SUPPLEMENTARY APPENDIX

Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia

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Supplement to: Phase 2 Study of Acalabrutinib in Ibrutinib-Intolerant Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia

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Eligibility criteria

Inclusion criteria

Eligible subjects will be considered for inclusion in this study if they meet all of the following criteria:

1. Men and women ≥18 years of age
2. Prior diagnosis of chronic lymphocytic leukemia (CLL) that meets published diagnostic criteria[1] as follows:
    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. No evidence of cyclin D1 rearrangement or BCL-1 overexpression
    d. Presence of ≥5 x 10^9 B lymphocytes/L (≥5000/μL) in the peripheral blood (at any point since diagnosis)
3. Must have received ≥1 prior therapy for CLL and not be appropriate for treatment or retreatment with purine analogue–based therapy as defined by ≥1 of the following criteria:
    a. Failure to respond (stable disease or disease progression on treatment) or progression-free interval of <3 years from treatment with a purine analogue–based therapy and anti-CD20 antibody–containing chemoimmunotherapy regimen after ≥2 cycles
    b. Age ≥70 years
    c. Age ≥65 years with the presence of 1 of the following comorbidities that might

place the subject at an unacceptable risk for treatment-related toxicity with purine analogue–based therapy, provided they have received ≥1 prior treatment including ≥2 cycles of an alkylating agent–based (or purine analogue–based) anti-CD20 antibody–containing chemoimmunotherapy regimen:

i. Cumulative Illness Rating Scale–Geriatric score ≥6

ii. Creatinine clearance <70 mL/min

d. History of purine analogue–associated autoimmune anemia, neutropenia or autoimmune thrombocytopenia

e. Fluorescence in situ hybridisation testing showing 17p deletion mutation or p53 mutation (by central laboratory)

4. Intolerant of ibrutinib, defined as:

   a. The subject has discontinued ibrutinib therapy due to grade 3 or 4 adverse events (AEs) that persisted in spite of optimal supportive care measures OR

   b. Subjects who had grade 2 AEs related to ibrutinib therapy, in spite of optimal supportive care measures, that persisted for ≥2 weeks or that recurred ≥2 times whether dose was reduced or discontinued

5. Measurable nodal disease by computed tomography defined as ≥1 lymph node >1.5 cm as measured in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended

6. Documented disease progression after stopping ibrutinib therapy as defined by the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria

7. Eastern Cooperative Oncology Group performance status of ≤2

8. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 3.9.10
9. 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. Highly effective forms of contraception are defined in Section 3.9.10
10. Men must agree to refrain from sperm donation during the study and for 2 days after the last dose of study drug
11. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty
12. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorisation to use protected health information (in accordance with national and local patient privacy regulations)

Exclusion criteria

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

1. Ongoing grade 3 or 4 AE attributed to ibrutinib therapy. Note: Patients may be eligible for enrolment once the ibrutinib-related AE improves to grade ≤2
2. Treatment with systemic anticancer therapy for CLL is prohibited between discontinuation of ibrutinib and enrolment in this trial
3. Prior exposure to a BCL-2 inhibitor (eg, venetoclax/ABT-199)
4. Prior malignancy (other than CLL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease-

free for ≥2 years

5. Significant cardiovascular disease such as uncontrolled or symptomatic untreated 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 QTc >480 msec at screening. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enrol in the study
6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass
7. Evidence of active Richter transformation or any evidence of disease progression on ibrutinib therapy or any Bruton tyrosine kinase inhibitor
8. Central nervous system involvement by CLL or related Richter transformation
9. Known history of HIV, serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection
    a. Subjects who are hepatitis B core antibody–positive and who are surface antigen–negative will need to have a negative polymerase chain reaction (PCR) result before enrolment. Those who are hepatitis B surface antigen–positive or hepatitis B PCR–positive will be excluded
    b. Subjects who are hepatitis C antibody–positive will need to have a negative PCR result before enrolment. Those who are hepatitis C PCR–positive will be excluded
10. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura

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 or equivalent for >2 weeks)

11. History of stroke or intracranial hemorrhage within 2 months before the first dose of study drug
12. History of bleeding diathesis (eg, hemophilia or von Willebrand disease)
13. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening
14. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug
15. Requires treatment with a strong CYP3A inhibitor/inducer
16. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to H_2 receptor antagonists or antacids are eligible for enrolment in this study
17. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug. Alternative anticoagulation therapy is permitted
18. Absolute neutrophil count $<0.75 \times 10^9$/L or platelet count $<50 \times 10^9$/L, unless there is bone marrow involvement
19. Total bilirubin >1.5 x upper limit of normal (ULN); or aspartate aminotransferase or alanine aminotransferase >3.0 x ULN

20. Estimated creatinine clearance of <30 mL/min, calculated using the formula of Cockcroft and Gault ([140 − age] • mass [kg]/[72 • creatinine mg/dL] • multiply by 0.85 if female)
21. Breastfeeding or pregnant
22. Concurrent participation in another therapeutic clinical trial

Exploratory analysis of molecular resistance to BTK inhibitors

An exploratory analysis of molecular resistance to BTK inhibitors was performed retrospectively using deep sequencing of *BTK* and *PLCG2* in patients with pretreatment samples. Sample B-cells were purified from blood using a negative-selection immunodensity method or an anti-CD19 immunoaffinity method (RosetteSep Human B Cells, Stemcell Technologies, Vancouver, Canada).[2,3] Next-generation sequencing was performed on B-cell genomic DNA using a custom-designed, amplicon-based, AmpliSeq library (Thermo Fisher Scientific, Waltham, MA) covering the entire coding regions of *BTK* and *PLCG2* and sequencing on the Ion Torrent platform (PGM or Ion Chef-S5 platforms, Thermo Fisher Scientific) as previously described.[2,3] Samples were sequenced to an average depth of 5400 reads, with a validated sensitivity of 0.3% allele fraction for mutations at the *BTK* C481 codon and 0.5% at other sites.

Statistical analysis

Data as of March 6, 2020, were included in the analysis. All safety and efficacy analyses included enrolled patients who received at least one dose of acalabrutinib. No formal tests of hypotheses were performed. Continuous variables were reported using descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized as the number and percentage of patients in a given

category; confidence intervals (CI) were provided as appropriate. For the primary endpoint, the ORR and the associated 95% exact (Clopper-Pearson) CI were reported. Time-to-event endpoints (DOR, PFS, OS, and TTNT) were analyzed using the Kaplan-Meier method; median time to event (months) was reported, and estimated event-free rates and 95% CIs were reported for selected landmarks.

References

1. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-5456.
2. Woyach JA, Ruppert AS, Guinn D, et al. BTK(C481S)-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol. 2017;35(13):1437-1443.
3. Jones D, Woyach JA, Zhao W, et al. PLCG2 C2 domain mutations co-occur with BTK and PLCG2 resistance mutations in chronic lymphocytic leukemia undergoing ibrutinib treatment. Leukemia. 2017;31(7):1645-1647.

Table S1. Prior systemic CLL therapies.

Prior therapy	N=60
Ibrutinib	60 (100)
Monotherapy	50 (83)
Combination therapy[a]	10 (17)
Anti-CD20 monoclonal antibody	43 (72)[b]
Rituximab	40 (67)
Ofatumumab	9 (15)
Systemic chemotherapy	36 (60)
Alkylator	32 (53)
Bendamustine	18 (30)
Nucleoside analog	25 (42)
Fludarabine	24 (40)
Steroid	7 (12)
Alemtuzumab	6 (10)
Lenalidomide	6 (10)
Investigational drug[c]	6 (10)
Idelalisib	2 (3)

Data presented are n (%).

CLL, chronic lymphocytic leukemia.

[a]Combinations included: ibrutinib + rituximab (n=3), ibrutinib + obinutuzumab, ibrutinib + rituximab + lenalidomide, ibrutinib + ublituximab, rituximab + bendamustine + ibrutinib, monalizumab + ibrutinib, ibrutinib + ofatumumab, and ibrutinib + lenalidomide (n=1 for each).

[b]Some patients received both agents.

[c]Investigational drugs included: antineoplastic agents, entospletinib, gossypol acetic acid, monalizumab, spebrutinib, and ublituximab.

Table S2. Adverse events leading to ibrutinib discontinuation.

