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List of Primary Investigators and Study Sites

Investigator Name (by Country)	No. of Patients Enrolled	Investigator Site
Australia		
Janowski, Wojciech	4	Calvary Mater Newcastle
Ma, David	1	St Vincent's Hospital Sydney
Mulligan, Stephen	1	Royal North Shore Hospital
Presgrave, Peter	2	Wollongong Hospital
Seymour, John	5	Peter MacCallum Cancer Center
Walker, Patricia	1	Frankston Hospital
Belgium		
Janssens, Ann	3	UZ Leuven
Van Den Neste, Eric	1	Clinique Universitaire Saint-LUC
Denmark		
Christiansen, Ilse	1	Aalborg Universitetshospital
Poulsen, Christian	3	Region Sjalland Sygehus Oest Roskilde
France		
Cymbalista, Florence	1	Hopital Avicenne
De Guibert, Sophie	2	The Public Hospital CHU de Rennes
Dupuis, Jehan	1	Hopital Henri Mondor
Lepretre, Stephane	5	Centre Henri Becquerel
Salles, Gilles	2	Centre Hospitalier Universitaire Lyon
Germany		
Schmidt, Burkhard	3	Hamatologisch Onkologische
Stilgenbauer, Stephan	4	University of Ulm
Hungary		

Egyed, Miklós	4	Somogy Megyei Kaposi Mor Oktato Korhaz
Illés, Árpád	15	Debreceni Egyetem Klinikai Koezpont
Nagy, Zsolt	3	Pecsi Tudomanyegyetem
Rosta, András	2	Orszogos Onkologiai Intezet
Israel		
Bairey, Osnat	2	Clalit Health Services through Rabin Medical Center
Braester, Andrei	2	Health Association of Western Galilee Medical Center - Nahar
Fineman, Riva	1	Rambam Health Corporation
Nagler, Arnon	3	The Chaim Sheba Medical Center
Preis, Meir	1	Lady Davis Carmel Medical Center
Ruchlemer, Rosa	1	Shaare Zedek Medical Center
Tadmor, Tamar	2	Bnai Zion Medical Center
Yeganeh, Shay	1	Baruch Padeh Poriya Medical Center
Italy		
Bosi, Alberto	2	Azienda Ospedaliera Universitaria Careggi
Cuneo, Antonio	2	Azienda Ospedaliero-Universitaria di Ferrara
Ghia, Paolo	6	Ospedale San Raffaele S.r.l.
Laurenti, Luca	1	Policlinico Universitario A Gemelli
Marasca, Roberto	3	Universita degli Studi di Modena e Reggio Emilia - Modena
Murru, Roberta	1	Ospedale Oncologico Regionale A Businco
Musuraca, Gerardo	2	IRCCS IRST Meldola
Tani, Monica	3	Ospedale Santa Maria delle Croci
Tedeschi, Alessandra	6	Azienda Ospedaliera Niguarda Ca Granda
Zinzani, Pier	1	University of Bologna

Netherlands		
Croon- de Boer, Fransien	3	Ikazia Ziekenhuis
de Heer, Koen	1	Flevoziekenhuis
Doorduijn, Jeanette	2	Erasmus University Medical Center
Houtenbos, Ilse	1	Spaarne Ziekenhuis
Kater, Arnon	3	AMC Medical Center
Levin, Mark	3	Albert Schweitzer Ziekenhuis
Mous, Rogier	1	Universitair Medisch Centrum Utrecht
Nijland, Marcel	3	Universitair Medisch Centrum Groningen
Posthuma, Ward	3	Reinier de Graaf Gasthuis
Schaar, Cees	1	Gelre Ziekenhuizen
Silbermann, Matthijs	2	Tergooiziekenhuizen
van der Klift, Marjolein	1	Amphia Ziekenhuis
van Kampen, Roel	3	Orbis Medisch Centrum
Veelken, Hendrik	2	Leids Universitair Medisch Centrum
New Zealand		
Corbett, Gillian	2	Tauranga Hospital
Elinder-Camburn, Anna	2	North Shore Hospital
Ganly, Peter	1	Canterbury Health Laboratories
Poland		
Ciepluch, Hanna	9	Wojewodzkie Centrum Onkologii
Czyz, Jaroslaw	24	Szpital Uniwersytecki Nr 2 im. Dr Jana Biziela w Bydgoszczy
Halka, Janusz	2	Samodzielny Publiczny Zaklad Opieki Zdrowotnej Ministerstwa Spraw Wewnetrznych I Administracji

Homenda, Wojciech	7	Wojewodzki Szpital Specjalistyczny im. Janusza Korczaka
Jurczak, Wojciech	55	Malopolskie Centrum Medyczne S.C
Knopinska-Posluszny, Wanda	10	Szpital Morski im. PCK
Mazur, Grzegorz	15	Uniwersytecki Szpital Kliniczny Jana Mikulicza Radeckiego
Robak, Tadeusz	29	Wojewdzki Szpital Specjalistyczne im. M. Kopernika w Lodzi
Woszczyk, Dariusz	3	Szpital Wojewódzki w Opolu Sp. z o.o
Spain		
De La Serna, Javier	2	Hospital Universitario 12 de Octubre
Garcia-Marco, Jose Antonio	10	Hospital Universitario Puerta de Hierro-Majadahonda
Garcia-Malo, Maria Dolores	1	Hospital General Universitario Morales Meseguer
González-Barca, Eva	2	Institut Catala d'Oncologia (ICO)
Hernández Rivas, José Angel	1	Hospital Infanta Leonor
Loscertales, Javier	2	La Princesa University Hospital Foundation for Biomedical Research
Moreno, Carolina	1	Hospital de La Santa Creu i Sant Pau
Osorio, Santiago	7	Hospital Gregorio Maranon
Yañez San Segundo, Lucrecia	3	Hospital Universitario Marques de Valdecilla
Turkey		
Demirkan, Fatih	5	Dokuz Eylul University Medical Faculty
Ferhanoglu, Ahmet Burhan	2	Koc University Medical Faculty American Hospital
Ilhan, Osman	7	Ankara University Medical Faculty Ibni Sina Hospital
Keklik, Muzaffer	2	Erciyes University School of Medicine

Vural, Filiz	4	Ege Universitesi Tip Fakultesi Hastanesi
Yagci, Munci	5	Gazi University Medical Faculty Gazi Hospital
Yenerel, Mustafa Nuri	18	Istanbul University Faculty of Medicine
United Kingdom		
Allsup, David	3	Hull And East Yorkshire Hospitals NHS Trust
Bloor, Adrian	3	The Christie NHS Foundation Trust
El-Sharkawi, Dima	3	The Royal Marsden NHS Foundation
Fegan, Christopher	1	University Hospital of Wales
Forconi, Francesco	3	University Hospital Southampton NHS Foundation Trust
Fox, Christopher	11	Nottingham University Hospitals NHS Trust
Hallam, Simon	1	Barts and the London School of Medicine and Dentistry
Hillmen, Peter	10	The Leeds Teaching Hospitals NHS Trust, Trust Headquarters
Hutchinson, Claire	1	Derriford Hospital
Kennedy, Ben	2	University Hospitals of Leicester NHS Trust
McCarthy, Helen	1	Royal Bournemouth and Christchurch Hospitals NHS Foundation
Paneesha, Shankaranarayana	7	Heart of England NHS Foundation Trust, of Birmingham Heartlands
Patten, Piers	2	King's College Hospital NHS Foundation Trust
Pettitt, Andrew	1	Royal Liverpool and Broadgreen University Hospitals NHS Trust
Ringshausen, Ingo	4	Cambridge University Hospitals NHS Foundation Trust
United States of America		
Allan, John	2	Weill Cornell Medical College

Bajaj, Madhuri	3	Illinois CancerCare
Barrientos, Jacqueline	1	Long Island Jewish Medical Center
Brander, Danielle	4	Duke University
Brody, Joshua	4	Mount Sinai
Byrd, John	22	The Ohio State University
Chanan-Khan, Asher	2	Mayo Clinic, Jacksonville
Charu, Veena	1	Pacific Cancer Medical Center, Inc
Chaves, Jorge	1	Northwest Medical Specialties
Coleman, Morton	6	Clinical Research Alliance Inc.
Dakhil, Shaker	3	Cancer Center of Kansas
Eradat, Herbert	1	University of California, Los Angeles
Holmes, Jarrod	1	St Joseph Heritage Healthcare
Isenalumhe, Leidy	9	Moffitt Cancer Center
Kahl, Brad	3	University of Wisconsin
Kay, Neil	12	Mayo Clinic Rochester
Kipps, Thomas	6	The Regents of the University of California
Kozloff, Mark	1	Ingalls Memorial Hospital
Lamanna, Nicole	1	Columbia University Medical Center
Leis, Jose	7	Mayo Clinic Phoenix
Lerner, Rachel	1	Park Nicollet Institute
Leslie, Lori	5	Hackensack University Medical Center
Murray, Christal	1	Scott and White Healthcare
Portell, Craig	1	University of Virginia
Schuster, Stephen	8	The Trustees of the University of Pennsylvania
Siddiqi, Tanya	6	City of Hope

Splichal, James	1	University Cancer and Blood Center, LLC
Thompson, Philip	3	MD Anderson Cancer Center

List of Independent Data Monitoring Committee Members

Name	Affiliation	Role
John Gribben, MD	Barts Cancer Institute Centre for Haemato-Oncology, Barts and the London School of Medicine, Queen Mary, University of London	Hematologist (Chairperson)
Michael Grever, MD	The Ohio State University Medical Center Department of Internal Medicine	Hematologist
Steven Dahlberg, MS	Statistical Consultant	Biostatistician

Supplementary Methods

Patient Eligibility

Inclusion Criteria

1. Men and women ≥18 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
3. Diagnosis of chronic lymphocytic leukemia (CLL) that meets published diagnostic criteria[1]:
    a. Monoclonal B cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥1 B cell marker (CD19, CD20, or CD23) and CD5
    b. Prolymphocytes may comprise ≤55% of blood lymphocytes
    c. Presence of ≥5 x 10^9 B lymphocytes/L (5000 µL) in the peripheral blood (at any point since diagnosis); this applies to CLL only
4. Must have ≥1 of the following high-risk prognostic factors:
    a. Presence of 17p del by central laboratory
    b. Presence of 11q del by central laboratory
5. Active disease meeting ≥1 of the following International Workshop on CLL (IWCLL) 2008 criteria for requiring treatment:
    a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin <10 g/dL) and/or thrombocytopenia (platelets <100,000/µL)
    b. Massive (i.e., ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly
    c. Massive nodes (i.e., ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy
    d. Progressive lymphocytosis with an increase of >50% over a 2-month period or a lymphocyte doubling time (LDT) of <6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte count obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of <30 x 10^9/L (30,000/µL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded
    e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy
    f. Constitutional symptoms documented in the subject's chart with supportive objective measures, as appropriate, defined as ≥1 of the following disease-related symptoms or signs:
        i. Unintentional weight loss ≥10% within the previous 6 months before Screening
        ii. Significant fatigue (ie, ECOG performance status 2 or worse; inability to work or perform usual activities)
        iii. Fevers >100.5°F or 38.0°C for ≥2 weeks before Screening without evidence of infection
        iv. Night sweats for >1 month before Screening without evidence of infection
6. Must have received ≥1 prior therapies for CLL

7. Meet the following laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥750 cells/μL (0.75 x 10^9/L) or ≥500 cells/μL (0.50 x 10^9/L) in patients with documented bone marrow involvement, and independent of growth factor support 7 days before assessment.
    b. Platelet count ≥30,000 cells/μL (30 x 10^9/L) without transfusion support 7 days before assessment. Patients with transfusion-dependent thrombocytopenia are excluded
    c. Serum aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) ≤3.0 x upper limit of normal (ULN)
    d. Total bilirubin ≤1.5 x ULN
    e. Estimated creatinine clearance (ie, estimated glomerular filtration rate using Cockcroft-Gault) ≥30 mL/min
8. Able to receive all outpatient treatment, all laboratory monitoring, and all radiologic evaluations at the institution that administers study drug for the entire study
9. Women who are sexually active and can bear children must agree to use highly effective forms of contraception while on the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer
10. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer
11. Men must agree to refrain from sperm donation during the study and for 2 days after the last dose of acalabrutinib or 90 days after the last dose of ibrutinib, whichever is longer
12. Must be willing and able to adhere to the study visit schedule, understand and comply with other protocol requirements, and provide written informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations). Note vulnerable subjects, as defined in the International Conference on Harmonisation (ICH) good clinical practices (GCP), are not allowed on this protocol (eg, prisoners or institutionalized subjects)

