Supplementary Appendix

Supplement to: Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2023;388:319-32. DOI: 10.1056/NEJMoa2211582

This appendix has been provided by the authors to give readers additional information about the work.

Table of Contents

List of Investigators

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Ting, Stephen	Box Hill Hospital/Eastern Health	Australia	3
Opat, Stephen	Monash Medical Centre	Australia	2
Marlton, Paula	Princess Alexandra Hospital	Australia	5
Leahy, Michael	Royal Perth Hospital	Australia	1
Tam, Constantine	St. Vincents Hospital, Melbourne	Australia	0
Hourigan, Matthew	Icon Cancer Foundation	Australia	1
Janowski, Wojt	Calvary Mater Newcastle	Australia	2
Walker, Patricia	Peninsula Private Hospital	Australia	2
Wickham, Nicholas	Ashford Cancer Centre Research	Australia	0
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Lemmens, Jan	Gasthuiszusters Antwerpen	Belgium	1
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HU, Jianda	Fujian Medical University Union Hospital	China	5
Weng, Jianyu	Guangdong General Hospital	China	1
Zhou, Keshu	Henan Cancer Hospital	China	19
Xu, Wei	Jiangsu Province Hospital	China	7
Feng, Ru	Nanfang Hospital	China	3
Zhang, Wei	Peking Union Hospital	China	6
Gao, Sujun	The First Bethune Hospital Of Jilin University	China	2
Pan, Ling	West China Hospital, Sichuan University	China	9
Yan, Dongmei	The Affiliated Hospital Of Xuzhou Medical University	China	0
Sun, Zimin	Anhui Province Hospital	China	0
Liu, Peng	Zhongshan Hospital Of Fudan University	China	2
Hu, Yu	Wuhan Union Hospital	China	5
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JING, Hongmei	Peking University Third Hospital	China	2
Yu, Kang	The First Affiliated Hospital Of Wenzhou Medical University	China	1
Jin, Jie	The First Affiliated School Of Zhejiang University	China	7
Wang, Zhao	Beijing Friendship Hospital-Capital Medical University	China	1
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Zhu, Xiongpeng	Quanzhou First Hospital Of Fujian Province	China	1
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Liu, Zhuogang	Shengjing Hospital	China	3

Li, Ping	Tongji Hospital Of Tongji University	China	3
Hajek, Roman	Fakultni Nemocnice Ostrava	Czech Republic	15
Simkovic, Martin	Fakultni Nemocnice Hradec Kralove	Czech Republic	20
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Tomowiak, Cecile	CHRU De Poitiers La Miletrie	France	1
Dartigeas, Caroline	CHRU Bretonneau	France	4
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Eichhorst, Barbara	Uniklinik Köln	Germany	1
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Wehler, Thomas	Evangelisches Krankenhaus Hamm	Germany	1
Liersch, Rudiger	Gemeinschaftspraxis Fur Hamatologie Und Onkologie	Germany	0
Riesenberg, Hendrik	Onkologische Schwerpunktpraxis Bielefeld	Germany	0
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Marasca, Roberto	Azienda Ospedaliero Universitaria Di Modena Policlinico	Italy	0
Cascavilla, Nicola	Ospedale Casa Sollievo Della Sofferenza IRCCS	Italy	0
Ghia, Paolo	Ospedale San Raffaele S.R.L. - PPDS	Italy	2
Tedeschi, Alessandra	ASST GOM Niguarda	Italy	8
Laurenti, Luca	Fondazione Policlinico Universitario Agostino Gemelli	Italy	2
Rossi, Giuseppe	ASST Degli Spedali Civili Di Brescia - Spedali Civili Di Brescia	Italy	0
Coscia, Marta	AO Città Della Salute E Della Scienza Di Torino	Italy	5
Levin, Mark-David	Albert Schweitzer Ziekenhuis	Netherlands	5
Schaar, Cornelis	Gelre Ziekenhuizen	Netherlands	1
Schreurs, John	Martini Ziekenhuis	Netherlands	0
Hughes, Marie	Tauranga Hospital	New Zealand	2
Chan, Henry	North Shore Hospital	New Zealand	10
Weinkove, Robert	Wellington Hospital	New Zealand	10

Islam, Shahid	Waikato Hospital	New Zealand	7
Liang, James	Middlemore Hospital	New Zealand	2
Ganly, Peter	Canterbury Health Laboratories	New Zealand	11
Jurczak, Wojciech	Pratia MCM Kraków	Poland	45
Robak, Tadeusz	Wojewodzkie Wielospecjalistyczne Centrum Onkologii I Traumatologii Im. M. Kopernika W Lodzi	Poland	19
Holojda, Jadwiga	Wojewodzki Szpital Specjalistyczny W Legnicy	Poland	3
Pluta, Andrzej	Szpital Specjalistyczny W Brzozowie	Poland	16
Ciepluch, Hanna	Copernicus PL Sp. Z O.O. Wojewodzkie Centrum Onkol	Poland	16
Mital, Andrzej	Uniwersyteckie Centrum Kliniczne - PPDS	Poland	22
Grosicki, Sebastian	SP ZOZ Zespol Szpitali Miejskich	Poland	35
Kazmierczak, Maciej	Examen Sp. Z O.O.	Poland	45
Piszcz, Jaroslaw	Interhem Opieka Szpitalna	Poland	15
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Garcia Marco, Jose Antonio	Hospital Universitario Puerta De Hierro	Spain	1
Gimeno, Eva	Hospital Del Mar	Spain	0
Rifon Roca, Jose	Clinica Universidad Navarra	Spain	0
Ferra Coll, Christelle	Hospital Universitario Germans Trias I Pujol	Spain	2
Casado Montero, Luis Felipe	Hospital Universitario De Toledo	Spain	3
Lopez Jimenez, Javier	Hospital Universitario Ramon Y Cajal	Spain	10
Yanez San Segundo, Lucrecia	Hospital Universitario Marques De Valdecilla	Spain	1
Ramirez Payer, Angel	Hospital Universitario Central De Asturias	Spain	0
De La Fuente, Adolfo	MD Anderson Cancer Center Madrid	Spain	0
Baltasar, Patricia	Hospital Universitario La Paz	Spain	1
Francesc, Bosch	Hospital Universitario Vall d'Hebrón - PPDS	Spain	2
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Roncero, Josep	Institut Catala D Oncologia- Hospital Josep Trueta	Spain	5
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Andersson, Per-Ola	Södra Älvsborgs Sjukhus Borås	Sweden	0
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Tombak, Anil	Mersin Universitesi Tip Fakultesi Hastanesi	Turkey	0
Kaynar, Leylagul	Erciyes University School Of Medicine	Turkey	0
Arslan, Onder	Ankara University Medical Faculty	Turkey	0
Hutchinson, Claire	Derriford Hospital	United Kingdom	2
Munir, Tahla	St James's University Hospital	United Kingdom	7
Forconi, Francesco	Southampton General Hospital	United Kingdom	2
Shah, Nimish	Norfolk And Norwich University Hospital	United Kingdom	2
Auer, Rebecca	Barts Health NHS Trust	United Kingdom	0
Bloor, Adrian	Christie Hospital	United Kingdom	0
Martinez De La Calle, Nicolas	Nottingham University Hospitals NHS Trust	United Kingdom	5
Marshall, Scott	Sunderland Royal Hospital	United Kingdom	2
Walewska, Renata	Royal Bournemouth Hospital	United Kingdom	3
Paneesha, Shankaranarayana	Birmingham Heartlands Hospital	United Kingdom	3
Patten, Piers	Kings College Hospital	United Kingdom	0
Preston, Gavin	NHS Grampian - PPDS	United Kingdom	1
Young, Moya	Kent & Canterbury Hospital	United Kingdom	5
Schuh, Anna	Genesiscare	United Kingdom	0
Brown, Jennifer	Dana Farber Cancer Institute	United States	5
Flinn, Ian	SCRI Tennessee Oncology Nashville	United States	5
Kingsley, Edwin	Comprehensive Cancer Centers Of Nevada - USOR	United States	3
Shadman, Mazyar	Fred Hutchinson Cancer Research Center	United States	8
Quick, Donald	Joe Arrington Cancer Research & Treatment Center	United States	1
Brander, Danielle	Duke University Medical Center	United States	4
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Yimer, Habte	Texas Oncology (Tyler) - USOR	United States	2
Ferrajoli, Alessandra	MD Anderson Cancer Center	United States	8

