Supplemental Information to: Hillmen P, Eichhorst B, Brown JR. et al. Zanubrutinib versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial

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

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*Number of patients among the first 415 patients enrolled in the study, the 415th patient was randomized on Dec 20, 2019.

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 with ClinicalTrials.gov.

Supplemental Methods

Inclusion criteria

Each patient eligible to participate in this study must meet **all** of the following criteria:

1. Age 18 years or older
2. Confirmed diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) that meets the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria[1]
3. CLL/SLL requiring treatment as defined by at least one of the following criteria:
    a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
    b. Massive (≥ 6 cm below left costal margin), progressive, or symptomatic splenomegaly
    c. Massive nodes (≥ 10 cm in longest diameter), or progressive or symptomatic lymphadenopathy
    d. Progressive lymphocytosis with an increase of > 50% over a two-month period or lymphocyte-doubling time of < 6 months. Lymphocyte-doubling time may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of two weeks over an observation period of two to three months. In patients with initial blood lymphocyte counts of < 30 x 10^9/L (30,000/mL), lymphocyte-doubling time should not be used as a single parameter to define treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL/SLL (e.g., infection) should be excluded
    e. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
        i. Unintentional weight loss of ≥ 10% within the previous 6 months
        ii. Significant fatigue
        iii. Fevers > 100.5°F or 38°C for ≥ 2 weeks without other evidence of infection
        iv. Night sweats for > 1 month without evidence of infection
4. Relapsed or refractory to at least one prior systemic therapy for CLL/SLL. A line of therapy is defined as completing at least two cycles of treatment of standard regimen according to current National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guidelines, or of an investigational regimen on a clinical trial
5. Measurable disease by computed tomography (CT)/magnetic resonance imaging. Measurable disease is defined as ≥ 1 lymph node > 1.5 cm in longest diameter and measurable in two perpendicular diameters or an extranodal lesion must measure > 10 mm in longest perpendicular diameter
6. Eastern Cooperative Oncology Group performance status of 0, 1, or 2
7. Life expectancy ≥ 6 months
8. Adequate bone marrow function as defined by
    a. Absolute neutrophil count (ANC) ≥ 1000/mm^3 (growth factor use is allowed), except for patients with bone marrow involvement, in which case ANC must be ≥ 750/mm^3

        i. The screening hematology values confirming patient meets the ANC requirement must be dated at least 14 days following the most recent administration of peg-filgrastim and at least seven days following the most recent administration of other myeloid growth factors (e.g., granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF])
    b. Platelet ≥ 75,000/mm^3 (may be posttransfusion), except for patients with bone marrow involvement by CLL, in which case the platelet count must be ≥ 30,000/mm^3
    c. Hemoglobin ≥ 7.5 g/dL (may be posttransfusion)
9. Patient must have adequate organ function defined as
    a. Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault equation or the Modification of Diet in Renal Disease equation, or as measured by nuclear medicine scan or 24-hour urine collection)
    b. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤ 2.5 × upper limit of normal unless due to CLL/SLL
    c. Serum total bilirubin < 3.0 × upper limit of normal (unless documented Gilbert syndrome)
10. Female patients of childbearing potential must practice highly effective methods of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib or ibrutinib
11. Male patients are eligible if vasectomized or if they agree to the use of barrier contraception with other highly effective methods during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib or ibrutinib
12. Ability to provide written informed consent and can understand and comply with the requirements of the study

Exclusion criteria

Each patient eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. Known prolymphocytic leukemia or history of, or currently suspected, Richter transformation (biopsy based on clinical suspicion may be needed to rule out transformation)
2. Clinically significant cardiovascular disease including the following:
    a. Myocardial infarction within six months before screening
    b. Unstable angina within three months before screening
    c. New York Heart Association class III or IV congestive heart failure
    d. History of clinically significant arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, Torsades de Pointes)
    e. QTcF > 480 milliseconds based on the Fridericia formula
    f. History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
    g. Uncontrolled hypertension as indicated by a minimum of two consecutive blood pressure measurements showing systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg at screening

3. Prior malignancy within the past three years, except for curatively treated basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, carcinoma in situ of the cervix or breast
4. History of severe bleeding disorder, such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
5. History of stroke or intracranial hemorrhage within 180 days before first dose of study drug
6. Severe or debilitating pulmonary disease
7. Unable to swallow study drug, or disease significantly affecting gastrointestinal function, such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
8. Active fungal, bacterial, and/or viral infection requiring systemic therapy
9. Known central nervous system involvement by leukemia or lymphoma
10. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or adverse events
11. Known infection with HIV or serologic status reflecting active viral hepatitis B or C infection as follows:
    a. Presence of hepatitis B surface antigen or hepatitis B core antibody. Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (< 20 IU), and if they are willing to undergo monitoring for HBV reactivation
    b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable
12. Moderate or severe hepatic impairment, i.e., Child-Pugh class B or C
13. Major surgery within four weeks of the first dose of study drug
14. Prior treatment with a Bruton tyrosine kinase (BTK) inhibitor
15. Last dose of prior therapy for CLL/SLL ≤ 14 days before randomization, with the following additional exclusion requirements:
    a. Treatment with monoclonal antibody-based therapy within 28 days of first dose of study drug
    b. Treatment with chimeric antigen receptor T-cell therapy within 180 days of first dose of study drug
    c. Treatment with Chinese herbal medicine with anticancer intent within 28 days of first dose of study drug
    d. Chemotherapy or radiation treatment within 21 days of first dose of study drug or hematopoietic stem cell transplantation within 90 days of first dose of study drug
16. Ongoing need for corticosteroid use during the trial. NOTE: systemic corticosteroids must be fully tapered off/stopped at least five days before the first dose of study drug
17. Toxicity from prior anticancer therapy that has not recovered to ≤grade 1 (except for alopecia, ANC, and platelet count; for ANC and platelet count, see inclusion criterion 8)

