Zanubrutinib Demonstrates Superior Progression-Free Survival Compared with Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Results from Final Analysis of ALPINE Randomized Phase 3 Study

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Bruton Tyrosine Kinase Inhibition in CLL: Background

- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation in CLL and B-cell lymphomas[1]
  - BCR signaling is dependent on BTK (Bruton's Tyrosine Kinase)
- Ibrutinib, a first-in-class, covalent BTK inhibitor, has transformed CLL therapy; however, it has properties that limit use
  - Treatment discontinuation from toxicities has been reported in 16%-23% of patients[3-6]
  - Exposure coverage between dosing intervals falls below IC_{50} and variable BTK occupancy at trough has been observed

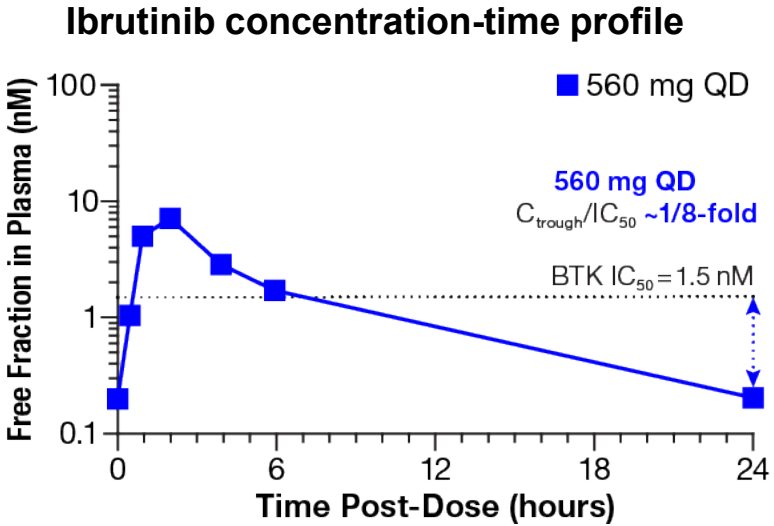

Figure adapted from Tam CS et al. *Expert Rev Clin Pharmacol*. 2021;14:11, 1329-1344

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Zanubrutinib: Differentiating Features and Background

- Zanubrutinib is a second-generation Bruton tyrosine kinase inhibitor (BTKi)
  - Zanubrutinib was designed to have greater BTK specificity than ibrutinib
  - Zanubrutinib has exposure coverage above its IC_{50}
  - Higher drug-concentration/IC_{50} ratios would be expected to lead to more sustained and complete BTK inhibition to improve efficacy
- Zanubrutinib has demonstrated superior PFS by IRC over chemoimmunotherapy in treatment-naive CLL/SLL patients without del(17p)[1]

[1]Tam CS, Brown JB, Kahl BS, et al. *Lancet Oncol*. 2022. https://doi.org/10.1016/S1470-2045(22)00293-5

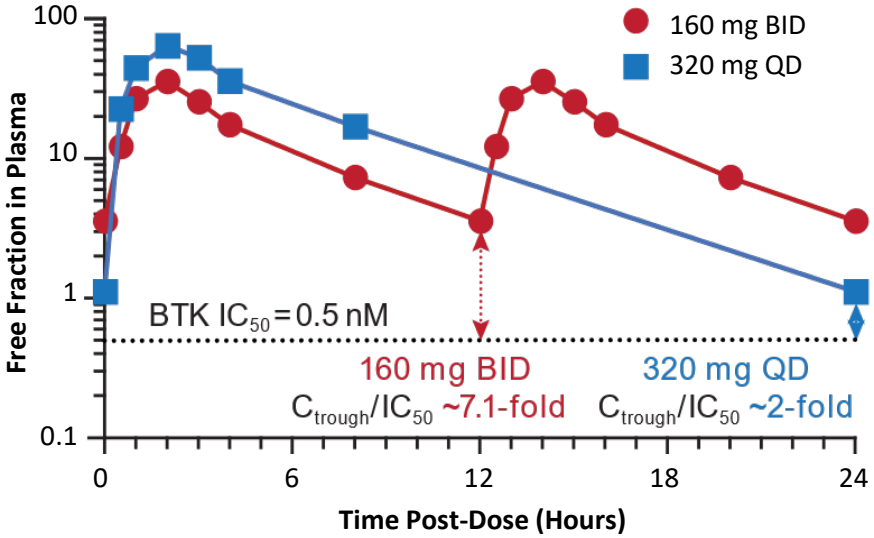


Figure modified from Ou YC, Tang Z, Novotny W, et al *Leukemia & Lymphoma.* 2021; 62(11):2612-2624.

