Treatment naïve and first relapse CLL: What is the rationale for treatment choice

Javier Pinilla-Ibarz, MD, PhD.
Senior Member
Head of Lymphoma section and
Director of Immunotherapy
Malignant Hematology Department

MOFFITT CANCER CENTER

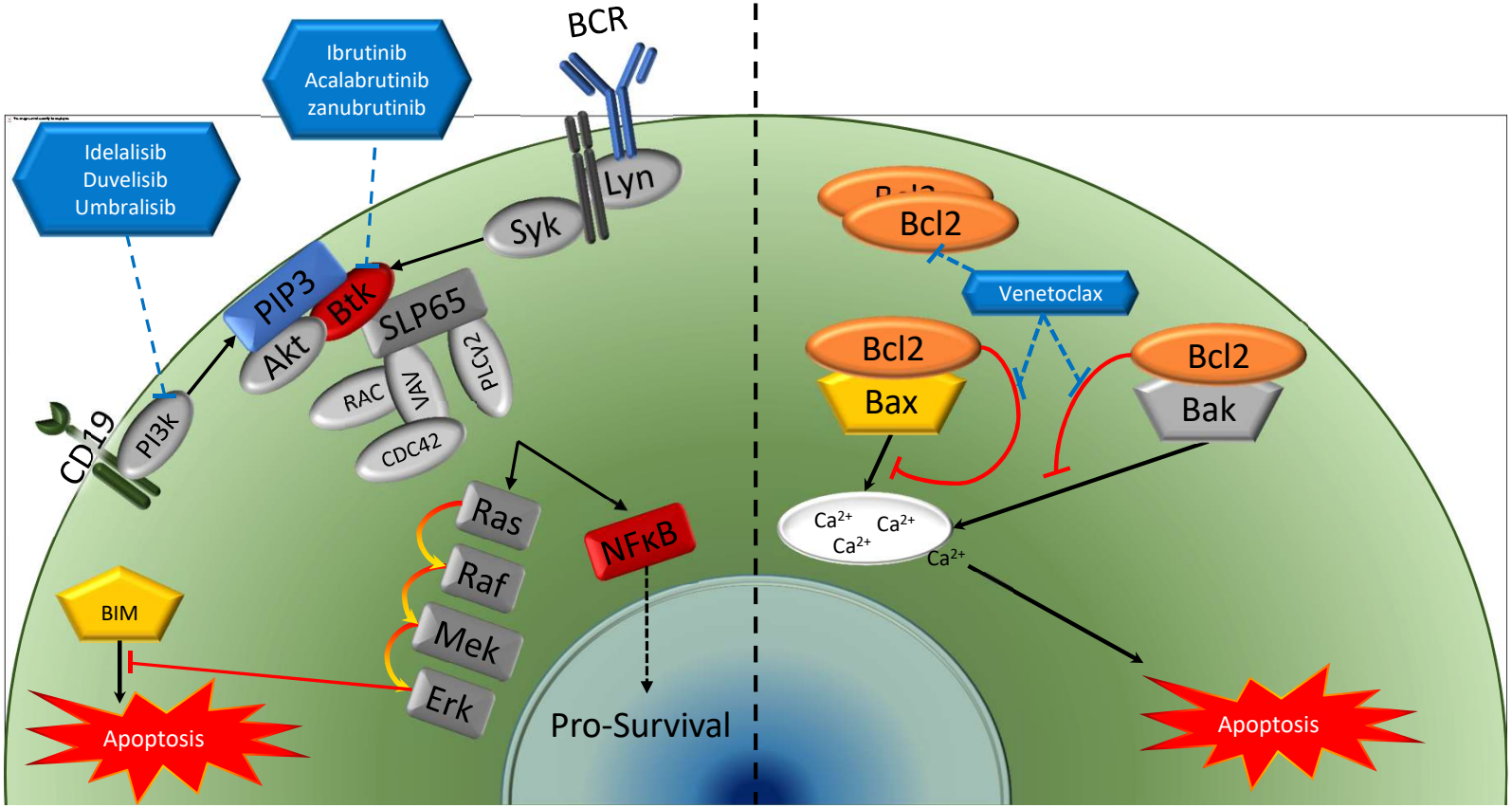
COI

- 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

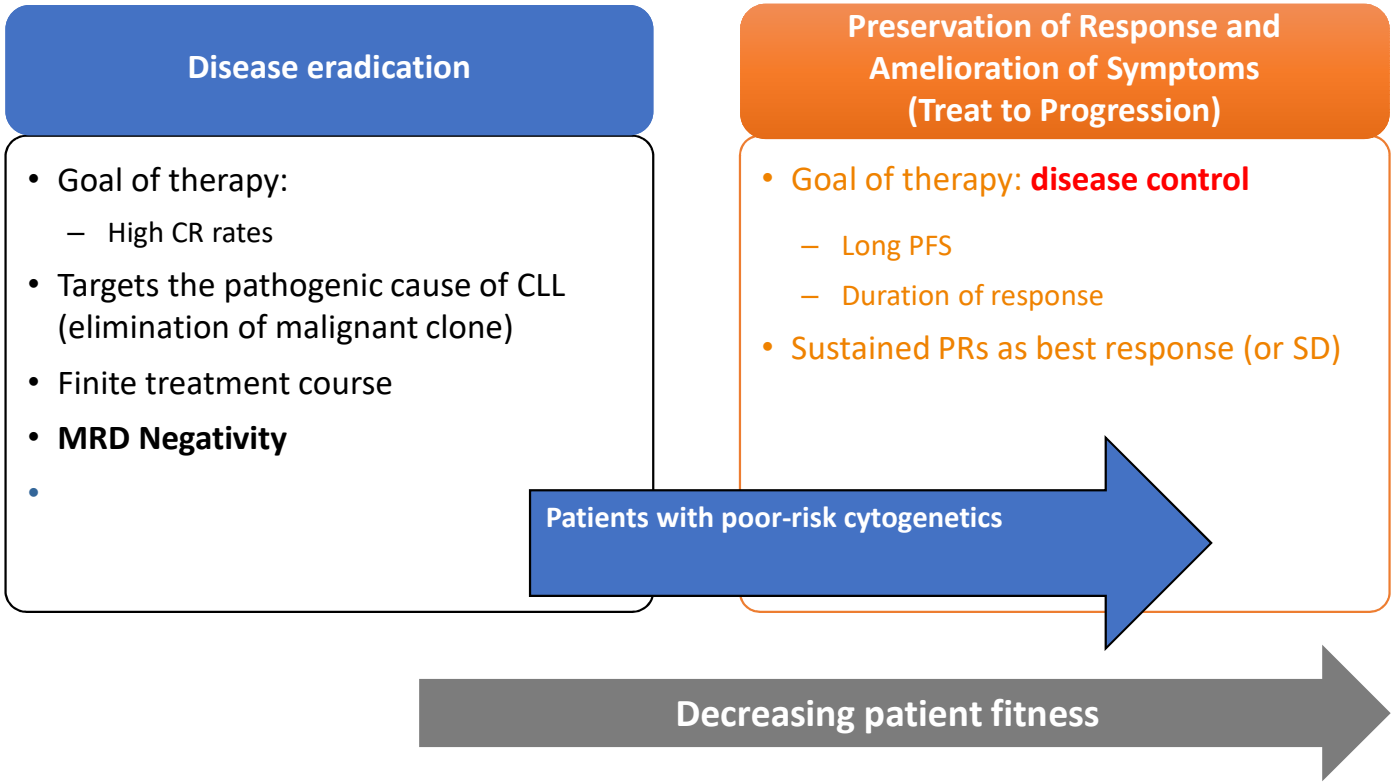
Blocking BCR signaling is a cytostatic mechanism

Blocking bcl2 pathways is a cytotoxic mechanism



The initial Changing Treatment Paradigm in CLL

- **Chemo/Chemoimmunotherapy**
- **BCR inhibitors**



The NEW ENGLAND JOURNAL of MEDICINE

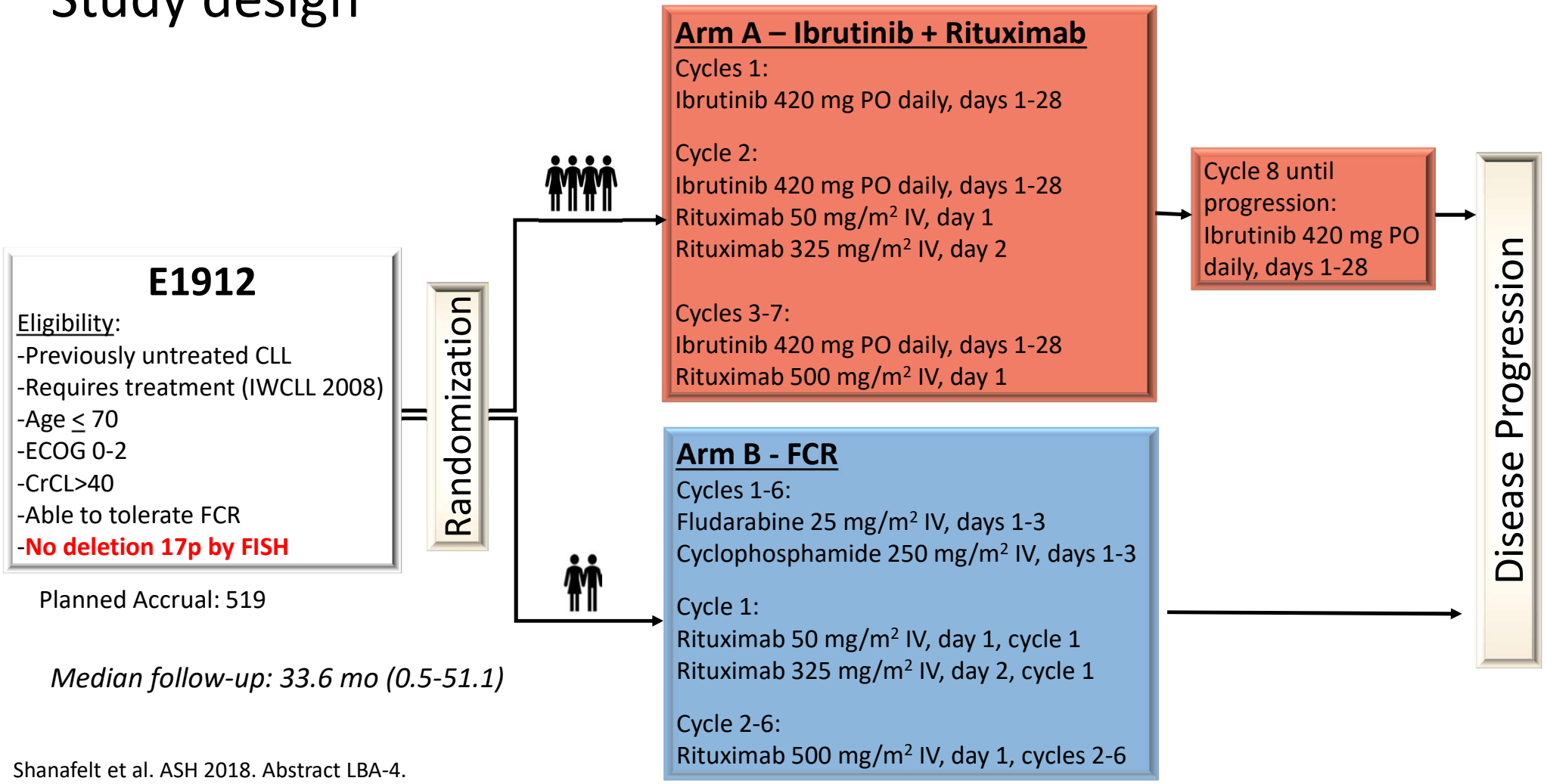
ORIGINAL ARTICLE

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

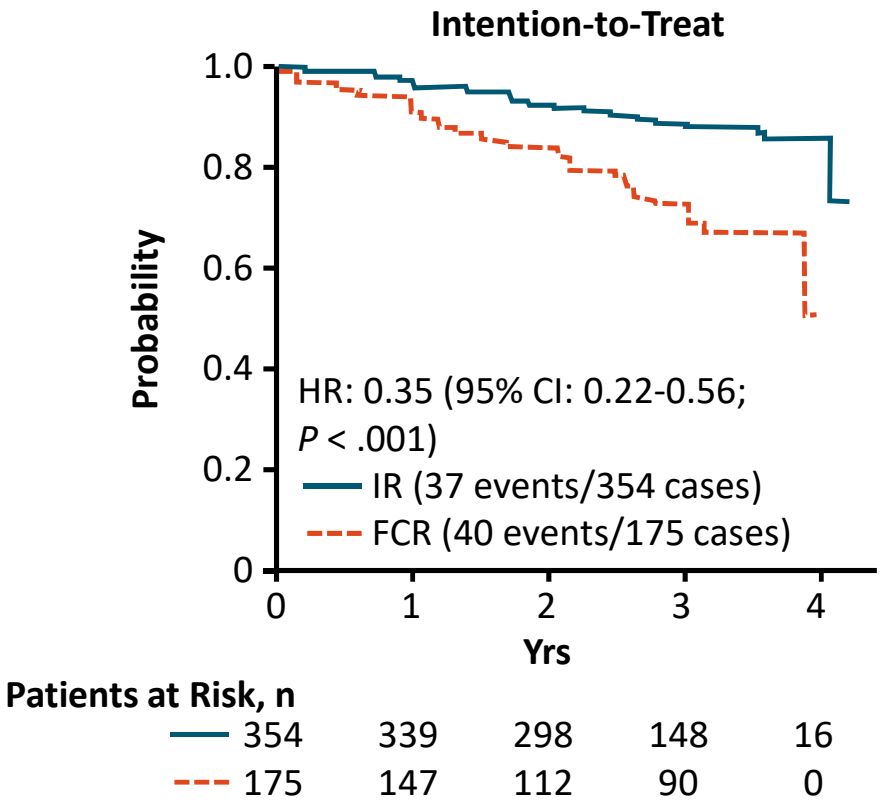
Study design

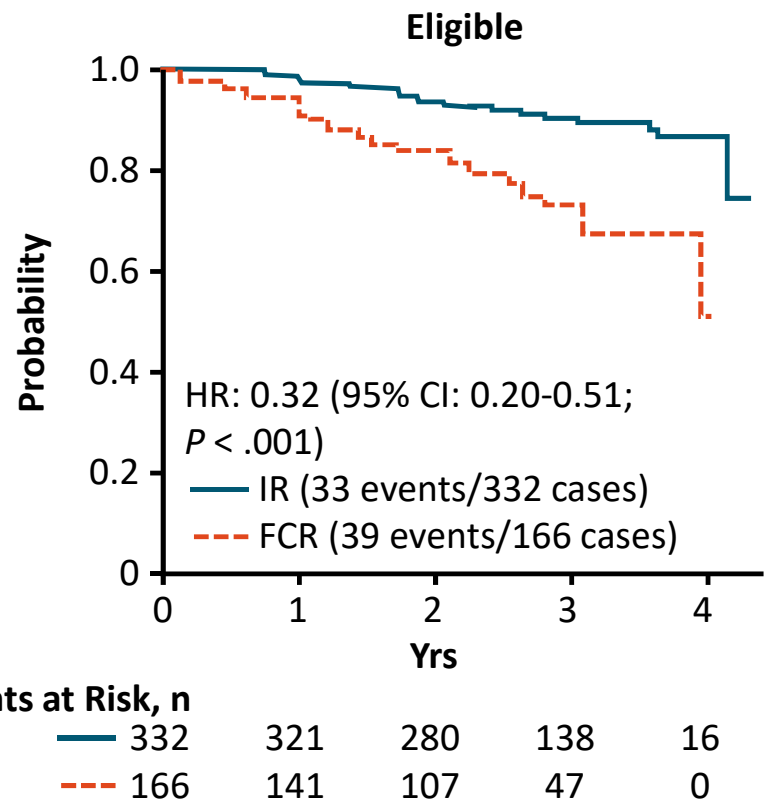


Median follow-up: 33.6 mo (0.5-51.1)

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

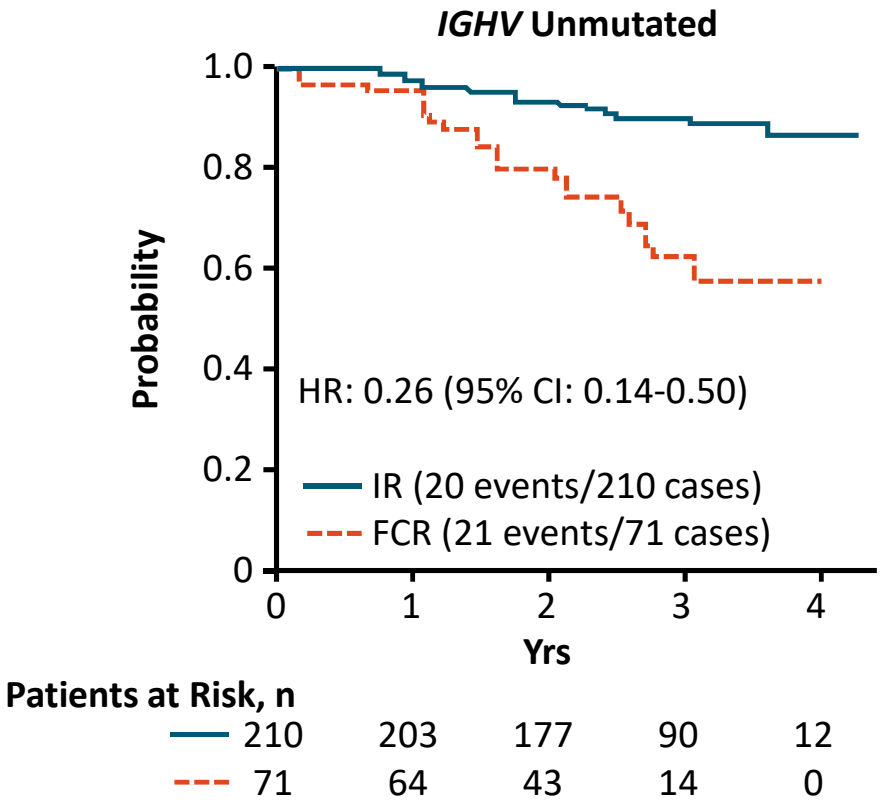
E1912: PFS (Primary Endpoint)