Preferred term	All treated subjects (N=60)			
	All grades[b] n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with ≥1 event[a]	60 (100)	20 (33.3)	36 (60.0)	4 (6.7)
Atrial fibrillation	14 (23.3)	5 (8.3)	8 (13.3)	1 (1.7)
Diarrhea	7 (11.7)	4 (6.7)	3 (5.0)	0
Arthralgia	6 (10.0)	2 (3.3)	4 (6.7)	0
Rash	6 (10.0)	2 (3.3)	4 (6.7)	0
Asthenia	2 (3.3)	2 (3.3)	0	0
Atrial flutter	2 (3.3)	0	2 (3.3)	0
Fatigue	2 (3.3)	0	2 (3.3)	0
Neutropenia	2 (3.3)	0	1 (1.7)	1 (1.7)
Arthritis	1 (1.7)	1 (1.7)	0	0
Aspartate aminotransferase increased	1 (1.7)	0	1 (1.7)	0
Cellulitis	1 (1.7)	0	1 (1.7)	0
Cough	1 (1.7)	1 (1.7)	0	0
Dizziness	1 (1.7)	1 (1.7)	0	0
Ecchymosis	1 (1.7)	1 (1.7)	0	0
Edema	1 (1.7)	1 (1.7)	0	0
Epistaxis	1 (1.7)	0	1 (1.7)	0
Febrile neutropenia	1 (1.7)	0	0	1 (1.7)
Gastritis	1 (1.7)	0	1 (1.7)	0
Gastrointestinal disorder	1 (1.7)	1 (1.7)	0	0
Glaucoma	1 (1.7)	0	0	1 (1.7)
Guillain-Barré syndrome	1 (1.7)	0	1 (1.7)	0
Hematuria	1 (1.7)	1 (1.7)	0	0
Hemorrhage	1 (1.7)	1 (1.7)	0	0
Headache	1 (1.7)	1 (1.7)	0	0
Hypersensitivity	1 (1.7)	0	1 (1.7)	0
Hypertension	1 (1.7)	0	1 (1.7)	0

Liver function test increased	1 (1.7)	1 (1.7)	0	0
Macular edema	1 (1.7)	0	1 (1.7)	0
Myalgia	1 (1.7)	0	1 (1.7)	0
Neutrophil count decreased	1 (1.7)	0	1 (1.7)	0
Pneumonia	1 (1.7)	0	1 (1.7)	0
Pulmonary hemorrhage	1 (1.7)	0	1 (1.7)	0
Rash, maculopapular	1 (1.7)	1 (1.7)	0	0
Retinal hemorrhage	1 (1.7)	1 (1.7)	0	0
Retinal vein occlusion	1 (1.7)	1 (1.7)	0	0
Stent-graft endoleak	1 (1.7)	0	1 (1.7)	0
Stomatitis	1 (1.7)	1 (1.7)	0	0
Thrombocytopenia	1 (1.7)	0	1 (1.7)	0
Uveitis	1 (1.7)	0	1 (1.7)	0

AEs leading to intolerance in patients with less than 2 months prior ibrutinib treatment: rash (n=3; two patients discontinued acalabrutinib [one due to squamous cell carcinoma of the lung and one due to endometrial cancer]); arthralgia/joint pain (n=2); atrial flutter (n=2); uveitis, hypersensitivity/allergic reaction, thrombocytopenia, severe pneumonia, maculopapular rash, stomatitis, and epistaxis (n=1 each); and neutropenia, diarrhea, fatigue, and edema (all in the same patient).

[a]Adverse events are not mutually exclusive; several patients experienced ≥1 adverse event.

[b]Grade 1 adverse events were not cause for ibrutinib discontinuation and were, therefore, not captured.

Table S3. Treatment-emergent adverse events with acalabrutinib.

Adverse event	All treated subjects (N=60)					
	All grades n (%)	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Diarrhea	32 (53.3)	18 (30.0)	11 (18.3)	3 (5.0)	0	0
Headache	25 (41.7)	20 (33.3)	4 (6.7)	1 (1.7)	0	0
Contusion	24 (40.0)	20 (33.3)	4 (6.7)	0	0	0
Dizziness	20 (33.3)	18 (30.0)	1 (1.7)	1 (1.7)	0	0
Upper respiratory tract infection	20 (33.3)	3 (5.0)	17 (28.3)	0	0	0
Cough	18 (30.0)	9 (15.0)	9 (15.0)	0	0	0
Nausea	15 (25.0)	10 (16.7)	5 (8.3)	0	0	0
Neutropenia[a]	15 (25.0)	0	3 (5.0)	7 (11.7)	5 (8.3)	0
Arthralgia	14 (23.3)	8 (13.3)	5 (8.3)	1 (1.7)	0	0
Fatigue	14 (23.3)	6 (10.0)	7 (11.7)	1 (1.7)	0	0
Pneumonia	13 (21.7)	0	4 (6.7)	7 (11.7)	0	2 (3.3)
Pyrexia	12 (20.0)	7 (11.7)	5 (8.3)	0	0	0
Back pain	10 (16.7)	4 (6.7)	5 (8.3)	1 (1.7)	0	0
Constipation	10 (16.7)	9 (15.0)	0	1 (1.7)	0	0
Dyspnea	10 (16.7)	7 (11.7)	3 (5.0)	0	0	0
Lymphocytosis[b]	10 (16.7)	0	2 (3.3)	8 (13.3)	0	0
Rash	10 (16.7)	6 (10.0)	4 (6.7)	0	0	0
Sinusitis	10 (16.7)	0	10 (16.7)	0	0	0
Thrombocytopenia[c]	10 (16.7)	3 (5.0)	2 (3.3)	3 (5.0)	2 (3.3)	0
Anemia	9 (15.0)	3 (5.0)	3 (5.0)	3 (5.0)	0	0
Cough syndrome, upper airway	9 (15.0)	6 (10.0)	3 (5.0)	0	0	0
Fall	8 (13.3)	4 (6.7)	2 (3.3)	2 (3.3)	0	0
Hematuria	8 (13.3)	5 (8.3)	2 (3.3)	1 (1.7)	0	0
Hypertension	8 (13.3)	2 (3.3)	4 (6.7)	2 (3.3)	0	0
Night sweats	8 (13.3)	4 (6.7)	4 (6.7)	0	0	0
Edema, peripheral	8 (13.3)	6 (10.0)	2 (3.3)	0	0	0
Urinary tract infection	8 (13.3)	0	7 (11.7)	1 (1.7)	0	0

Weight increased	8 (13.3)	3 (5.0)	5 (8.3)	0	0	0
Abdominal pain	7 (11.7)	2 (3.3)	4 (6.7)	1 (1.7)	0	0
Influenza-like illness	7 (11.7)	4 (6.7)	2 (3.3)	1 (1.7)	0	0
Chills	6 (10.0)	6 (10.0)	0	0	0	0
Depression	6 (10.0)	3 (5.0)	3 (5.0)	0	0	0
Hyperhidrosis	6 (10.0)	6 (10.0)	0	0	0	0
Insomnia	6 (10.0)	4 (6.7)	2 (3.3)	0	0	0
Nasal congestion	6 (10.0)	3 (5.0)	3 (5.0)	0	0	0
Basal cell carcinoma	5 (8.3)	0	3 (5.0)	2 (3.3)	0	0
Decreased appetite	5 (8.3)	2 (3.3)	2 (3.3)	1 (1.7)	0	0
Dry mouth	5 (8.3)	5 (8.3)	0	0	0	0
Hypoesthesia	5 (8.3)	5 (8.3)	0	0	0	0
Hypotension	5 (8.3)	4 (6.7)	1 (1.7)	0	0	0
Localized edema	5 (8.3)	3 (5.0)	2 (3.3)	0	0	0
Muscle spasms	5 (8.3)	3 (5.0)	1 (1.7)	1 (1.7)	0	0
Myalgia	5 (8.3)	5 (8.3)	0	0	0	0
Pain in extremity	5 (8.3)	4 (6.7)	0	1 (1.7)	0	0
Petechia	5 (8.3)	4 (6.7)	1 (1.7)	0	0	0
Pollakiuria	5 (8.3)	4 (6.7)	1 (1.7)	0	0	0
Pruritus	5 (8.3)	5 (8.3)	0	0	0	0
Skin lesion	5 (8.3)	3 (5.0)	2 (3.3)	0	0	0
Vomiting	5 (8.3)	3 (5.0)	2 (3.3)	0	0	0
Abdominal discomfort	4 (6.7)	2 (3.3)	2 (3.3)	0	0	0
Arthritis	4 (6.7)	3 (5.0)	1 (1.7)	0	0	0
Bronchitis	4 (6.7)	1 (1.7)	3 (5.0)	0	0	0
Dry skin	4 (6.7)	3 (5.0)	1 (1.7)	0	0	0
Ecchymosis	4 (6.7)	4 (6.7)	0	0	0	0
Epistaxis	4 (6.7)	4 (6.7)	0	0	0	0
Gastro-esophageal reflux disease	4 (6.7)	2 (3.3)	2 (3.3)	0	0	0
Hyperkalemia	4 (6.7)	3 (5.0)	1 (1.7)	0	0	0
Hyponatremia	4 (6.7)	0	1 (1.7)	3 (5.0)	0	0