18. Pregnant or lactating women
19. Vaccination with a live vaccine within 35 days prior to the first dose of study drug
20. Ongoing alcohol or drug addiction
21. Hypersensitivity to zanubrutinib, ibrutinib, or any of the other ingredients in either drug
22. Patient requires treatment with warfarin or other vitamin K antagonists
23. Requires ongoing treatment with a strong CYP3A inhibitor or inducer
24. Concurrent treatment for CLL/SLL outside of this clinical trial (includes the screening period)
25. Active and/or ongoing autoimmune anemia and/or autoimmune thrombocytopenia (e.g., idiopathic thrombocytopenia purpura) requiring treatment.

End of treatment

Patients should discontinue study treatment for the following:

- Withdrawal from the study
- Pregnancy
- The investigator or sponsor determines it is in the best interest of the patient
- Intercurrent illness that compromises the patient's ability to participate in the study
- Unequivocal disease progression confirmed by independent central review
    - patients with disease progression may continue study drug treatment with zanubrutinib if they are benefiting from study treatment in the judgement of the investigators, with approval from the medical monitor
- Need for prohibited medication
- Start of alternative anticancer therapy to treat the condition initially being evaluated in this study, or start of therapy for secondary malignancy that would interfere with assessment of zanubrutinib safety and efficacy
- Study drug interruption > 28 days (unless agreed by the investigator and the medical monitor)
- Significant, persistent, or recurrent adverse events

The investigator/patient may elect to discontinue study treatment for reasons other than those listed above but are not required to do so. Withdrawal of consent to the study is not required to discontinue study treatment.

Dose modification for toxicity

Zanubrutinib was interrupted for hematologic toxicity under any of the following conditions:

- Grade 4 neutropenia (that is persistent for at least 10 consecutive days)
- Grade 4 thrombocytopenia (that is persistent for at least 10 consecutive days)
- Grade 3 thrombocytopenia associated with significant bleeding
- Grade ≥ 3 febrile neutropenia

After a first occurrence, zanubrutinib may have been restarted at full dose upon recovery of the toxicity to grade ≤ 1 or baseline. If the same event recurred, patients restarted at one dose level lower (80 g BID) upon recovery of the toxicity to grade ≤1 or baseline. If the event recurred at 80 mg BID, zanubrutinib was once again interrupted until recovery to grade ≤ 1 or baseline and restarted at one dose level lower (80 mg once daily). A maximum of two dose reductions was allowed.

For nonhematologic toxicities, the following guidance was given:

Toxicity	**Action for Zanubrutinib**	**Restart Dose**
Grade ≥ 3 bleeding not considered related to study drug	Hold until recovery to less than or equal to grade 1	Restart at either the original dose or dose level (-1), at the discretion of the treating investigator
Grade ≥ 3 bleeding considered related to study drug	Hold until underlying condition has fully resolved. If underlying condition cannot be treated to full resolution, permanently discontinue zanubrutinib.	Restart at dose level (-1)
Any grade intracranial hemorrhage	Permanently discontinue zanubrutinib.	Not applicable
Atrial fibrillation (AF) that is symptomatic and/or incompletely controlled	Hold until AF is clinically controlled	Restart at either the original dose or dose level (-1), at the discretion of the treating investigator
Other grade ≥ 3 toxicity considered related to study drug, including inadequately controlled hypertension and/or liver or renal laboratory value abnormalities	Hold until recovery to less than or equal to baseline (BL) if BL is greater than grade 1; hold until less than or equal to grade 1 if BL is less than or equal to grade 1.	Restart at either the original dose level or dose level (-1), at the discretion of the treating investigator

For dose modification of ibrutinib, local prescribing guidelines appropriate for your country should be followed.

Central laboratory assessments
CLL/SLL is characterized by various mutations shown to be linked to favorable prognosis or poor prognosis.

Blood and bone marrow samples were used to investigate genetic alterations in the tumor cells, such as del(17p), del(11q), and 12q+, by fluorescence in situ hybridization using a specialized central laboratory, as well as mutation status of relevant genes including *TP53* by molecular techniques.

Efficacy assessments
Overall response to study treatment was assessed every three cycles up to C25 after which it was assessed every six cycles based on the modified iwCLL criteria with addition of treatment-related lymphocytosis (Table S1) for patients with CLL and the Lugano Classification for NHL (Table S2) for patients with SLL using CT-based response criteria.

PFS was defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first. Duration of response was defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first. Overall survival was defined as the time from randomization to the date of death due to any cause.

Safety assessments
Among the first 415 patients randomized, three patients from zanubrutinib arm and one patient from ibrutinib arm were not treated and are not included in the safety analyses.