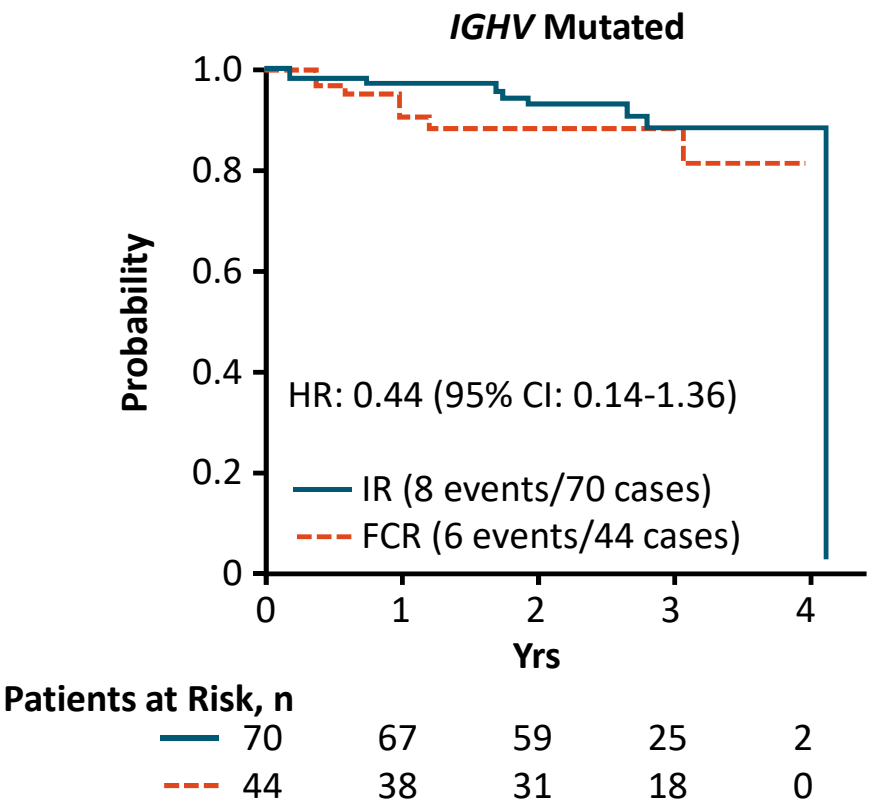




Shanafelt. ASH 2018. Abstr LBA-4. Shanafelt. NEJM. 2019;381:432.

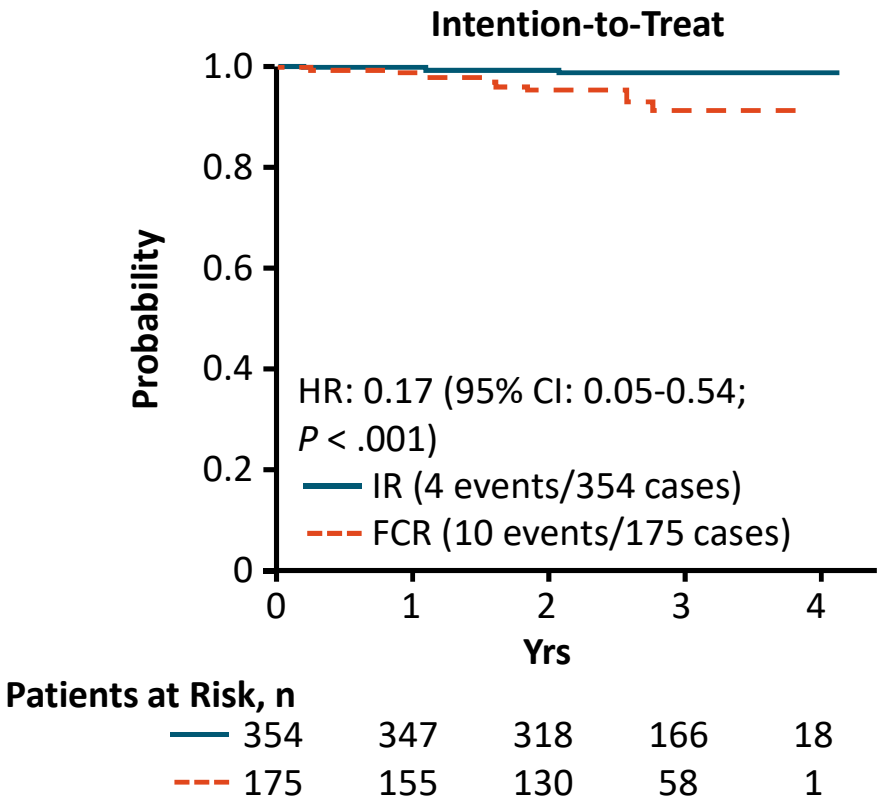
E1912: PFS by *IGHV* Status

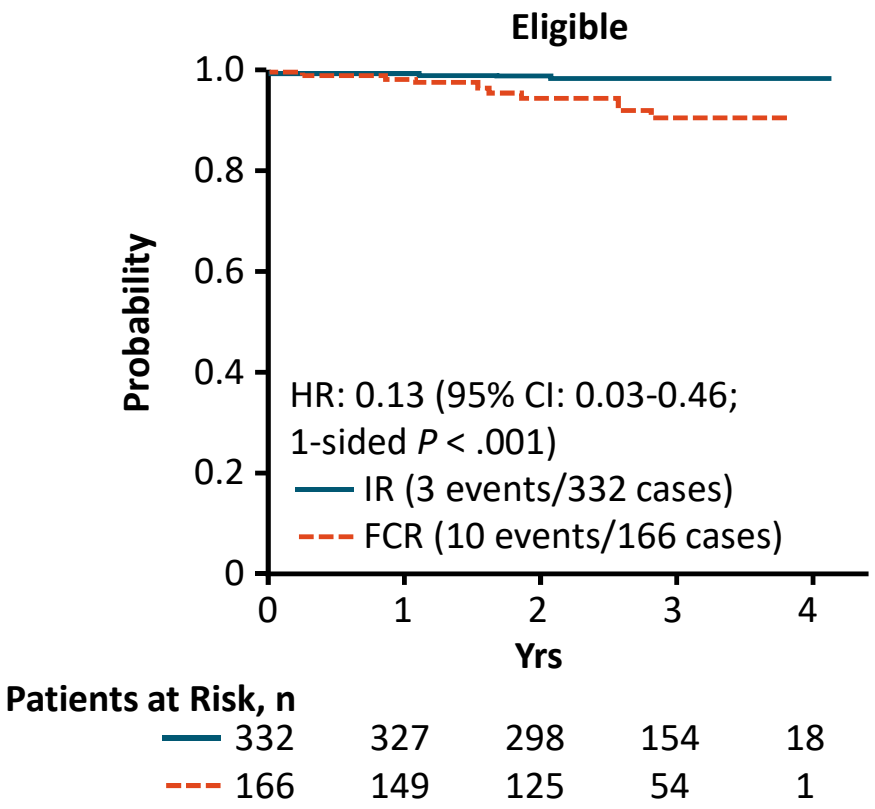




Shanafelt. ASH 2018. Abstr LBA-4. Shanafelt. NEJM. 2019;381:432.

E1912: OS





Shanafelt. ASH 2018. Abstr LBA-4. Shanafelt. NEJM. 2019;381:432.

The NEW ENGLAND JOURNAL of MEDICINE

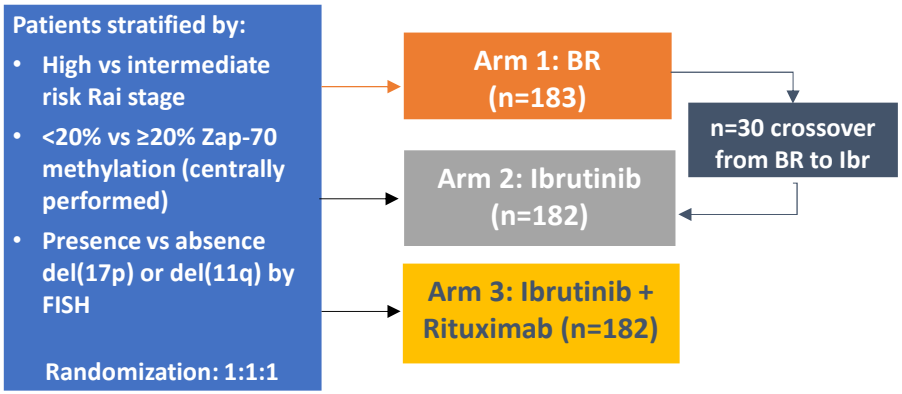
ORIGINAL ARTICLE

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

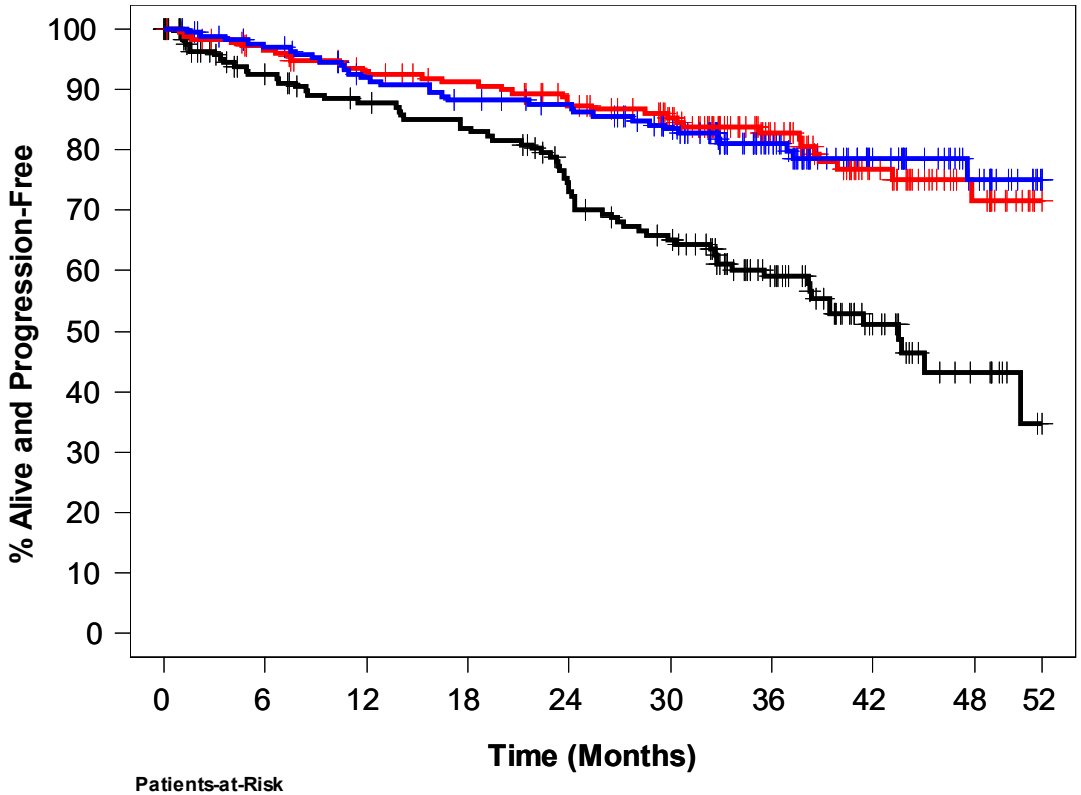


Primary endpoints: PFS
Secondary endpoints: OS, TTP, DOR. Proportion achieving MRD negativity, Biopsy proven CR, Toxicity

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)

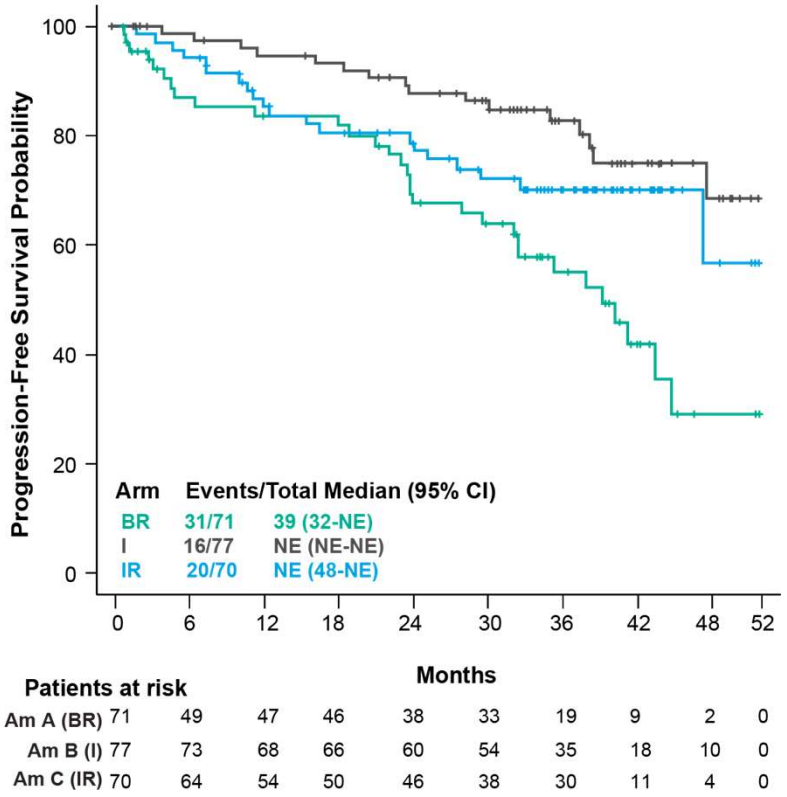
IR vs BR
HR: 0.38 (95% CI: 0.25-0.59)
(1-sided p value <0.001)

