Appendix for: ASCEND: The Phase 3, Randomized Trial of Acalabrutinib Versus Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory CLL

Paolo Ghia, MD, PhD, et al.

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List of investigators

Investigator Name	Investigator Site	Country	Enrolled
Cannell, Paul	Fiona Stanley Hospital	Australia	1
Harrup, Rosemary	Royal Hobart Hospital	Australia	1
Walker, Patricia Ann	Peninsula Health	Australia	1
Campbell, Philip	Barwon Health	Australia	3
Hahn, Uwe	The Queen Elizabeth Hospital	Australia	1
Baker, Ross	Perth Blood Institute	Australia	1
Tiley, Campbell	Gosford Hospital	Australia	1
Taylor, Kerry	Icon Cancer Foundation	Australia	3
Greil, Richard	Universitätsklinik für Innere Medizin Salzburg	Austria	3
Heibl, Sonja	Klinikum Wels-Grieskirchen	Austria	3
Heintel, Daniel	Wilhelminenspital der Stadt Wien	Austria	1
Geissler, Klaus	Krankenhaus Hietzing	Austria	1
Offner, Fritz	Universitair Ziekenhuis Gent	Belgium	3
Demuynck, Hilde	Jan Yperman Ziekenhuis	Belgium	1
Wu, Ka Lung	ZNA Stuivenberg	Belgium	1
Depaus, Julien	CHU UCL Namur - site Godinne	Belgium	1
Spasov, Emil	University Multiprofile Hospital for Active Treatment Sveti Georgi	Bulgaria	1
Tzvetkov, Nikolay	UMHAT Dr. Georgi Stranski EAD	Bulgaria	3
Sivcheva, Liliya	Multiprofile Hospital for Active Treatment Hristo Botev	Bulgaria	4
Dolan, Sean	Saint John Regional Hospital	Canada	4
Chen, Christine	Princess Margaret Hospital - Toronto	Canada	3
Owen, Carolyn	Alberta Health Services	Canada	2
Aw, Andrew	The Ottawa Hospital - General Campus	Canada	2
Cheung, Matthew	Sunnybrook Health Sciences Centre	Canada	1
Assouline, Sarit	McGill University - Jewish General Hospital	Canada	1
Pejsa, Vlatko	Klinicka Bolnica Dubrava	Croatia	2
Basic Kinda, Sandra	Klinički Bolnički Centar Zargeb (University Hospital Centre Zagreb)	Croatia	7
Mayer, Jiří	FN Brno	Czech Republic	10
Hájek, Roman	Fakultní nemocnice Ostrava	Czech Republic	7

Papajik, Tomáš	FN Olomouc	Czech Republic	4
Lysák, Daniel	Fakultní Nemocnice Plzeň	Czech Republic	13
Kozák, Tomáš	Fakultní Nemocnice Královske Vinohrady	Czech Republic	13
Šimkovič, Martin	Fakultni nemocnice Hradec Králové	Czech Republic	13
Leblond, Véronique	Groupe Hospitalier Pitié-Salpétrière	France	1
Aurran-Schleinitz, Thérése	Institut Paoli Calmettes	France	1
Etienne, Gabriel	Institut Bergonié	France	1
Mahé, Béatrice	Centre Hospitalier Universitaire de Nantes Hôtel Dieu	France	3
Tempescul, Adrian	Centre Hospitalier Universitaire Brest	France	1
Welslau, Manfred	Klinikum Aschaffenburg-Alzenau	Germany	1
Hebart, Holger	Stauferklinikum Schwäbisch Gmünd	Germany	2
Kwong, Yok Lam	Queen Mary Hospital	Hong Kong	1
Rosta, András	Országos Onkológiai Intézet	Hungary	1
Illés, Árpád	Debreceni Egyetem Belgyógyászati Klinika	Hungary	6
Jakucs, János	Békés Megyei Központi Kórház Pándy Kálmán Tagkórház	Hungary	3
Preis, Meir	Carmel Medical Center	Israel	2
Nemets, Anatoly	Barzilai Medical Center	Israel	1
Goldschmidt, Neta	Hadassah Medical Center	Israel	1
Ghia, Paolo	Ospedale San Raffaele	Italy	2
Musuraca, Gerardo	Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori	Italy	3
Marasca, Roberto	Universita Degli Studi di Modena-Azienda Ospedaliere Policlinco	Italy	1
Montillo, Marco	Azienda Socio Sanitaria Territoriale Grande Ospedale Metropolitano Niguarda	Italy	2
Rossi, Giuseppe	Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia	Italy	1
Spina, Michele	Centro di Riferimento Oncologico di Aviano	Italy	2
Gobbi, Marco	Azienda Ospedaliera Universitaria San Martino	Italy	2
Rambaldi, Alessandro	Azienda Ospedaliera Papa Giovanni XXIII	Italy	2
Ganly, Peter	Christchurch Hospital	New Zealand	2
Kilfoyle, Allanah	Palmerston North Hospital	New Zealand	2
Jurczak, Wojciech	Małopolskie Centrum Medyczne	Poland	15

Robak, Tadeusz	Wojewódzkie Wielospecjalistyczne Centrum Onkologii i Traumatologii im. M. Kopernika w Łodzi	Poland	9
Czyż, Jarosław	Szpital Uniwersytecki nr 2 im. dr. Jana Biziela w Bydgoszczy	Poland	12
Ciepłuch, Hanna	Copernicus Podmiot Leczniczy Wojewódzkiego Centrum Onkologii	Poland	4
Wach, Małgorzata	Samodzielny Publiczny Szpital Kliniczny nr 1 w Lublinie	Poland	14
Pluta, Andrzej	Szpital Specjalistyczny w Brzozowie Podkarpacki Ośrodek Onkologiczny im. Ks. B. Markiewicza	Poland	14
Kłoczko, Janusz	Uniwersytecki Szpital Kliniczny w Bialymstoku	Poland	1
Volodicheva, Elena	Tula Area Clinical Hospital	Russia	3
Pristupa, Alexander	Ryazan Regional Clinical Hospital	Russia	2
Alexeeva, Yulia	Almazov Federal North-West Medical Research Centre of Department of Health of Russian Federation	Russia	2
Konstantinova, Tatyana	Sverdlovsk Regional Clinical Hospital #1	Russia	1
Yablokova, Vera	Yaroslavl Regional Clinical Hospital	Russia	1
Kaplanov, Kamil	State Budgetary Healthcare Institution “Volgograd Regional Clinical Oncology Dispensary #1”	Russia	3
Chagorova, Tatyana	Regional Oncology Dispensary	Russia	1
Udovitsa, Dmitriy	State Healthcare Institution Oncologic Dispensary No. 2 - Health Department of Krasnodar Region	Russia	3
Hsieh, Wen-Son	ICON SOC Farrer Park Medical Clinic	Singapore	1
Ong, Shin Yeu	Singapore General Hospital	Singapore	4
Kafková, Adriana	HEMKO	Slovakia	1
Kim, Jin Seok	Severance Hospital, Yonsei University Health System	South Korea	1
Bang, Soo-Mee	Seoul National University Bundang Hospital	South Korea	2
Lee, Jae Hoon	Gachon University Gil Medical Center	South Korea	1
Sohn, Sang-Kyun	Kyungpook National University Hospital	South Korea	1
Jo, Jae-Cheol	Ulsan University Hospital	South Korea	2
De la Serna, Javier	Hospital Universitario 12 de Octubre	Spain	4
Garcia-Marco, Jose	Hospital Universitario Puerta de Hierro	Spain	1
Loscertales, Javier	Hospital Universitario de La Princesa	Spain	3