Spurgeon, Stephen	Oregon Health And Science University	United States	6
Graf, Solomon	VA Puget Sound Health Care System	United States	3
Chaudhry, Arvind	Medical Oncology Associates (Dba Summit Cancer Center)	United States	2
Coleman, Morton	Clinical Research Alliance Inc	United States	7
Freeman, Benjamin	Summit Medical Group	United States	4
Levy, Moshe	Texas Oncology-B.Charles A.Sammons Cancer Center	United States	0
Bryan, Locke	Augusta University	United States	1
Agrawal, Apurv	New Jersey Hematology Oncology Associates LLC	United States	0
Bhat, Seema	Ohio State University Comprehensive Cancer Center	United States	0
Hall, Ryan	CARTI Cancer Center	United States	3
Liles, Darla	Leo W. Jenkins Cancer Center	United States	0
Shunyakov, Leonid	Central Care Cancer Center	United States	0
Thirman, Michael	University Of Chicago Medical Center	United States	0
Twardy, Amanda	Oncology And Hematology Associates Of Southwest Virginia, Inc	United States	10
Hrom, John	Hattiesburg Hematology And Oncology Clinic	United States	3
Stevens, Don	Norton Cancer Institute - Pavilion	United States	1
Cull, Elizabeth	Prisma Health Cancer Institute	United States	0
Anz III, Bertrand	SCRI Tennessee Oncology Chattanooga	United States	5
Barrientos, Jacqueline	Northwell Health	United States	0
Bociek, Robert	University Of Nebraska Medical Center	United States	2
Klein, Leonard	Illinois Cancer Specialists (Niles) - USOR	United States	0
Lamanna, Nicole	Columbia University Medical Center	United States	1
O'Brien, Susan	University Of California Irvine Medical Center	United States	0
Sharman, Jeff	Willamette Valley Cancer Center	United States	6
Burke, John	Rocky Mountain Cancer Centers (Aurora) - USOR	United States	5

Santiago, Manuel	Texas Oncology - San Antonio Medical Center - USOR	United States	4
Courtright, Jay	Texas Oncology (Loop) - USOR	United States	0
Mcintyre, Kristi	Texas Oncology (Walnut) - USOR	United States	0
Ruxer, Robert	Texas Oncology-Fort Worth Cancer Center	United States	3
Farber, Charles	Atlantic Health System	United States	1
Melear, Jason	Texas Oncology (West 38) - USOR	United States	0
Zafar, Syed	SCRI Florida Cancer Specialists South	United States	2
Cultrera, Jennifer	SCRI Florida Cancer Specialists North	United States	3
Kambhampati, Suman	SCRI HCA Midwest Health	United States	1
Eradat, Herbert	David Geffen School Of Medicine At UCLA	United States	2

Trial Registration

ALPINE was registered with ClinicalTrials.gov on Nov 2, 2018, a day after the first patient was enrolled on Nov 1, 2018. However, trial registration occurred within the regulatory required timeline, which was up to 21 days after first patient consent. The first patient was the only patient enrolled before the trial was registered withClinicalTrials.gov.

Primary and Secondary Outcome Statistical Methods

Analysis of the primary endpoint of ORR included hypothesis testing of the noninferiority and superiority of zanubrutinib to ibrutinib. Noninferiority testing for ORR was performed using a stratified Wald test based on the stratified Mantel-Haenszel response ratio estimate against the noninferiority margin of 0.8558 on the log scale. Superiority testing was performed using a stratified Cochran-Mantel-Haenszel test. All stratified analyses were stratified by the four randomization stratification factors. Response rates for each treatment arm were calculated along with 95% confidence intervals.

Analysis of the key secondary endpoint of PFS included hypothesis testing of the noninferiority and superiority of zanubrutinib to ibrutinib. Noninferiority testing was performed using a stratified Wald test based on the hazard ratio estimate from a stratified Cox proportional hazards model against the noninferiority margin of 1.3319 on the log scale. Superiority testing was performed using a stratified log-rank test. The stratified hazard ratio was calculated along with its 95% confidence interval, and the distribution of PFS for each arm was summarized using the median and other quartiles as well as PFS rates at selected timepoints based on the Kaplan-Meier method.

The key secondary endpoint of atrial fibrillation/flutter incidence was analyzed based on incidence rates compared and tested using a chi-square test. While hypothesis testing was performed, the endpoint of atrial fibrillation/flutter was tested separately from the hierarchical testing of ORR and PFS. (See Statistical Analysis Plan for details on hypothesis testing and multiplicity adjustment)

Other secondary endpoints were analyzed with methods described above. Duration of response was analyzed for patients who achieved a response (partial response or higher). The distribution of duration of response for each arm was summarized using the median and other quartiles as well as event-free rates at selected timepoints. Treatment arm comparisons were not performed. Rate of PR-L (partial response with lymphocytosis) was summarized for each treatment arm along with corresponding 95% confidence intervals, and overall survival was summarized using

methods described for PFS including hazard ratio estimates, Kaplan-Meier estimates and corresponding confidence intervals. (See Statistical Analysis Plan for details on planned health-related quality-of-life analyses)

Sample Size Considerations

The sample size calculation is based on the primary efficacy analyses for the primary endpoint of overall response rate per investigator assessment. Assuming a response ratio (zanubrutinib arm / ibrutinib arm) of 1.03 (72% / 70%), 600 patients will provide more than 90% power to demonstrate the noninferiority of zanubrutinib to ibrutinib at the noninferiority margin of 0.8558 (response ratio) and a 1-sided alpha level of 0.025 when there is 1 interim analysis at 69% information fraction. The response rate for ibrutinib is approximated from published clinical data.[1] The noninferiority margin of 0.8558 was derived based on the ratio of overall response rates of ibrutinib versus active controls in the RESONATE and RESONATE 2 trials using a fixed-effect meta-analysis. The choice of noninferiority margin of 0.8558 retained 80% of the estimated treatment effect on the log scale.

Assuming a hazard ratio (HR) of 0.9 (zanubrutinib arm / ibrutinib arm), 205 PFS events are required to achieve 80% power at a 1-sided alpha of 0.025 to demonstrate the noninferiority of zanubrutinib to ibrutinib at the noninferiority margin of 1.3319 (HR) for the key secondary endpoint of PFS per investigator assessment. The noninferiority margin of 1.3319 was derived based on the hazard ratio of ibrutinib versus active controls in the RESONATE and RESONATE 2 trials using a fixed-effect meta-analysis. The choice of noninferiority margin of 1.3319 retained over 80% of the estimated treatment effect on the log scale.