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

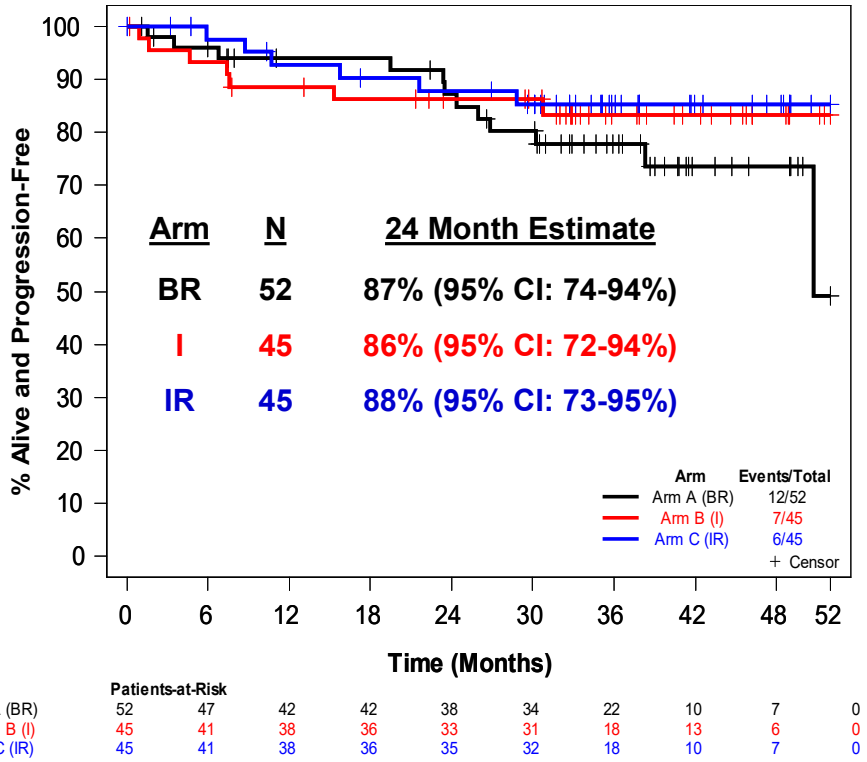
Woyach et al., ASH 2018,

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

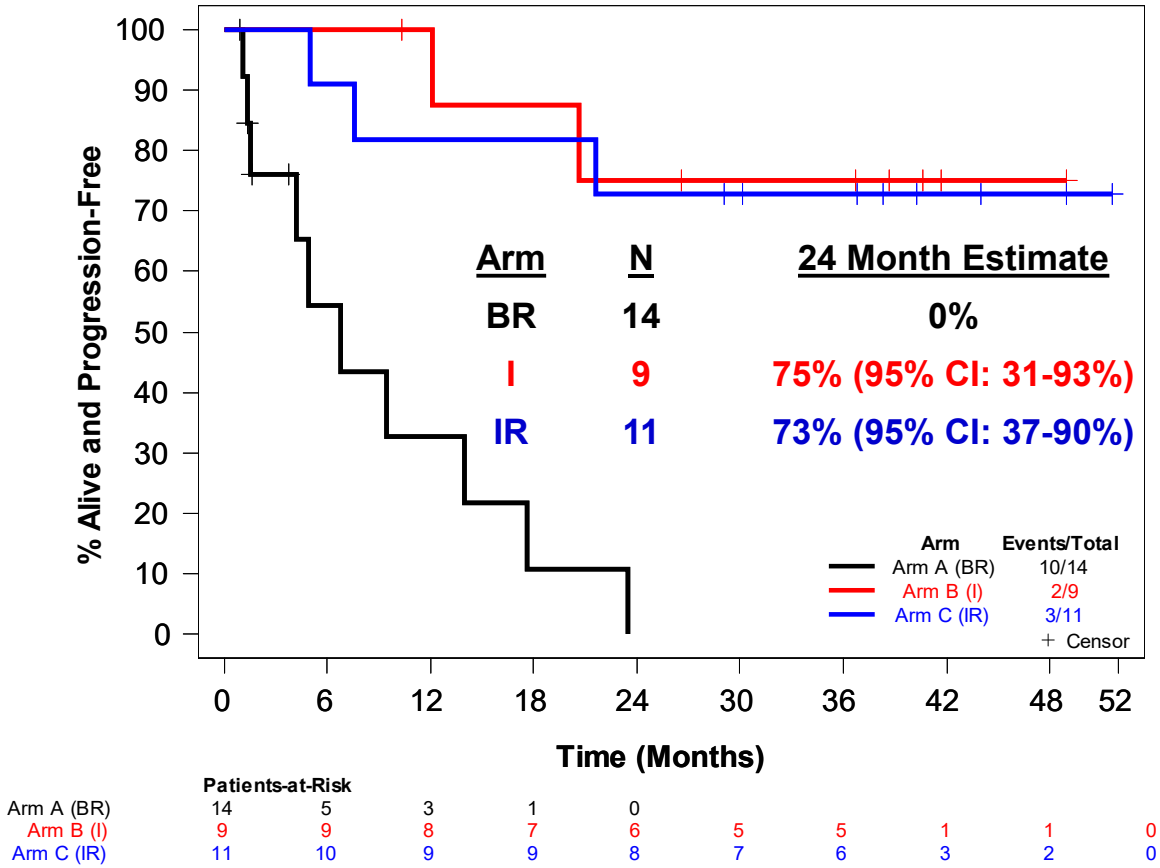
IGVH unmutated



IGVH Mutated



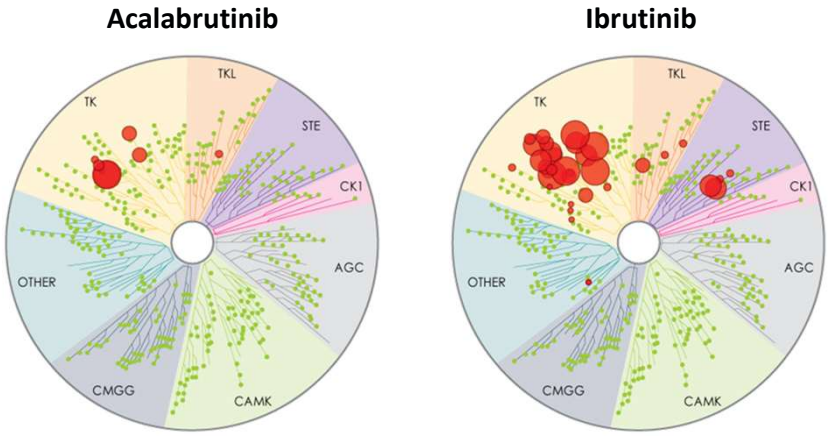
Del (17p13.1) Subgroup: Progression Free Survival Intention-to-Treat Patient Population



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

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

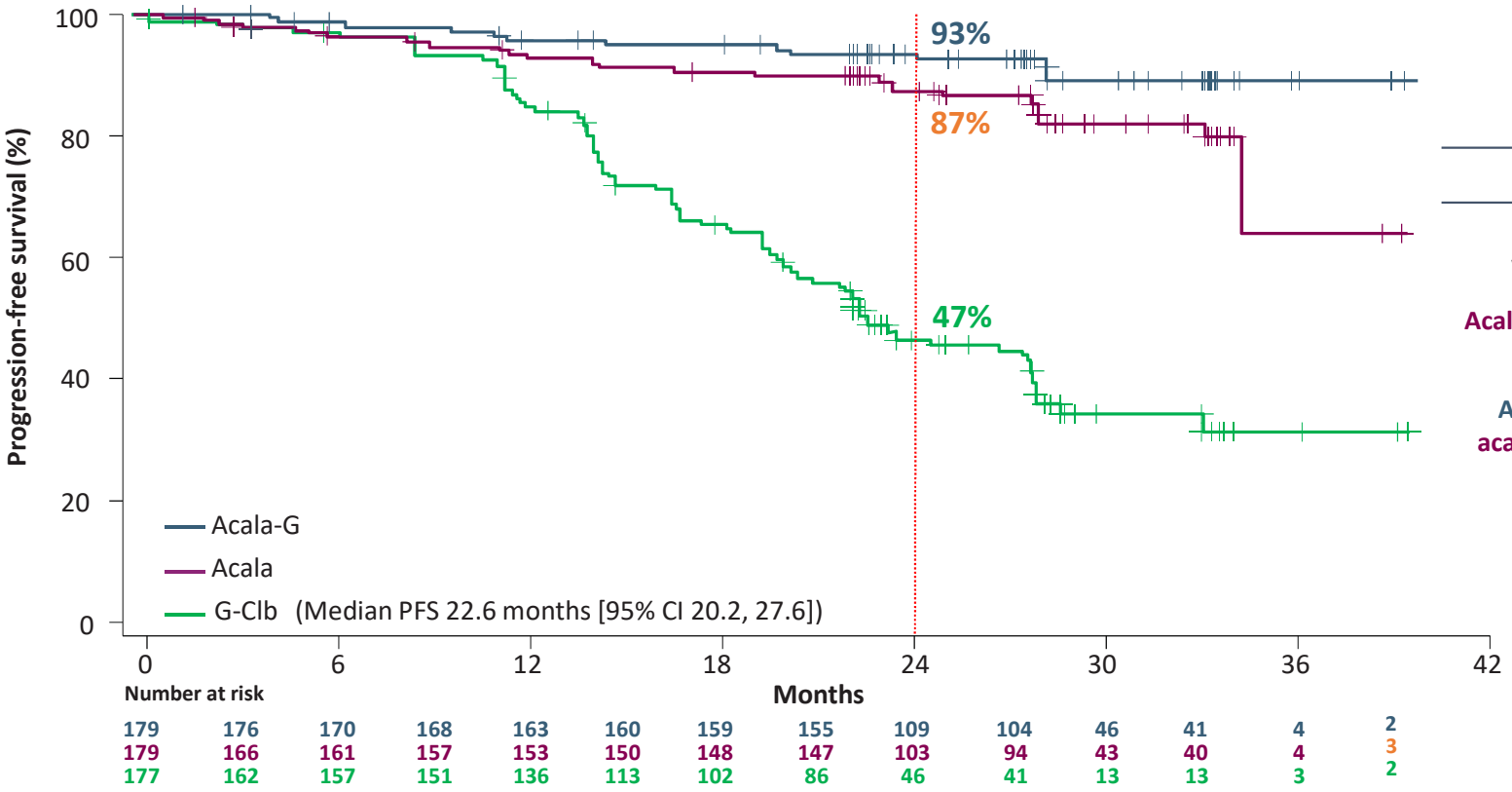
***Crossover** from G-Clb to acalabrutinib was allowed after IRC-confirmed progression*

- 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

Sharman et al ASH 2019

IRC-Assessed Progression-Free Survival

Median follow-up 28.3 months

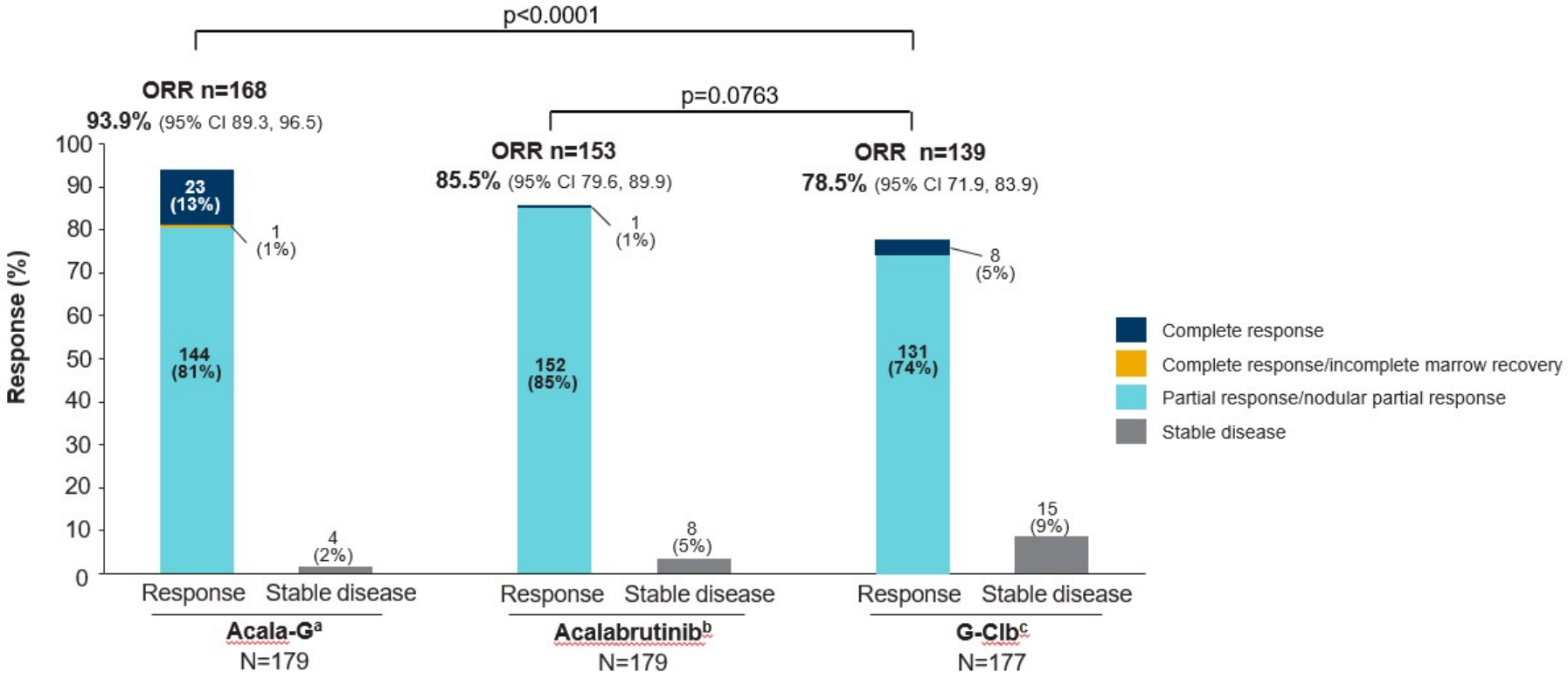


Hazard ratio (95% CI)	
Acala-G vs G-Clb	**0.10** (0.06, 0.17) p<0.0001
Acalabrutinib vs G-Clb	**0.20** (0.13, 0.30) p<0.0001
Acala-G vs acalabrutinib[a]	**0.49** (0.26, 0.95)

- Sharman et al ASH 2019

Sharman, ASH 2019

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

- Sharman et al ASH 2019

The New Changing Treatment Paradigm in CLL

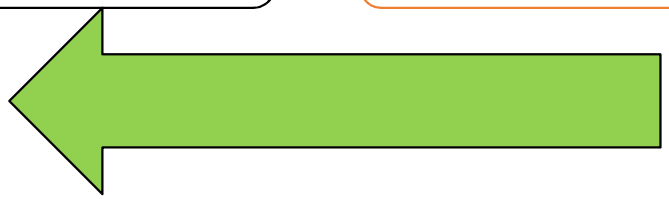
- **Bcl2 inhibitors**
- **BCR inhibitors**

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

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

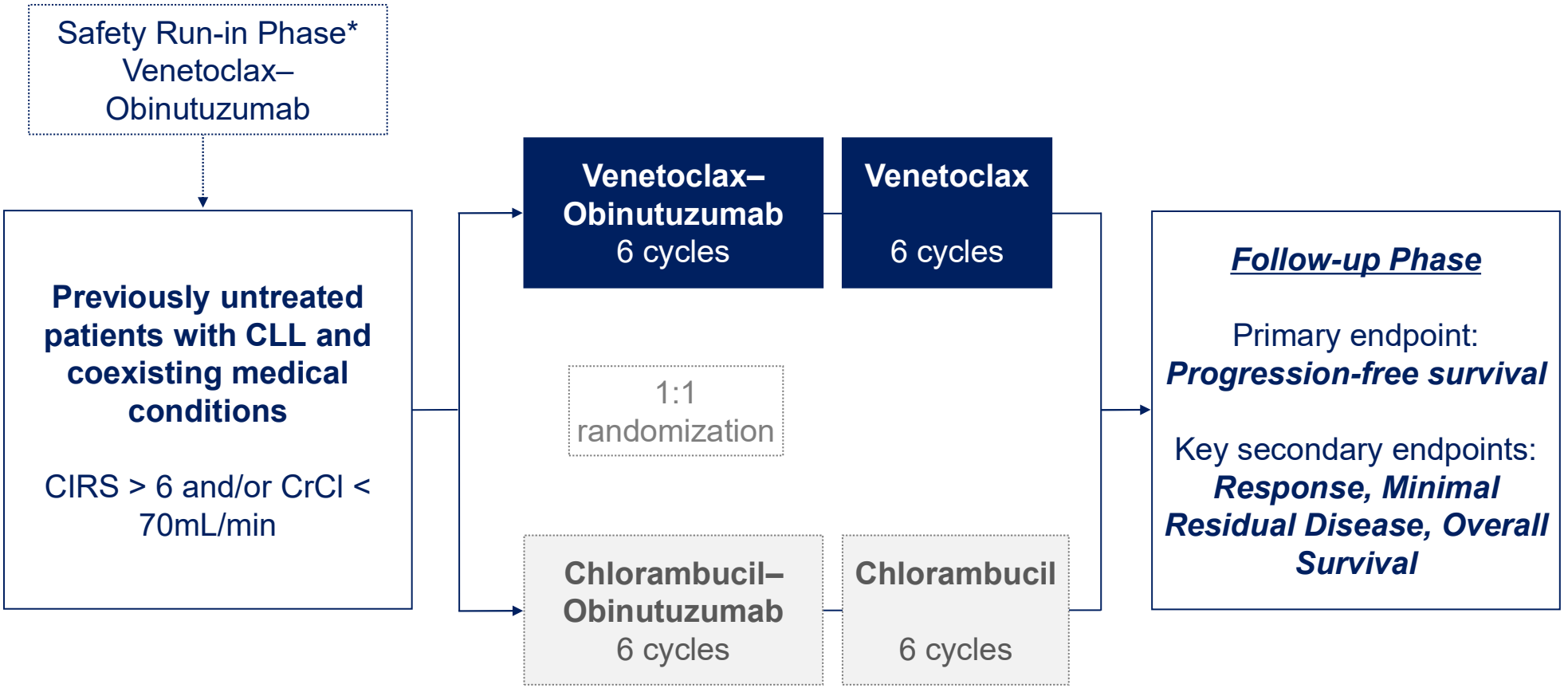
ORIGINAL ARTICLE

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

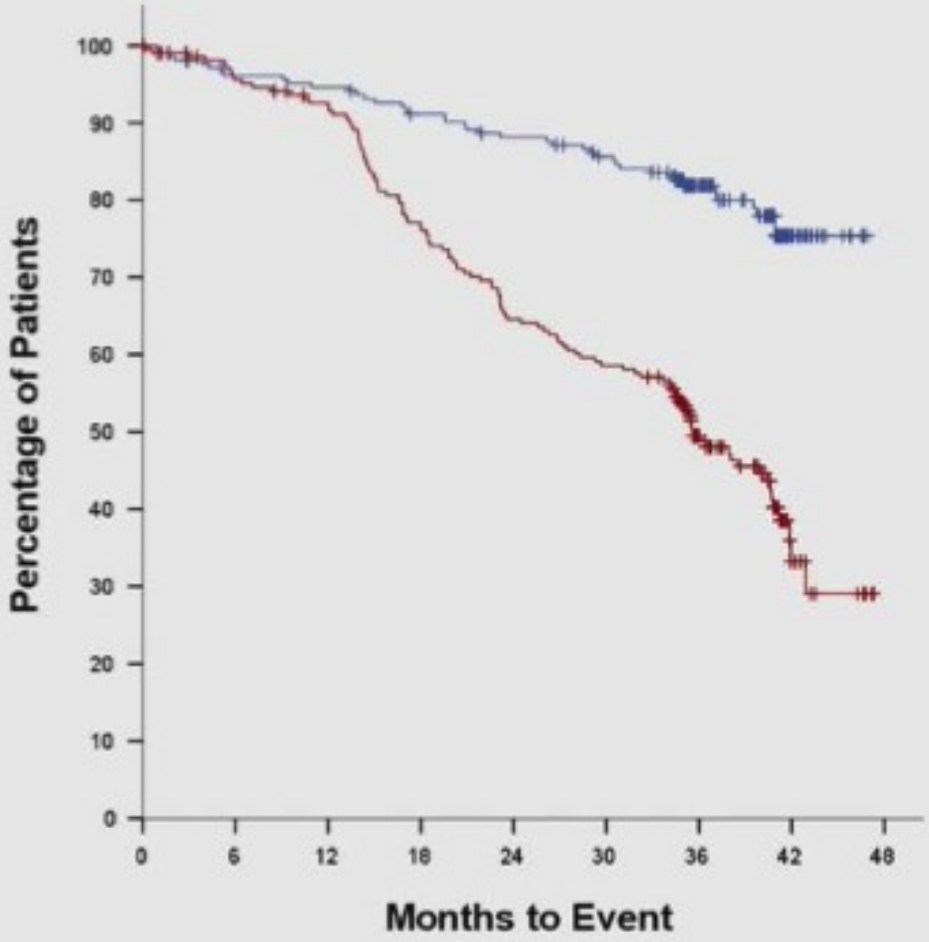
TRIAL DESIGN



CLL-14

PROGRESSION-FREE SURVIVAL

Median observation time 39.6 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 35.6 months

