Updates in CLL Therapy

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Disclosure Information

Susan O'Brien, MD

I have the following financial relationships to disclose:

Sponsor/Company	Affiliation(s)
AbbVie	Consultant
Acerta	Research Support
Alexion	Consultant
Alliance	Research Support
Amgen	Consultant
Aptose Biosciences Inc.	Consultant
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Eli Lilly and Company	Consultant
Gilead	Consultant/Research Support
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Juno Therapeutics	Consultant
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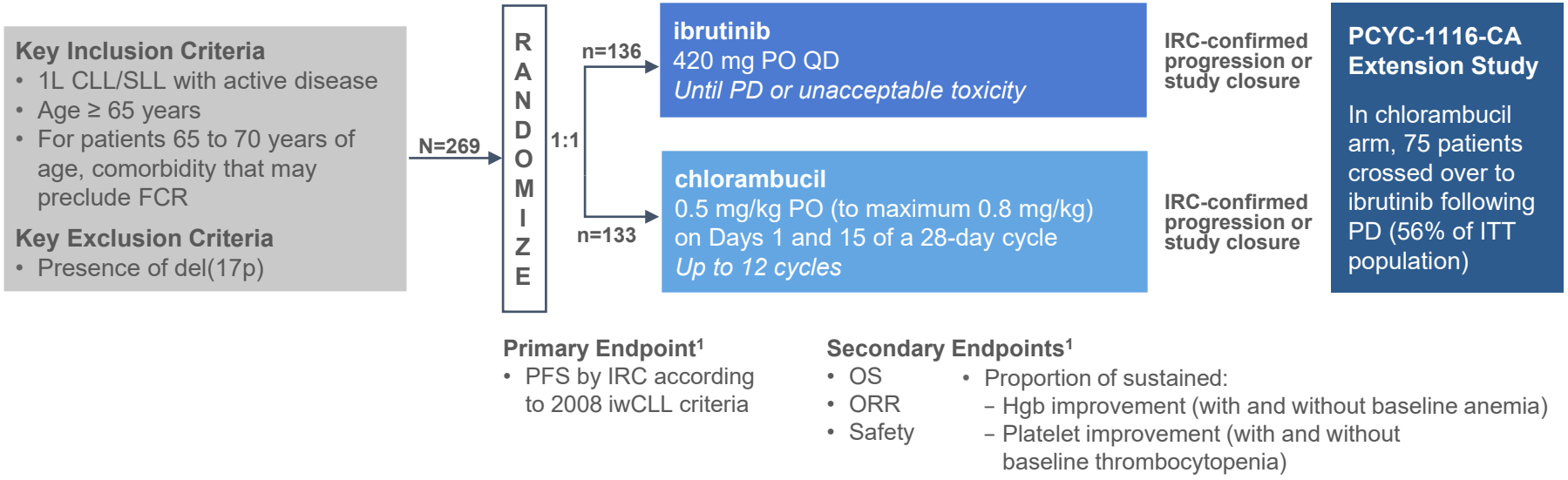
Pfizer	Consultant/Research Support
Pharmacyclics	Consultant/Research Support
Regeneron	Research Support
TG Therapeutics	Consultant/Research Support
Vaniam Group LLC	Consultant
Verastem	Consultant
Vida Ventures	Consultant

Updated January 2022

RESONATE-2: Phase 3 Trial in 1L CLL/SLL

Phase 3 randomized, multicenter, open-label trial of ibrutinib vs chlorambucil in patients ≥65 years of age with 1L CLL/SLL (NCT01722487)

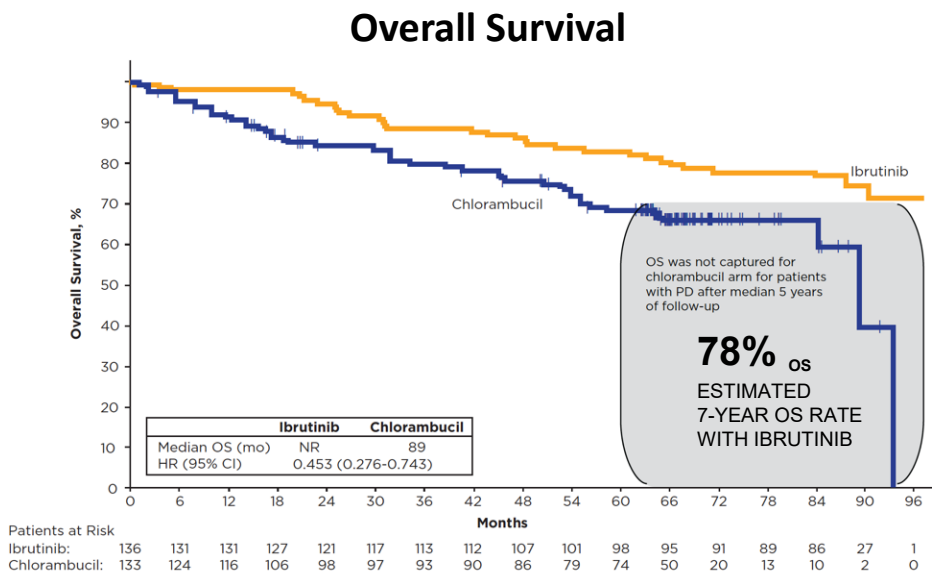


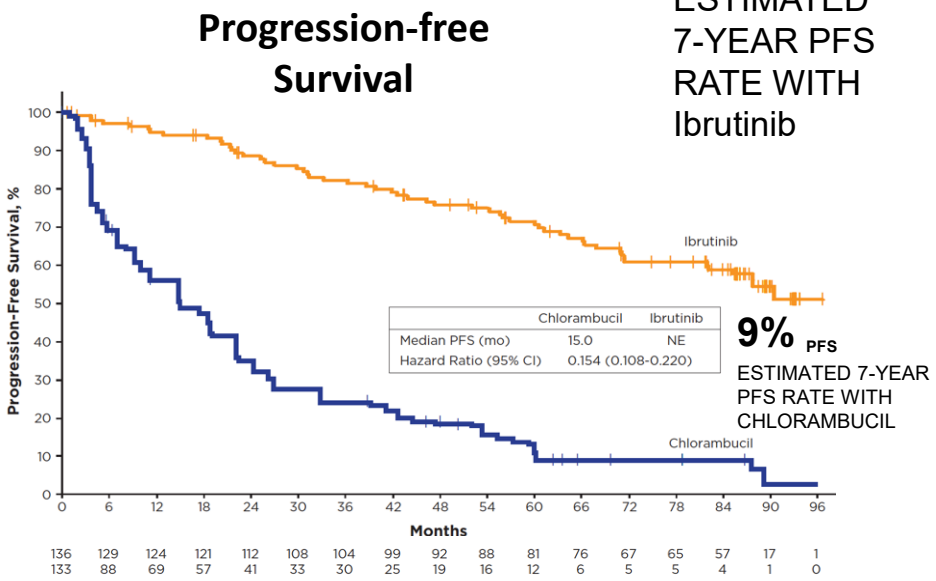
References:

1. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34(3):787-798.

2. Clinicaltrials.gov. Open-label phase 3 btk inhibitor ibrutinib vs chlorambucil patients 65 years or older with treatment-naive cll or sll. https://clinicaltrials.gov/ct2/show/NCT01722487.
Accessed May 2, 2022

Up to 8 Years of Follow-up in RESONATE-2: OS and PFS



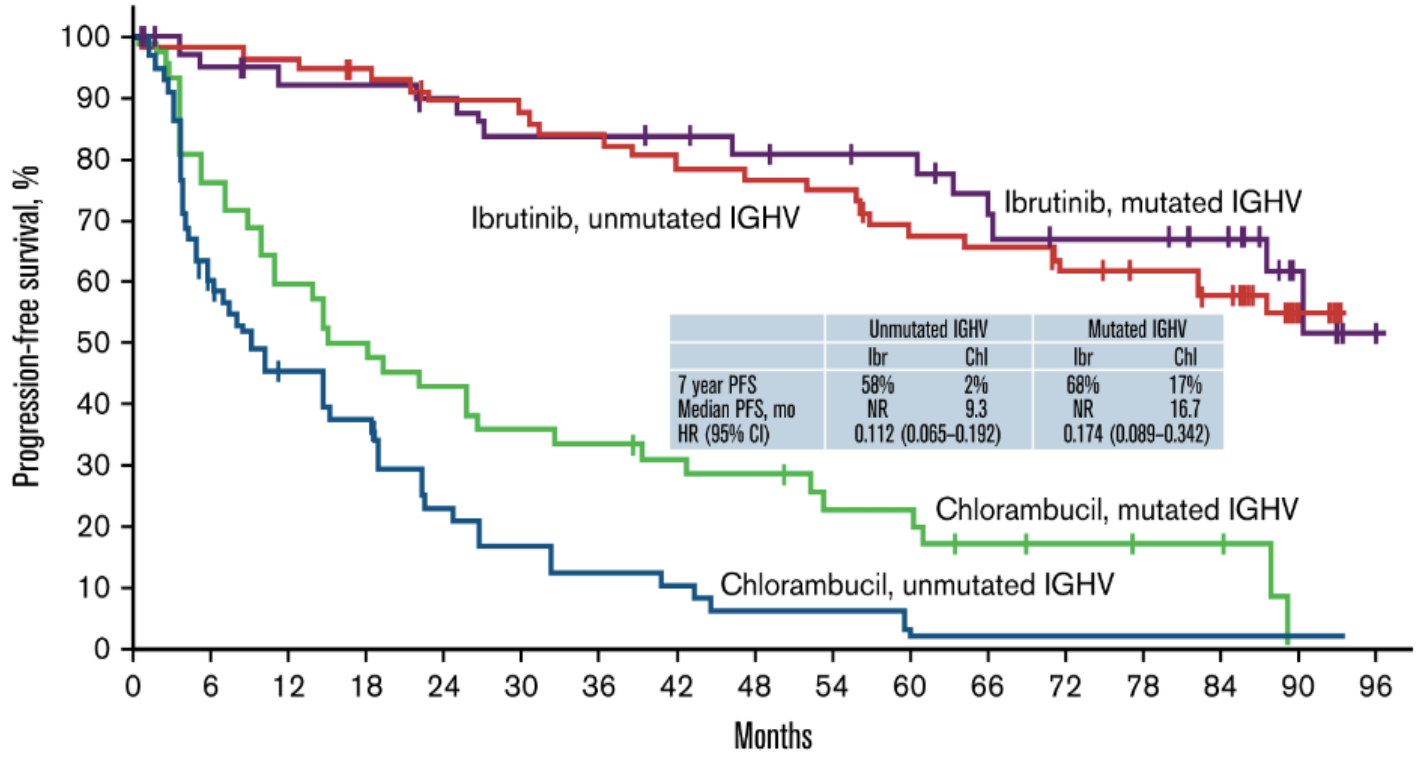


- **78%** taking Ibrutinib were estimated to be alive at 7 years
- **59%** taking Ibrutinib were estimated to be progression-free and alive at 7 years vs 9% of patients taking chlorambucil

Reference:

1. Barr PM, Owen C, Robak T, et al. Up to 8 years follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv*. 2022 Apr 4:bloodadvances.2021006434.doi:10.1182/bloodadvances.2021006434

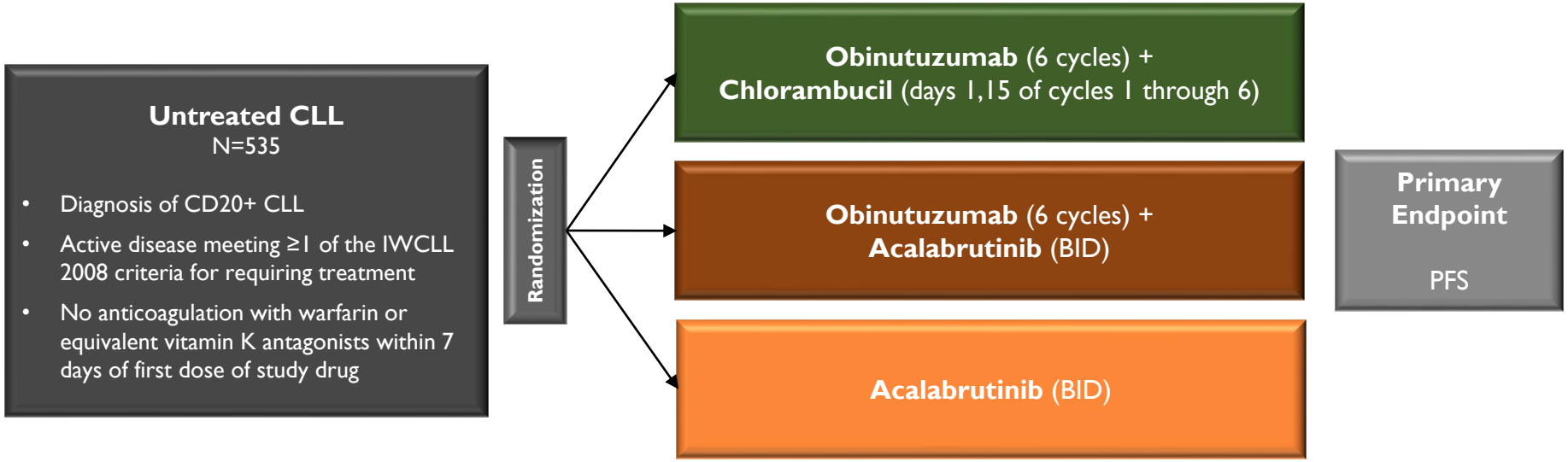
PFS by Mutation Status



Patients at risk																	
Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	22	19	19	16	6	1
Ibrutinib, unmutated IGHV:	58	57	56	53	49	48	46	43	42	41	36	35	32	30	27	10	0
Chlorambucil, mutated IGHV:	42	32	25	21	18	15	14	12	11	8	8	5	4	4	3	0	0
Chlorambucil, unmutated IGHV:	60	33	23	19	11	8	6	5	3	3	2	1	1	1	1	1	0