Statistical analysis
The sample size calculation was based on the noninferiority margin for overall response rate on the response ratio scale of 0.8558, the one-sided type I error of 0.025 and the assumed response ratio of 1.02 (72% / 70%). The assumed response ratio was referenced in Protocol Amendment 3.0 and yielded an updated sample size of approximately 600 patients, an increase from the previous sample size of approximately 400 patients.

To control the study-wide type I error, individual significance levels were adjusted for the following fixed sequence hierarchical testing procedure:

- first, the primary end point of overall response rate (ORR; noninferiority then superiority) would be tested at an interim analysis and a final analysis of ORR
- then, if ORR were statistically significant for the superiority of zanubrutinib over ibrutinib at either the interim or final analysis of ORR, the key secondary end point of progression-free survival (PFS; noninferiority then superiority) would be tested when approximately 205 PFS events have occurred

As this study has an interim and final analysis of the primary end point of ORR, significance levels for ORR testing were adjusted at each analysis of ORR based on an

O’Brien-Fleming alpha spending function. Hypothesis testing for ORR noninferiority was performed using a stratified Wald test of the log response ratio and for superiority using a stratified Cochran-Mantel-Haenszel test. Hypothesis testing for PFS noninferiority will be performed using a stratified Wald test of the log hazard ratio and for superiority using a stratified log-rank test. Stratified analyses were based on the randomization stratification factors, ie, age, geographic region, refractory status and del(17p)/*TP53* mutation status.

A sensitivity analysis of ORR using an alternative set of response confirmation rules (see Appendix C in the SAP) was performed that allowed PR-L to be subsequently confirmed as a best overall response of PR. To account for disease progression due to study drug interruption, ORR and BOR were summarized based on all disease assessments through the data cutoff date, disease progression or the start of new CLL/SLL therapy, whichever came first; however, disease progression that occurred 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. Additionally, to account for the impact of COVID-19, ORR was summarized for each treatment arm excluding patients who died due to COVID-19.

Atrial fibrillation rate, a prespecified key secondary end point, would be tested at the interim and final analyses of ORR using the same significance levels as the hypothesis tests of ORR but would be separate from the fixed sequence testing procedure for ORR and PFS. At the interim analysis of ORR, the analysis was restricted to dosed patients among the first 415 randomized, whereas at the final analysis of ORR, the analysis will include all dosed patients. Hypothesis testing was performed using an unstratified chi-squared test.

Sensitivity analyses of investigator-assessed overall response rate

The noninferiority of the primary endpoint of investigator-assessed overall response rate was analyzed in the per-protocol analysis set. Results were consistent with the investigator-assessed overall response rate for the first 415 randomized patients in the intent-to-treat (ITT) analysis set with a response ratio of 1.26 (95% CI: 1.11, 1.43). The overall response rate was higher for patients in the zanubrutinib arm (79.8% [95% CI: 73.6, 85.1]) compared with the ibrutinib arm (62.8% [95% CI: 55.8, 69.4]).

A sensitivity analysis of investigator-assessed overall response rate was performed that counted assessments of PR-L that were subsequently followed by PR or higher responses as confirmed best overall responses of PR for patients with CLL. Results indicated the noninferiority of zanubrutinib to ibrutinib with a response ratio of 1.11 (95% CI: 0.99, 1.24). The investigator-assessed overall response rate was higher for patients in the zanubrutinib arm (79.7% [95% CI: 73.6, 85.0]) compared with the ibrutinib arm (71.6% [95% CI: 65.0, 77.7]). This result supports the noninferiority of zanubrutinib to ibrutinib.

A sensitivity analysis of investigator-assessed overall response rate was summarized to account for disease progression due to study drug interruption. Results were consistent with the investigator-assessed overall response rate for the first 415 randomized patients in the ITT analysis set. The response ratio was 1.24 [95% CI: 1.10, 1.41], the ORR for zanubrutinib was 78.7% [95% CI 72.5, 84.1], and the ORR for ibrutinib was 63.0 [95% CI: 56.0, 69.6]).

To account for the impact of COVID-19, investigator-assessed overall response rate was summarized for each treatment arm excluding patients who died due to COVID-19. One patient (best response of PR) in the zanubrutinib arm and 4 patients (2 patients with best response of PR; 1 patient with PR-L; 1 patient with stable disease) in the ibrutinib arm who died because of COVID-19-related adverse event were excluded. Results were consistent with the investigator-assessed overall response rate for the first 415 randomized patients in the ITT analysis set. The response ratio was 1.24 [95% CI: 1.09, 1.41], the ORR for zanubrutinib was 78.2% [95% CI 71.9, 83.6], and the ORR for ibrutinib was 62.7 [95% CI: 55.7, 69.4]).

