Learning from BTK Inhibitors & Moving Forward the Therapeutic Field in CLL

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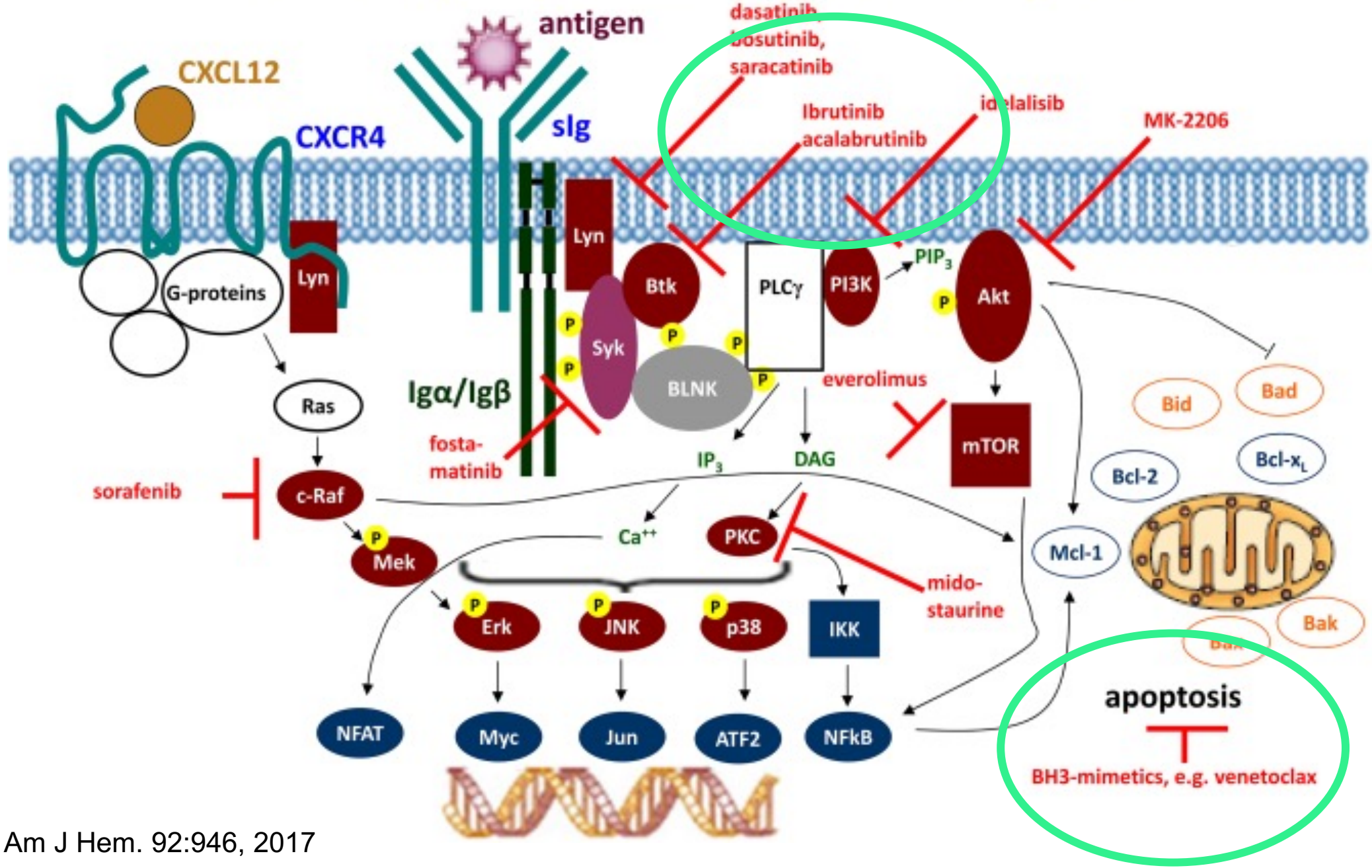
Survival signaling in CLL: targets of novel agents



Hallek, M., Am J Hem. 92:946, 2017

Generalizations about Treatments for CLL

- Treatment for indication, no early treatment - first-line & relapse CLL
- Most patients are >70 yrs, have comorbidities and more toxicities
- Del(17p)/*TP53*-M; complex = high-risk, even with continuous treatment
- Shorter PFS with finite-duration treatment for: IGHV-UM; del(17p); del(11q)
- Deeper response = longer remission with finite-duration therapy for both treatment-naïve and relapsed/refractory
- Progression while on targeted therapy is resistance
- Relapsed disease is not necessarily refractory to finite-duration targeted treatment – retreatment is option, remission duration important

Important for Selecting Treatment in CLL

- IGHV mutation status (for first line): **does not change**[1]
- del(17p) status by FISH: **can change**[2]
  - Know % of cells with deletion
- *TP53* mutation status: **can change**[2]
- *BTK* and *PLCG2* mutation status (in BTKi treated): **can change**[3]
- Age and comorbidities are considerations

1. Crombie. Am J Hematol. 2017;92:1393. 2. Chauffaille. Hematol Transfus Cell Ther. 2020;42:261. 3. Hallek. Am J Hematol. 2019;94:1266.

First-line Phase III Randomized Trials

- **CLL14** (CIRS >6; CrCl <70 mL/min)
  - **Venetoclax + Obinutuzumab** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **RESONATE-2**
  - **Ibrutinib** *vs.*
  - **Chlorambucil**
- **iLLUMINATE** (PCYC-1130) (>65yo or ≤65yo with comorbidities)
  - **Ibrutinib + Obinutuzumab** *vs.*
  - **Chlorambucil + Obinutuzumab**
- **Alliance** (A041202) (>65yo)
  - **Ibrutinib** *vs.*
  - **Ibrutinib + Rituximab** *vs.*
  - **BR**
- **ECOG E1912** [<70yo; non-del(17p)]
  - **Ibrutinib + Rituximab** *vs.*
  - **FCR**
- **ELEVATE-TN** (>65yo or younger with CIRS score >6, or CrCl <70 mL/min)
  - **Acalabrutinib** *vs.*
  - **Acalabrutinib + Obinutuzumab**
  - **Chlorambucil + Obinutuzumab**
- **SEQUOIA** [≥65 yo OR unsuitable for FCR; non-del(17p)]
  - **Zanubrutinib** *vs.*
  - **BR**

BTKi- *vs.* BCL-2i-based Treatment

BTK Inhibitor[1-4]

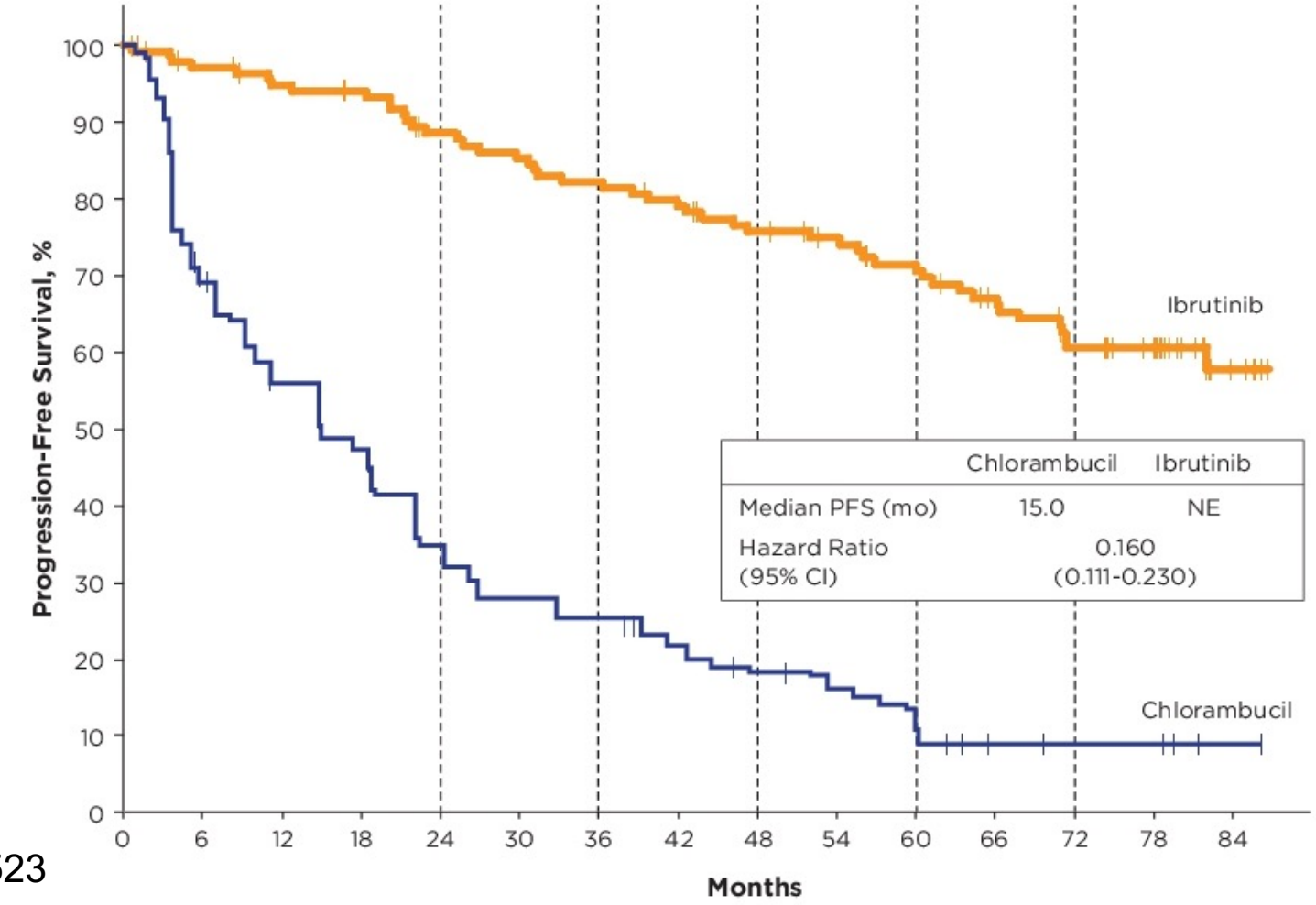
- Easier initiation
- Continuous and indefinite therapy
- Very low TLS risk
- More cardiac risk
- Some favor in del(17p)/ mutated-*TP53*

BCL-2 Inhibitor[4,5]

- Risk for TLS requires monitoring for initiation
- Includes CD20 mAb – immunosuppression
- Fixed duration
- GFR sensitivity
- Question if best for del(17p)/ mutated-*TP53*

1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

RESONATE-2: First-line, Age >65yrs
Ibrutinib Prolonged PFS Over Chlorambucil



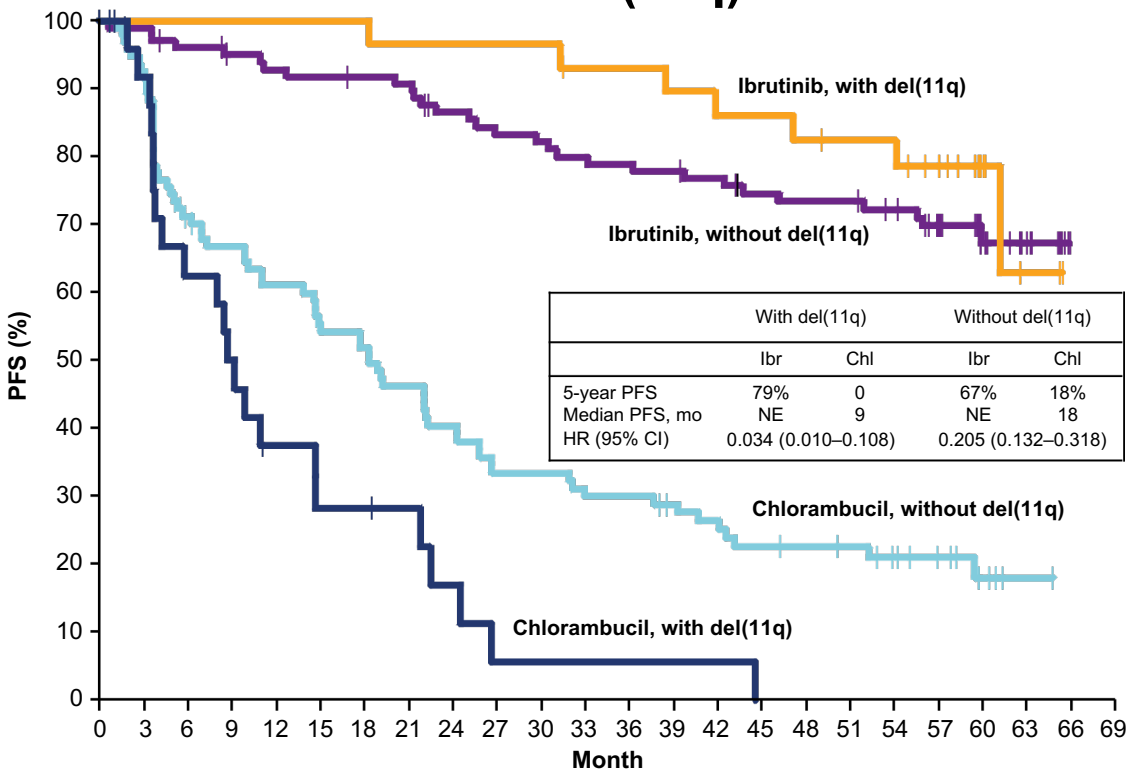
Barr et al. ASCO 2021, Poster 7523

Patients at Risk and PFS

Ibrutinib:	136	129	124	121	112	108	104	99	92	88	81	74	64	56	12
PFS, %:					89		82		76		71		61		
Chlorambucil:	133	88	69	57	41	33	30	25	19	16	12	6	5	5	1
PFS, %:					35		25		18		12		9		

Ibrutinib Overcomes Poor Prognosis of Del(11q) and Unmutated IGHV in RESONATE-2

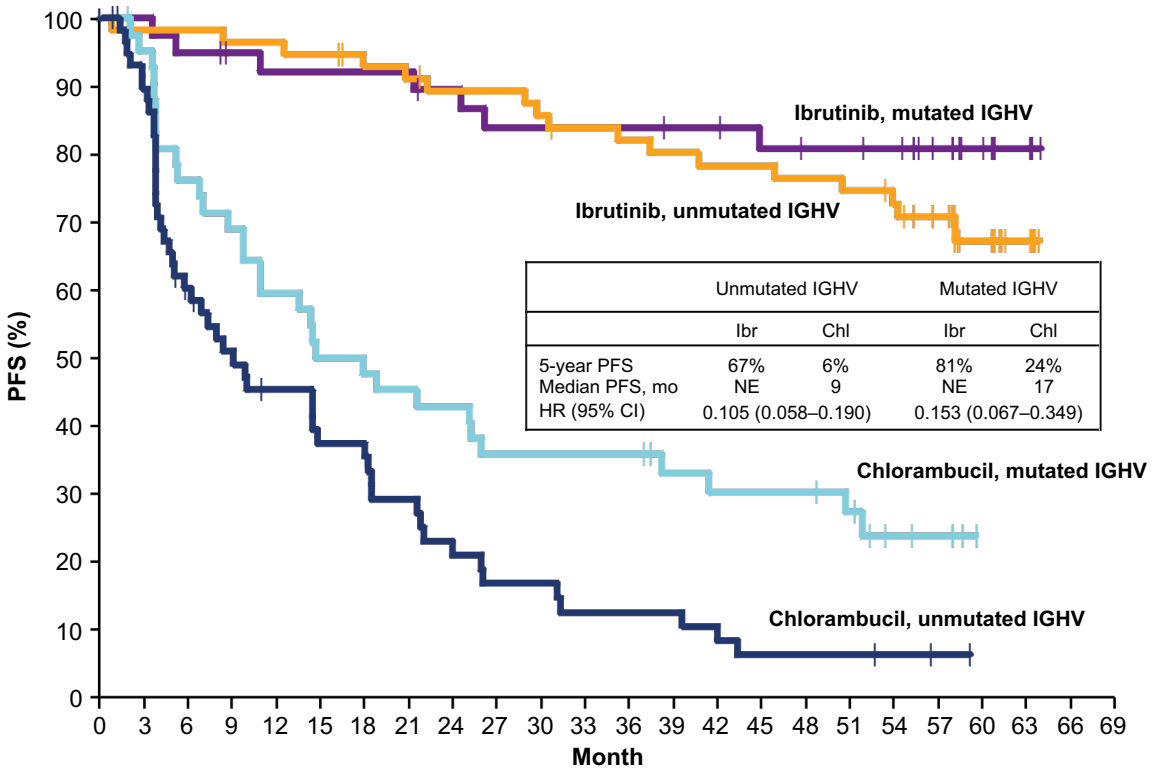
Del(11q)



	With del(11q)		Without del(11q)	
	Ibr	Chl	Ibr	Chl
5-year PFS	79%	0	67%	18%
Median PFS, mo	NE	9	NE	18
HR (95% CI)	0.034 (0.010–0.108)		0.205 (0.132–0.318)	

	Ibrutinib	
	With del(11q)	Without del(11q)
5-year PFS	79%	67%
Median PFS, mo	NE	NE
HR (95% CI)	0.719 (0.315–1.642)	

IGHV

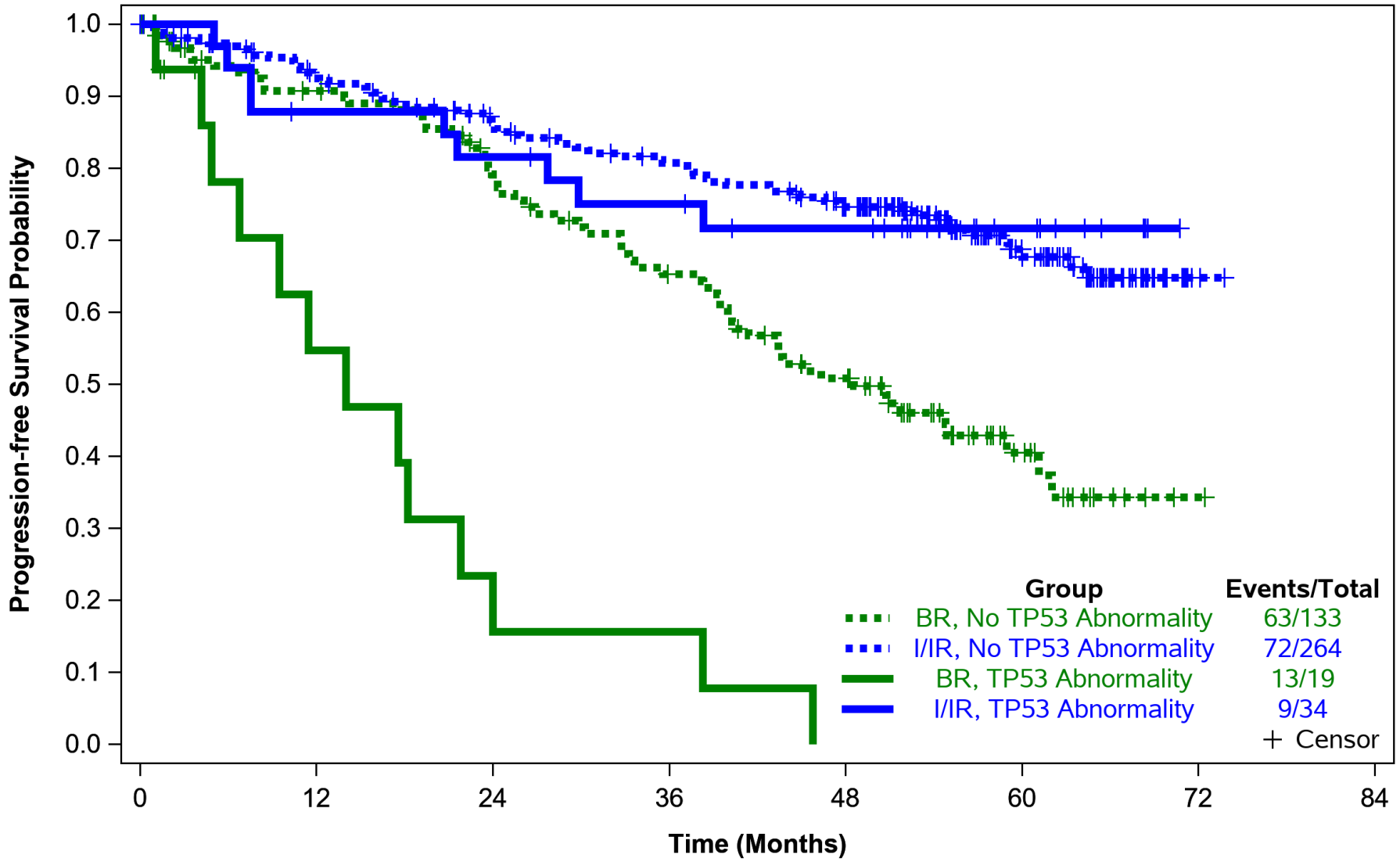


	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
5-year PFS	67%	6%	81%	24%
Median PFS, mo	NE	9	NE	17
HR (95% CI)	0.105 (0.058–0.190)		0.153 (0.067–0.349)	

	Ibrutinib	
	Unmutated IGHV	Mutated IGHV
5-year PFS	67%	81%
Median PFS, mo	NE	NE
HR (95% CI)	0.632 (0.262–1.525)	

Tedeschi A, et al. Presented at: European Hematology Association (EHA) Congress; June 14, 2019; Amsterdam, NL. Abstract S107.