Exclusion Criteria

Subjects will be ineligible for this study if they meet any of the following criteria:

1. Known central nervous system lymphoma or leukemia
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter transformation
3. Uncontrolled autoimmune hemolytic anemia (AIHA) or immune thrombocytopenic purpura (ITP) defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (>20 mg daily of prednisone daily or equivalent)
4. Prior exposure to ibrutinib or to a B cell receptor (BCR) inhibitor (eg Btk or phosphatidylinositol 3 kinase or Syk inhibitors) or a B cell lymphoma-2 (BCL-2) inhibitor (eg, ABT-199)
5. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days before first dose of study drug
6. Corticosteroid use >20 mg within 1 week before first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid

use, or as premedication for administration of study drug or contrast. For example, subjects requiring steroids at daily doses >20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded

7. Prior radio- or toxin-conjugated antibody therapy
8. Prior allogeneic stem cell or autologous transplant
9. Major surgery within 4 weeks before first dose of study drug
10. History of prior malignancy except for the following:
    a. Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years before Screening and felt to be at low risk for recurrence by treating physician
    b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer
    c. Adequately treated cervical carcinoma in situ without current evidence of disease
11. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval >480 msec at screening
12. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
13. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment
14. Known history of infection with human immunodeficiency virus
15. Serologic status reflecting active hepatitis B or C infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result before randomization. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded
16. History of stroke or intracranial hemorrhage within 6 months before randomization
17. History of bleeding diathesis (eg, hemophilia, von Willebrand disease)
18. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug
19. Requires treatment with a strong CYP3A inhibitor/inducer
20. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole)
21. Breastfeeding or pregnant
22. Concurrent participation in another therapeutic clinical trial
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening

Dose Modification Guidelines

Assessment of Toxicity

Dose modification decisions for patients with cytopenia (below the lower limit of the normal range) at baseline was based on the IWCLL 2008[1] grading scale for hematologic toxicity in CLL studies shown below.

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value	Absolute neutrophil count/µL§ (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

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be reported as grade 5.
†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is <20 x 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 (eg, <20 x 10^9/L [20,000/µL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
‡Hemoglobin (Hb) levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
§If the ANC reaches <1 x 10^9/L (1000/µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1 x 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 granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity but should be documented.

Acalabrutinib

Dose Delays
Treatment with acalabrutinib was held for any unmanageable, potentially study drug–related toxicity that was grade ≥3 in severity. Any other clinically important events for which dose delays were considered appropriate by the investigator had to be discussed with the medical monitor. Study drug could be held for a maximum of 28 consecutive days from expected dose because of toxicity. Study treatment was discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor.
Note: Temporary withholding of study drug (e.g., for drug-related toxicity, surgery, or intercurrent illness) for as few as 7 days could cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients could resume therapy and relevant clinical, laboratory, and/or radiologic assessments were performed

to document whether tumor control could be maintained or whether actual disease progression has occurred.

Dose Modifications and Discontinuation
The actions in the table below were followed for the following toxicities:

- Grade 4 absolute neutrophil count (<500/μL) for >7 days (neutrophil growth factors were permitted per American Society of Clinical Oncology guidelines[2] and use had to be recorded on the case report form)
- Grade 3 platelet decreases in the presence of significant bleeding
- Grade 4 platelet decreases
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other grade 4 toxicity or unmanageable grade 3 toxicity

Dose Modification Occurrence	**Action**
1st – 2nd	Hold acalabrutinib until recovery to grade ≤1 or baseline; may restart at original dose level
3rd	Hold acalabrutinib until recovery to grade ≤1 or baseline; restart at one dose level lower (100 mg once daily)
4th	Discontinue acalabrutinib

If acalabrutinib was reduced for apparent treatment-related toxicity, the dose did not need to be re-escalated, even if there was minimal or no toxicity with the reduced dose. However, if the patient tolerated a reduced dose of acalabrutinib for ≥4 weeks, then the dose could be increased to the next higher dose level at the discretion of the investigator. Such re-escalation was particularly warranted if further evaluation revealed that the adverse event (AE) that led to the dose reduction was not treatment-related. However, the maximum dose of acalabrutinib was 100 mg orally twice daily for this protocol. Any changes to the dosing regimen must be recorded in the Dosage Administration case report form.

Ibrutinib

Dose Delays
Treatment with ibrutinib was held for any unmanageable, potentially study drug–related toxicity that was grade ≥3 in severity. Any other clinically important events for which dose delays were considered appropriate by the investigator had to be discussed with the medical monitor. Study drug could be held for a maximum of 28 days from expected dose because of toxicity. Study treatment was discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the medical monitor.

Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as few as 7 days could cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients could resume therapy and relevant clinical, laboratory, and/or radiologic assessments were performed

to document whether tumor control could be maintained or whether actual disease progression has occurred.

Dose Modifications and Discontinuation
The actions in the table below were followed for the following toxicities:

- Grade 4 absolute neutrophil count (<500/μL) for >7 days (neutrophil growth factors were permitted per American Society of Clinical Oncology guidelines[2] and use had to be recorded on the case report form)
- Grade 3 platelet decreases in the presence of significant bleeding
- Grade 4 platelet decreases
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other grade 4 toxicity or unmanageable grade 3 toxicity

Dose Modification Occurrence	**Action**
1st	Hold ibrutinib until recovery to grade ≤1 or baseline; may restart at original dose level (420 mg daily)
2nd	Hold ibrutinib until recovery to grade ≤1 or baseline; may restart at 280 mg daily
3rd	Hold ibrutinib until recovery to grade ≤1 or baseline; may restart at 140 mg daily
4th	Discontinue ibrutinib

Note: If local regulations required following local prescribing information for dose modifications/discontinuation, and they differed from the aforementioned, then the local regulations were followed. Any changes to the dosing regimen were recorded in the Dosage Administration case report form.

Baseline Mutational Analyses

Baseline screening assessments included central laboratory testing of peripheral blood for del(17)(p13.1) (used for randomization stratification with >7% cutoff) and del(11)(q22.3) with >6% cutoff by fluorescence in situ hybridization (FISH; FDA-approved Vysis CLL FISH Probe Kit; Abbott Molecular) and stimulated karyotyping (stimulated with DSP30/IL2 and PHA/IL2 per karyotyping standard operating procedures for disease type CLL; Interpace Diagnostics). *TP53* mutational status was assessed by CLIA approved Sanger sequencing at an analytical sensitivity of 25% of mutant in a background of wild-type genomic DNA for exons 4-9. Complex karyotype was defined by 3 or more chromosomal abnormalities with one or more structural abnormalities. FISH, *TP53* mutation, IGHV mutational status, and complex karyotype (≥3 including del(13q)) were centrally determined.

Progression-Free Survival Censorship Criteria

For independent review committee (IRC)- and investigator-assessed progression-free survival (PFS) analyses, patients were censored for death, progression, and treatment discontinuation, including starting subsequent anticancer therapy and loss to follow-up or study exit.

Response Evaluations

Response assessments were in accordance with IWCLL 2008 criteria,[1] with the modification that treatment-related lymphocytosis in the absence of other signs of disease progression was not considered progressive disease. Radiographic imaging (computed tomography with contrast or magnetic resonance imaging) was performed at baseline and every 12 weeks until week 100, and then every 24 weeks until 5 years on study, then yearly until disease progression, regardless of study drug discontinuation. Bone marrow aspirate and biopsy were obtained to confirm complete responses after all other criteria had been met.

Definition of Efficacy Endpoints

Response Assessment Criteria (per IWCLL 2008, With Modification for Persistent Lymphocytosis[1,3])

Response	**Lymphocytes***	**Bone Marrow**	**Physical Exam† (Nodes, Liver, Spleen)**	**Peripheral Blood***
CR‡	Lymphocytes <4 x 10^9/L	Normocellular <30% lymphocytes; No B-lymphoid nodules	Normal (e.g., no lymph nodes >1.5 cm)	ANC >1.5 x 10^9/L§ Platelets >100 x 10^9/L§ Hemoglobin >11.0 g/dL (untransfused)§
Cri	Lymphocytes <4 x 10^9/L	Hypocellular <30% lymphocytes	Normal (e.g., no lymph nodes >1.5 cm)	Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity
PR‡	Lymphocytes <5 x 10^9/L or ≥50% decrease from baseline	Not assessed	≥50% reduction in lymphadenopathy‖ and/or in spleen or liver enlargement	ANC >1.5 x 10^9/L or platelets >100 x 10^9/L or 50% improvement over baseline§ or hemoglobin >11.0 g/dL or 50% improvement over baseline (untransfused)§

PRL‡	Lymphocytes <5 x 10^9/L	Not assessed	≥50% reduction in lymphadenopathy‖ and/or in spleen or liver enlargement	ANC >1.5 x 10^9/L or platelets >100 x 10^9/L or 50% improvement over baseline§ or hemoglobin >11.0 g/dL or 50% improvement over baseline (untransfused)§
SD	Absence of PD and failure to achieve at least a PR			
PD‡	Lymphocytes ≥50% increase over baseline	Not assessed	Increase ≥50% in lymphadenopathy or increase ≥50% in hepatomegaly or increase ≥50% in splenomegaly	Platelet decrease of ≥50% from baseline secondary to CLL or hemoglobin decrease of >2 g/dL from baseline secondary to CLL

ANC, absolute neutrophil count; CLL, chronic lymphocytic leukemia; CR, complete remission (response); Cri, CR with incomplete bone marrow recovery; PD, progressive disease; PR, partial remission (response); PRL, partial remission (response) with lymphocytosis; SD, stable disease.
*Baseline is defined as the most recent complete blood count and absolute lymphocyte count results prior to the first study dose, which could include cycle 1 day 1.
†Computed tomography scan of abdomen, pelvis, and thorax could be used if previously abnormal.
‡CR: all of the above CR criteria had to be met, and patients had to lack disease-related constitutional symptoms; PR: at least two of the above PR criteria for lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes plus one of the criteria for ANC, platelets, or hemoglobin had to be met; PRL: presence of lymphocytosis, ≥50% reduction in lymphadenopathy and/or in spleen or liver enlargement, and one of the criteria for ANC, platelets, or hemoglobin had to be met; PD: at least one of the above PD criteria had to be met, or transformation to a more aggressive histology (eg, Richter transformation). For PD as assessed by progressive cytopenias, a bone marrow biopsy was required for confirmation. Note: Isolated elevation of treatment-related lymphocytosis by itself was not considered PD unless the patient became symptomatic from this per Cheson 2012.[3]
§Without need for exogenous growth factors.
‖In the sum products of ≤6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes.

Definition of Serious Adverse Events

A serious AE (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death)
- Is life-threatening (with regards to determining if an AE is serious, “life-threatening” is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more

severe. If either the investigator or the sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening).
- Requires inpatient hospitalization >24 hours or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life threatening or require hospitalization, but may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsion that do not result in hospitalization, or development of drug dependency or drug abuse

Statistical Analysis

For any analyses based on the Cox proportional hazards model, the proportional hazards assumption was assessed by visual inspection of the Kaplan-Meier curves and if further investigation was needed, a test of the treatment and time interaction in the model and/or plots of Schoenfeld residuals was conducted.

Ad Hoc Analyses

Subgroup analyses of IRC-assessed PFS were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of the primary endpoint. Prognostic variables included: randomization stratification factors (presence of del(17)(p13.1) mutation [yes vs no], ECOG at randomization [0, 1 vs 2], number of prior therapies [1–3 vs ≥4; additionally analyze 1, 2, 3, 4, and ≥5 separately]); region (North America, Western Europe, Central and Eastern Europe, Asia Pacific); age group (<65 vs ≥65 years; <70 vs ≥70 years; <75 vs ≥75 years); sex (male vs female); race (white vs non-white); bulky disease (longest diameter of lymph node <5 cm vs ≥5cm or <10 cm vs ≥10 cm at baseline); Rai stage at screening (stage 0–II vs III–IV); cytopenias at baseline (yes vs no); presence of del(11)(q22.3) mutation (yes vs no); *TP53* mutation (mutated vs unmutated); IGHV (mutated vs unmutated); complex karyotype (yes vs no); β_2-microglobulin at baseline (≤3.5 mg/L vs >3.5 mg/L); high-risk features (del(17)(p13.1) and del(11)(q22.3) [yes vs no]; del(17)(p13.1) and/or *TP53* mutation [yes vs no]; del(17)(p13.1) and *TP53* mutation [yes vs no]; del(17)(p13.1) and del(11)(q22.3) and *TP53* mutation [yes vs no]; del(17)(p13.1) and unmutated IGHV [yes vs no]; del(17)(p13.1) and complex karyotype [yes vs no]; and del(11)(q22.3) and complex karyotype [yes vs no]). The HR and corresponding 95% CI for acalabrutinib/ibrutinib were calculated using an unstratified Cox proportional hazards model for each subgroup. A sensitivity analysis of the primary endpoint was performed in which PFS was analyzed as the time from date of randomization to the date of first IRC-assessed disease progression or death due to any cause, whichever came first, regardless of the use of subsequent anticancer therapy.