Musculoskeletal pain	4 (6.7)	1 (1.7)	3 (5.0)	0	0	0
Nocturia	4 (6.7)	2 (3.3)	2 (3.3)	0	0	0
Noncardiac chest pain	4 (6.7)	2 (3.3)	2 (3.3)	0	0	0
Rhinitis, allergic	4 (6.7)	3 (5.0)	1 (1.7)	0	0	0
Stomatitis	4 (6.7)	2 (3.3)	2 (3.3)	0	0	0
Tinnitus	4 (6.7)	3 (5.0)	1 (1.7)	0	0	0
Tremor	4 (6.7)	3 (5.0)	1 (1.7)	0	0	0
Alanine aminotransferase increased	3 (5.0)	1 (1.7)	1 (1.7)	1 (1.7)	0	0
Cardiac failure, congestive	3 (5.0)	0	0	3 (5.0)	0	0
Chest pain	3 (5.0)	1 (1.7)	0	2 (3.3)	0	0
Clostridium difficile infection	3 (5.0)	0	3 (5.0)	0	0	0
Hemoptysis	3 (5.0)	2 (3.3)	1 (1.7)	0	0	0
Hypokalemia	3 (5.0)	1 (1.7)	0	2 (3.3)	0	0
Large intestine polyp	3 (5.0)	2 (3.3)	1 (1.7)	0	0	0
Lower respiratory tract infection	3 (5.0)	0	2 (3.3)	1 (1.7)	0	0
Malaise	3 (5.0)	2 (3.3)	1 (1.7)	0	0	0
Oropharyngeal pain	3 (5.0)	2 (3.3)	1 (1.7)	0	0	0
Otitis media	3 (5.0)	0	2 (3.3)	1 (1.7)	0	0
Pain	3 (5.0)	3 (5.0)	0	0	0	0
Paresthesia	3 (5.0)	3 (5.0)	0	0	0	0
Peripheral swelling	3 (5.0)	3 (5.0)	0	0	0	0
Productive cough	3 (5.0)	3 (5.0)	0	0	0	0
Purpura	3 (5.0)	3 (5.0)	0	0	0	0
Rash, maculopapular	3 (5.0)	2 (3.3)	1 (1.7)	0	0	0
Sepsis	3 (5.0)	0	0	0	3 (5.0)	0
Skin infection	3 (5.0)	1 (1.7)	2 (3.3)	0	0	0
Skin laceration	3 (5.0)	3 (5.0)	0	0	0	0
Squamous cell carcinoma of skin	3 (5.0)	0	3 (5.0)	0	0	0

Syncope	3 (5.0)	0	0	3 (5.0)	0	0
Urinary retention	3 (5.0)	1 (1.7)	2 (3.3)	0	0	0
Vertigo	3 (5.0)	3 (5.0)	0	0	0	0
Weight decreased	3 (5.0)	0	3 (5.0)	0	0	0
Abdominal distension	2 (3.3)	2 (3.3)	0	0	0	0
Actinic keratosis	2 (3.3)	0	2 (3.3)	0	0	0
Alopecia	2 (3.3)	2 (3.3)	0	0	0	0
Anxiety	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Arthropod bite	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Asthenia	2 (3.3)	2 (3.3)	0	0	0	0
Atrial fibrillation	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Blood creatinine increased	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Bone pain	2 (3.3)	2 (3.3)	0	0	0	0
Bronchopulmonary aspergillosis	2 (3.3)	0	0	0	1 (1.7)	1 (1.7)
Cardiac murmur	2 (3.3)	2 (3.3)	0	0	0	0
Cataract	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Cellulitis	2 (3.3)	0	1 (1.7)	1 (1.7)	0	0
Clostridium difficile colitis	2 (3.3)	0	1 (1.7)	1 (1.7)	0	0
Conjunctivitis	2 (3.3)	0	2 (3.3)	0	0	0
Dyspnea, exertional	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Dysuria	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Ear discomfort	2 (3.3)	2 (3.3)	0	0	0	0
Ear pain	2 (3.3)	2 (3.3)	0	0	0	0
Edema	2 (3.3)	2 (3.3)	0	0	0	0
Folliculitis	2 (3.3)	0	2 (3.3)	0	0	0
Gait disturbance	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Hemorrhoids	2 (3.3)	2 (3.3)	0	0	0	0
Herpes zoster	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Hiatus hernia	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Hyperkeratosis	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0

Hypersensitivity	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Hyperuricemia	2 (3.3)	2 (3.3)	0	0	0	0
Hypogammaglobuli-nemia	2 (3.3)	0	2 (3.3)	0	0	0
Hypomagnesemia	2 (3.3)	2 (3.3)	0	0	0	0
Hypophosphatemia	2 (3.3)	0	0	2 (3.3)	0	0
Influenza	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Lethargy	2 (3.3)	2 (3.3)	0	0	0	0
Leukocytosis	2 (3.3)	0	0	2 (3.3)	0	0
Ligament sprain	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Lymph node pain	2 (3.3)	2 (3.3)	0	0	0	0
Lymphedema	2 (3.3)	0	2 (3.3)	0	0	0
Memory impairment	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Micturition urgency	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Migraine with aura	2 (3.3)	2 (3.3)	0	0	0	0
Neck pain	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Nephrolithiasis	2 (3.3)	1 (1.7)	0	1 (1.7)	0	0
Onychoclasis	2 (3.3)	2 (3.3)	0	0	0	0
Oral herpes	2 (3.3)	2 (3.3)	0	0	0	0
Palpitations	2 (3.3)	2 (3.3)	0	0	0	0
Pleural effusion	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Postprocedural hemorrhage	2 (3.3)	2 (3.3)	0	0	0	0
Respiratory failure	2 (3.3)	0	0	2 (3.3)	0	0
Rhinorrhea	2 (3.3)	2 (3.3)	0	0	0	0
Sinus bradycardia	2 (3.3)	2 (3.3)	0	0	0	0
Sleep apnea syndrome	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Squamous cell carcinoma	2 (3.3)	0	2 (3.3)	0	0	0
Tooth infection	2 (3.3)	0	2 (3.3)	0	0	0
Transaminases increased	2 (3.3)	1 (1.7)	0	0	1 (1.7)	0
Vitamin D deficiency	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0
Vulvovaginal mycotic	2 (3.3)	1 (1.7)	1 (1.7)	0	0	0

infection						
Abdominal pain, lower	1 (1.7)	0	1 (1.7)	0	0	0
Acanthoma	1 (1.7)	0	1 (1.7)	0	0	0
Acne	1 (1.7)	1 (1.7)	0	0	0	0
Acute kidney injury	1 (1.7)	1 (1.7)	0	0	0	0
Adjustment disorder with depressed mood	1 (1.7)	1 (1.7)	0	0	0	0
Adnexa uteri cyst	1 (1.7)	1 (1.7)	0	0	0	0
Ankle fracture	1 (1.7)	0	1 (1.7)	0	0	0
Anticonvulsant drug level increased	1 (1.7)	1 (1.7)	0	0	0	0
Aortic stenosis	1 (1.7)	0	0	1 (1.7)	0	0
Apnea	1 (1.7)	0	0	1 (1.7)	0	0
Arachnoid cyst	1 (1.7)	0	1 (1.7)	0	0	0
Arrhythmia	1 (1.7)	1 (1.7)	0	0	0	0
Ascites	1 (1.7)	1 (1.7)	0	0	0	0
Asthma	1 (1.7)	0	1 (1.7)	0	0	0
Barrett esophagus	1 (1.7)	0	1 (1.7)	0	0	0
Blister	1 (1.7)	1 (1.7)	0	0	0	0
Blood blister	1 (1.7)	0	1 (1.7)	0	0	0
Blood phosphorus decreased	1 (1.7)	0	1 (1.7)	0	0	0
Bone lesion	1 (1.7)	1 (1.7)	0	0	0	0
Bronchiectasis	1 (1.7)	0	1 (1.7)	0	0	0
Bronchiolitis	1 (1.7)	0	1 (1.7)	0	0	0
Bronchitis, chronic	1 (1.7)	1 (1.7)	0	0	0	0
Cardiomyopathy	1 (1.7)	0	0	1 (1.7)	0	0
Cardiorenal syndrome	1 (1.7)	0	0	1 (1.7)	0	0
Carpal tunnel syndrome	1 (1.7)	0	1 (1.7)	0	0	0
Cerebrovascular accident	1 (1.7)	0	1 (1.7)	0	0	0
Cheilitis	1 (1.7)	1 (1.7)	0	0	0	0
Cholangitis	1 (1.7)	0	0	1 (1.7)	0	0

