Selecting the Appropriate BTKi in the Treatment of Relapsed CLL

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

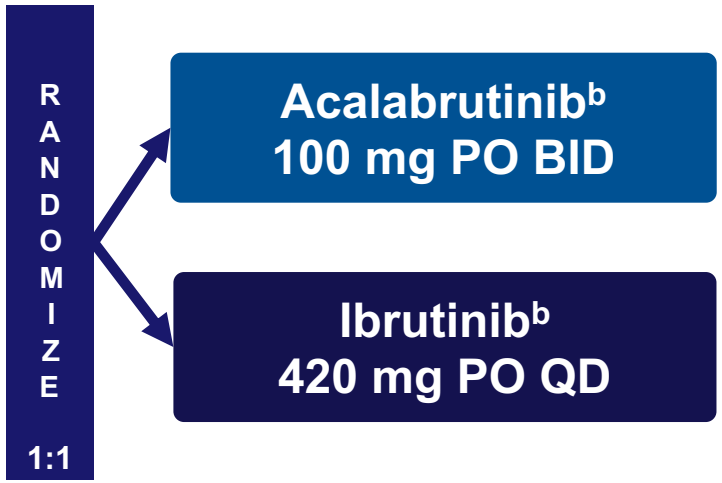
Patients (N = 533)

Key Inclusion Criteria

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

Stratification

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



Primary endpoint

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

Secondary endpoints (hierarchic order)

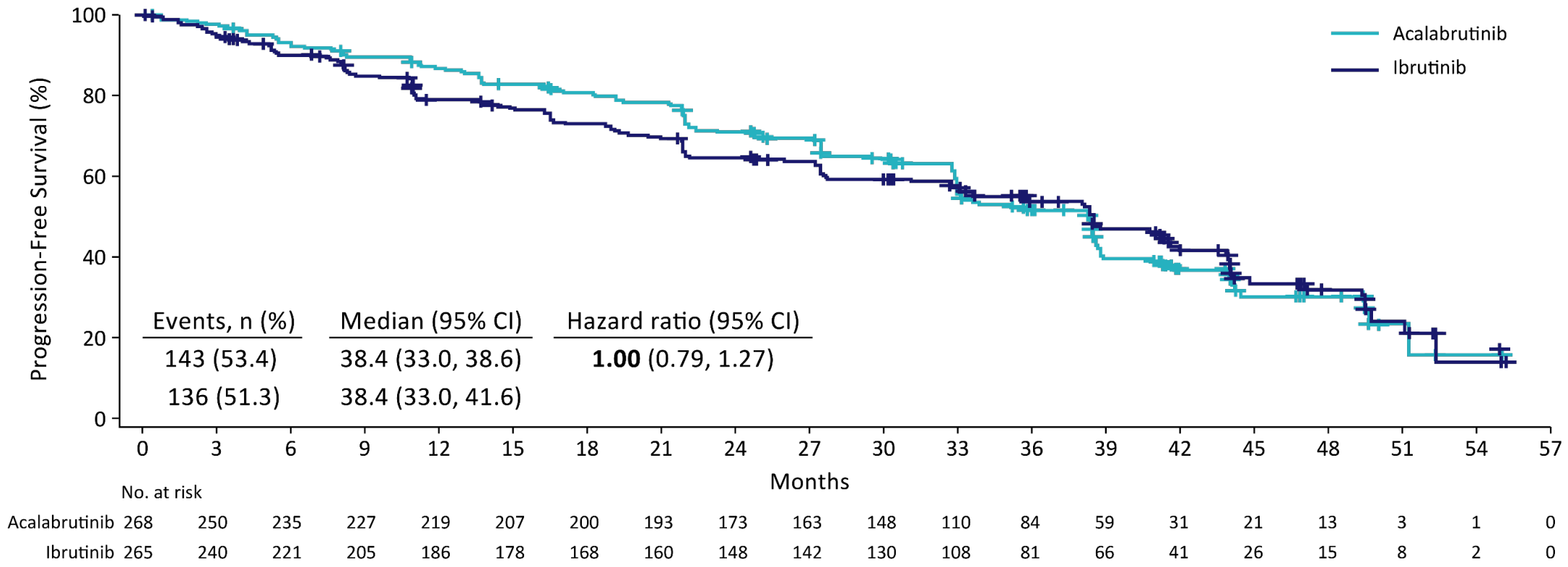
- Incidence of any-grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

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;111:5446-5456.

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

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



Median follow-up: 40.9 months (range, 0.0–59.1).
IRC, independent review committee; PFS, progression-free survival.

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

ELEVATE-RR: Events of Clinical Interest

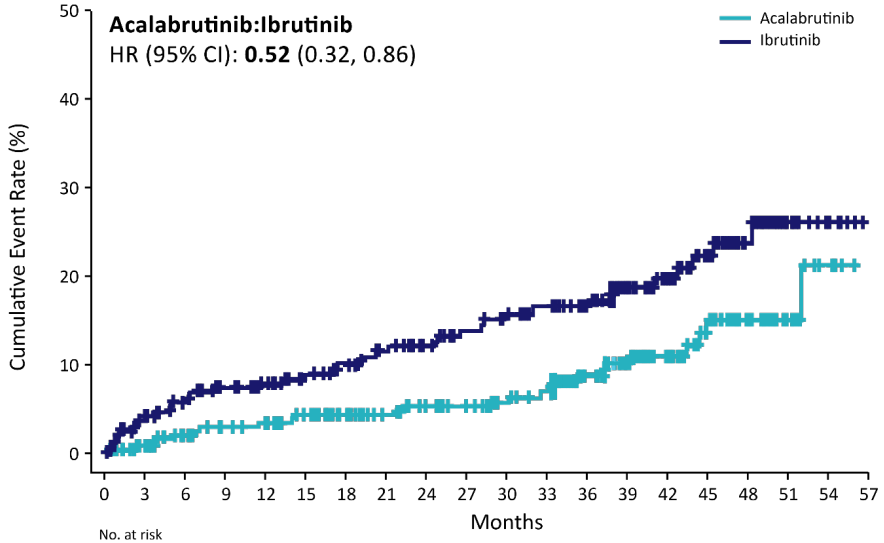
Events, n (%)	Any Grade		Grade ≥3	
	Acalabrutinib (n = 266)	Ibrutinib (n = 263)	Acalabrutinib (n = 266)	Ibrutinib (n = 263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a,*]	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	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 **red** for terms with statistical differences.
*Two-sided *P* value for event comparisons <.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.