Subgroup analyses of treatment-emergent adverse events were performed using the same subgroups as the primary analysis to investigate the benefit:risk for acalabrutinib versus ibrutinib. For each of the following treatment-emergent adverse event types, the risk difference (Arm A – Arm B) and its corresponding 95% CI for each subgroup were calculated based on normal approximation (with the use of Wilson's score): grade 3 or higher treatment-emergent

adverse events; treatment-emergent adverse events leading to dose interruption; and treatment-emergent adverse events leading to discontinuation of treatment. Additional subgroups were considered as appropriate.

Time to next treatment was analyzed using Kaplan-Meier methods and a stratified Cox proportional hazards model.

Exploratory Endpoint Analyses

Exploratory endpoints included investigator-assessed PFS; investigator- and IRC-assessed event-free survival (defined as the time from date of randomization to the date of first disease progression, any-cause death, start of subsequent anticancer therapy, or discontinuation of treatment due to adverse events); investigator- and IRC-assessed overall response rate (ORR); improvement of disease-related symptoms (defined as constitutional symptoms including weight loss, fever, night sweats, and fatigue; not reported); incidence, time to onset, and duration of lymphocytosis (on-treatment absolute lymphocyte count (ALC) >400,000 µL; not reported); medical resource utilization (not reported); potential predictive biomarkers (not reported); acalabrutinib pharmacokinetics (not reported); patient-reported outcomes (not reported); duration of investigator- and IRC-assessed response (not reported); and time to initial investigator- and IRC-assessed response (not reported).

The exploratory endpoints of investigator-assessed PFS and investigator- and IRC-assessed event-free survival were analyzed using Kaplan-Meier methods and a stratified Cox proportional hazards model. Statistical results for exploratory endpoints were considered descriptive. Exploratory analyses were performed using the intent-to-treat population unless specified otherwise.

Overall Response Rate

ORR was defined as the proportion of patients who achieved a best overall response assessment of complete response (CR), CR with incomplete bone marrow recovery (CRi), nodular partial response (nPR), or partial response (PR) according to the IWCLL 2008 criteria,[1] as assessed by the IRC or the investigator before initiation of subsequent anticancer therapy.

ORR was summarized by number and percentage of patients, and its corresponding 95% CI was calculated based on a normal approximation using Wilson's score method and summarized by treatment arm. ORR was compared between treatment arms using the Cochran-Mantel-Haenszel (CMH) test adjusted for stratification factors.

ORR including partial response with lymphocytosis assessed by IRC and investigators was also analyzed with the same analysis method used for ORR.

A subgroup analysis for ORR assessed by IRC was performed using the same subgroups as the primary analysis. The ORR and its corresponding 95% CI were calculated separately by arm for each subgroup.

Treatment-emergent Diarrhea, Major Bleeding Events, Lymphocytosis and Second Primary Malignancies

The incidences of treatment-emergent diarrhea, major bleeding events (any hemorrhagic event that was serious, grade 3 or higher in severity, or that was a central nervous system hemorrhage [any severity grade]), and secondary malignancies were summarized by treatment arm. The incidence of patients with at least one occurrence of treatment-related lymphocytosis, defined as an elevation in ALC of 50% or higher compared with baseline and a post-baseline assessment of <5000/μL were summarized. ALC at peak and time to peak ALC for patients who meet the above criteria for lymphocytosis were summarized by descriptive statistics.

Improvement and/or Resolution of Disease-related Symptoms

Disease-related symptoms were defined as constitutional symptoms including weight loss, fever, night sweats, and fatigue. For each symptom, the number and percentage of patients with symptoms absent at each post-baseline timepoint was summarized in the subset of patients with symptoms present at baseline.

Post Hoc Analyses

Descriptive two-sided P-values for between treatment group comparisons of the incidences of any-grade and grade 3 or higher adverse events were generated based on Barnard's exact test without multiplicity adjustment. Cumulative incidences of events of clinical interest and common adverse events were assessed using Kaplan-Meier methods and a Cox proportional hazards model. Patients with a history of cardiac events, atrial fibrillation, and hypertension were identified based on assessments of medical history records. Risk factors for atrial fibrillation were based on medical review of medical history records. Exposure-adjusted frequencies for events of clinical interest were calculated as (total number of treatment-emergent adverse events for each event of clinical interest category by treatment) x 100 / (sum of treatment-emergent period of all patients in respective treatment in months). Time to onset of Richter transformation was calculated as the date of Richter transformation minus the date of first treatment dose plus one.

Censoring Rules

PFS data were censored at:

- Randomization for patients who had no baseline assessments or no adequate post-baseline assessment
- Date of last adequate assessment for patients with no IRC-assessed progressive disease (PD) or death at the time of the data cutoff, or before the patient was lost to follow-up or exited the study
- Date of last adequate assessment before the start of subsequent anticancer therapy, for patients without IRC-assessed PD or death before starting subsequent anticancer therapy
- Date of last adequate assessment before the missed visits, for patients with IRC-assessed PD or death immediately after ≥2 consecutively missed visits

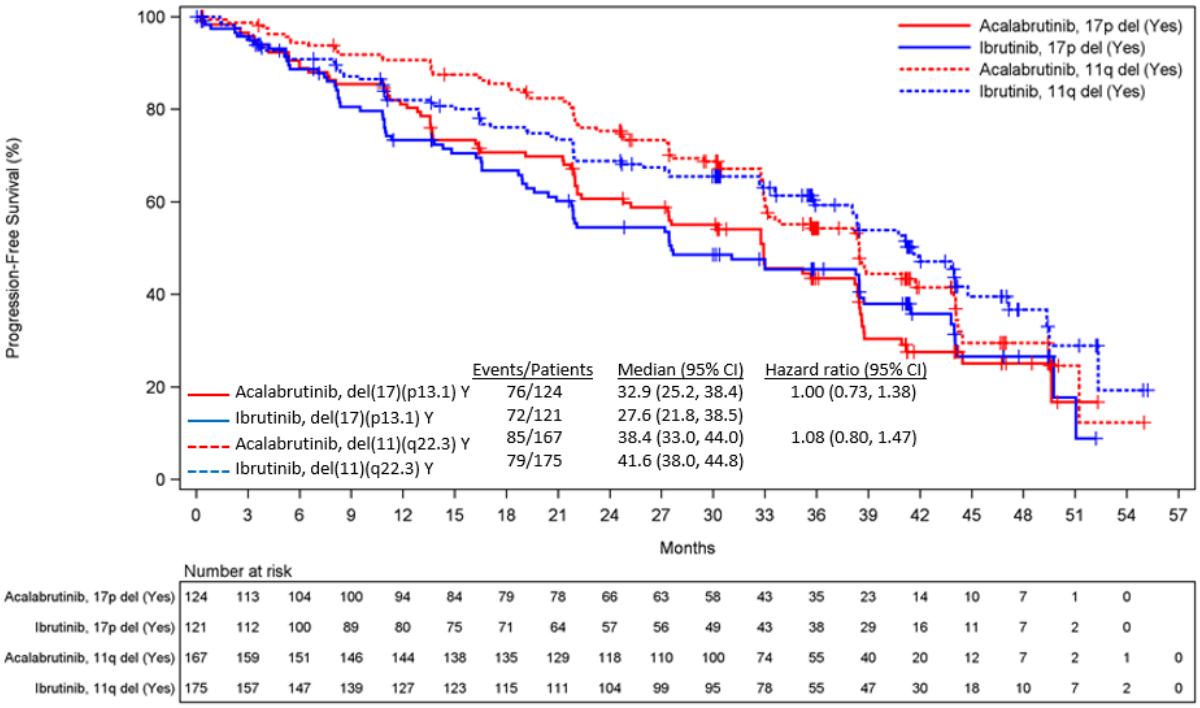
Overall survival (OS) data were censored at randomization for patients who were lost to follow-up immediately after randomization. For patients not known to have died, OS data were censored at the last known date that the patient was alive before the analysis cutoff date or before the patient was lost to follow-up or study exit.

For ORR, patients with missing data were considered nonresponders.

Incidences of atrial fibrillation/flutter, grade ≥3 infections, or Richter transformation were required to be reported at each occurrence and if not reported, the subject was considered to not have the event.

SUPPLEMENTARY FIGURES

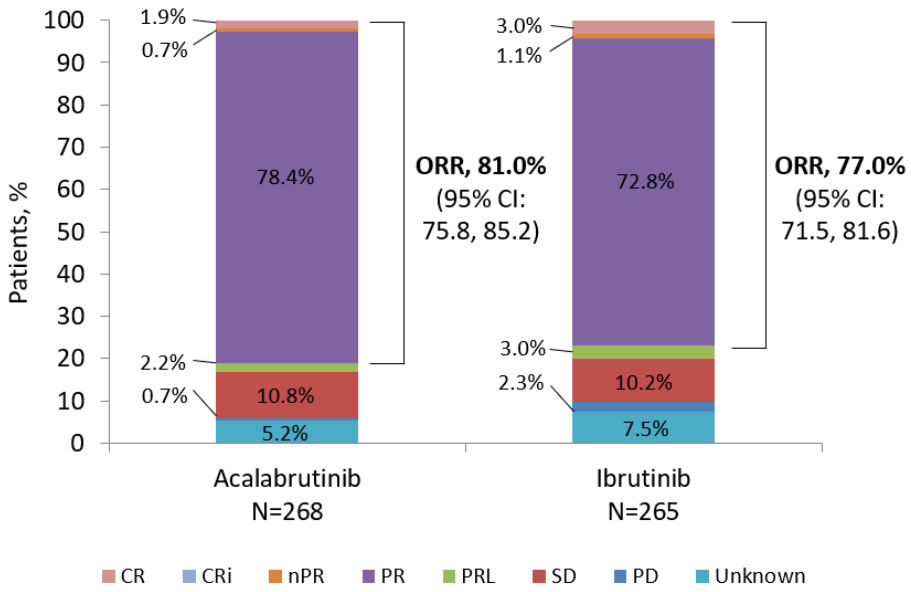
Figure S1. Kaplan-Meier Curve of Independent Review Committee–Assessed Progression-Free Survival in Patients With del(17)(p13.1) or del(11)(q22.3)



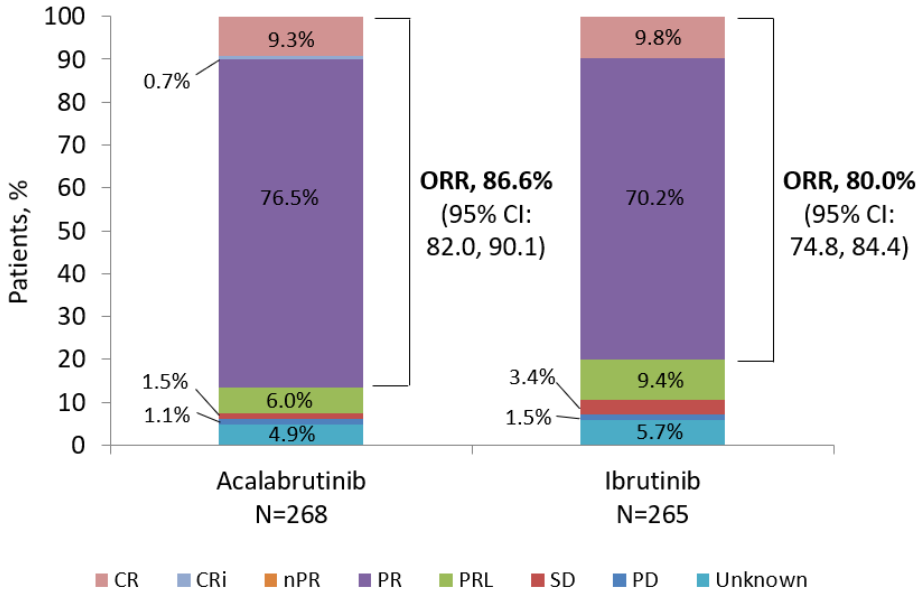
CI, confidence interval.