Progression-free Survival Sensitivity Analyses

The non-inferiority of the key secondary endpoint of PFS will also be analyzed in the Per-protocol Analysis Set. Per protocol population is defined as including patients who received any dose of study drug and had no critical protocol deviation. To account for disease progression due to study drug interruption, PFS was summarized where disease progression that occurs within 6 weeks of a study drug interruption of at least 7 days was not counted as disease progression for the purpose of this sensitivity analysis. To account for the impact of COVID-19, PFS was summarized for each treatment arm while additionally censoring deaths due to COVID-19. Additionally, alternative censoring rules were applied for new CLL/SLL therapies for patients who did not have progressive disease assessment prior starting new anti-cancer therapy.

Adverse Event of Special Interest Categories and Search Terms

Adverse Event of Special Interest Category	Search Criteria
Hemorrhage	Hemorrhage terms (excluding laboratory terms) (SMQ) Narrow
Major hemorrhage	Major hemorrhage: • Subdural hematoma PT • Subdural hemorrhage PT • All Hemorrhage PT if AE SOC is 'Nervous system disorders • Serious or grade 3 and above Hemorrhage PT if AESOC is not 'Nervous system disorders
Atrial fibrillation and/or flutter	Atrial fibrillation PT, Atrial flutter PT
Hypertension	Hypertension (SMQ) Narrow
Second primary malignancies Skin cancers	Malignant Tumors (SMQ) Narrow Subcategory - skin cancers: skin malignant tumors (SMQ) Narrow
Tumor lysis syndrome	Tumor lysis syndrome (SMQ) Narrow
Infection Opportunistic Infections	Infections: Infections and Infestations SOC Subcategory - Opportunistic infections: Opportunistic infections (SMQ) Narrow
Neutropenia	Neutropenia PT, Neutrophil count decreased PT, Febrile neutropenia PT, Agranulocytosis PT, Neutropenic infection PT, Neutropenic sepsis PT
Thrombocytopenia	Thrombocytopenia PT, Platelet count decreased PT
Anemia	Anemia PT, Hemoglobin decreased PT

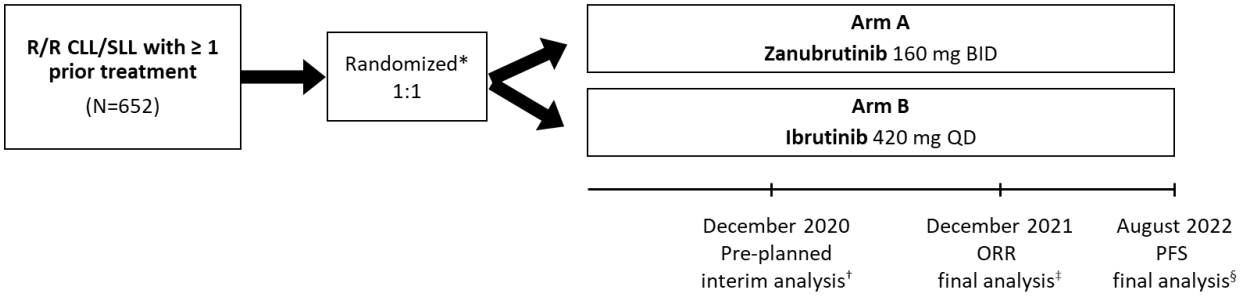
AE, adverse events; PT, preferred term; SMQ, standardized MedDRA query; SOC, system organ class

Representativeness of Study Participants

Disease under investigation	Relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia
Special considerations	
Sex and gender	CLL/SLL affects men more than women (1.9:1) and this gender effect seems to be stable across all ethnicities.[2,3]
Age	CLL/SLL typically affects older adults; median age at diagnosis is 70 years.[3]
Race or ethnic group	CLL/SLL occurs in patients of White/Caucasian ethnicity more frequently than other populations.[2] Incidence of CLL is 5-10-fold less in Asian populations than Caucasian/White populations. Incidence of CLL is lower among African Americans than among White/Caucasians and age adjusted survival is inferior.[4] Compared with other populations, African Americans with CLL have higher adverse prognostic features, such as deletions of the short arm of chromosome 17 (del[17p]; *see other considerations*). [5]
Geography	Incidence and mortality of CLL/SLL are highest in Central and Western Europe, North America, and Australia and lower in Asia.[2]
Other considerations	Del(17p) and abnormalities in the *TP53* gene are the most important prognostic and predictive markers for treatment decisions in CLL[6] as they are correlated with unfavorable outcomes with current standard treatments for CLL. These alterations occur in up to 30% to 40% of relapsed/refractory cases.[7]
Overall representativeness of this trial	The participants in the present trial demonstrated the expected ratio of men to women with a median age of 67 years. As most participants from this multiregional study were from Europe, United States, and New Zeeland/Australia, 81% of participants were Caucasian/White, which is consistent with the general population. Asian patients represented 14% of the study population; less than 1.0% of the study participants were African American. Nearly one-fourth of participants in ALPINE were high-risk with del(17p) and/or *TP53* mutations. While this rate is at the lower bound end, it remains within reported values in the general population of patients with R/R CLL.

Supplemental Figures

Figure S1. Study Design

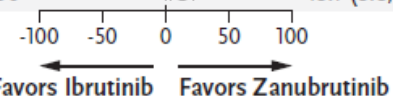


*Stratification factors: age, geographic region, refractory status, and del(17p)/*TP53* mutation status.
†ORR interim analysis scheduled approximately 12 months after the enrollment of the first 415 patients.
‡ORR final analysis scheduled approximately 12 months after enrollment completion.
§PFS final analysis scheduled when approximately 205 PFS events were observed.
BID denotes twice daily, CLL chronic lymphocytic leukemia, ORR overall response rate, PFS progression-free survival, QD once daily, R/R relapsed/refractory, SLL small lymphocytic lymphoma.
ALPINE enrolled 652 patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. Patients were randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily until disease progression or unacceptable toxicity.

Figure S2. Subgroup Analysis for Investigator- and Independent Review Committee–Assessed Overall Response Rate (ITT Population, N=652)

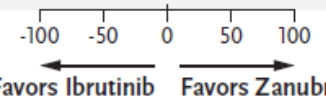
A. Investigator-Assessed ORR

Subgroup	Zanubrutinib *Response/Subjects*	Ibrutinib *Response/Subjects*	Rate Difference (95% CI)[a], %
Age group			
<65 years	113/126	99/125	10.5 (1.6, 19.4)
≥65 years	160/201	142/200	8.6 (0.2, 17.0)
Sex			
Male	179/213	168/232	11.6 (4.1, 19.2)
Female	94/114	73/93	4.0 (-6.9, 14.8)
Geographic region			
Asia	40/49	33/45	8.3 (-8.6, 25.2)
Australia/New Zealand	21/28	24/30	-5.0 (-26.5, 16.5)
Europe	164/198	146/191	6.4 (-1.6, 14.4)
North America	48 /52	38/59	27.9 (13.7, 42.1)
Prior lines of therapy			
1–3	252/303	219/295	8.9 (2.4, 15.5)
>3	21/24	22/30	14.2 (-6.5, 34.8)
Baseline ECOG performance status			
0	111/129	88/122	13.9 (4.0, 23.9)
≥1	162/198	153/203	6.4 (-1.6, 14.4)
Baseline del17p/TP53 mutation status			
Present	61/75	48/75	17.3 (3.3, 31.3)
Absent	211/251	193/250	6.9 (0.0, 13.8)
Bulky disease[b]			
Yes	125/145	114/149	9.7 (0.9, 18.5)
No	148/182	127/176	9.2 (0.4, 17.9)
Baseline Beta-2 microglobulin			
≤3.5 mg/L	82/105	63/92	9.6 (-2.7, 22.0)
>3.5 mg/L	152/176	138/183	11.0 (2.9, 19.0)
Baseline IGHV mutation status			
Unmutated	205/239	180/239	10.5 (3.4, 17.5)
Mutated	60/79	48/70	7.4 (-7.0, 21.8)
Disease stage			
Binet state of A/B or Ann Arbor stage I/II bulky	151/182	142/189	7.8 (-0.4, 16.1)
Binet stage C or Ann Arbor stage III/IV	122/145	99/135	10.8 (1.3, 20.3)
Complex karyotype			
Yes	48/56	52/70	11.4 (-2.3, 25.2)
No	133/153	96/130	13.1 (3.8, 22.3)