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

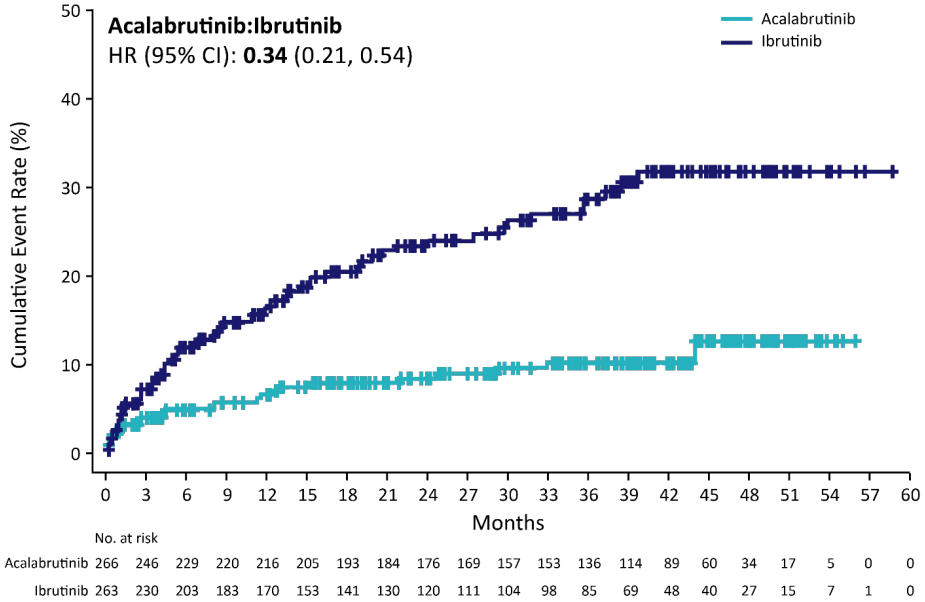
Lower Cumulative Incidences of Any Grade Atrial Fibrillation/Flutter and Hypertension With Acalabrutinib

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

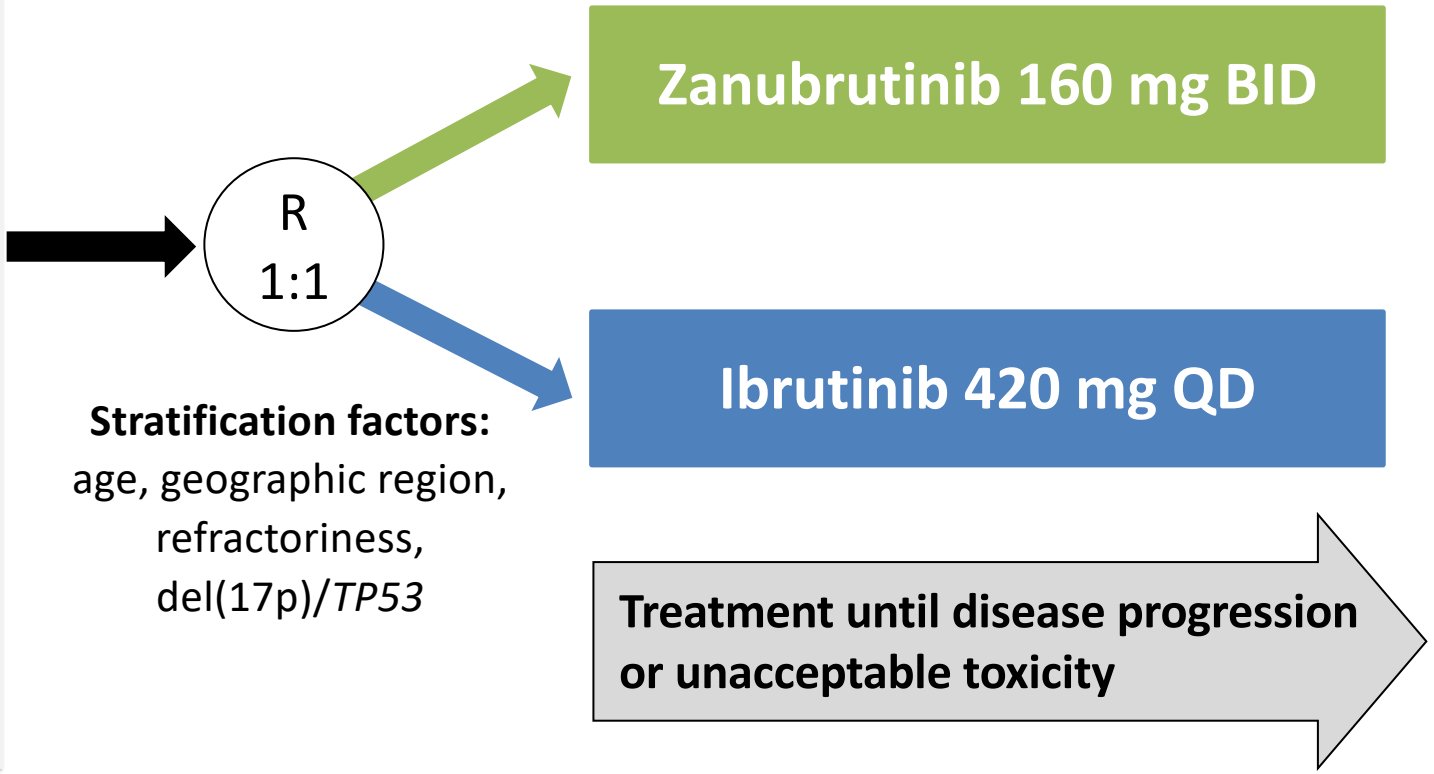
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