Supplemental Tables

TABLE S1. Modified iwCLL classification for response for CLL[1,2]

Parameter	Complete Response	Partial Response[b]	Partial Response with Lymphocytosis[c]	Progressive Disease[d]
Group A				
Lymphadenopathy[e]	None > 1.5 cm	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50% or new lesion
Hepatomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	
Marrow[f]	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines Crig	50% reduction in marrow infiltrate, or B-lymphoid nodules[h]	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B				
Platelet count	> 100,000/μL	> 100,000/μL or increase ≥ 50% over baseline	> 100,000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils[f]	> 1500/μL	> 1500/μL or > 50% improvement over baseline	> 1500/μL or > 50% improvement over baseline	

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Note: BTK inhibition may cause lymphocytosis due to a redistribution of leukemia cells from the lymphoid tissues to the blood. In such cases, increased blood lymphocytosis may not be a sign of treatment failure or progressive disease. The opposite may occur during periods of temporary holds of BTK inhibitors (due to adverse events or other reasons), and leukemia cells may redistribute from the blood to lymphoid tissue; this also may not be a sign of treatment failure or progressive disease. Isolated increase in lymph

nodes and/or splenomegaly during periods of study drug hold may occur leading to PD. Sites should do their best to obtain CT scans and perform response assessments using the time allotted in assessment windows to avoid this situation. Patient may continue study treatment post-first assessed PD if it is perceived that the patient will benefit from continued treatment. After the second assessment of PD, the patient must discontinue from study treatment. In rare instances, after discussion with the Medical Monitor, the patient may remain on study treatment even after the second assessment of PD.
Group A criteria define the tumor load; Group B criteria define the function of the hematopoietic system (or marrow).
Abbreviations: CLL, chronic lymphocytic leukemia; CRi, CR with incomplete bone marrow recovery; CT=computed tomography; iwCLL, International Workshop on CLL; PD, progressive disease; PR, partial response.
[a]Complete response: all the criteria must be met, and patients must lack disease-related constitutional symptoms.
[b]Partial response: at least 2 of the criteria of group A plus 1 of the criteria of Group B must be met. *If only one Group A parameter is abnormal at baseline, then one Group A parameter is sufficient. Bone marrow results are not required as a Group A parameter to determine PR unless that is the only Group A parameter abnormal at baseline.*
[c]Partial response with lymphocytosis: blood lymphocytes decreased <50% or increased from baseline + otherwise meeting criteria for PR.
[d]Progressive disease: at least 1 of the above progressive disease criteria must be met; Stable disease: is absence of progressive disease and failure to achieve at least a PR-L.
[e]Sum of the products of multiple lymph nodes (as evaluated by CT scans, or by physical examination).
[f] These parameters are irrelevant for some response categories.
[g]Complete response with incomplete marrow recovery: all the criteria met for complete response except for hypocellular bone marrow.
[h]Nodular partial response: all the criteria met for complete response except for the presence of lymphoid nodules in the bone marrow.

TABLE S2. The Lugano classification for CT-based response for SLL[3]

Response and Site	CT-Based Response
Complete	
Lymph nodes and extralymphatic sites	Complete radiologic response (all the following): Target nodes/nodal masses must regress to ≤1.5 cm in longest transverse diameter of a lesion No extralymphatic sites of disease
Nonmeasured lesion	Absent
Organ enlargement	Regress to normal
New lesions	None
Bone marrow	Normal by morphology, if indeterminate, IHC negative
Partial	
Lymph nodes and extralymphatic sites	Partial remission (all the following): ≥ 50% decrease in sum of the product of the perpendicular diameters for multiple lesions of up to 6 target measurable nodes and extranodal sites and no criteria for PD are met When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Absent/normal, regressed, but no increase
Organ enlargement	Spleen must have regressed by > 50% in length beyond normal
New lesions	None
Bone marrow	Not applicable
No response or stable disease	
Target nodes/nodal masses, extranodal lesions	Stable disease < 50% decrease from baseline in sum of the product of the perpendicular diameters for multiple lesions of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	No increase consistent with progression
Organ enlargement	No increase consistent with progression
New lesions	None

Bone marrow	Not applicable
Progressive disease[a]	Progressive disease requires at least 1 of the following cross products of the longest transverse diameter of a lesion and perpendicular diameter progression: An individual node/lesion must be abnormal with: longest transverse diameter of a lesion > 1.5 cm and Increase by ≥ 50% from cross product of the longest transverse diameter of a lesion and perpendicular diameter nadir and An increase in longest transverse diameter of a lesion or shortest axis perpendicular to the longest transverse diameter of a lesion from nadir 0.5 cm for lesions ≤ 2 cm 1 .0 cm for lesions > 2 cm In the setting of splenomegaly[†], the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly[b]
Individual target nodes/nodal masses	
Nonmeasured lesions	New or clear progression of pre-existing nonmeasured lesions
New lesions	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1 .0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent involvement

Modified with permission from Chason BD, et al. *J Clin Oncol* 2014.[3]

Abbreviations: CT, computed tomography; IHC, immunohistochemistry; PD, progressive disease.

[a]Temporary withholding of study drug (e.g., for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

Isolated increase in lymph nodes and/or splenomegaly during periods of study drug hold may occur leading to PD. Sites should do their best to obtain CT scans and perform response assessments using the time allotted in assessment windows to avoid this situation. Patients may continue study treatment post-first assessed PD if it is perceived that the patient will benefit from continued treatment. After the second assessment of PD, the patient must discontinue from study treatment. In rare instances, after

discussion with the Medical Monitor, the patient may remain on study treatment even after the second assessment of PD.
[b]Splenomegaly defined as vertical spleen length > 13 cm.