Yañez San Segundo, Lucrecia	Hospital Universitario Marqués de Valdecilla	Spain	1
Ferra Coll, Christelle	Hospital Universitari Germans Trias i Pujol	Spain	2
Jarque Ramos, Isidro	Hospital Universitari i Politecnic La Fe de Valencia	Spain	2
Gonzalez Diaz, Marcos	Hospital Universitario de Salamanca	Spain	1
Lauri, Birgitta	Sunderby Sjukhus	Sweden	2
Karlsson, Claes	Karolinska University Hospital Solna	Sweden	1
Andersson, Per-Ola	Södra Älvsborgs Sjukhus - Borås	Sweden	1
Wang, Tso-Fu	Hualien Tzu Chi Hospital Buddhist Tzu Chi Medical Foundation	Taiwan	1
Kryachok, Iryna	National Cancer Institute	Ukraine	6
Kaplan, Polina	Dnipropetrovsk City Multifield Clinical Hospital Number 4	Ukraine	6
Pylypenko, Halyna	Municipal Institution Cherkasy Regional Oncology Dispensary Cherkasy Regional Council	Ukraine	4
Rekhtman, Grygoriy	Khmelnytsky Regional Hospital	Ukraine	2
Lysa, Tamila	O.F. Gerbachevsky Zhytomyr Regional Clinical Hospital	Ukraine	2
Dyagil, Iryna	State Institution "National Research Center of Radiation Medicine of the NAMS of Ukraine"	Ukraine	2
Glushko, Natalia	Ivano-Frankivsk Regional Clinical Hospital	Ukraine	3
Ringshausen, Ingo	Cambridge University Hospitals NHS Foundation Trust	United Kingdom	2
Jacob, Abraham	The Royal Wolverhampton NHS Trust	United Kingdom	2
Avery, Eric	Nebraska Hematology Oncology	United States	2
Burhani, Nafisa	Joliet Oncology Hematology Associates, Ltd	United States	2

Independent data monitoring committee members

Name	Affiliation	Role
Steven Dahlberg, MS	Statistical Consultant, Bellevue, WA, USA	Chair
John Allan, MD	Department of Medicine, Weill Cornell Medical College, New York, NY, USA	Member
Simon Rule, MD	Department of Haematology, Derriford Hospital, Devon, United Kingdom	Member

Supplemental methods

Eligibility criteria

Inclusion criteria

Eligible patients were considered for inclusion in this study if they met **all** the following criteria:

1. Men and women ≥18 years of age
2. ECOG performance status of 0 to 2
3. Diagnosis of CLL that meets published diagnostic criteria [Hallek 2008]:
    1. 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.
    2. Prolymphocytes may comprise ≤55% of blood lymphocytes.
    3. Presence of ≥5 x 10^9 B lymphocytes/l (5000/µl) in the peripheral blood (at any point since initial diagnosis).
4. Must have documented CD20-positive CLL
5. Active disease meeting ≥1 of the following IWCLL 2008 criteria for requiring treatment:
    1. 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).
    2. Massive (ie, ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly.
    3. Massive nodes (ie, ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy.
    4. Progressive lymphocytosis with an increase of >50% over a 2-month period or a LDT of <6 months. LDT may be obtained by linear regression extrapolation of ALC obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients 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.
    5. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy.
    6. Constitutional symptoms documented in the patient's chart with supportive objective measures, as appropriate, defined as ≥1 of the following disease-related symptoms or signs:
        1. Unintentional weight loss ≥10% within the previous 6 months before screening.
        2. Significant fatigue (ECOG performance score 2; inability to work or perform usual activities).
        3. Fevers higher than 100.5°F or 38.0°C for ≥2 weeks before screening without evidence of infection.
        4. Night sweats for >1 month before screening without evidence of infection.
6. Meet the following laboratory parameters:
    1. 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.

2. Platelet count ≥50,000 cells/µl (50 x 10^9/l), or ≥30,000 cells/µl (30 x 10^9/l) in patients with documented bone marrow involvement, and without transfusion support 7 days before assessment. Patients with transfusion-dependent thrombocytopenia are excluded. If an investigator has chosen bendamustine/rituximab as the Arm B treatment, platelets must be ≥75,000 cells/µl (75 x 10^9/l).
3. Serum AST and ALT ≤2.0 x ULN.
4. Total bilirubin ≤1.5 x ULN.
5. 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].

7. Must have received ≥1 prior systemic therapies for CLL. Note: Single-agent steroids or localized radiation are not considered a prior line of therapy. If a single-agent anti-CD20 antibody was previously administered, patients must have received ≥2 doses.
8. 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, 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer.
9. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer.
10. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of idelalisib, 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longer.
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 authorization to use protected health information (in accordance with national and local patient privacy regulations).

Exclusion criteria

Patients were ineligible for this study if they met **any** of the following criteria:

1. Known CNS lymphoma or leukemia
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
3. Uncontrolled AIHA or 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 or equivalent).
4. Prior exposure to a BCL-2 inhibitor (eg, venetoclax/ABT-199) or a BCR inhibitor (eg, BTK inhibitors or PI3K inhibitors). Prior bendamustine is allowed if Investigator's choice for treatment in Arm B is idelalisib with rituximab. Bendamustine retreatment is allowed if the prior response to bendamustine lasted >24 months.
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 daily prednisone equivalent 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, patients 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 transplant or prior autologous transplant within 6 months of first dose of study drug(s) or presence of graft-*vs*-host disease or receiving treatment for graft-*vs*-host disease.
9. Major surgical procedure within 30 days of first dose of study drug. Note: If a patient had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
10. History of prior malignancy except for the following:
    1. Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and felt to be at low risk for recurrence by treating physician.
    2. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer.
    3. Adequately treated carcinoma in situ without current evidence of disease.
11. Significant cardiovascular disease such as uncontrolled or untreated 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 QTc >480 msec (calculated using Fridericia's formula: QT/RR0.33) at screening. Exception: Patients with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll on study.
12. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
13. Received a live virus vaccination within 28 days of first dose of study drug.
14. Known history of infection with HIV or any uncontrolled active systemic infection (eg, bacterial, viral or fungal).
15. Active CMV infection (active viremia as evidenced by positive polymerase chain reaction [PCR] result for CMV DNA).
16. Serologic status reflecting active hepatitis B or C infection.
    1. Patients who are anti-HBc positive and who are surface antigen negative will need to have a negative PCR result before randomization. Those who are HbsAg-positive or hepatitis B PCR positive will be excluded.
    2. Patients who are hepatitis C antibody positive will need to have a negative PCR result before randomization. Those who are hepatitis C PCR positive will be excluded.
17. Ongoing, drug-induced liver injury, alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, ongoing extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.
18. History of or ongoing drug-induced pneumonitis.
19. History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.
20. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug.