Barr PM, Owen C, Robak T et al Blood Adv 2022 April

ELEVATE TN: Obinutuzumab/Chlorambucil, Acalabrutinib/Obinutuzumab or Acalabrutinib in Frontline CLL (Phase III): 5 Year Follow-up

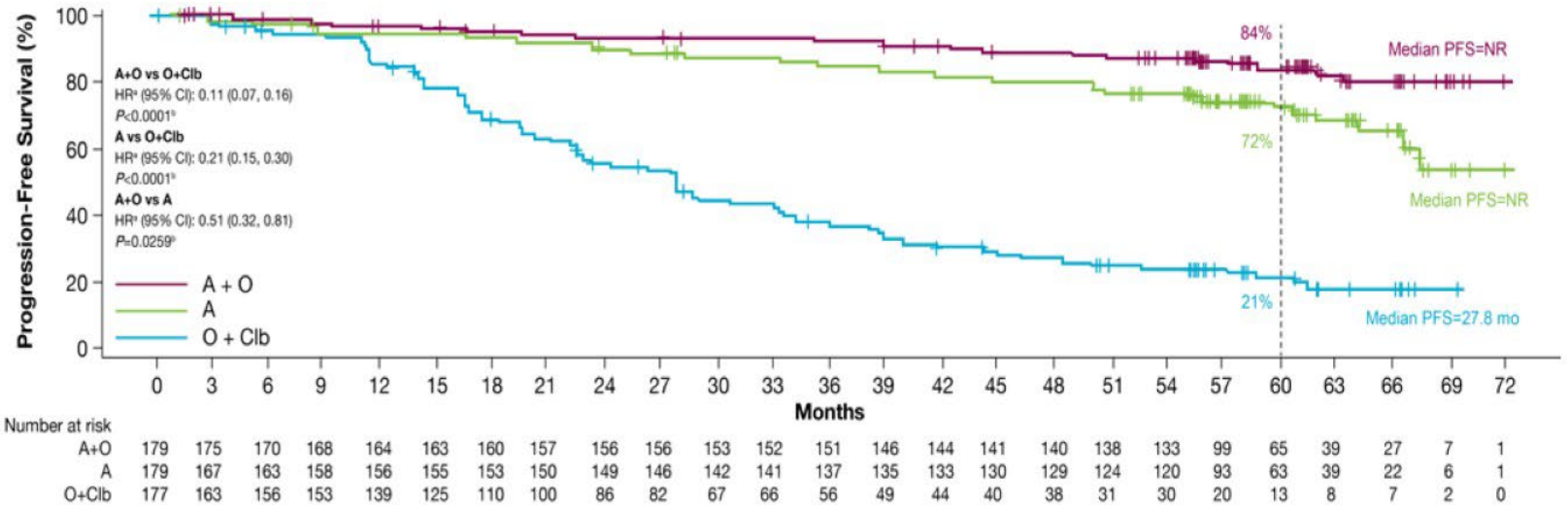


Sharman JP et al. ASCO 2022.

Investigator-assessed PFS

- Median PFS was significantly longer for acalabrutinib containing arms than obinutuzumab and chlorambucil
- At 60 months, estimated PFS rates were in favor of A+O (84%) and A (72%)

A. Investigator-assessed PFS



[a]Hazard ratio based on Cox proportional-hazard model stratified by 17p deletion status (yes vs no based on interactive voice/web response system). [b]P-value based on log-rank test stratified by 17p deletion status (yes vs no based on interactive voice/web response system).

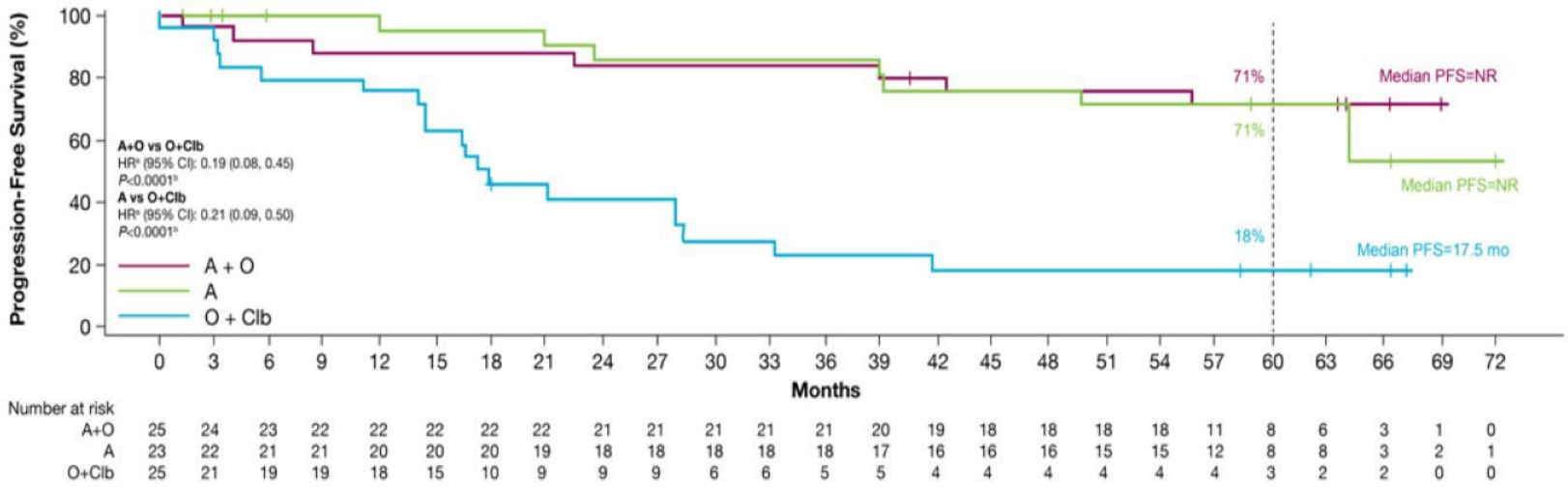
A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; NR = not reached; O = Obinutuzumab; PFS = progression free survival; vs = versus.

Sharman JP et al. Poster Presented at: ASCO; June 3-7, 2022; Chicago, Illinois.

Investigator-assessed PFS in Patients With Del(17p) and/or Mutated *TP53*

- PFS benefit was consistent in patients with del(17p) and/or mutated *TP53*

B. Investigator-assessed PFS in Patients With del(17p) and/or Mutated *TP53*



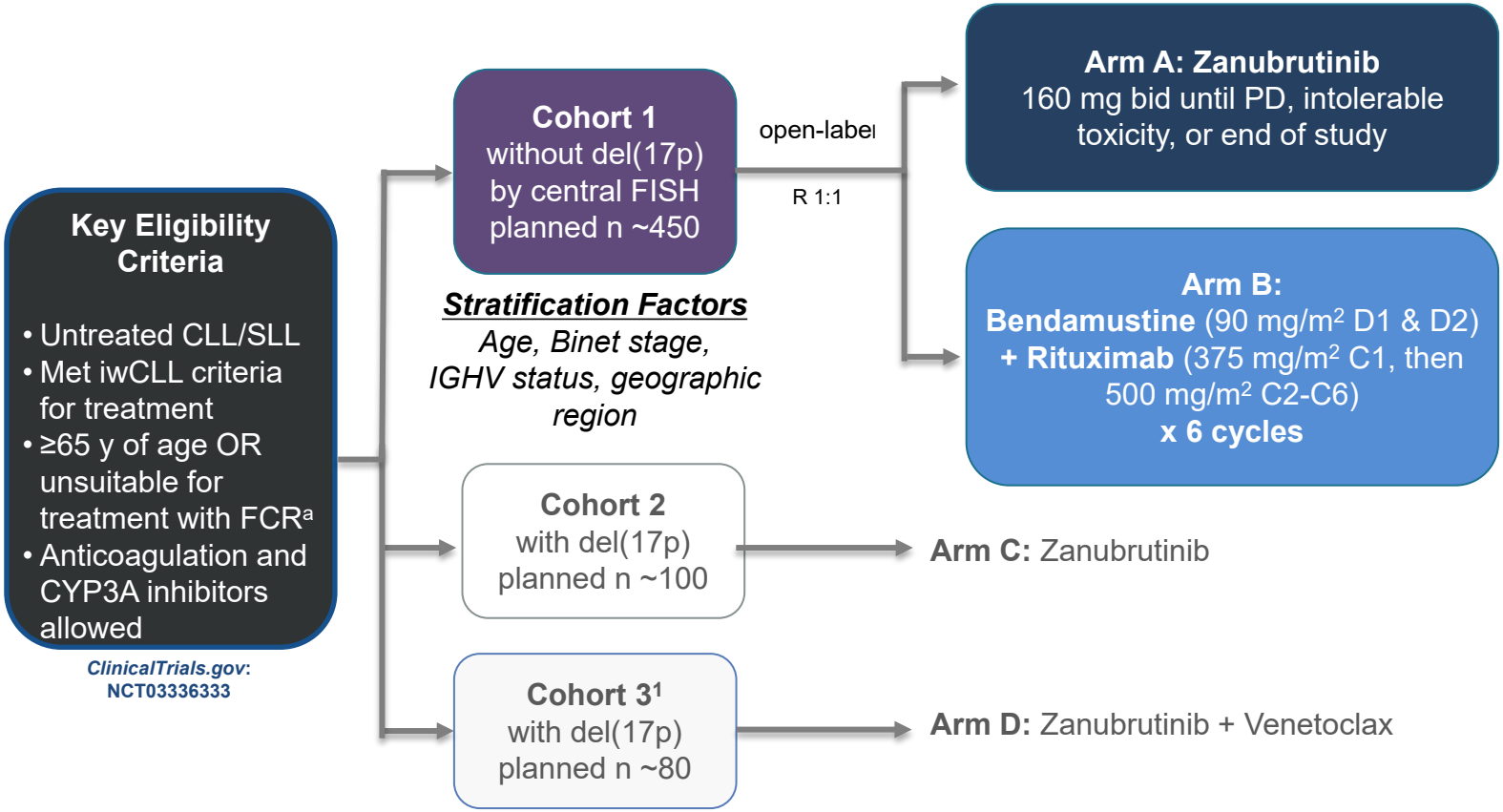
[a]Hazard ratio was based on unstratified Cox-Proportional-Hazards model; [b]P-value was based on unstratified log-rank test.

A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; NR = not reached; O = Obinutuzumab; PFS = progression free survival; *TP53* = tumour protein p53; vs = versus.

Sharman JP et al. Poster Presented at: ASCO; June 3-7, 2022; Chicago, Illinois.

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.

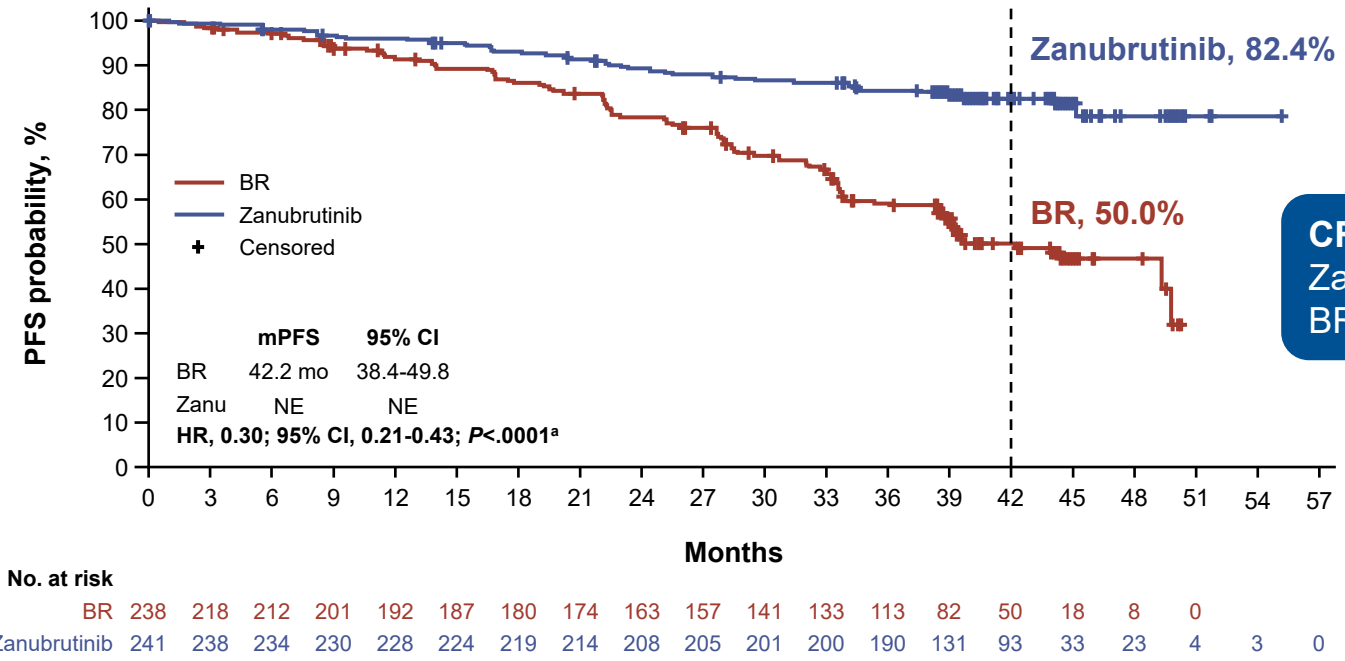
C, cycle; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CYP3A, cytochrome P450, family 3, subfamily A; D, day; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in-situ hybridization; IRC, independent review committee; IGHV, gene 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.