TABLE S3. Grading scale for hematologic toxicity in CLL studies[1]

Grade	Decrease in Platelets[b] or Hgb[c] (Nadir) From Pretreatment Value	Absolute Neutrophil Count/μL[d] (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

Reproduced with permission from Hallek M, et al *Blood* 2008.[1]

Abbreviations: ANC, absolute neutrophil count; CL, chronic lymphocytic leukemia; G-CSF, granulocyte colony-stimulating factor; Hgb, hemoglobin; WBC, white blood cell.

[a]Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring because of toxicity at any level of decrease from pretreatment will be reported as grade 5.

[b]Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is < 20×10^9/L (20,000/μL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (e.g., < 20×10^9/L [20,000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

[c]Hgb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hgb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

[d]If the ANC reaches < 1×10^9/L (1000/μL), it should be judged to be grade 3 toxicity. Other decreases in the WBC, or in circulating neutrophils, are not to be considered because a decrease in the WBC is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1×10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity but should be documented.

TABLE S4. Summary of deaths

Death Summary, n (%)	**Zanubrutinib (n = 204)**	**Ibrutinib (n = 207)**
Total number of deaths	11 (5.4)	19 (9.2)
Cause of death		
Adverse event[a]	4 (2.0)	9 (4.3)
COVID-19	1 (0.5)	4 (1.9)
Disease under study	6 (2.9)	9 (4.3)
Indeterminate	1 (0.5)	1 (0.5)
Deaths within 30 days of last dose date	8 (3.9)	12 (5.8)
Cause of death		
Adverse event[a]	4 (2.0)	7 (3.4)
COVID-19	1 (0.5)	3 (1.4)
Disease under study	4 (2.0)	4 (1.9)
Indeterminate	0 (0.0)	1 (0.5)
Deaths >30 days of last dose date	3 (1.5)	7 (3.4)
Cause of death		
Adverse event[a]	0 (0.0)	2 (1.0)
COVID-19	0 (0.0)	1 (0.5)
Disease under study	2 (1.0)	5 (2.4)
Indeterminate	1 (0.5)	0 (0.0)

[a]Lethal adverse events are listed in Table S11.

TABLE S5. Progression-free survival events per investigator assessment

Progression-Free Survival Events, n (%)	Zanubrutinib (n = 207)	Ibrutinib (n = 208)
All progression-free survival events	21 (10.1)	44 (21.2)
Progressive disease	15 (7.2)	30 (14.4)
Decrease in platelet count	0 (0.0)	1 (0.5)
Increase in lymph nodes	10 (4.8)	23 (11.1)
Increase in lymph nodes/extralymphatic sites	1 (0.5)[a]	2 (1.0)
New enlarged lymph nodes	1 (0.5)	1 (0.5)
New or increase in splenomegaly	0 (0.0)	2 (1.0)
New symptomatic disease	2 (1.0)[a]	1 (0.5)[b]
Other	1 (0.5)	0 (0.0)
Death	6 (2.9)	14 (6.7)
Censoring	186 (89.9)	164 (78.8)
Ongoing	179 (86.5)	155 (74.5)
Discontinued from study	7 (3.4)	9 (4.3)

[a]Three patients in the zanubrutinib arm had biopsy-confirmed Richter transformation; 1 patient is included in the 'Increase in lymph nodes/extralymphatic sites' category and 2 patients are included in the 'New symptomatic disease (includes transformation)' category.
[b]One patient in the ibrutinib arm had biopsy-confirmed Richter transformation; this patient is included in the new symptomatic disease category.

TABLE S6. Adverse events leading to treatment discontinuation

Adverse Event Preferred Term, n (%)	Zanubrutinib (N = 204)	Ibrutinib (N = 207)
Any AE leading to discontinuation	16 (7.8)	27 (13.0)
Pneumonia	1 (0.5)	2 (1.0)
Atrial fibrillation	0 (0.0)	2 (1.0)
COVID-19 pneumonia	0 (0.0)	2 (1.0)
Diarrhea	1 (0.5)	1 (0.5)
Acute respiratory failure	0 (0.0)	1 (0.5)
Anemia	0 (0.0)	1 (0.5)
Anal squamous cell carcinoma	0 (0.0)	1 (0.5)
Blood bilirubin increased	0 (0.0)	1 (0.5)
Bronchitis	0 (0.0)	1 (0.5)
Cardiac arrest	0 (0.0)	1 (0.5)
Cardiac failure	0 (0.0)	1 (0.5)
Central nervous system hemorrhage	0 (0.0)	1 (0.5)
Cerebral infarction	0 (0.0)	1 (0.5)
Cholecystitis	1 (0.5)	0 (0.0)
COVID-19	1 (0.5)	0 (0.0)
Dyspnea	0 (0.0)	1 (0.5)
Epistaxis	0 (0.0)	1 (0.5)
Hemolytic anemia	0 (0.0)	1 (0.5)
Hemorrhoids	1 (0.5)	0 (0.0)
Hypertension	0 (0.0)	1 (0.5)
Infection	1 (0.5)	0 (0.0)
Laryngeal cancer	1 (0.5)	0 (0.0)
Malaise	1 (0.5)	0 (0.0)
Myocardial infarction	0 (0.0)	1 (0.5)
Neutropenia	1 (0.5)	0 (0.0)
Oedema peripheral	0 (0.0)	1 (0.5)
Oral mucosal blistering	1 (0.5)	0 (0.0)
Palpitations	0 (0.0)	1 (0.5)
Pneumonia cryptococcal	1 (0.5)	0 (0.0)
Rash	1 (0.5)	0 (0.0)
Rash maculo-papular	0 (0.0)	1 (0.5)
Respiratory tract infection	1 (0.5)	0 (0.0)
Septic shock	0 (0.0)	1 (0.5)
Sinusitis	1 (0.5)	0 (0.0)
Skin hemorrhage	1 (0.5)	0 (0.0)
Small cell lung cancer metastatic	1 (0.5)	0 (0.0)
Swelling face	0 (0.0)	1 (0.5)
Thrombocytopenia	0 (0.0)	1 (0.5)
Thymoma malignant	0 (0.0)	1 (0.5)
Ventricular fibrillation	0 (0.0)	1 (0.5)