B. IRC-Assessed ORR

Subgroup	Zanubrutinib Response/Subjects	Ibrutinib Response/Subjects	Rate Difference (95% CI)[a], %
Age group			
<65 years	117/126	98/125	14.5 (6.0, 23.0)
≥65 years	165/201	148/200	8.1 (0.0, 16.2)
Sex			
Male	185/213	170/232	13.6 (6.3, 20.9)
Female	97/114	76/93	3.4 (-6.9, 13.6)
Geographic region			
Asia	43/49	35/45	10.0 (-5.2, 25.2)
Australia/New Zealand	22/28	23/30	1.9 (-19.5, 23.4)
Europe	169/198	150/191	6.8 (-0.8, 14.4)
North America	48/52	38/59	27.9 (13.7, 42.1)
Prior lines of therapy			
1–3	260/303	223/295	10.2 (3.9, 16.5)
>3	22/24	23/30	15.0 (-3.7, 33.7)
Baseline ECOG performance status			
0	115/129	89/122	16.2 (6.7, 25.7)
≥1	167/198	157/203	7.0 (-0.7, 14.7)
Baseline del17p/TP53 mutation status			
Present	64/75	53/75	14.7 (1.6, 27.7)
Absent	217/251	193/250	9.3 (2.5, 16.0)
Bulky disease[b]			
Yes	127/145	116/149	9.7 (1.2, 18.3)
No	155/182	130/176	11.3 (3.0, 19.6)
Baseline Beta-2 microglobulin			
≤3.5 mg/L	88/105	67/92	11.0 (-0.5, 22.5)
>3.5 mg/L	153/176	140/183	10.4 (2.5, 18.3)
Baseline IGHV mutation status			
Unmutated	212/239	184/239	11.7 (5.0, 18.4)
Mutated	61/79	48/70	8.6 (-5.6, 22.9)
Disease stage			
Binet state of A/B or Ann Arbor stage I/II bulky	157/182	142/189	11.1 (3.2, 19.1)
Binet stage C or Ann Arbor stage III/IV	125/145	104/135	9.2 (0.1, 18.2)
Complex karyotype			
Yes	46/56	53/70	6.4 (-7.8, 20.6)
No	140/153	98/130	16.1 (7.5, 24.7)



All subgroups, with the exception of complex karyotype were prespecified.

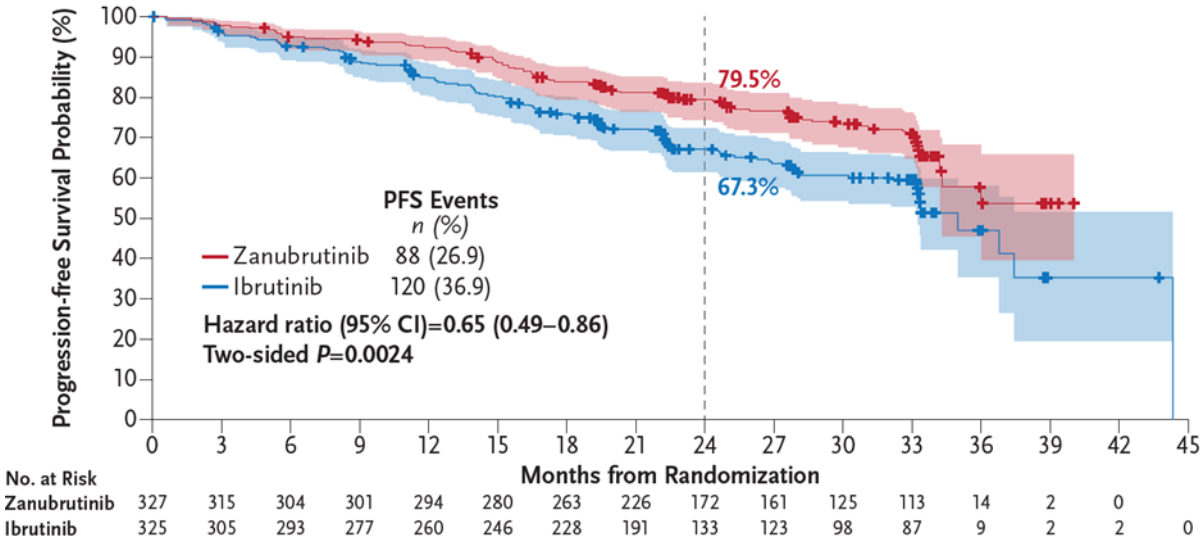
[a]Rate difference (zanubrutinib minus ibrutinib) and 95% CI were unstratified for subgroups.

[b]Bulky disease is derived from any target lesion longest diameter ≥5 cm.

ECOG denotes Eastern Cooperative Oncology Group, IGHV immunoglobulin heavy chain variable region, IRC Independent Review Committee, ORR overall response rate.

Figure S3. Independent-Review Committee Assessed Progression-Free Survival in ITT and del(17p)/*TP53* Mutation Populations

A. ITT population



Noninferiority 1-sided *P* <0.0001.