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



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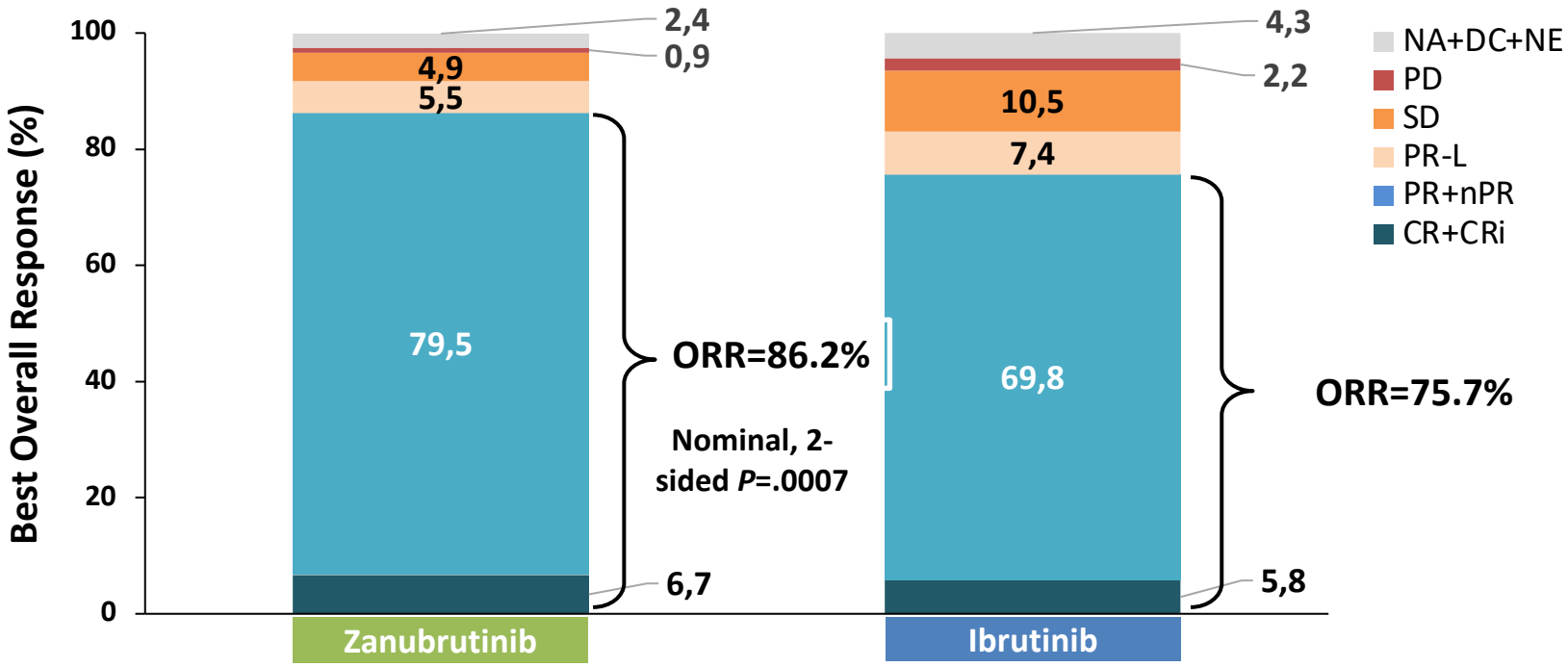
Zanubrutinib Showed Higher ORR Assessed by IRC



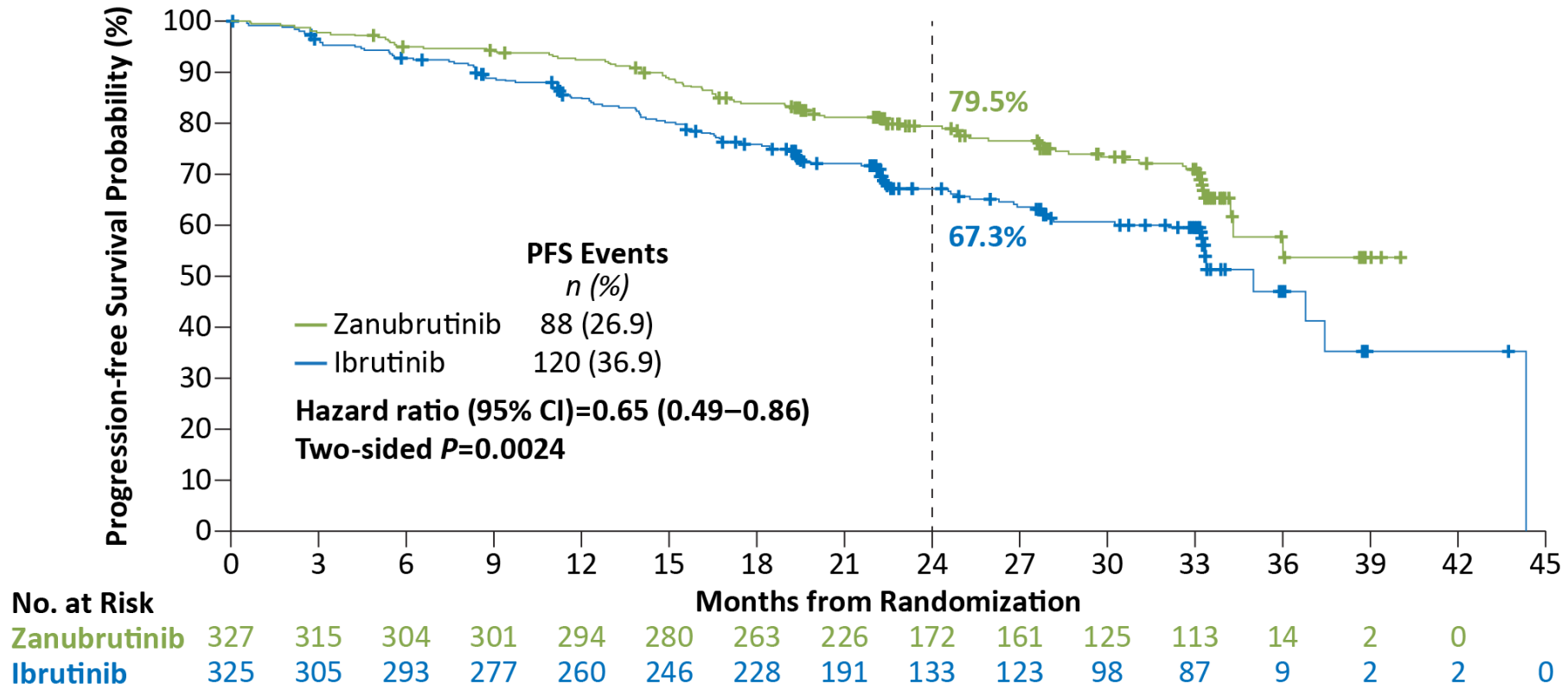
CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