Abbreviation: AE, adverse event.

TABLE S7. Cardiac adverse events leading to treatment discontinuation

Cardiac Adverse Event, n (%)	Treatment Discontinuation	
	Zanubrutinib (n=204)	Ibrutinib (n =207)
Any event in cardiac disorders SOC	0 (0.0)	7 (3.4)
Atrial fibrillation	0 (0.0)	2 (1.0)
Palpitations	0 (0.0)	1 (0.5)
Cardiac failure	0 (0.0)	1 (0.5)
Cardiac arrest	0 (0.0)	1 (0.5)
Myocardial infarction	0 (0.0)	1 (0.5)
Ventricular fibrillation	0 (0.0)	1 (0.5)

Abbreviation: SOC, system organ class.

TABLE S8. Adverse events of special interest grade ≥3 or leading to treatment discontinuation

Adverse Event of Special Interest, n (%)	Grade ≥ 3		Treatment Discontinuation	
	Zanubrutinib (n = 204)	Ibrutinib (n = 207)	Zanubrutinib (n = 204)	Ibrutinib (n = 207)
Any event	91 (44.6)	85 (41.1)	10 (4.9)	13 (6.3)
Anemia	4 (2.0)	7 (3.4)	0 (0.0)	1 (0.5)
Atrial fibrillation and flutter	2 (1.0)	4 (1.9)	0 (0.0)	2 (1.0)
Hemorrhage	6 (2.9)	6 (2.9)	1 (0.5)	2 (1.0)
Major hemorrhage[a]	6 (2.9)	6 (2.9)	0 (0.0)	1 (0.5)
Hypertension	22 (10.8)	22 (10.6)	0 (0.0)	1 (0.5)
Infections	26 (12.7)	37 (17.9)	6 (2.9)	6 (2.9)
Opportunistic infections[b]	1 (0.5)	2 (1.0)	1 (0.5)	0 (0.0)
Neutropenia	38 (18.6)	31 (15.0)	1 (0.5)	0 (0.0)
Second primary malignancy	10 (4.9)	4 (1.9)	2 (1.0)	2 (1.0)
Skin cancers	3 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	7 (3.4)	7 (3.4)	0 (0.0)	1 (0.5)
Tumor lysis syndrome	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Includes hemorrhages that were serious or grade ≥ 3 or CNS hemorrhages of all grades.
[b]Includes one patient with pneumonia cryptococcal in the zanubrutinib arm and one each of osteomyelitis fungal, *Pneumocystis jirovecii* pneumonia, and pneumonia legionella in the ibrutinib arm.

TABLE S9. COVID-19–related adverse events

COVID-19–Related Adverse Event, n (%)	Zanubrutinib (n = 204)	Ibrutinib (n = 207)
Patients with any COVID-19-related AE	11 (5.4)	11 (5.3)
COVID-19	7 (3.4)	7 (3.4)
COVID-19 pneumonia	3 (1.5)	4 (1.9)
Suspected COVID-19	2 (1.0)	0 (0.0)
SARS-CoV-2 test positive	0 (0.0)	1 (0.5)
Patients with grade 5 COVID-19 AEs	1 (0.5)	3 (1.4)

Abbreviation: AE, adverse event.

TABLE S10. Fatal adverse events

Grade 5 Adverse Event, n (%)	Zanubrutinib (n = 204)	Ibrutinib (n = 207)
Number of patients with grade 5 AE[a]	8 (3.9)	12 (5.8)
COVID-19 pneumonia	0 (0.0)	3 (1.4)
Malaise	2 (1.0)	0 (0.0)
Myocardial infarction	0 (0.0)	2 (1.0)
Cardiac arrest	0 (0.0)	1 (0.5)
Central nervous system hemorrhage	0 (0.0)	1 (0.5)
Cerebral infarction	0 (0.0)	1 (0.5)
Colitis	1 (0.5)	0 (0.0)
COVID-19	1 (0.5)	0 (0.0)
Death	0 (0.0)	1 (0.5)
Infection	1 (0.5)	0 (0.0)
Influenza	0 (0.0)	1 (0.5)
Jaundice	1 (0.5)	0 (0.0)
Mobility decreased	1 (0.5)	0 (0.0)
Multiple organ dysfunction syndrome	0 (0.0)	1 (0.5)
Pneumonia	1 (0.5)	1 (0.5)
Pneumonia cryptococcal	1 (0.5)	0 (0.0)
Respiratory failure	0 (0.0)	1 (0.5)
Respiratory tract infection	1 (0.5)	0 (0.0)
Sepsis	1 (0.5)	0 (0.0)
Septic shock	0 (0.0)	1 (0.5)

Abbreviation: AE, adverse event.