ALPINE Study Design

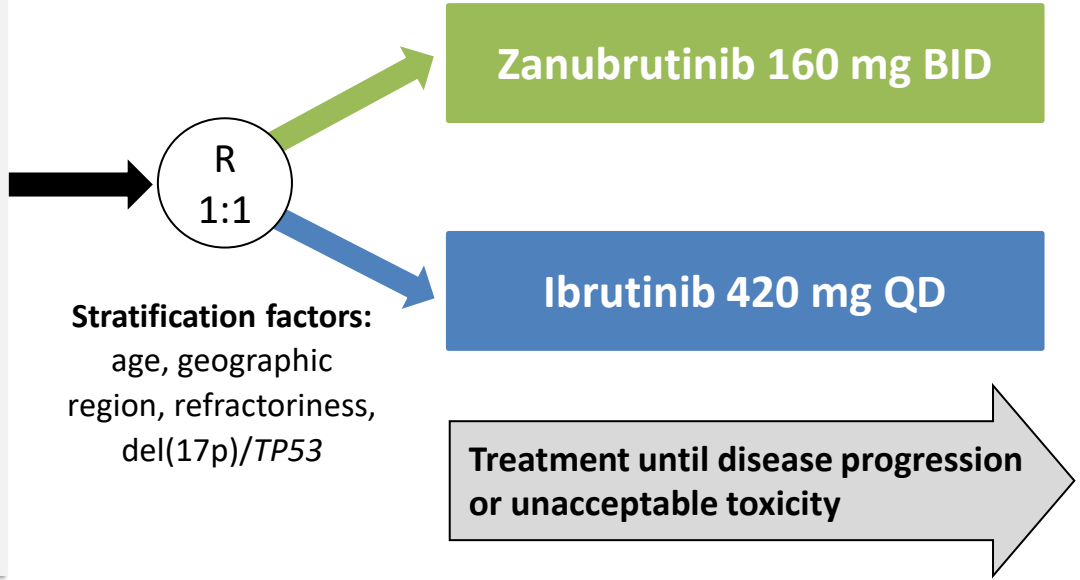
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

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



Endpoints and Statistical Design

Primary Endpoint

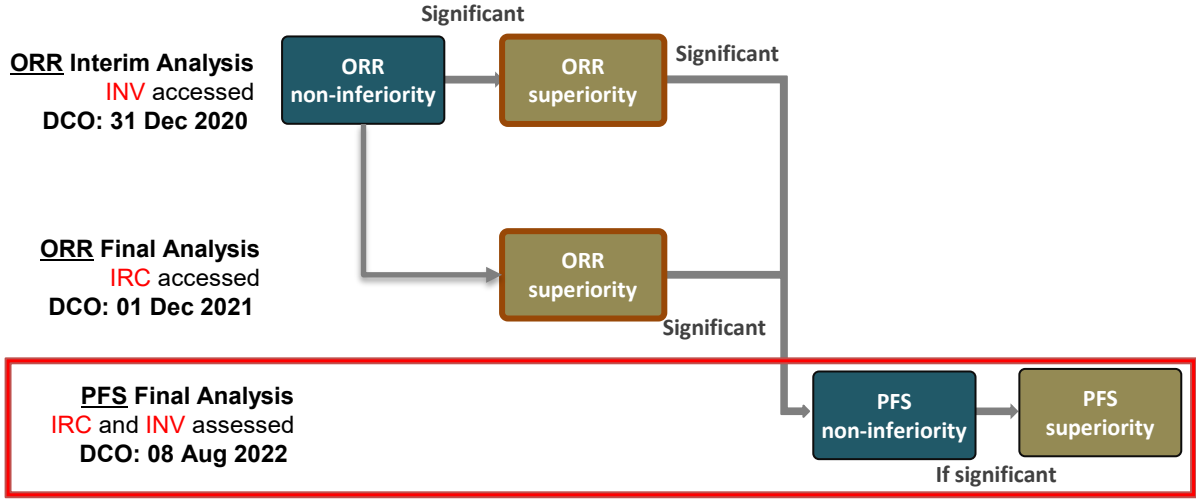
- ORR (PR+CR) noninferiority and superiority (by investigator)