B. del[17p]/*TP53*^{mut} population

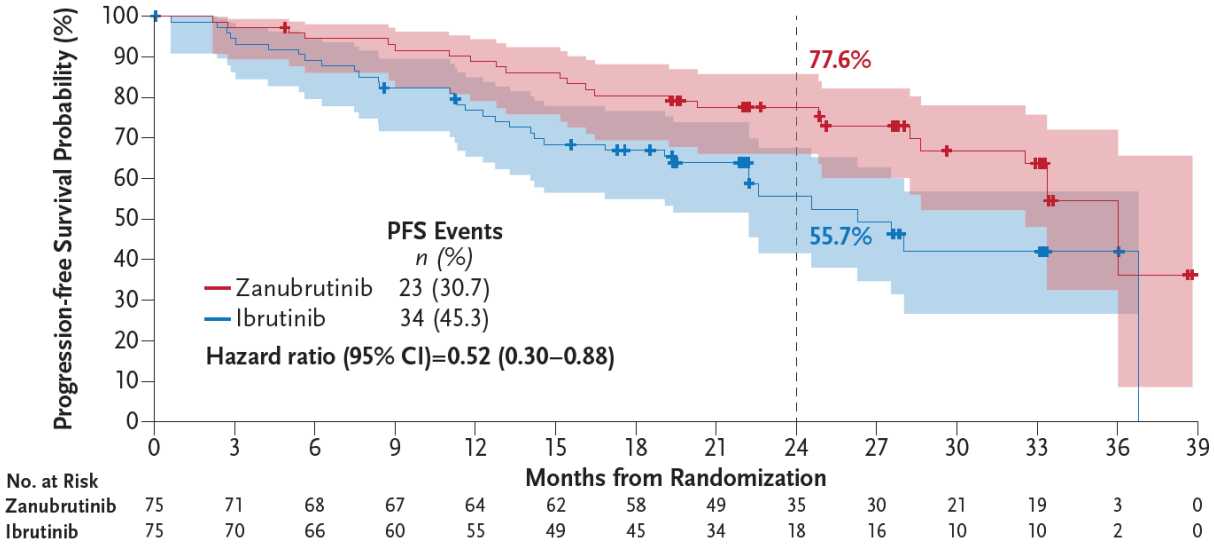
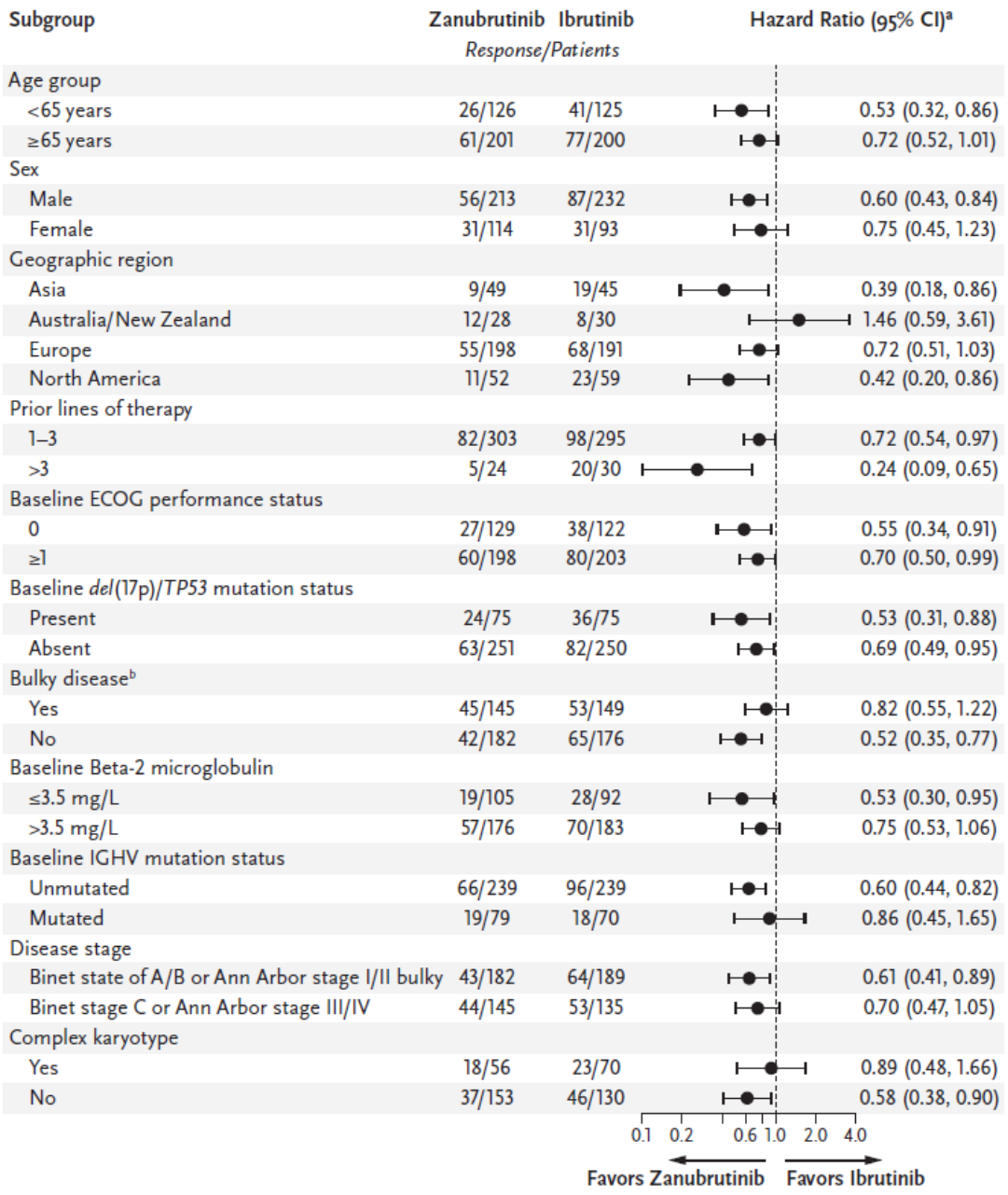
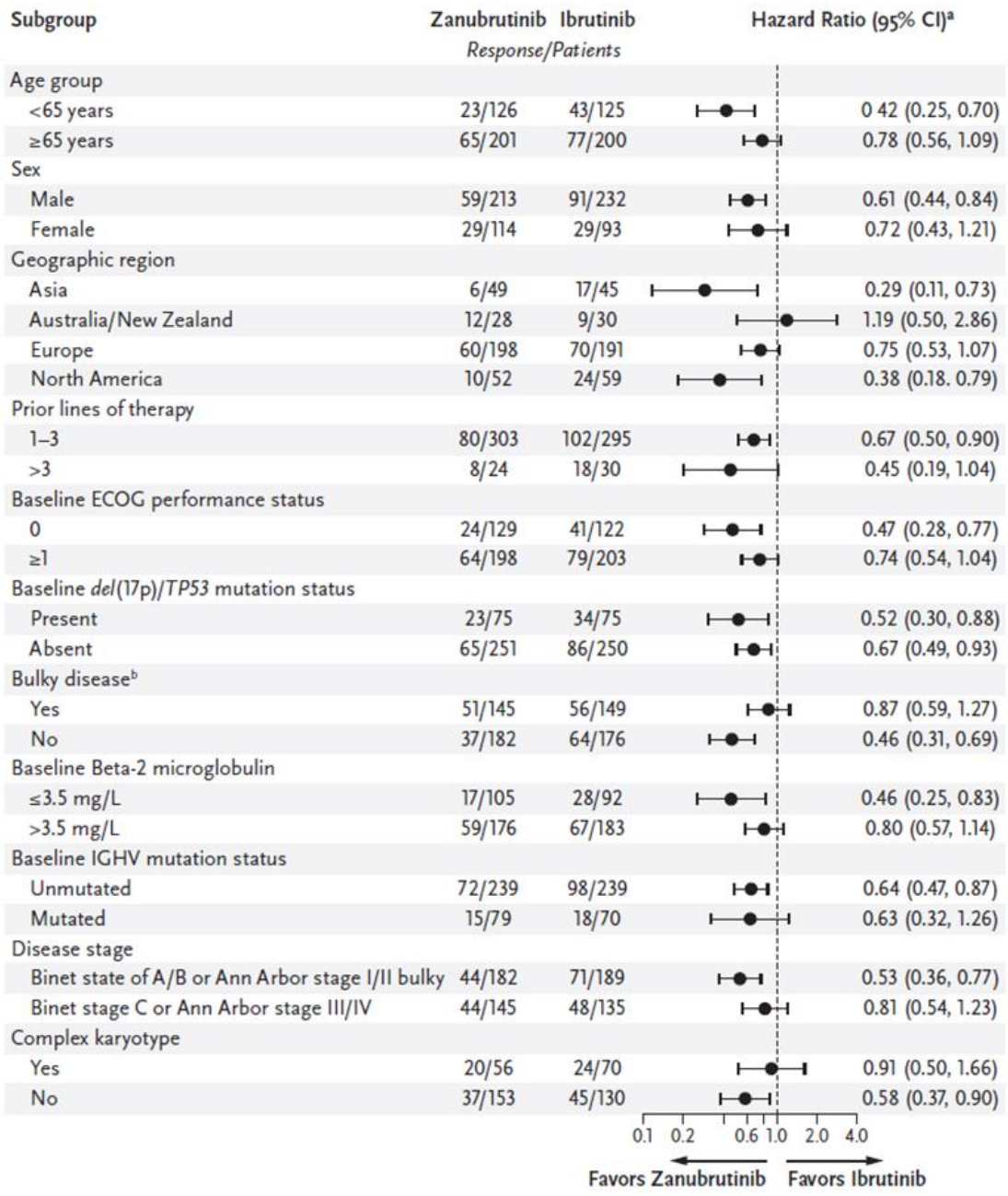