Tam et al Lancet Oncol 2022 Aug; 23(8): 1031-43

Cohort 1: PFS in Patients Without del(17p)

Median follow-up: 43.7 months



CR/CRi rates:
Zanubrutinib, 17.4%;
BR, 21.8%

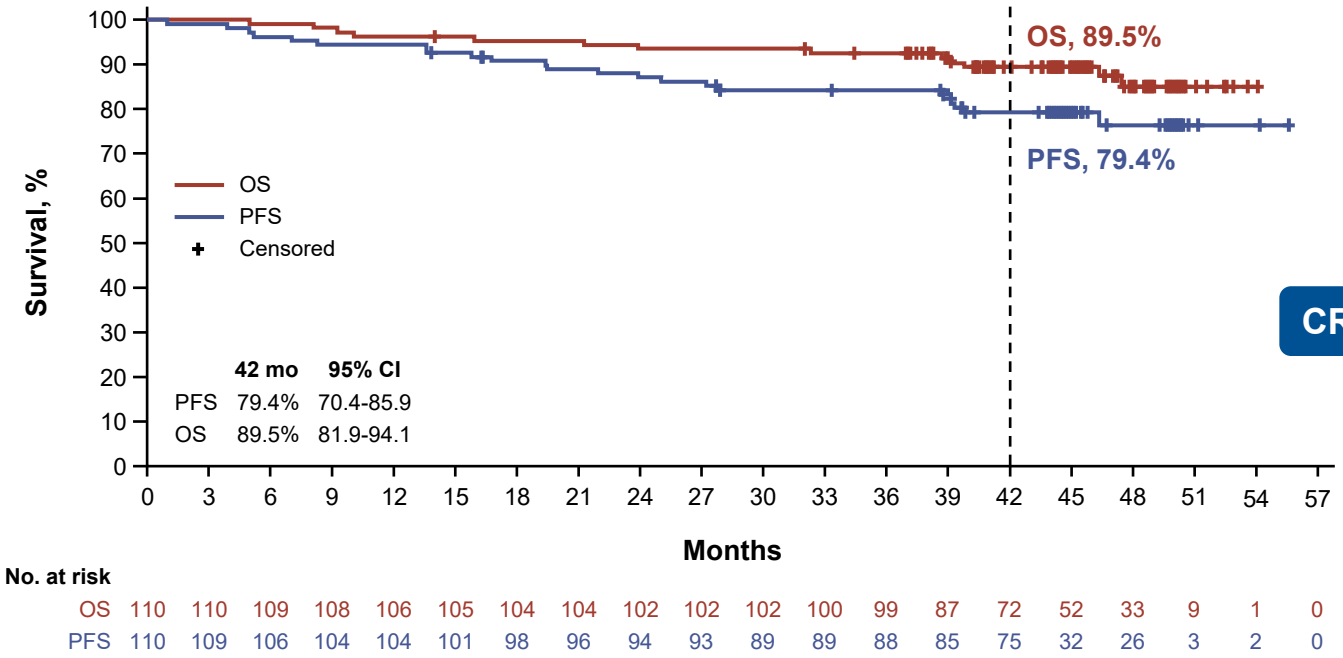
BR, bendamustine plus rituximab; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; del(17p), deletion in chromosome 17p; HR, hazard ratio; mPFS, median progression-free survival; NE, not evaluable; PFS, progression-free survival; zanu, zanubrutinib.

[a] Descriptive *P* value.

Shadman et al ICML 2023

Cohort 2: PFS and OS in Patients With del(17p)

Median follow-up: 47.9 months

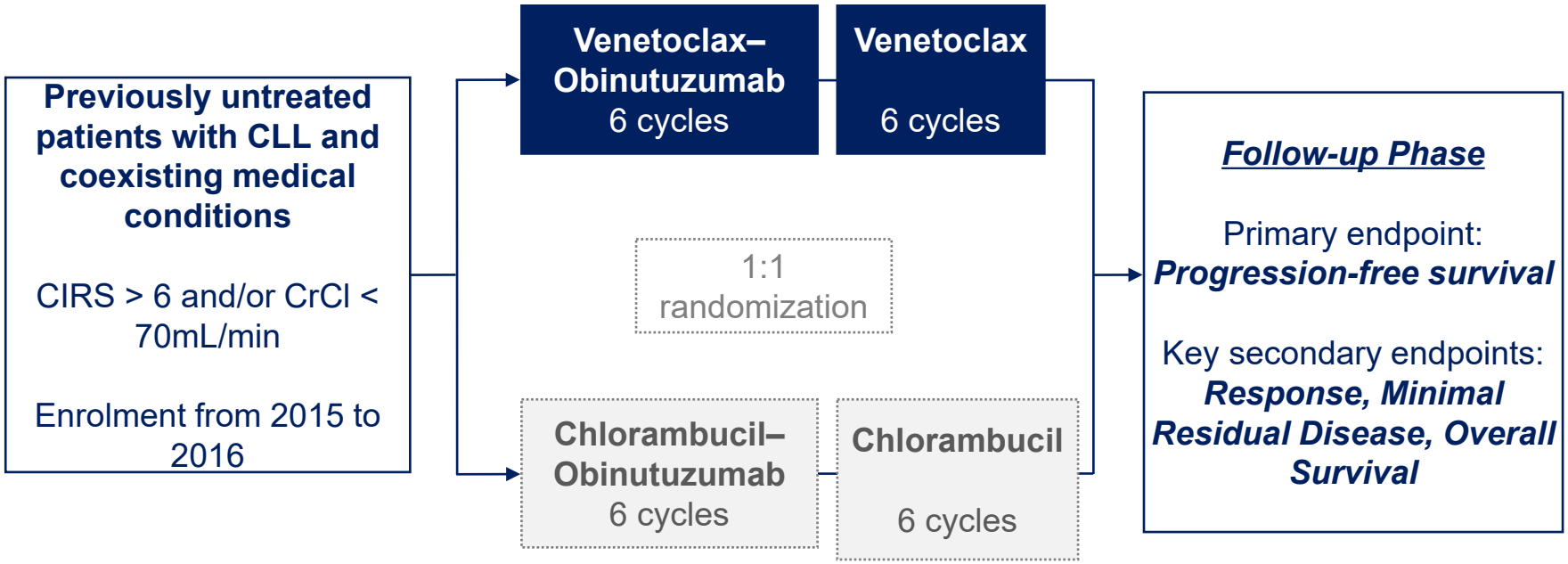


CR/CRi rate, 14.5%

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; del(17p), deletion in chromosome 17p; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Shadman et al IMCL 2023

CLL14 TRIAL DESIGN

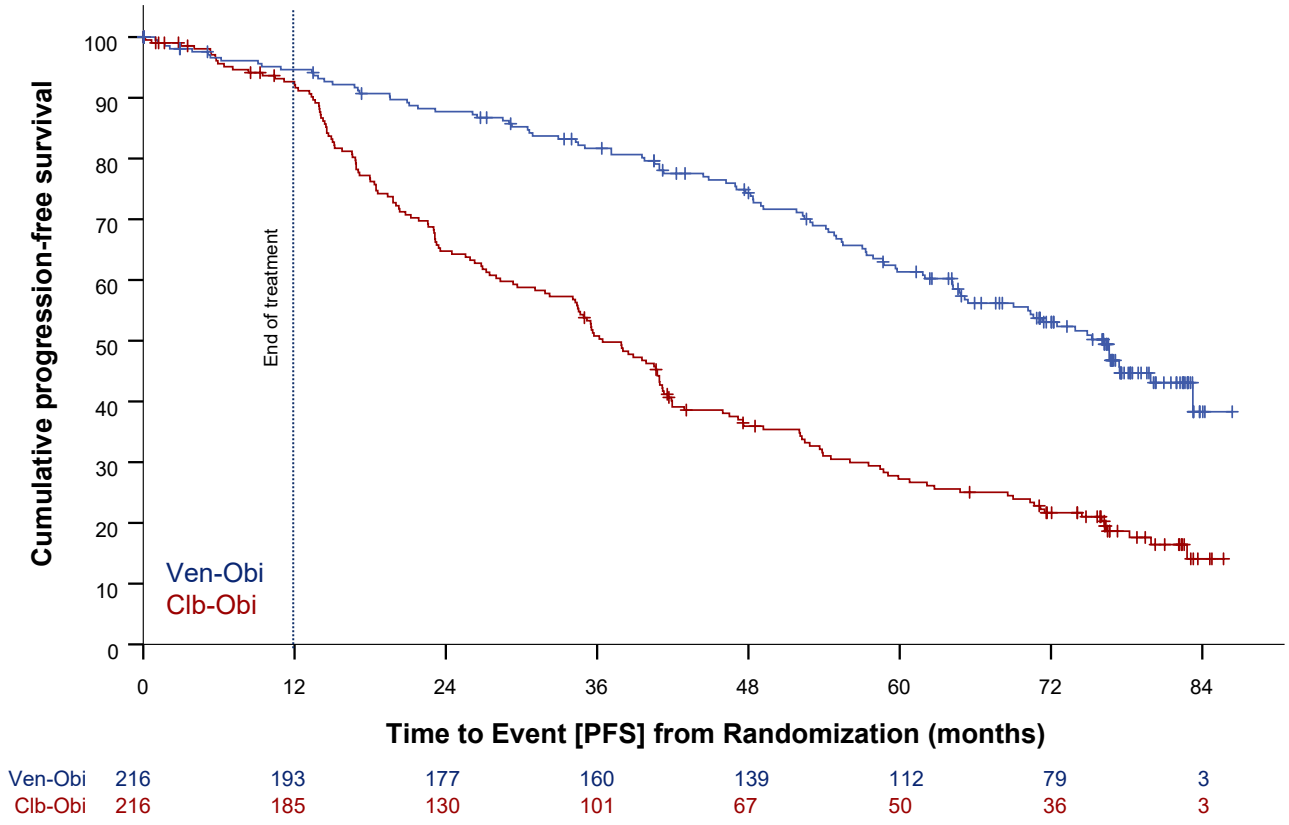


Current median observation time: 76.4 months

Al Sawaf et al EHA 2023

PROGRESSION-FREE SURVIVAL

Investigator-assessed PFS



Median PFS

Ven-Obi: 76.2 months

Clb-Obi: 36.4 months

6-year PFS rate

Ven-Obi: 53.1%

Clb-Obi: 21.7%

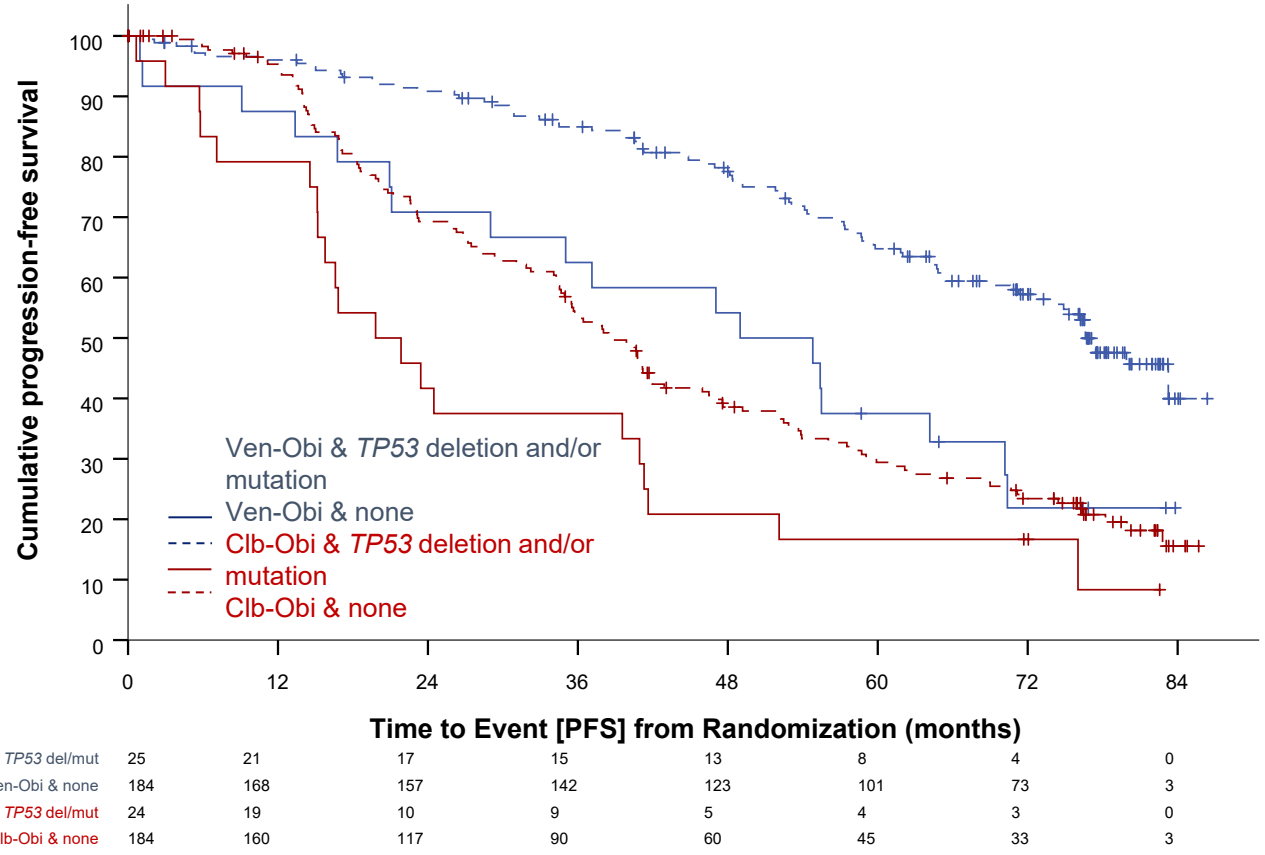
HR 0.40, 95% CI [0.31-0.52]