21. History of bleeding diathesis (eg, hemophilia, von Willebrand disease).
22. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
24. Requires treatment with a strong CYP3A inhibitor/inducer.
25. Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
26. Breast feeding or pregnant.
27. Concurrent participation in another therapeutic clinical trial.
28. Prothrombin time/INR or aPTT (in the absence of a Lupus anticoagulant) >2.0 x ULN. Exception: Patients receiving warfarin are excluded, however, those receiving other anticoagulant therapy who have a higher INR/aPTT may be permitted to enroll to this study after discussion with the medical monitor.
29. History of confirmed progressive multifocal leukoencephalopathy (PML).

Dose modification guidelines

Acalabrutinib

The actions in the table below should be followed for the following toxicities (according to CTCAE criteria version 4.03 or higher)

- Grade 4 ANC (<500/µl) for >7 days (neutrophil growth factors are permitted per ASCO guidelines [Smith 2015] and use must be recorded on the electronic case report form (eCRF)
- Grade 3 platelet count decreases in presence of significant bleeding
- Grade 4 platelet count 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

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 orally once daily)
4th	Discontinue acalabrutinib

If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the patient tolerates a reduced dose of acalabrutinib for ≥4 weeks then the dose may be increased to the next higher dose level, at the discretion of the Investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. However, the maximum dose of acalabrutinib is 100 mg orally twice daily for this protocol.

Any changes to the dosing regimen must be recorded in the Dosage Administration eCRF.

Idelalisib

Idelalisib dose reductions are described in the tables below. For severe or life-threatening toxicities related to idelalisib, withhold drug until toxicity is resolved. If resuming idelalisib after interruption for severe or life-threatening toxicities, reduce the dose to 100 mg PO BID. Recurrence of severe or life-threatening idelalisib-related toxicity upon rechallenge should result in permanent discontinuation of idelalisib. If idelalisib is discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.
Idelalisib may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Idelalisib should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the Medical Monitor.

Pneumonitis	**Any symptomatic pneumonitis**		
	Discontinue idelalisib in patients with any severity of symptomatic pneumonitis		
ALT/AST	**>3 to 5×ULN**	**>5 to 20×ULN**	**>20×ULN**
	Maintain idelalisib dose. Monitor at least weekly until ≤1 x ULN	Withhold idelalisib. Monitor at least weekly until ALT/AST are ≤1 x ULN, then may resume idelalisib at 100 mg PO BID	Discontinue idelalisib permanently
Bilirubin	**>1.5 to 3×ULN**	**>3 to 10×ULN**	**>10×ULN**
	Maintain idelalisib dose. Monitor at least weekly until ≤1 x ULN	Withhold idelalisib. Monitor at least weekly until bilirubin is ≤1 x ULN, then may resume idelalisib at 100 mg PO BID	Discontinue idelalisib permanently
Diarrhea*	**Moderate diarrhea**	**Severe diarrhea or hospitalization**	**Life-threatening diarrhea**
	Maintain idelalisib dose Monitor at least weekly until resolved	Withhold idelalisib. Monitor at least weekly until resolved, then may resume idelalisib at 100 mg PO BID	Discontinue idelalisib permanently
Neutropenia	**ANC 1.0 to <1.5 Gi/l**	**ANC 0.5 to <1.0 Gi/l**	**ANC <0.5 Gi/l**
	Maintain idelalisib dose	Maintain idelalisib dose. Monitor ANC at least weekly	Interrupt idelalisib. Monitor ANC at least weekly until ANC ≥0.5 Gi/l, then may resume idelalisib at 100 mg PO BID

Thrombocytopenia	**Platelets 50 to <75 Gi/l**	**Platelets 25 to <50 Gi/l**	**Platelets <25 Gi/l**
	Maintain idelalisib dose	Maintain idelalisib dose. Monitor platelet counts at least weekly	Interrupt idelalisib. Monitor platelet counts at least weekly, may resume idelalisib at 100 mg PO BID when platelets ≥25 Gi/l
Infections	**Grade ≥3 sepsis or pneumonia**		
	Interrupt idelalisib until infection has resolved		
	Evidence of CMV infection or viremia		
	Hold idelalisib in patients with evidence of CMV infection of any grade or viremia (PCR above the lower limit of quantitation or positive antigen test). Idelalisib may be restarted once patient has PCR below the lower limit of quantitation; as per Investigator discretion. If idelalisib is resumed, monitor (by PCR or antigen test) for CMV reactivation at least monthly.		
	Evidence of PJP infection		
	Hold idelalisib in patients with suspected PJP infection of any grade. Permanently discontinue idelalisib in patients with active or confirmed PJP infection.		

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; Gi/l = giga/liter; PO = orally; ULN = upper limit of normal.
*Moderate diarrhea: increase of 4 to 6 stools per day over baseline; severe diarrhea: increase of ≥7 stools per day over baseline.

Bendamustine
Bendamustine administration should be delayed in the event of grade 4 hematologic toxicity or clinically significant grade ≥2 nonhematologic toxicity. Once nonhematologic toxicity has recovered to grade ≤1 and/or the blood counts have improved (ANC ≥1 x 10^9/l, platelets ≥75 x 10^9/l), bendamustine can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted (see Warnings and Precautions in prescribing information). If bendamustine is discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

Dose modifications for hematologic toxicity: for grade ≥3 toxicity, reduce the dose to 50 mg/m^2 IV on Days 1 and 2 of each cycle; if grade ≥3 toxicity recurs, reduce the dose to 25 mg/m^2 IV on Days 1 and 2 of each cycle.
Dose modifications for nonhematologic toxicity: for clinically significant grade ≥3 toxicity, reduce the dose to 50 mg/m^2 IV on Days 1 and 2 of each cycle.

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

Patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine should be considered if there are signs of (opportunistic) infections.

Accommodations should be made in the event of doses of bendamustine held or delayed due to toxicity to permit a full six cycles to be received, wherever possible. See further instructions for data entry in such cases in the eCRF guidelines. Locally and/or regionally approved minor schedule variations in administration of bendamustine + rituximab may be accommodated, provided the doses of both bendamustine and rituximab remain the same as specified in the protocol, and the total doses per cycle remain the same as per protocol, with modifications for toxicity as provided above.

In the event of dosing delays due to toxicity, when possible, dosing of both bendamustine and rituximab should be held, and readministered together once toxicity has resolved to grade 1 or better (or to study baseline). In such cases, the cycle schedule will be shifted accordingly (see instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/MRI scans will remain fixed, however.

Study drug (bendamustine) may be held a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment (bendamustine) should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by Medical Monitor.

Rituximab
No dose modification is allowed for rituximab. If rituximab is discontinued, patients can continue to receive idelalisib or bendamustine as outlined in this protocol. If bendamustine or idelalisib are discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol. The initial dose of rituximab may be divided for administration, per local or institutional standards.

Central laboratory assessments and gene mutation analysis

Baseline assessments conducted at screening included immunophenotyping of circulating lymphocytes, central analysis of genomic aberrations with fluorescence in situ hybridization (FISH), mutational analysis of the immunoglobulin heavy-chain variable-region (IGHV) gene and *TP53* by DNA sequencing, and evaluation of lymph-node size.

