable (N=23)

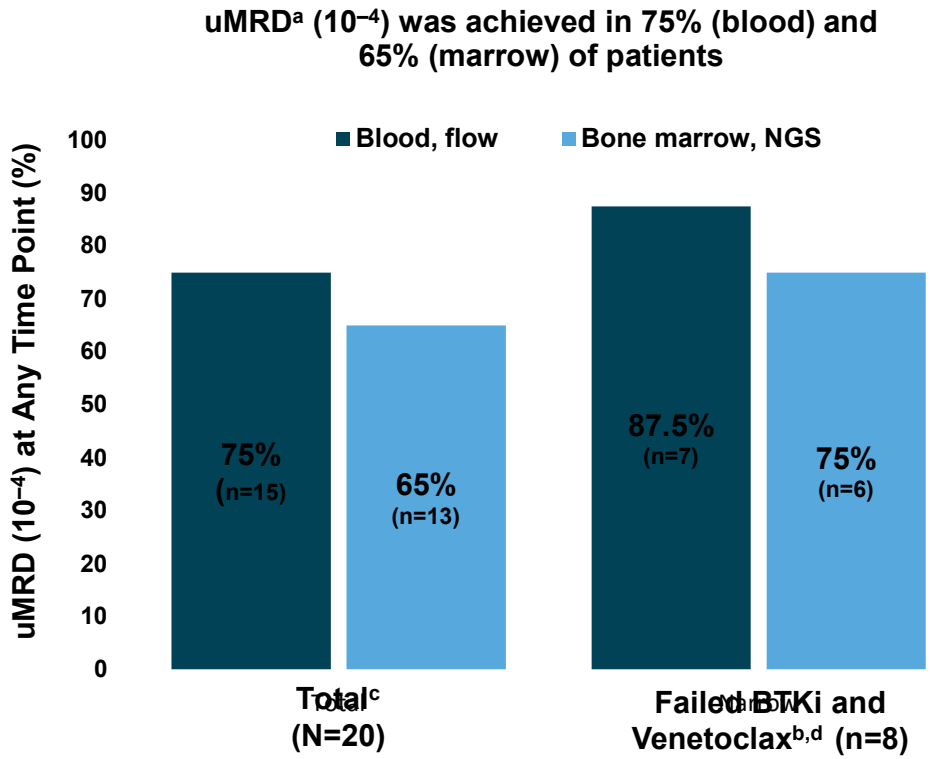
ClinicalTrials.gov identifier: NCT03331198.

[a]One patient received nonconforming product. [b]Failure defined as SD or PD as best response, or PD after previous response, or discontinuation due to intolerance (unmanageable toxicity). Ineligibility defined as requirement for full-dose anticoagulation or history of arrhythmia. [c]Complex cytogenetic abnormalities, del(17p), *TP53* mutation, or unmutated IGHV. [d]Guo W, et al. *Contemp Clin Trials.* 2017;58:23-33.

BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CY, cyclophosphamide; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FLU, fludarabine; IGHV, immunoglobulin heavy-chain variable region; mTPI, modified toxicity probability interval for dose escalation; PD, progressive disease; SD, stable disease; SLL, small lymphocytic lymphoma.

Best Overall Response and Undetectable MRD





Median study follow-up: 11 months

All percentages are rounded to whole numbers except those ending in .5. [a]Evaluable for response defined as having a pretreatment assessment and ≥1 postbaseline assessment. One patient was not evaluable for response. [b]Failed venetoclax defined as discontinuation due to PD or <PR after ≥3 months of therapy. [c]Evaluable for MRD was defined as patients with detectable MRD at baseline. Two patients were not evaluable for MRD. [d]One patient in this subset was not evaluable for MRD. BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; MRD, minimal residual disease; NGS, next-generation sequencing; nPR, nodular partial response; PD, progressive disease; PR, partial response; SD, stable disease; uMRD, undetectable minimal residual disease.

Conclusions

- Ibrutinib has show superior PFS vs chemoimmunotherapy in 4 phase III trials and has become an excellent front line therapy.
- Anti-CD20 does not seem to add benefit to ibrutinib on front line therapy.
- Acalabrutinib offer a new alternative for BTK inhibition.
- IgHV mutational status is a valid marker for therapy stratification in all patients and younger ones when chemo-immunotherapy is considered.
- Obinutuzumab + Venetoclax is now offering a time limited therapy in the front line settings with excellent results and high MRD- status.
- Ibrutinib+venetoclax will soon be a new alternative in the near future.
- Second line options keep increasing from dublets and triplets venetoclax combination to new BTK inhibitors and CART

Thank you

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