3-year PFS rate

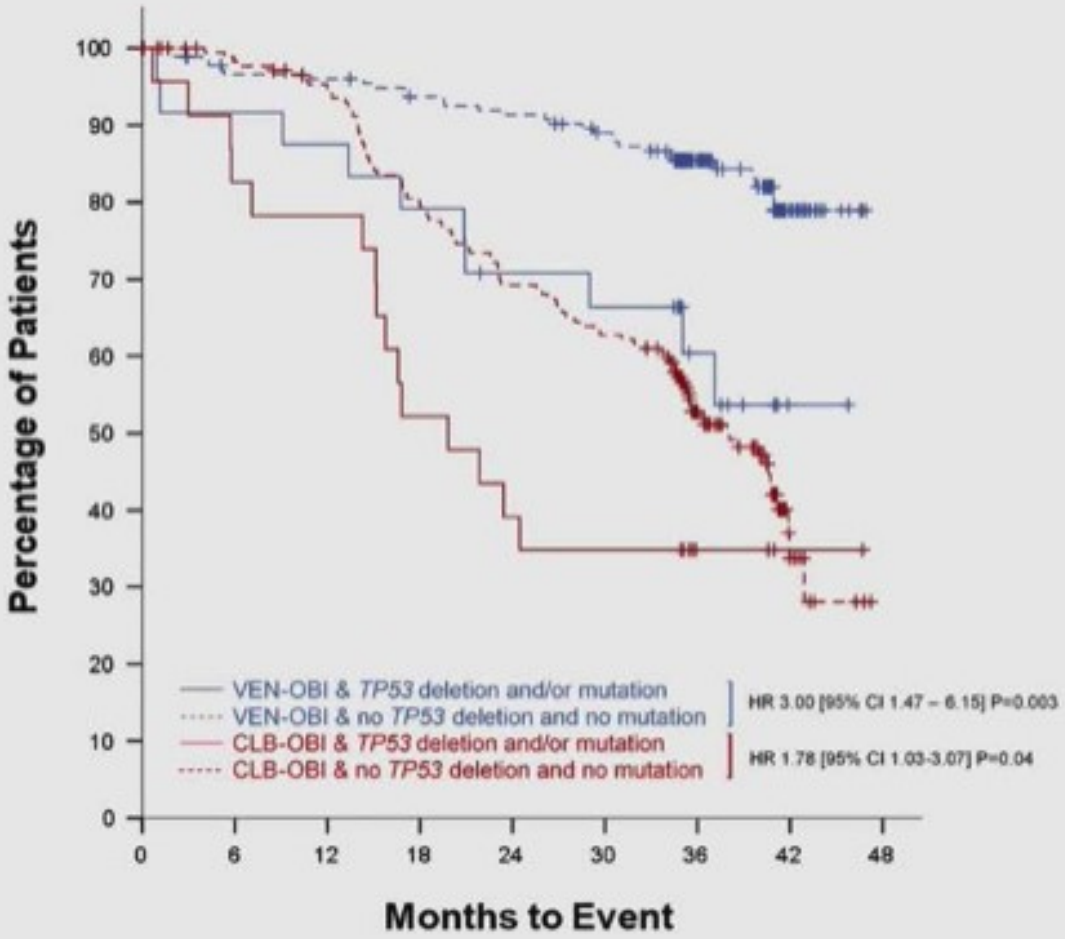
Ven-Obi: 81.9%

Clb-Obi:49.5%

HR 0.31, 95% CI [0.22-0.44], P<0.0001

PROGRESSION-FREE SURVIVAL

According to *TP53*del/mut status



Median PFS

Ven-Obi without TP53del/mut: not reached

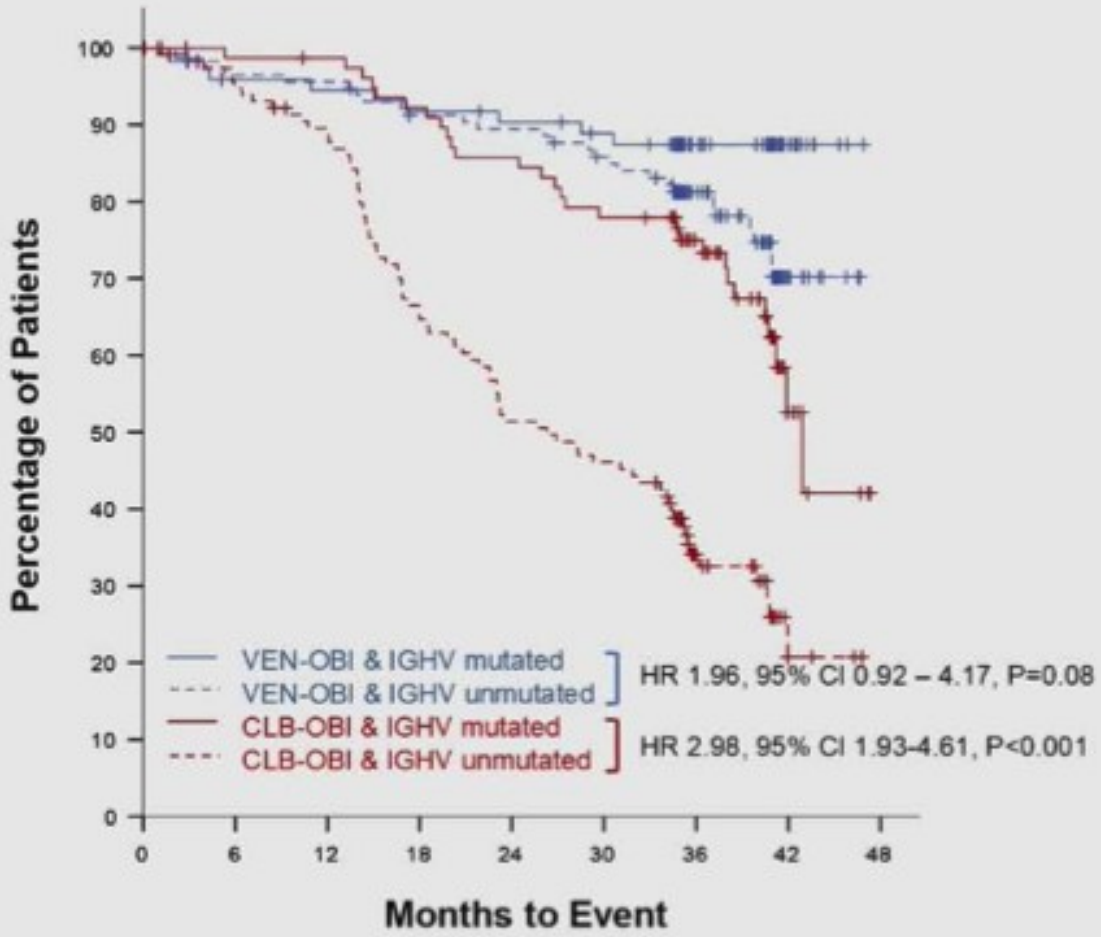
Ven-Obi with TP53del/mut: not reached

Clb-Obi without TP53del/mut : 19.8 months

Clb-Obi with TP53del/mut : 38.0 months

PROGRESSION-FREE SURVIVAL

According to *IGHV* status



Median PFS

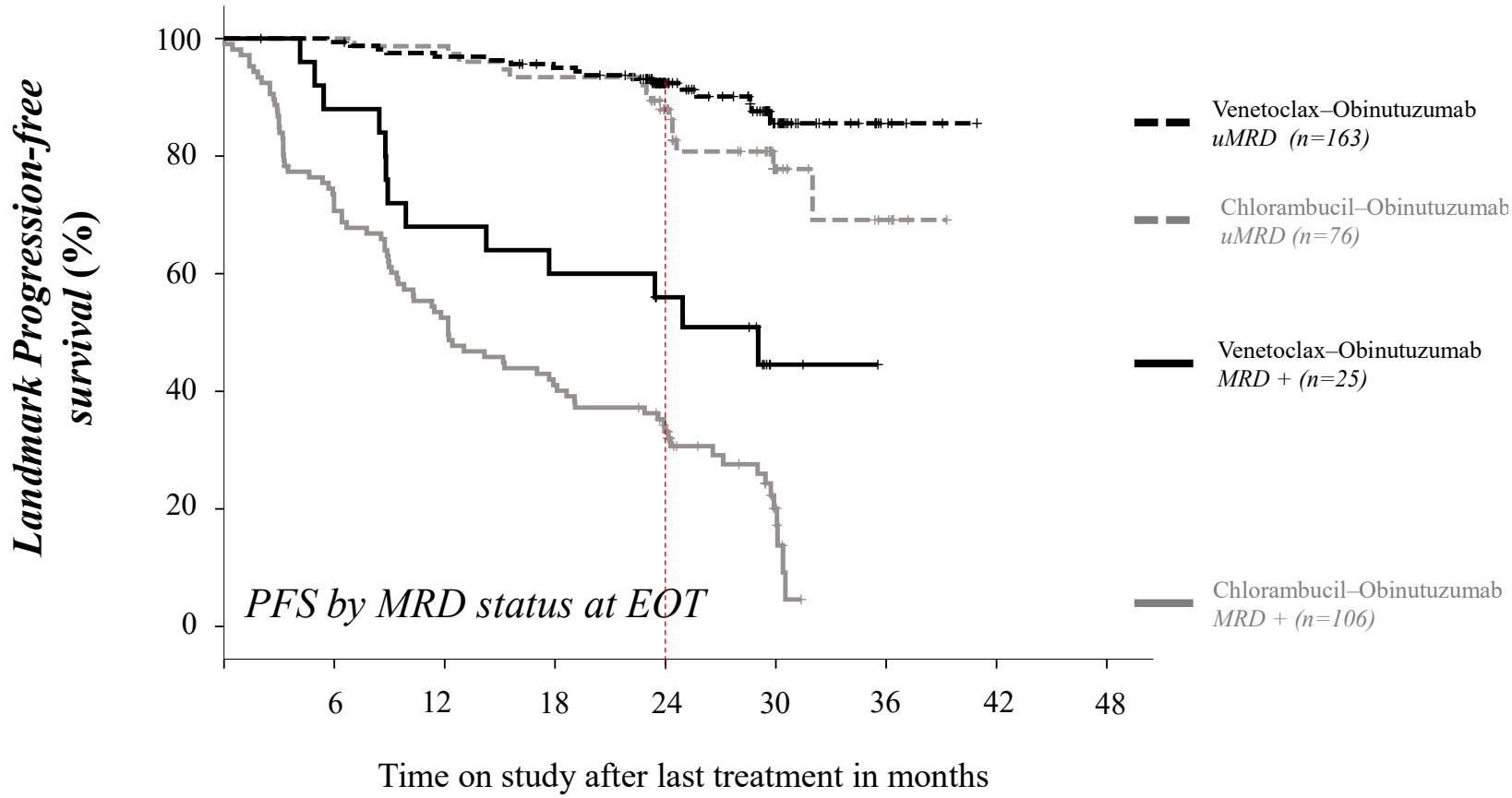
Ven-Obi IGHV*mut*: not reached

Ven-Obi IGHV*unmut*: not reached

Clb-Obi IGHV*mut*: 42.9 months

Clb-Obi IGHV*unmut*: 26.3 months

PFS by MRD status at EOT



The Very New Changing Treatment Paradigm in CLL

- **Bcl2 inhibitors+ BCRi**

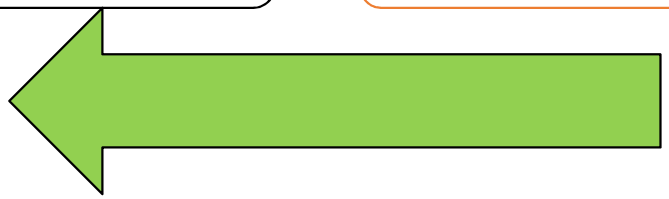
- **BCR inhibitors**

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

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)



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.

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

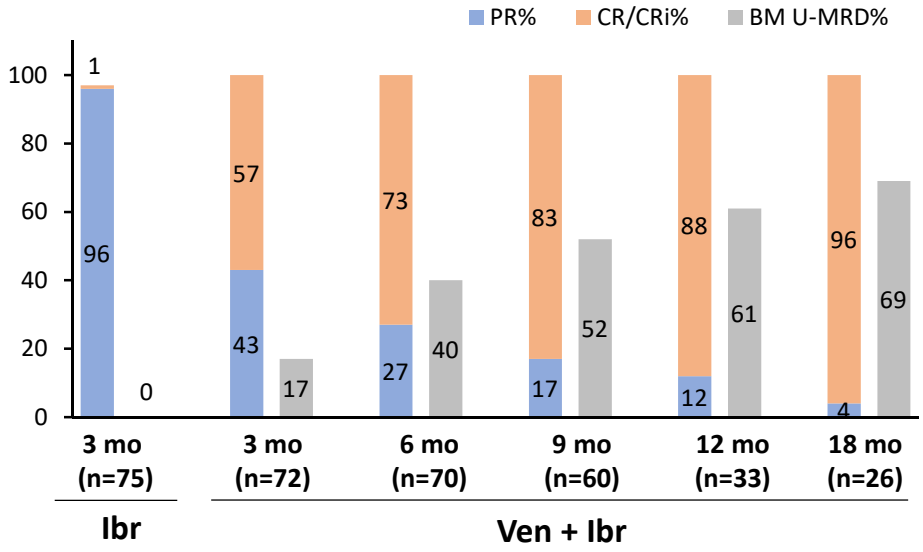
Patients with MRD-positive CLL continued Ibr

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

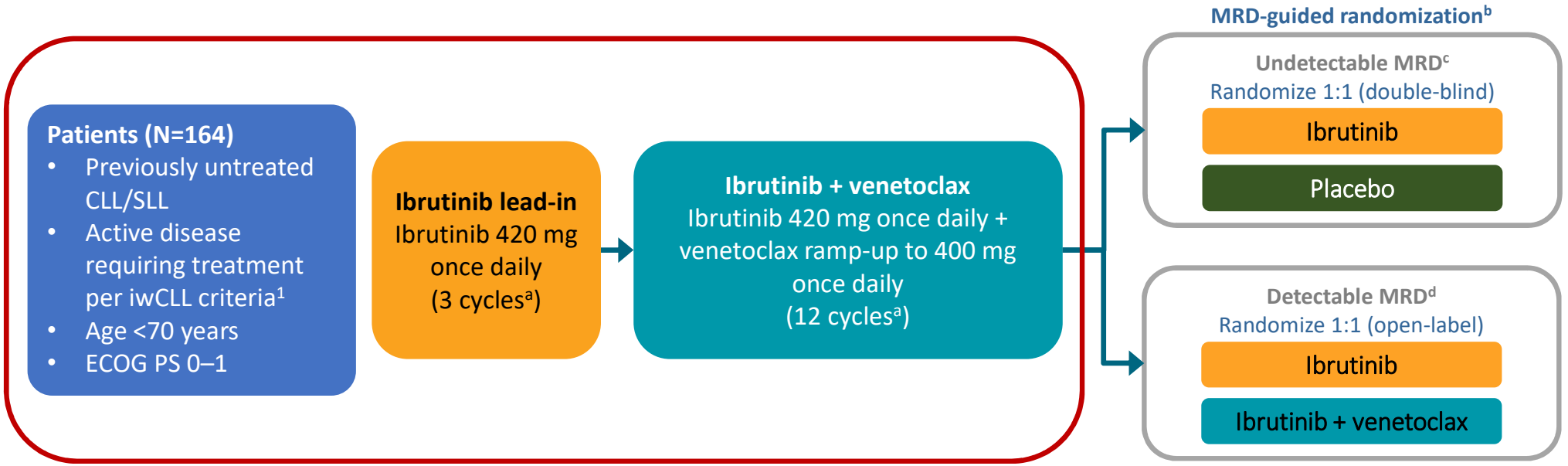
Jain et al. ASH 2018. Abstract 186.
https://clinicaltrials.gov/ct2/show/NCT02756897.