Key Secondary Endpoints

- PFS
- Incidence of atrial fibrillation

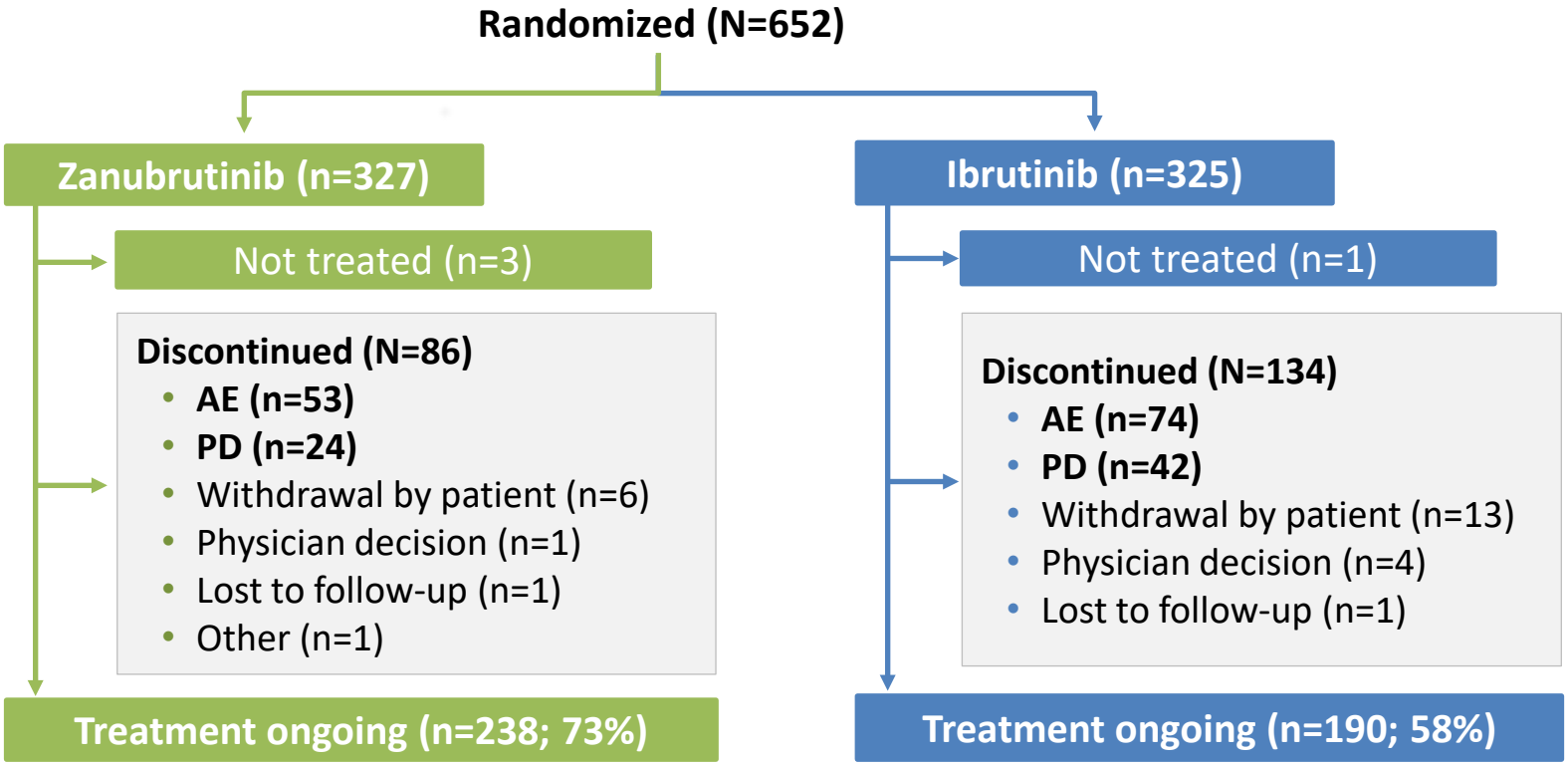
Other Secondary Endpoints

- DoR, OS
- Time to treatment failure
- PR-L or higher
- Patient-reported outcomes
- Safety



Overall response rate noninferiority and superiority were demonstrated in the ORR interim and final analyses; PFS was tested for noninferiority under hierarchical testing when 205 events had occurred

Patient Disposition



AE, adverse event; PD, progressive disease.