A central laboratory tested peripheral blood samples obtained at baseline for all patients. FISH probes were used for cytogenetic profiling; testing assessed abnormalities in chromosomes 13q, 12, 11q, and 17p (Vysis CLL FISH Probe kit; Abbott Molecular). The mutational status of genes known to be involved in CLL prognosis was assessed with genomic profiling. For IGHV gene mutation, standard Sanger sequencing was used; assay sensitivity was 10% and the cutoff was 2%. For *TP53* mutations, both Sanger and next-generation sequencing methods were employed. The sensitivity for Sanger sequencing was 20%, and 5% for next-generation sequencing. The average coverage for all amplicons was over 1000 reads. If locally assessed FISH results confirming the status of del(17p) before randomization were available, these could be used only

for stratification purposes; all analyses used FISH cytogenetics and *TP53* mutation status as determined by central laboratory assessment. Complex karyotype was defined as ≥3 cytogenetic abnormalities based on karyotyping (conventional cytogenetics) by the central laboratory. Computed tomographic scans with contrast or magnetic resonance imaging dye was performed in all patients at baseline, every 12 weeks through cycle 25, and then every 24 weeks thereafter until disease progression.

Definition of study endpoints and timing of assessments

Endpoint	Definition and analysis method
Independent review committee-assessed progression-free survival (PFS)*	Time from the date of randomization until disease progression (assessed by the IRC per IWCLL 2008 criteria) or death from any cause, whichever occurs first. Patients not meeting these criteria and alive by the analysis data cutoff date will be censored, and the detailed censoring rules will be specified in the SAP. Pretreatment radiologic tumor assessment were obtained within 30 days before the first dose. Radiologic tumor assessment was performed every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on cycle 4 day 1, the second on treatment scan on cycle 7 day 1, and so on through cycle 25, and then every 24 weeks (± 14 days) thereafter. For bendamustine-treated patients, the second radiologic tumor assessment occurred at the next 12-week interval (± 14 days) regardless of whether the patient was on study drug. CT or MRI scans could be performed ≤7 days before response evaluation. CT or MRI scans were performed until disease progression was confirmed, regardless of whether or not the patient remained on treatment. In the event disease progression was suspected due to physical examination or laboratory test, a CT or MRI scans was performed to confirm disease progression. If the sole measurable lesion was within the field of prior radiotherapy, there must be evidence of disease progression in that lesion that had not been previously irradiated. A stratified log-rank test was used for the primary comparison of PFS. Additionally, a stratified Cox regression model was used to provide the estimated PFS HR and 2-sided 95% CIs for acalabrutinib relative to investigator's choice. Kaplan-Meier (KM) curves are presented for each treatment arm. Median PFS and its 95% CI, as well as landmark PFS and associated 95% CI at selected times, were provided. Sensitivity analyses performed are described in the SAP.
Investigator-assessed PFS	Time from randomization until disease progression (assessed by the Investigator per IWCLL 2008 criteria) or death from any cause, whichever occurs first. Analysis methods for investigator-assessed PFS will be similar to those described for PFS as assessed by the independent review committee per IWCLL 2008 criteria.
Investigator-assessed overall response rate (ORR)	The proportion of patients who achieve a CR, CRi, nPR, or PR over the course of the study per investigator assessment. Patients who do not

	have any postbaseline response assessment were considered to be nonresponders. Overall response assessments were based upon evaluation of physical exams, recording of symptoms, radiologic evaluations, and hematologic evaluations per the schedule of assessments. Response evaluations were done every 12 weeks (± 14 days) with the first on-treatment radiologic assessment occurring on cycle 4 day 1, the second on treatment scan on cycle 7 day 1, and so on through Cycle 25, and then every 24 weeks (± 14 days) thereafter. Hematology results were performed within 7 days of CT/MRI scans. Bone marrow biopsies/aspirates to confirm a CR were performed within 8-12 weeks of the CT/MRI scan, which showed suspected CR. Patients who had signs and symptoms of disease progression outside of the scheduled study visits and assessments were evaluated by the investigator with a physical exam and a CBC with differential to determine if disease progression was present. Any suspected case of disease progression was confirmed with a CT scan if one was not obtained. ORR was compared between treatment arms using the Cochran-Mantel-Haenszel chi-square test, adjusted for randomization stratification factors.
Independent review committee-assessed ORR	Summarized and analyzed similarly to investigator-assessed ORR.
Overall survival	Time from date of randomization until date of death due to any cause. Patients who have not died by the analysis data cutoff date were censored at the last date known to be alive before the cutoff date. Patients known to be alive or dead after the data cutoff date were censored at the data cutoff date. The analysis methods for OS were similar to those described for PFS.
Investigator- and independent review committee-assessed duration of response	Time from the first documentation of objective response to the earlier time of disease progression (assessed by the investigator or IRC per IWCLL 2008 criteria) or death from any cause. The same censoring rules and analysis methods were applied as described for PFS.
Time to next treatment (TTNT)	Time from randomization to institution of nonprotocol-specified treatment for CLL. The analysis methods for TTNT were similar to those described for PFS. For crossover patients, TTNT was defined as time from initial treatment of acalabrutinib to institution of nonprotocol-specified treatment for CLL.

Secondary endpoints also included patient-reported outcome using the FACIT-Fatigue instrument, which will be presented in a separate analysis.

Response assessment criteria (per iwCLL 2008, with modification for persistent lymphocytosis[22,23])

Response*	Lymphocytes	Bone Marrow	Physical Examination[a] (Nodes, Liver, Spleen)	Peripheral Blood

CR	Lymphocytes <4 x 10^9/l	Normocellular <30% lymphocytes No B-lymphoid nodules	Normal (eg, no lymph nodes >1.5 cm)	ANC >1.5 x 10^9/l[b] Platelets >100 x 10^9/l[b] Hemoglobin > 11.0 g/dl (untransfused)[b]
CRi	Lymphocytes <4 x 10^9/l	Hypocellular <30% lymphocytes No B-lymphoid nodules	Normal (eg, no lymph nodes >1.5 cm)	Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity
nPR	CR with the presence of lymphoid nodules in the bone marrow, which reflect residual disease			
PR	Lymphocytes <5 x 10^9/l or ≥50% decrease from baseline	Not assessed	≥50% reduction in lymphadenopathy[c] 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[b] or Hemoglobin >11.0 g/dl or 50% improvement over baseline (untransfused)[b]
PRL	Lymphocytes ≥5 x 10^9/l and <50% decrease from baseline	Not assessed	≥50% reduction in lymphadenopathy[c] 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[b] or Hemoglobin >11.0 g/dl or 50% improvement over baseline (untransfused)[b]
SD	Absence of PD and failure to achieve at least a PR			
PD	Lymphocytes ≥50% increase over baseline, with ≥5000 B lymphocytes/µl	Not assessed (except to confirm PD as assessed by progressive cytopenias)	Appearance of any new lesion or de novo appearance of hepatomegaly or splenomegaly or	Platelets decrease of ≥50% from baseline secondary to CLL or Hemoglobin decrease of >2

			Increase ≥50% in lymphadenopathy or Increase ≥50% in hepatomegaly or Increase ≥50% in splenomegaly	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; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; nPR = nodular partial remission; PD = progressive disease; PR = partial remission (response); PRL = partial remission (response) with lymphocytosis; SD = stable disease.