Cholelithiasis	1 (1.7)	0	0	1 (1.7)	0	0
Chronic kidney disease	1 (1.7)	0	0	1 (1.7)	0	0
Chronic myelomonocytic leukemia	1 (1.7)	0	0	1 (1.7)	0	0
Chronic obstructive pulmonary disease	1 (1.7)	0	0	1 (1.7)	0	0
Chronic sinusitis	1 (1.7)	0	1 (1.7)	0	0	0
Cold sweat	1 (1.7)	1 (1.7)	0	0	0	0
Colitis	1 (1.7)	0	0	1 (1.7)	0	0
Confusional state	1 (1.7)	0	0	1 (1.7)	0	0
Conjunctival hemorrhage	1 (1.7)	1 (1.7)	0	0	0	0
Cyst	1 (1.7)	1 (1.7)	0	0	0	0
Deep vein thrombosis	1 (1.7)	0	1 (1.7)	0	0	0
Dental caries	1 (1.7)	1 (1.7)	0	0	0	0
Dermal cyst	1 (1.7)	1 (1.7)	0	0	0	0
Dermatitis acneiform	1 (1.7)	1 (1.7)	0	0	0	0
Diastasis recti abdominis	1 (1.7)	0	1 (1.7)	0	0	0
Disturbance in attention	1 (1.7)	1 (1.7)	0	0	0	0
Diverticulitis	1 (1.7)	0	0	1 (1.7)	0	0
Drug hypersensitivity	1 (1.7)	1 (1.7)	0	0	0	0
Dry eye	1 (1.7)	1 (1.7)	0	0	0	0
Dysarthria	1 (1.7)	1 (1.7)	0	0	0	0
Dyspepsia	1 (1.7)	0	1 (1.7)	0	0	0
Dysphagia	1 (1.7)	0	1 (1.7)	0	0	0
Ear infection	1 (1.7)	0	1 (1.7)	0	0	0
Encephalopathy	1 (1.7)	0	0	1 (1.7)	0	0
Endometrial cancer	1 (1.7)	0	0	1 (1.7)	0	0
Enterocolitis	1 (1.7)	0	0	1 (1.7)	0	0
Enterocolitis, infectious	1 (1.7)	0	1 (1.7)	0	0	0
Eosinophilia	1 (1.7)	1 (1.7)	0	0	0	0

Escherichia bacteremia	1 (1.7)	0	0	1 (1.7)	0	0
Esophagitis	1 (1.7)	1 (1.7)	0	0	0	0
Eye contusion	1 (1.7)	1 (1.7)	0	0	0	0
Face injury	1 (1.7)	1 (1.7)	0	0	0	0
Feeling cold	1 (1.7)	1 (1.7)	0	0	0	0
Fluid overload	1 (1.7)	0	1 (1.7)	0	0	0
Folate deficiency	1 (1.7)	0	1 (1.7)	0	0	0
Gastric polyps	1 (1.7)	1 (1.7)	0	0	0	0
Gastritis	1 (1.7)	0	1 (1.7)	0	0	0
Gastroenteritis	1 (1.7)	0	1 (1.7)	0	0	0
Gastrointestinal adenocarcinoma	1 (1.7)	0	0	1 (1.7)	0	0
Gastrointestinal hemorrhage	1 (1.7)	0	1 (1.7)	0	0	0
Gingivitis	1 (1.7)	0	1 (1.7)	0	0	0
Glomerulosclerosis	1 (1.7)	1 (1.7)	0	0	0	0
Goitre	1 (1.7)	1 (1.7)	0	0	0	0
Groin pain	1 (1.7)	0	1 (1.7)	0	0	0
Hemangioma of bone	1 (1.7)	1 (1.7)	0	0	0	0
Hemangioma of skin	1 (1.7)	1 (1.7)	0	0	0	0
Hematochezia	1 (1.7)	1 (1.7)	0	0	0	0
Hematoma	1 (1.7)	1 (1.7)	0	0	0	0
Hemoglobin decreased	1 (1.7)	0	1 (1.7)	0	0	0
Helicobacter infection	1 (1.7)	1 (1.7)	0	0	0	0
Hiccups	1 (1.7)	1 (1.7)	0	0	0	0
Hip fracture	1 (1.7)	0	0	0	1 (1.7)	0
Hordeolum	1 (1.7)	1 (1.7)	0	0	0	0
Hot flush	1 (1.7)	1 (1.7)	0	0	0	0
Hyperglycemia	1 (1.7)	1 (1.7)	0	0	0	0
Hyperlipidemia	1 (1.7)	0	1 (1.7)	0	0	0
Hyperparathyroidism	1 (1.7)	1 (1.7)	0	0	0	0
Hypersomnia	1 (1.7)	1 (1.7)	0	0	0	0

Hypertrichosis	1 (1.7)	1 (1.7)	0	0	0	0
Hypoacusis	1 (1.7)	1 (1.7)	0	0	0	0
Hypocalcemia	1 (1.7)	0	1 (1.7)	0	0	0
Hypoglycemia	1 (1.7)	0	1 (1.7)	0	0	0
Hypothermia	1 (1.7)	1 (1.7)	0	0	0	0
Hypovolemia	1 (1.7)	0	1 (1.7)	0	0	0
Immunodeficiency	1 (1.7)	1 (1.7)	0	0	0	0
Increased appetite	1 (1.7)	1 (1.7)	0	0	0	0
Increased tendency to bruise	1 (1.7)	0	1 (1.7)	0	0	0
Infected bite	1 (1.7)	0	1 (1.7)	0	0	0
Inflammation	1 (1.7)	1 (1.7)	0	0	0	0
Inguinal hernia	1 (1.7)	0	0	1 (1.7)	0	0
Injection-site hemorrhage	1 (1.7)	0	0	1 (1.7)	0	0
Intermittent claudication	1 (1.7)	0	0	1 (1.7)	0	0
Iron deficiency	1 (1.7)	0	1 (1.7)	0	0	0
Iron deficiency anemia	1 (1.7)	0	1 (1.7)	0	0	0
Joint range of motion decreased	1 (1.7)	0	1 (1.7)	0	0	0
Joint swelling	1 (1.7)	1 (1.7)	0	0	0	0
Kidney infection	1 (1.7)	0	1 (1.7)	0	0	0
Laryngeal inflammation	1 (1.7)	1 (1.7)	0	0	0	0
Left ventricular dysfunction	1 (1.7)	1 (1.7)	0	0	0	0
Lentigo maligna	1 (1.7)	0	0	1 (1.7)	0	0
Limb injury	1 (1.7)	0	1 (1.7)	0	0	0
Liver function test abnormal	1 (1.7)	0	0	1 (1.7)	0	0
Liver function test increased	1 (1.7)	0	0	1 (1.7)	0	0
Localized infection	1 (1.7)	0	1 (1.7)	0	0	0
Lumbar spinal stenosis	1 (1.7)	0	0	1 (1.7)	0	0

Malignant melanoma in situ	1 (1.7)	0	1 (1.7)	0	0	0
Melanocytic nevus	1 (1.7)	0	1 (1.7)	0	0	0
Middle ear effusion	1 (1.7)	0	1 (1.7)	0	0	0
Migraine	1 (1.7)	0	1 (1.7)	0	0	0
Mitral valve incompetence	1 (1.7)	0	1 (1.7)	0	0	0
Musculoskeletal chest pain	1 (1.7)	0	1 (1.7)	0	0	0
Musculoskeletal stiffness	1 (1.7)	1 (1.7)	0	0	0	0
Nail infection	1 (1.7)	0	1 (1.7)	0	0	0
Nasopharyngitis	1 (1.7)	0	1 (1.7)	0	0	0
Neuralgia	1 (1.7)	0	1 (1.7)	0	0	0
Neuropathy, peripheral	1 (1.7)	1 (1.7)	0	0	0	0
Nightmare	1 (1.7)	1 (1.7)	0	0	0	0
Ocular hyperemia	1 (1.7)	0	1 (1.7)	0	0	0
Onychomycosis	1 (1.7)	0	1 (1.7)	0	0	0
Oral blood blister	1 (1.7)	1 (1.7)	0	0	0	0
Oral fungal infection	1 (1.7)	0	1 (1.7)	0	0	0
Oral pain	1 (1.7)	1 (1.7)	0	0	0	0
Osteoarthritis	1 (1.7)	1 (1.7)	0	0	0	0
Osteoporosis	1 (1.7)	1 (1.7)	0	0	0	0
Osteosclerosis	1 (1.7)	1 (1.7)	0	0	0	0
Pancytopenia	1 (1.7)	0	1 (1.7)	0	0	0
Patella fracture	1 (1.7)	0	1 (1.7)	0	0	0
Peripheral coldness	1 (1.7)	1 (1.7)	0	0	0	0
Plantar fasciitis	1 (1.7)	0	1 (1.7)	0	0	0
Pneumonia aspiration	1 (1.7)	0	0	1 (1.7)	0	0
Pneumonia, mycoplasmal	1 (1.7)	0	0	1 (1.7)	0	0
Pneumonia, respiratory syncytial viral	1 (1.7)	0	0	1 (1.7)	0	0
Pneumonia, viral	1 (1.7)	0	1 (1.7)	0	0	0