- 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

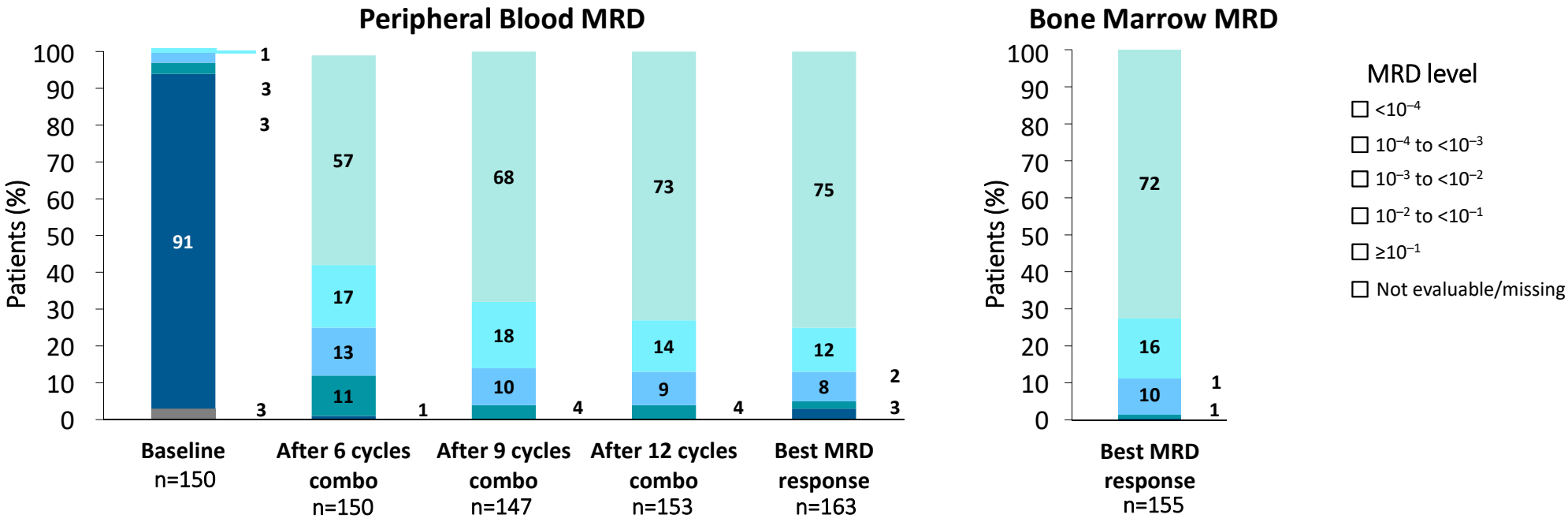
CAPTIVATE-MRD Cohort: Study Design



- 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.

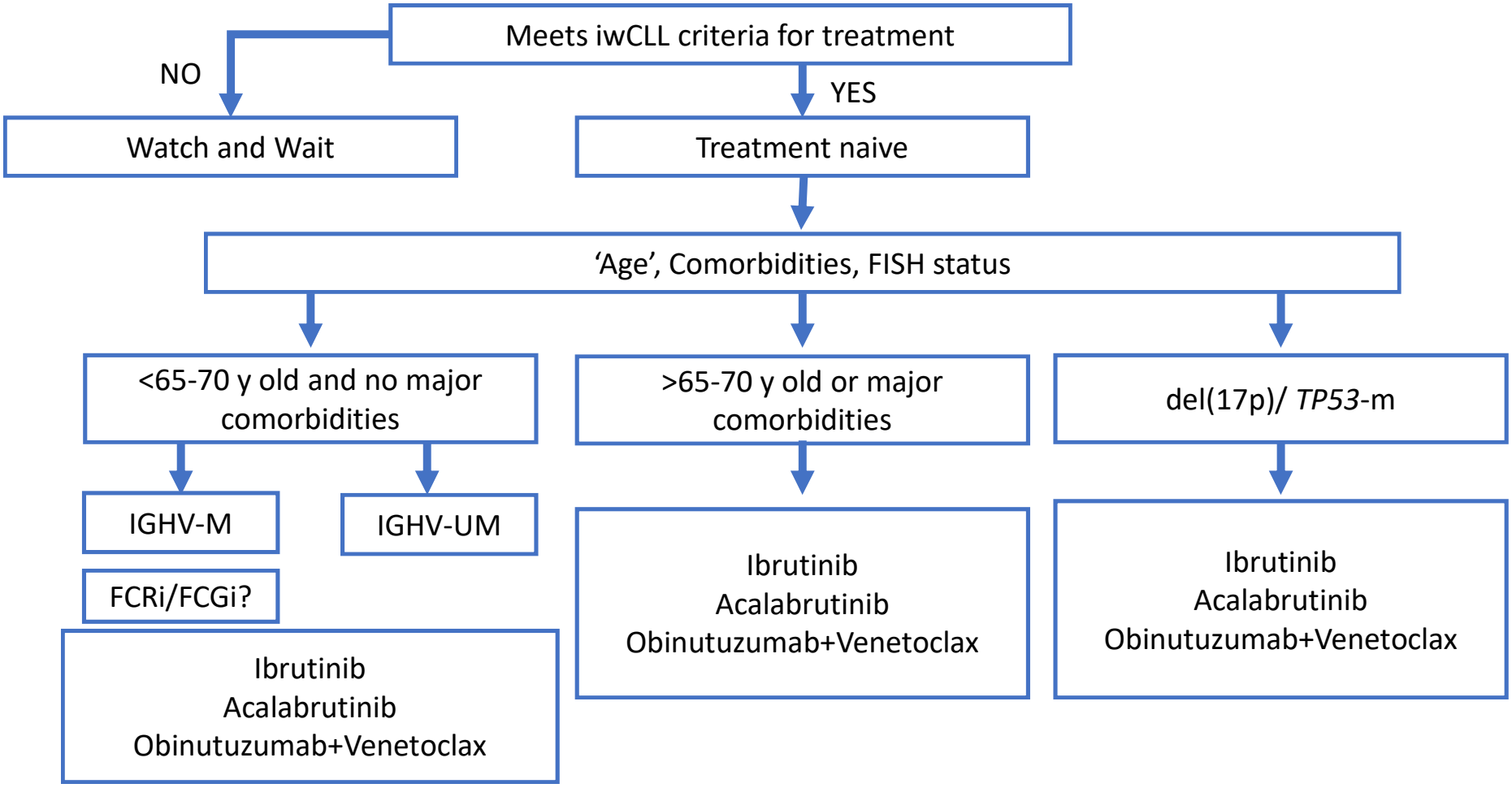
High Rates of Undetectable MRD Sustained Over Time in MRD-Evaluable Patients



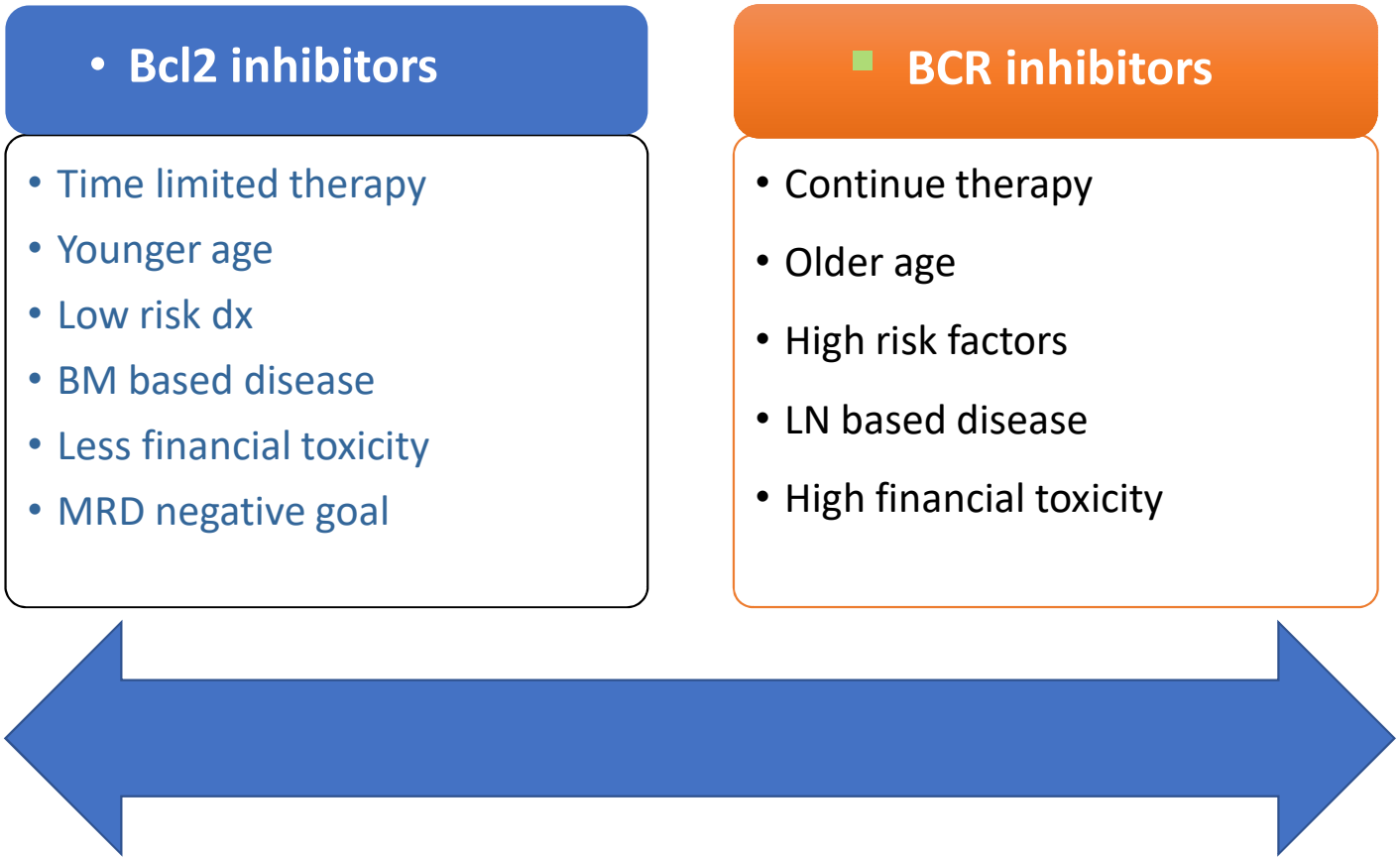
- Proportion of patients with undetectable MRD in peripheral blood increased over the 12 cycles of combination therapy

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

CLL Front Line Treatment Algorithm 2020

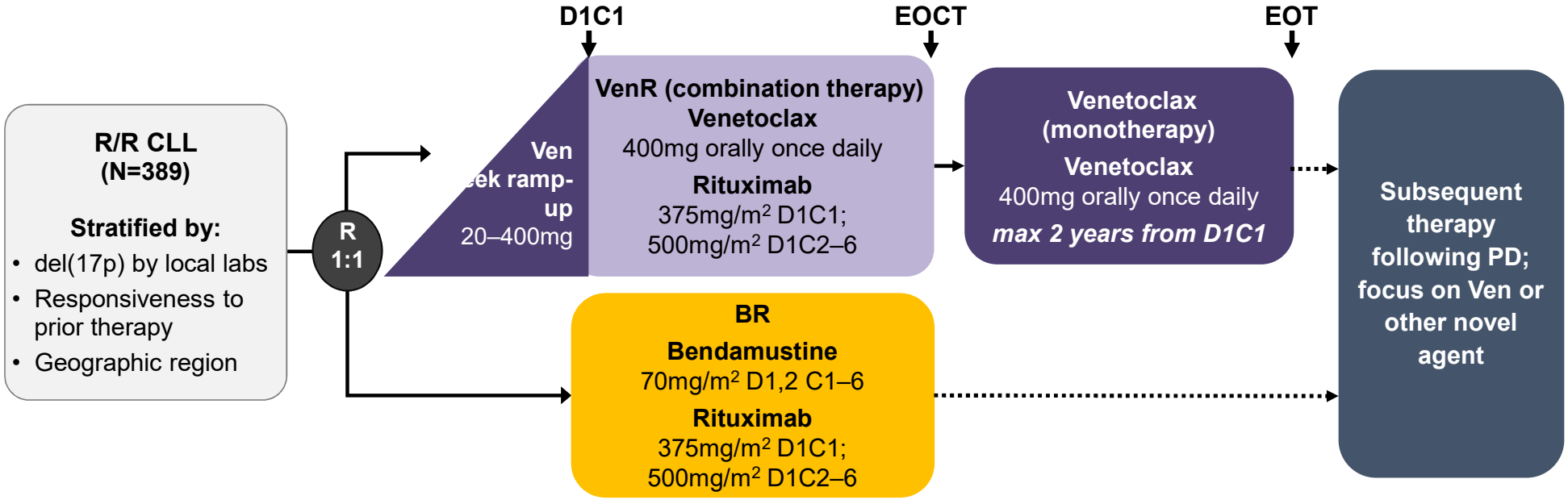


The alternatives Treatment Paradigm in CLL



Treatment for Relapsed/Refractory CLL

MURANO study design

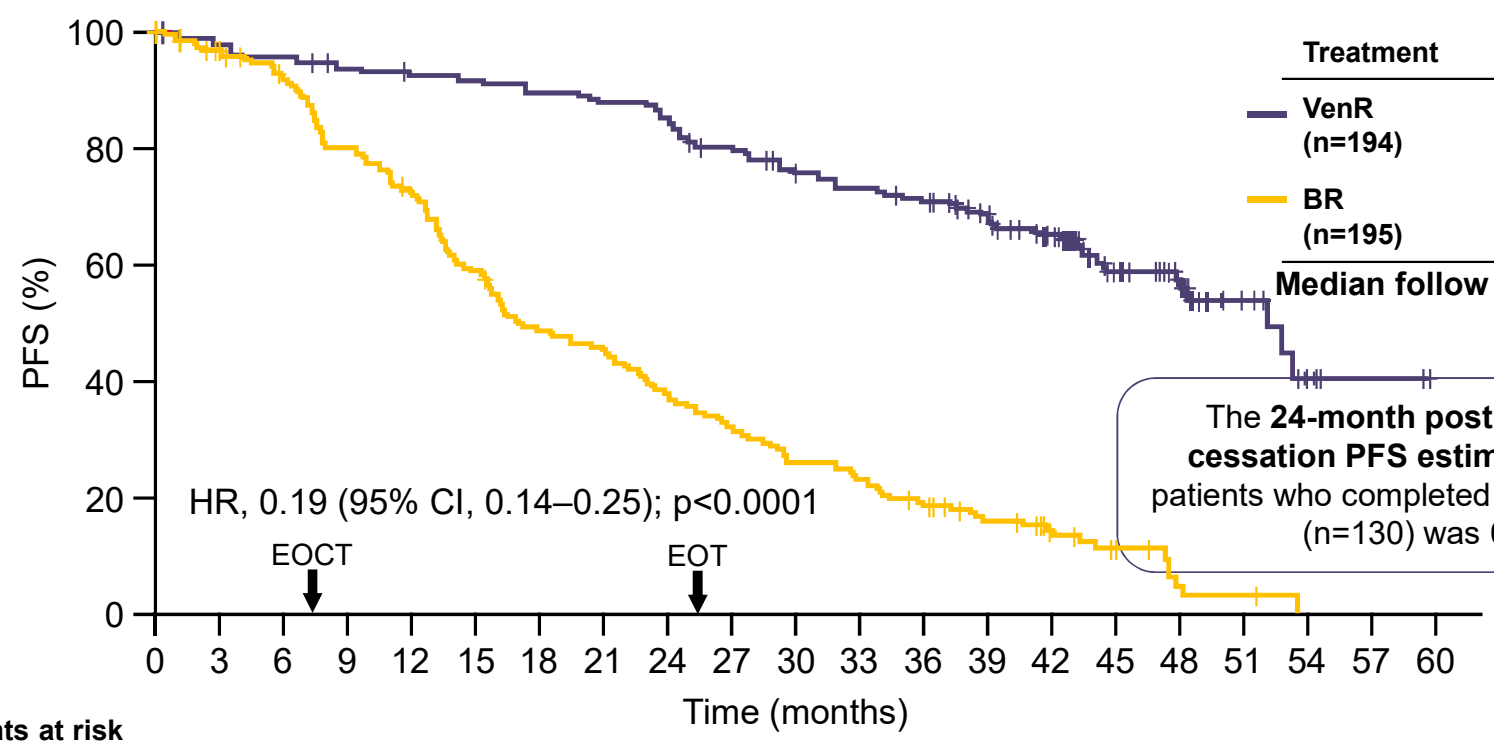


- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoint:** rates of clearance of MRD
- Clinical response and MRD* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

*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



Treatment	4-yr PFS, % (95% CI)
VenR (n=194)	57.3 (49.4–65.3)
BR (n=195)	4.6 (0.1–9.2)