Figure S2. Overall Response Rate as Assessed by (A) Independent Review Committee and (B) Investigators

A.



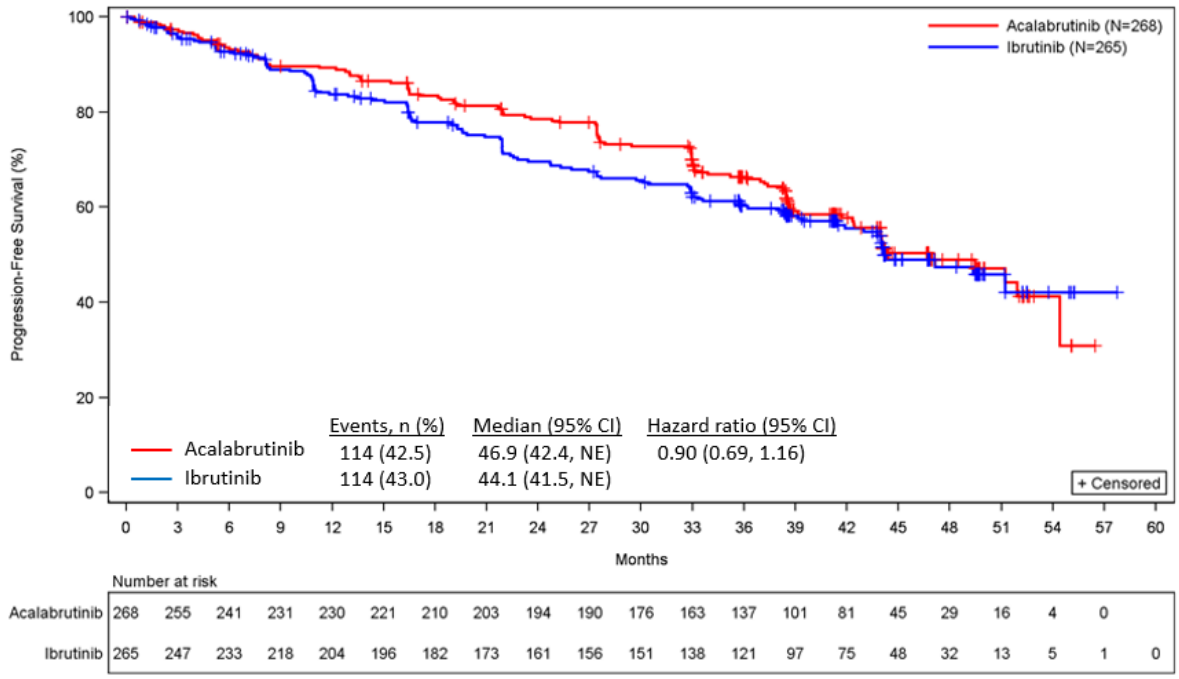
B.



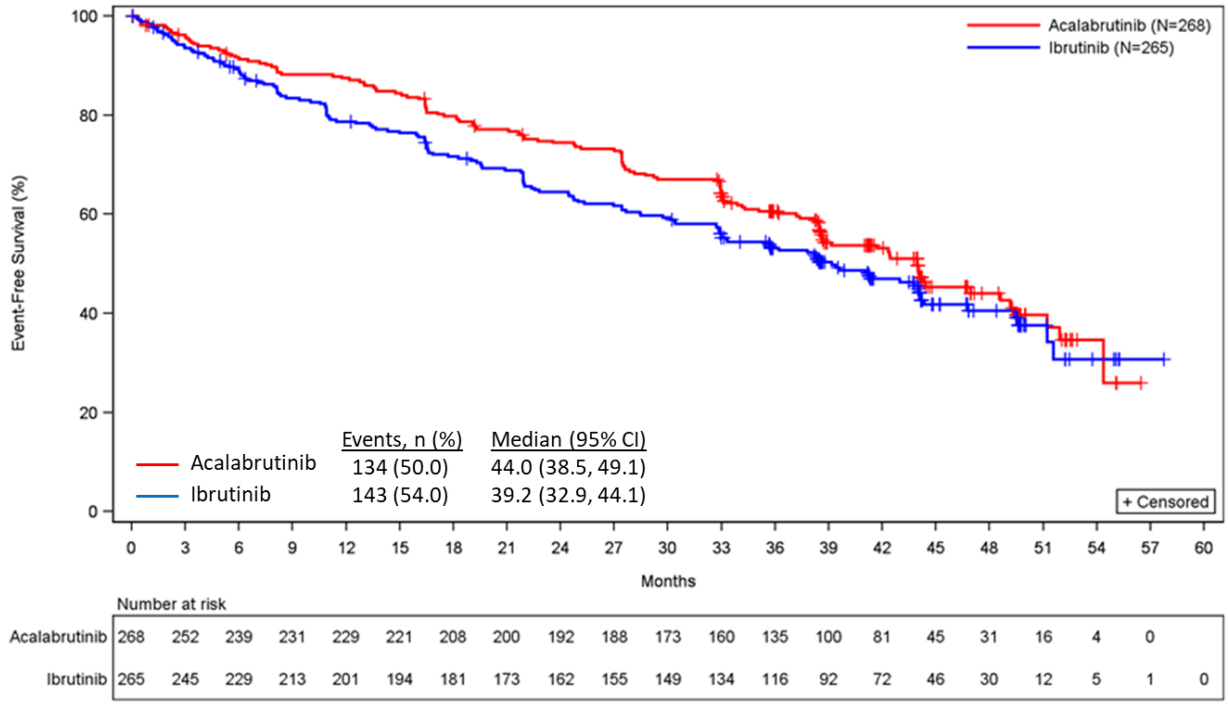
CR, complete response; CRi, complete response with incomplete blood count recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; PRL, partial response with lymphocytosis; SD, stable disease.

Figure S3. Kaplan-Meier Curve of Investigator-Assessed (A) Progression-Free Survival, (B) Event-Free Survival, and (C) Time to Next Treatment*

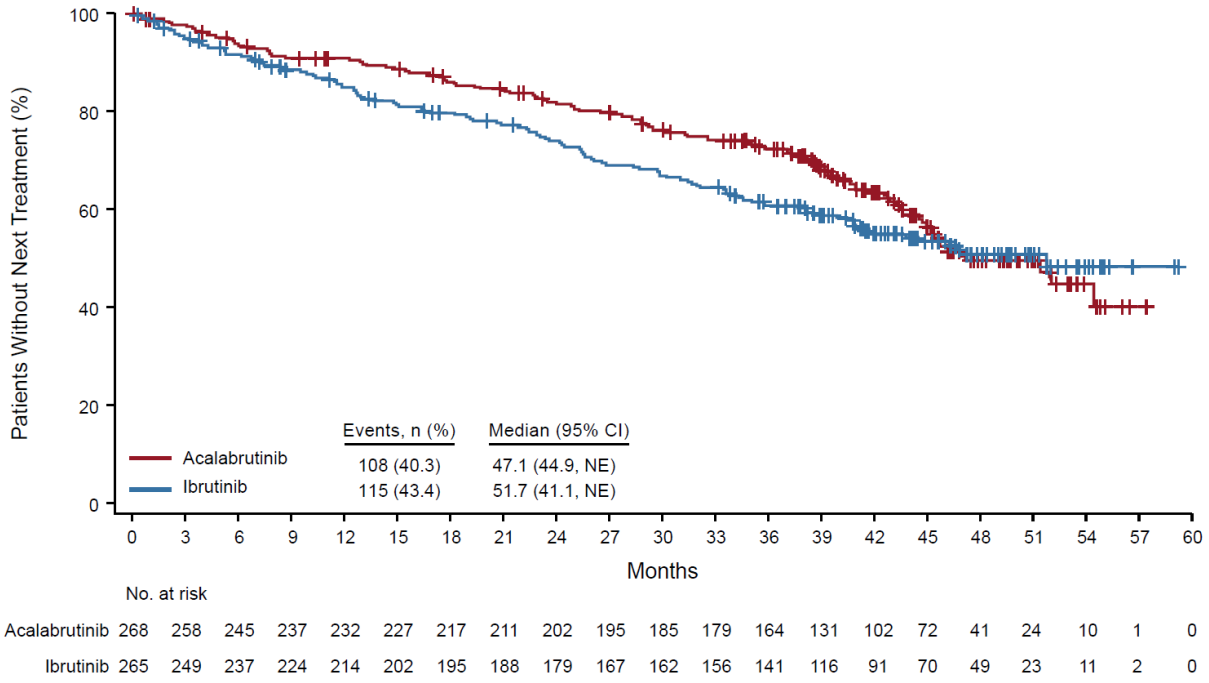
A.



B.



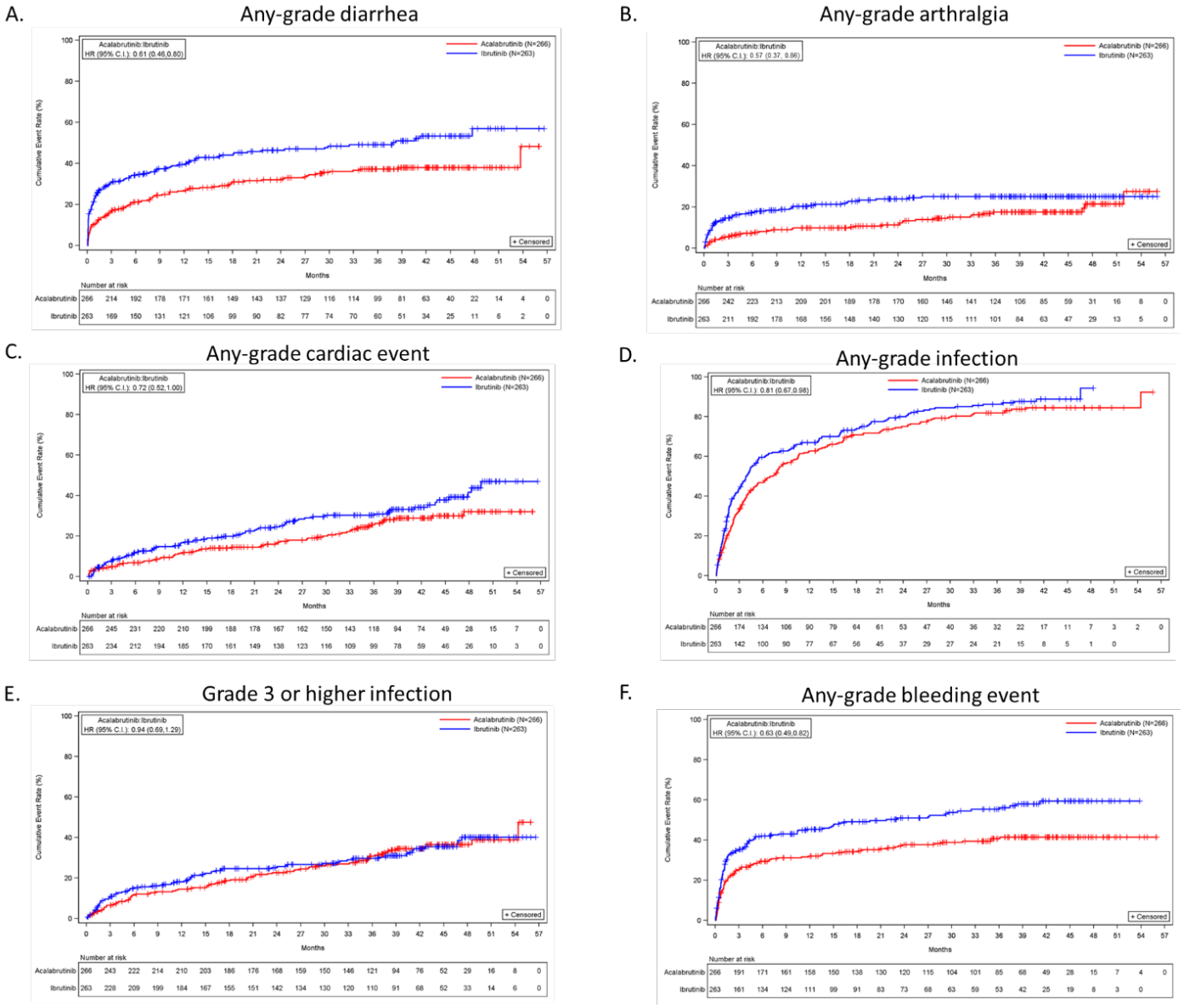
C.