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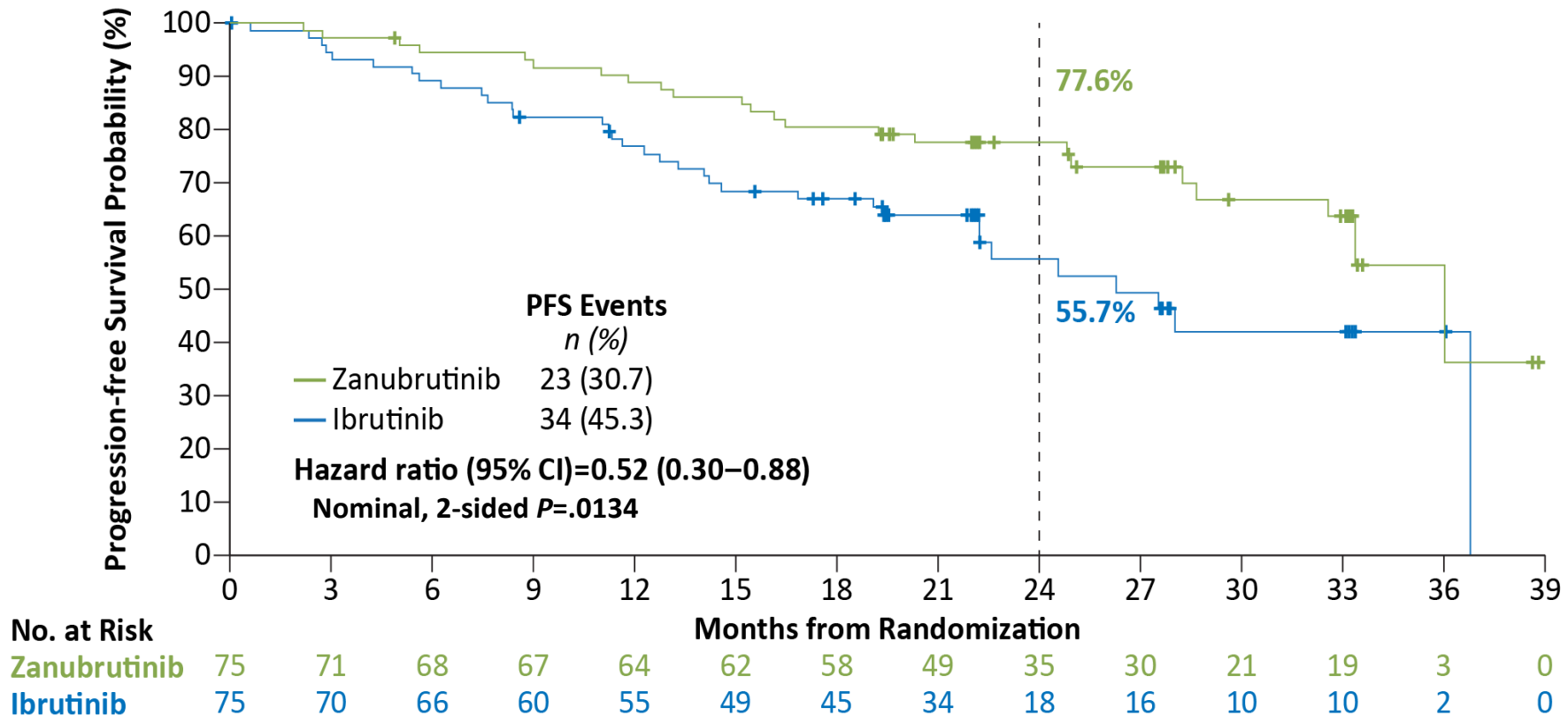
Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}



PFS data assessed by IRC

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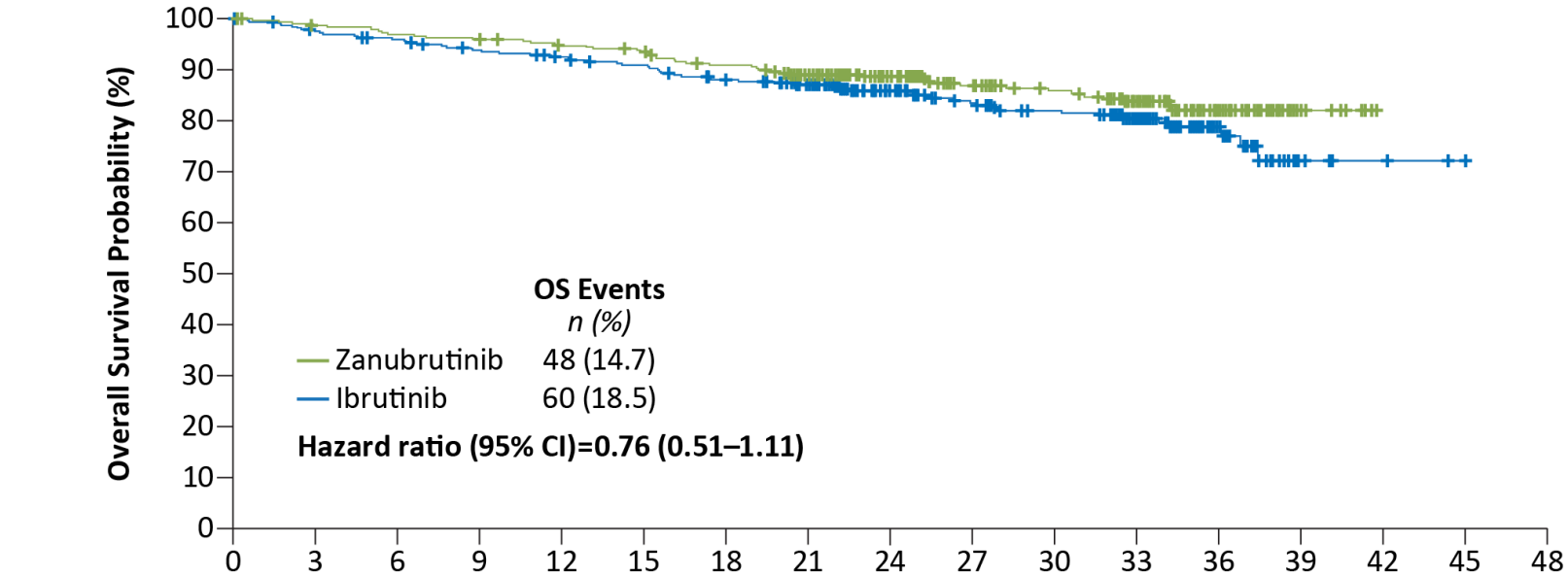
Data cutoff: 8 Aug 2022