P<0.0001

Al Sawaf et al EHA 2023

PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 76.4 months



Ven-Obi & *TP53* del/mut	25	21	17	15	13	8	4	0
Ven-Obi & none	184	168	157	142	123	101	73	3
Clb-Obi & *TP53* del/mut	24	19	10	9	5	4	3	0
Clb-Obi & none	184	160	117	90	60	45	33	3

Median PFS

Ven-Obi & no *TP53*del/mut: 76.6 m

Ven-Obi & *TP53*del/mut: 51.9 m

HR 2.29, 95% CI [1.37-3.83], p=0.001

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

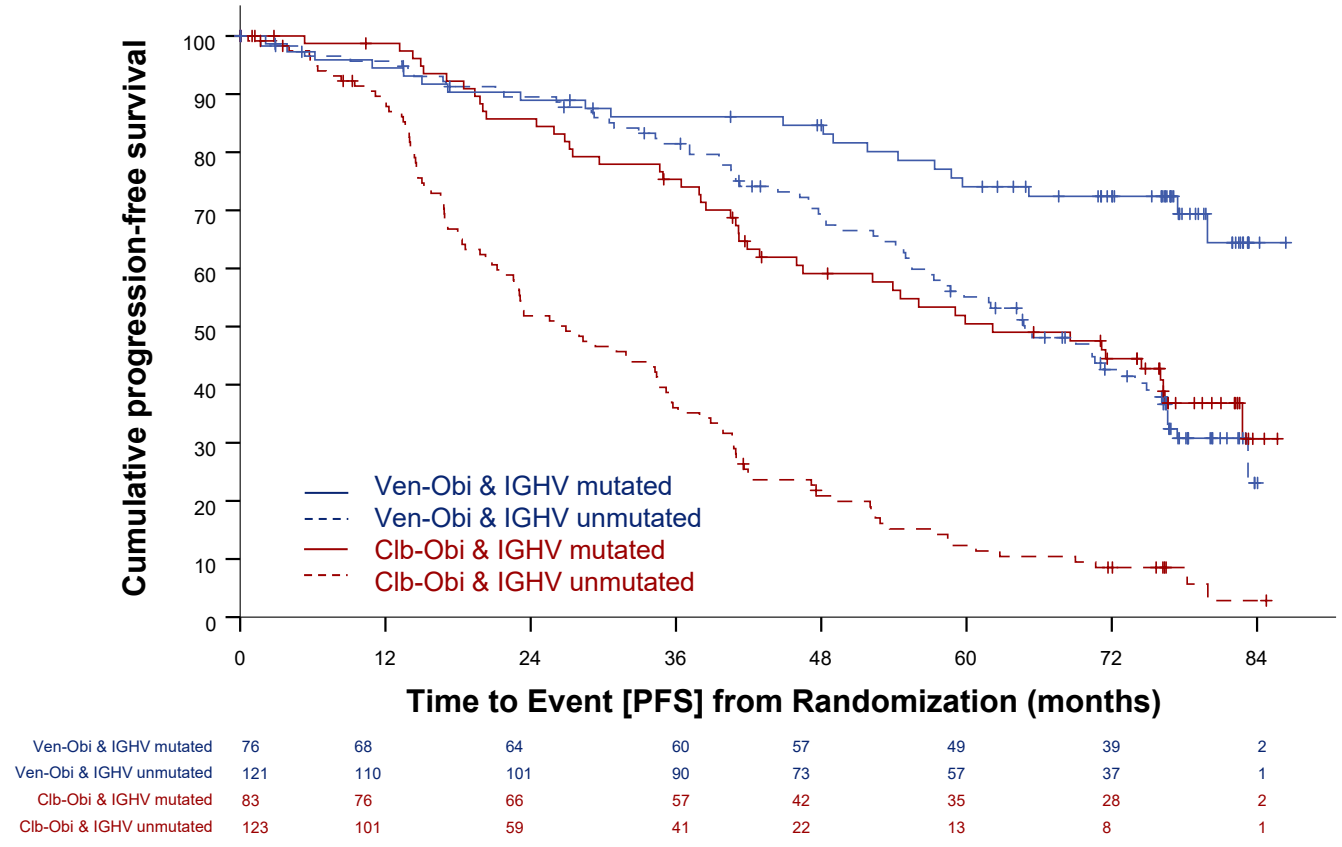
Clb-Obi & *TP53*del/mut: 20.8 m

HR 1.66, 95% CI [1.05-2.63], p=0.03

Al Sawaf et al EHA 2023

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

HR 0.38, 95%CI [0.23-0.61], p<0.001

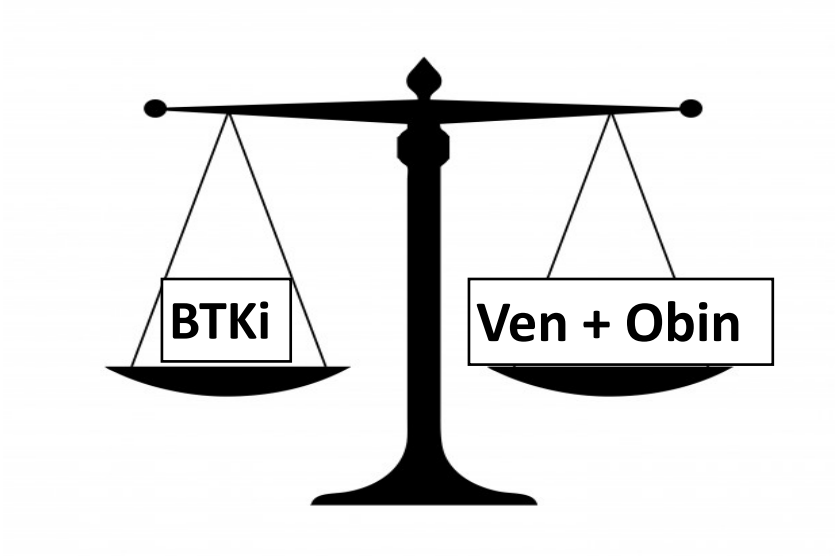
Clb-Obi & IGHVmut: 62.2 m

Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

Al Sawaf et al EHA 2023

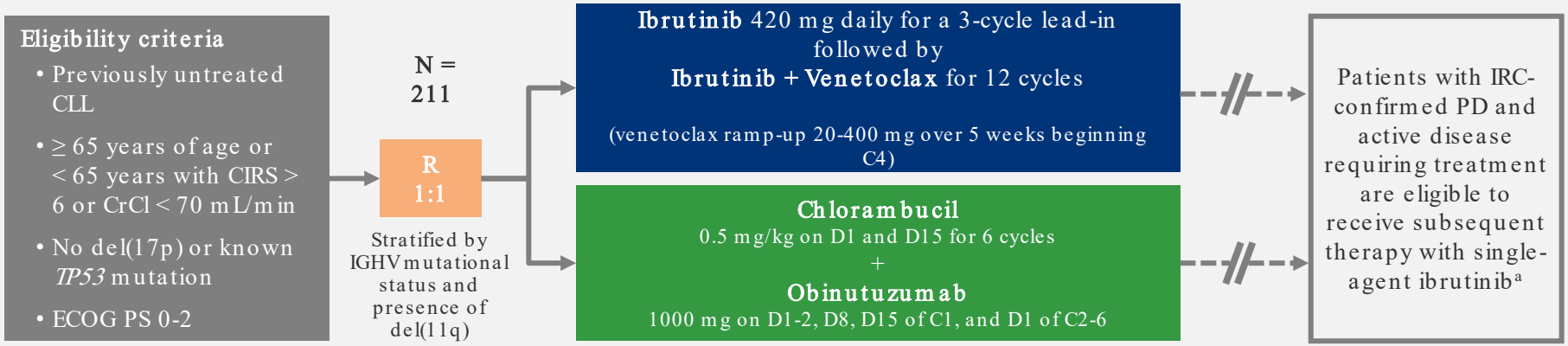
Frontline BTKi vs. Ven + Obinutuzumab: Factors to Consider



- Convenience (no infusions, TLS monitoring)
- Long term efficacy data
- Phase 3 data compared to FCR and BR
- More data for efficacy of ven at time of ibrutinib progression

- Potential for 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long term adherence
- Potential for cost-saving if 1-year of therapy is durable

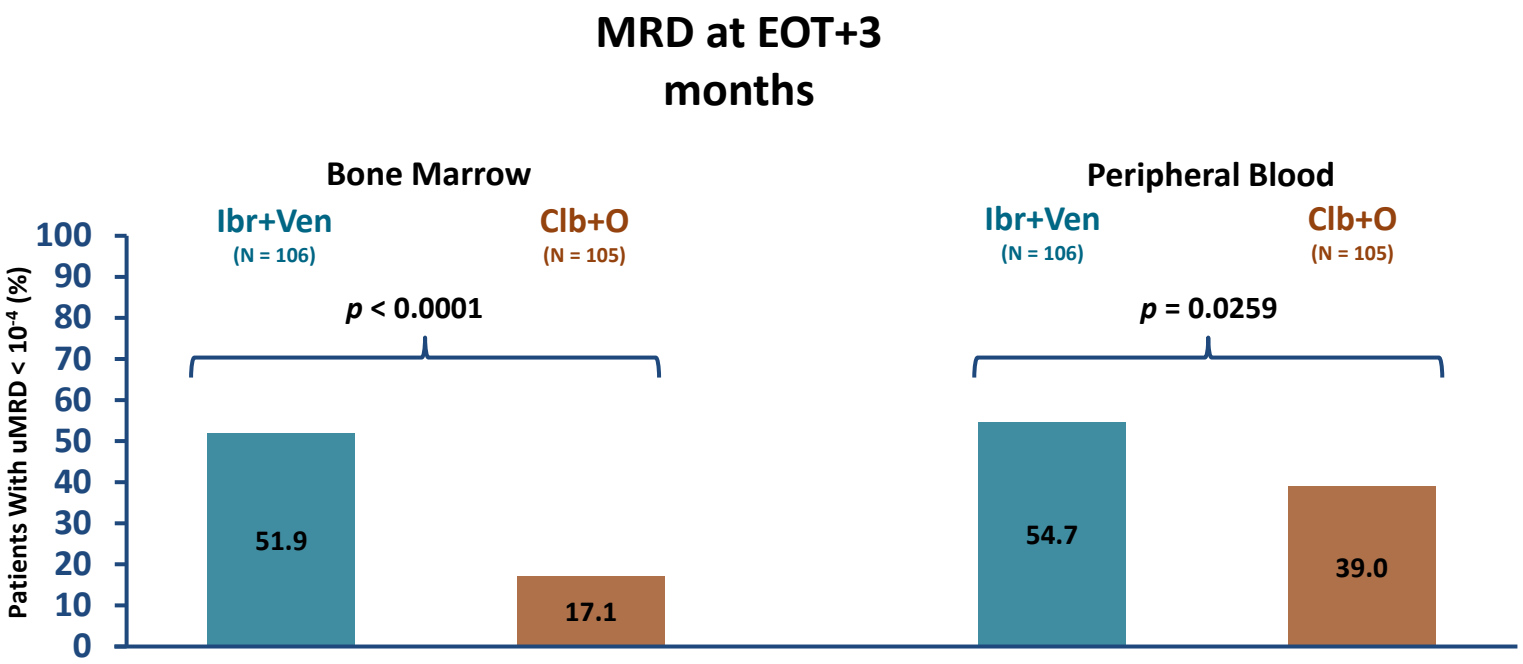
Phase 3 GLOW Study (NCT03462719)



- **Primary end point: IRC-assessed PFS**
- Key secondary end points: uMRD rates, response rates, overall survival, time to next treatment, and safety
- Current analysis
  - Median study follow-up of 46 months (range, 1.7-51.7)
  - MRD assessed in peripheral blood in responders by NGS