*At 36 months, 72.2% (95% CI 66.2, 77.4) of acalabrutinib patients versus 60.7% (95% CI 54.3, 66.4) of ibrutinib patients had not started subsequent anticancer therapy.

CI, confidence interval; NE, not evaluable.

Figure S4. Cumulative Incidence of (A) Any-Grade Diarrhea, (B) Any-Grade Arthralgia,[a] (C) Any-Grade Cardiac Event, (D) Any-Grade Infection, (E) Grade 3 or Higher Infection, and (F) Any-Grade Bleeding Events Over Time



[a]The HR for any-grade arthralgia was estimated from 0 to 33 months (time interval where the proportional hazards assumption is met); from 33 months onward, there were 6 versus 0 arthralgia events with acalabrutinib versus ibrutinib, respectively, so a HR could not be estimated. The overall HR was 0.61 (95% CI: 0.41, 0.90) and can be interpreted as an average over time.

HR, hazard ratio; CI, confidence interval.

Figure S5. Second Primary Malignancies Excluding Non-Melanoma Skin Cancer

Shown are treatment-emergent and non-treatment-emergent second primary malignancies from the time of treatment. The median time to onset of second primary malignancies was 526.0 days (range, 13 to 1133) in the acalabrutinib arm and 453.5 days (range, 42 to 1282) in the ibrutinib arm.

SUPPLEMENTAL TABLES

Table S1. Additional Patient Baseline Characteristics

Characteristic	Acalabrutinib (N=268)	Ibrutinib (N=265)
Time from initial diagnosis to randomization, median (range) ─ months	84.8 (1.6–434.0)	73.0 (1.4–278.0)
Time from prior treatment to randomization, median (range) ─ months	19.0 (0.0–174.8)	18.9 (0.0–183.4)
Binet stage		
A	31 (11.6)	29 (10.9)
B	112 (41.8)	106 (40.0)
C	104 (38.8)	114 (43.0)
Not done	21 (7.8)	16 (6.0)
Cytogenetic subgroup		
del(17)(p13.1) and/or del(11)(q22.3)	267 (99.6)*	265 (100.0)
del(17)(p13.1) and del(11)(q22.3)	21 (7.8)	30 (11.3)
del(17)(p13.1) and/or *TP53* mutation	136 (50.7)	135 (50.9)
del(17)(p13.1) and *TP53* mutation	85 (31.7)	97 (36.6)
del(17)(p13.1) and del(11)(q22.3) and *TP53* mutation	12 (4.5)	20 (7.5)
del(17)(p13.1) and unmutated IGHV	92 (34.3)	105 (39.6)
del(17)(p13.1) and complex karyotype	67 (25.0)	68 (25.7)
del(11)(q22.3) and complex karyotype	70 (26.1)	74 (27.9)
β2-microglobulin >3.5 mg/L		
>3.5 mg/L	207 (77.2)	214 (80.8)
≤3.5 mg/L	58 (21.6)	51 (19.2)
Missing	3 (1.1)	0

Prior RBC transfusion within 28 days before randomization	12 (4.5)	10 (3.8)
Prior platelet transfusion within 28 days before randomization	0	1 (0.4)
Constitutional symptoms		
Any constitutional symptom	144 (53.7)	135 (50.9)
Weight loss	23 (8.6)	30 (11.3)
Fever	12 (4.5)	20 (7.5)
Night sweats	122 (45.5)	110 (41.5)
Fatigue	37 (13.8)	42 (15.8)
Missing	9 (3.4)	4 (1.5)
Creatinine clearance, median (range) ─ mL/min	87.0 (30.0–261.0)	87.0 (22.0–237.0)
Absolute lymphocyte count, median (range), 10^9/L	40.9 (0.8–361.5)	47.2 (1.1–445.8)
Absolute neutrophil count, median (range), 10^9/L	4.4 (0.0–111.3)	4.8 (0.3–100.7)
Platelet count, median (range), 10^9/L	124.0 (14.0–408.0)	120.0 (17.0–419.0)
Hemoglobin level, median (range), g/dL	11.8 (5.5–17.3)	11.8 (6.4–17.0)

Data are presented as no. (%) unless otherwise specified.
*One patient was randomized without any genetic testing and was discontinued from the study prior to treatment.
IGHV, immunoglobulin heavy chain variable region; RBC, red blood cell; *TP53*, tumor protein p53.

Table S2. Prior Therapies

Prior therapy*, no (%)	Acalabrutinib (N=268)	Ibrutinib (N=265)
Alkylators	242 (90.3)	240 (90.6)
Anti-CD20 monoclonal antibodies	227 (84.7)	229 (86.4)
Purine analogues	172 (64.2)	158 (59.6)
Steroids	62 (23.1)	62 (23.4)
Chemotherapy†	39 (14.6)	37 (14.0)
Alemtuzumab	16 (6.0)	11 (4.2)
Lenalidomide (monotherapy and in combination)	5 (1.9)	13 (4.9)
Mitoxantrone	3 (1.1)	5 (1.9)
Experimental antibodies	1 (0.4)	3 (1.1)
PI3K inhibitors (monotherapy and in combination)	1 (0.4)	0
Other‡	10 (3.7)	6 (2.3)

*A patient was only counted once for each category.
†Includes doxorubicin, bleomycin, vinca/alkaloids, etoposide, and platinum-based regimens.
‡Other therapies included monoclonal antibody (N=4), experimental NOS (N=3), alkylator (N=2), and IVIG (N=1)-based regimens in the acalabrutinib arm and experimental NOS (N=2), CDK-inhibitor/anti-CD20 (N=2), anti-CD20 (N=1), and mTOR kinase inhibitor (N=1)-based regimens in the ibrutinib arm.
CDK, cyclin-dependent kinase; IVIG, intravenous immunoglobulin; NOS, not otherwise specified.

Table S3. Summary of Deaths

Event, no. (%)	Acalabrutinib (N=266)	Ibrutinib (N=263)
Death	62 (23.3)*	73 (27.8)
Primary cause of death		
CLL disease progression	21 (7.9)	22 (8.4)
Richter transformation	3 (1.1)	7 (2.7)
Other†	5 (1.9)	3 (1.1)
Unknown	5 (1.9)	8 (3.0)
Adverse event	28 (10.5)	33 (12.5)
Within 30 days of last dose‡	17 (6.4)	25 (9.5)
Infections and infestations	12 (4.5)	15 (5.7)
Pneumonia	4 (1.5)	3 (1.1)
Sepsis	2 (0.8)	4 (1.5)
Brain abscess	1 (0.4)	0
Cerebral aspergillosis	1 (0.4)	0
COVID-19	1 (0.4)	2 (0.8)
Pneumocystis jirovecii pneumonia	1 (0.4)	0
Septic shock	1 (0.4)	2 (0.8)
Urinary tract infection	1 (0.4)	0
Biliary sepsis	0	1 (0.4)
Meningitis	0	1 (0.4)
Salmonella sepsis	0	1 (0.4)
Upper respiratory tract infection	0	1 (0.4)
Cardiac disorders	1 (0.4)	2 (0.8)
Cardiorespiratory arrest	1 (0.4)	0

Cardiac arrest	0	1 (0.4)
Cardiac failure	0	1 (0.4)
General disorders and administration site conditions	1 (0.4)	0
Pyrexia	1 (0.4)	0
Sudden cardiac death	0	1 (0.4)
Nervous system disorders	1 (0.4)	0
Cerebrovascular accident	1 (0.4)	0
Renal and urinary disorders	1 (0.4)	1 (0.4)
Renal failure	1 (0.4)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1 (0.4)
Dyspnea	1 (0.4)	0
Respiratory failure	0	1 (0.4)
Gastrointestinal disorders	0	1 (0.4)
Ileus	0	1 (0.4)
Metabolism and nutrition disorders	0	2 (0.8)
Cachexia	0	1 (0.4)
Tumor lysis syndrome	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.4)
Lung adenocarcinoma	0	1 (0.4)
Vascular disorders	0	1 (0.4)
Circulatory collapse	0	1 (0.4)
Beyond 30 days after last dose‡	11 (4.1)	8 (3.0)
Infections and infestations	4 (1.5)	4 (1.5)
Fungal infection	1 (0.4)	0

Pneumonia	1 (0.4)	2 (0.8)
Progressive multifocal leukoencephalopathy	1 (0.4)	0
Respiratory tract infection	1 (0.4)	0
Sepsis	0	1 (0.4)
Urosepsis	0	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.1)	1 (0.4)
Acute myeloid leukemia	1 (0.4)	0
Lung adenocarcinoma	1 (0.4)	0
Lung squamous cell carcinoma metastatic	1 (0.4)	0
Malignant melanoma	0	1 (0.4)
Cardiac disorders	1 (0.4)	0
Myocardial infarction	1 (0.4)	0
Injury, poisoning and procedural complications	1 (0.4)	0
Subdural hematoma	1 (0.4)	0
Metabolism and nutrition disorders	1 (0.4)	0
Tumor lysis syndrome	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1 (0.4)
Alveolitis	1 (0.4)	0
Respiratory failure	0	1 (0.4)
Hepatobiliary disorders	0	1 (0.4)
Hepatic cirrhosis	0	1 (0.4)
Immune system disorders	0	1 (0.4)

Hemophagocytic lymphohistiocytosis	0	1 (0.4)

*One patient randomized to the acalabrutinib arm died before receiving treatment and was not included in the safety population.
†Causes of death reported as “other” included death preferred terms of respiratory failure related to bacterial pneumonia (N=1), atrial fibrillation (N=1), septic shock (bacterial) (N=1), cerebral hemorrhage (N=1), and acute respiratory failure (N=1) in the acalabrutinib arm and codeine and dihydrocodeine toxicity (N=1), heart failure (N=1), and infection complications (N=1) in the ibrutinib arm. All occurred over 30 days after the last treatment dose in both arms.
‡Deaths occurring after the start of subsequent anticancer therapy were included in the “beyond 30 days after last dose” category regardless of time after last dose.
CLL, chronic lymphocytic leukemia.

Table S4. Subsequent Chronic Lymphocytic Leukemia Therapies in Patients Without Richter Transformation

	Acalabrutinib (N=258)	**Ibrutinib (N=252)**
Patients who received ≥1 subsequent therapy	60 (23.3)	56 (22.2)
Number of subsequent therapies		
Median (range)	1 (1–6)	1 (1–7)
1	35 (13.6)	33 (13.1)
2	18 (7.0)	11 (4.4)
3	4 (1.6)	4 (1.6)
≥4	3 (1.2)	8 (3.2)
Subsequent therapy		
Venetoclax	39 (15.1)	33 (13.1)
Anti-CD20 monoclonal antibody	23 (8.9)	24 (9.5)
Ibrutinib*	12 (4.7)	16 (6.3)
Alkylators other than bendamustine	4 (1.6)	13 (5.2)
Other BTK inhibitors	4 (1.6)	2 (0.8)
Steroid	4 (1.6)	7 (2.8)
Acalabrutinib*	3 (1.2)	1 (0.4)
PI3K inhibitors (monotherapy and in combination)	3 (1.2)	6 (2.4)
Chemotherapy†	2 (0.8)	8 (3.2)
Stem cell transplant	2 (0.8)	2 (0.8)
Alemtuzumab	1 (0.4)	0
Bendamustine	1 (0.4)	6 (2.4)
Purine analogues	1 (0.4)	3 (1.2)
Experimental antibodies	0	3 (1.2)

Platinum-based regimens	0	1 (0.4)
Other‡	5 (1.9)	3 (1.2)

Data are reported as no. (%) unless otherwise specified.
A patient was only counted once per regimen; only regimens with an indication of CLL were included.
*Additional details are provided in **Table S5**.
†Includes patients treated with doxorubicin, bleomycin, and vinca/alkaloids.
‡Other subsequent CLL therapies included experimental systemic therapies (N=3), ATR inhibitor (N=1), and AXL-kinase inhibitor (N=1) in the acalabrutinib group and ATR inhibitor (N=1), experimental systemic therapy (N=1), and TGR1202 + ublituximab and CAR-T cells (N=1) in the ibrutinib group.
CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia.