*CR: all of the above CR criteria have to be met, and patients have 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 have to be met; PRL: presence of lymphocytosis, plus ≥50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the criteria for ANC, platelets or hemoglobin have to be met; PD: at least one of the above PD criteria has to be met, or transformation to a more aggressive histology (eg, Richter's syndrome). For PD as assessed by progressive cytopenias, a bone marrow biopsy is required for confirmation. Note: Isolated elevation of treatment-related lymphocytosis by itself will not be considered PD unless patient becomes symptomatic from this per Cheson 2012.

[a]Computed tomography (CT) scan of abdomen, pelvis, and thorax may be used if previously abnormal.

[b]Without need for exogenous growth factors.

[c]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.

Hematologic improvement assessment

Hematologic improvement in the subset of patients with cytopenia(s) is defined as follows for each parameter:

Improvement to hemoglobin >11 g/dl from baseline or increase ≥50% over baseline
Improvement to platelet counts >100 x 10^9/l from baseline or increase ≥50% over baseline
Improvement to ANC >1.5 x 10^9/l or increase ≥50% over baseline

Sustained hematologic improvement is defined as improvement in cytopenia by ≥50%, or hemoglobin (Hgb) >11 g/dl, platelets >100 x 10^9/l, ANC >1.5 x 10^9/l with the duration of improvement lasting for at least 2 months without blood transfusion or growth factors. The proportion of patients achieving sustained hematologic improvement will be summarized by treatment arm.

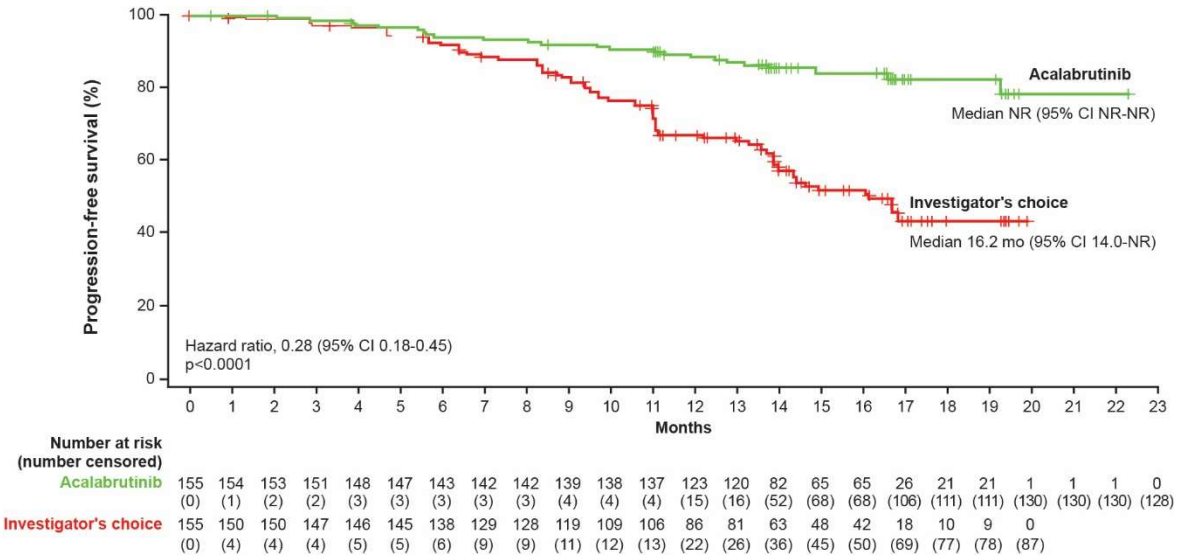
Details of statistical analysis

Five sensitivity analyses of IRC-assessed progression-free survival were conducted to test for the potential impact of differences in modeling or censoring approaches: (1) an unstratified log-rank test, (2) progression-free survival analyses without censoring at subsequent anti-cancer therapy to assess potential confounding of treatment effect estimates by subsequent therapy, (3) progression-free survival analyses without censoring of death or disease progression after ≥2 missed response assessment at the date of last adequate response assessment, (4) progression-free survival analyses excluding patients with important protocol deviation, (5) progression-free survival analyses using eCRF-recorded stratification factors.

To adjust for multiple testing, the prespecified hierarchical testing of two key secondary efficacy endpoints was performed in the following order: IRC-assessed ORR and OS. Because the study met its primary endpoint, a formal statistical test of IRC-assessed ORR between the two arms was performed at the two-sided significance level of 0.05 using a stratified Cochran–Mantel–Haenszel test. As this endpoint was not statistically significant, *P* values for the subsequent hierarchically tested endpoints could be considered only descriptive.

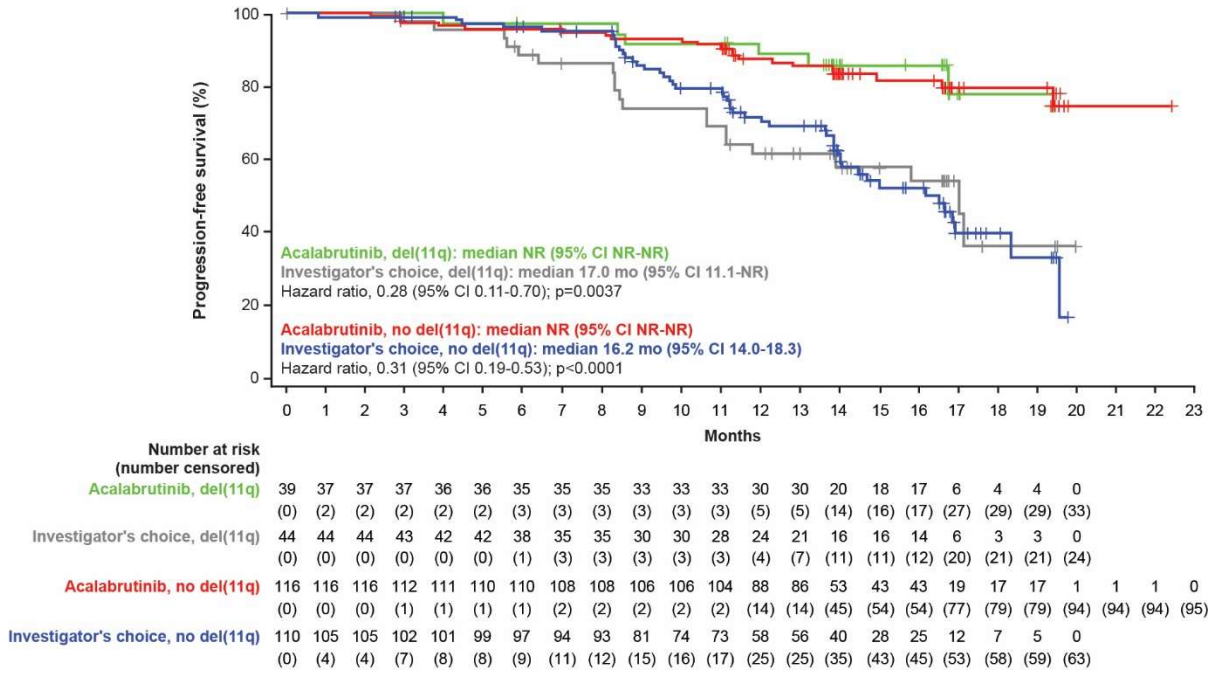
Distributions of time-to-event endpoints, including PFS, OS, duration of response, and time to next treatment were estimated using the Kaplan–Meier method. All efficacy analyses were conducted in the intention-to-treat population. Safety was analyzed according to actual treatment received in all randomized patients who received ≥1 dose of any study medication were included in the safety analyses. Statistical analyses were performed using SAS v9.4.