Median follow up: 48 months

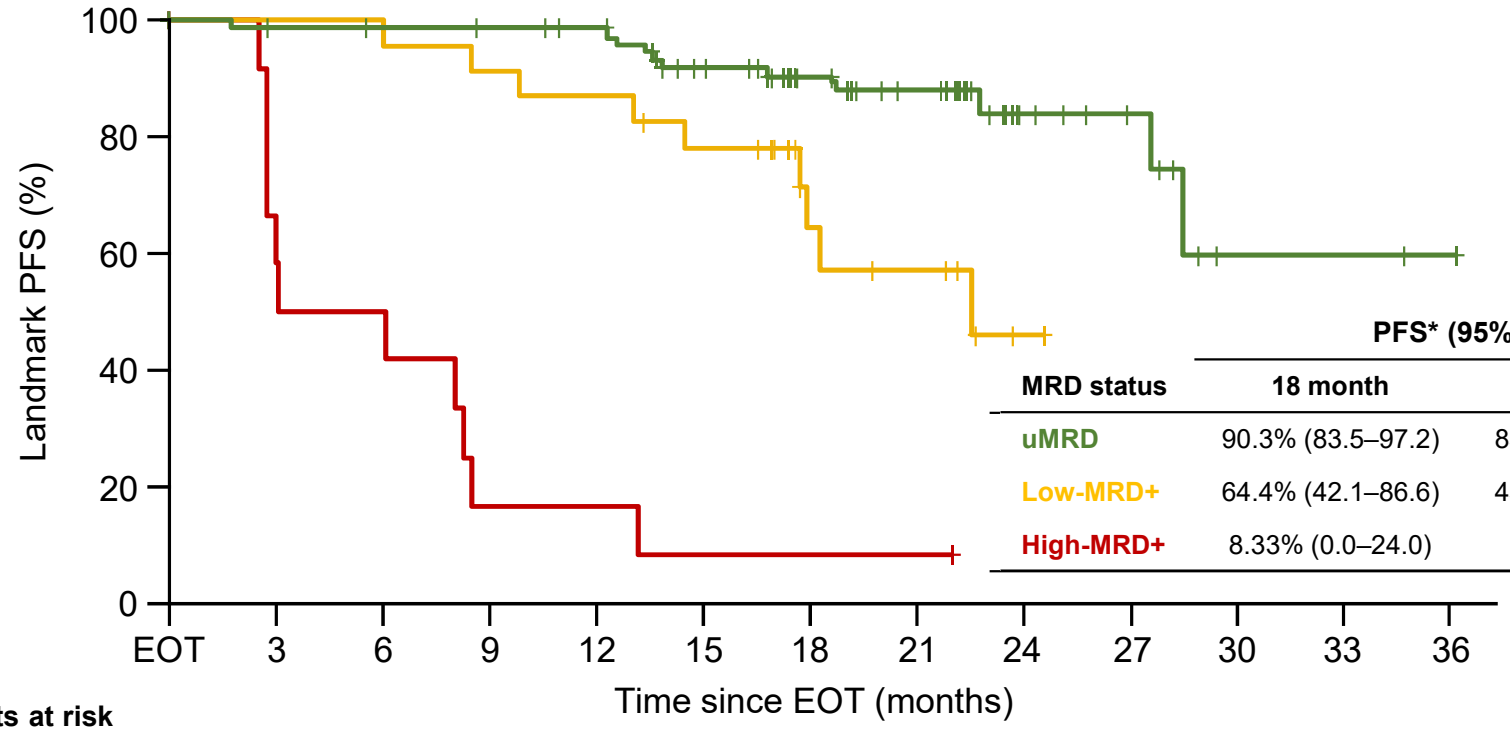
The **24-month post-treatment cessation PFS estimate** in VenR patients who completed 2 years of Ven (n=130) was **68%**

No. of patients at risk

VenR	194	190	185	179	176	174	170	167	161	150	141	134	130	118	101	55	40	14	7	2	-
BR	195	178	165	143	129	104	85	80	66	56	45	40	32	23	14	9	3	2	-	-	-

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

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



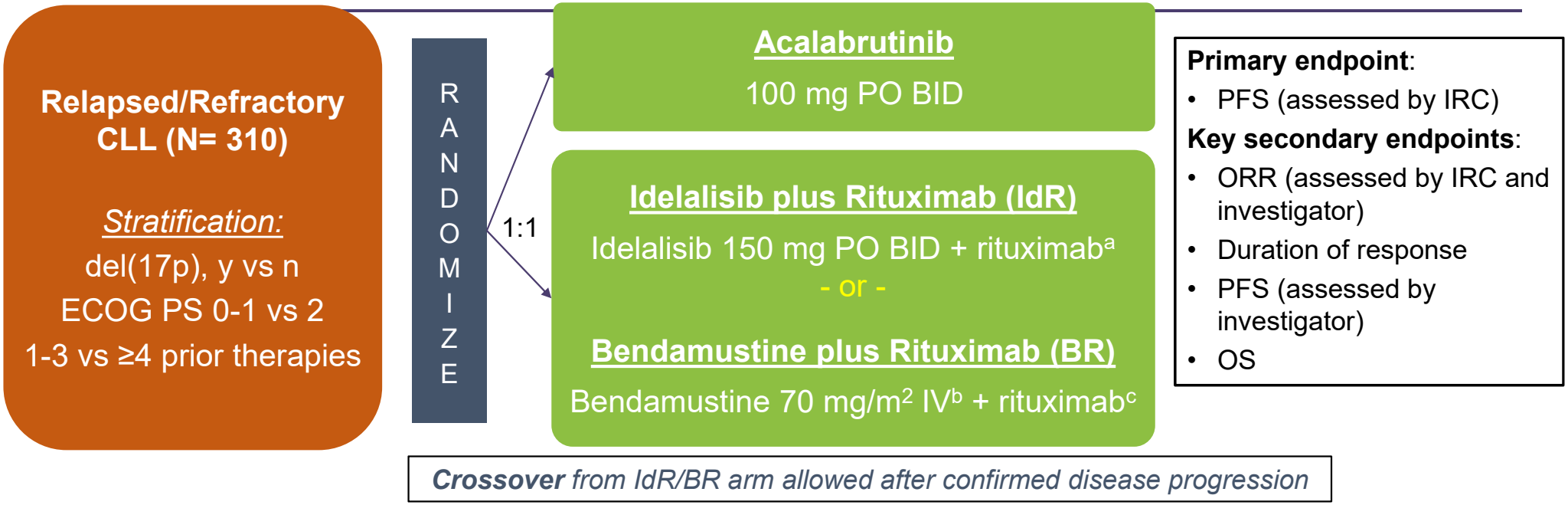
MRD status	PFS* (95% CI) 18 month	24 month
uMRD	90.3% (83.5–97.2)	83.9% (72.9–94.9)
Low-MRD+	64.4% (42.1–86.6)	45.7% (18.1–73.4)
High-MRD+	8.33% (0.0–24.0)	NE

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

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.

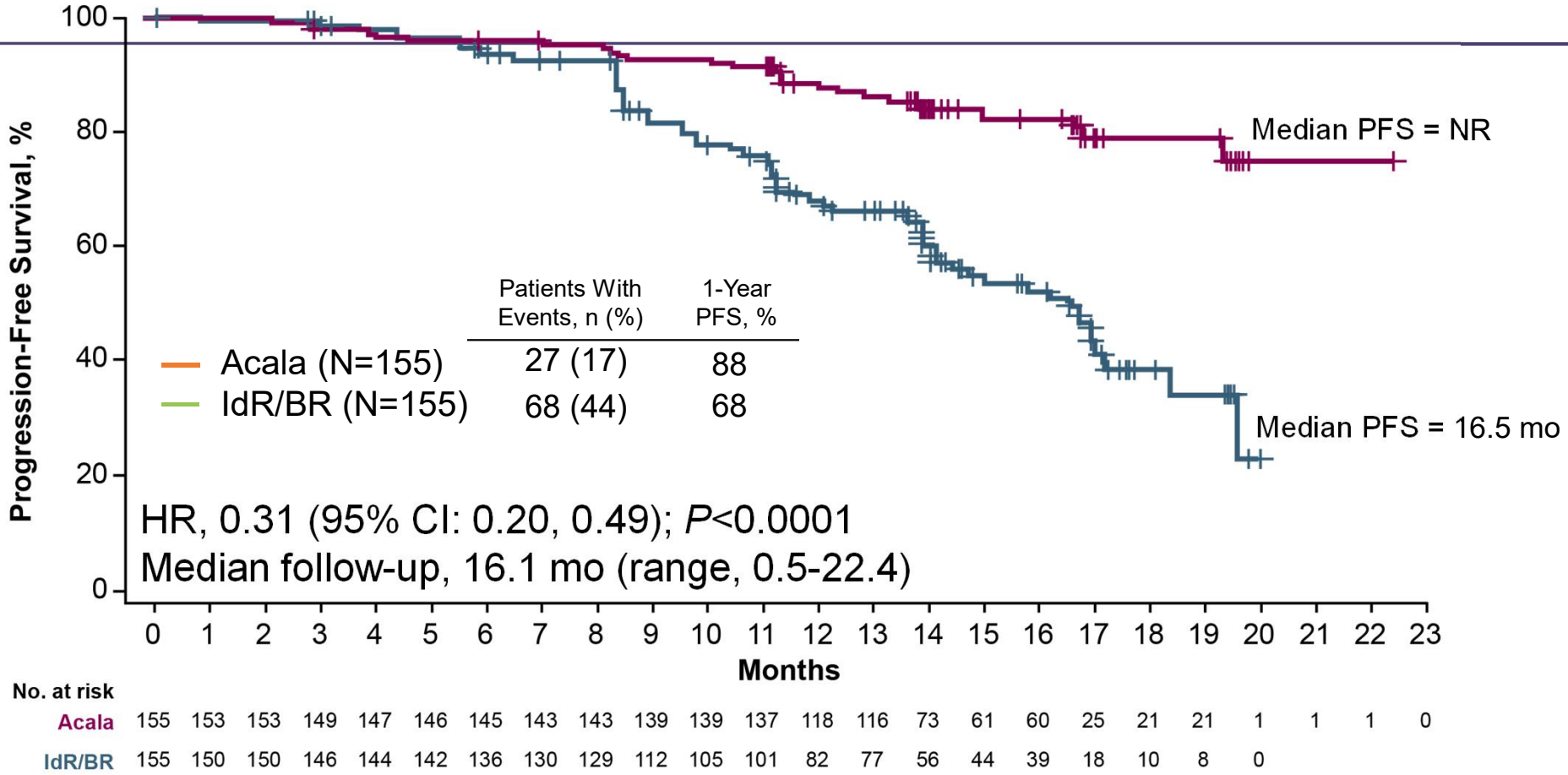
[b]On day 1 and day 2 of each cycle.

[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.

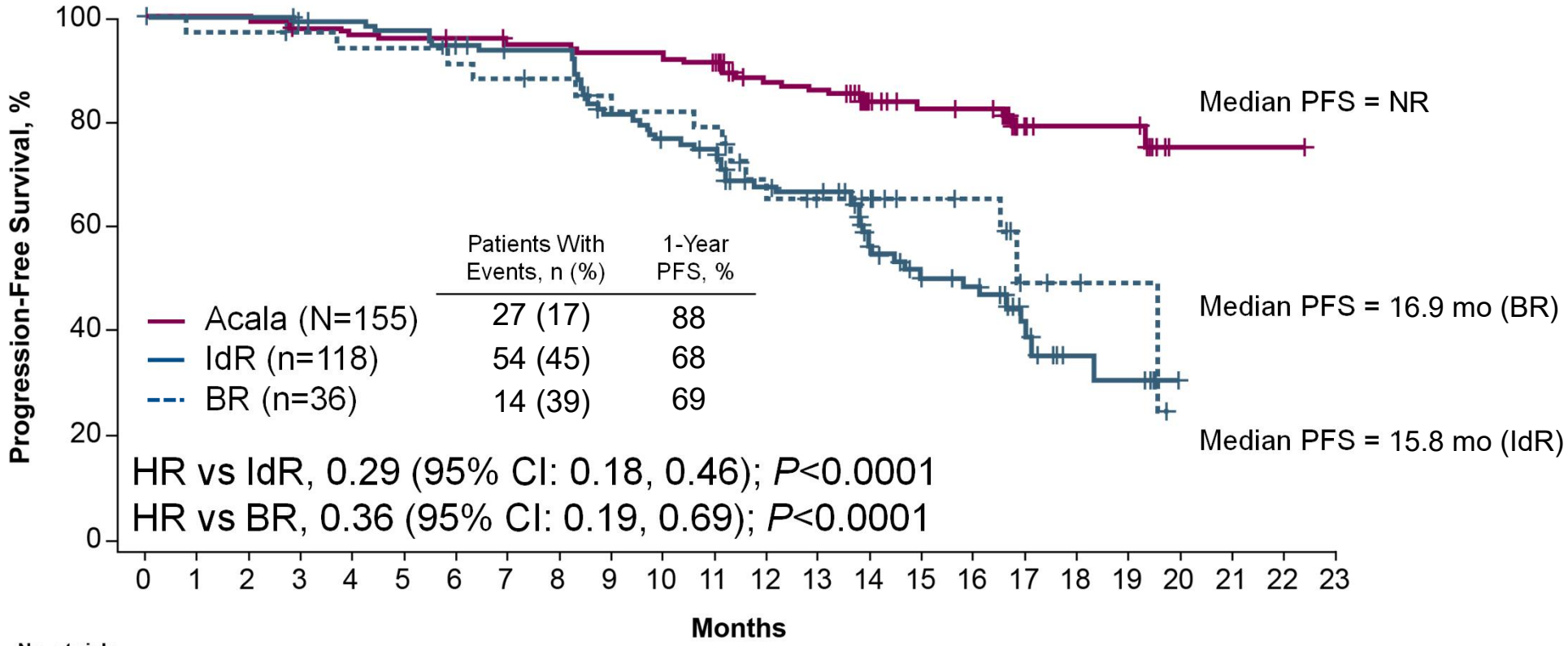
Ghia, EHA 2019

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.

IRC-Assessed PFS Superior for Acalabrutinib vs IdR or BR

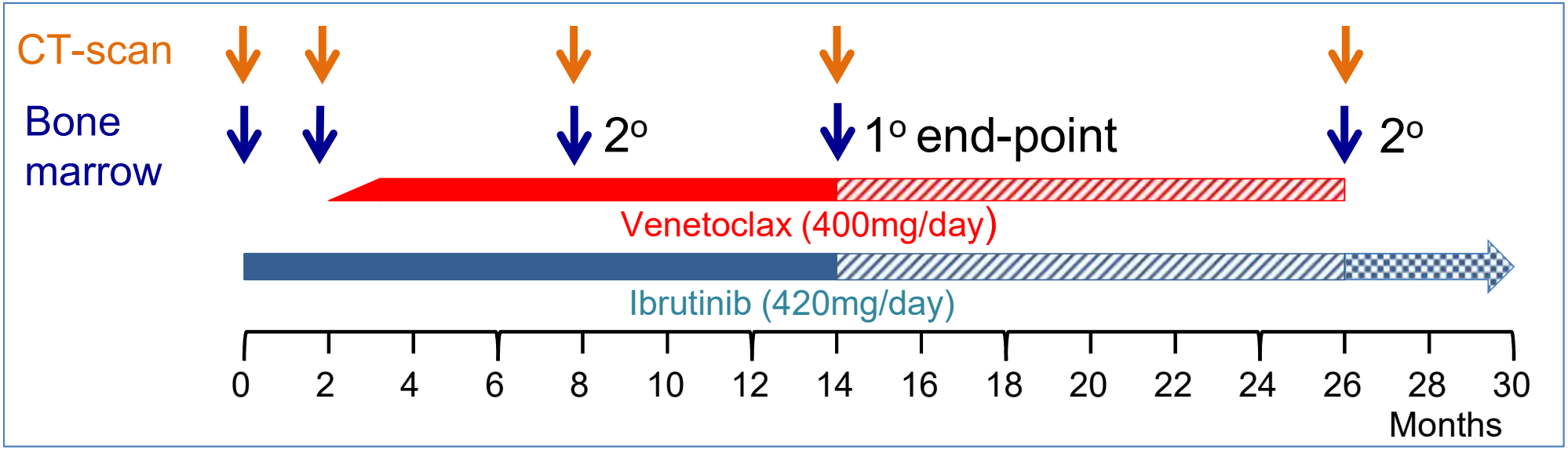


No. at risk

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.