Polycythemia	1 (1.7)	1 (1.7)	0	0	0	0
Portal hypertension	1 (1.7)	0	1 (1.7)	0	0	0
Postoperative hypertension	1 (1.7)	0	0	1 (1.7)	0	0
Precancerous skin lesion	1 (1.7)	0	1 (1.7)	0	0	0
Procedural pain	1 (1.7)	0	0	1 (1.7)	0	0
Prostatic obstruction	1 (1.7)	1 (1.7)	0	0	0	0
Prostatic-specific antigen increased	1 (1.7)	1 (1.7)	0	0	0	0
Pseudomonas infection	1 (1.7)	0	1 (1.7)	0	0	0
Pulmonary mass	1 (1.7)	1 (1.7)	0	0	0	0
Pulmonary edema	1 (1.7)	0	1 (1.7)	0	0	0
Pulmonary sepsis	1 (1.7)	0	0	1 (1.7)	0	0
Pyelitis	1 (1.7)	1 (1.7)	0	0	0	0
Pyelonephritis	1 (1.7)	0	0	1 (1.7)	0	0
Pyuria	1 (1.7)	0	1 (1.7)	0	0	0
Rash, erythematous	1 (1.7)	1 (1.7)	0	0	0	0
Renal tubular necrosis	1 (1.7)	0	0	1 (1.7)	0	0
Respiratory fume inhalation disorder	1 (1.7)	1 (1.7)	0	0	0	0
Respiratory tract infection	1 (1.7)	0	0	1 (1.7)	0	0
Retinal tear	1 (1.7)	0	1 (1.7)	0	0	0
Retinopathy	1 (1.7)	1 (1.7)	0	0	0	0
Rhinitis	1 (1.7)	0	1 (1.7)	0	0	0
Rhinovirus infection	1 (1.7)	1 (1.7)	0	0	0	0
Rib fracture	1 (1.7)	0	1 (1.7)	0	0	0
Sciatica	1 (1.7)	0	1 (1.7)	0	0	0
Scoliosis	1 (1.7)	0	1 (1.7)	0	0	0
Scratch	1 (1.7)	1 (1.7)	0	0	0	0
Seborrheic keratosis	1 (1.7)	1 (1.7)	0	0	0	0
Sensory loss	1 (1.7)	1 (1.7)	0	0	0	0
Sinus headache	1 (1.7)	1 (1.7)	0	0	0	0

Sinus tachycardia	1 (1.7)	1 (1.7)	0	0	0	0
Skin abrasion	1 (1.7)	1 (1.7)	0	0	0	0
Skin burning sensation	1 (1.7)	0	1 (1.7)	0	0	0
Skin discoloration	1 (1.7)	1 (1.7)	0	0	0	0
Skin exfoliation	1 (1.7)	0	1 (1.7)	0	0	0
Skin hemorrhage	1 (1.7)	1 (1.7)	0	0	0	0
Skin hyperpigmentation	1 (1.7)	1 (1.7)	0	0	0	0
Skin mass	1 (1.7)	0	0	1 (1.7)	0	0
Skin papilloma	1 (1.7)	1 (1.7)	0	0	0	0
Sleep disorder	1 (1.7)	1 (1.7)	0	0	0	0
Spinal fracture	1 (1.7)	0	0	1 (1.7)	0	0
Spinal osteoarthritis	1 (1.7)	0	1 (1.7)	0	0	0
Spinal pain	1 (1.7)	1 (1.7)	0	0	0	0
Splenic rupture	1 (1.7)	0	0	1 (1.7)	0	0
Spontaneous hemorrhage	1 (1.7)	1 (1.7)	0	0	0	0
Sputum discolored	1 (1.7)	0	1 (1.7)	0	0	0
Squamous cell carcinoma of lung	1 (1.7)	0	1 (1.7)	0	0	0
Stress urinary incontinence	1 (1.7)	0	1 (1.7)	0	0	0
Subdural hematoma	1 (1.7)	0	1 (1.7)	0	0	0
Synovial cyst	1 (1.7)	1 (1.7)	0	0	0	0
Tachycardia	1 (1.7)	1 (1.7)	0	0	0	0
Tendon disorder	1 (1.7)	0	1 (1.7)	0	0	0
Thermal burn	1 (1.7)	0	1 (1.7)	0	0	0
Thrombophlebitis, superficial	1 (1.7)	0	1 (1.7)	0	0	0
Thyroid mass	1 (1.7)	1 (1.7)	0	0	0	0
Tinea infection	1 (1.7)	1 (1.7)	0	0	0	0
Toothache	1 (1.7)	1 (1.7)	0	0	0	0
Transfusion reaction	1 (1.7)	0	0	1 (1.7)	0	0
Transient acantholytic	1 (1.7)	1 (1.7)	0	0	0	0

dermatosis						
Tumor flare	1 (1.7)	0	1 (1.7)	0	0	0
Umbilical hernia	1 (1.7)	0	1 (1.7)	0	0	0
Urinary incontinence	1 (1.7)	1 (1.7)	0	0	0	0
Vaginal hemorrhage	1 (1.7)	0	1 (1.7)	0	0	0
Varices, esophageal	1 (1.7)	0	1 (1.7)	0	0	0
Ventricular arrhythmia	1 (1.7)	0	1 (1.7)	0	0	0
Ventricular fibrillation	1 (1.7)	0	0	0	0	1 (1.7)
Vision blurred	1 (1.7)	1 (1.7)	0	0	0	0
Vitreous floaters	1 (1.7)	1 (1.7)	0	0	0	0
Vitreous hemorrhage	1 (1.7)	1 (1.7)	0	0	0	0
Wheezing	1 (1.7)	0	1 (1.7)	0	0	0
Wrist fracture	1 (1.7)	1 (1.7)	0	0	0	0

[a]Includes events of neutropenia and decreased neutrophil count.

[b]Includes events of lymphocytosis and increased lymphocyte count.

[c]Includes events of thrombocytopenia and decreased platelet count.

Table S4. Ibrutinib-intolerance adverse events recurring with acalabrutinib.

Category of adverse event	Adverse event with ibrutinib	Adverse event with acalabrutinib	Worst grade with ibrutinib	Worst grade with acalabrutinib	Change in grade
Diarrhea	Diarrhea	Diarrhea	3	2	Lower
	Diarrhea	Diarrhea	2	2	No change
	Diarrhea	Diarrhea	2	1	Lower
	Diarrhea	Diarrhea	3	3	No change
	Diarrhea	Diarrhea	3	1	Lower
Hemorrhage	Epistaxis	Contusion	3	2	Lower
	Hematuria	Hematuria	2	1	Lower
	Hemorrhage	Subdural hematoma	2	2	No change
	Pulmonary hemorrhage	Contusion	3	1	Lower
	Retinal hemorrhage	Hematuria	2	2	No change
Musculoskeletal pain	Arthralgia	Arthritis	2	1	Lower
	Arthritis	Arthralgia	2	2	No change
Cardiac arrhythmia	Atrial fibrillation	Atrial fibrillation	2	1	Lower
	Atrial fibrillation	Atrial fibrillation	3	2	Lower
Rash	Rash	Rash	3	1	Lower
	Rash	Rash	3	2	Lower
	Rash, maculopapular	Rash	2	1	Lower
Cough	Cough	Cough	2	1	Lower
Dizziness	Dizziness	Dizziness	2	1	Lower
Fatigue	Fatigue	Fatigue	3	3	No change
	Asthenia	Asthenia	2	1	Lower
Headache	Headache	Headache	2	2	No change
Infection	Cellulitis	Cellulitis	3	2	Lower
Liver-related investigations	Liver function test increased	Liver function test increased	2	3	Higher

Neutropenia	Neutropenia	Neutropenia	3	3	No change
Stomatitis	Stomatitis	Stomatitis	2	1	Lower
Rhinitis	Stent-graft endoleak	Rhinitis	3	2	Lower
Two patients experienced >1 adverse event defined as intolerance.					