CU Niemann et al ASH 2022

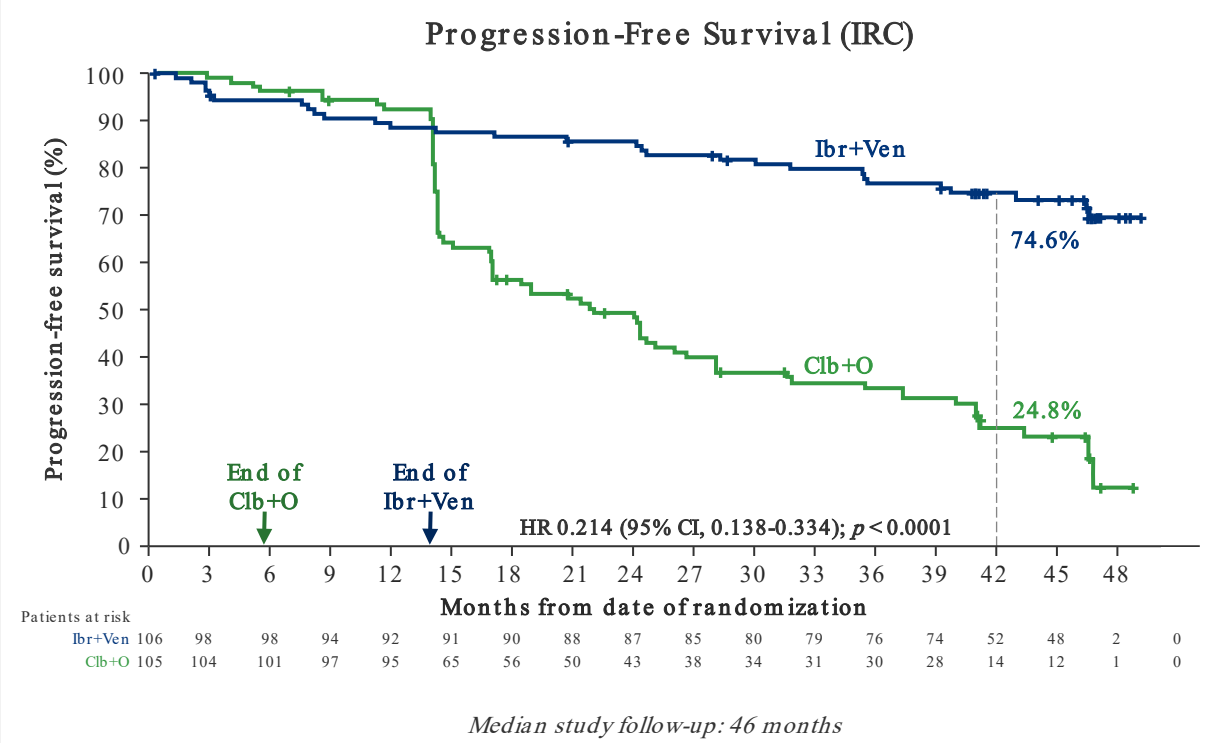
uMRD Rate < 10^{-4} Was Significantly Higher in Both Compartments With Ibr+Ven



- Rate of uMRD was significantly higher with Ibr+Ven vs Clb+O in BM and PB
- uMRD concordance in PB/BM: **92.9%** for Ibr+Ven vs **43.6%** for Clb+O

MRD results by next-generation sequencing at EOT+3.
BM, bone marrow; EOT, end of treatment; PB, peripheral blood.

GLOW: Progression-Free Survival by IRC Remained Superior For Ibr+Ven Versus Clb+O With 4 Years of Study Follow-up



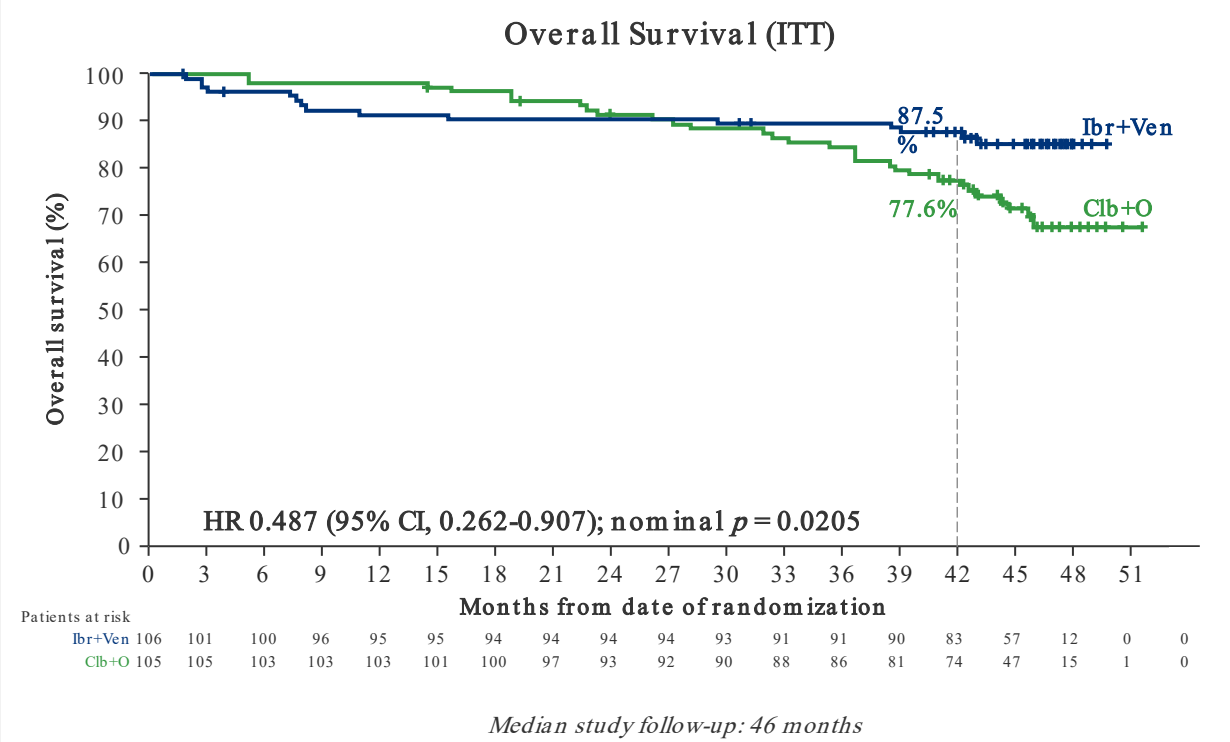
Median study follow-up: 46 months

- **Ibr+Ven reduced the risk of progression or death by 79%** versus Clb+O
  - HR 0.214 (95% CI, 0.138-0.334); $p < 0.0001$
- Estimated 3.5-year PFS rates:
  - **74.6%** for Ibr+Ven
  - **24.8%** for Clb+O

IRC, independent review committee; CI, confidence interval; HR, hazard ratio.

CU Niemann et al ASH 2022

GLOW: Ibr+Ven Improved Overall Survival Versus Clb+O With 4 Years of Study Follow-up



Median study follow-up: 46 months

- In the Clb+O arm, 39/41 patients requiring subsequent treatment received a BTKi or venetoclax
- The majority of deaths in the Clb+O arm occurred while off any treatment
- More infection-related deaths were seen in the Clb+O arm

Causes of Death

n (%)	Ibr+Ven (N = 106)	Clb+O (N = 105)
PD	1 (0.9)	2 (1.9)
Infections	4 (3.8)	11 (10.5)
Other[a]	10 (9.4)	17 (16.2)
TOTAL	15 (14.2)	30 (28.6)

CU Niemann et al ASH 2022

[a]Cause and number (Ibr+Ven arm, Clb+O arm) of "other" deaths: general/unknown (4, 5), cardiac (2, 4), central nervous system (2, 3), neoplasm (1, 3), euthanasia (1, 0), hepatobiliary (0, 1), respiratory (0, 1).
ITT, intent to treat; BTKi, Bruton's tyrosine kinase inhibitor; PD, progressive disease; HR hazard ratio; CI, confidence interval.

Where are we heading in 1L CLL?

Ongoing phase 3 trials:

- CLL13/GAIA: FCR/BR vs. VR, vs. VO, vs. IVO (n=920)
- UK NCRI FLAIR: FCR vs. I vs. IV (vs. IR) (n=1,522)
- Alliance A041702: IO vs. IVO (older pts, n=454)
- ECOG EA9161: IO vs. IVO (younger pts, n=720)
- ACE-CL-311: FCR/BR vs AV vs AVO (n=780)
- CLL GLOW: IV vs. Chl/O (n=200)
- MAJIK: AV vs VO (n=600)

Near future:

- CLL17: I vs. IV vs. VO (n=882)

Which BTK Inhibitor?

ELEVATE-RR: Phase 3 Randomized Non-inferiority Open-Label Trial Comparing Ibrutinib to Acalabrutinib in High Risk R/R Patients

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]

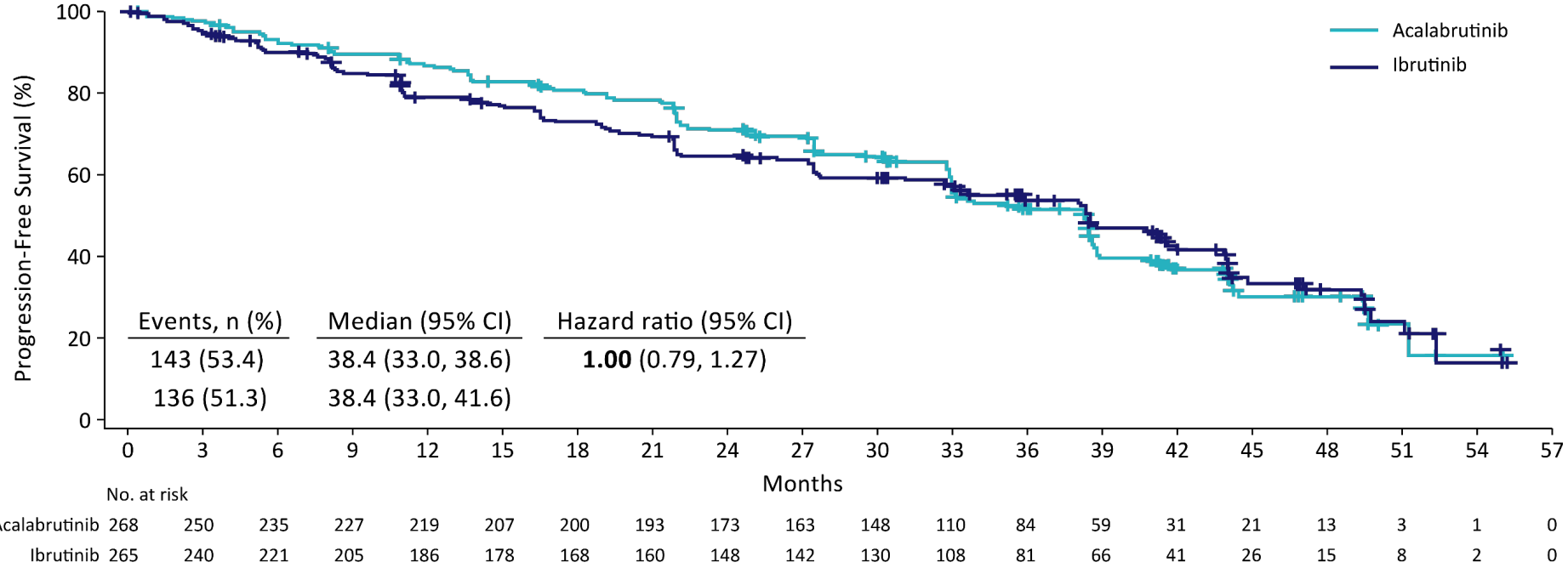
Secondary endpoints (hierarchical order):

- 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; 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.

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.

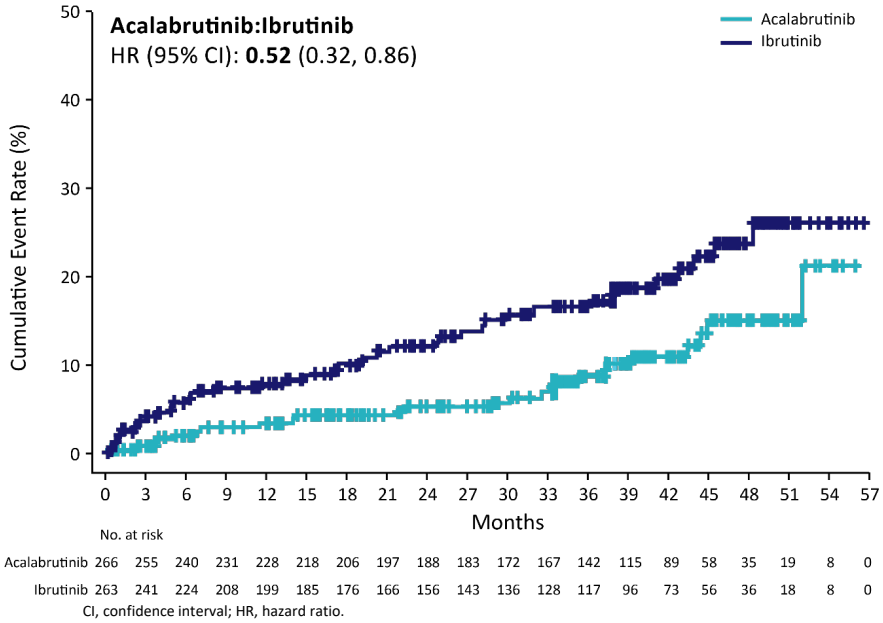
Events of Clinical Interest

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold red** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.
[c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies; UTI, urinary tract infection.