Figure A1. Investigator-assessed progression-free survival for acalabrutinib and investigator's choice therapy in the intention-to-treat population.



CI = confidence interval; NR = not reached.

Figure A2. Independent review committee-assessed progression-free survival for acalabrutinib and investigator's choice therapy by del(11q) status in the intention-to-treat population.

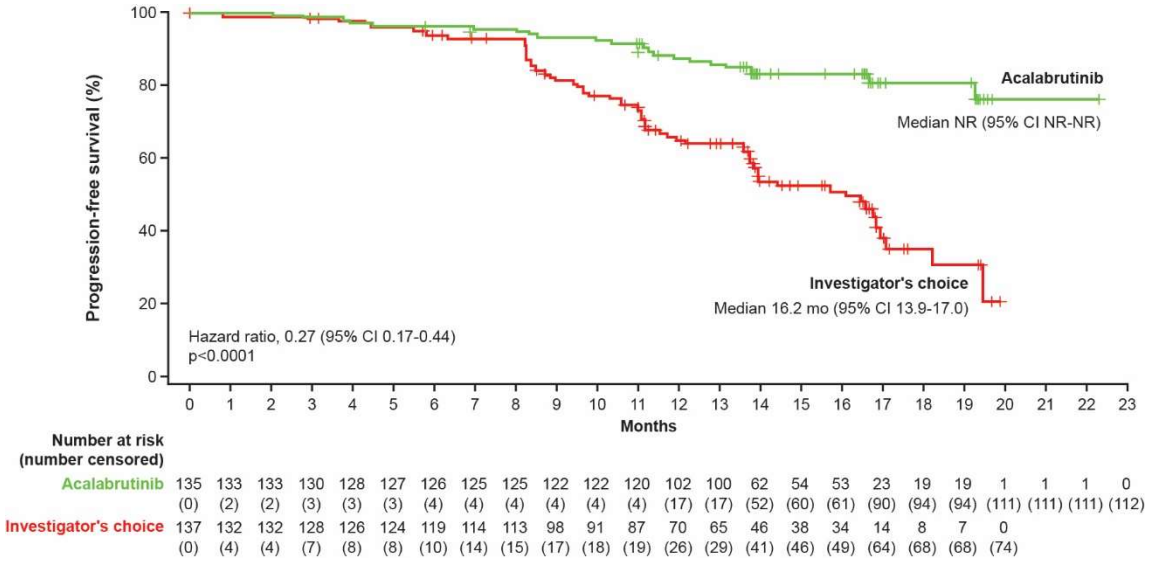


Number at risk (number censored)																								
Acalabrutinib, del(11q)	39 (0)	37 (2)	37 (2)	37 (2)	36 (2)	36 (2)	35 (3)	35 (3)	35 (3)	33 (3)	33 (3)	33 (3)	30 (5)	30 (5)	20 (14)	18 (16)	17 (17)	6 (27)	4 (29)	4 (29)	0 (33)			
Investigator's choice, del(11q)	44 (0)	44 (0)	44 (0)	43 (0)	42 (0)	42 (0)	38 (1)	35 (3)	35 (3)	30 (3)	30 (3)	28 (3)	24 (4)	21 (7)	16 (11)	16 (11)	14 (12)	6 (20)	3 (21)	3 (21)	0 (24)			
Acalabrutinib, no del(11q)	116 (0)	116 (0)	116 (0)	112 (1)	111 (1)	110 (1)	110 (1)	108 (2)	108 (2)	106 (2)	106 (2)	104 (2)	88 (14)	86 (14)	53 (45)	43 (54)	43 (54)	19 (77)	17 (79)	17 (79)	1 (94)	1 (94)	1 (94)	0 (95)
Investigator's choice, no del(11q)	110 (0)	105 (4)	105 (4)	102 (7)	101 (8)	99 (8)	97 (9)	94 (11)	93 (12)	81 (15)	74 (16)	73 (17)	58 (25)	56 (25)	40 (35)	28 (43)	25 (45)	12 (53)	7 (58)	5 (59)	0 (63)			

CI = confidence interval; NR = not reached.

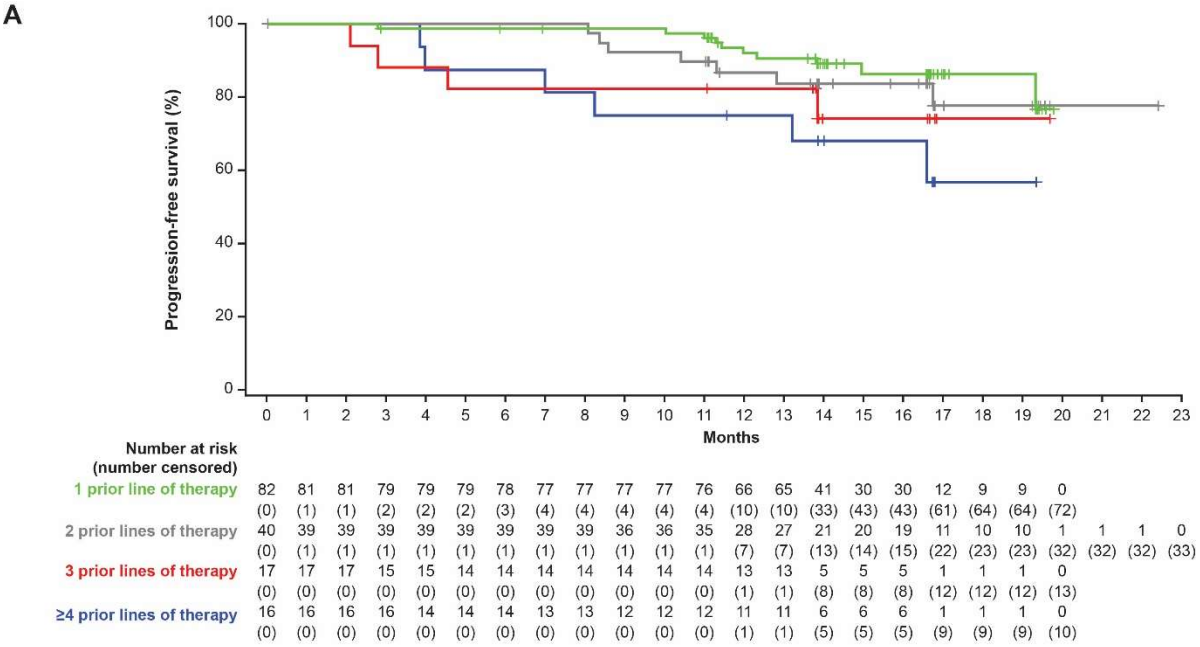
Figure A3. Independent review committee-assessed progression-free survival in patients with high-risk cytogenetic features receiving acalabrutinib and investigator's choice therapy in the intention-to-treat population.

High-risk cytogenetic features included having any combination of chromosome del(17p), *TP53* mutation, chromosome del(11q), or unmutated *IGHV*.