Overall Survival

Fewer deaths with zanubrutinib compared with ibrutinib



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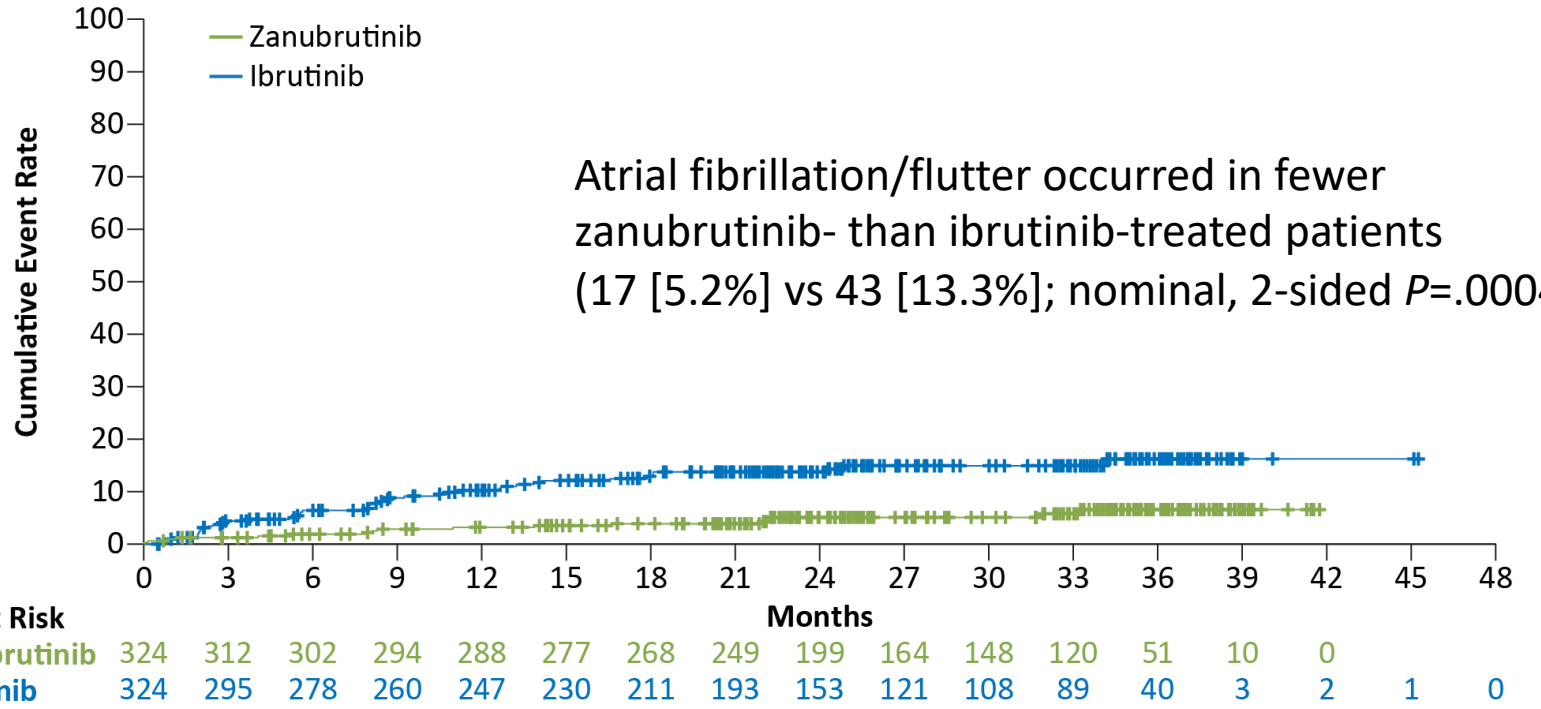
Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



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

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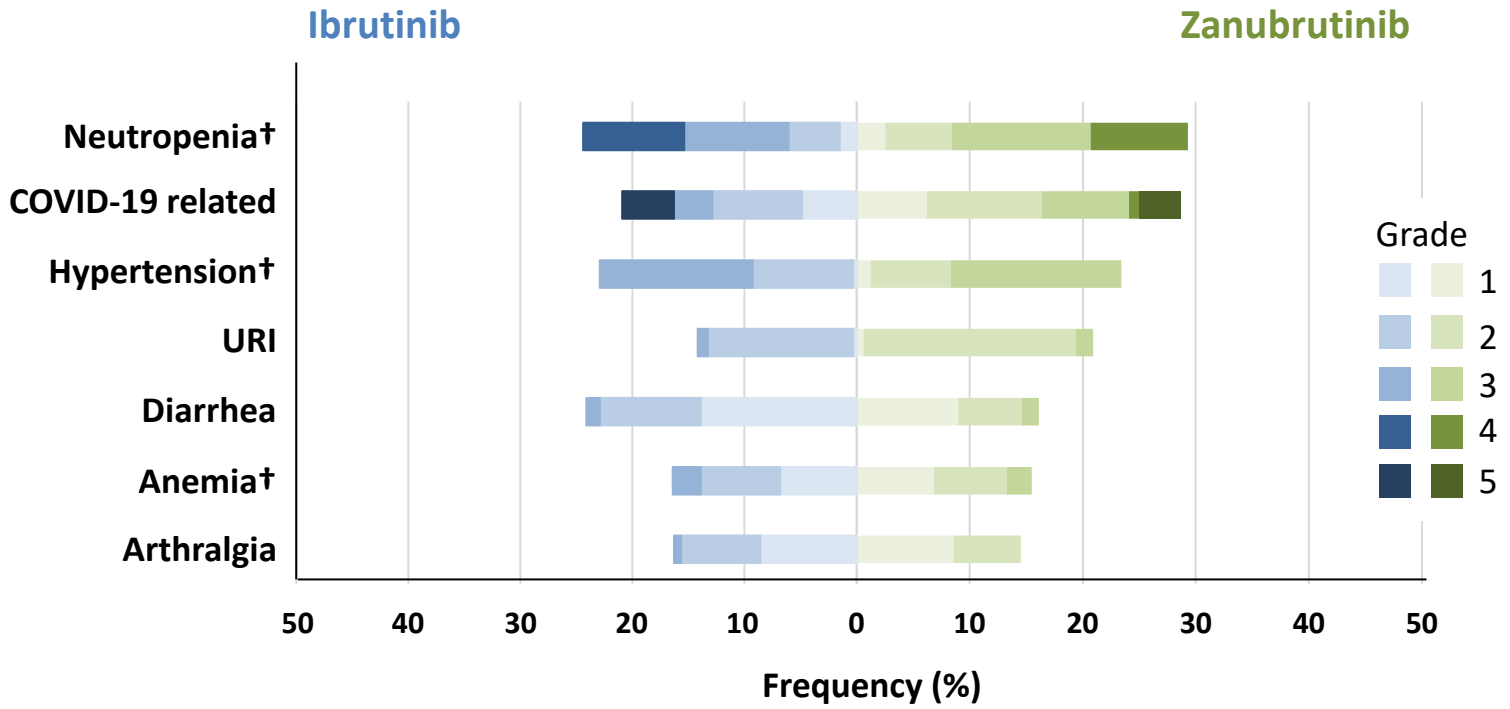
Most Common Adverse Events*