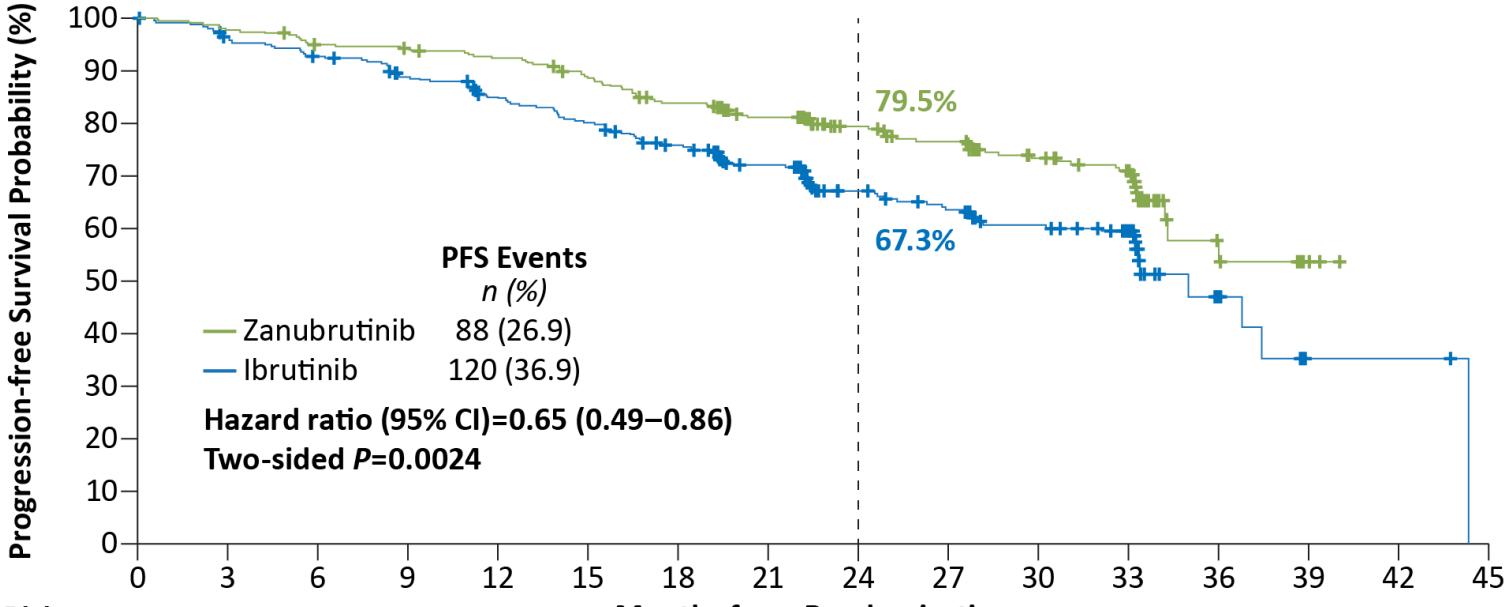
Balanced Demographics and Disease Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range) ≥65 years, n (%)	**67 (35-90)** 201 (61.5)	**68 (35-89)** 200 (61.5)
Male, n (%)	**213 (65.1)**	**232 (71.4)**
ECOG PS ≥1, n (%)	**198 (60.6)**	**203 (62.5)**
Prior lines of systemic therapy, median (range) >3 prior lines, n (%)	**1 (1-6)** 24 (7.3)	**1 (1-12)** 30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%) del(17p) *TP53*^{mut} without del(17p)	**75 (22.9)** 45 (13.8) 30 (9.2)	**75 (23.1)** 50 (15.4) 25 (7.7)
del(11q), n (%)	**91 (27.8)**	**88 (27.1)**
IGHV mutational status, n (%) Mutated **Unmutated**	 79 (24.2) **239 (73.1)**	 70 (21.5) **239 (73.5)**
Complex karyotype*	**56 (17.1)**	**70 (21.5)**
Bulky disease (≥5 cm), n (%)	**145 (44.3)**	**149 (45.8)**

*Complex karyotype is defined as having ≥3 abnormalities.

Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months

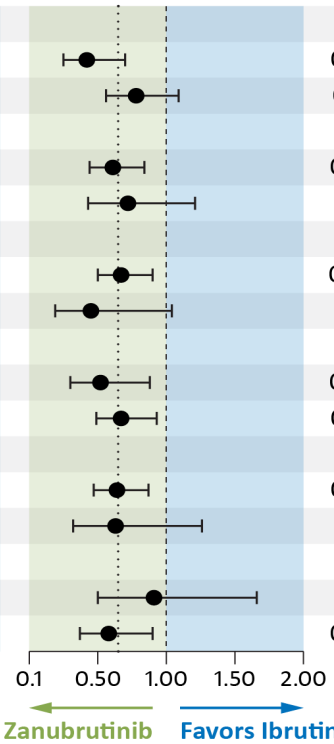


No. at Risk																
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0	
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