CI = confidence interval; IGHV = immunoglobulin heavy chain variable; NR = not reached.

Figure A4. Independent review committee-assessed progression-free survival in patients receiving acalabrutinib (Panel A) and investigator's choice therapy (Panel B) by prior lines of therapy in the intention-to-treat population.



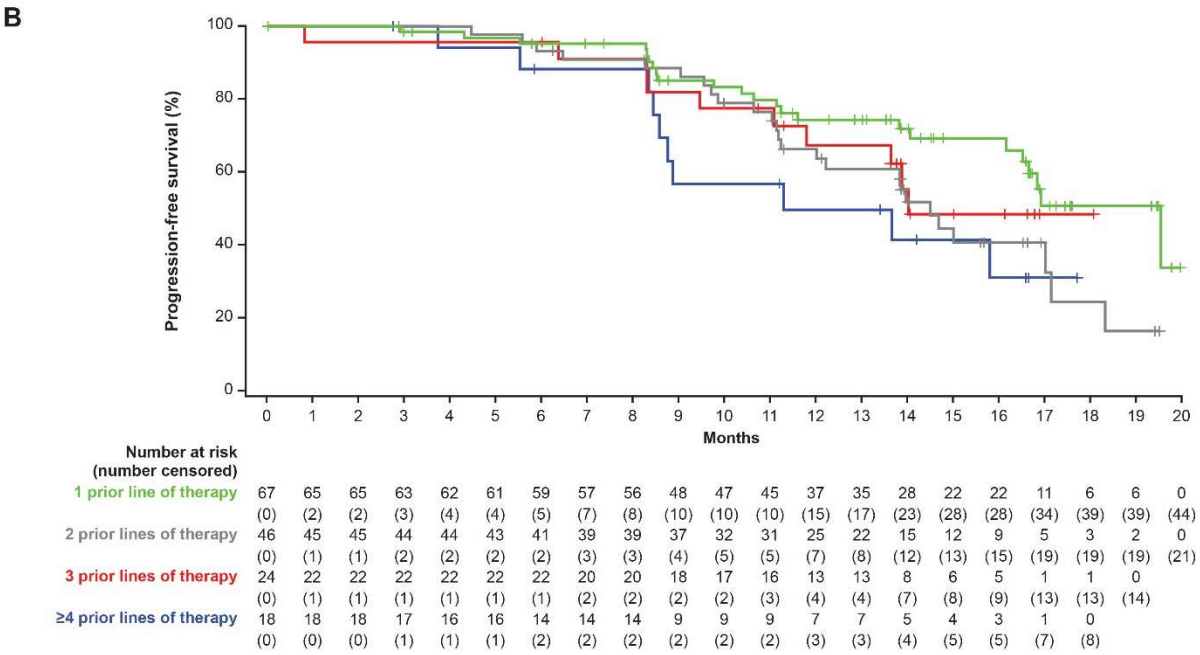
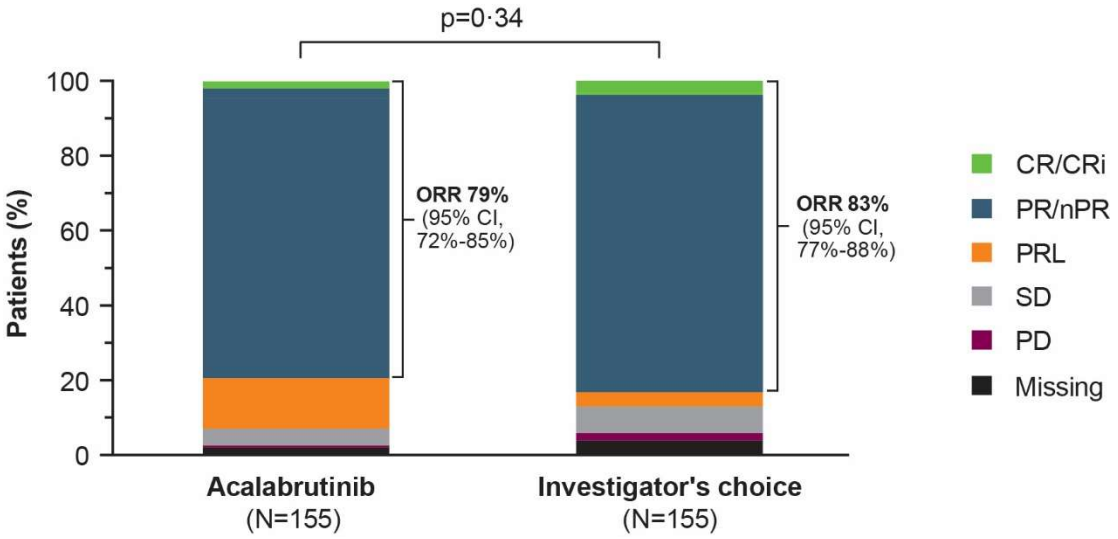


Figure A5. Investigator-assessed overall response rate



CI = confidence interval; CR = complete response; Cri = CR with incomplete bone marrow recovery; nPR = nodular partial remission; ORR = overall response rate; PD = progressive disease; PR = partial response; PRL = partial remission (response) with lymphocytosis; SD = stable disease.