Data cutoff: 8 Aug 2022

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

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Comparison of Patients on Elevate RR and Alpine

Characteristics	Acalabrutinib (n=268)	Zanubrutinib (N=327)
Median age, years (range)	66 (41–89)	67 (35–90)
Bulky disease, (>5 cm), n(%)	128 (47.8)	145 (44.3)
Lines of prior therapy, median (range)	**2** (1–9)	**1** (1–6)
Del(17p) present, n (%)	124 (**45.5**)	45 (**13.8**)
Del(17p) and/or *TP*53 mutation, n(%)	137 (**51**)	75 (**22.9**)
IGHV unmutated n (%)	220 (82.1)	239 (73.1)
Complex karyotype, n (%)	124 (**46.3**)	56 (**17.1**)

Final Analysis From RESONATE: 6-Year Follow-Up in Patients With Previously Treated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma on Ibrutinib

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Thomas J. Kipps, MD, PhD[11]; Carol Moreno, MD, PhD[12]; Marco Montillo, MD[13]; Jan A. Burger, MD, PhD[14]; John C. Byrd, MD[15]; Peter Hillmen, MBChB, PhD[16]; Sandra Dai, PhD, MS[17]; Anita Szoke, MD[17];
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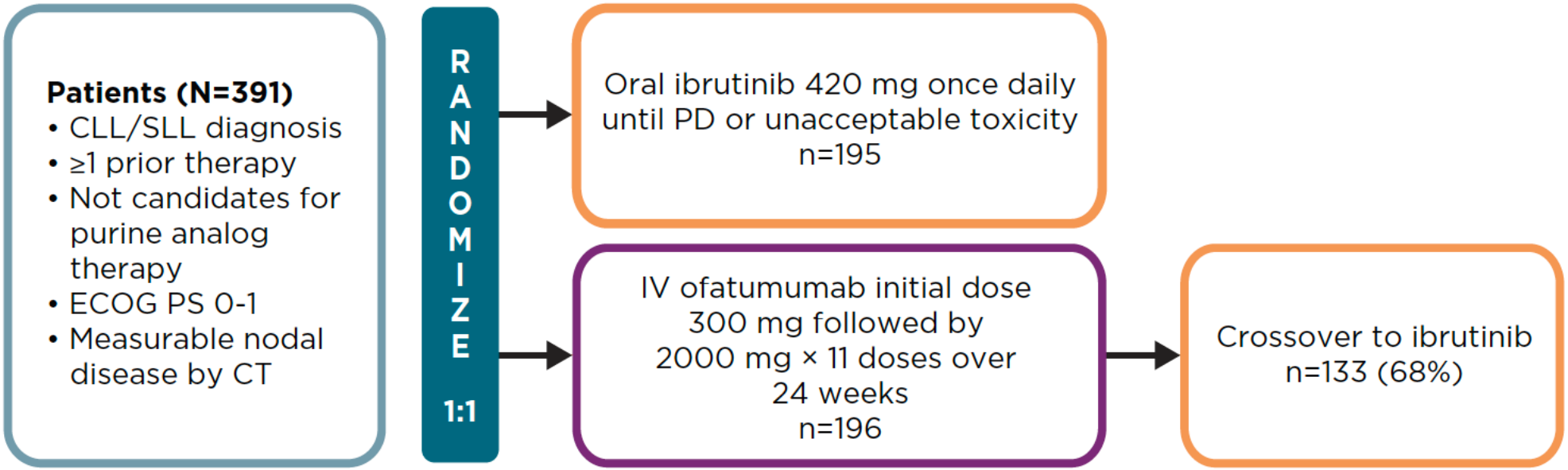
ASCO 2019

Methods
Figure 1. Study Design



Primary end point: Progression-free survival
Secondary end points: Overall response rate, overall survival, safety

CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PD, progressive disease.

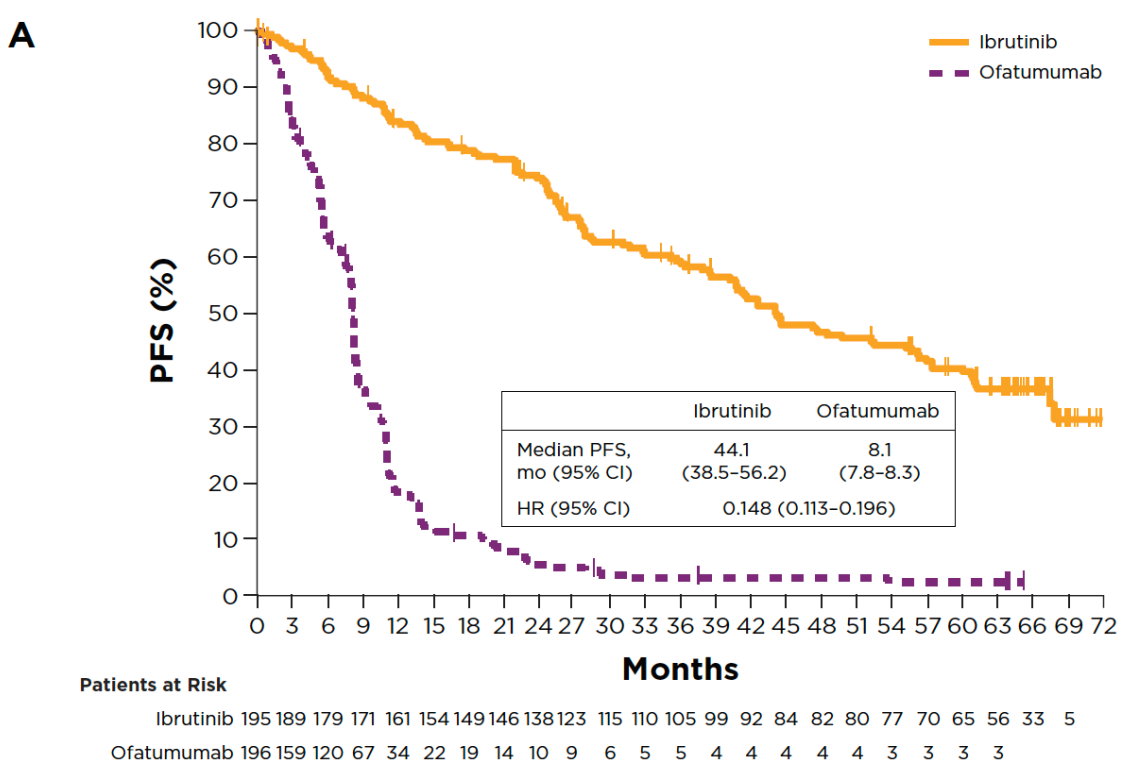
Poster presented at the 2019 ASCO Annual Meeting; May 31 – June 4, 2019; Chicago, IL, USA.