Interaction: Treatment Group and TP53 Abnormalities



Treatment Effect
I/IR vs BR

No TP53 Abn
Hazard Ratio 0.39
95% CI: 0.27-0.55

TP53 Abn
Hazard Ratio 0.07
95% CI: 0.03-0.18

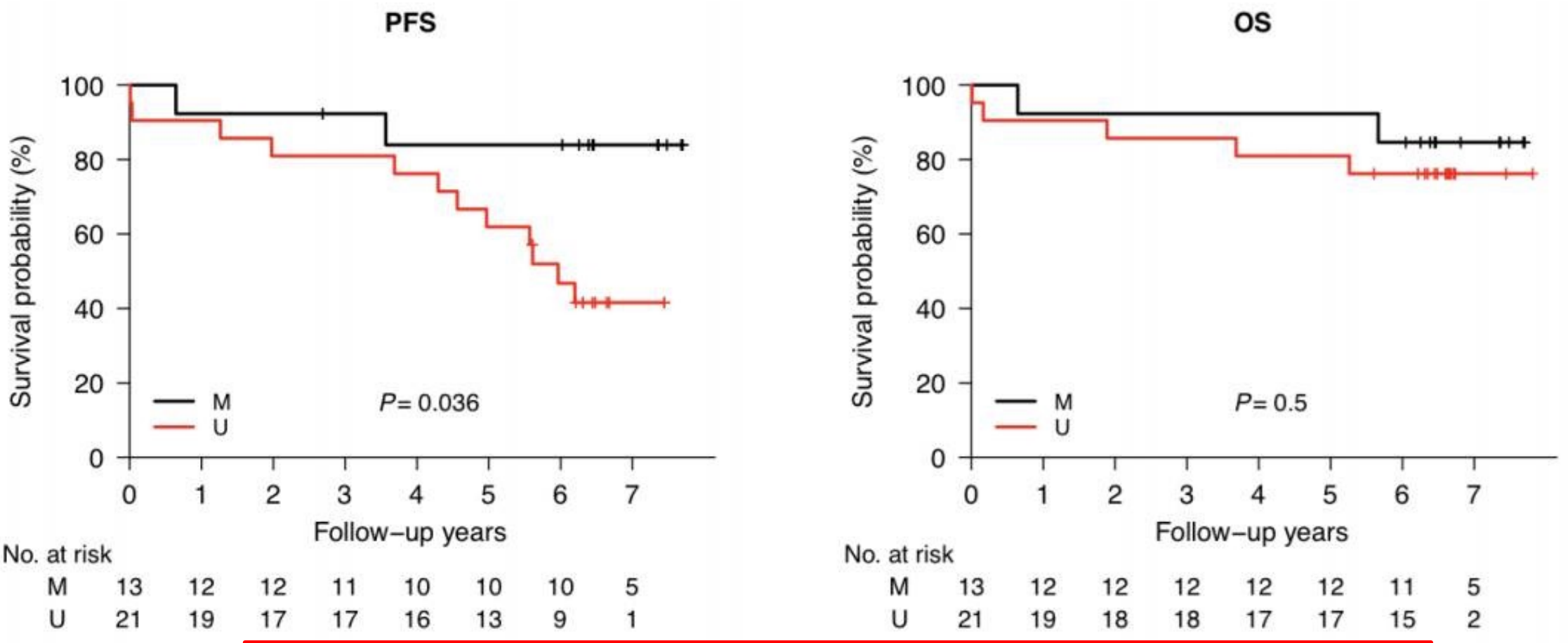
Interaction P = 0.0006

Woyach, et al. ASH 2021, Abstract #639

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Long-Term Follow-Up for Untreated Patients with CLL and *TP53* Abnormalities by IGHV Mutation Status

Survival by IGHV region gene mutation status

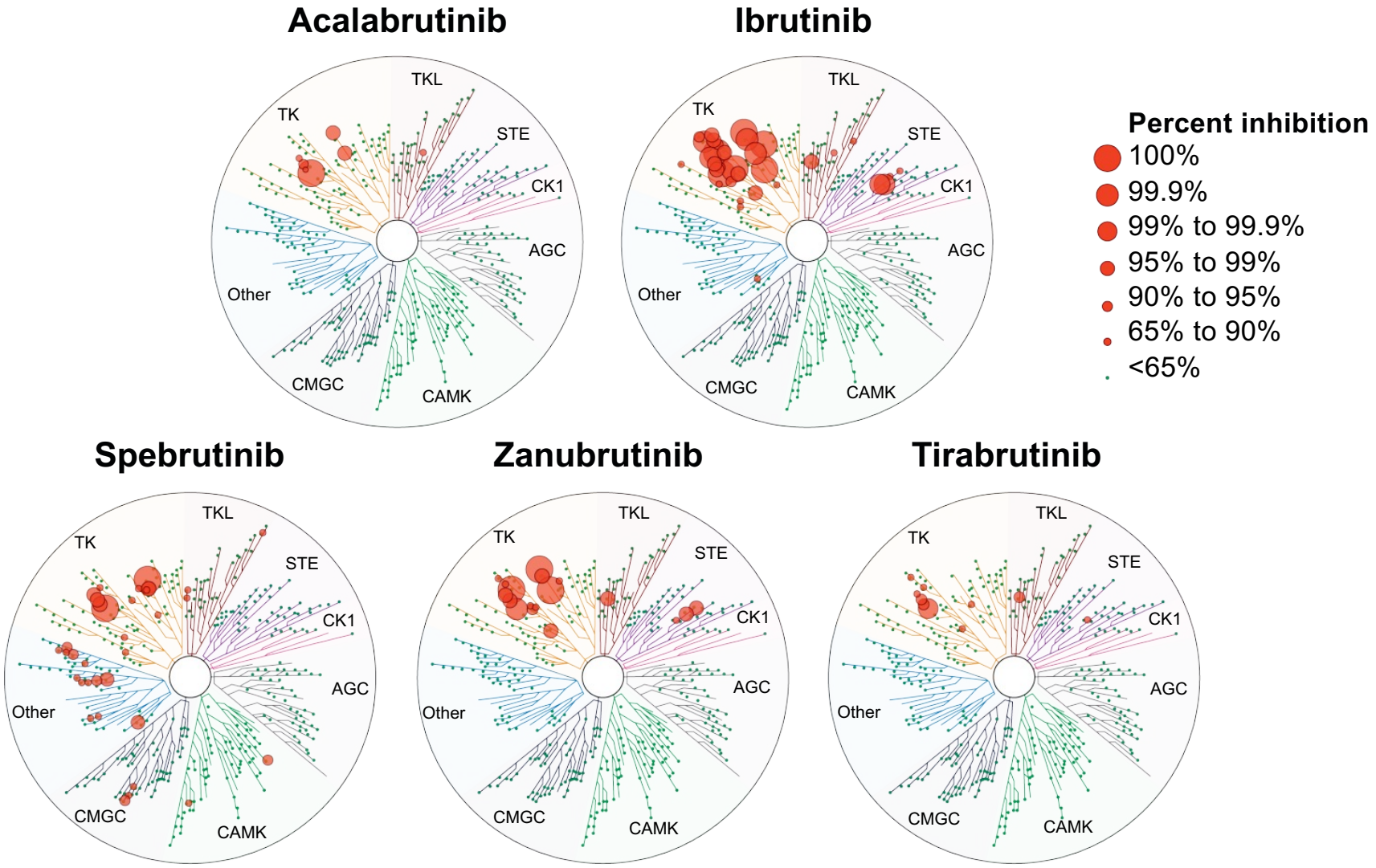


61% 6y PFS in untreated TP53 abnormal cohort

OS = overall survival.

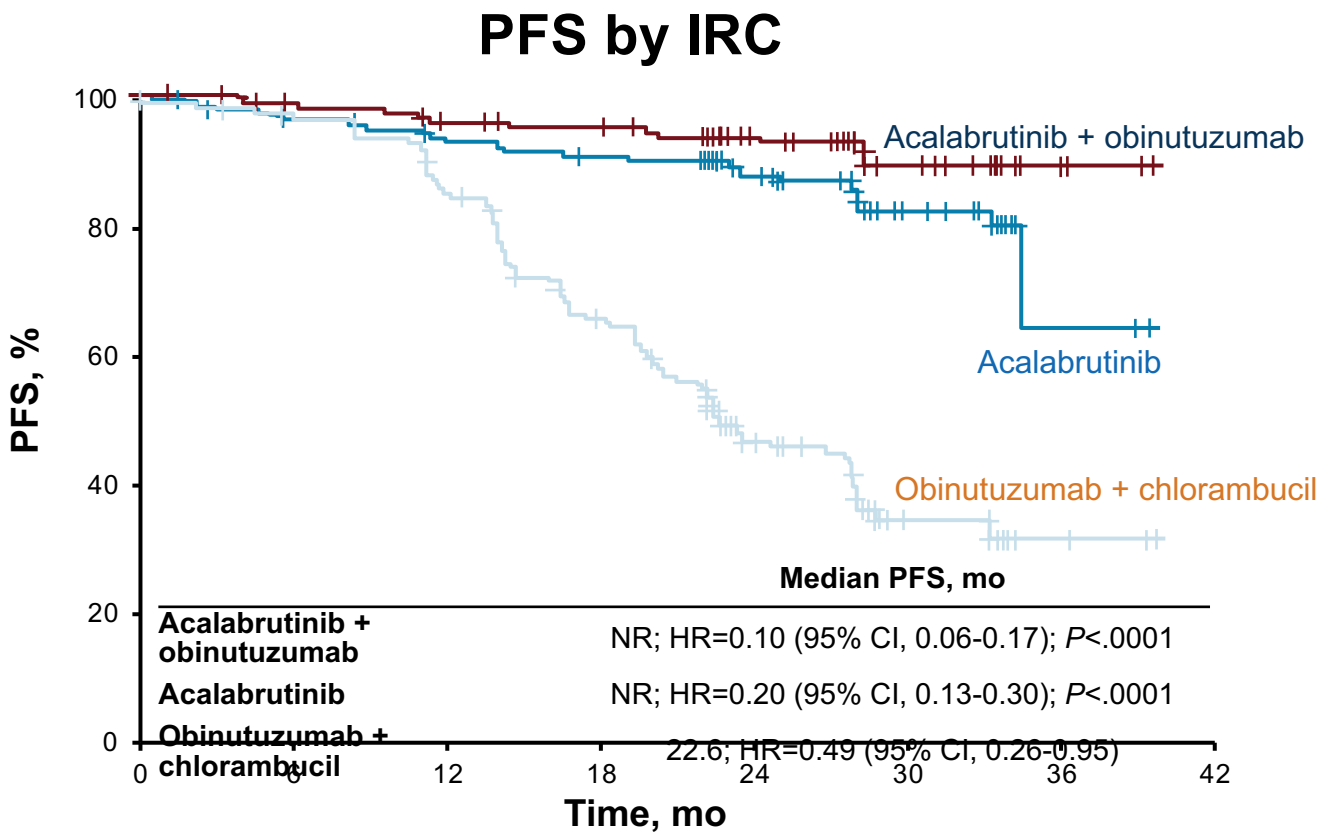
Ahn IE, et al. *N Engl J Med*. 2020;383(5):498-500.

Differences in Overall Kinase Selectivity Among BTKi[1]



1. Kaptein A et al. 60th American Society of Hematology Annual Meeting & Exposition (ASH 2018). Abstract 1871.

ELEVATE-TN: PFS (Primary Endpoint)



Estimated PFS at 24 months

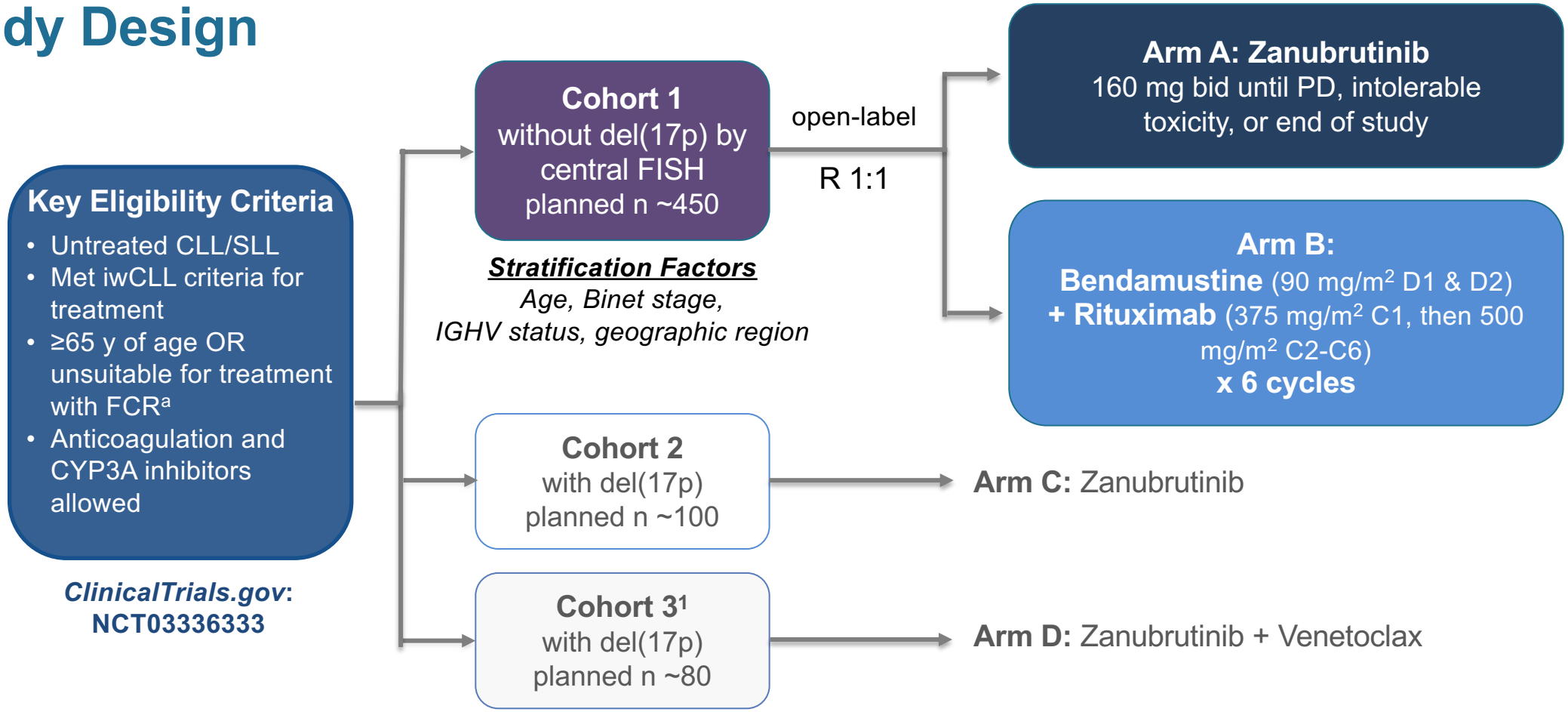
- 93% with acalabrutinib + obinutuzumab (95% CI, 87%-96%)
- 87% with acalabrutinib monotherapy (95% CI, 81%-92%)
- 47% with obinutuzumab + chlorambucil (95% CI, 39%-55%)

Post-hoc analysis: HR for PFS between acalabrutinib-obinutuzumab and acalabrutinib monotherapy was 0.49 (95% CI, 0.26-0.95)

IRC = independent review committee.

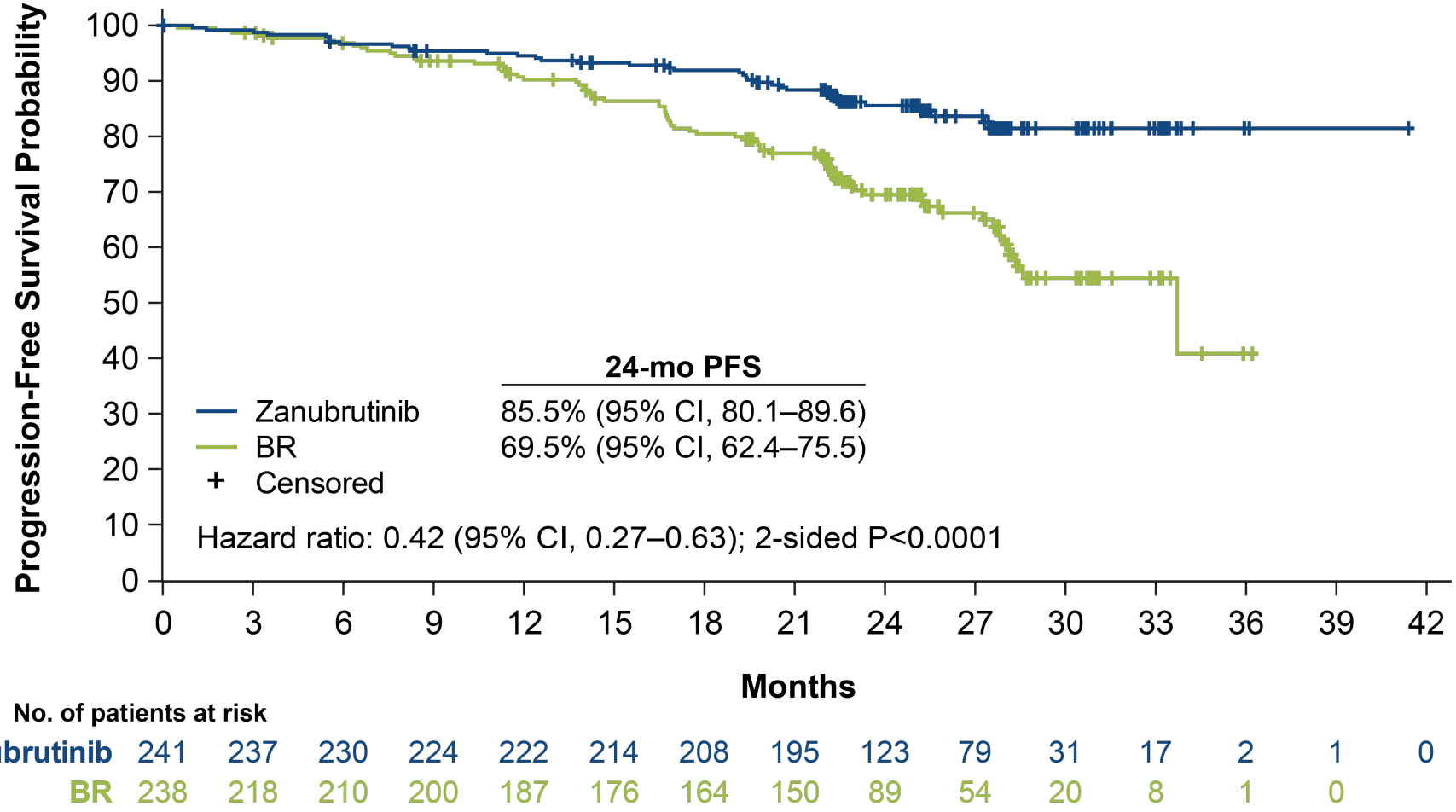
Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291.

SEQUOIA (BGB-3111-304)
Study Design



[a]Defined as Cumulative Illness Rating Scale >6, creatinine clearance <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years.
C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CYP3A, cytochrome P450, family 3, subfamily A; D, day; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in-situ hybridization; IRC, independent review committee; IGHV, gene encoding the immunoglobulin heavy chain variable region; iwCLL, International Workshop on CLL; ORR, overall response rate; PD, progressive disease; R, randomized.
1. Tedeschi A, et al. ASH 2021. Abstract 67.