Treatment Schedule and Stopping Rules



Stopping rules: Duration of therapy is double time to MRD4 negative

1) MRD negative (<0.01%) at M8 stop I+V at M14
2) MRD negative (<0.01%) at M14 or M26 stop I+V at M26
3) MRD positive (≥0.01%) at M26 continue ibrutinib monotherapy

Hillmen *et al.* ASH 2018; Abst 182

Primary end-point: undetectable MRD4 (<0.01%) in BM after 12 months I+V

All at Month 14	PB MRD negative	BM MRD negative	Trephine normal
All patients	**28/49 (57%)**	**19/49 (39%)**	**39/48 (81%)**
FCR/BR rel <36 months	14/20 (70%)	9/20 (45%)	18/19 (95%)
Prior idelalisib	6/9 (67%)	5/9 (56%)	7/9 (78%)

49/50 patients have reached at least Month 14 and have had a bone marrow MRD PB or BM <0.01% CLL cells (10^{-4}) by flow cytometry

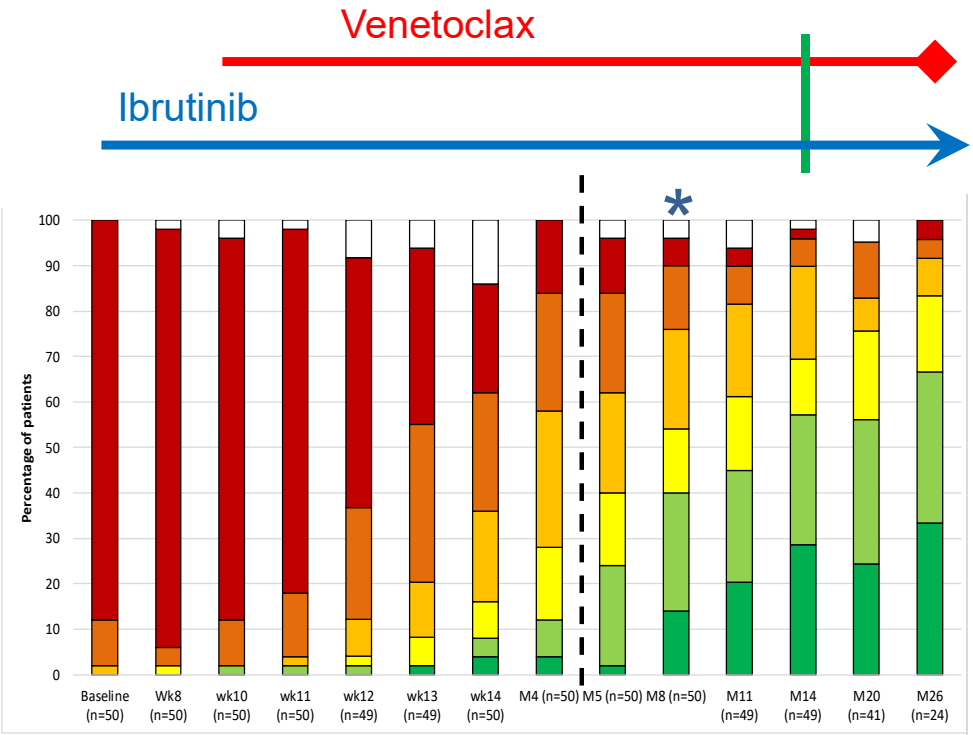
Using statistical significance (alpha) of 2.5% and statistical power of 95.5%, the A'Hern design requires at least 10 of 50 patients to achieve MRD-eradication in the marrow to approve the combined treatment. Assumptions: Ibr+Ven 30% MRD eradication; Ibr monotherapy <10% MRD eradication

Hillmen *et al.* ASH 2018; Abst 182

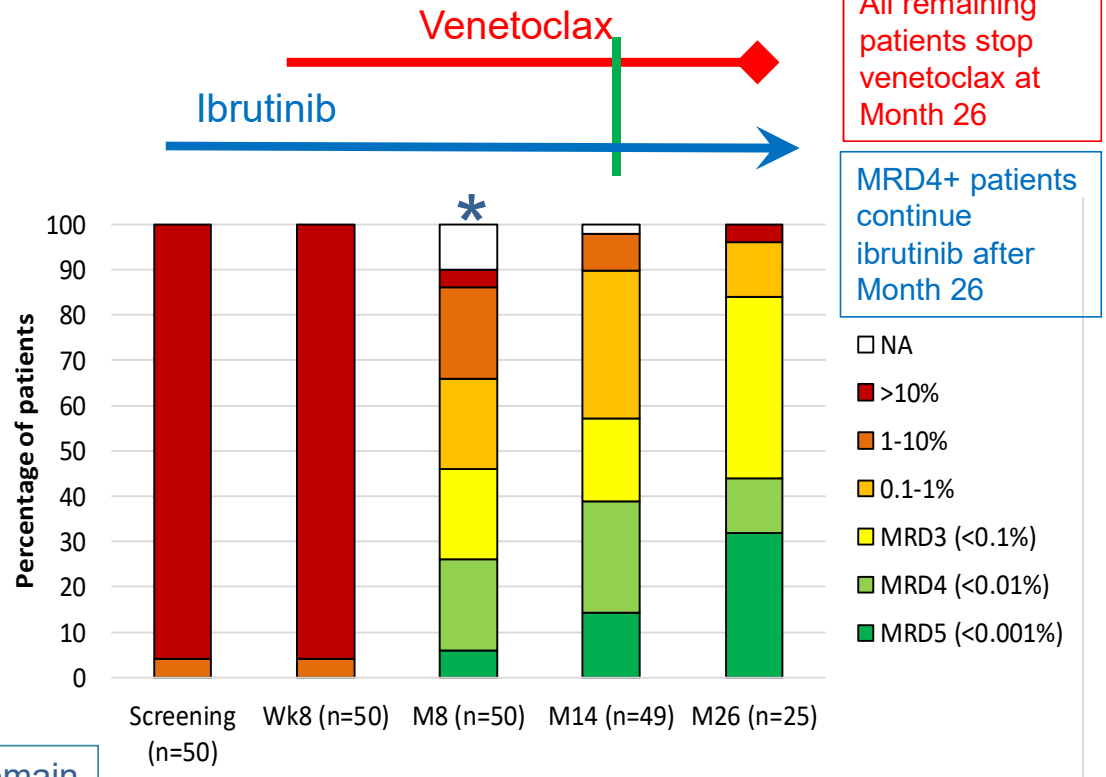
MRD level by time-point (up to Month 26)

Date of data lock:
05 November 2018

Peripheral Blood



Bone Marrow

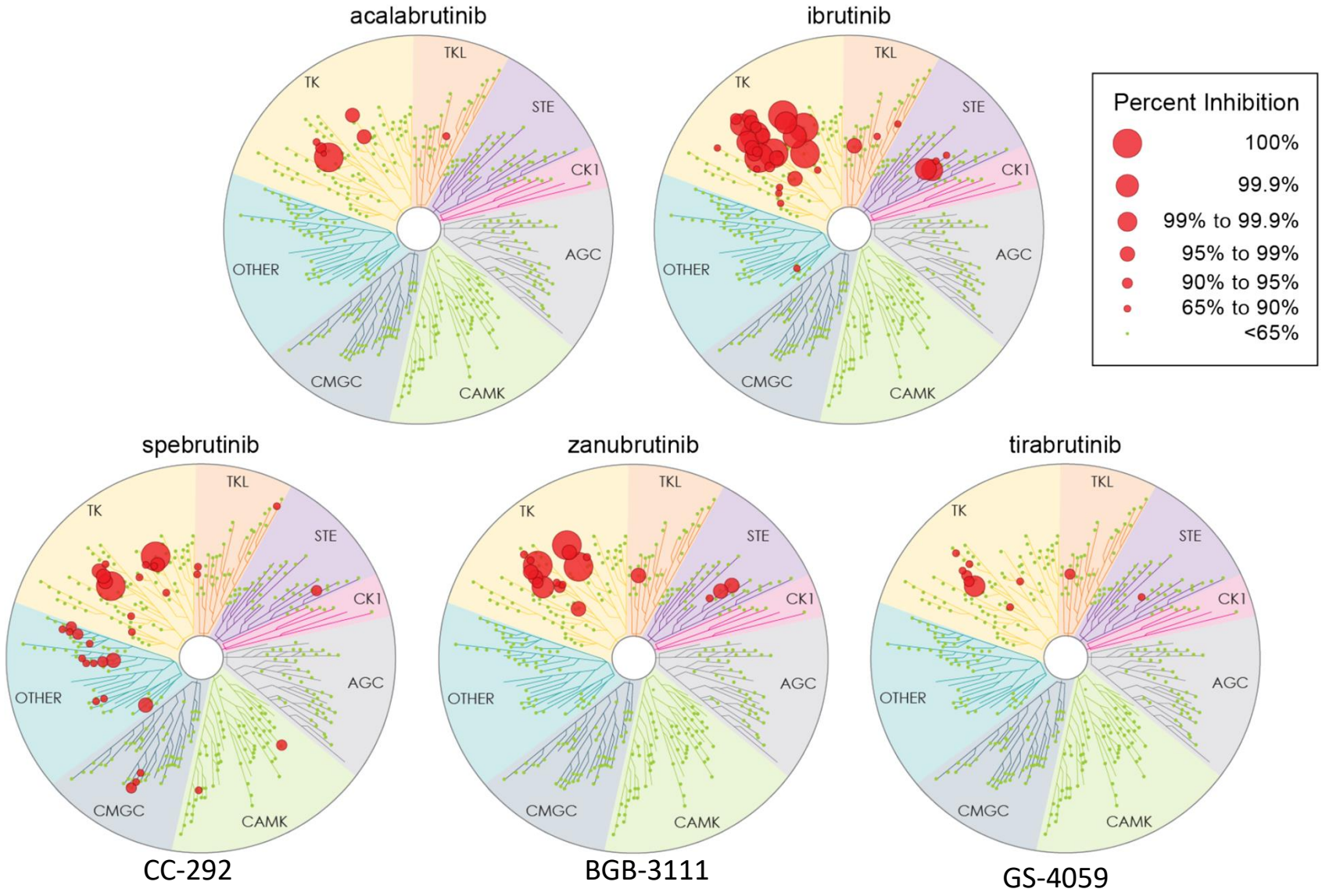


All remaining patients stop venetoclax at Month 26

MRD4+ patients continue ibrutinib after Month 26

*PB & BM MRD negative pts at Month 8 & 14 stop I+V → All 6 reaching M26 remain MRD negative to date

Hillmen *et al.* ASH 2018; Abst 182



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]

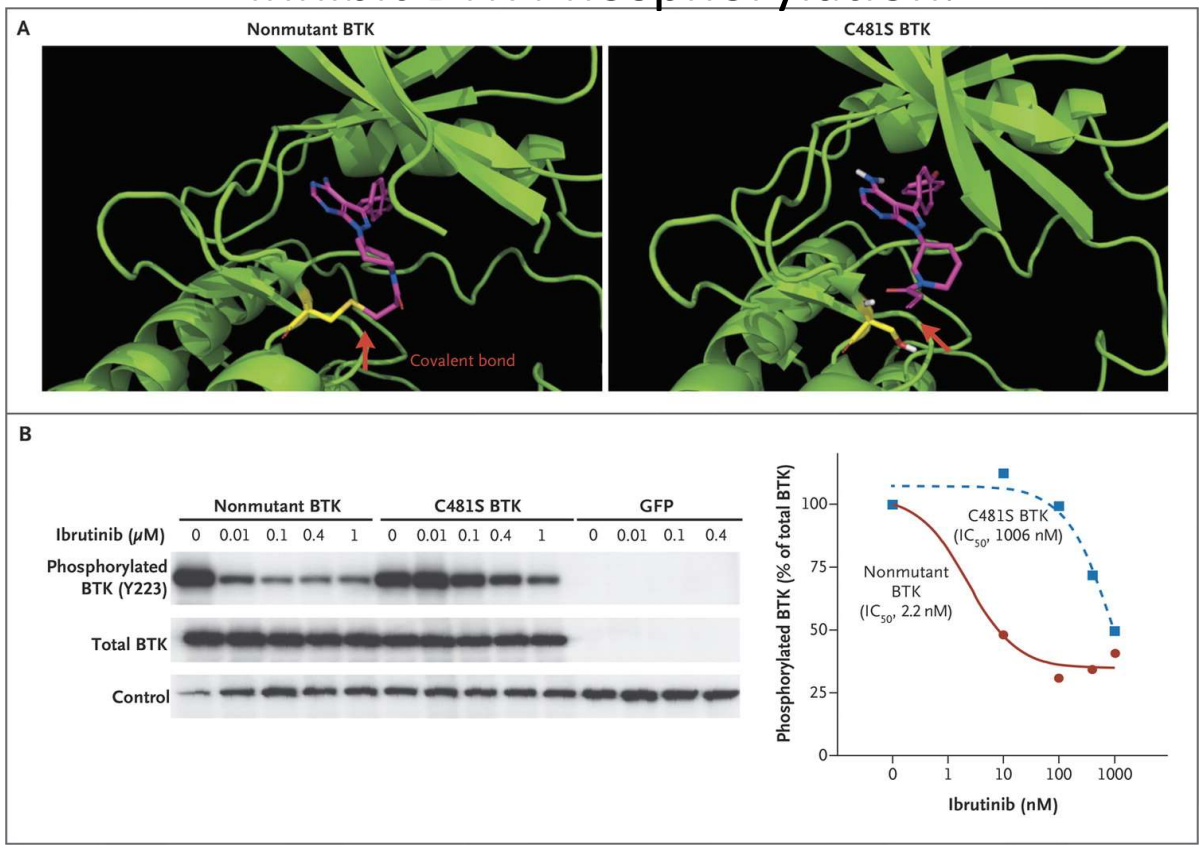
[1]Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; [2]University of Western Australia, Perth, Western Australia, Australia; [3]North Shore Hospital, Auckland, New Zealand; [4]Monash Health, Clayton, Victoria, Australia; [5]Monash University, Clayton, Victoria, Australia; [6]Department 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

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)

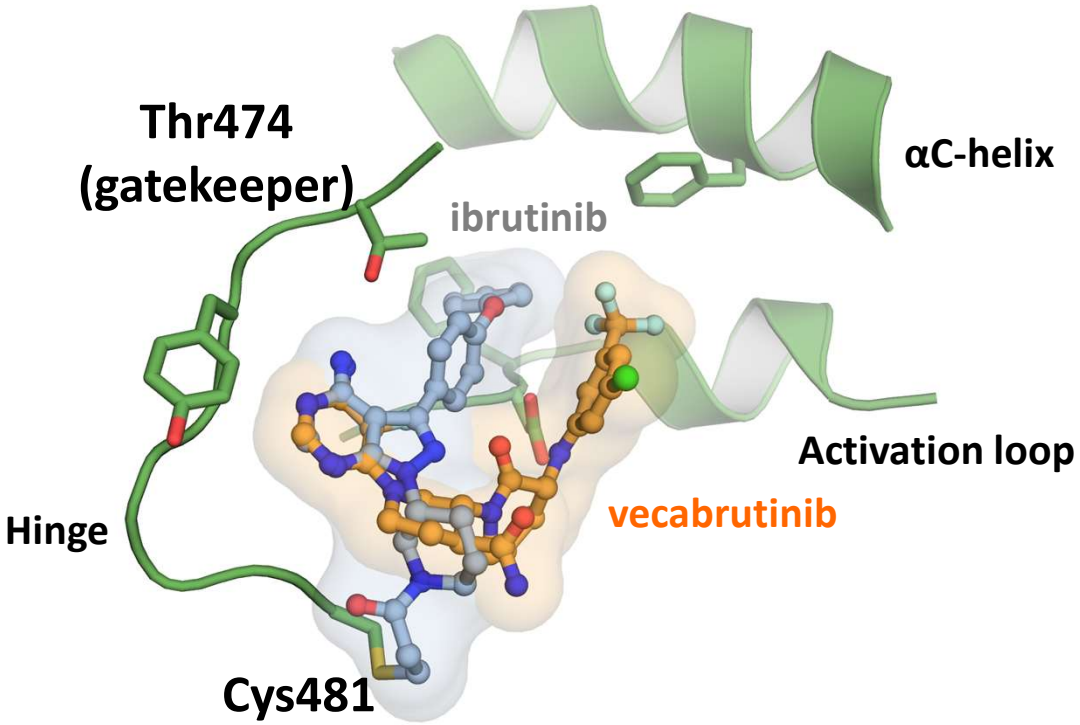
Data cutoff: May 8, 2019.
CR, complete response; CRi, complete response with incomplete bone marrow recovery; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve.
[a]As of data cutoff (May 8, 2019), 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.