PFS Favored Zanubrutinib Across Subgroups

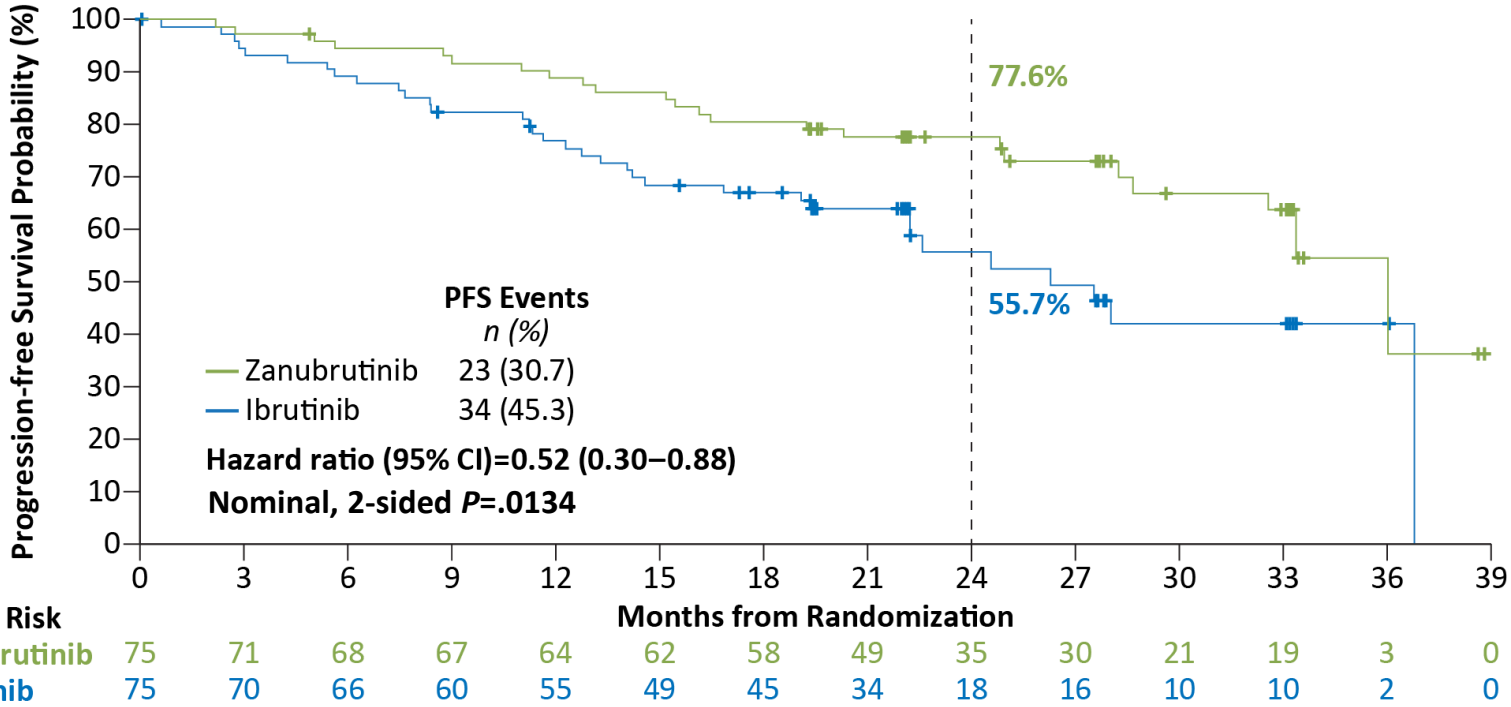
Subgroup	Zanubrutinib Response/Patients	Ibrutinib Response/Patients	Hazard Ratio (95% CI)[a]
Age group			
<65 years	23/126	43/125	0 42 (0.25, 0.70)
≥65 years	65/201	77/200	0.78 (0.56, 1.09)
Sex			
Male	59/213	91/232	0.61 (0.44, 0.84)
Female	29/114	29/93	0.72 (0.43, 1.21)
Prior lines of therapy			
1–3	80/303	102/295	0.67 (0.50, 0.90)
>3	8/24	18/30	0.45 (0.19, 1.04)
Baseline *del*(17p)/*TP53* mutation status			
Present	23/75	34/75	0.52 (0.30, 0.88)
Absent	65/251	86/250	0.67 (0.49, 0.93)
Baseline IGHV mutation status			
Unmutated	72/239	98/239	0.64 (0.47, 0.87)
Mutated	15/79	18/70	0.63 (0.32, 1.26)
Complex karyotype			
Yes	20/56	24/70	0.91 (0.50, 1.66)
No	37/153	45/130	0.58 (0.37, 0.90)



Data cutoff: 8 Aug 2022

[a]Hazard ratio and 95% CI were unstratified for subgroups.