Table S5. Recurrence of intolerance AEs in patients previously treated with ibrutinib in combination with other agents.

Patient age, yrs	Ibrutinib combination	During ibrutinib		During Acalabrutinib				
		AE leading to intolerance (grade)	Day of onset	AE recurrence (grade)	Day of onset	AE outcome	Action taken	Patient outcome
62	IBR+OBIN	Diarrhea (2)	2	-	-	-	-	Treatment ongoing
73	IBR+R	Dizziness (2), GI disorder (2), ecchymosis (2)	428	Dizziness (1)	8	Ongoing	Dose not changed	Treatment ongoing
52	IBR+R+LEN	Neutropenia (4)	97	-	-	-	-	Treatment ongoing
66	IBR+UTX	Rash (2)	1	-	-	-	-	Death due to disease progression
43	IBR+R+Benda	Asthenia (2), bronchiectasis (2)	1345	Asthenia (1)	255	Resolved	Dose not changed	Treatment ongoing
72	IBR+Mona	Epistaxis (3)	43	Contusion (2)	30	Ongoing	Dose not changed	Treatment ongoing
71	IBR+R	Atrial fibrillation (3)	434	-	-	-	-	Treatment ongoing
67	IBR+R	Pulmonary hemorrhage (3), atrial fibrillation (2)	1688	Contusion (1)	15	Resolved	Dose not changed	Withdrawal from study (physician decision); subsequent death due to disease progression
70	IBR+OFA	Atrial fibrillation (3)	1721	-	-	-	-	Treatment ongoing
74	IBR+LEN	Arthritis (2)	956	Arthralgia (2)	43	Ongoing	Dose not changed	Death due to Richter syndrome

Benda, bendamustine; GI, gastrointestinal; IBR, ibrutinib; LEN, lenalidomide; Mona, monalizumab; NE, not evaluable; OBIN, obinutuzumab; OFA, ofatumumab; PR, partial response; R, rituximab; SD, stable disease; UTX, ublituximab.

Table S6. *BTK* and *PLCG2* mutations at baseline.

Patient	Best response to ibrutinib	Best response to acalabrutinib	Duration of acalabrutinib response, months	Gene	Amino acid substitution	Nucleotide change	VAF, %
1[a]	PR	Not evaluable	2.16	*BTK*	p.C481R	c.1441T>C	74.9
				BTK	p.C481S	c.1441T>A	9.6
				BTK	p.C481S	c.1442G>C	6.7
				BTK	p.C481Y	c.1442G>A	4.9
				BTK	p.C481S	c.1442_1443delGCinsCT	4.1
2	CR	SD	15.01	*BTK*	p.C481S	c.1442G>C	30.7
				BTK	p.C481S	c.1441T>A	0.3
				PLCG2	p.L845F	c.2535A>T	3.3
				PLCG2	p.L845F	c.2535A>C	2.7
				PLCG2	p.R665W	c.1993C>T	0.6
3	Unknown	PR	25.10	*PLCG2*	p.D993N	c.2977G>A	33.1

[a]Due to local testing confirming a *C481* mutation, the patient was removed from the trial before any tumor assessment was performed.

BTK, Bruton tyrosine kinase gene; CR, complete response; *PLCG2*, phospholipase C gamma 2 gene; PR, partial response; SD, stable disease; VAF, variant allele frequency.

Table S7. *BTK* and *PLCG2* status at treatment termination (n=5)

Patient	Best response to ibrutinib	*BTK / PLCG2* status at baseline (VAF)	Best response to acalabrutinib	Duration of response, months	*BTK / PLCG2* status at treatment termination (VAF)
1	Unknown	ND	PRL	11.53	ND
2	Unknown	ND	PR	15.67	ND
3	Unknown	ND	SD	11.00	ND
4	PR	ND	PR	14.29	*PLCG2* p.D1140N c.3418G>A (38.3%) *BTK* p.T474I c.1421C>T (2.2%) *BTK* p.C481S c.1441T>A (1.0%) *BTK* p.C481S c.1442G>C (0.3%)
5	CR	*BTK* p.C481S c.1442G>C (30.7%) *BTK* p.C481S c.1441T>A (0.3%) *PLCG2* p.L845F c.2535A>T (3.3%) *PLCG2* p.L845F c.2535A>C (2.7%) *PLCG2* p.R665W c.1993C>T (0.6%)	SD	15.01	*BTK* p.C481S c.1442G>C (90.2%)

BTK, Bruton tyrosine kinase gene; CR, complete response; ND, no mutations detected with deep sequencing of sorted B cells; *PLCG2*, phospholipase C gamma 2 gene; PR, partial response; PRL, partial response with treatment-induced lymphocytosis; SD, stable disease; VAF, variant allele frequency.

Figure S1. Time to next treatment (TTNT) after acalabrutinib. The median time to next treatment was not reached.