Figure S4. Subgroup Analysis for Investigator- and Independent Review Committee–Assessed Progression-Free Survival (ITT Population, N=652)

A. Investigator-assessed PFS

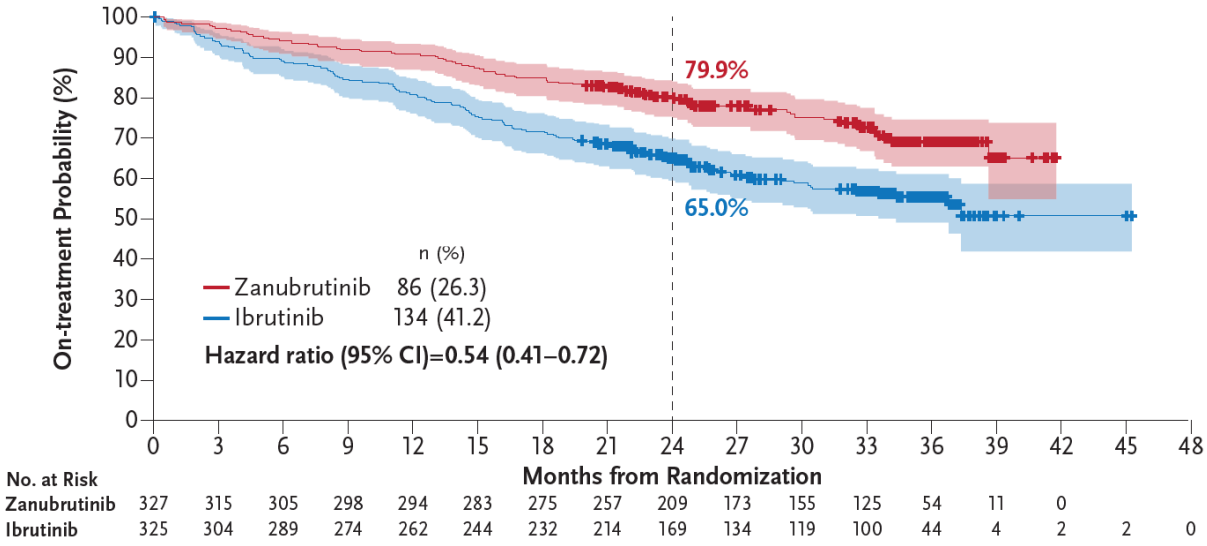


B. IRC-assessed PFS



All subgroups, with the exception of complex karyotype were prespecified.
[a]Hazard ratio (zanubrutinib over ibrutinib) and 95% CI were unstratified for subgroups.
[b]Bulky disease is derived from any target lesion longest diameter ≥5 cm.
ECOG denotes Eastern Cooperative Oncology Group, IGHV immunoglobulin heavy chain variable region, IRC Independent Review Committee, ORR overall response rate; PFS, progression-free survival.

Figure S5. Time-to-Treatment Failure



Supplemental Tables

Table S1. Investigator- and Independent Review Committee–Assessed Best Response Rate in All Patients; Data Cut-Off 1 December 2021 (ITT Population, N=652)

Best Response, n (%)	ITT Population	
	Zanubrutinib (n=327)	Ibrutinib (n=325)
Investigator Assessed		
ORR, % (95% CI)	**79.5* (74.7, 83.8)**	**71.1 (65.8, 75.9)**
CR or CRi	16 (4.9)	9 (2.8)
PR or nPR	244 (74.6)	222 (68.3)
PR-L	32 (9.8)	35 (10.8)
SD	25 (7.6)	39 (12.0)
PD	1 (0.3)	6 (1.8)
Discontinue prior to first assessment, NA or NE	9 (2.8)	14 (4.3)
IRC Assessed		
ORR, % (95% CI)	**80.4† (75.7, 84.6)**	**72.9 (67.7, 77.7)**
CR or CRi	13 (4.0)	8 (2.5)
PR or nPR	250 (76.5)	229 (70.5)
PR-L	33 (10.1)	32 (9.8)
SD‡	20 (6.1)	35 (10.8)
PD	3 (0.9)	7 (2.2)
Discontinue prior to first assessment, NA or NE	8 (2.4)	14 (4.3)

*Noninferiority 1-sided *P* <0.0001, superiority 2-sided *P*=0.0133 (superiority met at ORR IA with data cut-off 31 Dec 2020). Both *P*-values are descriptive.

†Noninferiority 1-sided *P* <0.0001, superiority 2-sided *P*=0.0264.

‡Includes 2 patients in zanubrutinib arm with response of non-progressive disease.

P-value was calculated for noninferiority via stratified test statistic against a null response ratio of 0.8558 and for superiority via stratified Cochran-Mantel-Haenszel test statistic.

CI denotes confidence interval; CR, complete response; CRi, CR with incomplete bone marrow recovery; IA, interim analysis; IRC, independent review committee; ITT, intent-to-treat; NA, not assessed; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD stable disease.

Table S2. Investigator- and Independent Review Committee–Assessed Best Response Rate in ITT Population and in Patients With del(17p)/*TP53* Mutation

Best Response, n (%)	ITT Population		del(17p)/*TP53* Mutation	
	Zanubrutinib (n=327)	Ibrutinib (n=325)	Zanubrutinib (n=75)	Ibrutinib (n=75)
Investigator Assessed				
ORR, % **95% CI**	**83.5** **79.0–87.3**	**74.2** **69.0–78.8**	**81.3** **70.7–89.4**	**64.0** **52.1–74.8**
CR or CRi	23 (7.0)	16 (4.9)	5 (6.7)	3 (4.0)
PR or nPR	250 (76.5)	225 (69.2)	56 (74.7)	45 (60.0)
PR-L	21 (6.4)	27 (8.3)	6 (8.0)	9 (12.0)
SD	23 (7.0)	37 (11.4)	5 (6.7)	13 (17.3)
PD	1 (0.3)	6 (1.8)	0	2 (2.7)
Discontinue prior to first assessment, NA or NE	9 (2.8)	14 (4.3)	3 (4.0)	3 (4.0)
IRC Assessed				
ORR, % **95% CI**	**86.2** **82.0–89.8**	**75.7** **70.7–80.3**	**85.3** **75.3–92.4**	**70.7** **59.0–80.6**
CR or CRi	22 (6.7)	19 (5.8)	6 (8.0)	4 (5.3)
PR or nPR	260 (79.5)	227 (69.8)	58 (77.3)	49 (65.3)
PR-L	18 (5.5)	24 (7.4)	4 (5.3)	7 (9.3)
SD*	16 (4.9)	34 (10.5)	3 (4.0)	8 (10.7)
PD	3 (0.9)	7 (2.2)	1 (1.3)	4 (5.3)
Discontinue prior to first assessment, NA or NE	8 (2.4)	14 (4.3)	3 (4.0)	3 (4.0)

*Includes 2 patients in zanubrutinib arm (1 in del(17p)/TP53 subgroup) with response of non-progressive disease.
Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
CI denotes confidence interval; CR, complete response; CRi, CR with incomplete bone marrow recovery; IRC, independent review committee; ITT, intent-to-treat; NA, not assessed; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD stable disease.