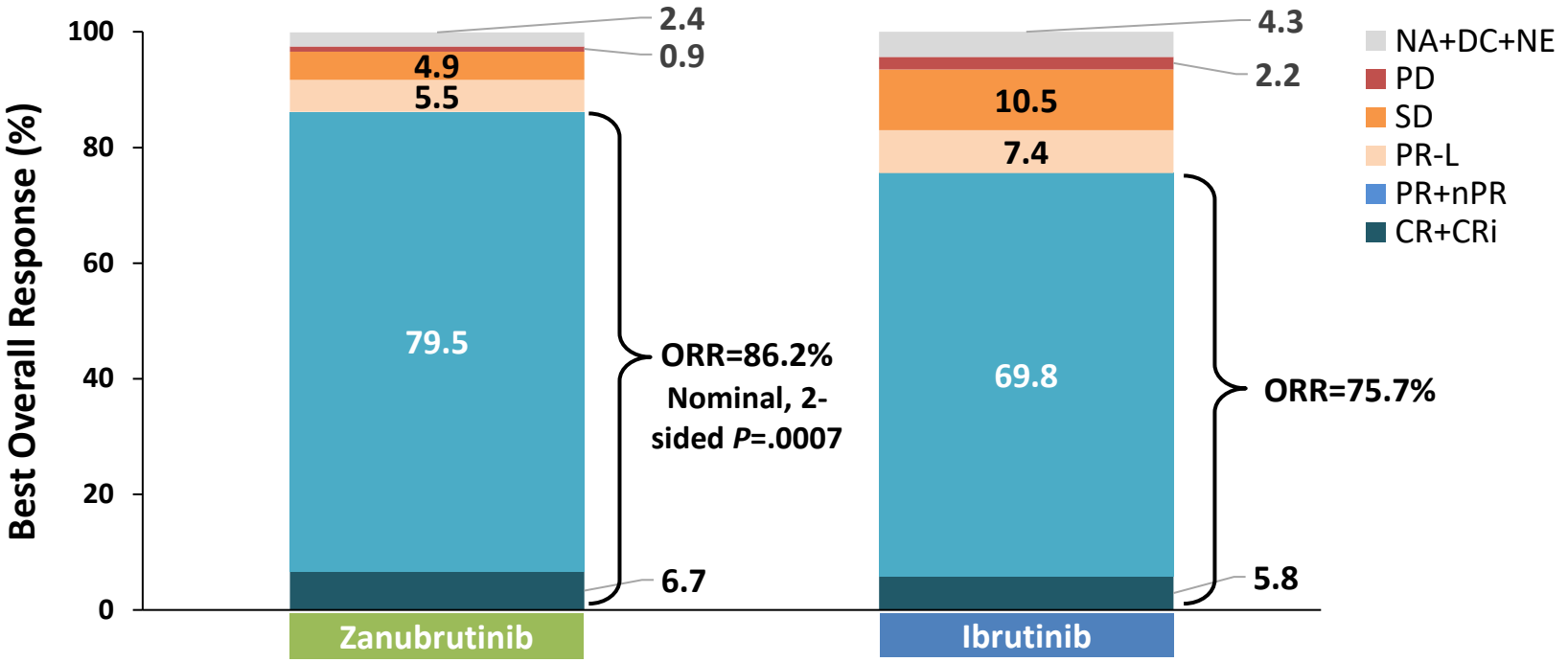
Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}