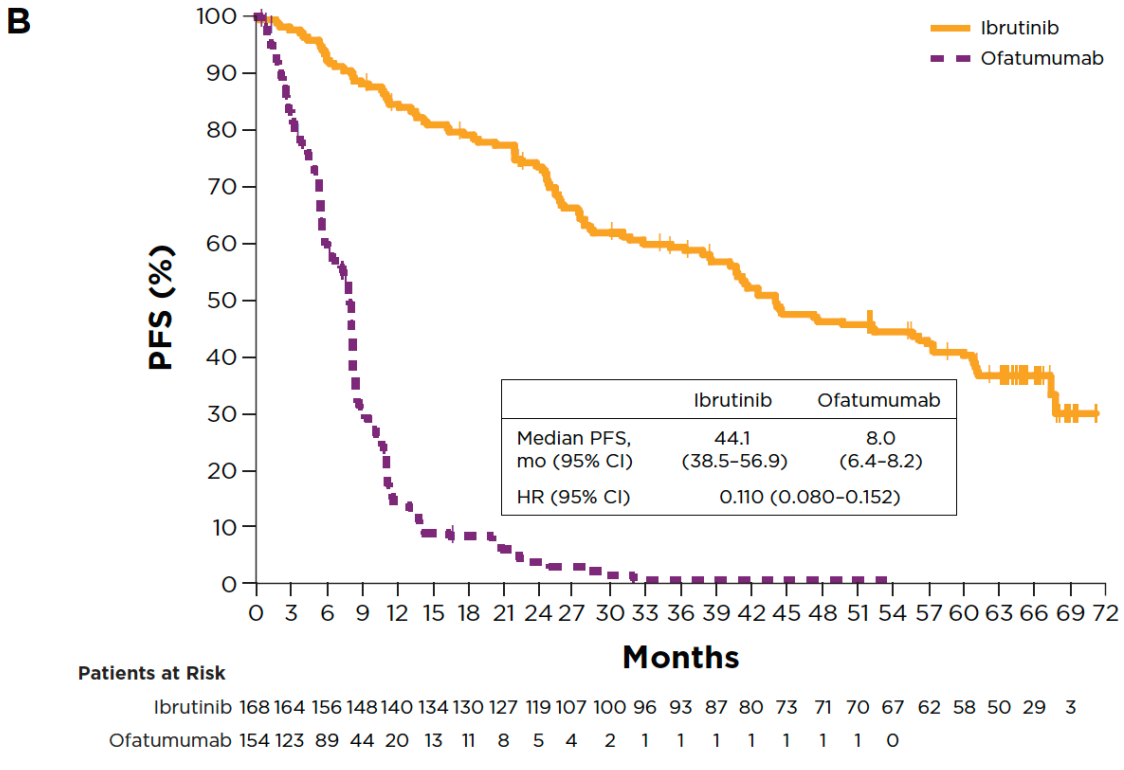
Table 2. Baseline Patient Characteristics and Disease Demographics

Parameters	Ibrutinib n=195	Ofatumumab n=196
Age, y		
Median (range)	67 (30–86)	67 (37–88)
≥70 y, n (%)	78 (40)	80 (41)
Rai stage at screening, n (%)		
0	5 (3)	2 (1)
I	51 (26)	42 (21)
II	30 (15)	39 (20)
III	23 (12)	35 (18)
IV	86 (44)	78 (40)
ECOG PS, n (%)		
0	79 (41)	80 (41)
1	116 (59)	116 (59)
Number of prior therapies, median (range)	3 (1–12)	2 (1–13)
Number of prior therapies, n (%)		
1	35 (18)	53 (27)
2	57 (29)	53 (27)
≥3	103 (53)	90 (46)

Poster presented at the 2019 ASCO Annual Meeting; May 31 – June 4, 2019; Chicago, IL, USA.

Figure 2. PFS in the (A) ITT Population and (B) Genomic High-Risk Population Patients with Del(17p), *TP53* Mutation, Del(11q), and/or Unmutated *IGHV* Status