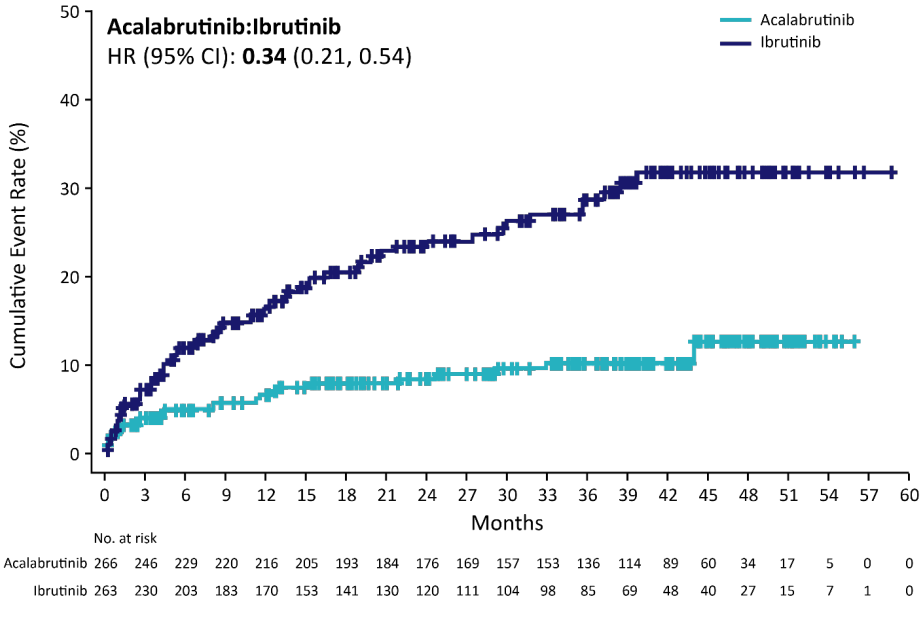
Lower Cumulative Incidences of Any Grade Atrial Fibrillation/Flutter and Hypertension With Acalabrutinib

Afib/Flutter



CI, confidence interval; HR, hazard ratio.

Hypertension



Byrd et al J Clin Oncol 2021 Nov 1;39(31):3441-3452.

ALPINE Study Design

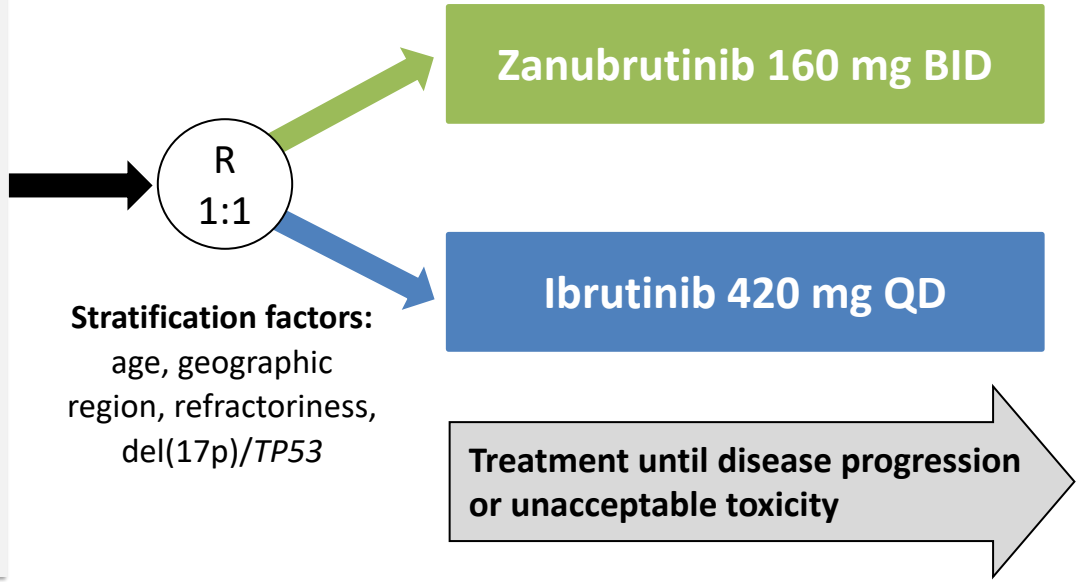
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

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

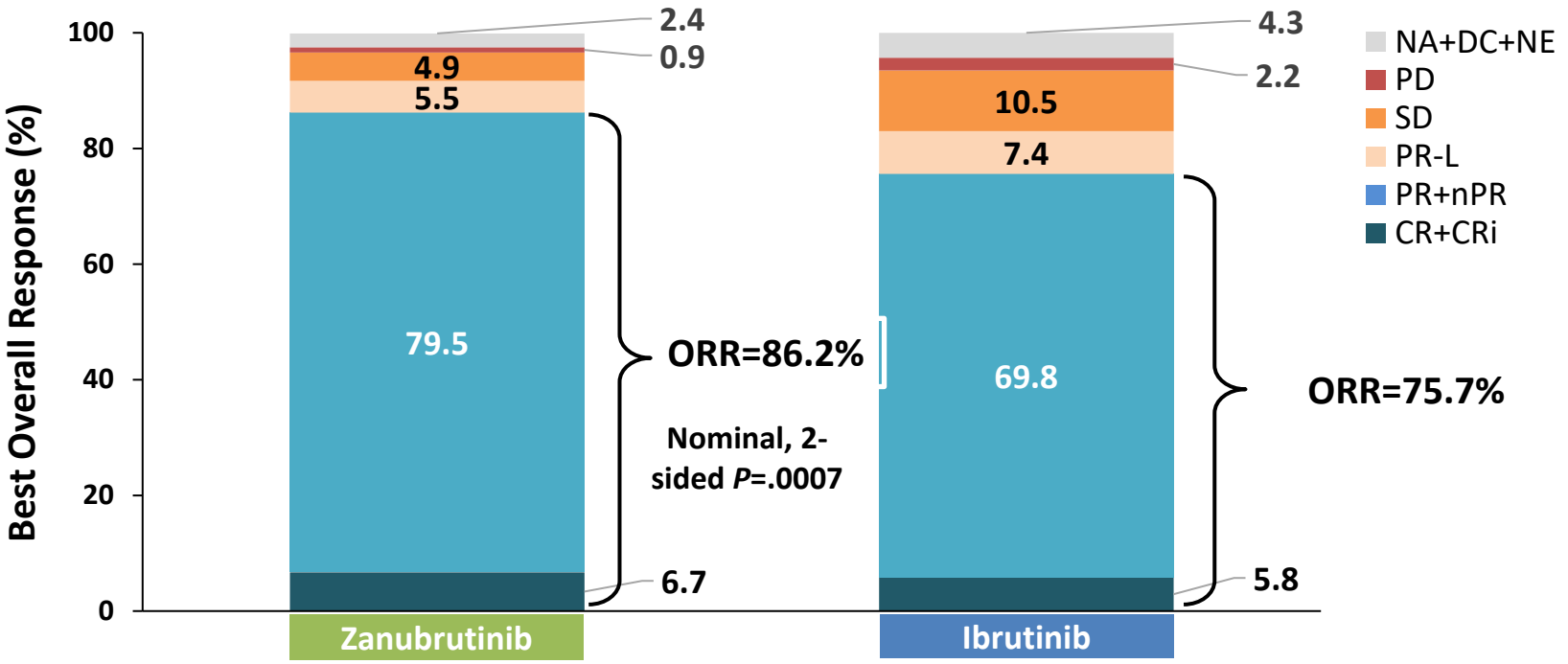
Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



JR Brown et al N Engl J Med. 2023 Jan 26;388(4):319-332

Zanubrutinib Showed Higher ORR Assessed by IRC



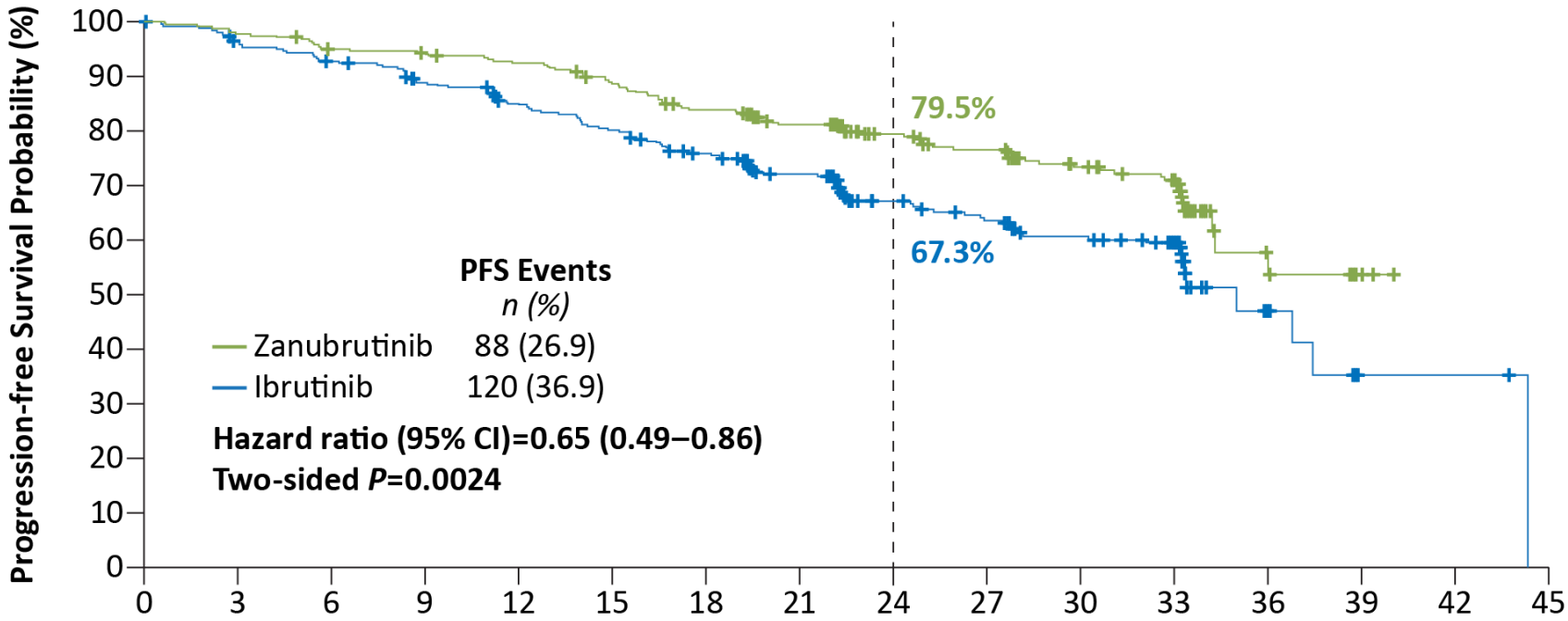
CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Data cutoff: 8 Aug 2022

JR Brown et al N Engl J Med. 2023 Jan 26;388(4):319-332

Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



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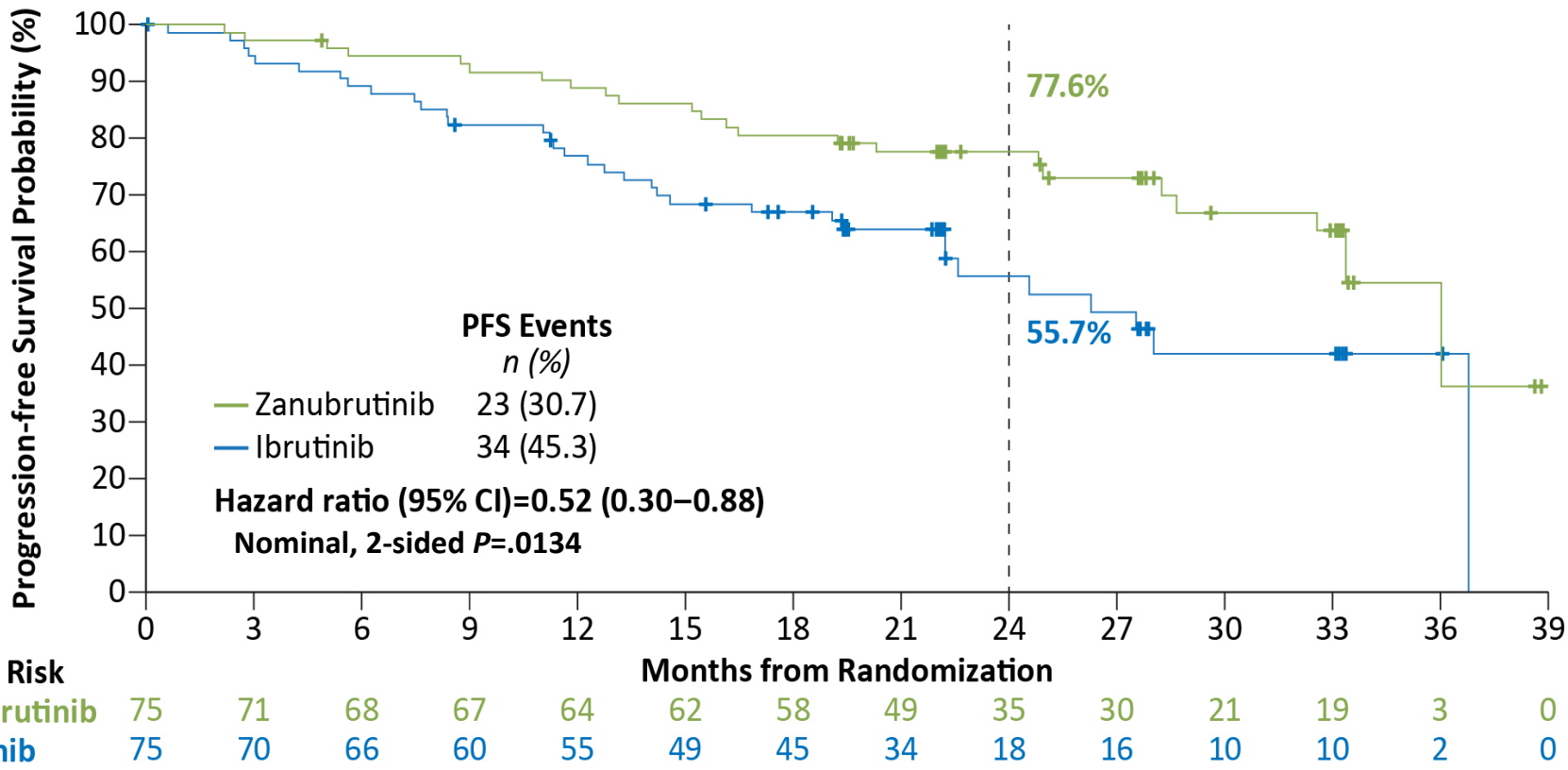
Data cutoff: 8 Aug 2022

Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}



No. at Risk														
Zanubrutinib	75	71	68	67	64	62	58	49	35	30	21	19	3	0
Ibrutinib	75	70	66	60	55	49	45	34	18	16	10	10	2	0

PFS data assessed by IRC

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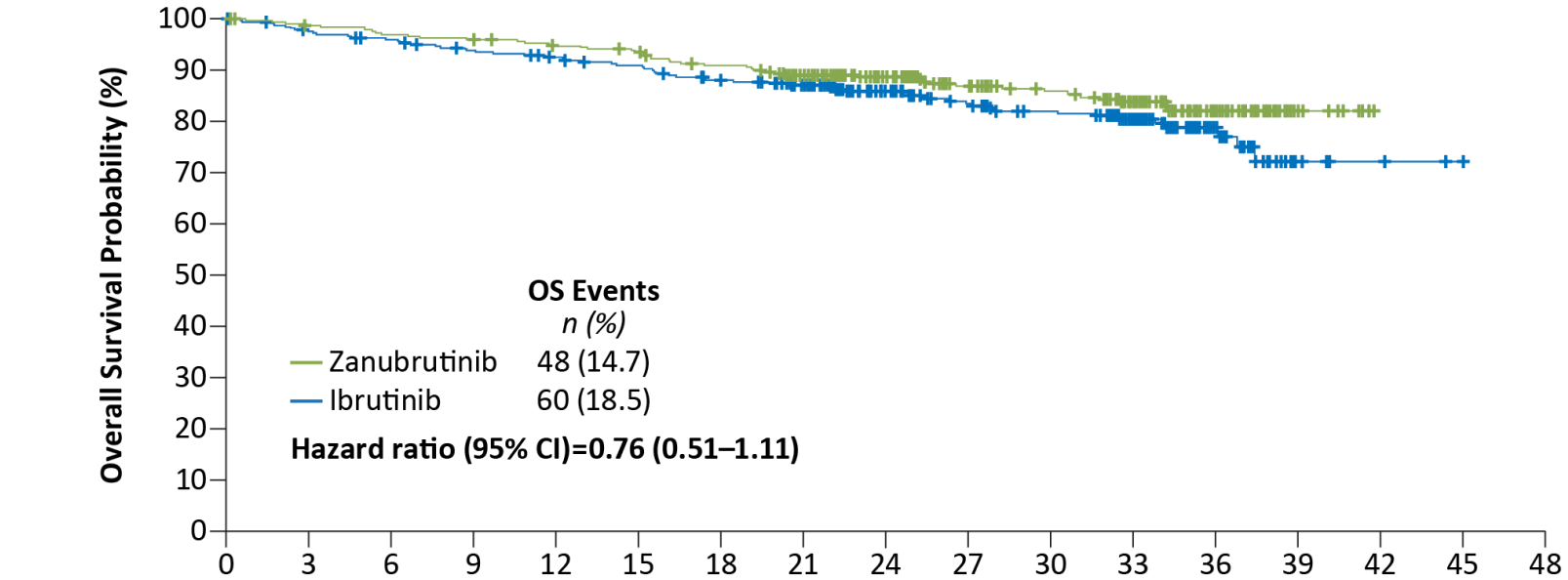
Data cutoff: 8 Aug 2022

Overall Survival

Fewer deaths with zanubrutinib compared with ibrutinib

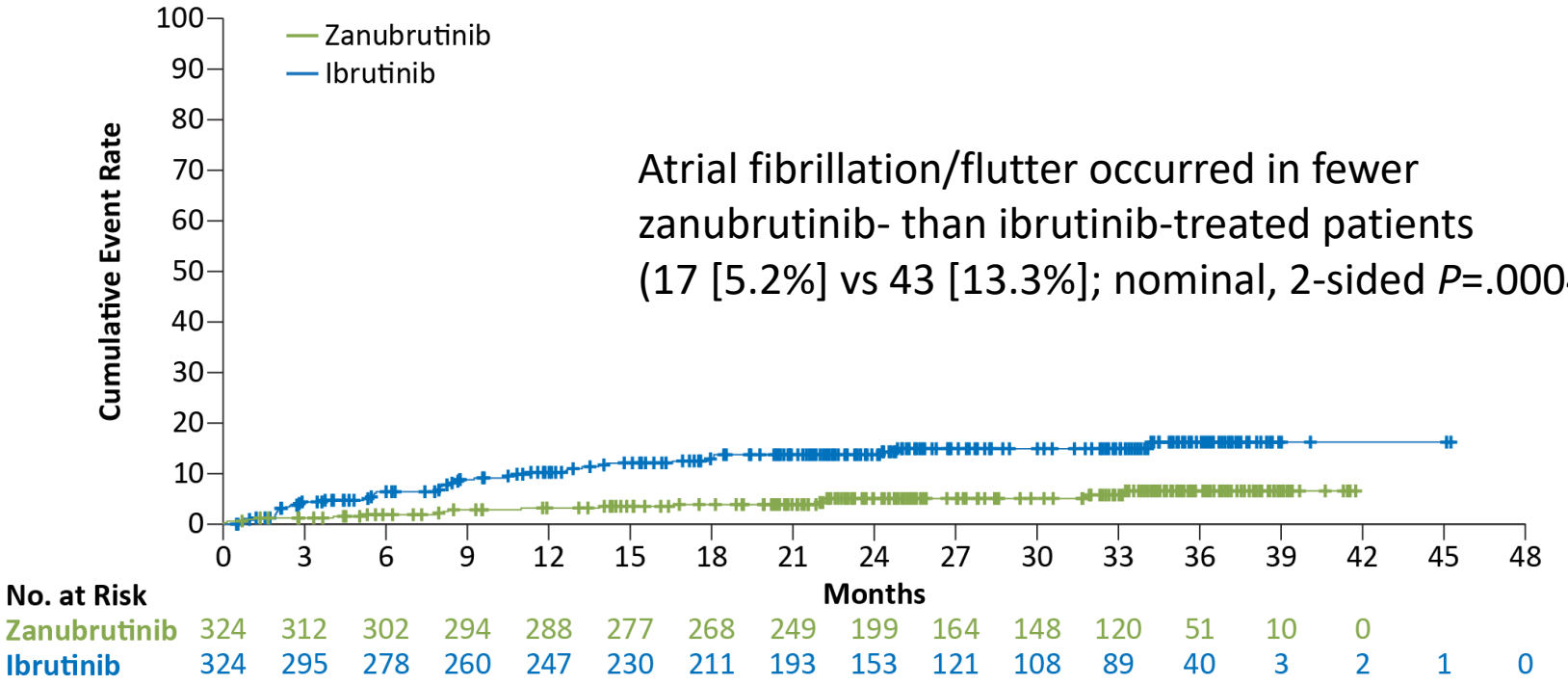


No. at Risk																	
Zanubrutinib	327	319	313	310	303	298	287	268	224	185	169	134	56	8	0		
Ibrutinib	325	314	307	297	290	283	271	255	200	171	156	124	50	7	3	1	0

Data cutoff: 8 Aug 2022

JR Brown N Engl J Med. 2023 Jan 26;388(4):319-332

Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib

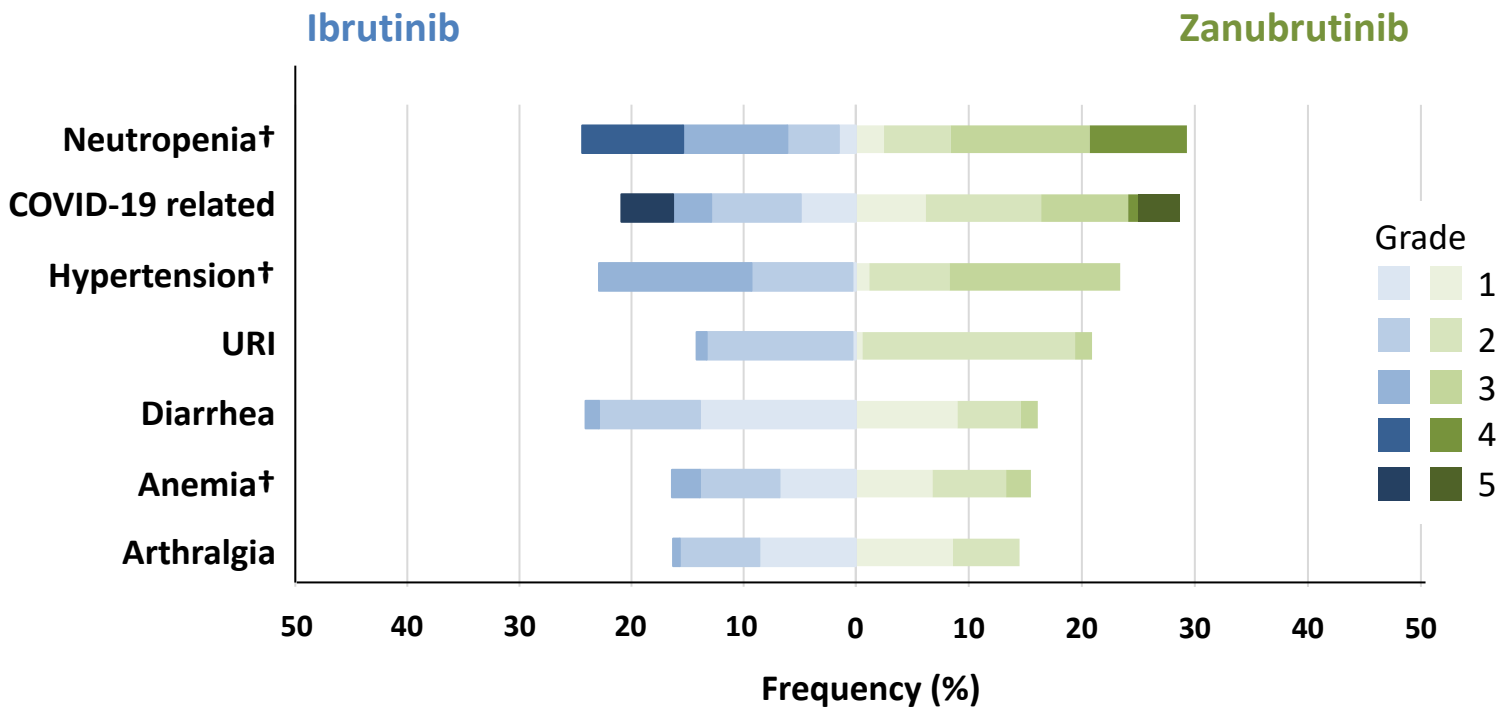


Atrial fibrillation/flutter occurred in fewer zanubrutinib- than ibrutinib-treated patients (17 [5.2%] vs 43 [13.3%]; nominal, 2-sided *P*=.0004)

Data cutoff: 8 Aug 2022

JR Brown N Engl J Med. 2023 Jan 26;388(4):319-332

Most Common Adverse Events*



Data cutoff: 8 Aug 2022

*Adverse events occurring in ≥15% of patients in either arm.
†Pooled terms.

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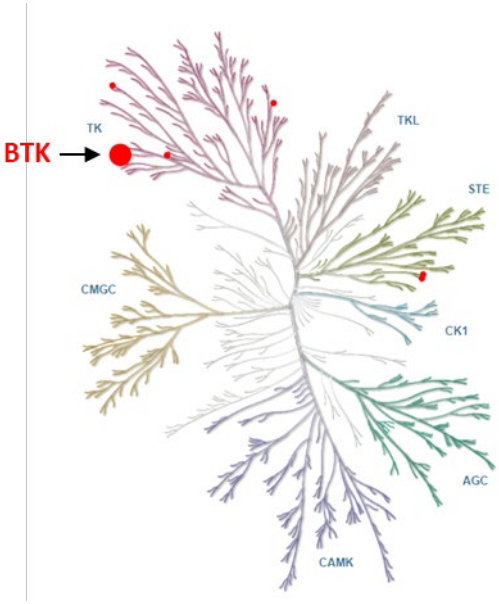
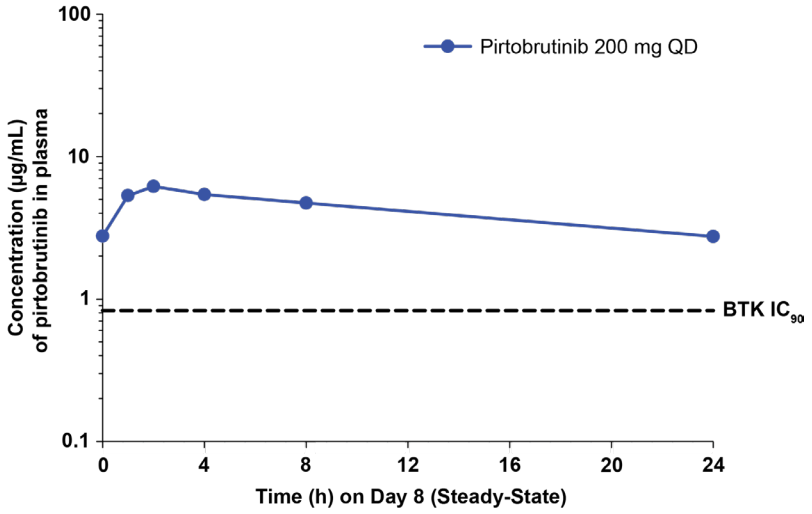
Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