[a]Multiple grade 5 adverse events were reported for some patients, and some patients' primary cause of death, as reported in Table S5, was not an adverse event.

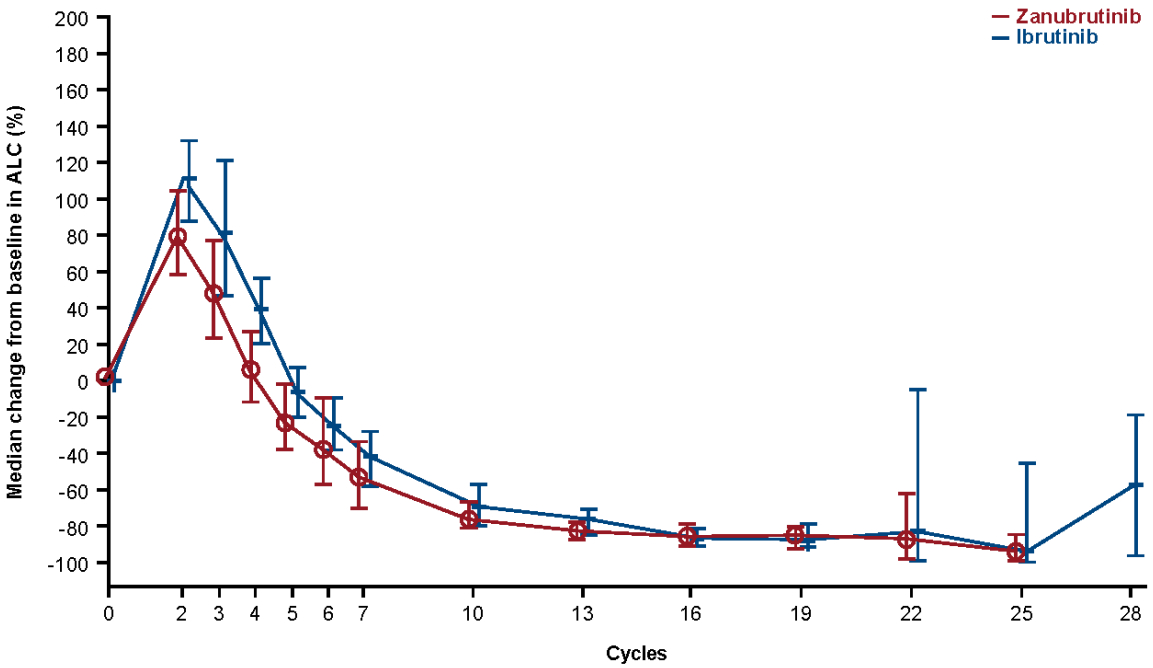
TABLE S11. Overall Response Rate by Independent Central Review Committee

Best Response, n (%)	All Patients		del(17p)/*TP53*	
	Zanubrutinib (n = 207)	**Ibrutinib (n = 208)**	**Zanubrutinib (n = 41)**	**Ibrutinib (n = 38)**
ORR 95% CI	158 (76.3) 69.9, 81.9	134 (64.4) 57.5, 70.9	33 (80.5) 65.1, 91.2	21 (55.3) 38.3, 71.4
CR or CRi	3 (1.4)	2 (1.0)	1 (2.4)	0 (0.0)
PR or nPR	155 (74.9)	132 (63.5)	32 (78.0)	21 (55.3)
PR-L	19 (9.2)	36 (17.3)	2 (4.9)	6 (15.8)
SD	21 (10.1)	25 (12.0)	3 (7.3)	7 (18.4)
Non-PD	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
PD	1 (0.5)	4 (1.9)	0 (0.0)	2 (5.3)
Discontinue prior to first assessment, NA or NE	7 (3.4)	9 (4.3)	3 (7.3)	2 (5.3)

Abbreviations: CR, complete response; Cri, CR with incomplete bone marrow recovery; del(17p), deletion of the short arm of chromosome 17; 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.

Supplemental Figures

FIG S1. Median percent change from baseline in absolute lymphocyte count over time. Median percent change from baseline in absolute lymphocyte count at each study visit. Transient peripheral lymphocytosis is observed with BTK inhibitors as leukemia cells are redistributed from lesions to the blood. Baseline is defined as the C1D1 value. Error bars represent 95% confidence intervals. ALC, absolute lymphocyte count.



No. of subjects													
Zanubrutinib	204	193	191	186	188	185	173	180	169	142	68	19	4
Ibrutinib	207	198	189	188	187	173	170	163	159	121	54	9	3	2

FIG S2. Progression-free survival by independent central review committee.