SEQUOIA (BGB-3111-304)
Progression-Free Survival Per IRC Assessment



BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

ELEVATE-RR:
Phase 3 Randomized Non-inferiority Open-Label Trial

Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1–3 vs ≥4)

RANDOMIZE 1:1

Acalabrutinib[b]
100 mg PO BID

Ibrutinib[b]
420 mg PO QD

Primary endpoint

- Non-inferiority on IRC-assessed PFS[c]

Secondary endpoints (hierarchical order):

- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

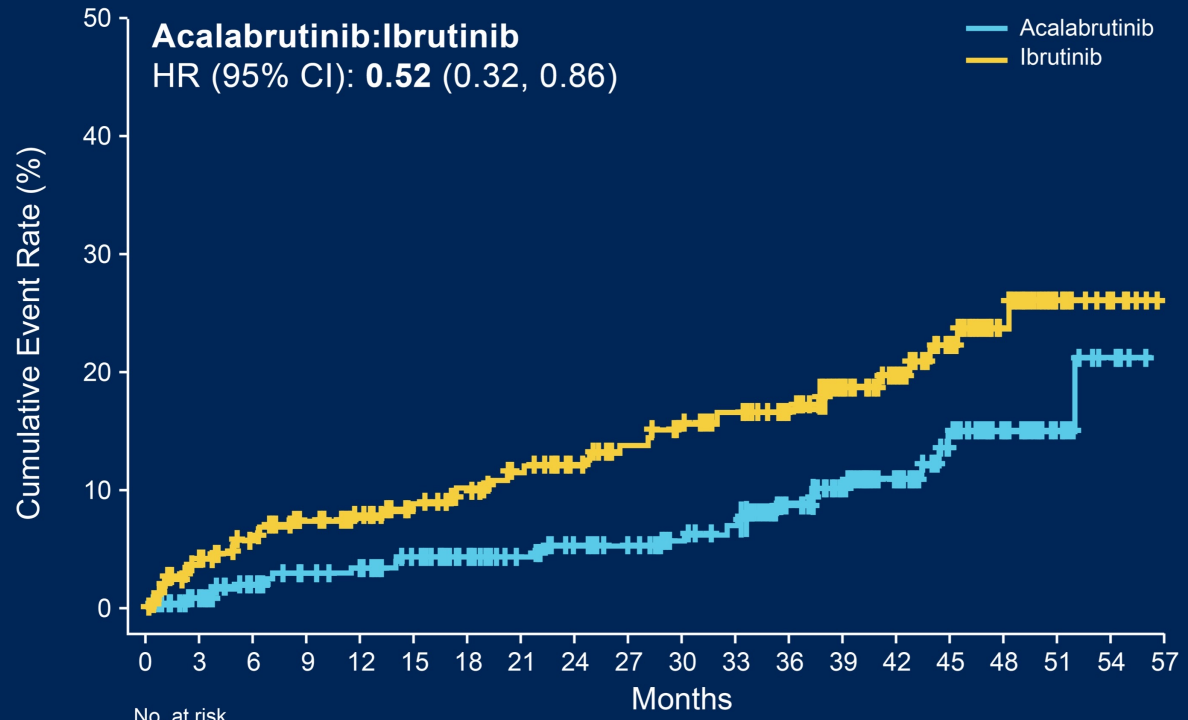
Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor (eg, BTK , PI3K, or Syk inhibitors), or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006).
[a]By central laboratory testing; [b]continued until disease progression or unacceptable toxicity; [c]conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.
Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily.

1. Hallek M, et al. *Blood*. 2008;111:5446-56.

Lower Cumulative Incidences of Any Grade Atrial Fibrillation/Flutter and Hypertension With Acalabrutinib

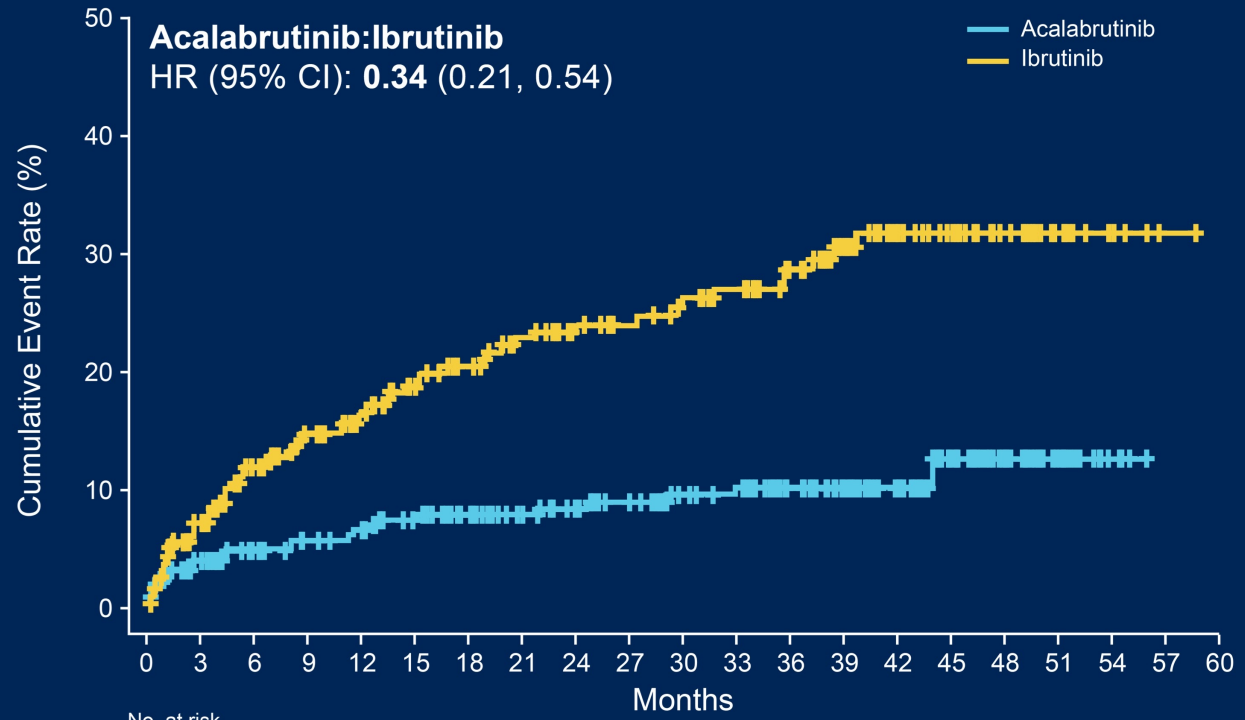
Afib/Flutter



No. at risk

Acalabrutinib	266	255	240	231	228	218	206	197	188	183	172	167	142	115	89	58	35	19	8	0
Ibrutinib	263	241	224	208	199	185	176	166	156	143	136	128	117	96	73	56	36	18	8	0

Hypertension



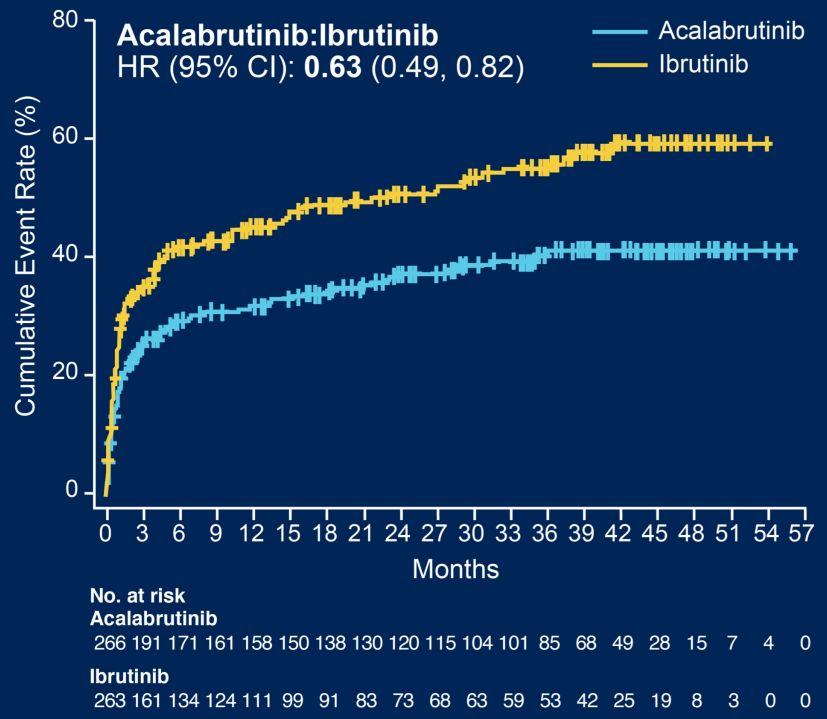
No. at risk

Acalabrutinib	266	246	229	220	216	205	193	184	176	169	157	153	136	114	89	60	34	17	5	0	0
Ibrutinib	263	230	203	183	170	153	141	130	120	111	104	98	85	69	48	40	27	15	7	1	0

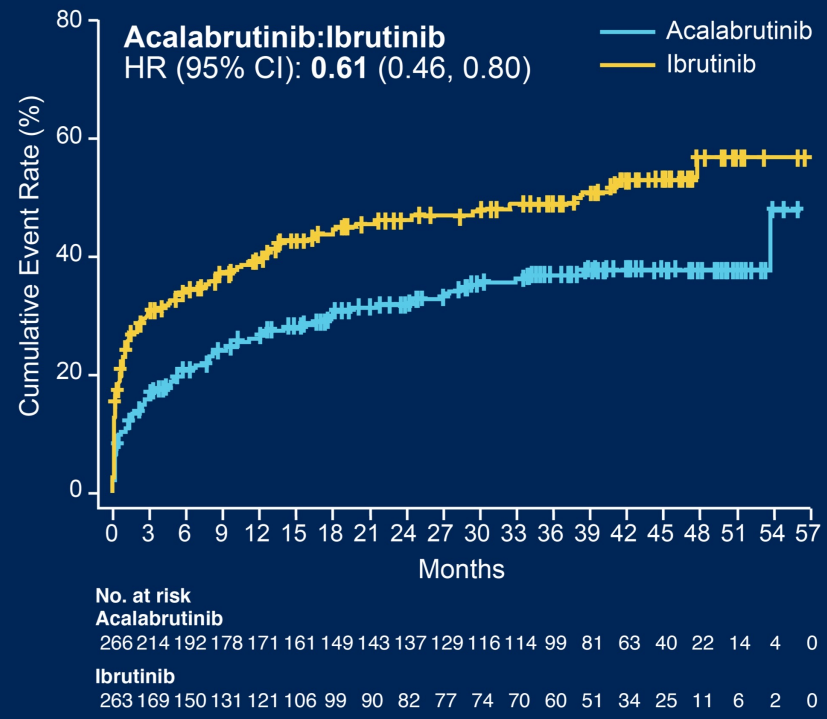
CI, confidence interval; HR, hazard ratio.

Lower Cumulative Incidences of Any-Grade Bleeding, Diarrhea, and Arthralgia Events With Acalabrutinib

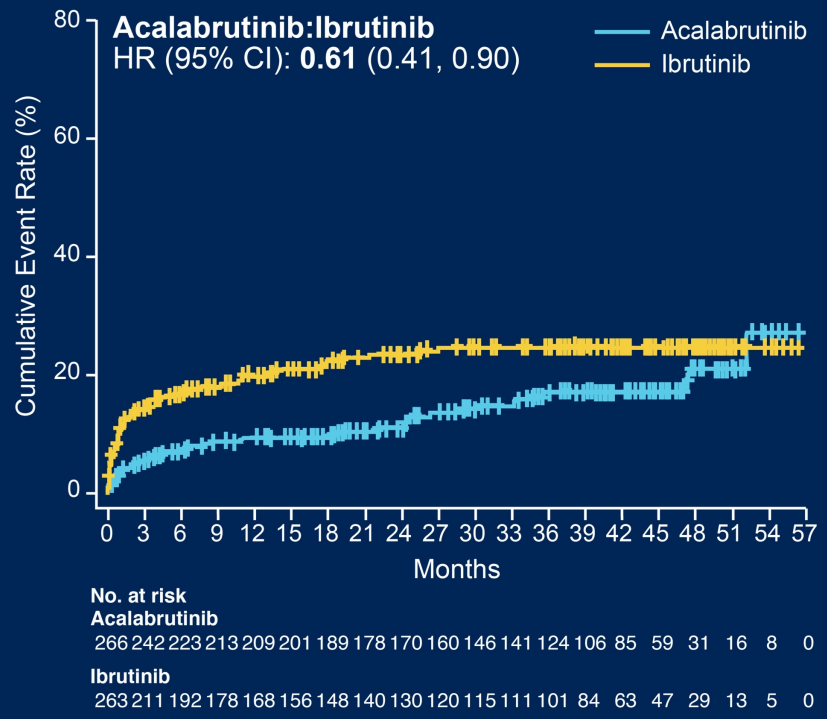
Bleeding Events



Diarrhea

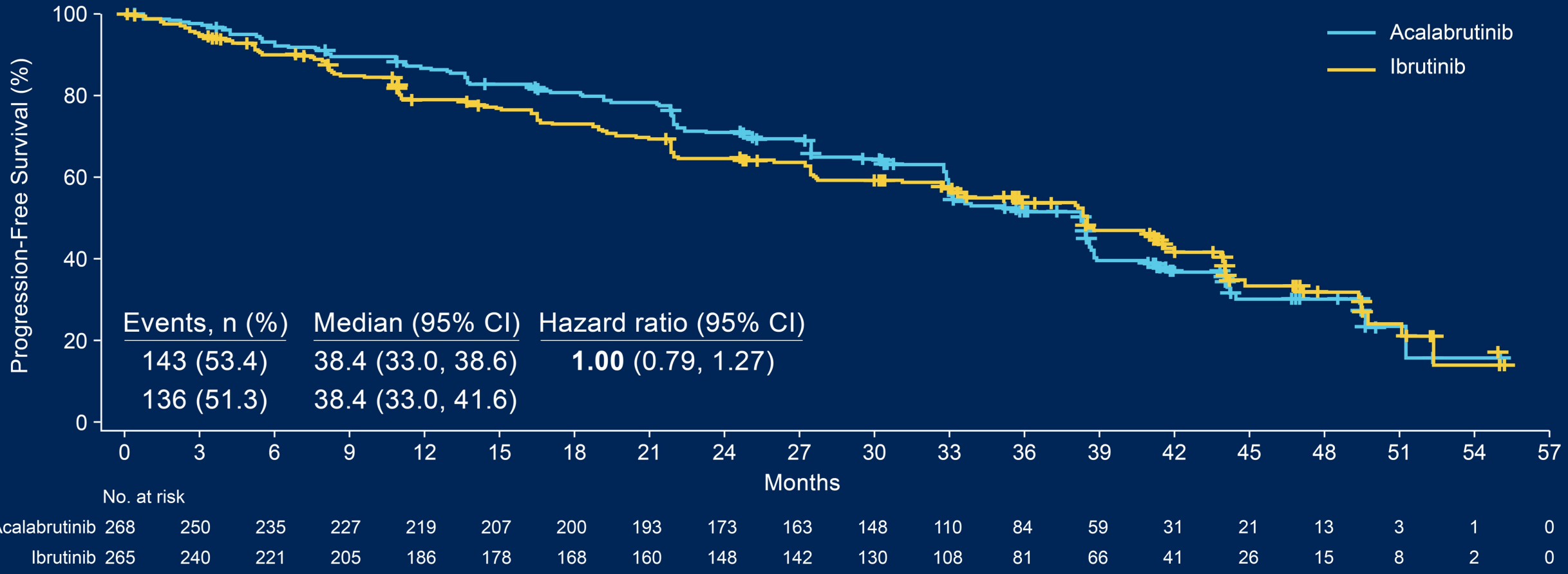


Arthralgia



CI, confidence interval; HR, hazard ratio.

Primary Endpoint: Non-inferiority Met on IRC-Assessed PFS



Median follow-up: 40.9 months (range, 0.0–59.1).

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

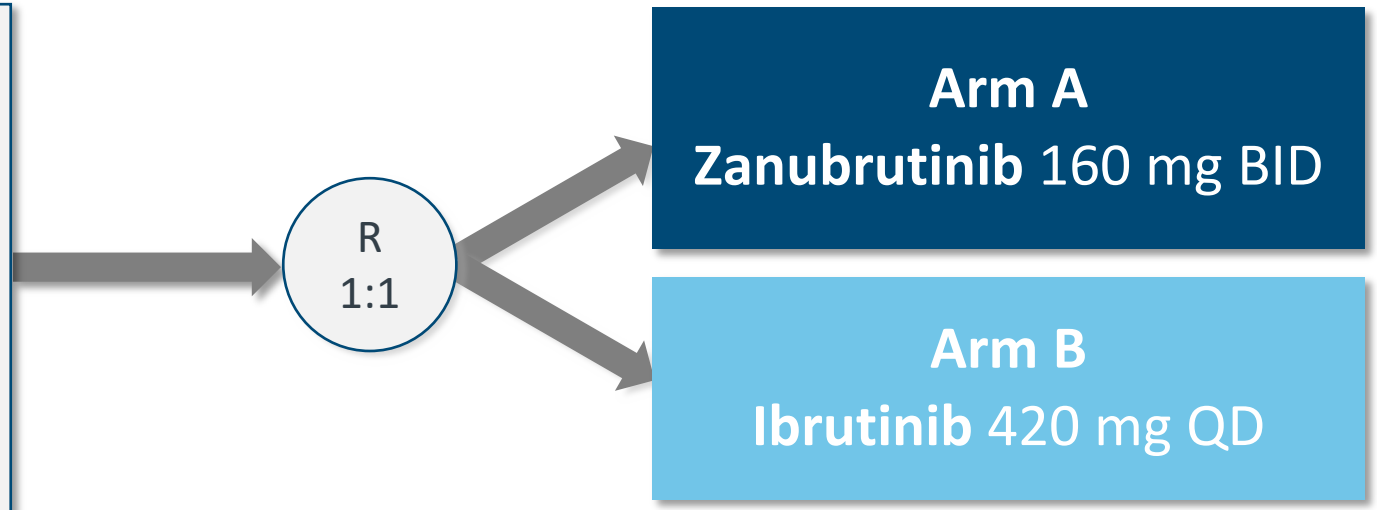
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



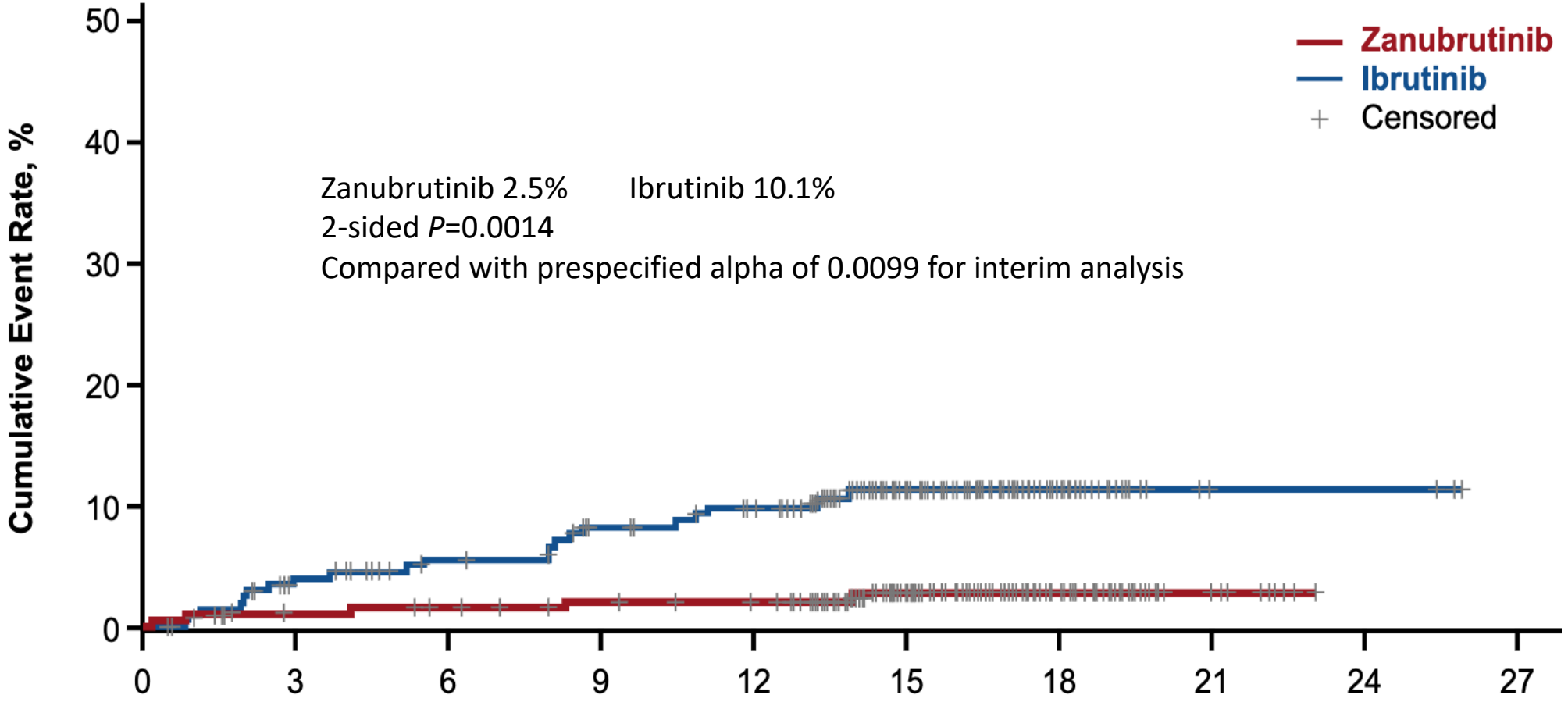
Stratification Factors

- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

BID, twice daily; BTK, Bruton tyrosine kinase' CLL, chronic lymphocytic leukemia; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Hillmen et al., EHA 2021