PFS data assessed by IRC

Data cutoff: 8 Aug 2022

Zanubrutinib Showed Higher ORR Assessed by IRC

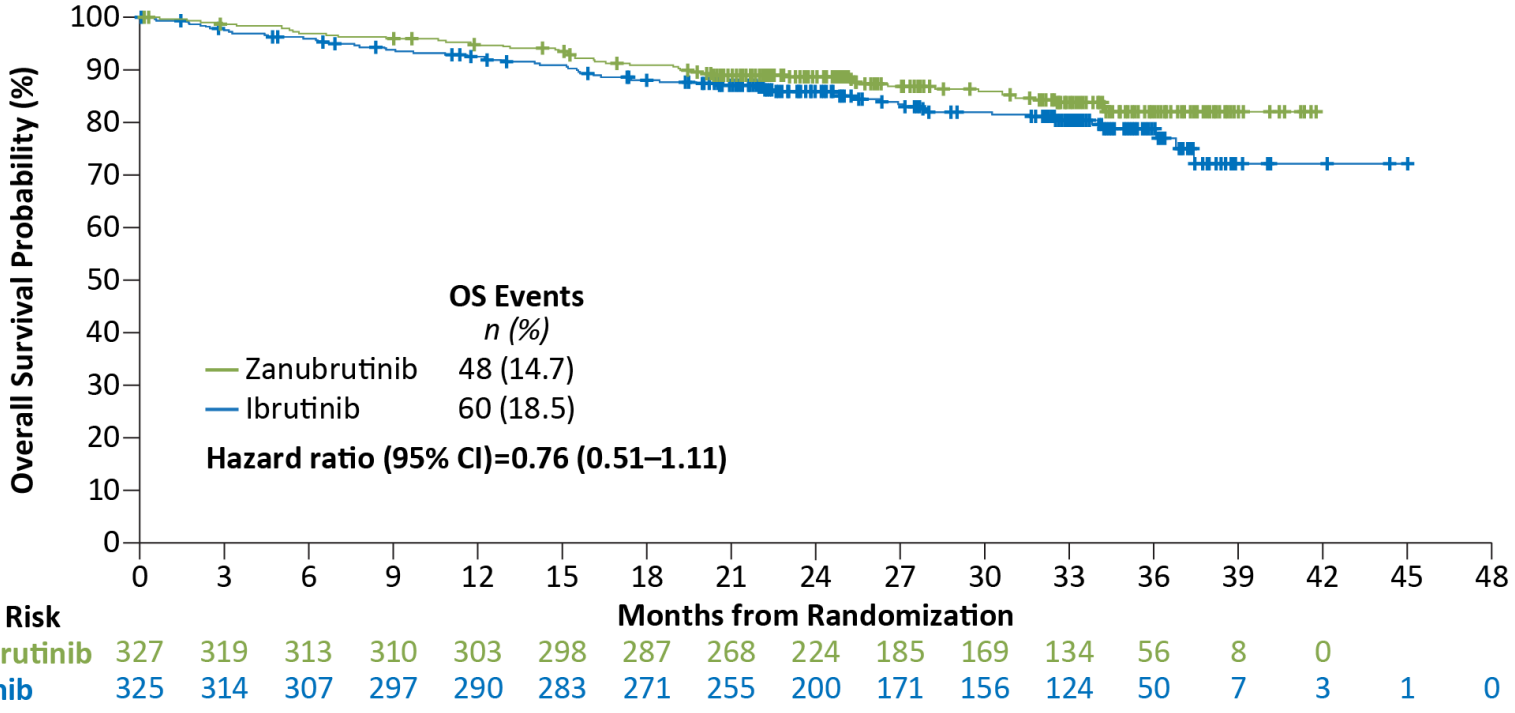


CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Data cutoff: 8 Aug 2022

Overall Survival

Fewer deaths with zanubrutinib compared with ibrutinib



Data cutoff: 8 Aug 2022

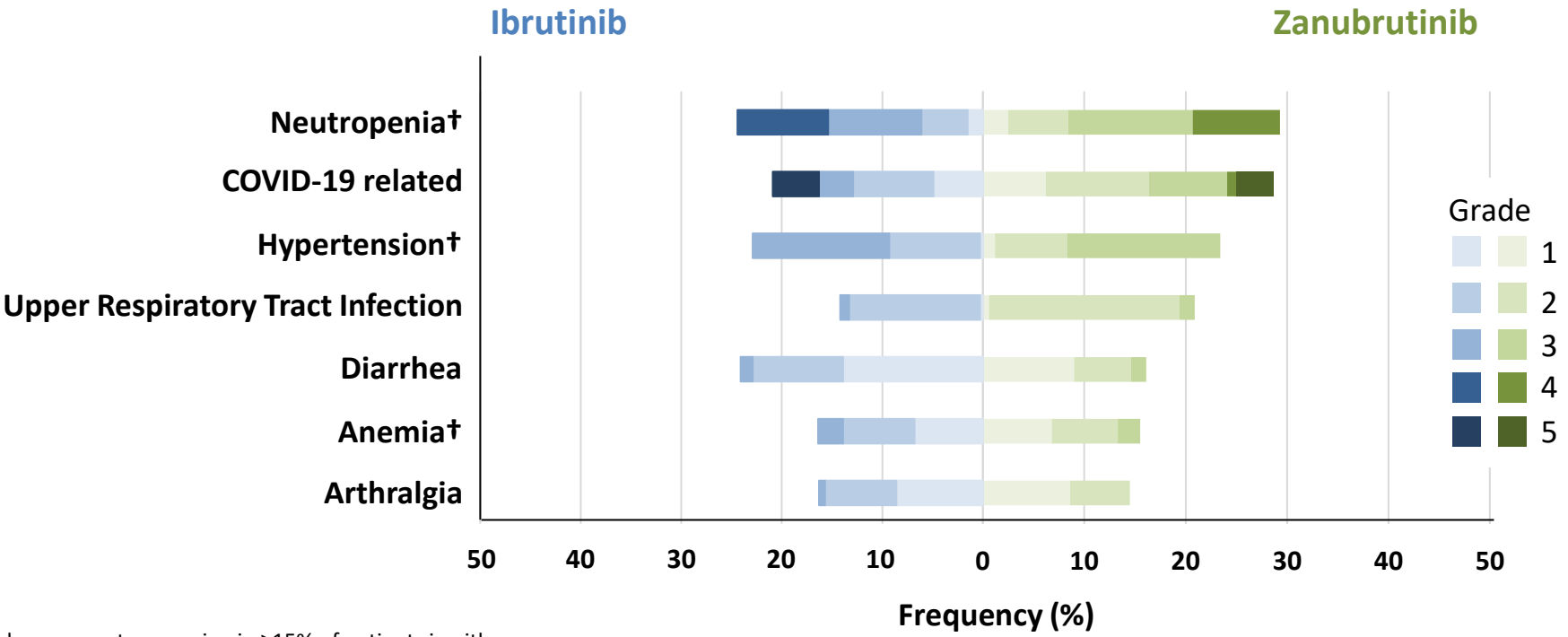
Overall Safety/Tolerability Summary

Zanubrutinib safety profile was favorable to ibrutinib

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**28.4**	**24.3**
Any grade adverse event	**318 (98.1)**	**321 (99.1)**
Grade 3 to 5	218 (67.3)	228 (70.4)
Grade 5	33 (10.2)	36 (11.1)
Serious adverse event	**136 (42.0)**	**162 (50.0)**
Adverse events leading to		
Dose reduction	**40 (12.3)**	**55 (17.0)**
Dose interruption	**162 (50.0)**	**184 (56.8)**
Treatment discontinuation	**50 (15.4)**	**72 (22.2)**

Data cutoff: 8 Aug 2022

Most Common Adverse Events*



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

†Pooled terms.