Highly Selective for BTK[6,7]



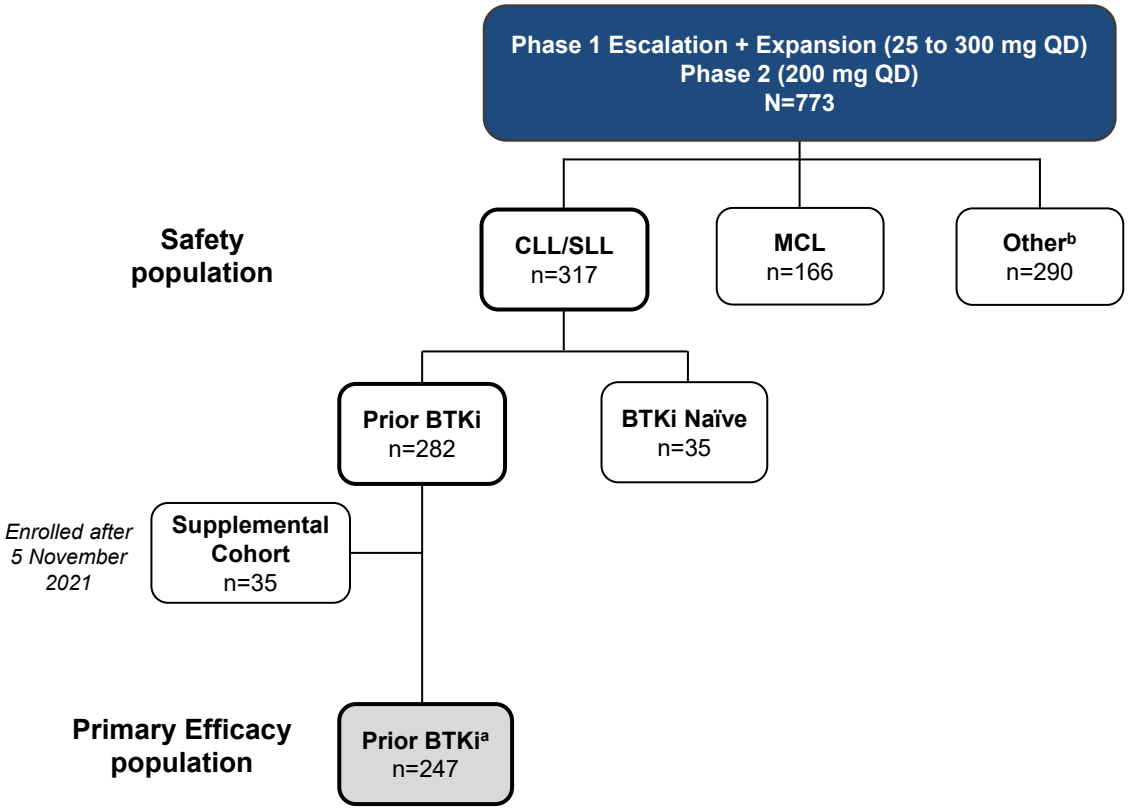
Plasma Exposures Exceeded BTK IC_{90} Throughout Dosing Interval



- Inhibits both wildtype and C481-mutant BTK with equal low nM potency, and has favorable oral pharmacology that enables continuous BTK inhibition throughout the dosing interval regardless of intrinsic rate of BTK turnover
- Pirtobrutinib is well tolerated and demonstrates promising efficacy in poor-prognosis B-cell malignancy patients following prior therapy, including prior cBTKi[1]

cBTKi, covalent Bruton tyrosine kinase inhibitor. [6]Mato et al, *Lancet*, 2021:397:892-901. [7]Brandhuber et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DOR (iwCLL) as assessed by IRC

Primary efficacy population[a]

- Enrolled in phase 1 or 2
- Treated with prior BTK inhibitor containing regimen
- Received one or more doses of pirtobrutinib monotherapy

DOR, duration of response: ORR, overall response rate; ECOG PS, Eastern Cooperative Oncology Group Performance Score; MTD, maximum tolerated dose; IRC, independent review committee; QD, daily;
Data cutoff date of 29 July 2022. [a]To ensure adequate follow-up, the primary efficacy population included all CLL/SLL patients who enrolled prior to 5 November 2021. [b]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

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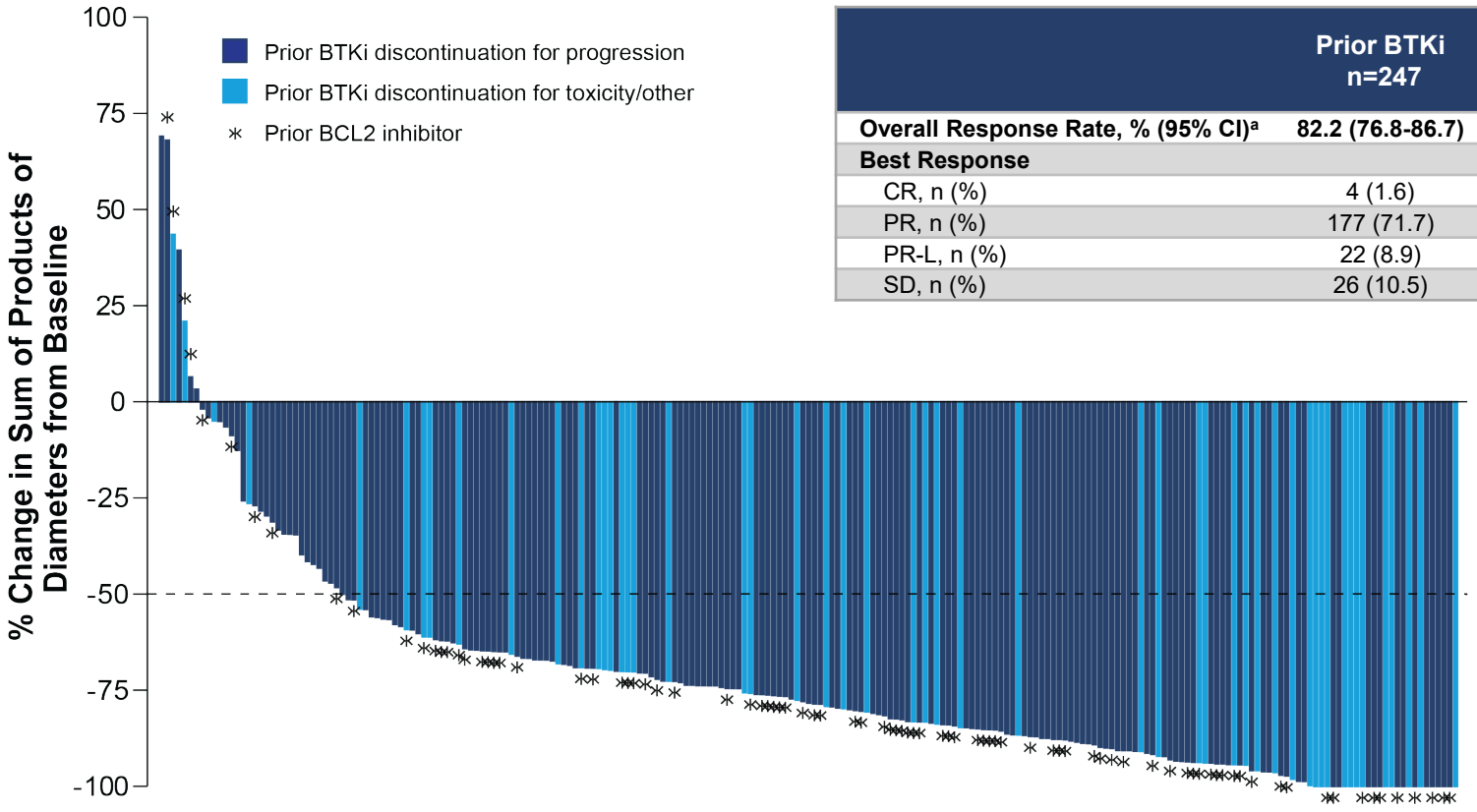
CLL/SLL Patient Characteristics

Characteristics	n=247
Median age, years (range)	69 (36-88)
Male, n (%)	168 (68)
Histology	
CLL	246 (>99)
SLL	1 (<1)
Rai staging[a]	
0-II	131 (53)
III-IV	102 (41)
Bulky Disease ≥5 cm, n (%)	78 (32)
ECOG PS, n (%)	
0	133 (54)
1	97 (39)
2	17 (7)
Median number of prior lines of systemic therapy, n (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	247 (100)
Anti-CD20 antibody	217 (88)
Chemotherapy	195 (79)
BCL2 inhibitor	100 (41)
PI3K inhibitor	45 (18)
CAR-T	14 (6)
Allogeneic stem cell transplant	6 (2)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)

Baseline Molecular Characteristics[b]	
Mutation status, n/n available (%)	
BTK C481-mutant	84/222 (38)
BTK C481-wildtype	138/222 (62)
PLCG2-mutant	18/222 (8)
PLCG2-wildtype	204/222 (92)
High Risk Molecular Features, n/n available (%)	51/176 (29)
17p deletion	87/222 (39)
TP53 mutation	90/193 (47)
17p deletion and/or *TP53* mutation	48/170 (28)
Both 17p deletion and *TP53* mutation	168/198 (85)
IGHV unmutated	24/57 (42)
Complex Karyotype	44/176 (25)
11q deletion	
Reason for prior BTKi discontinuation[c], n (%)	
Progressive disease	190 (77)
Toxicity/Other	57 (23)

ECOG PS, Eastern Cooperative Oncology Group Performance Score; Data cutoff date of 29 July 2022. [a]14 patients had missing data for Rai staging data. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control. [c]In the event more than one reason was noted for discontinuation, disease progression took priority.

Pirtobrutinib Efficacy in CLL/SLL Patients who Received Prior BTKi Treatment



	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Data cutoff date of 29 July 2022. Data for 24 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

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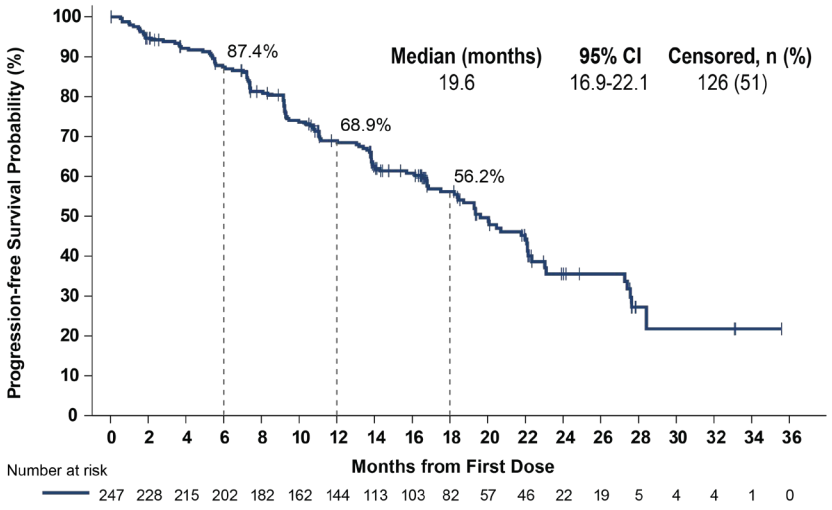
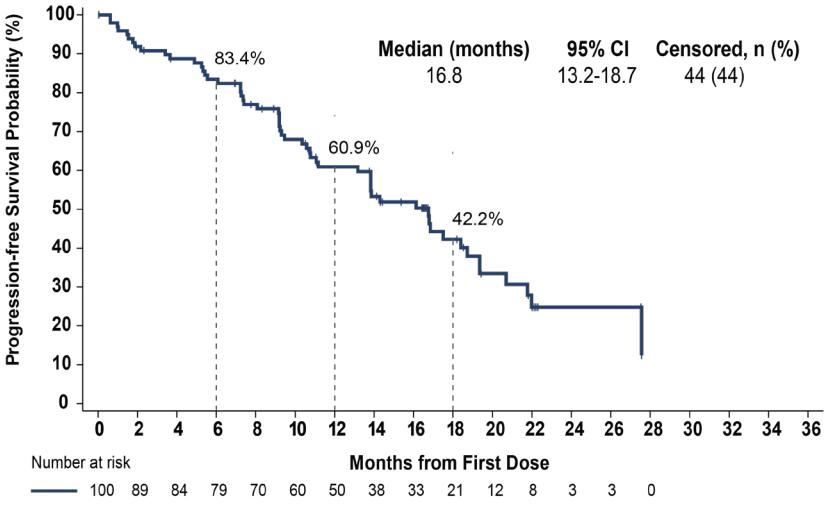
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

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Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and CLL/SLL safety profiles are consistent[h]

Data cutoff date of 29 July 2022.. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]CLL/SLL safety population data can be found via QR code.

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CONCLUSIONS

- BTKi produce long remissions with continuous therapy
- Ven/Obinutuzumab is finite 1 year therapy with high rates of uMRD
- Small molecule combinations result in high rates of uMRD
  - Do we need antibody with small molecules?
  - Results of retreatment after finite regimens?
- In relapsed patients zanubrutinib and acalabrutinib produce less atrial fibrillation than ibrutinib
  - zanubrutinib shows greater ORR and longer PFS with a trend for better OS
  - Acalabrutinib reduces the incidence of HTN