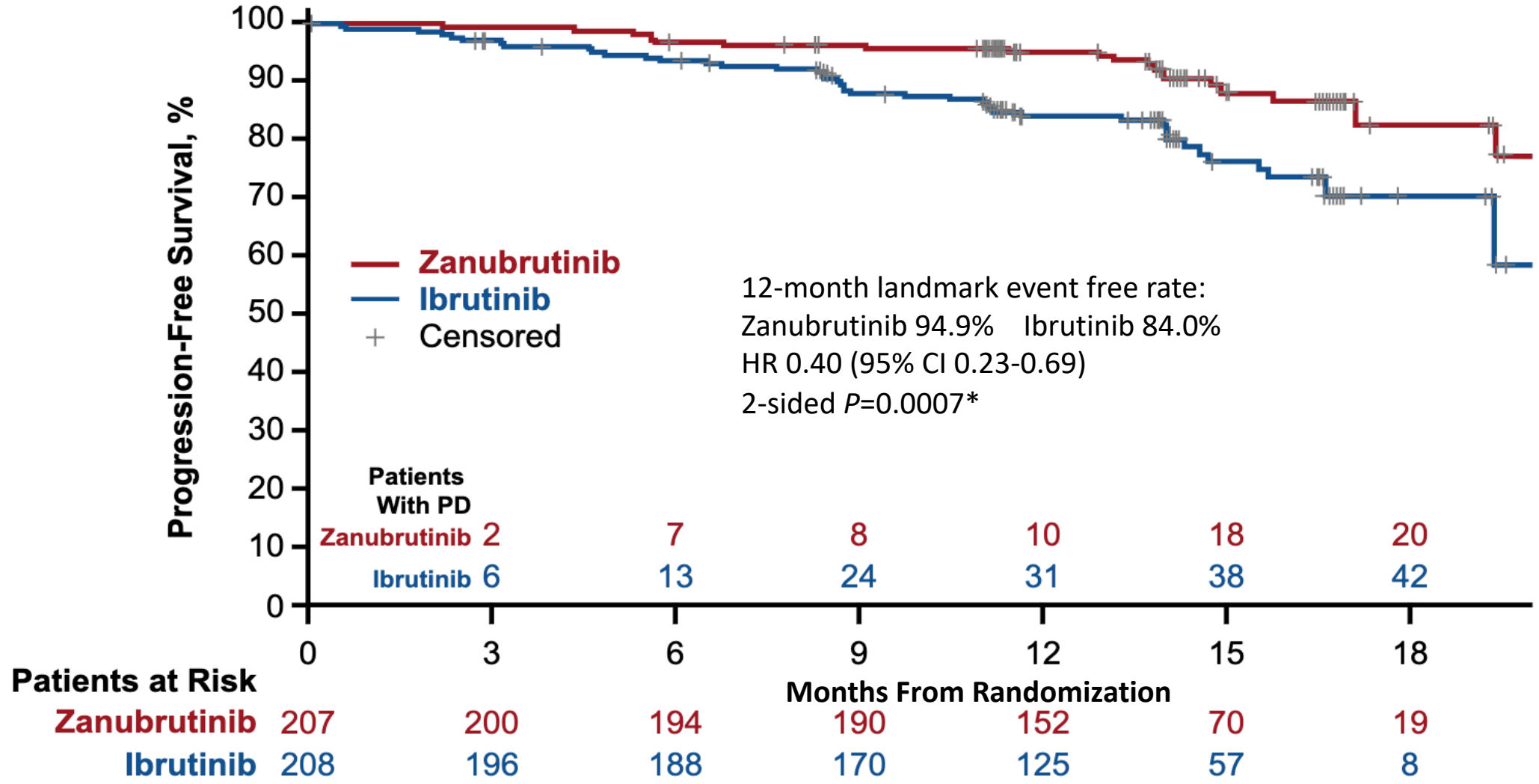
Atrial Fibrillation/Flutter



Patients at Risk										
Zanubrutinib	204	197	194	190	187	114	40	9	0	0
Ibrutinib	207	190	179	168	160	91	26	3	3	0

Hillmen et al., EHA 2021

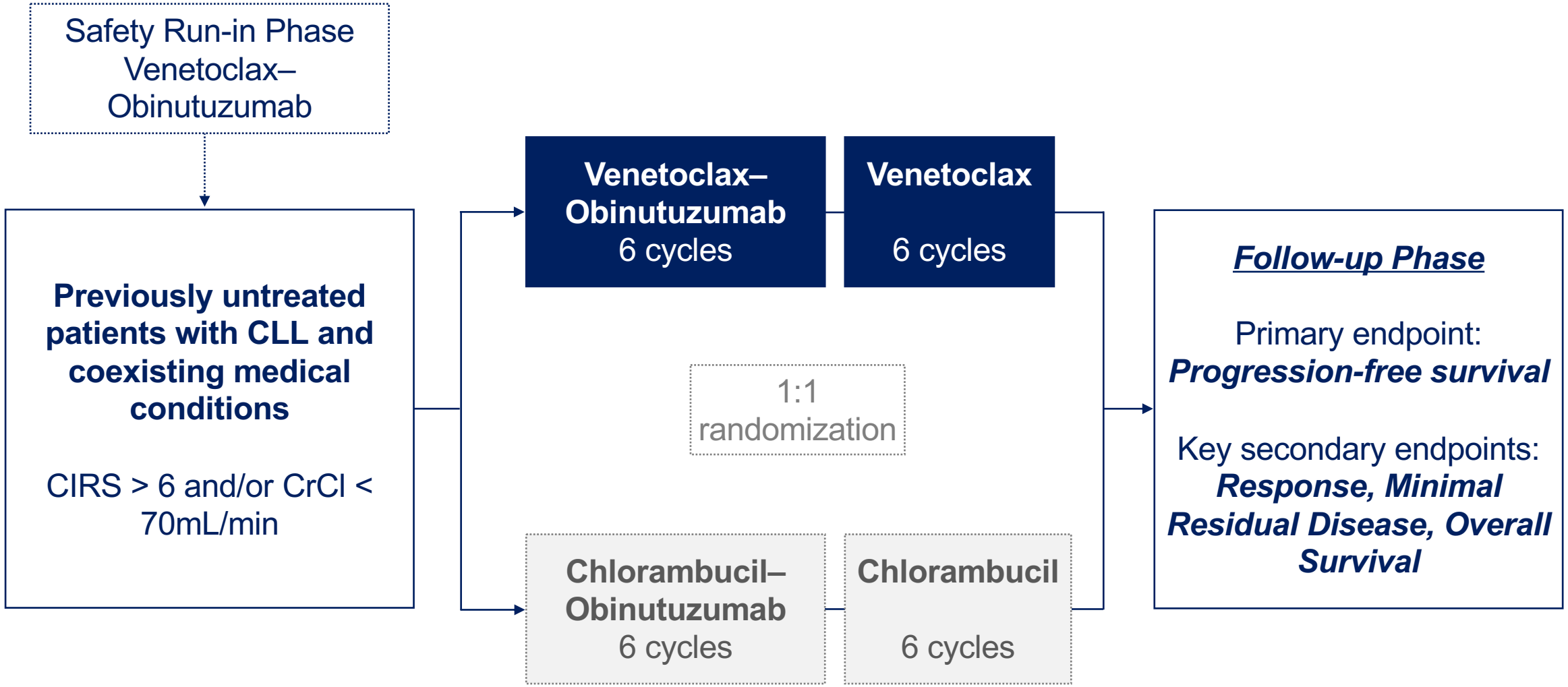
PFS by Investigator Assessment



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.
PFS, progression-free survival.

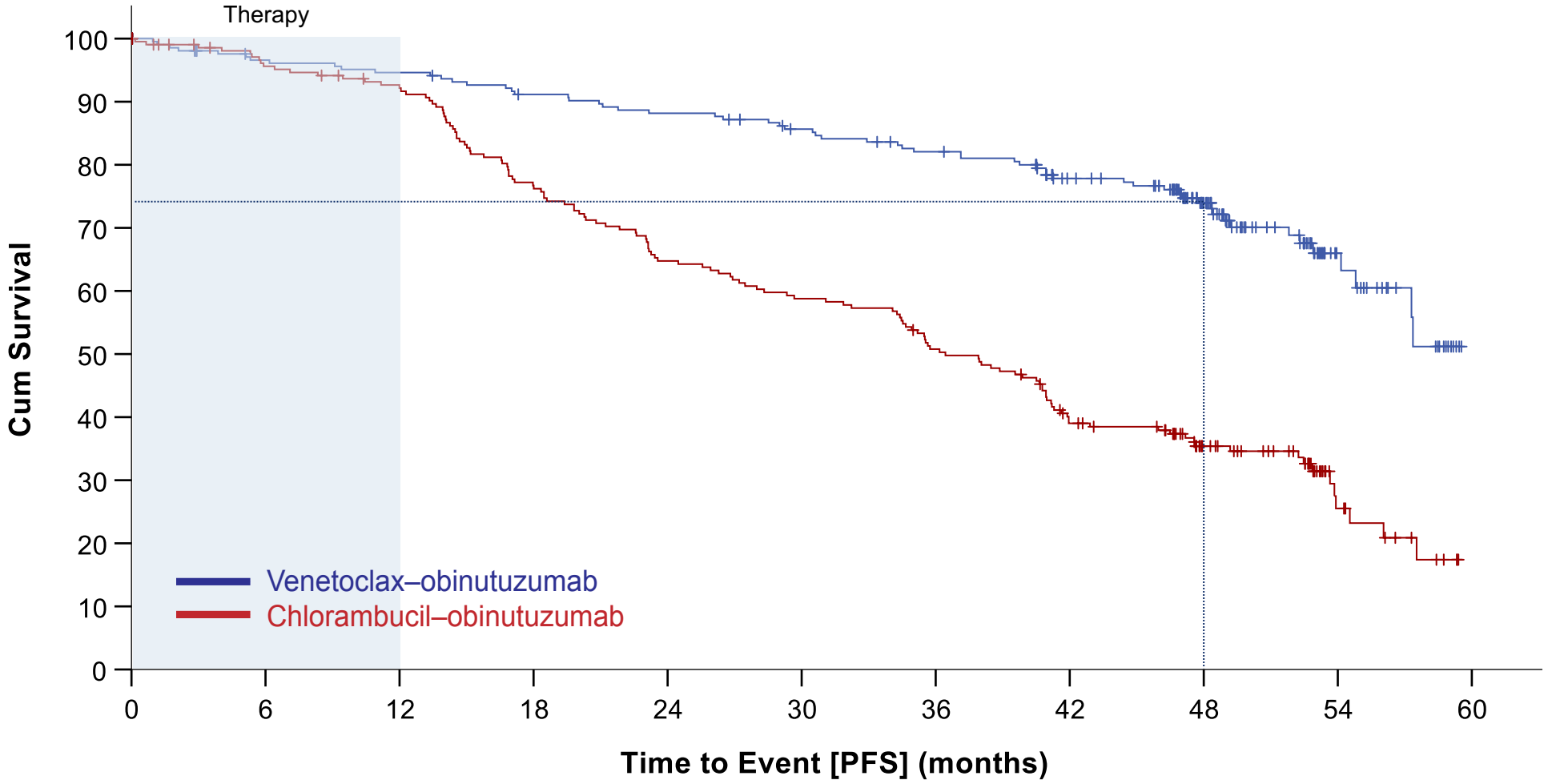
Hillmen et al., EHA 2021

CLL14: Trial Design



Progression-free Survival

Median observation time 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

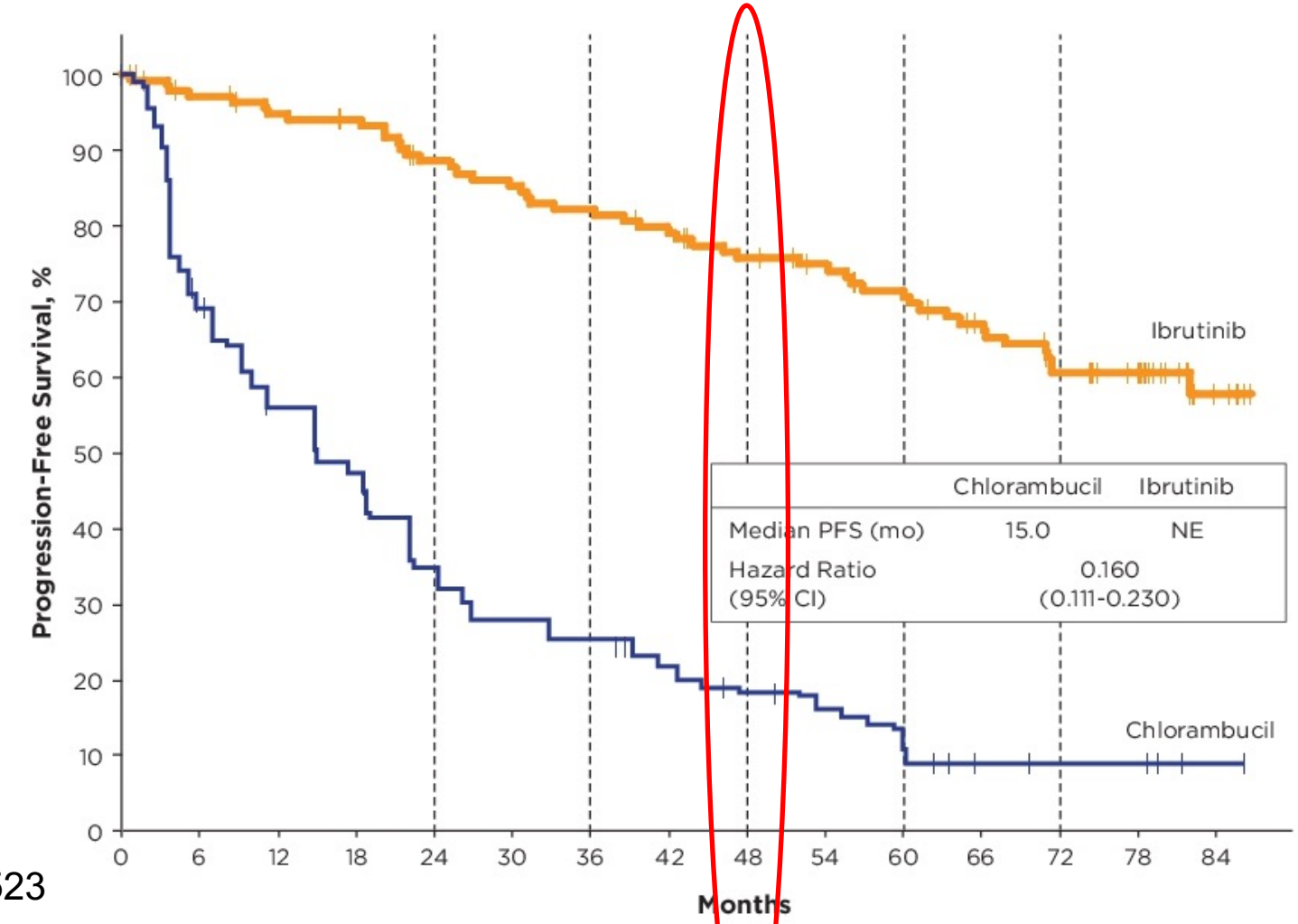
Ven-Obi: 74.0%

Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]
P<0.0001

Al-Sawaf et al. EHA 2021, Abstract S146

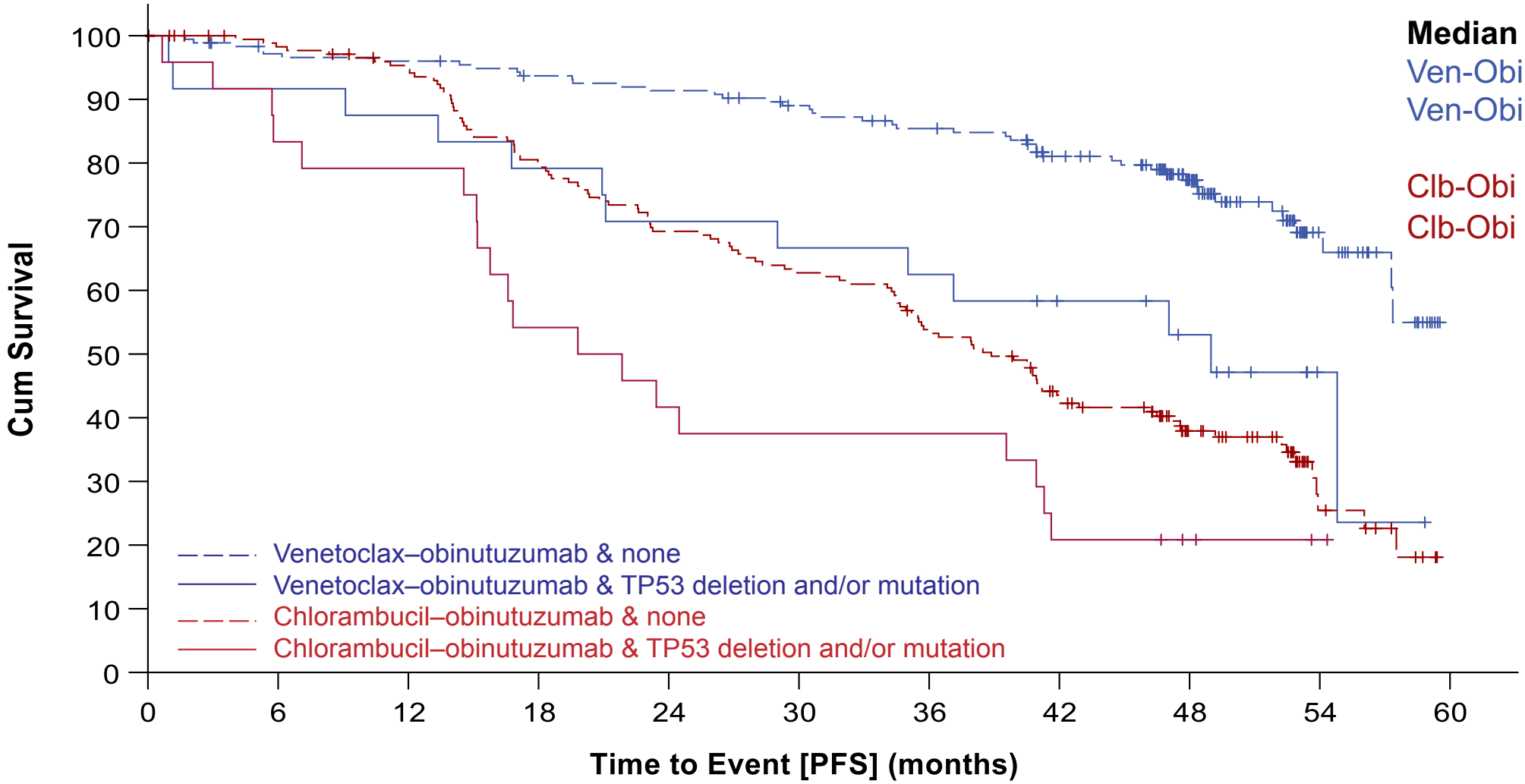
RESONATE-2: First-line, Age >65yrs
Ibrutinib Prolonged PFS Over Chlorambucil



Barr et al. ASCO 2021, Poster 7523

Progression-free Survival – *TP53* Status

Median observation time 52.4 months



Median PFS

Ven-Obi & no *TP53*del/mut: NR

Ven-Obi & *TP53*del/mut: 49.0 m

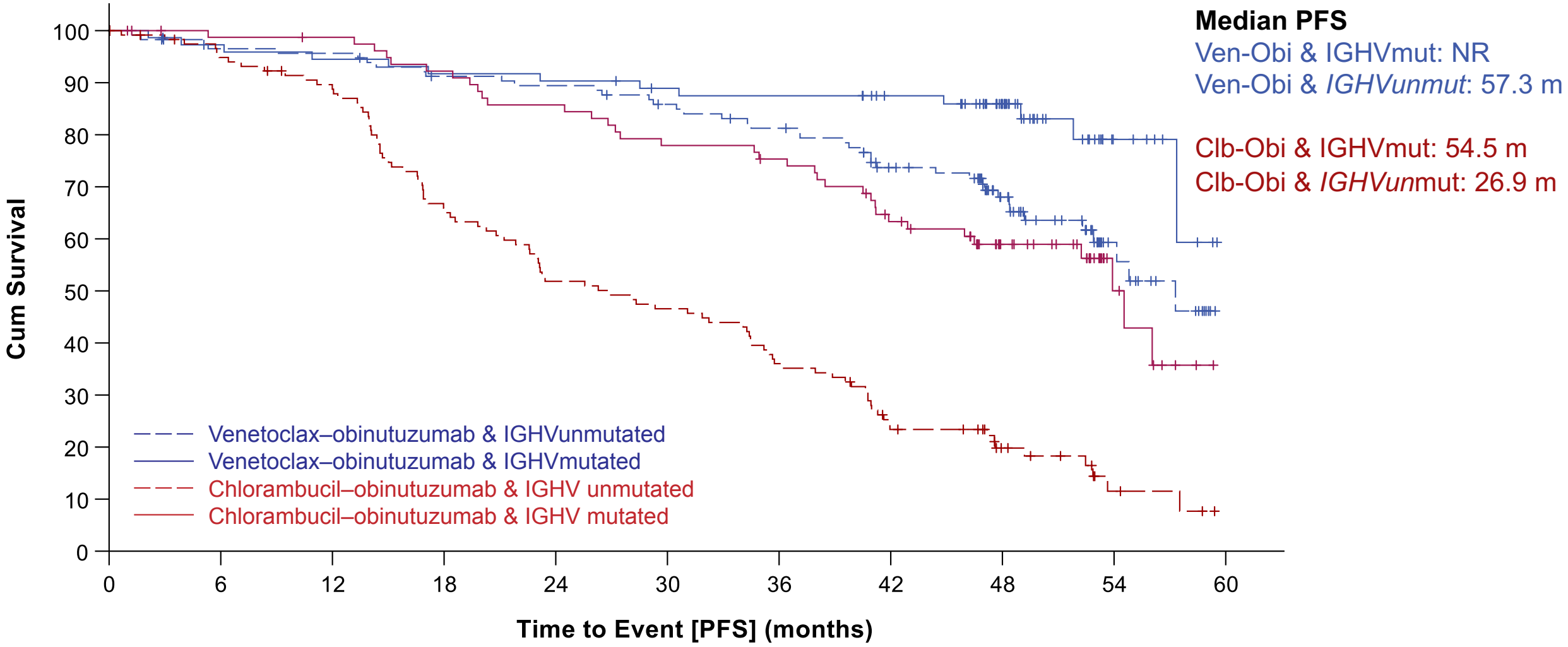
Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 20.8 m