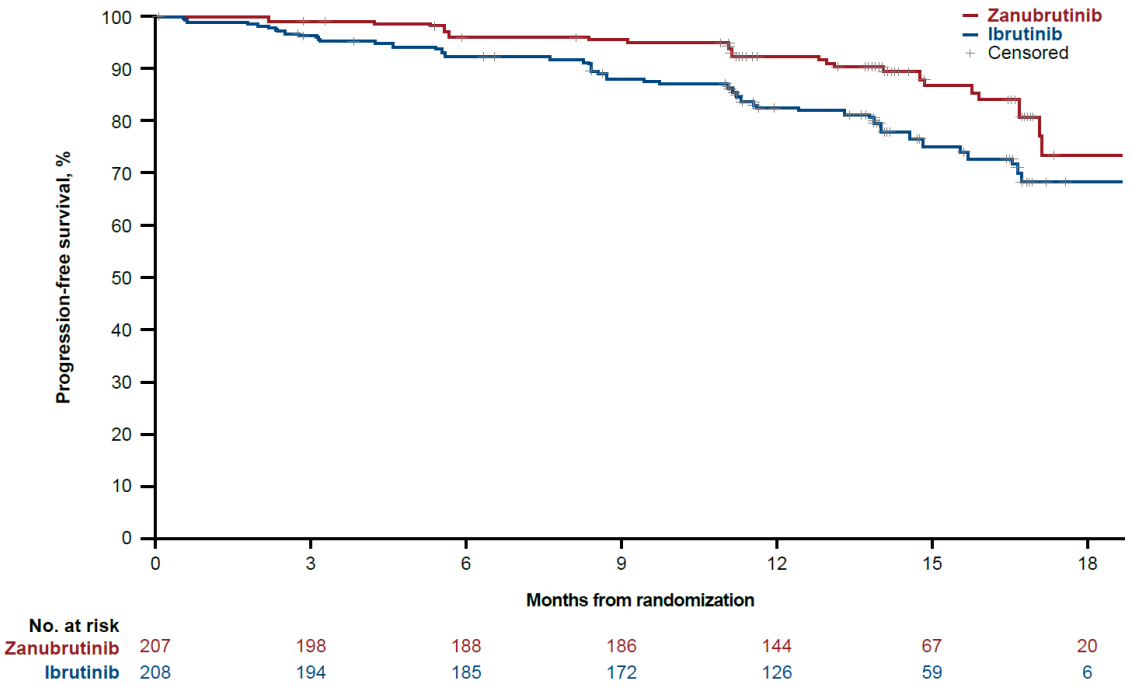
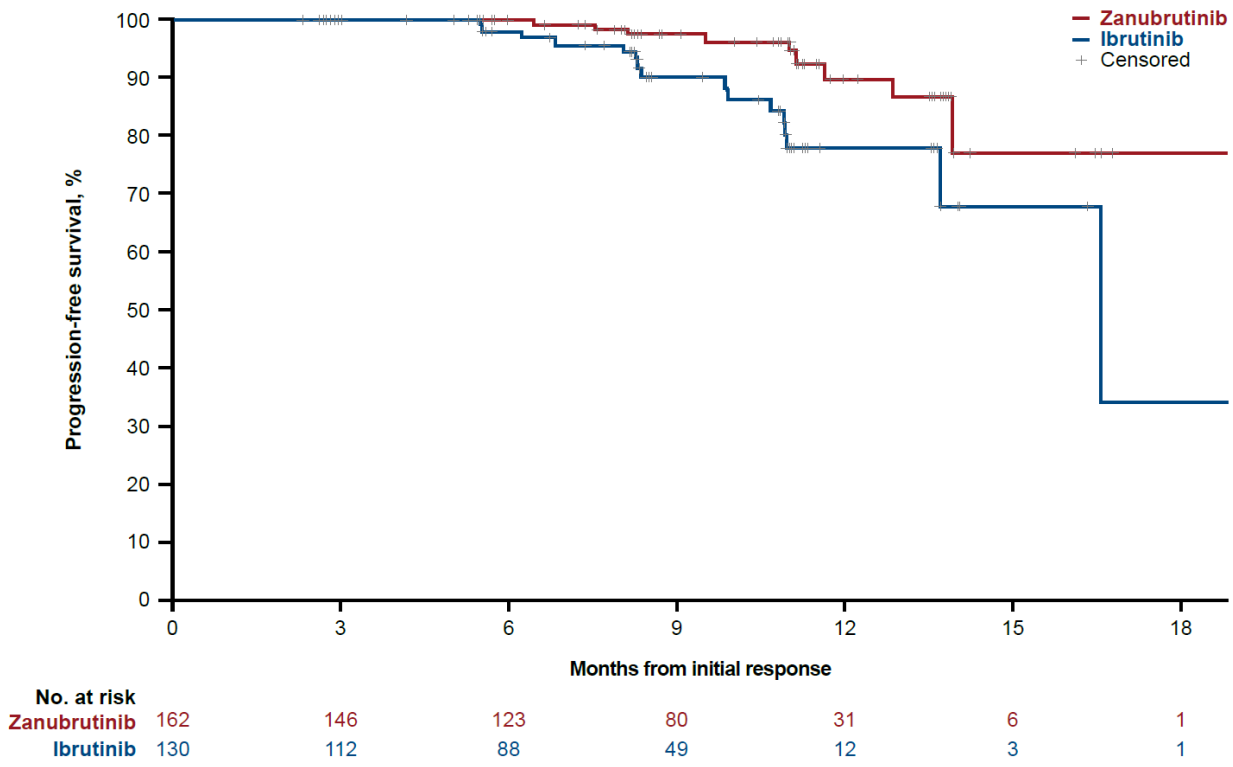


FIG S3. Duration of response in the first 415 randomized patients by investigator assessment.



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