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

Phase 1b/2 Study of Vecabrutinib in R/R B-Cell Malignancies[1,2]

- Vecabrutinib is a reversible, noncovalent inhibitor of wild-type and C481S-mutated BTK with nanomolar potency

R/R B-Cell Malignancies

Key inclusion criteria include

- CLL/SLL, MCL, WM, MZL, DLBCL-ABC, or FL
- ≥2 lines of tx, including covalent BTKi for CLL/SLL, MCL, and WM

Key exclusion criteria include

- Demonstrated BTKi intolerance

→

Phase 1b

BID in 3+3 design

- 25 mg
- 50 mg
- 100 mg
- 200 mg
- 300 mg
- 400 mg

→

Phase 2

CLL/SLL

- ≥1 prior tx w/ BTK C481x mutation
- ≥1 prior tx w/o BTK C481x mutation
- ≥2 prior tx w/ BTK C481x mutation
- ≥1 prior tx ibrutinib intolerant

Primary endpoints: MTD, RP2D (Phase 1b); ORR (Phase 2)

Secondary endpoints: Safety, pharmacokinetics

Baseline Characteristic	Cohorts 1-5 (N=29)
Indication	23 CLL, 3 WM, 2 MCL, 1 MZL
Median age (range)	68 (47-77)
Median prior tx (range)	4 (2-9)
≥1 chemotx, n (%)	22 (76)
Covalent BTKi, n (%)	29 (100): 24 ibr, 5 acala
Venetoclax, n (%)	12 (41)
CAR T, n (%)	2 (7)
del17p / del13q / trisomy 12, n (%)	13 (46) / 11 (38) / 6 (21)

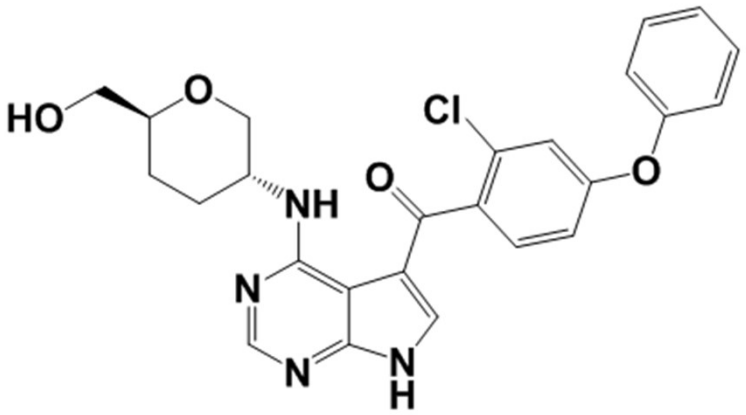
Efficacy in Cohorts 1-5

- INV-assessed SD was observed in 7/15 evaluable pts (4 BTK C481S, 3 BTK C481 wild-type)
- 7/15 evaluable pts discontinued tx due to PD at or before first response assessment; 1/15 withdrew consent

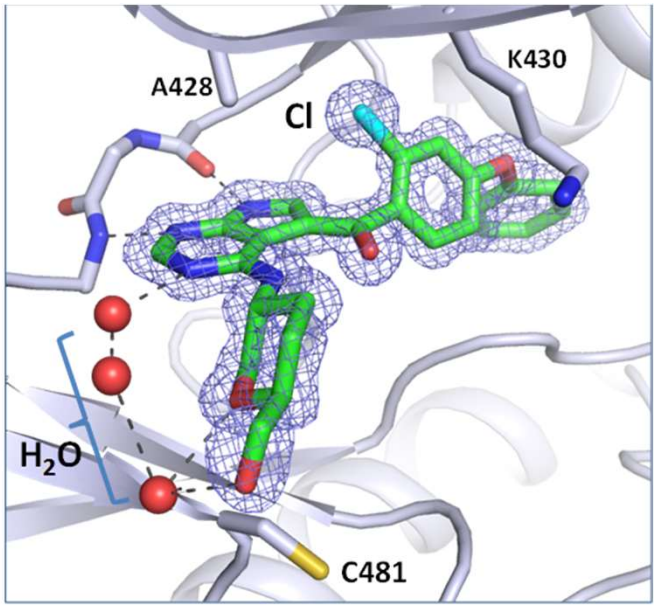
Safety	Cohorts 1-5
SAEs	10 SAEs in 7 pts, none considered drug-related
Most common any grade TEAEs, n (%)	(n=29)
Anemia	10 (35)
Headache	8 (28)
Night sweats	7 (24)
Most common drug-related TEAEs, n (%)	(n=29)
Headache	3 (10)
Nausea	3 (10)

1. Allan JN, et al. ASH 2019. Abstract 3041. 2. Study NCT03037645. ClinicalTrials.gov website. Accessed June 13, 2020.

ARQ 531



ARQ 531

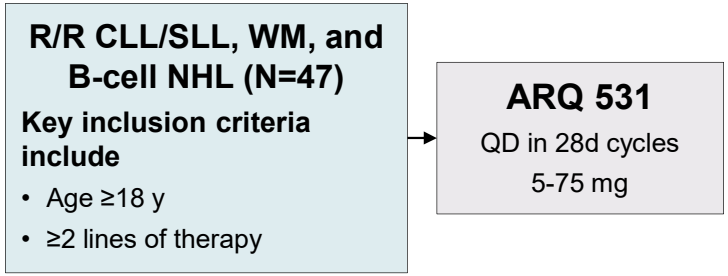


- Reversible inhibition of BTK
- Occupies the ATP binding pocket – non C481
- Orally bioavailable

Reiff et al, Cancer Discovery, in press

Phase 1/2 Study of ARQ 531 in R/R B-Cell Malignancies[1,2]

- ARQ 531 is a potent and reversible inhibitor of both WT and C481S-mutant BTKi



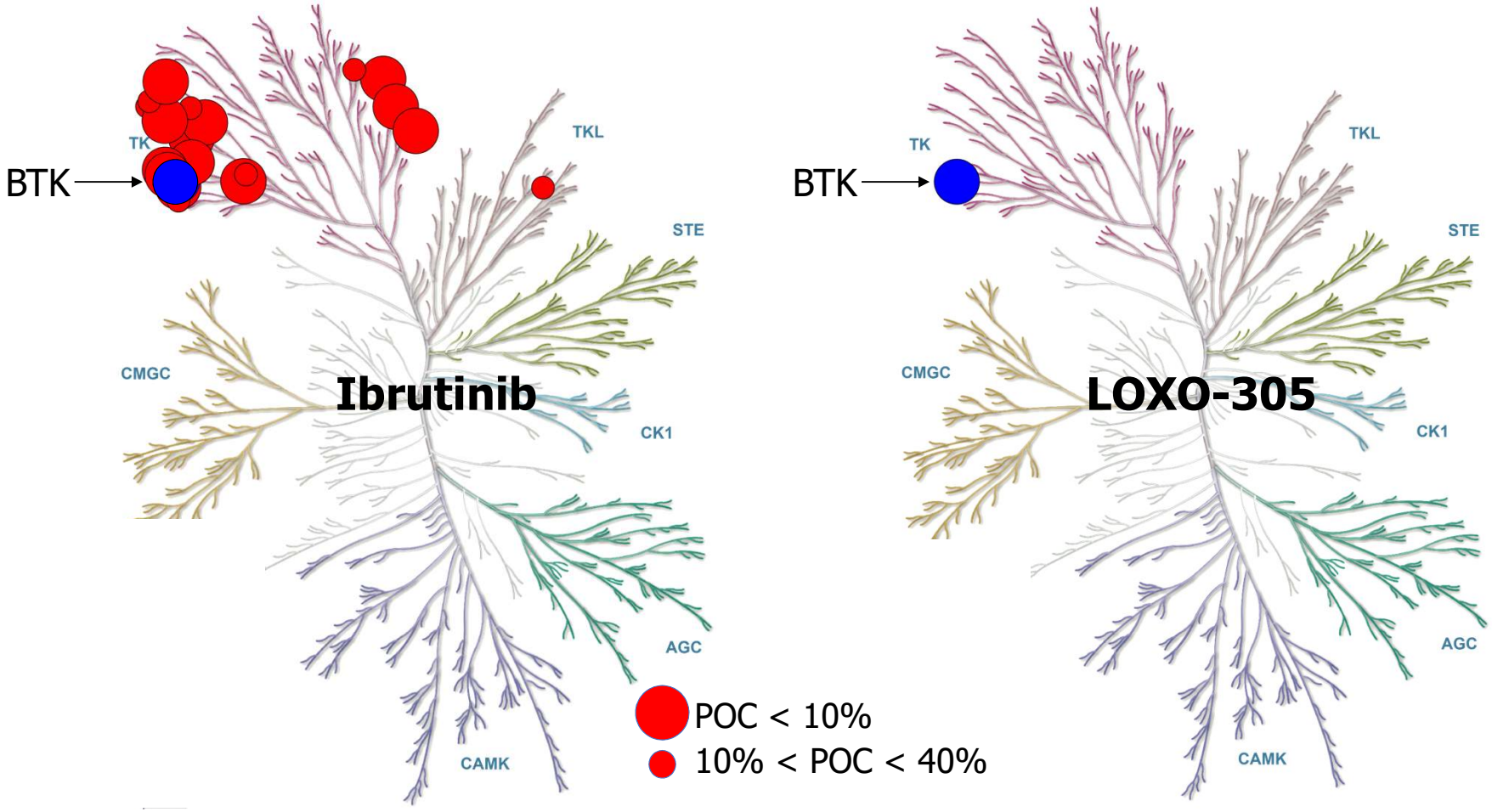
Primary Endpoints: RP2D, safety
Secondary Endpoints: pharmacokinetics, ORR, DOR

Key Findings:

- **89% ORR** (8/9) was achieved in R/R CLL pts (7/8 with C481S-mutant BTKi) dosed at ≥65 mg QD
- **100% PR** (5/5) was achieved in cycle 9
- Low incidence of associated toxicities and **no a-fib or bleeding** across all disease types
- **65 mg QD** was selected as the RP2D for further studies

1. ArQule press release. Published December 9, 2019. 2. Study NCT03162536. ClinicalTrials.gov website. Accessed April 29, 2020.

LOXO-305



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

BRUIN Phase 1 Trial of LOXO-305 in R/R B-Cell Malignancies

- LOXO-305 is a highly potent and selective non-covalent inhibitor of both WT and C481S-mutant BTKi

R/R CLL or B-cell NHL (N=28)

Key inclusion criteria include

- Age ≥18 y
- ECOG PS 0-2
- ≥2 lines of therapy, including BTKi-intolerant

→

LOXO-305

QD in 28d cycles

- 25 mg (n=5)
- 50 mg (n=6)
- 100 mg (n=9)
- 150 mg (n=5)
- 200 mg (n=3)

Key Endpoints: safety, MTD, RP2D, pharmacokinetics, ORR, DOR

Baseline Characteristic	CLL (n=16)
Median age, y (range)	68 (52-79)
Median prior tx (range)	4 (2-5)
Prior BTKi, n (%)	12 (75)
Reason for discontinuing prior BTKi, n (%)	(n=12)
Progressive disease	6 (50)
Intolerance	3 (25)
Other	3 (25)
del(17p), n/N (%)	4/12 (33)
IGHV-unmut, n/N (%)	10/14 (71)

Efficacy, n (%)	CLL		
	Best response (n=13)	Response at Cycle 3 (n=8)	Response at Cycle 5 (n=8)
ORR	10 (77)	4 (50)	7 (88)
CR	0	0	0
PR+PR-L	10 (77)	4 (50)	7 (88)

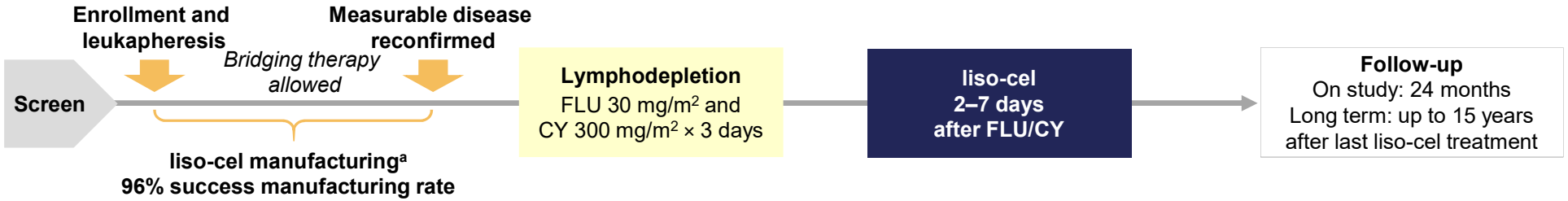
- Responses were observed in BTKi-resistant CLL regardless of C481S status

Safety, n (%)	All Doses and Patients (N=28)	
	TEAEs (≥10%)	Tx-related AEs
Fatigue	7 (25)	2 (7)
Diarrhea	5 (18)	3 (11)
Anemia	4 (14)	3 (11)
Maculopapular rash	4 (14)	4 (14)
Arthralgia	3 (11)	2 (7)
Back pain	3 (11)	0
Hyperbilirubinemia	3 (11)	1 (4)
Contusion	3 (11)	1 (4)

- No grade 3/4 AEs among most common AEs; 2 grade 3 tx-related AEs: 1 leukocytosis (dose hold), 1 neutropenia (no dose modification)
- No observations of AEs associated with covalent BTKis (a-fib, major bleeding)
- No DLTs reported and MTD not reached

Mato A, et al. ASH 2019. Abstract 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

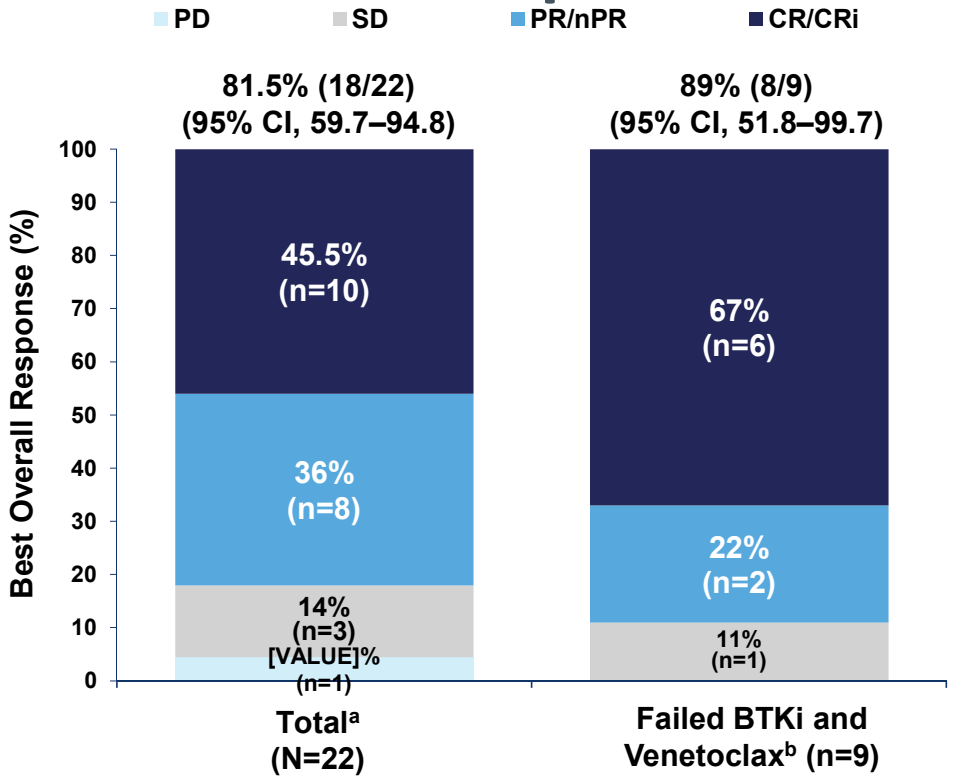
Dose Level	Dose	Evaluable (N=23)
[redacted]		

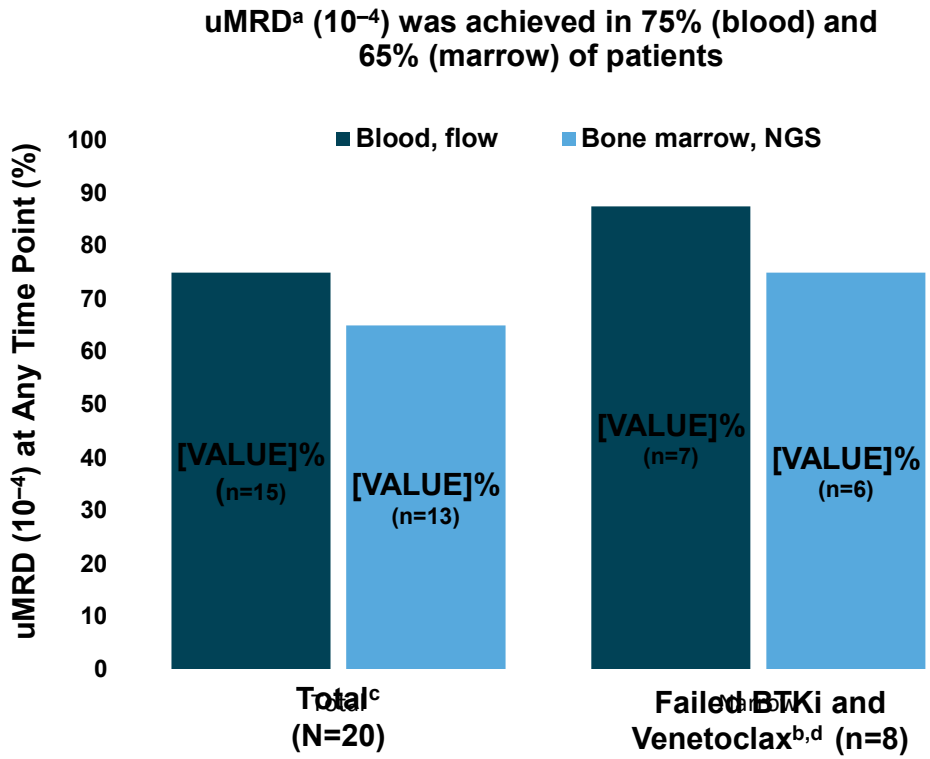
ClinicalTrials.gov identifier: NCT03331198.

[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.

So how we sequence therapies in RR CLL

- Venetoclax combinations are effective after BTKi failure.
- Is likely that second re treatment with venetoclax may be achieved.
- BTKi are also effective after venetoclax failure.
- At the end long term therapy will be more likely to be used in RR CLL

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 doublets and triplets venetoclax combination to new BTK inhibitors and CART

Thank you

javier.pinilla@moffitt.org