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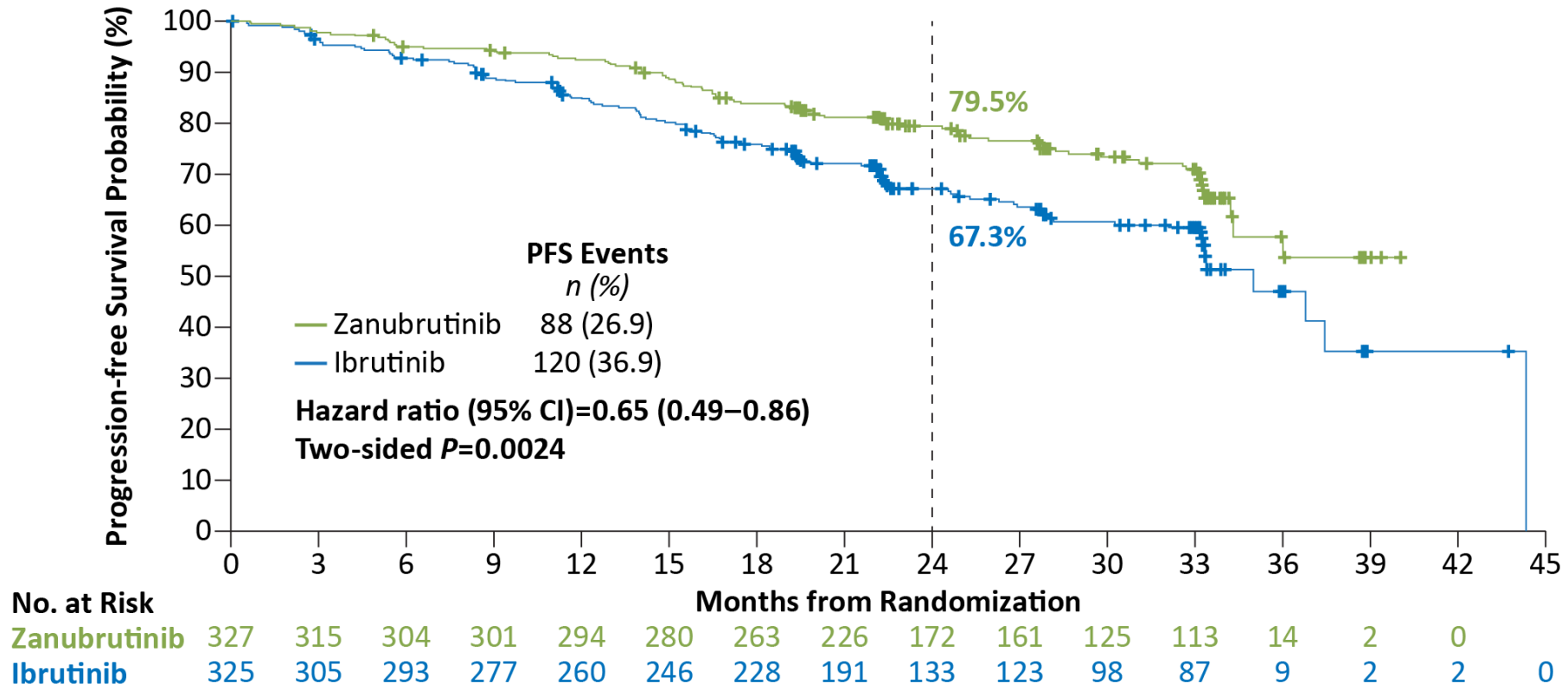

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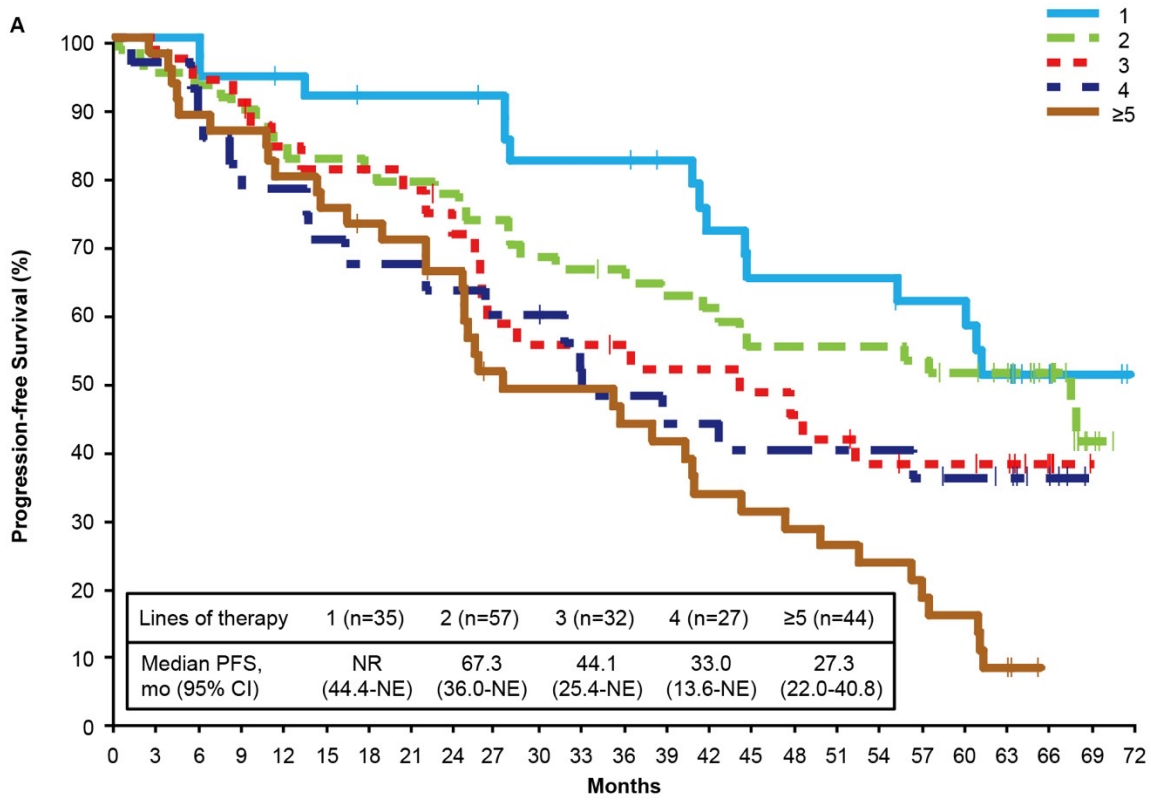
Final Analysis of RESONATE: PFS by Line of Therapy



Patients at Risk

1:	35	35	34	33	32	31	30	30	30	29	26	26	26	24	21	19	19	19	19	17	16	14	7	2
2:	57	54	53	51	47	46	45	44	42	40	37	36	34	33	32	29	29	29	29	28	26	24	18	3
3:	32	31	29	28	26	25	25	24	22	18	17	17	16	15	15	14	13	12	10	9	9	8	4	
4:	27	26	24	21	21	19	18	18	17	16	16	12	12	11	11	10	10	10	10	9	8	7	4	
≥5:	44	43	39	38	35	33	31	30	27	20	19	19	17	16	13	12	11	10	9	7	6	3		

What’s the Moral of My Story?

None of these comparator trials were blinded