Al-Sawaf et al. EHA 2021, Abstract S146

Progression-free Survival – IGHV Status

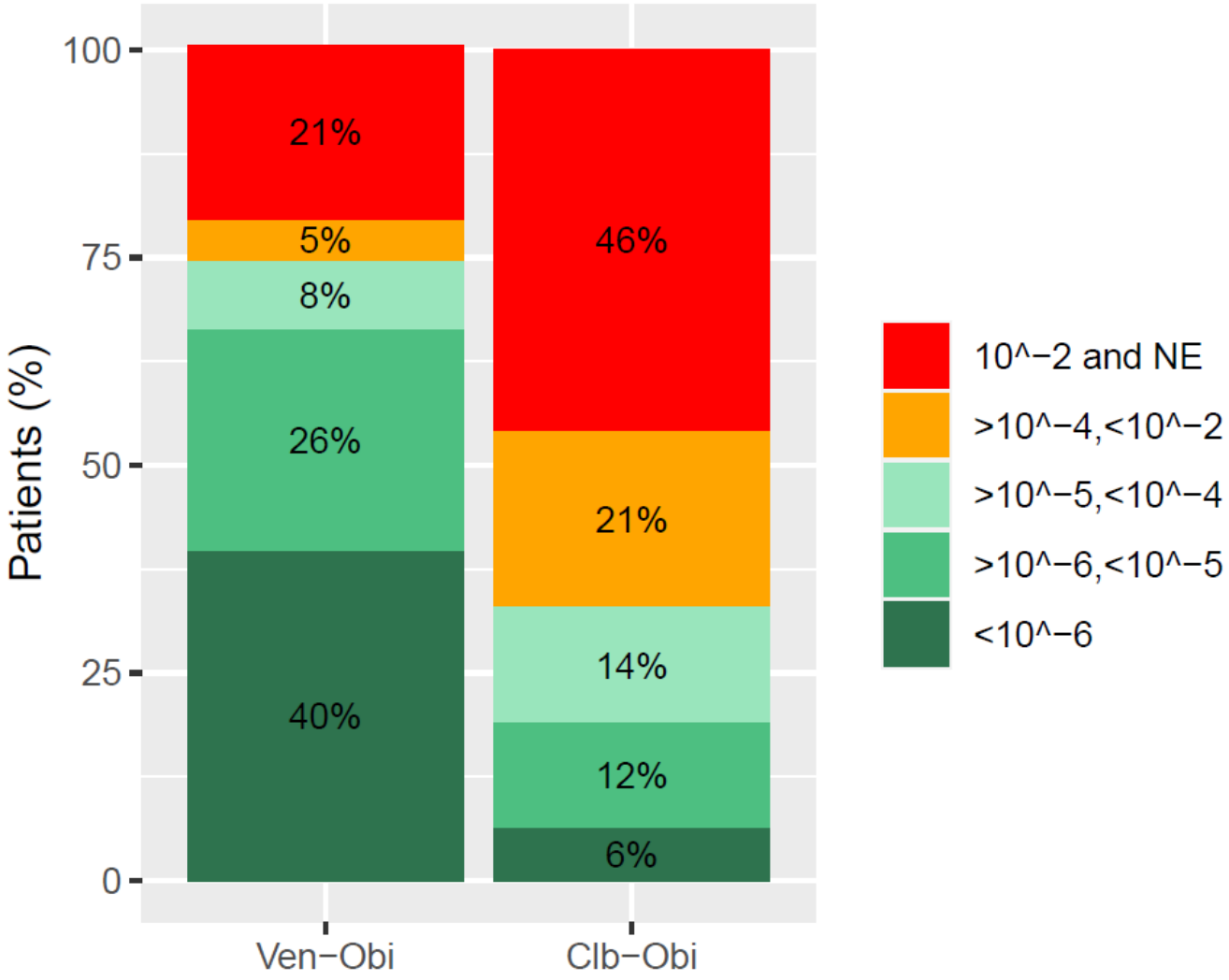
Median observation time 52.4 months



Al-Sawaf et al. EHA 2021, Abstract S146

CLL14 MRD Results

MRD by NGS at EoT



uMRD rate at EoT

- **Ven-Obin: 74%**
- **Clb-Obin: 32%**

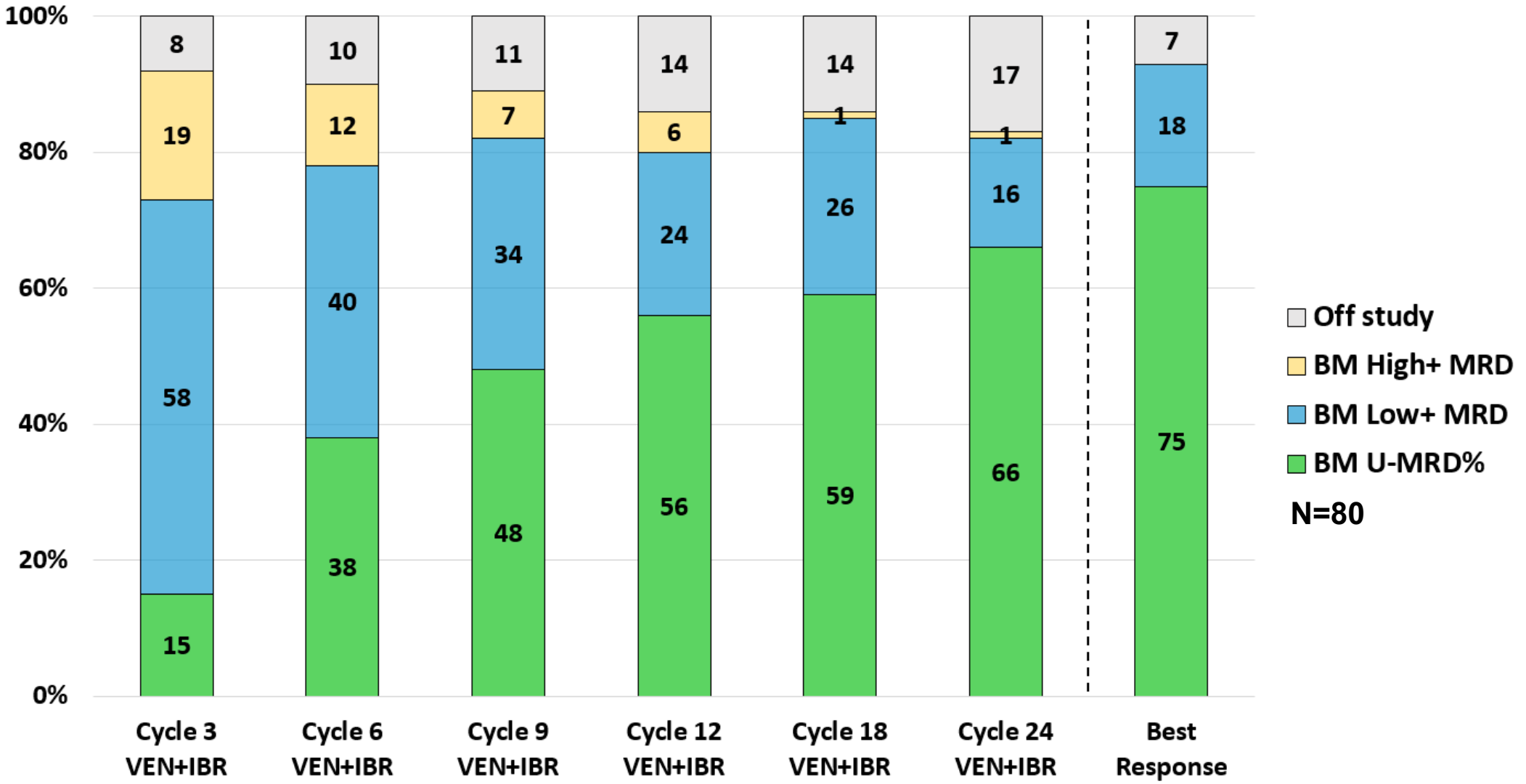
What happens *after* treatment completion?

Fischer et al, N Engl J Med, 2019
Al-Sawaf et al, Lancet Oncol, 2020

CLL14: Most Common ≥ Grade 3 Adverse Events

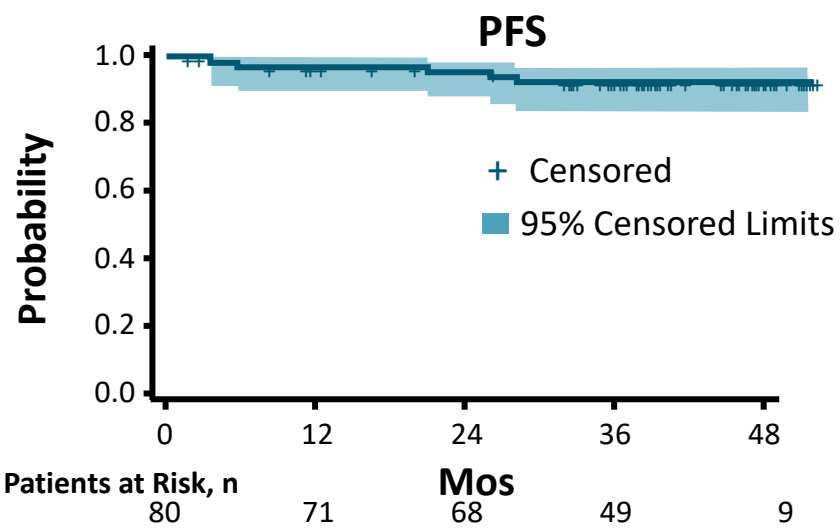
	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	**After Treatment**	**During Treatment**	**After Treatment**
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	13.7%	0.5%	15.0%	0.0%
Anemia	7.5%	1.5%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneunomia	3.3%	3.0%	2.8%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

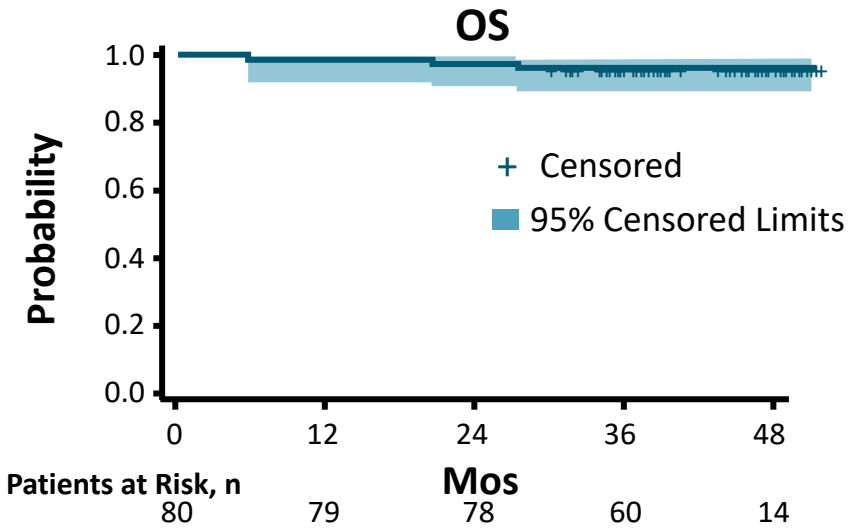
Firstline IBR+VEN BM MRD Responses Over Time

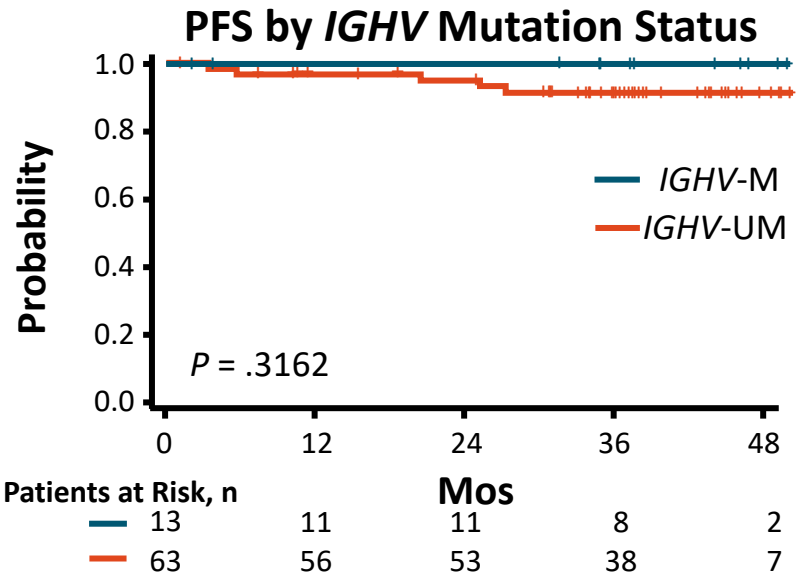


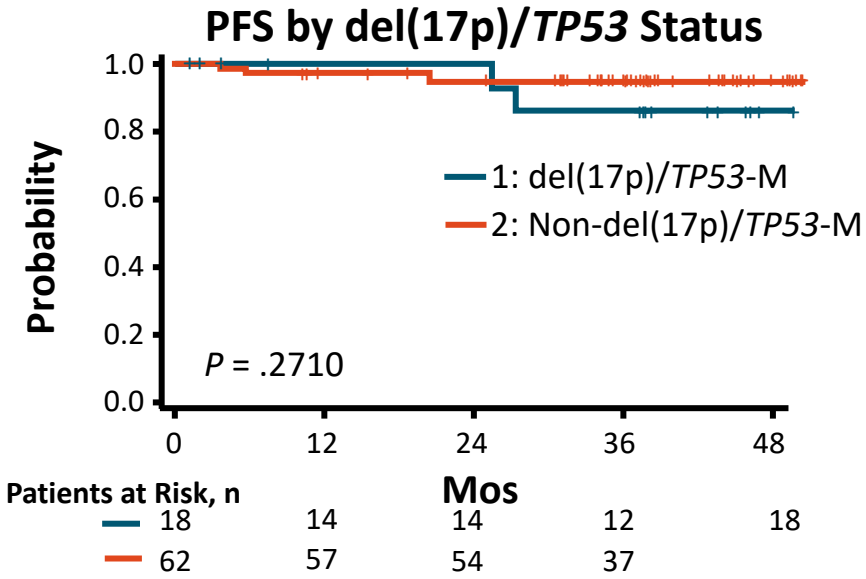
Jain et al., JAMA Oncology, 2021

Frontline Ibrutinib + Venetoclax: Survival Outcomes





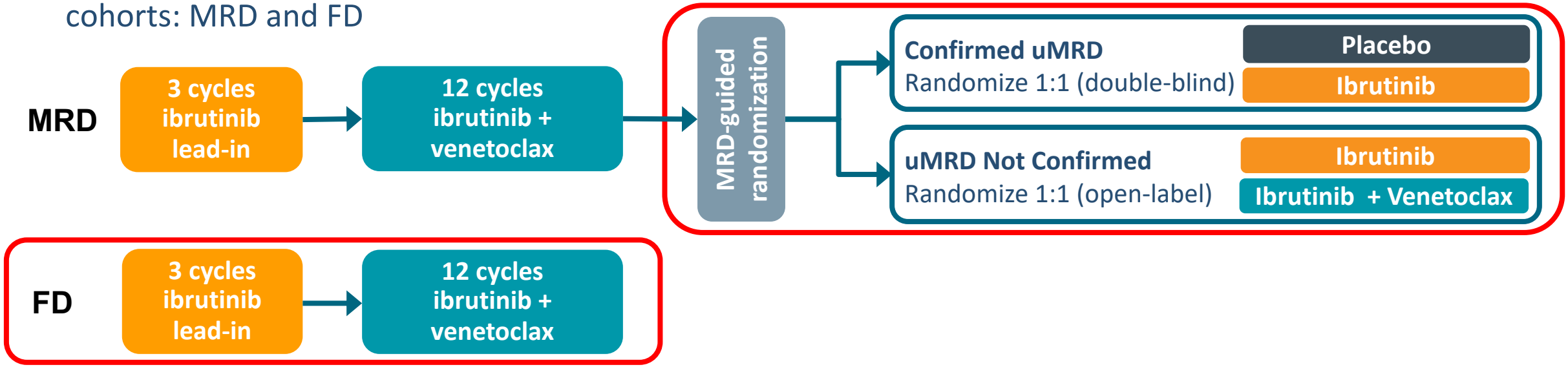




Jain et al., JAMA Oncology, 2021

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises 2 cohorts: MRD and FD



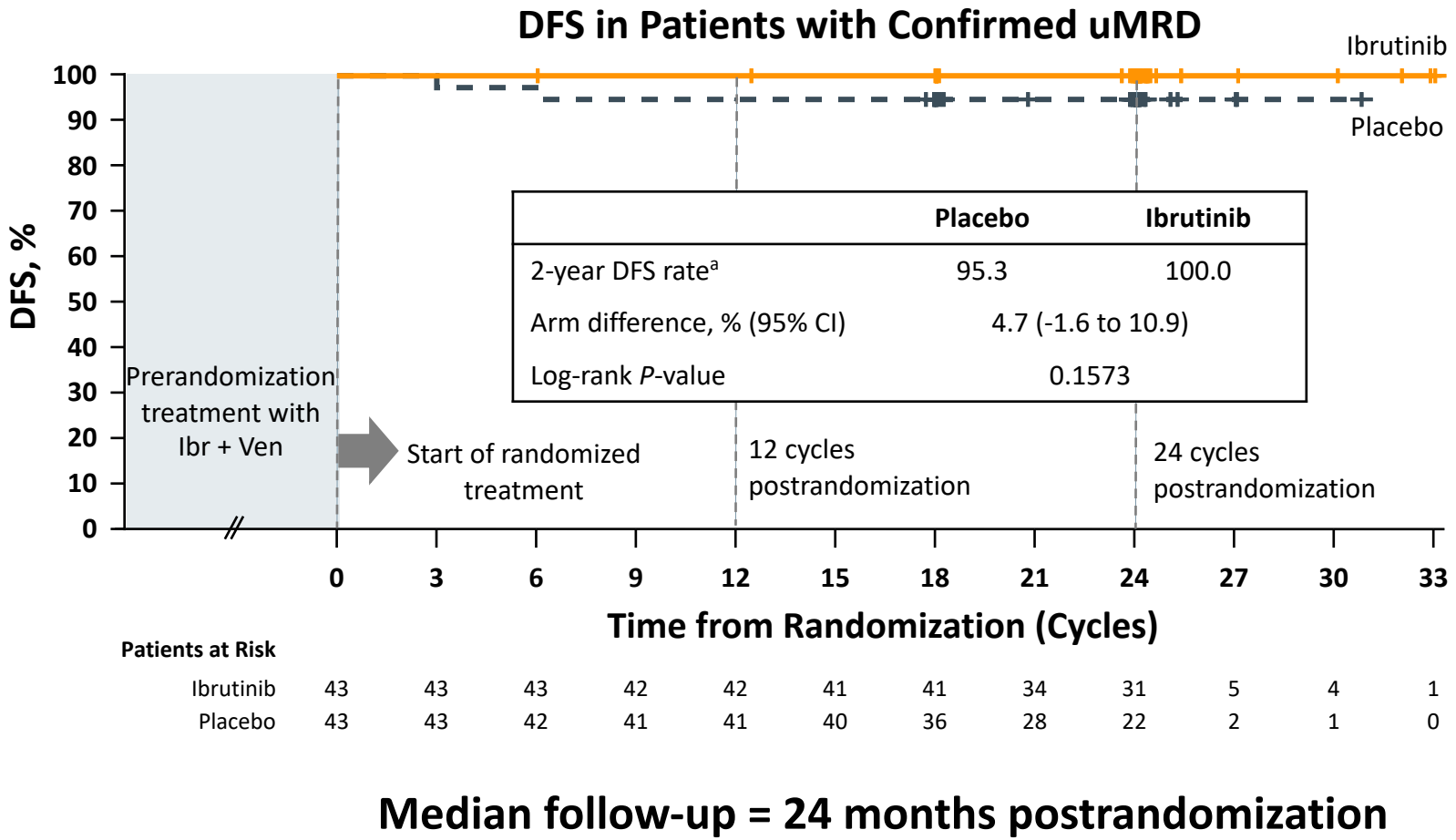
- Results from the MRD cohort demonstrated uMRD in more than two-thirds of patients treated with 12 cycles of ibrutinib + venetoclax (PB, 75%; BM, 68%), and 30-month PFS rates of ≥95% irrespective of subsequent MRD-guided randomized treatment[1]

- Primary analysis results from the FD cohort of CAPTIVATE are presented

BM, bone marrow; MRD, minimal residual disease; FD, fixed-duration; PB, peripheral blood; PFS, progression-free survival.