Data cutoff: 8 Aug 2022

Zanubrutinib Had A Favorable Cardiac Profile

Lower rate of cardiac events, serious cardiac events, treatment discontinuation, and deaths

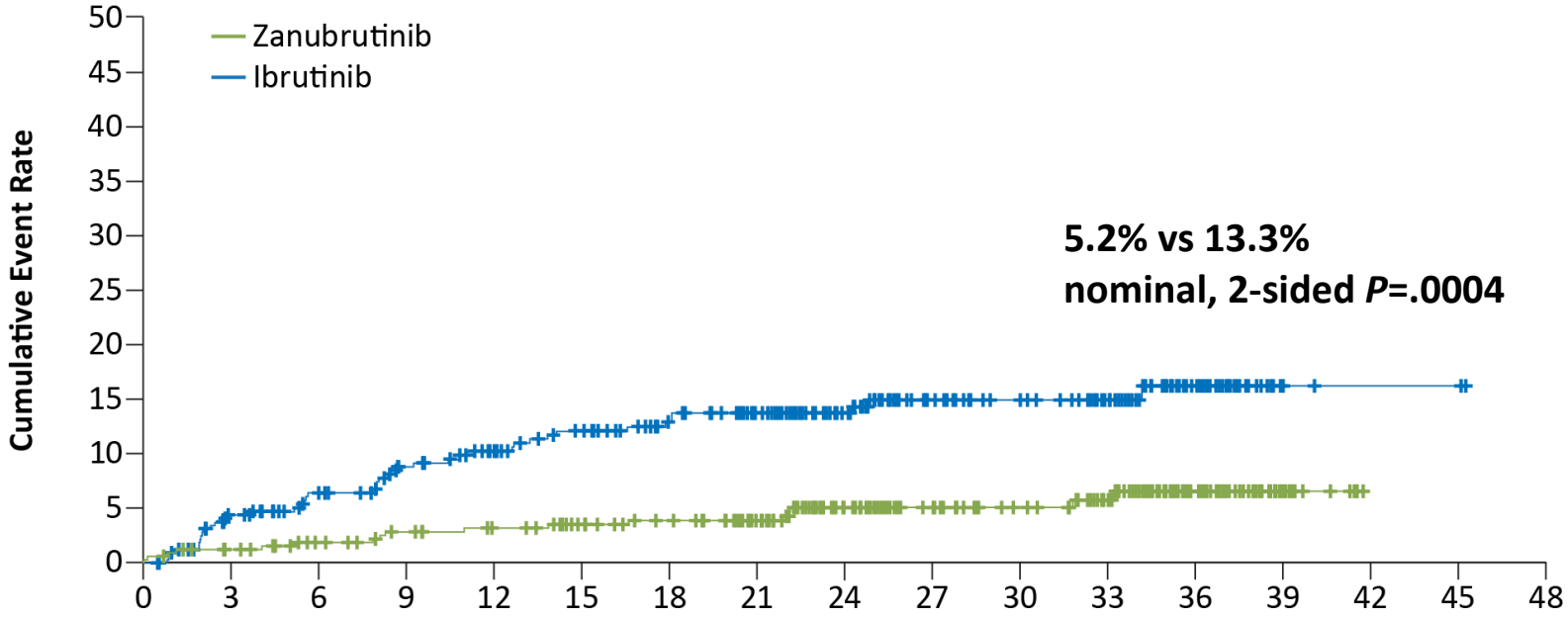
- Lower rate of serious cardiac adverse events reported with zanubrutinib
  - A fib/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac adverse events	**6 (1.9%)**	**25 (7.7%)**
Cardiac adverse events leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)*
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)*
Congestive cardiomyopathy	0	1 (0.3)*
Myocardial infarction	0	1 (0.3)*
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

Data cutoff: 8 Aug 2022

*Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



No. at Risk																
Zanubrutinib	324	312	302	294	288	277	268	249	199	164	148	120	51	10	0	
Ibrutinib	324	295	278	260	247	230	211	193	153	121	108	89	40	3	2	1	0

Data cutoff: 8 Aug 2022

Conclusions

- Zanubrutinib demonstrated superior PFS over ibrutinib in patients with relapsed/refractory CLL/SLL
  - PFS benefit seen across all major subgroups, including the del(17p)/*TP53*^{mut} population
- Zanubrutinib has a favorable safety profile compared with ibrutinib
  - Lower rate of grade ≥3 and serious AEs, fewer AEs leading to treatment discontinuation and dose reduction
  - Zanubrutinib has a better cardiac profile than ibrutinib with lower rates of atrial fibrillation, serious cardiac events, cardiac events leading to treatment discontinuation, and fatal cardiac events
- ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors in patients with relapsed/refractory CLL/SLL; **zanubrutinib has now proven superiority to ibrutinib in both PFS and ORR.**

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