Table S3. Investigator- and Independent Review Committee-Assessed Duration of Response (N=652)

	ITT Population	
	Zanubrutinib (n=327)	**Ibrutinib (n=325)**
Investigator Assessed		
Number of Responders	273	241
Events, n (%)	**53 (19.4)**	**62 (25.7)**
Progressive Disease	33 (12.1)	45 (18.7)
Death	20 (7.3)	17 (7.1)
Median Duration of Response, mo (95% CI)	NE (31.3, NE)	33.9 (33.9, NE)
24-month Event-free Rate, % (95% CI)	79.5 (73.1-84.6)	71.3 (63.8-77.5)
IRC Assessed		
Number of Responders	282	246
Events, n (%)	**60 (21.3)**	**69 (28.0)**
Progressive Disease	40 (14.2)	52 (21.1)
Death	20 (7.1)	17 (6.9)
Median Duration of Response, mo (95% CI)	NE (31.3, NE)	33.9 (32.2, 41.4)
24-month Event-free Rate, % (95% CI)	77.4 (71.0-82.5)	67.8 (60.1-74.3)

Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
CI denotes confidence interval; IRC, independent review committee; mo, months; NE, not estimable.

Table S4. Summary of Progressive Disease by Investigator-Assessment (N=652)

	ITT Population	
	Zanubrutinib (n=327)	**Ibrutinib (n=325)**
Patients with Progressive Disease*	**54 (16.5)**	**78 (24.0)**
Primary Method of Detection		
Increase in lymph nodes	40 (12.2)	61 (18.8)
New enlarged lymph nodes	3 (0.9)	6 (1.8)
New or increase in splenomegaly	8 (2.4)	6 (1.8)
New symptomatic disease	3 (0.9)	4 (1.2)
Decreased in platelet count	0	1 (0.3)
Patients with Disease Transformation	**5 (1.5)**	**4 (1.2)**

*Isolated lymphocytosis was not a criterion for progressive disease

Table S5. Sensitivity Analyses for Investigator- and Independent Review Committee-Assessed Progression-Free Survival

PFS HR (95% CI)	**Investigator Assessment**	**Independent Review Assessment**
Per protocol population (N=646)	0.64 (0.48, 0.85)	0.64 (0.48, 0.85)
Alternative Censoring Rules (ITT, N=652)	0.65 (0.49, 0.87)	0.63 (0.48, 0.84)
Accounting for Drug Interruption (ITT, N=652)	0.71 (0.52, 0.96)	0.71 (0.53, 0.95)
Accounting for Death due to COVID-19 (ITT, N=652)	0.62 (0.46, 0.84)	0.62 (0.45, 0.84)

Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
PFS, progression-free survival.

Table S6. Most Frequent Treatment-Emergent Adverse Events (>10%) in Either Arm (Safety Population; N=648)

TEAE by Preferred Term, n (%)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 TEAE	**318 (98.1)**	**321 (99.1)**
COVID-19	75 (23.1)	58 (17.9)
Neutropenia	74 (22.8)	59 (18.2)
Hypertension	71 (21.9)	64 (19.8)
Upper respiratory tract infection	68 (21.0)	46 (14.2)
Diarrhea	52 (16.0)	78 (24.1)
Anemia	49 (15.1)	51 (15.7)
Arthralgia	47 (14.5)	53 (16.4)
Contusion	44 (13.6)	34 (10.5)
Cough	38 (11.7)	34 (10.5)
Pneumonia	34 (10.5)	40 (12.3)
Rash	33 (10.2)	40 (12.3)
Fatigue	31 (9.6)	43 (13.3)
Pyrexia	27 (8.3)	33 (10.2)
Atrial fibrillation	15 (4.6)	40 (12.3)
Muscle spasms	10 (3.1)	41 (12.7)

TEAE, treatment-emergent adverse event.

Table S7. Adverse Events Leading to Death (Safety Population; N=648)

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Patients With ≥1 TEAE Leading to Death*	**33 (10.2)**	**36 (11.1)**
Infections and infestations	**22 (6.8)**	**22 (6.8)**
COVID-19	6 (1.9)	8 (2.5)
COVID-19 pneumonia	7 (2.2)	7 (2.2)
Pneumonia	4 (1.2)	4 (1.2)
Sepsis	2 (0.6)	0
Septic shock	0	2 (0.6)
Bacterial sepsis	1 (0.3)	0
Infection	1 (0.3)	0
Influenza	0	1 (0.3)
Lower respiratory tract infection bacterial	1 (0.3)	0
Pneumonia bacterial	1 (0.3)	0
Pneumonia cryptococcal	1 (0.3)	0
Pneumonia fungal	1 (0.3)	0
Pneumonia pseudomonal	1 (0.3)	0
Respiratory tract infection	1 (0.3)	0
General disorders and administration site conditions	**5 (1.5)**	**4 (1.2)**
Death	2 (0.6)	2 (0.6)
Malaise	2 (0.6)	0
Multiple organ dysfunction syndrome	1 (0.3)	1 (0.3)
Pyrexia	0	1 (0.3)
Cardiac disorders	**0 (0)**	**6 (1.9)**
Cardiac arrest	0	2 (0.6)
Myocardial infarction	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)
Congestive cardiomyopathy	0	1 (0.3)
Nervous system disorders	**2 (0.6)**	**3 (0.9)**
Central nervous system hemorrhage	0	1 (0.3)
Cerebral hemorrhage	1 (0.3)	0
Cerebral infarction	0	1 (0.3)
Cerebrovascular accident	0	1 (0.3)
Ischemic stroke	1 (0.3)	0
Respiratory, thoracic, and mediastinal disorders	**3 (0.9)**	**2 (0.6)**
Respiratory failure	1 (0.3)	1 (0.3)
Acute respiratory failure	1 (0.3)	0
Pulmonary embolism	0	1 (0.3)
Pulmonary edema	1 (0.3)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**3 (0.9)**	**0**
Neuroendocrine carcinoma	2 (0.6)	0
Adenocarcinoma of colon	1 (0.3)	0
Injury, poisoning, and procedural complications	**1 (0.3)**	**1 (0.3)**
Craniocerebral injury	1 (0.3)	0
Subdural hematoma	0	1 (0.3)

Gastrointestinal disorders	**1 (0.3)**	**0**
Colitis	1 (0.3)	0
Hepatobiliary disorders	**1 (0.3)**	**0**
Jaundice	1 (0.3)	0
Metabolism and nutrition disorders	**0**	**1 (0.3)**
Hypercalcemia	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	**1 (0.3)**	**0**
Mobility decreased	1 (0.3)	0
Renal and urinary disorders	**0**	**1 (0.3)**
Acute kidney injury	0	1 (0.3)
Vascular disorders	**1 (0.3)**	**0**
Aortic aneurysm rupture	1 (0.3)	0

*A total of 12 patients were reported to have more than 1 adverse event leading to death.
Patient 1 was reported to have grade 5 influenza and respiratory failure.
Patient 2 was reported to have grade 5 COVID-19 and COVID-19 pneumonia.
Patient 3 was reported to have grade 5 COVID-19 pneumonia and myocardial infarction.
Patient 4 was reported to have grade 5 COVID-19 pneumonia, cerebrovascular accident, and pulmonary embolism.
Patient 5 was reported to have grade 5 COVID-19 and respiratory failure.
Patient 6 was reported to have grade 5 COVID-19 and acute respiratory failure.
Patient 7 was reported to have grade 5 COVID-19 pneumonia and pneumonia bacterial.
Patient 8 was reported to have grade 5 lower respiratory tract infection bacterial, multiple organ dysfunction syndrome, pneumonia pseudomonal, and sepsis.
Patient 9 was reported to have grade 5 colitis and sepsis.
Patient 10 was reported to have grade 5 mobility decreased, malaise, and jaundice.
Patient 11 was reported to have grade 5 craniocerebral injury and cerebral hemorrhage.
Patient 12 was reported to have grade 5 bacterial sepsis and pneumonia.