1. Wierda WG et al. ASH 2020, Abstract #123.

MRD Cohort: No New DFS Events Occurred Since Primary Analysis



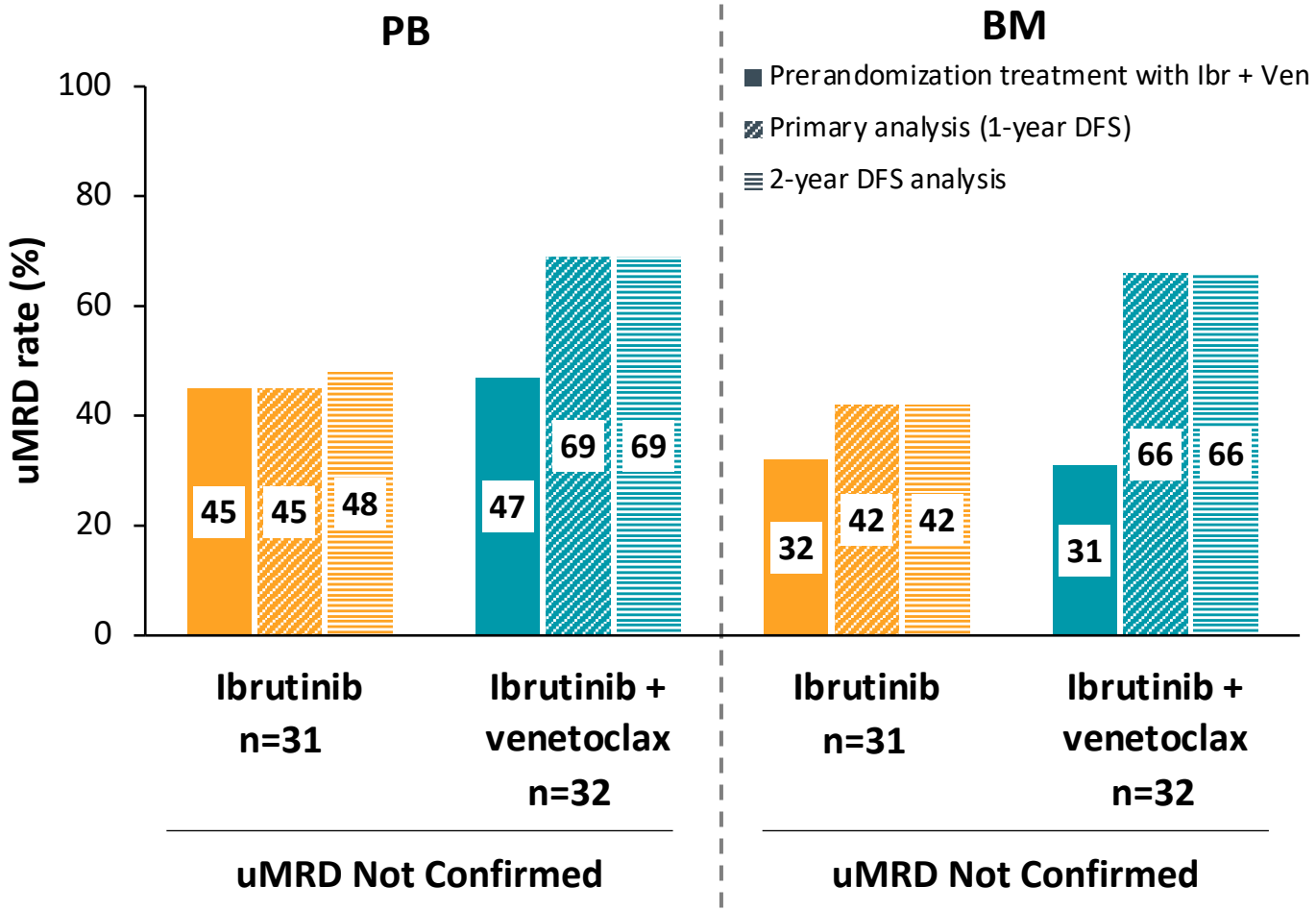
Median follow-up = 24 months postrandomization

- DFS was defined as freedom from MRD relapse (≥10^{-2} confirmed on 2 separate occasions) and without PD or death starting from randomization after 15 cycles of treatment
- In the additional year of follow-up since the 1-year DFS primary analysis, no new MRD relapses, PD, or deaths occurred in patients with Confirmed uMRD randomized to ibrutinib or placebo

DFS, disease-free survival; PD, progressive disease.
[a]24 cycles postrandomization.
Tick marks indicate patients with censored data.

Ghia, et al. CAPTIVATE-MRD; ASH 2021, Abstract #68

MRD Cohort: Best uMRD Rates Improved With Further Treatment in uMRD Not Confirmed Population



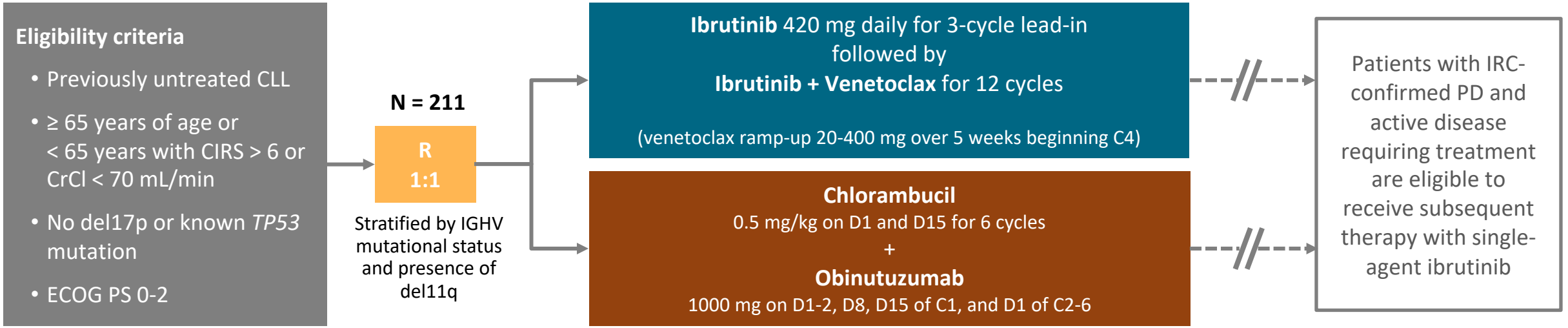
- As with CR rates, greatest uMRD rate improvements occurred during the first year of randomized treatment
  - Greater improvements with ibrutinib + venetoclax than with ibrutinib
- Improvements in uMRD rates were similar between patients achieving CR or PR

PR, partial response.

[a]Confirmed uMRD defined as having uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over ≥2 assessments ≥3 months apart and in both PB and BM; the best uMRD rates in the Confirmed uMRD population were 100% in both PB and BM.

- Ghia, et al. CAPTIVATE-MRD; ASH 2021, Abstract #68

Phase 3 GLOW Study Design (NCT03462719)

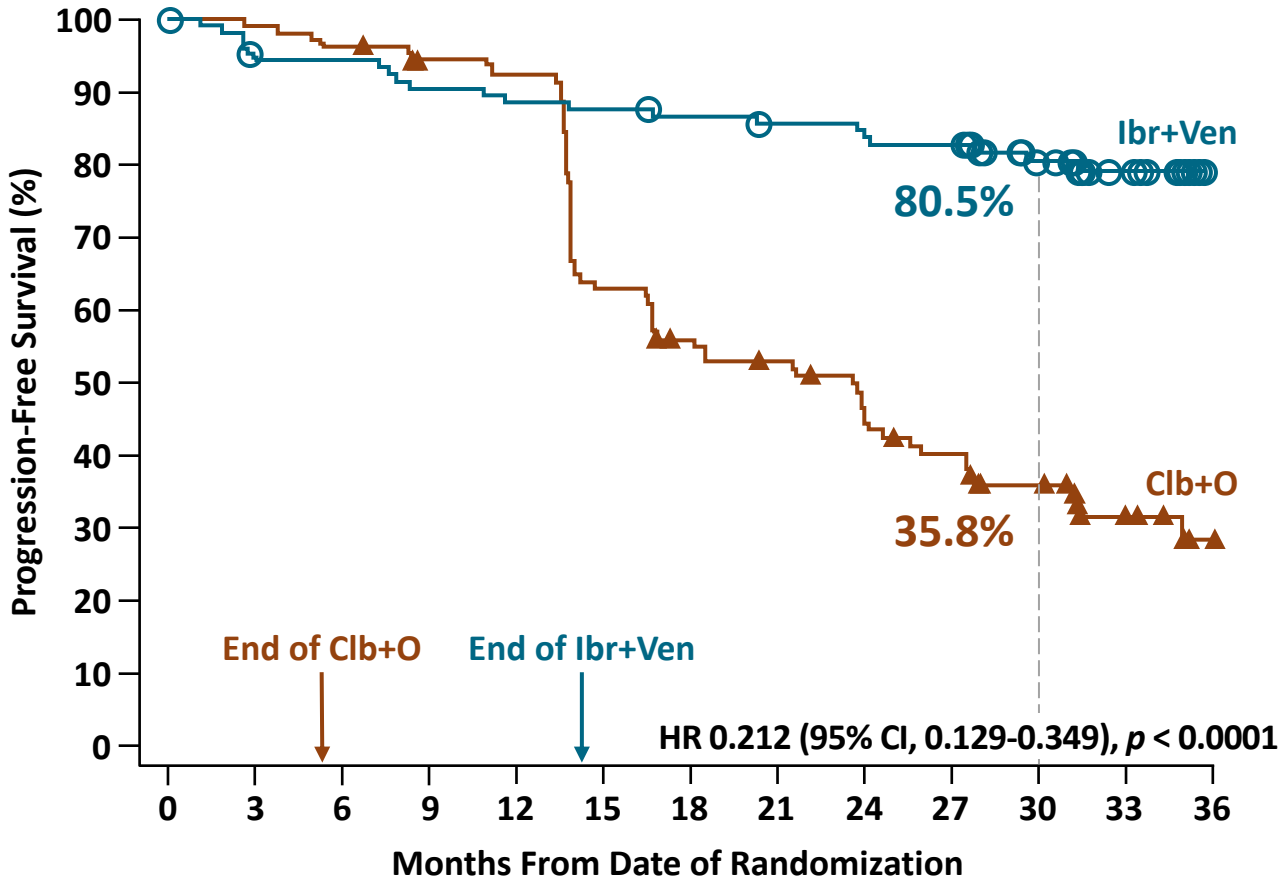


- **Study primary endpoint:** PFS as assessed by IRC
- **Current MRD analysis:**
  - MRD evaluated via NGS and reported with cutoffs of < 10^{-4} and < 10^{-5} (not all samples had sufficient cell yield to be analyzed at < 10^{-6}). NGS analysis not yet available beyond EOT+12 time point
  - PB/BM concordance calculated for patients with uMRD in PB at EOT+3 who had a paired BM sample
  - PFS results updated with 34.1 months of follow-up

BM, bone marrow; C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; EOT+3, 3 months after EOT; EOT+12, 12 months after EOT; IRC, independent review committee; NGS, next-generation sequencing; PB, peripheral blood; PD, progressive disease; R, randomization; uMRD, undetectable minimal residual disease.

Munir T, et al. ASH 2021, Abstract #70

GLOW: Superior Progression-Free Survival With Ibr+Ven vs Clb+O Was Maintained With Median 34.1 Months of Follow-up



Patients at risk

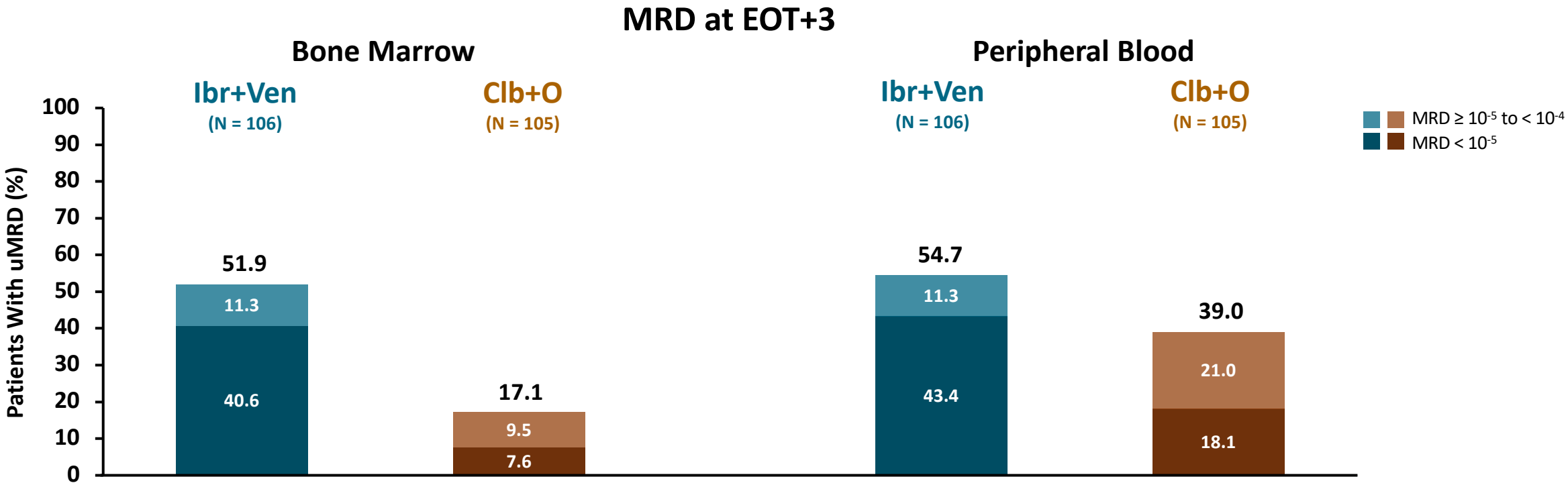
Ibr+Ven	106	98	98	94	92	91	89	87	86	84	71	42	1
Clb+O	105	104	101	96	94	64	55	51	43	37	30	13	3

- IRC-assessed PFS for Ibr+Ven was superior to Clb+O at primary analysis (median 27.7 months of follow-up)
  - HR 0.216 (95% CI, 0.131-0.357; $p < 0.0001$)
- **With median follow-up of 34.1 months:**
  - IRC-assessed PFS remained superior for Ibr+Ven (HR 0.212, 95% CI, 0.129-0.349; $p < 0.0001$)
  - 30-month PFS: 80.5% for Ibr+Ven vs 35.8% for Clb+O
  - Overall survival HR 0.76 (95% CI, 0.35-1.64), with 11 deaths for Ibr+Ven vs 16 for Clb+O

CI, confidence interval; HR, hazard ratio; OS, overall survival.

Munir T, et al. ASH 2021, Abstract #70

GLOW: uMRD Rate < 10^{-5} Was Higher With Ibr+Ven vs Clb+O in Both Compartments



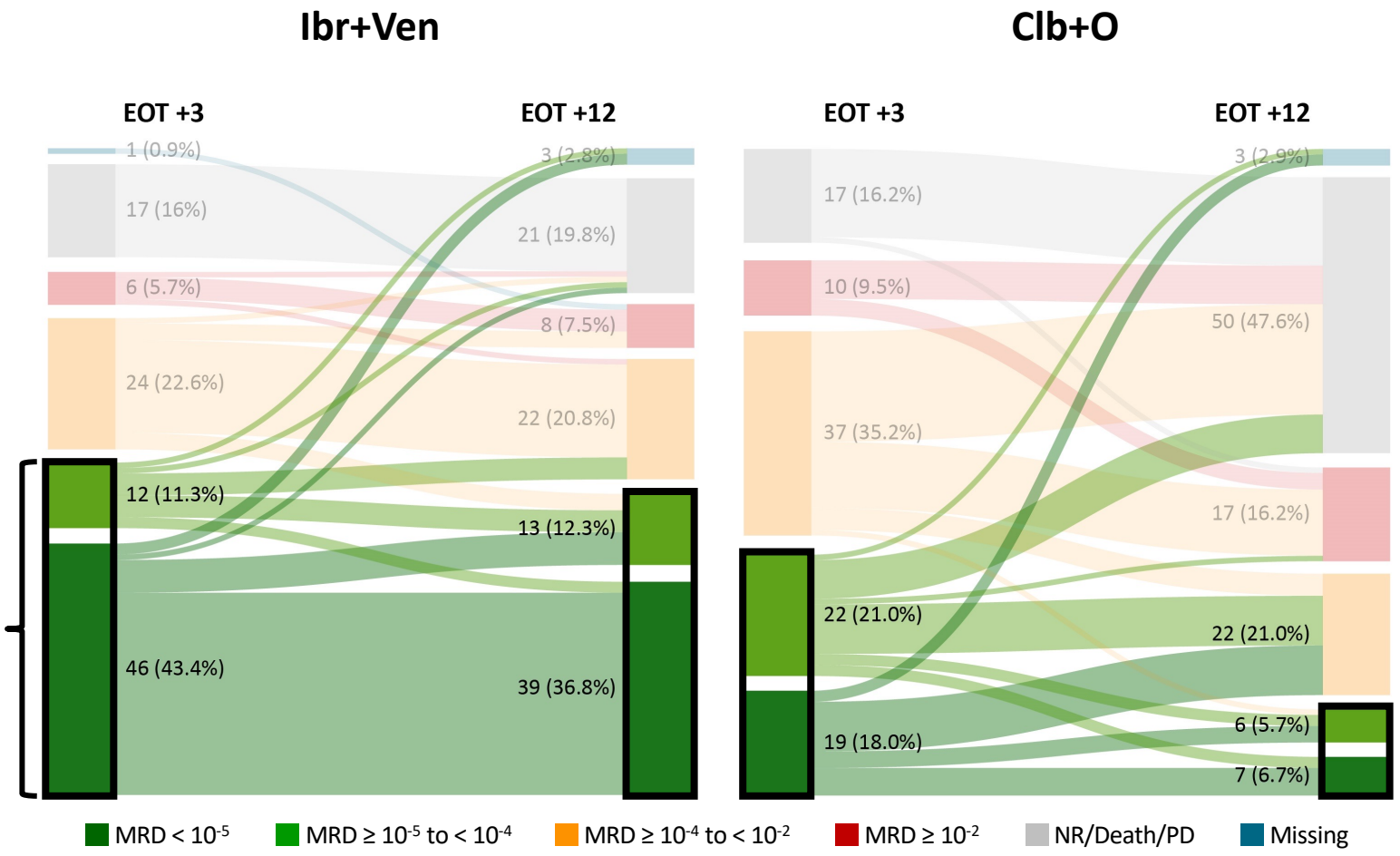
- In the Ibr+Ven arm, but not the Clb+O arm, most patients with uMRD < 10^{-4} had deep responses of uMRD < 10^{-5}
- uMRD concordance at < 10^{-5} in PB/BM: **90.9%** for Ibr+Ven vs **36.8%** for Clb+O

MRD results by next-generation sequencing at EOT+3. Note: Numbers may not add up due to rounding.
BM, bone marrow; EOT, end of treatment; PB, peripheral blood.

Munir T, et al. ASH 2021, Abstract #70

GLOW: uMRD in PB Was Better Sustained With Ibr+Ven From EOT+3 to EOT+12

- **84.5%** (49/58) of patients had sustained uMRD < 10^{-4} and **80.4%** (37/46) had sustained uMRD < 10^{-5} with Ibr+Ven[a]
  - 29.3% (12/41) and 26.3% (5/19) with Clb+O
- uMRD < 10^{-4} rate decreased 6% with Ibr+Ven vs 27% with Clb+O



[a]Sustained uMRD rate is calculated on a per-patient basis, not using intent-to-treat MRD rates at EOT+3 and EOT+12.
EOT, end of treatment; NR, nonresponder; PB, peripheral blood; PD, progressive disease.