Table S5. Summary of Patients Without Richter Transformation Who Received Acalabrutinib or Ibrutinib as Subsequent CLL Therapy

Randomization arm	**Acalabrutinib**		**Ibrutinib**	
Subsequent anticancer therapy	**Acalabrutinib**	**Ibrutinib**	**Acalabrutinib**	**Ibrutinib**
Patients, no. (%)	3 (1.2)	12 (4.7)	1 (0.4)	16 (6.3)
Reason for treatment discontinuation, no.				
AE/SAE	0	2*	0	3†
Disease progression	3	7	1	7
Investigator discretion	0	1	0	3
Other‡	0	2	0	3
Anticancer regimen, no.				
Monotherapy	2	3	0	6
Combination (regimen)	1 (venetoclax and rituximab)	9 (venetoclax and rituximab)	1 (chlorambucil, obinutuzumab, venetoclax, and rituximab)	10 (venetoclax, bendamustine, idelalisib, and anti-CD20 mAb)

*Hepatitis B reactivation (N=1) and neutropenia/leukopenia (N=1).

†Squamous cell carcinoma (N=1; this patient also later received venetoclax), polycythemia vera (N=1; patient withdrew due to beginning hydroxyurea and aspirin for the AE and started new ibrutinib treatment 2 days later), and parainfluenza (N=1; patient also had a suspected CNS infection, demyelinating appearance on MRI).

‡Other reasons included moving to a different center/out of town (N=2) in the acalabrutinib arm and discrepancy in IRC versus investigator response (N=1; per investigator assessment, the patient had a partial response while assessment per independent

review committee was disease progression), early termination for second primary malignancy (N=1), and prohibited concomitant medication use (N=1) in the ibrutinib arm.
AE, adverse event; CNS, central nervous system; mAb, monoclonal antibody; MRI, magnetic resonance imaging; SAE, serious adverse event.

Table S6. Treatment Exposure and Dose Modifications by Study Drug

	Acalabrutinib* **(N=266)**	**Ibrutinib** **(N=263)**
Treatment status, no. (%)		
Ongoing	124 (46.6)	109 (41.4)
Discontinued	142 (53.4)	154 (58.6)
Duration of exposure, months		
Median	38.3	35.5
Range	0.3–55.9	0.2–57.7
Relative dose intensity, %		
Median	99.0	98.7
Range	37.2–100.4	30.2–100.1
Patients with dose withholding, no. (%)†	115 (43.2)	131 (49.8)
Adverse event	81 (30.5)	92 (35.0)
Procedure	39 (14.7)	50 (19.0)
Patient error	8 (3.0)	6 (2.3)
Investigator decision	1 (0.4)	7 (2.7)
Other	12 (4.5)	16 (6.1)
Patients with dose reduction, no. (%)‡	35 (13.2)	40 (15.2)
Adverse event	14 (5.3)	16 (6.1)
Patient error	12 (4.5)	3 (1.1)
Investigator decision	2 (0.8)	3 (1.1)
Procedure	1 (0.4)	0
Other	8 (3.0)	10 (3.8)
Unknown	11 (4.1)	23 (8.7)

*One patient who was randomized to the ibrutinib treatment arm received acalabrutinib during the study and was included in the acalabrutinib safety population.

[†]Defined as missing dose for ≥7 consecutive days; a subject is counted once per reason.
[‡]Defined as taking a lower dose level for ≥3 consecutive days.

Table S7. Adverse Events Occurring in at Least 10% (Any Grade) or at Least 5% (Grade 3 and Higher) of Patients in Any Treatment Group

	Acalabrutinib (N=266)			Ibrutinib (N=263)		
	Any grade	**Grade 1–2**	**Grade ≥3**	**Any grade**	**Grade 1–2**	**Grade ≥3**
Summary of adverse events						
Any	260 (97.7)	77 (28.9)	183 (68.8)	256 (97.3)	59 (22.4)	197 (74.9)
Serious	143 (53.8)	17 (6.4)	126 (47.4)	154 (58.6)	16 (6.1)	138 (52.5)
Led to drug discontinuation (any grade)	39 (14.7)	3 (1.1)	36 (13.5)	56 (21.3)	20 (7.6)	36 (13.7)
Most common adverse events						
Occurring in greater than 30% of patients (any grade)						
Diarrhea	92 (34.6)	89 (33.5)	3 (1.1)	121 (46.0)	108 (41.1)	13 (4.9)
Headache	92 (34.6)	88 (33.1)	4 (1.5)	53 (20.2)	53 (20.2)	0
Occurring in 20–30% of patients (any grade)						
Cough	77 (28.9)	75 (28.2)	2 (0.8)	56 (21.3)	55 (20.9)	1 (0.4)
Upper respiratory tract infection	71 (26.7)	66 (24.8)	5 (1.9)	65 (24.7)	64 (24.3)	1 (0.4)
Pyrexia	62 (23.3)	54 (20.3)	8 (3.0)	50 (19.0)	48 (18.3)	2 (0.8)
Anemia	58 (21.8)	27 (10.2)	31 (11.7)	49 (18.6)	15 (5.7)	34 (12.9)

Neutropenia	56 (21.1)	4 (1.5)	52 (19.5)	65 (24.7)	5 (1.9)	60 (22.8)
Fatigue	54 (20.3)	45 (16.9)	9 (3.4)	44 (16.7)	44 (16.7)	0
Arthralgia	42 (15.8)	42 (15.8)	0	60 (22.8)	58 (22.1)	2 (0.8)
Hypertension	23 (8.6)	12 (4.5)	11 (4.1)	60 (22.8)	37 (14.1)	23 (8.7)
Occurring in 10–20% of patients (any grade)						
Nausea	47 (17.7)	47 (17.7)	0	49 (18.6)	48 (18.3)	1 (0.4)
Pneumonia	47 (17.7)	19 (7.1)	28 (10.5)	43 (16.3)	20 (7.6)	23 (8.7)
Thrombocytopenia	40 (15.0)	14 (5.3)	26 (9.8)	35 (13.3)	17 (6.5)	18 (6.8)
Dyspnea	37 (13.9)	31 (11.7)	6 (2.3)	23 (8.7)	22 (8.4)	1 (0.4)
Bronchitis	34 (12.8)	31 (11.7)	3 (1.1)	23 (8.7)	21 (8.0)	2 (0.8)
Constipation	31 (11.7)	31 (11.7)	0	37 (14.1)	35 (13.3)	2 (0.8)
Contusion	31 (11.7)	31 (11.7)	0	48 (18.3)	47 (17.9)	1 (0.4)
Nasopharyngitis	29 (10.9)	29 (10.9)	0	27 (10.3)	27 (10.3)	0
Dizziness	28 (10.5)	28 (10.5)	0	26 (9.9)	26 (9.9)	0
Vomiting	28 (10.5)	27 (10.2)	1 (0.4)	36 (13.7)	33 (12.5)	3 (1.1)
Peripheral edema	26 (9.8)	26 (9.8)	0	38 (14.4)	37 (14.1)	1 (0.4)
Rash	26 (9.8)	24 (9.0)	2 (0.8)	33 (12.5)	33 (12.5)	0
Myalgia	25 (9.4)	23 (8.6)	2 (0.8)	27 (10.3)	26 (9.9)	1 (0.4)

Atrial fibrillation	24 (9.0)	12 (4.5)	12 (4.5)	41 (15.6)	32 (12.2)	9 (3.4)
Urinary tract infection	22 (8.3)	19 (7.1)	3 (1.1)	36 (13.7)	30 (11.4)	6 (2.3)
Back pain	20 (7.5)	20 (7.5)	0	34 (12.9)	32 (12.2)	2 (0.8)
Epistaxis	19 (7.1)	18 (6.8)	1 (0.4)	28 (10.6)	27 (10.3)	1 (0.4)
Muscle spasms	16 (6.0)	16 (6.0)	0	35 (13.3)	33 (12.5)	2 (0.8)
Dyspepsia	10 (3.8)	10 (3.8)	0	32 (12.2)	32 (12.2)	0

Data are reported as no. (%). Adverse events are reported as individual MedDRA preferred terms.

Table S8. Serious Adverse Events Occurring in ≥3 Patients in Any Treatment Group by System Organ Class

	Acalabrutinib (N=266)		Ibrutinib (N=263)	
SAE, no. (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any SAE	143 (53.8)	126 (47.4)	154 (58.6)	138 (52.5)
Infections and infestations	77 (28.9)	71 (26.7)	78 (29.7)	72 (27.4)
Pneumonia	27 (10.2)	25 (9.4)	26 (9.9)	22 (8.4)
Pneumocystis jirovecii pneumonia	5 (1.9)	5 (1.9)	0	0
Pneumonia pseudomonal	5 (1.9)	5 (1.9)	0	0
Bronchitis	4 (1.5)	2 (0.8)	2 (0.8)	2 (0.8)
Cellulitis	3 (1.1)	1 (0.4)	3 (1.1)	2 (0.8)
Influenza	3 (1.1)	3 (1.1)	3 (1.1)	3 (1.1)
Sepsis	3 (1.1)	3 (1.1)	7 (2.7)	7 (2.7)
Upper respiratory tract infection	3 (1.1)	3 (1.1)	1 (0.4)	1 (0.4)
Urinary tract infection	2 (0.8)	2 (0.8)	4 (1.5)	4 (1.5)
Lower respiratory tract infection	1 (0.4)	1 (0.4)	4 (1.5)	4 (1.5)
Blood and lymphatic system disorders	26 (9.8)	22 (8.3)	23 (8.7)	22 (8.4)
Anemia	14 (5.3)	11 (4.1)	13 (4.9)	11 (4.2)

Thrombocytopenia	5 (1.9)	5 (1.9)	2 (0.8)	2 (0.8)
Febrile neutropenia	4 (1.5)	4 (1.5)	5 (1.9)	5 (1.9)
Neutropenia	3 (1.1)	3 (1.1)	1 (0.4)	1 (0.4)
Cardiac disorders	15 (5.6)	15 (5.6)	24 (9.1)	18 (6.8)
Atrial fibrillation	6 (2.3)	6 (2.3)	14 (5.3)	7 (2.7)
Angina pectoris	3 (1.1)	3 (1.1)	0	0
Cardiac failure	3 (1.1)	3 (1.1)	5 (1.9)	5 (1.9)
General disorders and administration site conditions	14 (5.3)	10 (3.8)	13 (4.9)	7 (2.7)
Pyrexia	10 (3.8)	6 (2.3)	5 (1.9)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (5.3)	12 (4.5)	22 (8.4)	17 (6.5)
Prostate cancer	1 (0.4)	1 (0.4)	5 (1.9)	2 (0.8)
Nervous system disorders	14 (5.3)	11 (4.1)	12 (4.6)	7 (2.7)
Cerebrovascular accident	3 (1.1)	1 (0.4)	1 (0.4)	1 (0.4)
Syncope	3 (1.1)	3 (1.1)	3 (1.1)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	13 (4.9)	9 (3.4)	21 (8.0)	13 (4.9)
Dyspnea	3 (1.1)	3 (1.1)	2 (0.8)	1 (0.4)
Pleural effusion	0	0	5 (1.9)	4 (1.5)

Gastrointestinal disorders	11 (4.1)	10 (3.8)	25 (9.5)	17 (6.5)
Diarrhea	2 (0.8)	2 (0.8)	3 (1.1)	2 (0.8)
Abdominal pain	1 (0.4)	1 (0.4)	5 (1.9)	4 (1.5)
Injury, poisoning and procedural complications	8 (3.0)	6 (2.3)	10 (3.8)	9 (3.4)
Metabolism and nutrition disorders	7 (2.6)	7 (2.6)	10 (3.8)	9 (3.4)
Renal and urinary disorders	5 (1.9)	3 (1.1)	9 (3.4)	8 (3.0)
Acute kidney injury	2 (0.8)	2 (0.8)	6 (2.3)	4 (1.5)
Hepatobiliary disorders	4 (1.5)	3 (1.1)	1 (0.4)	1 (0.4)
Musculoskeletal and connective tissue disorders	4 (1.5)	2 (0.8)	8 (3.0)	7 (2.7)
Vascular disorders	4 (1.5)	2 (0.8)	4 (1.5)	4 (1.5)
Eye disorders	3 (1.1)	3 (1.1)	0	0
Investigations	3 (1.1)	3 (1.1)	1 (0.4)	0
Immune system disorders	0	0	3 (1.1)	2 (0.8)

Patients with multiple severity grades for a given SAE were counted only once under the maximum severity.
SAE, serious adverse event.