Table S8. Summary of COVID-19 Related Treatment Emergent Adverse Events* (Safety Population; N=648)

TEAE related to COVID-19, n(%)	**Zanubrutinib (n=324)**	**Ibrutinib (n=324)**
Patients with any COVID-19 TEAE*	93 (28.7)	70 (21.6)
Grade 3 or higher	40 (12.3)	28 (8.6)
Leading to treatment discontinuation	12 (3.7)	16 (4.9)
Fatal	12 (3.7)	15 (4.6)

*COVID-19-related TEAE denotes any COVID-19 related preferred terms: COVID-19, COVID-19 pneumonia, post-acute COVID-19 syndrome, suspected COVID-19.

Table S9. All Cardiac Adverse Events (Safety Population; N=648)

Cardiac TEAEs, n (%)	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac Adverse Events		
Any event in cardiac disorders SOC	**69 (21.3)**	**96 (29.6)**
Atrial fibrillation	15 (4.6)	40 (12.3)
Palpitations	9 (2.8)	13 (4.0)
Atrioventricular block first degree	5 (1.5)	3 (0.9)
Cardiac failure	5 (1.5)	6 (1.9)
Sinus bradycardia	5 (1.5)	7 (2.2)
Angina pectoris	4 (1.2)	7 (2.2)
Sinus tachycardia	4 (1.2)	1 (0.3)
Supraventricular extrasystoles	4 (1.2)	3 (0.9)
Arrhythmia supraventricular	3 (0.9)	0
Bundle branch block left	3 (0.9)	0
Myocardial ischemia	3 (0.9)	1 (0.3)
Ventricular extrasystoles	3 (0.9)	3 (0.9)
Atrial flutter	2 (0.6)	3 (0.9)
Bundle branch block right	2 (0.6)	3 (0.9)
Coronary artery disease	2 (0.6)	1 (0.3)
Supraventricular tachycardia	2 (0.6)	1 (0.3)
Ventricular arrhythmia	2 (0.6)	1 (0.3)
Acute coronary syndrome	1 (0.3)	0
Acute myocardial infarction	1 (0.3)	0
Aortic valve stenosis	1 (0.3)	0
Arrhythmia	1 (0.3)	2 (0.6)
Arteriosclerosis coronary artery	1 (0.3)	0
Bradyarrhythmia	1 (0.3)	0
Cardiac failure congestive	1 (0.3)	2 (0.6)
Coronary artery insufficiency	1 (0.3)	0
Defect conduction intraventricular	1 (0.3)	0
Dilatation atrial	1 (0.3)	0
Extrasystoles	1 (0.3)	2 (0.6)
Left atrial hypertrophy	1 (0.3)	0
Left ventricular dysfunction	1 (0.3)	0
Left ventricular failure	1 (0.3)	0
Mitral valve incompetence	1 (0.3)	2 (0.6)
Myocardial fibrosis	1 (0.3)	0
Myocardial infarction	1 (0.3)	3 (0.9)
Pericardial effusion	1 (0.3)	0
Sinus arrhythmia	1 (0.3)	1 (0.3)
Sinoatrial block	1 (0.3)	0
Tachycardia	1 (0.3)	2 (0.6)
Ventricular hypokinesia	1 (0.3)	0
Bradycardia	0	3 (0.9)
Cardiac arrest	0	3 (0.9)
Cardiac discomfort	0	3 (0.9)
Congestive cardiomyopathy	0	3 (0.9)

Ventricular fibrillation	0	2 (0.6)
Aortic valve incompetence	0	1 (0.3)
Atrial tachycardia	0	1 (0.3)
Atrioventricular block	0	1 (0.3)
Cardiac disorder	0	1 (0.3)
Cardiac failure acute	0	1 (0.3)
Cardiac failure chronic	0	1 (0.3)
Sinus node dysfunction	0	1 (0.3)
Cardiac adverse events leading to treatment discontinuation		
Any TEAE in cardiac disorders SOC	**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)

SOC based on MedDRA version 24.0 denotes system organ class.
TEAE, treatment-emergent adverse event.

Table S10. Adverse Events of Special Interest* (Safety Population; N=648)

AESI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	**Ibrutinib (n=324)**	**Zanubrutinib (n=324)**	**Ibrutinib (n=324)**
≥1 AESI	**294 (90.7)**	**300 (92.6)**	**186 (57.4)**	**184 (56.8)**
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (4.3)	11 (3.4)	12 (3.7)
Hypertension	76 (23.5)	74 (22.8)	49 (15.1)	44 (13.6)
Infections	231 (71.3)	237 (73.1)	86 (26.5)	91 (28.1)
Opportunistic infection	7 (2.2)	10 (3.1)	5 (1.5)	5 (1.5)
Neutropenia†	95 (29.3)	79 (24.4)	68 (21.0)	59 (18.2)
Secondary primary malignancies	40 (12.3)	43 (13.3)	22 (6.8)	17 (5.2)
Skin cancers	21 (6.5)	28 (8.6)	7 (2.2)	4 (1.2)
Thrombocytopenia	42 (13.0)	50 (15.4)	11 (3.4)	17 (5.2)
Tumor lysis syndrome	1 (0.3)	0	1 (0.3)	0

* Specific related MedDRA preferred terms were pooled for each AESI category and summarized.
†Febrile neutropenia was reported in 4(1.2%) vs 3(0.9%) patients treated with zanubrutinib and ibrutinib, respectively.
AESI, adverse events of special interest.

Table S11. Treatment-Emergent Adverse Events of Special Interest Opportunistic Infections. (Safety Population; N=648)

Opportunistic Infections, n (%)	**Zanubrutinib (n=324)**	**Ibrutinib (n=324)**
Pneumonia fungal	2 (0.6)	2 (0.6)
Bronchopulmonary aspergillosis	2 (0.6)	1 (0.3)
Pneumocystis jirovecii pneumonia	1 (0.3)	2 (0.6)
Fungal abscess central nervous system	1 (0.3)	0
Pneumonia cryptococcal	1 (0.3)	0
Herpes ophthalmic	0	2 (0.6)
Ophthalmic herpes zoster	0	1 (0.3)
Osteomyelitis fungal	0	1 (0.3)
Pneumonia legionella	0	1 (0.3)
Pulmonary tuberculosis	0	1 (0.3)

One patient in the ibrutinib arm experienced both pneumonia legionella and pneumocystis jirovecii pneumonia

TEAE, treatment-emergent adverse event.

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