Munir T, et al. ASH 2021, Abstract #70

Select Ongoing Phase III Clinical Trials in First-line CLL

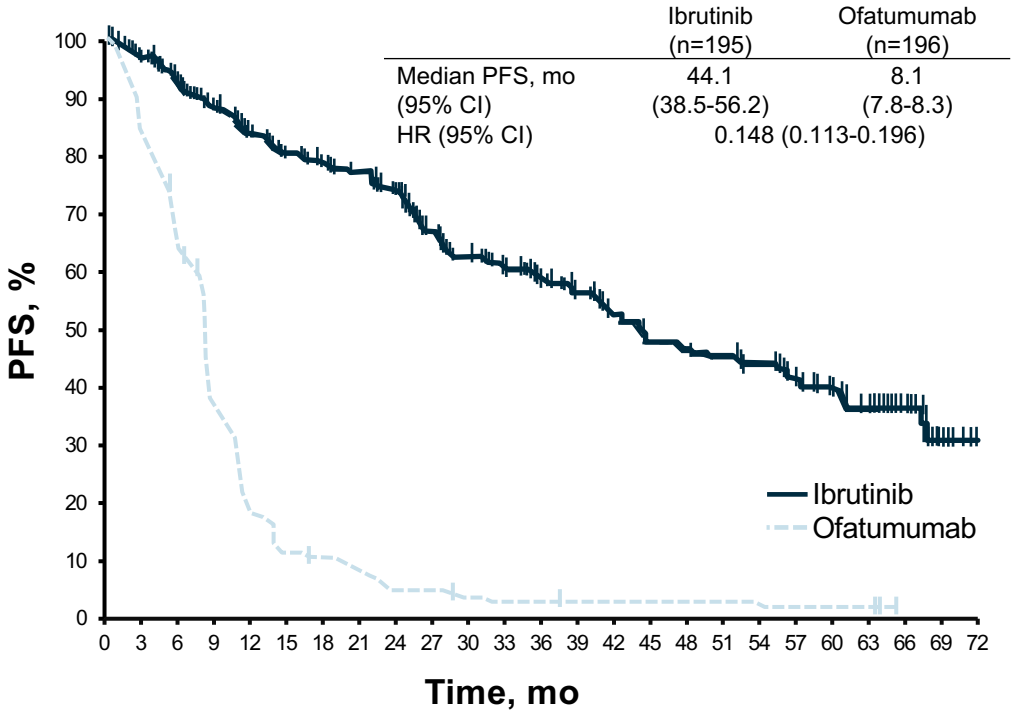
Trial	Subgroup	N	Status*	MRD	Treatment Arms			
GAIA/CLL13 (NCT02950051)	Fit pts	920	Enrolled	Primary	IbrVenOb	VenOb	VenR	FCR/BR
EA9161 (NCT03701282)	Fit, 18-69 yo	720	Enrolled	Secondary	IbrVenOb	IbrOb		
SEQUOIA (NCT03336333)	All pts	680	Enrolled	No	Zanub			BR
ACE-CL-311 (NCT03836261)	All pts	780	Enrolling	Secondary	AcaVenOb	AcaVen		FCR/BR
CRISTALLO (NCT04285567)	Fit pts	165	Enrolling	Primary	VenOb			FCR/BR
A041702 (NCT03737981)	≥70 yo	454	Enrolling	Secondary	IbrVenOb	IbrOb		
CLL17 (NCT04608318)	All pts	897	Enrolling	Secondary	Ibr	VenOb	IbrVen	
BRUIN CLL-313 (NCT05023980)	All pts (no del(17p)	250	Enrolling	No	Pirto			BR
MAJIC (NCT05057494)	All	600	Pending	Primary	AcaVen	VenOb		

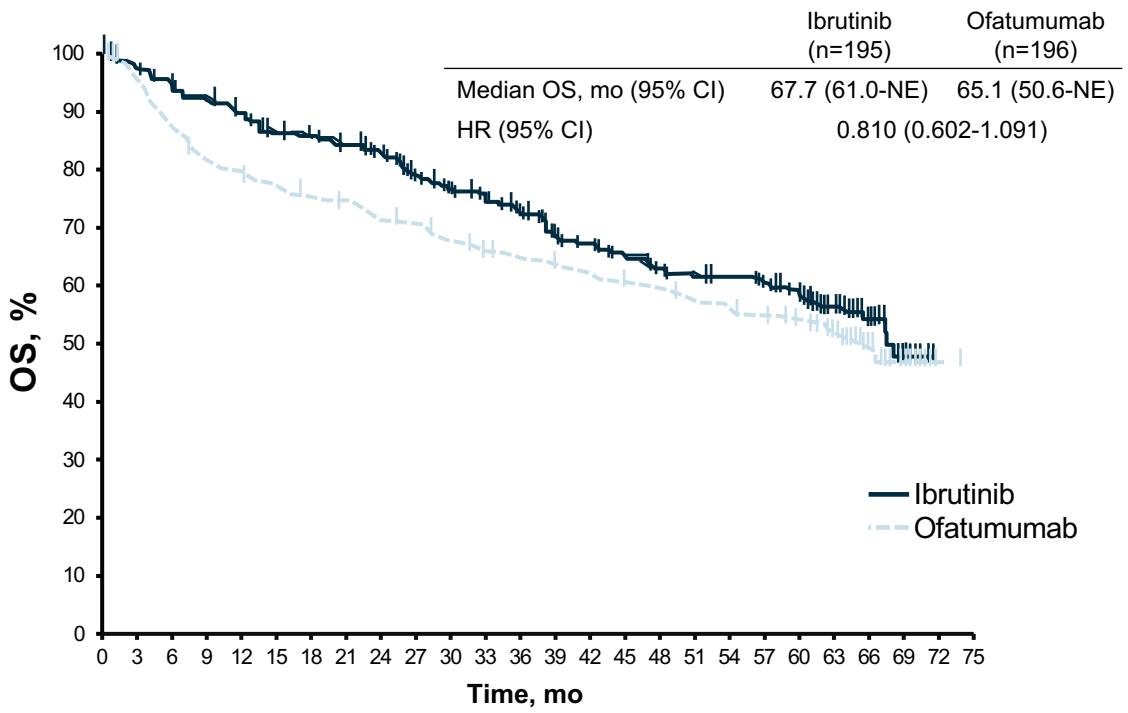
*Enrolling patients as of May 2022.

Considerations for Patients With Rel / Ref CLL

- Important factors for selecting treatment for R/R CLL:
  - First-line therapy
  - Toxicities from first-line therapy
  - Age and comorbidities (eg, fitness, cardiac issues, renal insufficiency)
  - Current disease status (eg, repeat cytogenetics/FISH, imaging, BM test if necessary to elucidate immune cytopenias)
  - Others: social support, financial, ease of administration (eg, hospitalization requirement, visit frequency, COVID-19)

RESONATE: Phase 3 Study in Relapsed CLL
Ibrutinib vs Ofatumumab—Outcomes





Final RESONATE findings: Ibrutinib safety profile remained consistent with prior reports

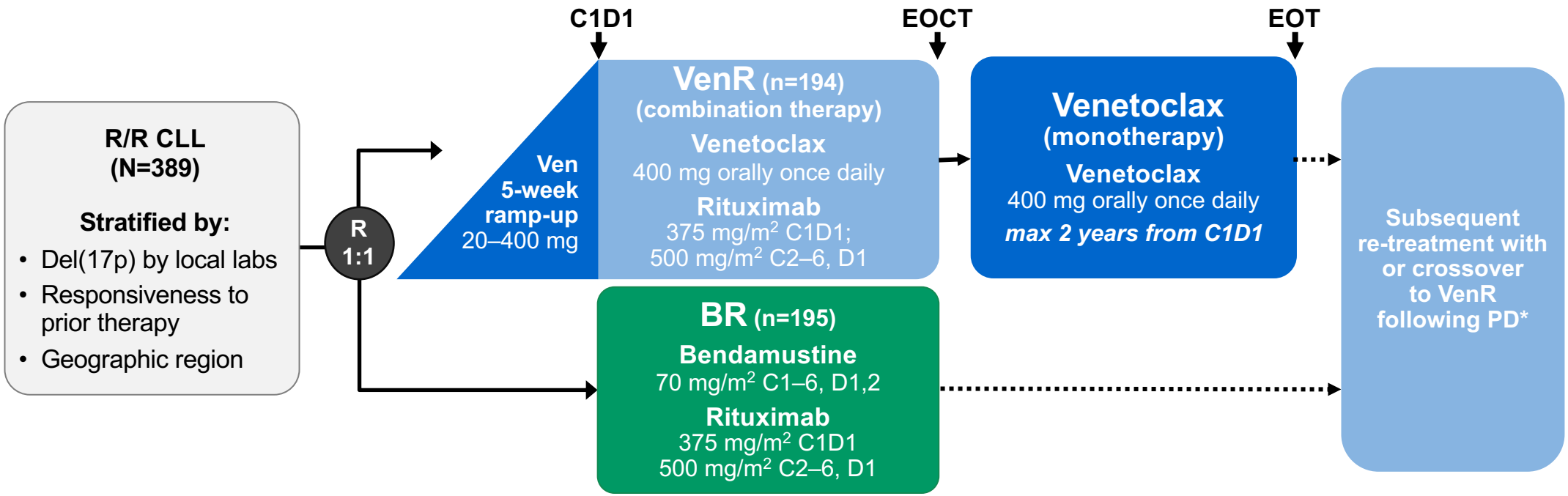
- Cumulatively, all-grade (grade ≥3) hypertension and atrial fibrillation occurred in 21% (9%) and 12% (6%) of patients, respectively
- 16% discontinued ibrutinib because of AEs
- **Peripheral neuropathy:** All grade = 13%, grade ≥3 = 0.5%
- **CHF:** All grade = 5%, grade ≥3 = 3%
- **Ventricular arrhythmia:** All grade: 1%, no grade ≥3 events

CHF = congestive heart failure.

Byrd JC, et al. *N Engl J Med*. 2014;371(3):213-223. Byrd JC, et al. *J Clin Oncol*. 2017;35(15 Suppl):7510. Munir T, et al. *Am J Hematol*. 2019;94(12):1353-1363.

MURANO Study (NCT02005471)

- Global, Phase III, open-label, randomized study[1]



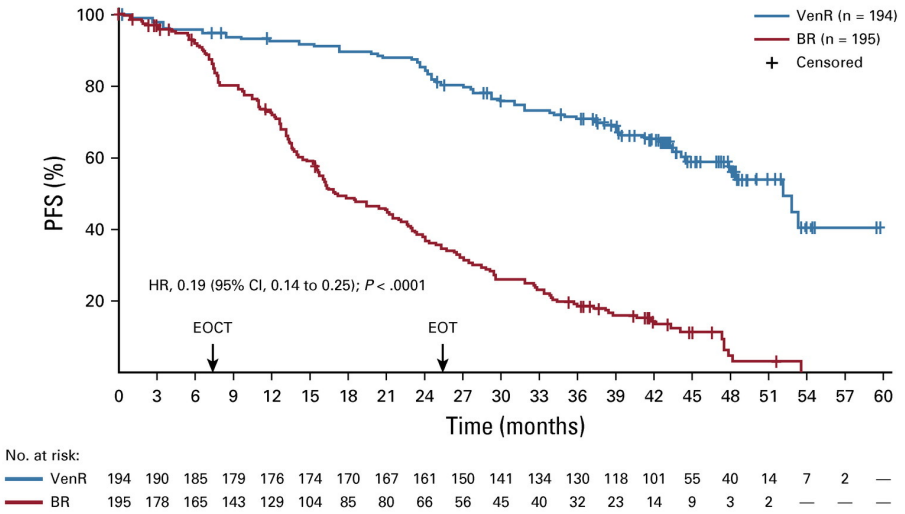
- At 48 months of follow up, deep responses with uMRD were associated with favorable PFS[2]

*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria
BR, bendamustine-rituximab; C, cycle; D, day; EOCT, end of combination treatment; EOT, end of treatment; PFS, progression-free survival; R, randomization; R/R CLL, relapsed refractory chronic lymphocytic leukemia; (u)MRD, (undetectable) minimal residual disease; PD, progressive disease; VenR, venetoclax-rituximab

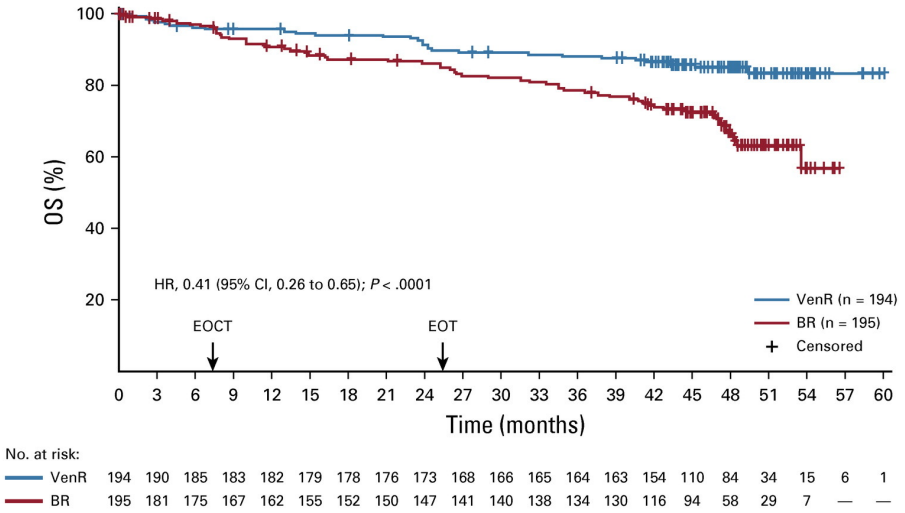
1. Seymour JF, et al. N Engl J Med 2018;378(12):1107–1120.
2. Kater AP, et al. J Clin Oncol 2020; DOI https://doi.org/10.1200/JCO.20.00948.

Kater et al. ASH 2020 Abstract #125

MURANO: PFS and OS - 4-yr Results



Progression-free Survival



Overall Survival

Kater, A et al. JCO 38:4042, 2020

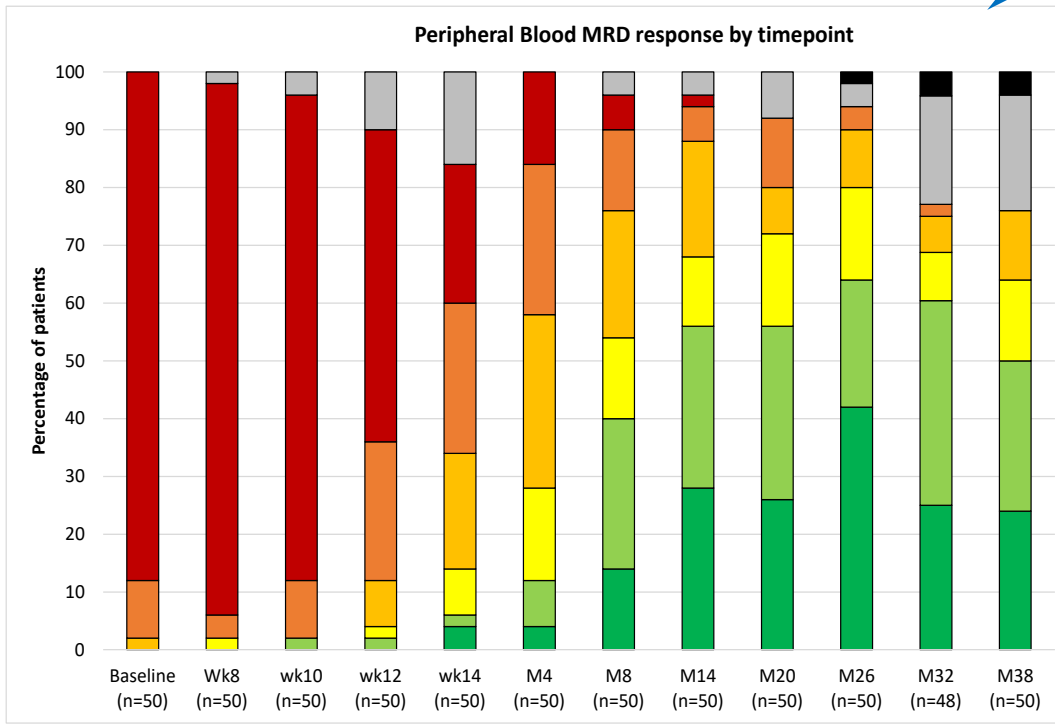
CLARITY: MRD level by time-point (up to Month 38)

At month 38, MRD4 (<0.01%) negative rates were 50% and 40% in peripheral blood and bone marrow respectively in all evaluable patients*

Blood

Venetoclax

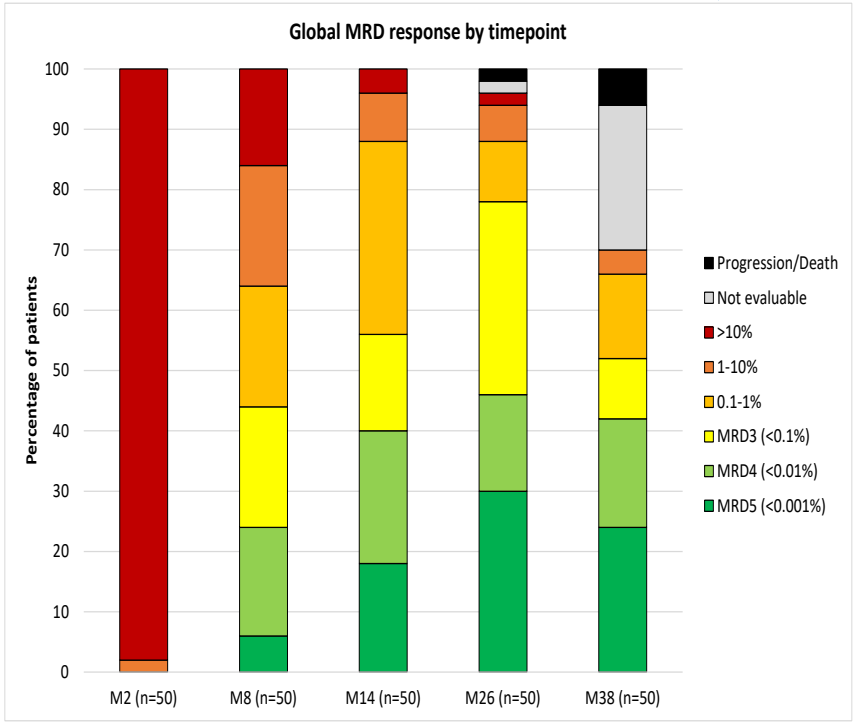
Ibrutinib



Marrow

Venetoclax

Ibrutinib



*Data missing at month 38 due to Covid Pandemic

Date of data lock: 6th Nov, 2020

M14 M26 M38

M14 M26 M38

Munir et al. ASH 2020 Abstract #124

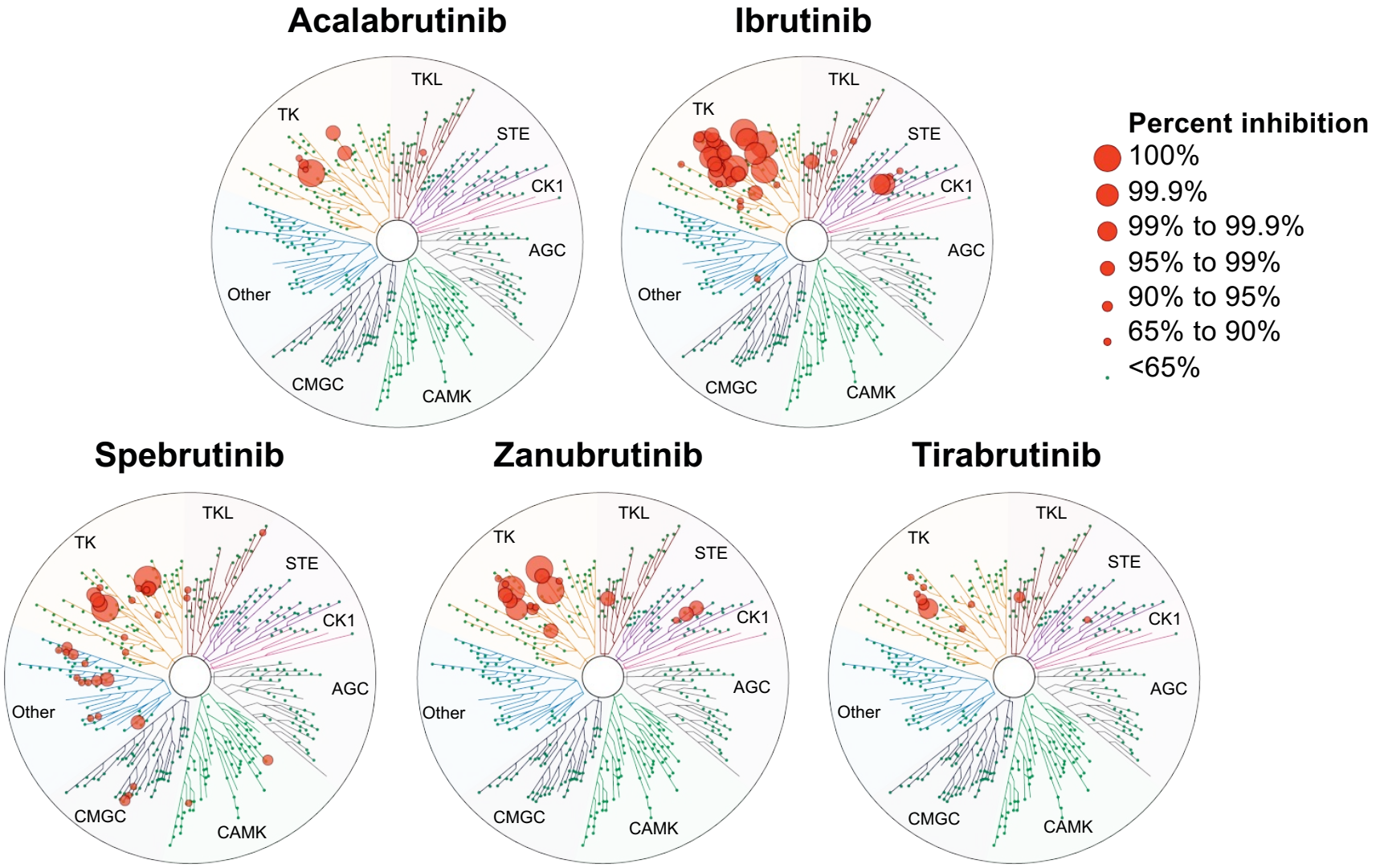
Differentiated Kinase Inhibition Profile

		Tec Family Kinases					Inhibition of Other Kinases
	IC_{50} (nM)	BTK	ITK	Tec#	TXK*	BMX*	Notable target kinases
Irreversible (covalent)	Ibrutinib	0.5	10.7	78	2.0	0.8	>10 more: EGFR family
	Acalabrutinib	5.1	>1000	93	368	46	Selective
	Zanubrutinib	0.22	30	1.9	n/a	n/a	N/A (not published)
Reversible (non-covalent)	Vecabrutinib	3	14	14	474	224	Selective -4 non-Tec family kinases: SRC family, NEK11
	ARQ 531	4.23	>10000	5.8	36.4	5.23	>20 more: SRC & TRK families, RAF1, MEK1
	LOXO-305	3.15	>5000	1234	209	1155	Very selective
	CG-806	8.4	4.3	>1000	n/a	14.5	18 w/ IC_{50} <10 nM: FLT3 (wt, ITD) c-MET, TRK family & Aurora kinases

***Determined with vecabrutinib free base (also relevant for SRC and EGFR); #Activated (also relevant for LCK).**

Neuman LL, et al. *Blood*. 2016;128(22):2032. Honigberg LA, et al. *PNAS*. 2010;107(29):13075-13080. Byrd JC, et al. *N Engl J Med*. 2016;374(4):323-332. Tam CS, et al. *Blood*. 2016;128(22):642. Eathiraj S, et al. Presented at: Pan Pacific Lymphoma Conference; July 18-22, 2016; Koloa, HI. Brandhuber B, et al. Presented at: Society of Hematologic Oncology (SOHO) Annual Meeting; September 12, 2018; Houston, TX. Zhang H, et al. Presented at: EHA Congress; June 15, 2018; Stockholm, SE.