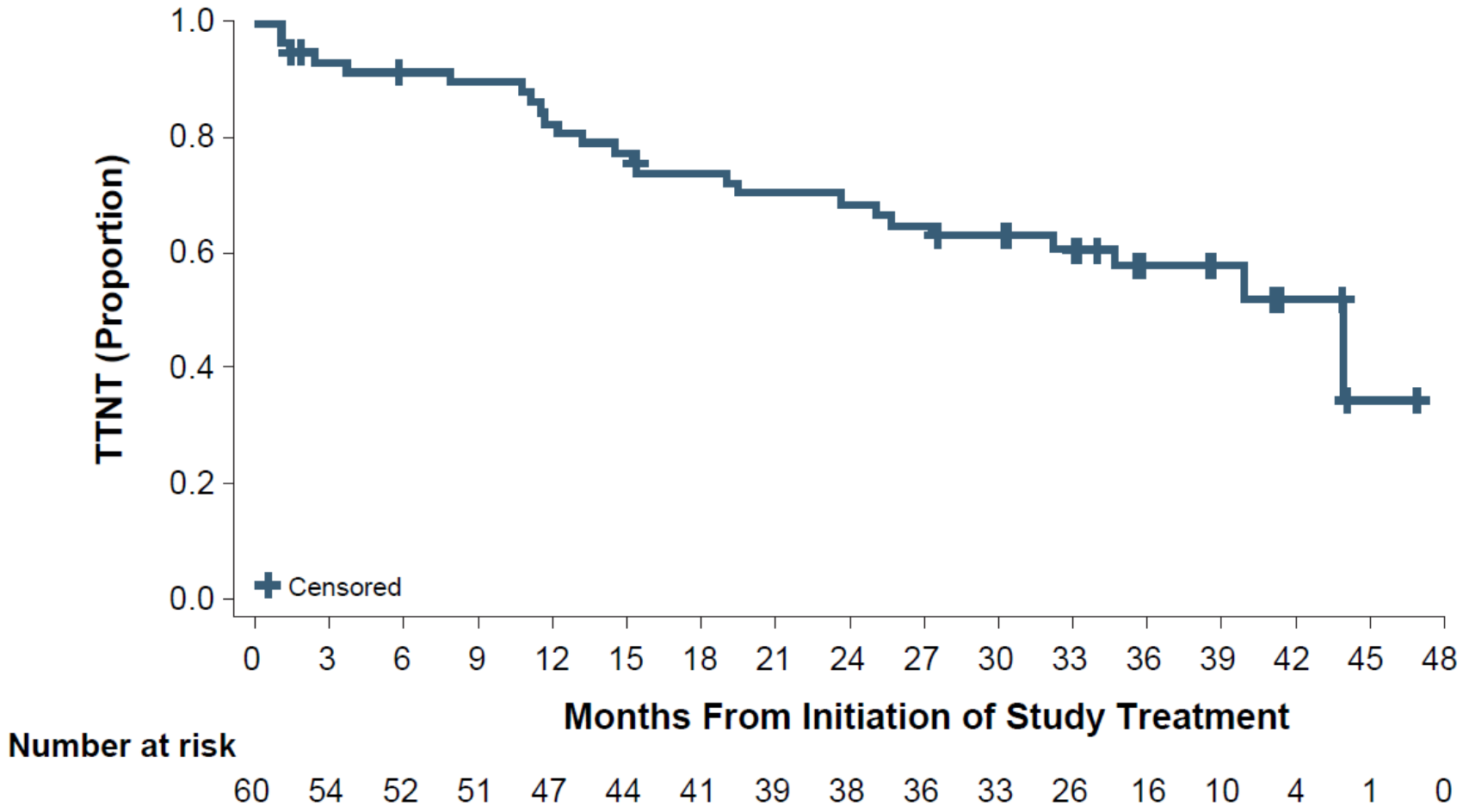
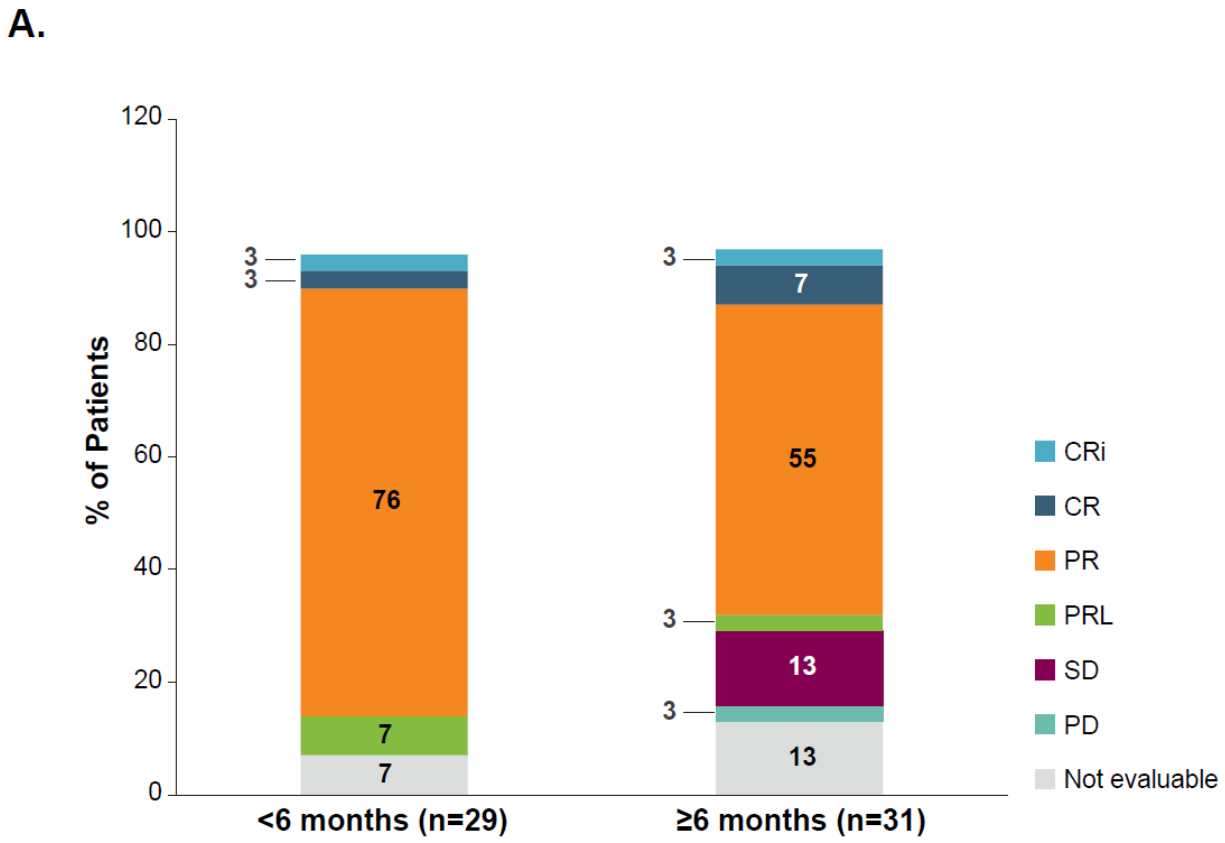
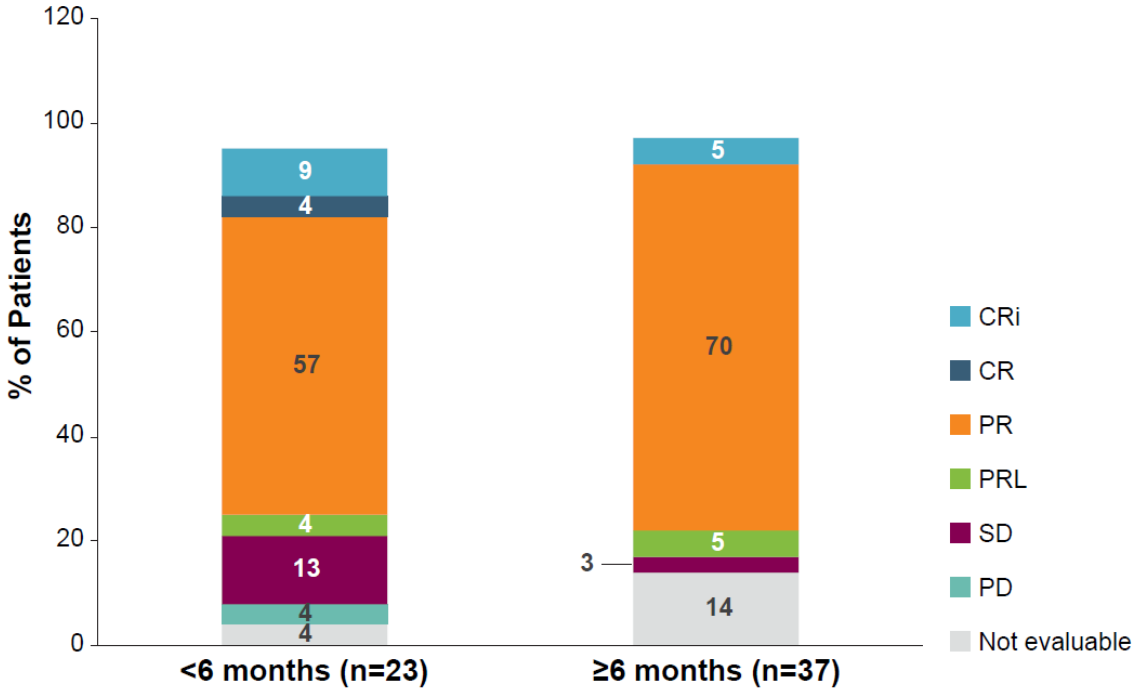


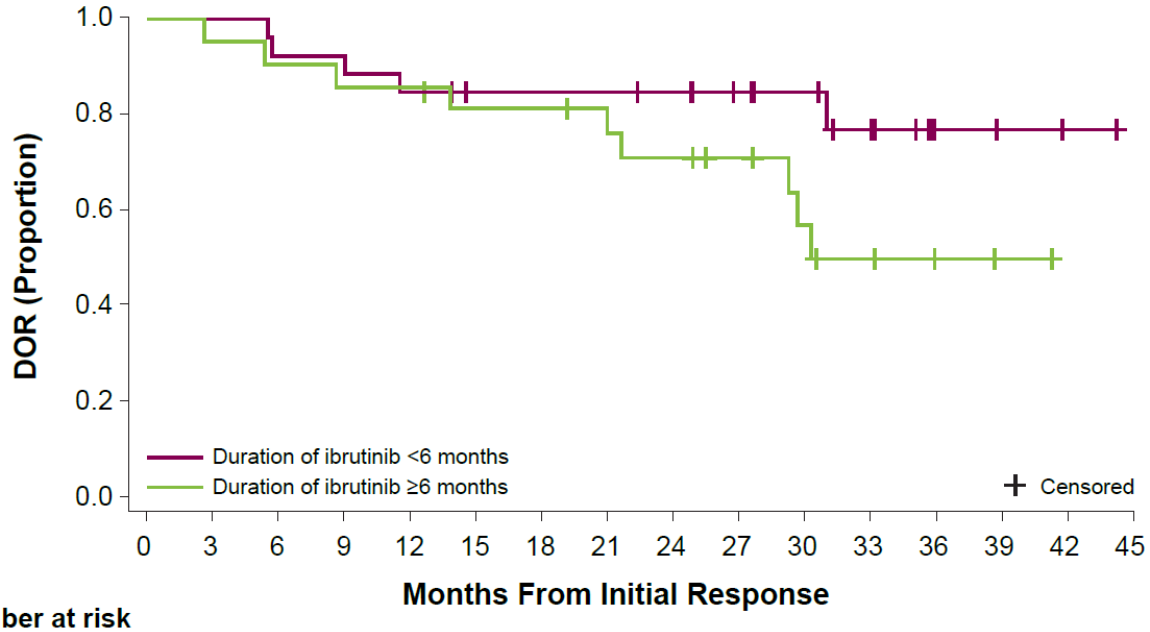
Figure S2. Objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS) by duration of ibrutinib treatment (A, C, and E) and by duration of treatment hold after ibrutinib discontinuation (B, D, and F). Duration of treatment hold after ibrutinib is calculated as first date of acalabrutinib dosing to last dose date of ibrutinib dosing + 1. CR, complete remission; Cri, complete remission with incomplete bone marrow recovery; PD, progressive disease; PR, partial remission; PRL, partial remission with lymphocytosis; SD, stable disease.