Table S9. Adverse Events of Any Grade Leading to Treatment Discontinuation

AEs leading to treatment discontinuation, no. (%)	Acalabrutinib(N=266)		Ibrutinib (N=263)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	39 (14.7)	36 (13.5)	56 (21.3)	36 (13.7)
Cardiac events	2 (0.8)	2 (0.8)	11 (4.2)	4 (1.5)
Cardiorespiratory arrest	1 (0.4)	1 (0.4)	0	0
Myocardial infarction	1 (0.4)	1 (0.4)	0	0
Atrial fibrillation	0	0	7 (2.7)	2 (0.8)
Cardiac arrest	0	0	1 (0.4)	1 (0.4)
Mitral valve incompetence	0	0	1 (0.4)	0
Pericardial effusion	0	0	1 (0.4)	1 (0.4)
Tachyarrhythmia	0	0	1 (0.4)	0
Cytopenia	7 (2.6)	6 (2.3)	2 (0.8)	2 (0.8)
Anemia	3 (1.1)	2 (0.8)	0	0
Neutropenia	2 (0.8)	2 (0.8)	1 (0.4)	1 (0.4)
Febrile neutropenia	1 (0.4)	1 (0.4)	0	0
Thrombocytopenia	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Hemorrhage	2 (0.8)	2 (0.8)	4 (1.5)	3 (1.1)
Hemorrhage	0	0	1 (0.4)	0
Major hemorrhage	2 (0.8)	2 (0.8)	3 (1.1)	3 (1.1)
Gastrointestinal hemorrhage	1 (0.4)	1 (0.4)	0	0
Hemorrhage intracranial	1 (0.4)	1 (0.4)	0	0
Pulmonary hematoma	0	0	1 (0.4)	1 (0.4)
Rectal hemorrhage	0	0	1 (0.4)	1 (0.4)

Skin hemorrhage*	0	0	1 (0.4)	1 (0.4)
Infections	17 (6.4)	16 (6.0)	18 (6.8)	17 (6.5)
Hepatitis B reactivation	2 (0.8)	2 (0.8)	0	0
Pneumonia	2 (0.8)	2 (0.8)	5 (1.9)	4 (1.5)
Appendicitis	1 (0.4)	1 (0.4)	0	0
Aspergillus infection	1 (0.4)	1 (0.4)	0	0
Brain abscess	1 (0.4)	1 (0.4)	0	0
Bronchopulmonary aspergillosis	1 (0.4)	0	0	0
COVID-19	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
COVID-19 pneumonia	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Cerebral aspergillosis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Hepatitis B	1 (0.4)	1 (0.4)	0	0
Herpes zoster meningoencephalitis	1 (0.4)	1 (0.4)	0	0
Pneumonia pseudomonal	1 (0.4)	1 (0.4)	0	0
Pneumonia staphylococcal	1 (0.4)	1 (0.4)	0	0
Postoperative wound infection	1 (0.4)	1 (0.4)	0	0
Sepsis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Biliary sepsis	0	0	1 (0.4)	1 (0.4)
Epstein-Barr virus infection reactivation	0	0	1 (0.4)	1 (0.4)
Escherichia pyelonephritis	0	0	1 (0.4)	1 (0.4)
Influenza	0	0	1 (0.4)	1 (0.4)
Parainfluenza virus infection	0	0	1 (0.4)	1 (0.4)
Pneumonia bacterial	0	0	1 (0.4)	1 (0.4)
Septic shock	0	0	2 (0.8)	2 (0.8)
Upper respiratory tract infection	0	0	1 (0.4)	1 (0.4)

Interstitial lung disease/pneumonitis	0	0	1 (0.4)	0
Interstitial lung disease	0	0	1 (0.4)	0
Second primary malignancies	6 (2.3)	6 (2.3)	5 (1.9)	5 (1.9)
Acute myeloid leukemia	1 (0.4)	1 (0.4)	0	0
Adenocarcinoma	1 (0.4)	1 (0.4)	0	0
Mesothelioma malignant	1 (0.4)	1 (0.4)	0	0
Ovarian cancer metastatic	1 (0.4)	1 (0.4)	0	0
Sarcoma	1 (0.4)	1 (0.4)	0	0
Squamous cell carcinoma of the vulva	1 (0.4)	1 (0.4)	0	0
Adenocarcinoma of colon	0	0	1 (0.4)	1 (0.4)
Lung adenocarcinoma	0	0	2 (0.8)	2 (0.8)
Malignant melanoma	0	0	1 (0.4)	1 (0.4)
Squamous cell carcinoma of lung	0	0	1 (0.4)	1 (0.4)
Tumor lysis syndrome	1 (0.4)	1 (0.4)	0	0
Other	4 (1.5)	3 (1.1)	15 (5.7)	5 (1.9)
Amyloidosis	0	0	1 (0.4)	1 (0.4)
Arthralgia	0	0	1 (0.4)	0
Crohn’s disease	0	0	1 (0.4)	0
Diarrhea	0	0	1 (0.4)	0
Dyspnea	0	0	1 (0.4)	0
Hemolytic anemia	0	0	1 (0.4)	1 (0.4)
Hypotension[†]	1 (0.4)	1 (0.4)	0	0
Ileus	0	0	1 (0.4)	1 (0.4)
Ingrowing nail	0	0	1 (0.4)	0
Peripheral edema	1 (0.4)	0	1 (0.4)	0

Pleural effusion‡	0	0	1 (0.4)	1 (0.4)
Polycythemia vera	0	0	1 (0.4)	0
Pyrexia§	2 (0.8)	2 (0.8)	0	0
Respiratory failure‖	0	0	1 (0.4)	1 (0.4)
Sarcoidosis	0	0	1 (0.4)	0
Spinal pain	0	0	1 (0.4)	0
Uveitis	0	0	1 (0.4)	0

AE, adverse event; CLL, chronic lymphocytic leukemia; ECI, event of clinical interest; INR, international normalized ratio.
*Due to spontaneous bleeding from an oral ulcer and with an elevated INR.
†In the setting of *Clostridium difficile* infection; subsequent death due to Richter transformation.
‡Due to CLL infiltration.
§Death occurred within 0 to 2 days due to AE with no defined cause.
‖AE began 2 days after atrial fibrillation onset, with death 2 days later due to respiratory failure.

Table S10. Summary of Cardiac Events

Cardiac events, no. (%)	Acalabrutinib (N=266)		Ibrutinib (N=263)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any cardiac event	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Cardiac arrhythmias	44 (16.5)	14 (5.3)	60 (22.8)	16 (6.1)
Atrial fibrillation	24 (9.0)	12 (4.5)	41 (15.6)	9 (3.4)
Tachycardia	7 (2.6)	0	7 (2.7)	0
Sinus bradycardia	5 (1.9)	0	3 (1.1)	0
Arrhythmia	2 (0.8)	1 (0.4)	2 (0.8)	0
Bradycardia	2 (0.8)	0	0	0
Bundle branch block right	2 (0.8)	0	1 (0.4)	0
Extrasystoles	2 (0.8)	0	1 (0.4)	0
Sinus tachycardia	2 (0.8)	0	6 (2.3)	0
Arrhythmia supraventricular	1 (0.4)	0	0	0
Atrial flutter	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)
Atrial tachycardia	1 (0.4)	0	0	0
Atrioventricular block	1 (0.4)	0	1 (0.4)	1 (0.4)

Atrioventricular block second degree	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Bifascicular block	1 (0.4)	0	0	0
Bradyarrhythmia	1 (0.4)	0	0	0
Cardiac flutter	1 (0.4)	0	0	0
Cardiorespiratory arrest	1 (0.4)	1 (0.4)	0	0
Atrioventricular block first degree	0	0	1 (0.4)	0
Bundle branch block left	0	0	2 (0.8)	1 (0.4)
Cardiac arrest	0	0	2 (0.8)	2 (0.8)
Sinus node dysfunction	0	0	1 (0.4)	0
Supraventricular tachycardia	0	0	2 (0.8)	1 (0.4)
Tachyarrhythmia	0	0	1 (0.4)	0
Ventricular arrhythmia	0	0	1 (0.4)	0
Ventricular extrasystoles	0	0	1 (0.4)	0
Ventricular fibrillation	0	0	1 (0.4)	1 (0.4)
Cardiac disorders, signs and symptoms NEC	10 (3.8)	0	14 (5.3)	0
Palpitation	10 (3.8)	0	12 (4.6)	0
Cardiovascular disorder	0	0	1 (0.4)	0
Hyperdynamic left ventricle	0	0	1 (0.4)	0
Coronary artery disorders	9 (3.4)	5 (1.9)	10 (3.8)	5 (1.9)

Angina pectoris	6 (2.3)	3 (1.1)	3 (1.1)	1 (0.4)
Myocardial ischemia	2 (0.8)	1 (0.4)	4 (1.5)	2 (0.8)
Myocardial infarction	1 (0.4)	1 (0.4)	0	0
Coronary artery disease	0	0	3 (1.1)	2 (0.8)
Heart failures	6 (2.3)	5 (1.9)	9 (3.4)	8 (3.0)
Cardiac failure	4 (1.5)	4 (1.5)	7 (2.7)	7 (2.7)
Cardiac failure chronic	1 (0.4)	1 (0.4)	3 (1.1)	1 (0.4)
Cardiac failure congestive	1 (0.4)	0	0	0
Left ventricular failure	1 (0.4)	0	0	0
Pericardial disorders	3 (1.1)	2 (0.8)	3 (1.1)	2 (0.8)
Pericardial effusion	3 (1.1)	1 (0.4)	2 (0.8)	1 (0.4)
Cardiac tamponade	1 (0.4)	1 (0.4)	0	0
Pericarditis	1 (0.4)	0	2 (0.8)	2 (0.8)
Cardiac valve disorders	1 (0.4)	0	5 (1.9)	2 (0.8)
Aortic valve disease	1 (0.4)	0	2 (0.8)	0
Tricuspid valve disease	1 (0.4)	0	0	0
Mitral valve disease	0	0	1 (0.4)	1 (0.4)
Mitral valve incompetence	0	0	3 (1.1)	2 (0.8)

Myocardial disorders	4 (1.5)	0	4 (1.5)	0
Cardiomyopathy	1 (0.4)	0	1 (0.4)	0
Ischemic cardiomyopathy	1 (0.4)	0	0	0
Ventricular hypertrophy	1 (0.4)	0	0	0
Ventricular hypokinesia	1 (0.4)	0	0	0
Left ventricular hypertrophy	0	0	2 (0.8)	0
Ventricular dysfunction	0	0	1 (0.4)	0

NEC, not elsewhere classifiable.