Differences in Overall Kinase Selectivity Among BTKi[1]

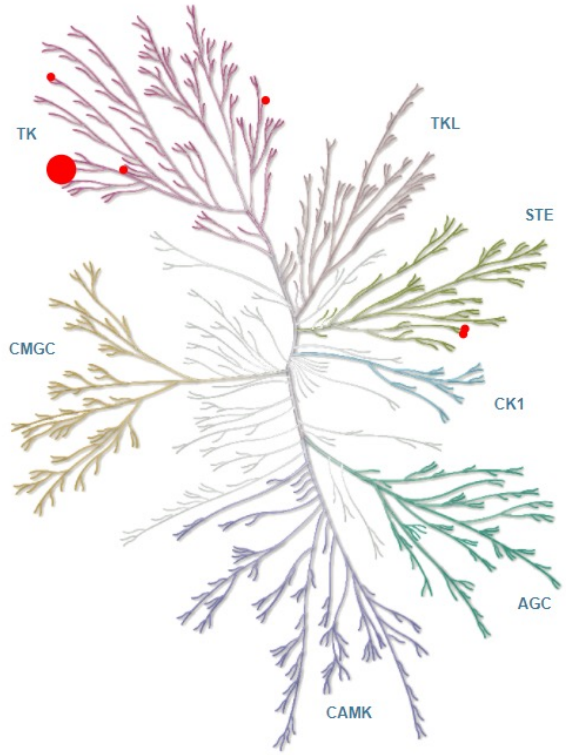


1. Kaptein A et al. 60th American Society of Hematology Annual Meeting & Exposition (ASH 2018). Abstract 1871.

Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

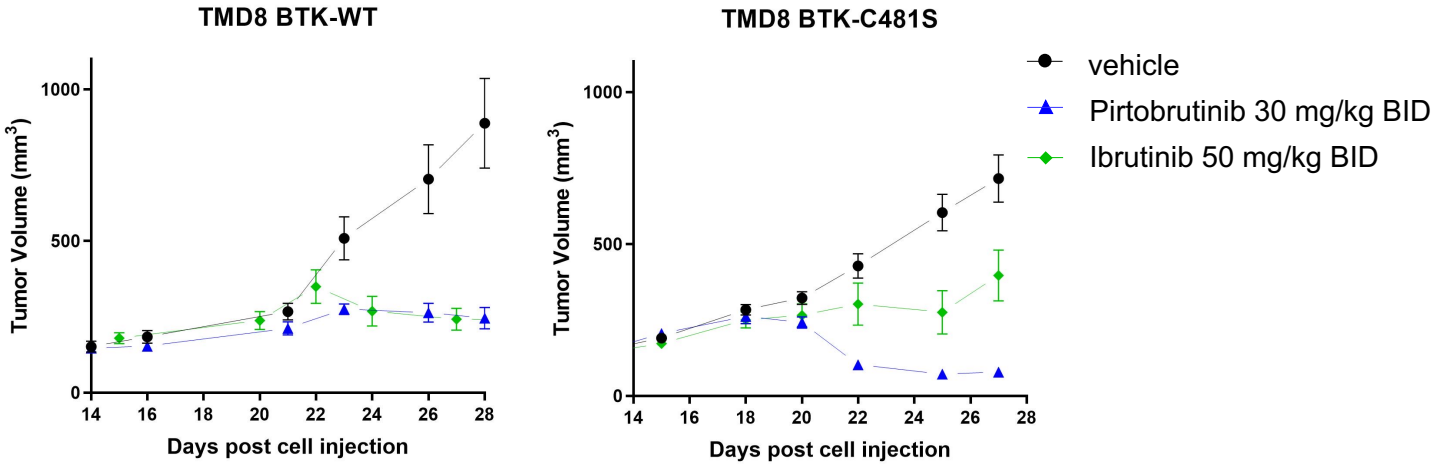
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S

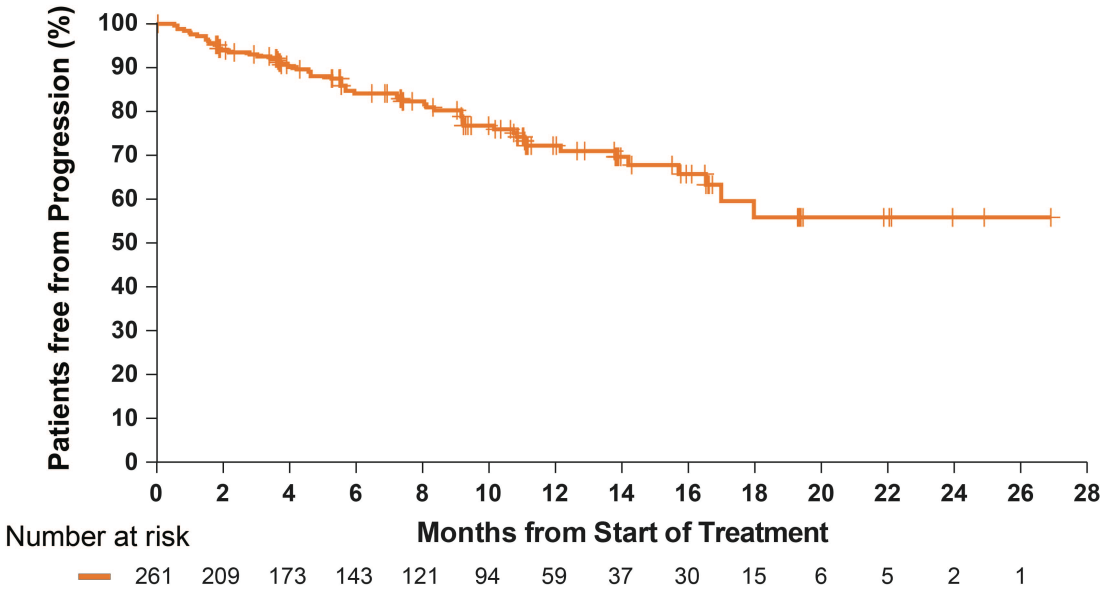


- >300-fold selectivity for BTK vs 370 other kinases[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]
- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- Due to reversible binding mode, BTK inhibition not impacted by a high intrinsic rate of BTK turnover[2]

BID, twice-daily; BTK, Bruton tyrosine kinase. [1]Mato et al, *Lancet*, 2021:397:892-901. [2]Brandhuber BJ, et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

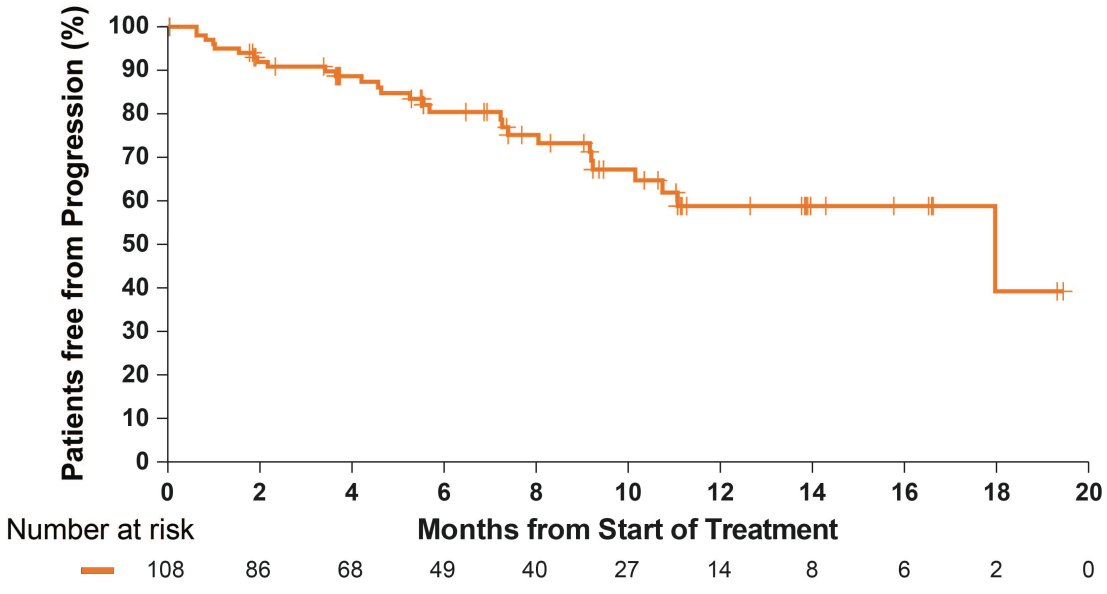
Progression-free Survival in BTK Pre-treated CLL/SLL Patients

PFS in at least BTK pre-treated patients
Median prior lines = 3



Median PFS: Not Estimable (95% CI: 17.0 months – Not Estimable)

PFS in at least BTK and BCL2 pre-treated patients
Median prior lines = 5



Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

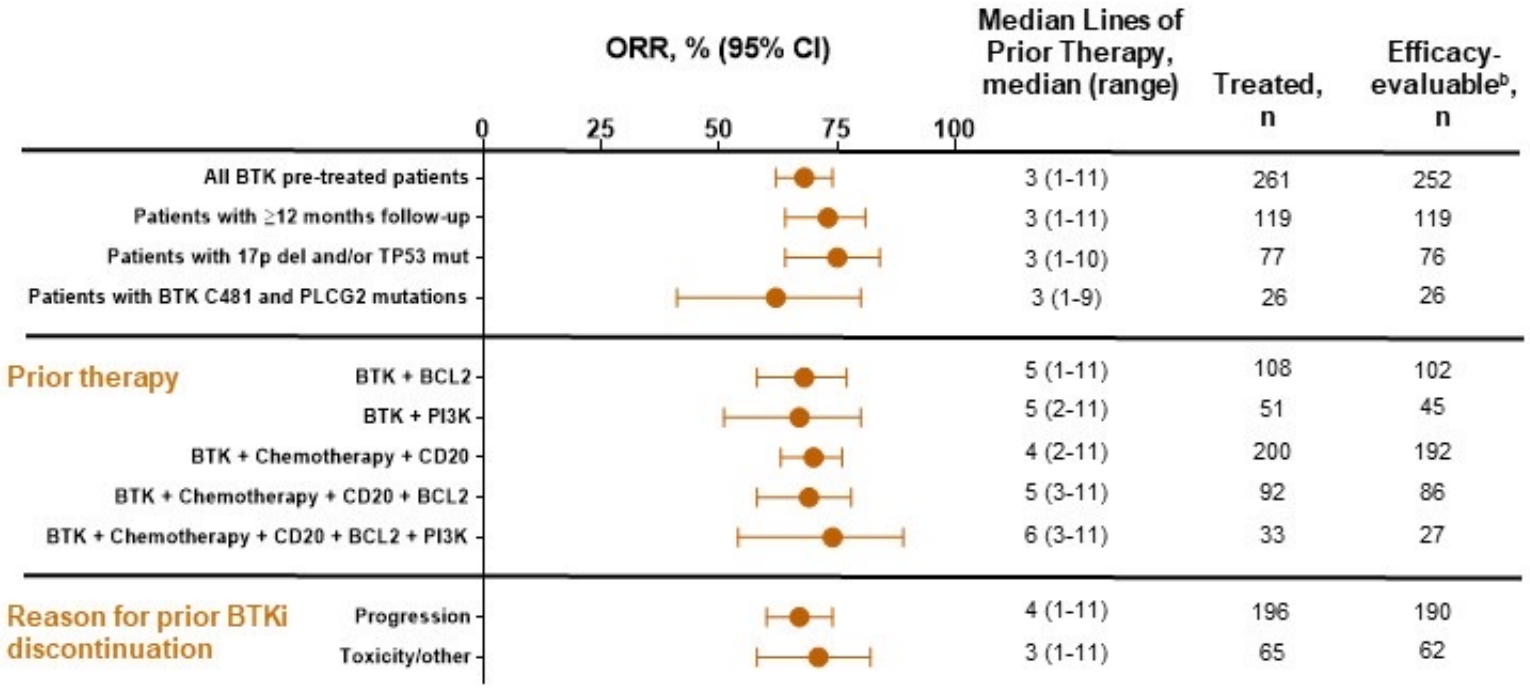
- 74% (194/261) of BTK pre-treated patients remain on pirtobrutinib
- Median follow-up of 9.4 months (range, 0.3 – 27.4) for all BTK pre-treated patients

Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment.

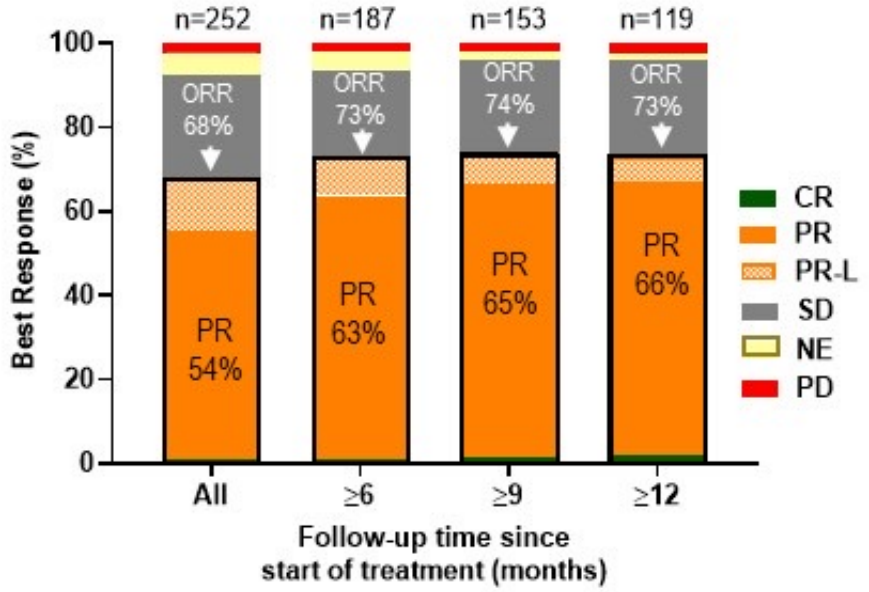
Mato et al. ASH 2021 Abstract #391

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients

Pirtobrutinib Efficacy Regardless of Other Prior Therapy[a]



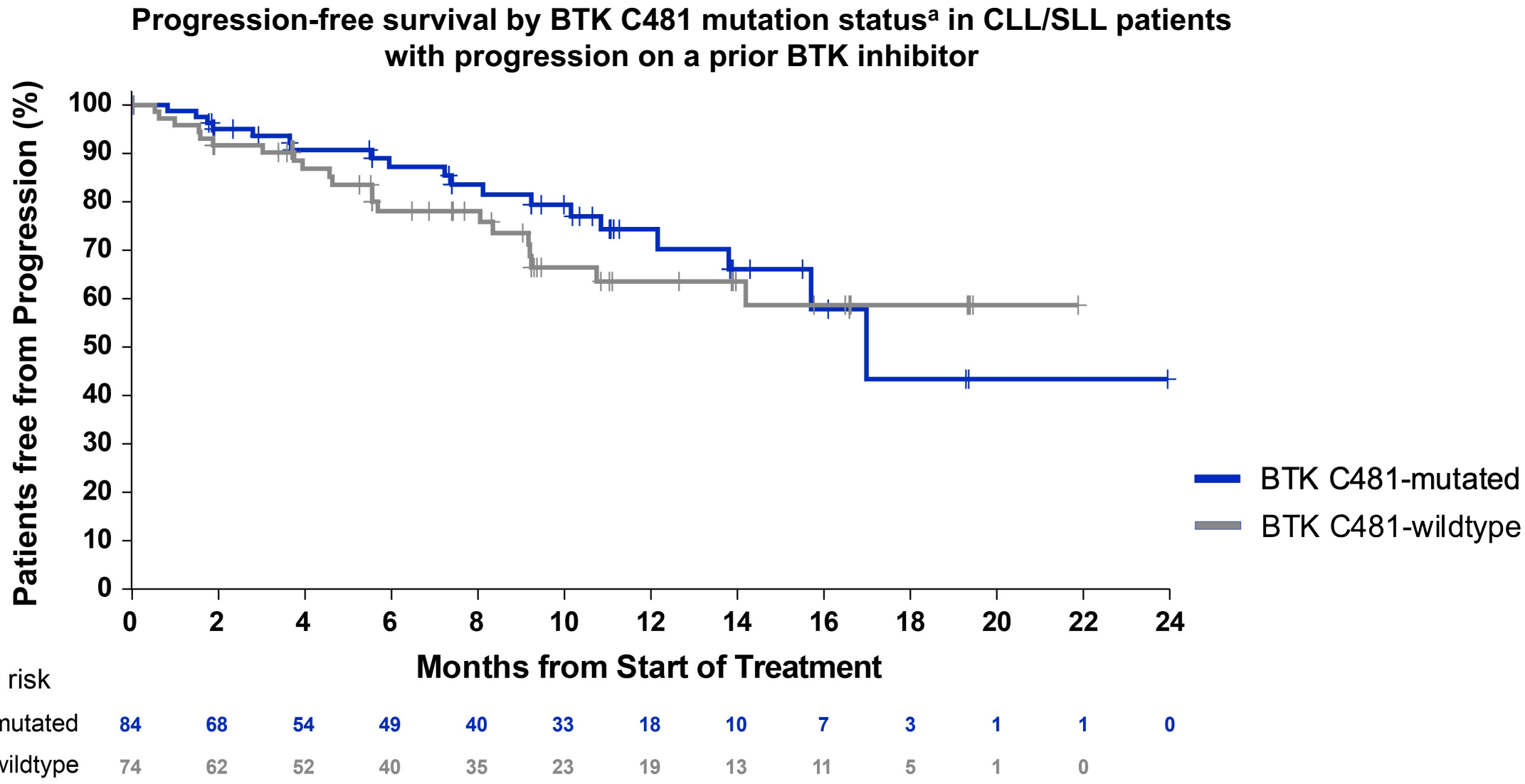
Overall Response Rate Over Time[c]



Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Efficacy evaluable patients are those who had at least one evaluable post-baseline assessment or had discontinued treatment prior to first post-baseline assessment. [c]Includes the BTK pre-treated efficacy-evaluable CLL/SLL patients at the time of data cutoff. Data at each timepoint includes the BTK pre-treated efficacy-evaluable CLL/SLL patients who had the opportunity to be followed for at least the indicated amount of time.

Mato et al. ASH 2021 Abstract #391

BTK C481 Mutation Status is not Predictive of Pirtobrutinib Benefit



Mato et al. ASH 2021 Abstract #391

Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment. [a]BTK C481 mutation status was centrally determined and based on pre-treatment samples.

Conclusions

- Covalent BTKi-based treatment is highly effective, well-tolerated continuous treatment in first-line and R/R CLL
- Venetoclax-based (+CD20 mAb) treatments result in deep remissions (uMRD) correlated with long PFS and OS
- Combined targeted therapy (ibrutinib + venetoclax) results in deep remissions (uMRD) with finite-duration treatment
- Pirtobrutinib (LOXO-305), a reversible BTKi, is well-tolerated and has activity in irreversible BTKi-refractory CLL