B.



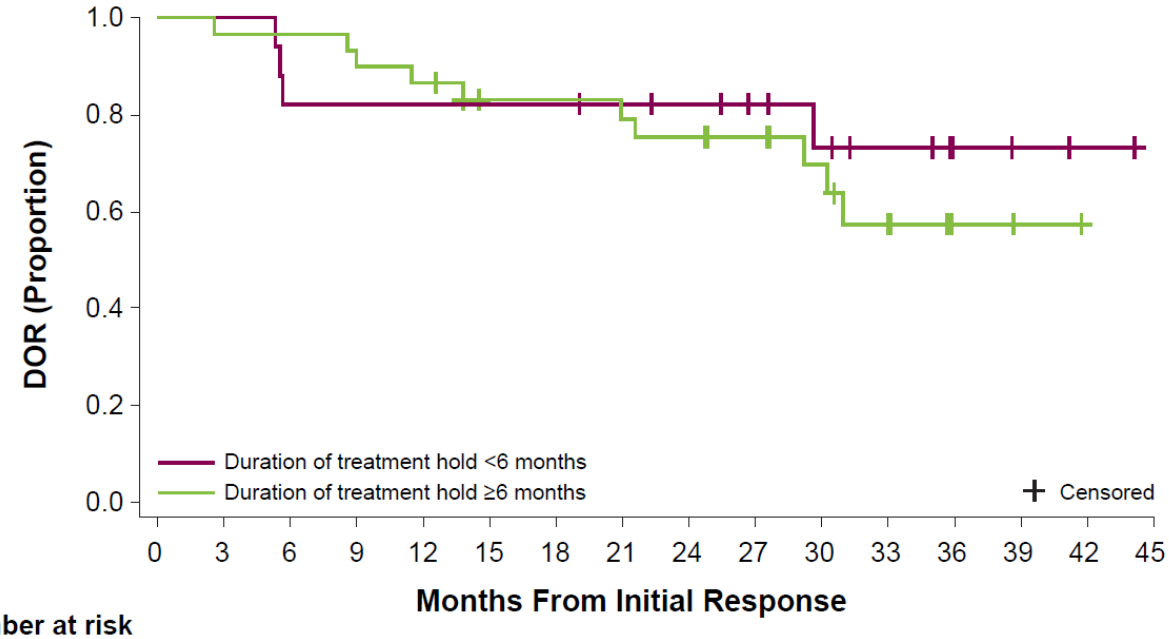
C.



Number at risk

IBR <6 mo	26	26	24	24	22	19	19	19	18	15	12	9	3	2	1	0
IBR ≥6 mo	21	20	19	18	18	17	17	15	14	12	8	6	3	1	0	

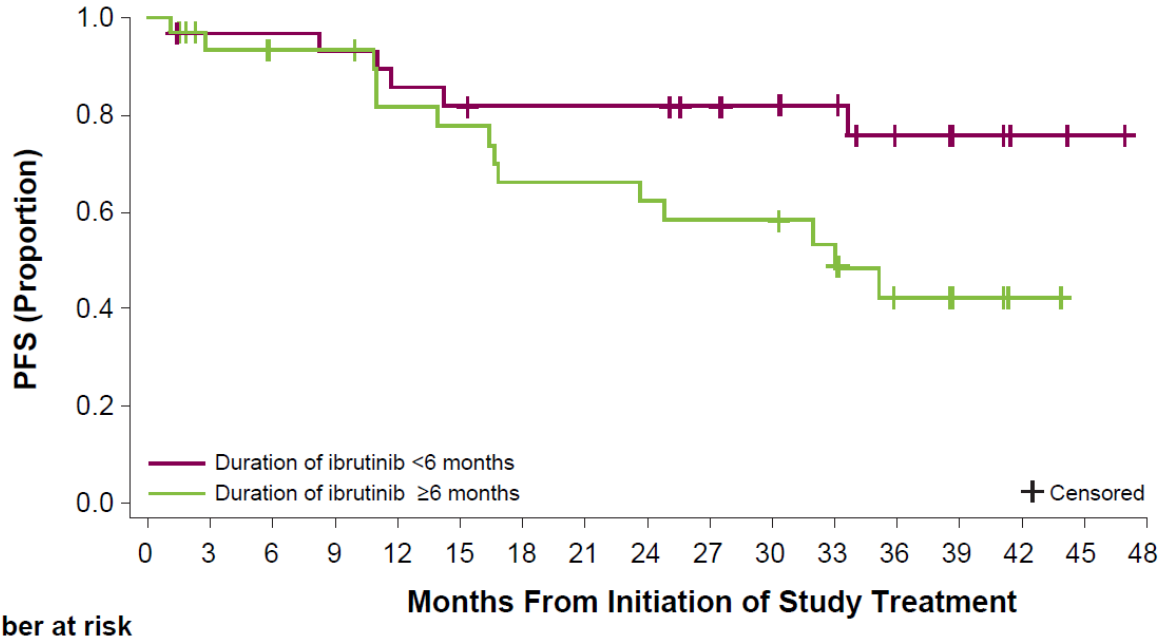
D.



Number at risk

Tx hold <6 mo	17	17	14	14	14	14	14	13	12	10	8	6	3	2	1	0
Tx hold ≥6 mo	30	29	29	28	26	22	22	21	20	17	12	9	3	1	0	

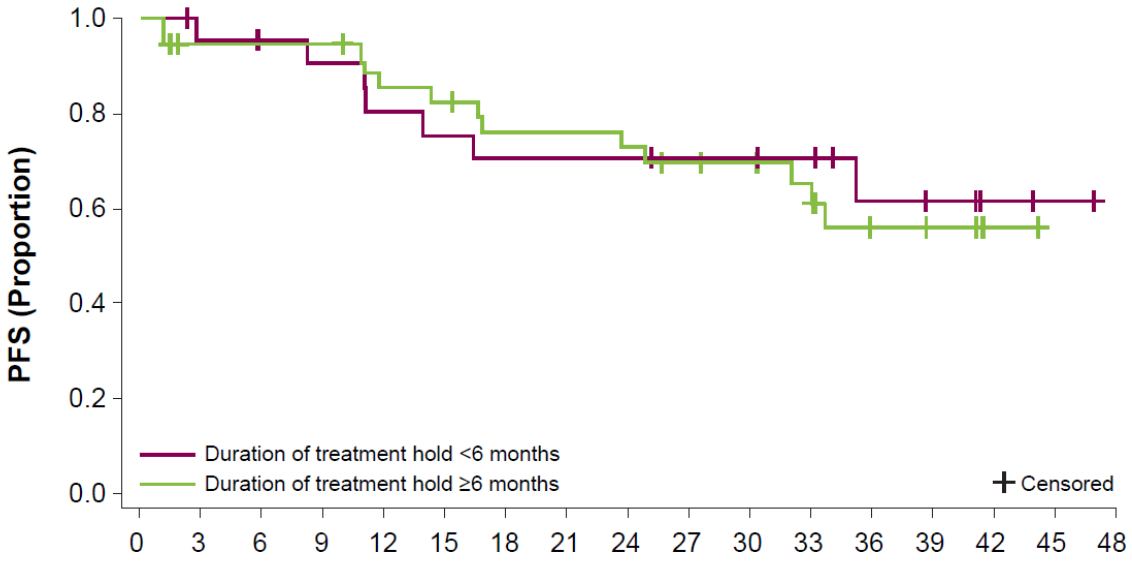
E.



Number at risk

IBR <6 mo	29	27	27	26	23	22	21	21	21	19	17	14	8	4	2	1	0
IBR ≥6 mo	31	26	24	24	21	20	17	17	16	15	15	11	6	4	1	0	

F.



Number at risk

Tx hold <6 mo	23	21	19	18	16	15	14	14	14	13	13	10	7	4	2	1	0
Tx hold ≥6 mo	37	32	32	32	28	27	24	24	23	21	19	15	7	4	1	0	