Table S11. Summary of Grade ≥3 Infections

Type of infection, no. (%)	Acalabrutinib (N=266)	Ibrutinib (N=263)
Any grade ≥3 infection	82 (30.8)	79 (30.0)
Infections by region		
Central nervous system and spinal infections		
Brain abscess	2 (0.8)	0
Meningitis	0	1 (0.4)
Meningitis aseptic	0	1 (0.4)
Pneumonia, upper respiratory, and respiratory		
Pneumonia, all		
Pneumonia*	28 (10.5)	23 (8.7)
Pneumocystis jirovecii pneumonia	5 (1.9)	0
Pneumonia pseudomonal	5 (1.9)	0
Pneumococcal infection	1 (0.4)	1 (0.4)
Pneumonia acinetobacter	1 (0.4)	0
Pneumonia bacterial	1 (0.4)	1 (0.4)
Pneumonia hemophilus	1 (0.4)	1 (0.4)
Pneumonia klebsiella	1 (0.4)	0
Pneumonia mycoplasmal	1 (0.4)	0
Pneumonia staphylococcal	1 (0.4)	0
Pneumonia streptococcal	1 (0.4)	1 (0.4)
Pneumonia viral	1 (0.4)	0
Pneumonia influenzal	0	1 (0.4)
Pneumonia pneumococcal	0	1 (0.4)
Upper respiratory and respiratory		

Upper respiratory tract infection	5 (1.9)	1 (0.4)
Bronchitis	3 (1.1)	2 (0.8)
Influenza	3 (1.1)	3 (1.1)
COVID-19 pneumonia	2 (0.8)	1 (0.4)
Respiratory tract infection	2 (0.8)	2 (0.8)
Chronic sinusitis	1 (0.4)	1 (0.4)
COVID-19	1 (0.4)	2 (0.8)
Lower respiratory tract infection	1 (0.4)	4 (1.5)
Acute sinusitis	0	1 (0.4)
Infective exacerbation of bronchiectasis	0	1 (0.4)
Metapneumovirus infection	0	1 (0.4)
Parainfluenzae virus infection	0	1 (0.4)
Peritonsillar abscess	0	1 (0.4)
Respiratory syncytial virus infection	0	1 (0.4)
Rhinovirus infection	0	1 (0.4)
Sinusitis	0	2 (0.8)
Tonsillitis	0	1 (0.4)
Sepsis		
Sepsis	4 (1.5)	7 (2.7)
Neutropenic sepsis	3 (1.1)	0
Septic shock	2 (0.8)	2 (0.8)
Escherichia sepsis	2 (0.8)	0
Clostridial sepsis	1 (0.4)	0
Urosepsis	1 (0.4)	0
Acinetobacter sepsis	0	1 (0.4)
Bacteremia	0	1 (0.4)

Bacterial sepsis	0	1 (0.4)
Biliary sepsis	0	1 (0.4)
Klebsiella sepsis	0	1 (0.4)
Pseudomonal sepsis	0	1 (0.4)
Salmonella sepsis	0	1 (0.4)
Gastrointestinal		
Appendicitis	2 (0.8)	2 (0.8)
Clostridium difficile colitis	2 (0.8)	0
Diarrhea infectious	1 (0.4)	0
Gastrointestinal infection	1 (0.4)	0
Clostridium difficile infection	0	2 (0.8)
Gastroenteritis	0	2 (0.8)
Kidney, bladder, and reproductive tract		
Escherichia urinary tract infection	3 (1.1)	2 (0.8)
Urinary tract infection	3 (1.1)	6 (2.3)
Urinary tract infection bacterial	1 (0.4)	1 (0.4)
Cystitis	0	1 (0.4)
Escherichia pyelonephritis	0	1 (0.4)
Hydrocele male infected	0	1 (0.4)
Urinary tract infection enterococcal	0	1 (0.4)
Urinary tract infection pseudomonal	0	1 (0.4)
Ear, eye, mouth/dental		
Gingivitis	1 (0.4)	0
Mastoiditis	1 (0.4)	0
Otitis media acute	1 (0.4)	0
Tooth abscess	1 (0.4)	0

Otitis media	0	2 (0.8)
Tooth infection	0	2 (0.8)
Muscle, bone and joint infections		
Abscess jaw	1 (0.4)	0
Arthritis bacterial	0	1 (0.4)
Bone abscess	0	1 (0.4)
Skin, soft tissue, and wound infections		
Bezold abscess	1 (0.4)	0
Blister infected	1 (0.4)	0
Cellulitis	1 (0.4)	2 (0.8)
Dermatitis infected	1 (0.4)	0
Groin abscess	1 (0.4)	0
Postoperative wound infection	1 (0.4)	0
Skin bacterial infection	1 (0.4)	1 (0.4)
Wound infection staphylococcal	1 (0.4)	0
Abscess limb	0	1 (0.4)
Cellulitis staphylococcal	0	1 (0.4)
Hematoma infection	0	1 (0.4)
Infected bite	0	1 (0.4)
Infected skin ulcer	0	1 (0.4)
Post procedural cellulitis	0	1 (0.4)
Skin infection	0	1 (0.4)
Soft tissue infection	0	2 (0.8)
Wound infection	0	1 (0.4)
Other infections by pathogen		
Bacterial infections		

Hemophilus infection	1 (0.4)	1 (0.4)
Meningococcal infection	1 (0.4)	0
Proteus infection	1 (0.4)	0
Staphylococcal infection	1 (0.4)	2 (0.8)
Stenotrophomonas infection	1 (0.4)	0
Acinetobacter infection	0	1 (0.4)
Bacterial infection	0	1 (0.4)
Campylobacter infection	0	1 (0.4)
Enterobacter infection	0	1 (0.4)
Nocardiosis	0	2 (0.8)
Fungal infections		
Bronchopulmonary aspergillosis	3 (1.1)	1 (0.4)
Aspergillus infection	1 (0.4)	0
Cerebral aspergillosis	1 (0.4)	1 (0.4)
Cryptococcosis	1 (0.4)	0
Oral candidiasis	1 (0.4)	0
Oral fungal infection	1 (0.4)	0
Candida infection	0	1 (0.4)
Onychomycosis	0	1 (0.4)
Viral infections		
Hepatitis B reactivation	2 (0.8)	0
Hepatitis B	1 (0.4)	0
Herpes zoster	1 (0.4)	4 (1.5)
Herpes zoster meningoencephalitis	1 (0.4)	0
Oral herpes	1 (0.4)	0
Picornavirus infection	1 (0.4)	0

Enterovirus infection	0	1 (0.4)
Epstein-Barr virus infection reactivation	0	1 (0.4)
Gastroenteritis norovirus	0	1 (0.4)
Hepatitis E	0	1 (0.4)
Varicella zoster virus infection	0	1 (0.4)
Not elsewhere classifiable (NEC)		
Infection	0	2 (0.8)

Patients with multiple severity grades for a given adverse event were counted only once under the maximum severity.
*Includes events with preferred term of pneumonia.

Table S12. Incidence, Time to Onset, Subtypes, Prior and Subsequent Therapies, and Outcomes in Patients With Richter Transformation

	Acalabrutinib (N=266)	**Ibrutinib (N=263)**
Patients with at least one RT, no. (%)	10	13
Time to RT onset, median (Q1, Q3) ─ months	7.1 (4.2, 24.5)	11.5 (8.4, 25.3)
RT patients with del(17)(p13.1), no. (%)	6 (60.0)	6 (46.2)
Number of prior therapies, median (Q1, Q3)	2 (1, 3)	1 (1, 2)
Prior treatment with purine analogues, no. (%)	8 (80.0)	7 (53.8)
Histology		
Diffuse large B cell lymphoma	7 (70.0)	11 (84.6)
Other*	3 (30.0)	2 (15.4)
Deaths among patients with RT[†]	8 (80.0)	11 (84.6)
Time from onset of RT diagnosis to death, median (Q1, Q3) ─ months	3.2 (0.2, 14.4)	1.7 (1.1, 3.2)

Percentages are based on the number of patients with Richter transformation.
*Other histologies included Burkitt lymphoma (N=1), Hodgkin's disease (N=1), and prolymphocytic leukemia (N=1) in the acalabrutinib arm and peripheral T cell lymphoma (N=1) and plasmoblastic lymphoma (N=1) in the ibrutinib arm.
[†]Causes of death were RT (N=3), PD (N=2), cerebrovascular accident (N=1), septic shock (N=1), and unknown (N=1) in the acalabrutinib group and RT (N=7), PD (N=3), and codeine and dihydrocodeine toxicity (N=1) in the ibrutinib group.
PD, progressive disease; Q, quartile; RT, Richter transformation.

Table S13. Additional Events of Clinical Interest

Events, no. (%)	Acalabrutinib (N=266)		Ibrutinib (N=263)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Bleeding events*	101 (38.0)	10 (3.8)	135 (51.3)	12 (4.6)
Major bleeding events†	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Cytopenias	108 (40.6)	78 (29.3)	113 (43.0)	94 (35.7)
Anemia	58 (21.8)	31 (11.7)	49 (18.6)	34 (12.9)
Neutropenia	62 (23.3)	58 (21.8)	68 (25.9)	63 (24.0)
Thrombocytopenia	42 (15.8)	27 (10.2)	36 (13.7)	18 (6.8)
Hepatotoxicity	15 (5.6)	5 (1.9)	22 (8.4)	4 (1.5)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
Interstitial lung disease/pneumonitis*	7 (2.6)	1 (0.4)	17 (6.5)	2 (0.8)
Second primary malignancies	50 (18.8)	23 (8.6)	36 (13.7)	15 (5.7)
Any second primary malignancy excluding non-melanoma skin cancers	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)
Tumor lysis syndrome	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)

*Two-sided P-value for any-grade event comparisons <0.05 without multiplicity adjustment.
†Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or that was a central nervous system hemorrhage (any severity grade).

Table S14. Summary of Major Bleeding Events

	Acalabrutinib (N=266)		Ibrutinib (N=263)	
Events, no. (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any major bleeding event*	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Brain				
Hemorrhage intracranial	2 (0.8)	2 (0.8)	1 (0.4)	1 (0.4)
Cerebral hemorrhage	1 (0.4)	0	0	0
Subdural hematoma	1 (0.4)	1 (0.4)	1 (0.4)	0
Gastrointestinal/Genitourinary				
Abdominal wall hematoma	1 (0.4)	1 (0.4)	0	0
Gastrointestinal hemorrhage	1 (0.4)	1 (0.4)	0	0
Hematuria	0	0	2 (0.8)	2 (0.8)
Mallory-Weiss syndrome	0	0	1 (0.4)	0
Rectal hemorrhage	0	0	1 (0.4)	1 (0.4)
Upper gastrointestinal hemorrhage	0	0	1 (0.4)	1 (0.4)
Skin/Joint/Mucosal				
Epistaxis	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Thrombocytopenic purpura	1 (0.4)	1 (0.4)	0	0

Contusion	0	0	1 (0.4)	1 (0.4)
Hemarthrosis	0	0	1 (0.4)	1 (0.4)
Immune thrombocytopenia	0	0	1 (0.4)	1 (0.4)
Skin hemorrhage	0	0	1 (0.4)	1 (0.4)
Eye				
Vitreous hemorrhage	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Retinal hemorrhage	0	0	1 (0.4)	0
Hematomas				
Hematoma	2 (0.8)	2 (0.8)	0	0
Mediastinal hematoma	1 (0.4)	0	0	0
Hematoma infection	0	0	1 (0.4)	1 (0.4)
Pulmonary hematoma	0	0	1 (0.4)	1 (0.4)
Tumor hemorrhage[†]	0	0	1 (0.4)	1 (0.4)

*Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or that was a central nervous system hemorrhage (any severity grade).
[†]Bleeding from a tumor of the salivary gland.

Table S15. Summary of Any Grade Second Primary Malignancies

Events, no. (%)	Acalabrutinib (N=266)	Ibrutinib (N=263)
Second primary malignancies	50 (18.8)	36 (13.7)
Non-melanoma skin cancer	28 (10.5)	20 (7.6)
Basal cell carcinoma	14 (5.3)	10 (3.8)
Squamous cell carcinoma of skin	14 (5.3)	10 (3.8)
Bowen's disease	3 (1.1)	0
Keratoacanthoma	1 (0.4)	1 (0.4)
Skin cancer	1 (0.4)	1 (0.4)
Second primary malignancies excluding non-melanoma skin cancer	24 (9.0)	20 (7.6)
Prostate cancer	3 (1.1)	6 (2.3)
Lip squamous cell carcinoma	2 (0.8)	0
Lung adenocarcinoma	2 (0.8)	2 (0.8)
Lung neoplasm malignant	2 (0.8)	2 (0.8)
Acute myeloid leukemia	1 (0.4)	0
Adenocarcinoma	1 (0.4)	0
Burkitt's lymphoma	1 (0.4)	0
Cutaneous T cell lymphoma	1 (0.4)	0
Diffuse large B cell lymphoma	1 (0.4)	0
Leukemic infiltration pulmonary	1 (0.4)	0
Malignant melanoma	1 (0.4)	3 (1.1)
Mesothelioma malignant	1 (0.4)	0
Mucoepidermoid carcinoma of salivary gland	1 (0.4)	0
Non-small cell lung cancer	1 (0.4)	0

Ovarian cancer metastatic	1 (0.4)	0
Renal cancer	1 (0.4)	0
Renal cell carcinoma	1 (0.4)	0
Sarcoma	1 (0.4)	0
Squamous cell carcinoma	1 (0.4)	0
Squamous cell carcinoma of the vulva	1 (0.4)	0
Adenocarcinoma of colon	0	1 (0.4)
Bladder cancer	0	1 (0.4)
Bladder transitional cell carcinoma	0	1 (0.4)
Malignant melanoma in situ	0	1 (0.4)
Malignant neoplasm of conjunctiva	0	1 (0.4)
Papillary thyroid cancer	0	1 (0.4)
Prostate cancer stage II	0	1 (0.4)
Squamous cell carcinoma of lung	0	2 (0.8)
Squamous cell carcinoma of the parotid gland	0	1 (0.4)
Transitional cell carcinoma	0	1 (0.4)

Includes events occurring within the treatment-emergent period.

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