Figure A6. Sustained hematologic improvement

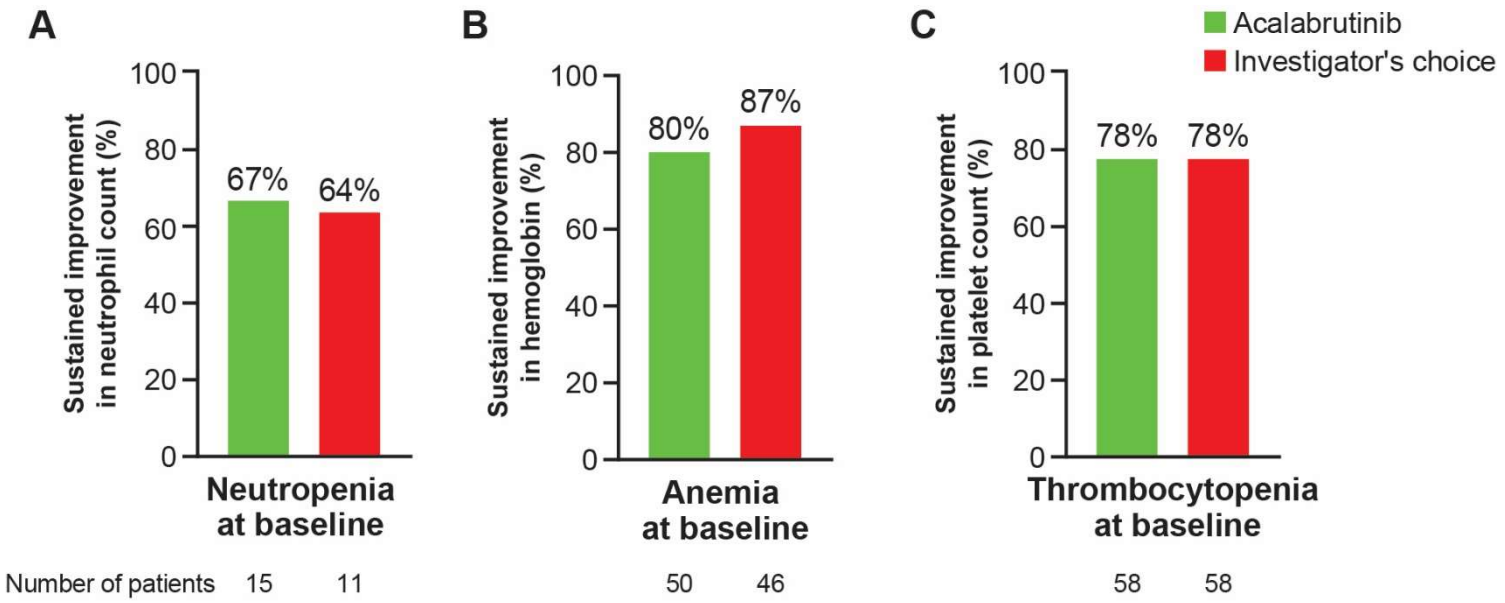
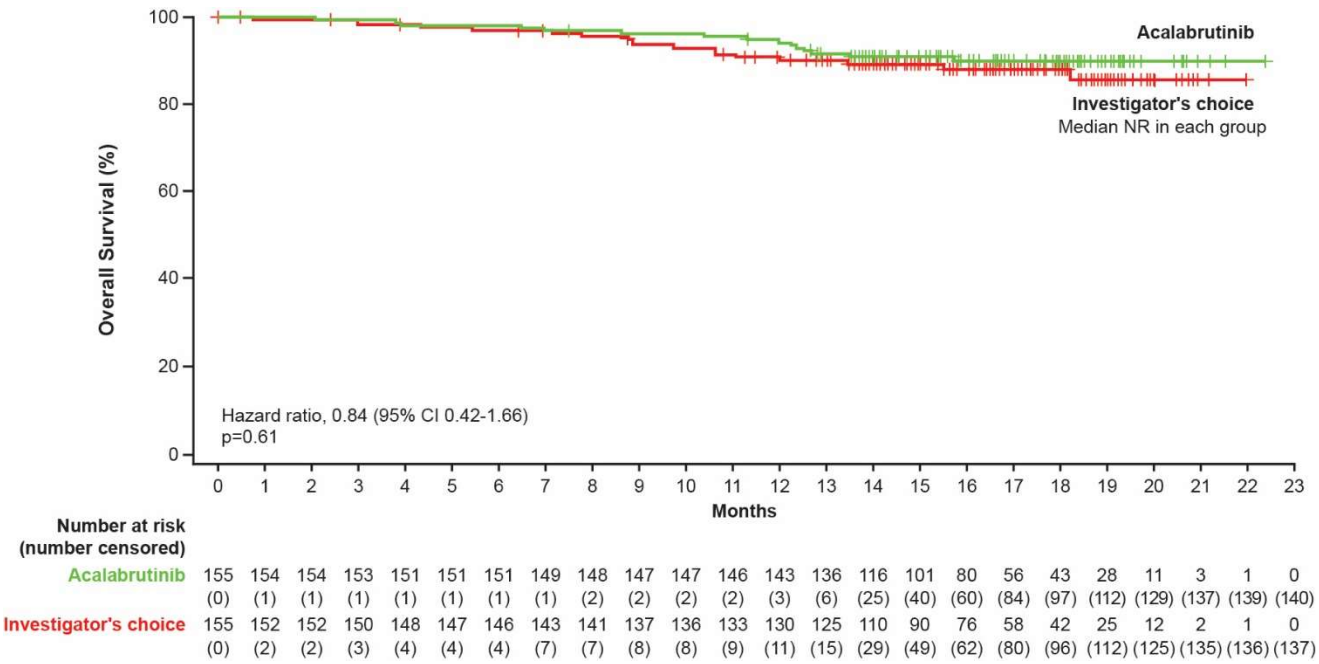
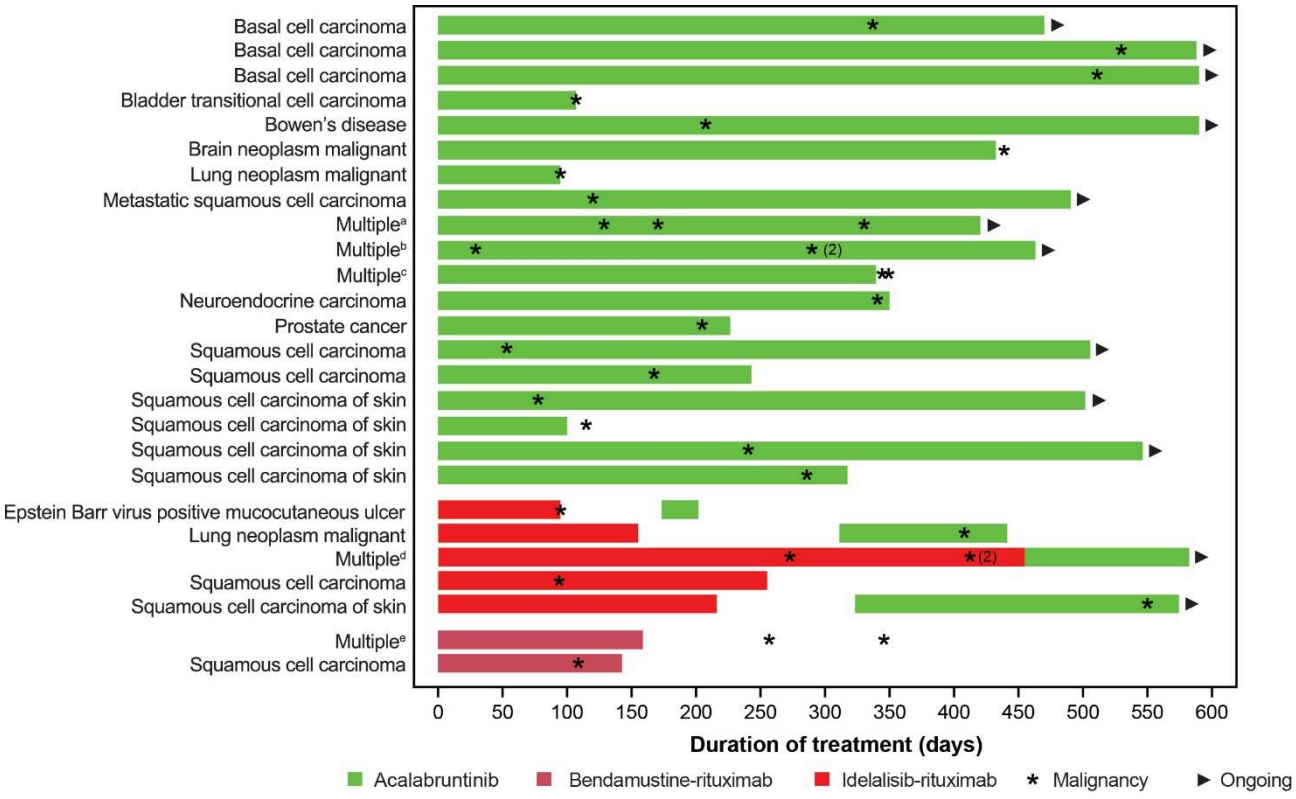


Figure A7. Kaplan-Meier curve of overall survival in patients receiving acalabrutinib or investigator's choice therapy in the intention-to-treat population.



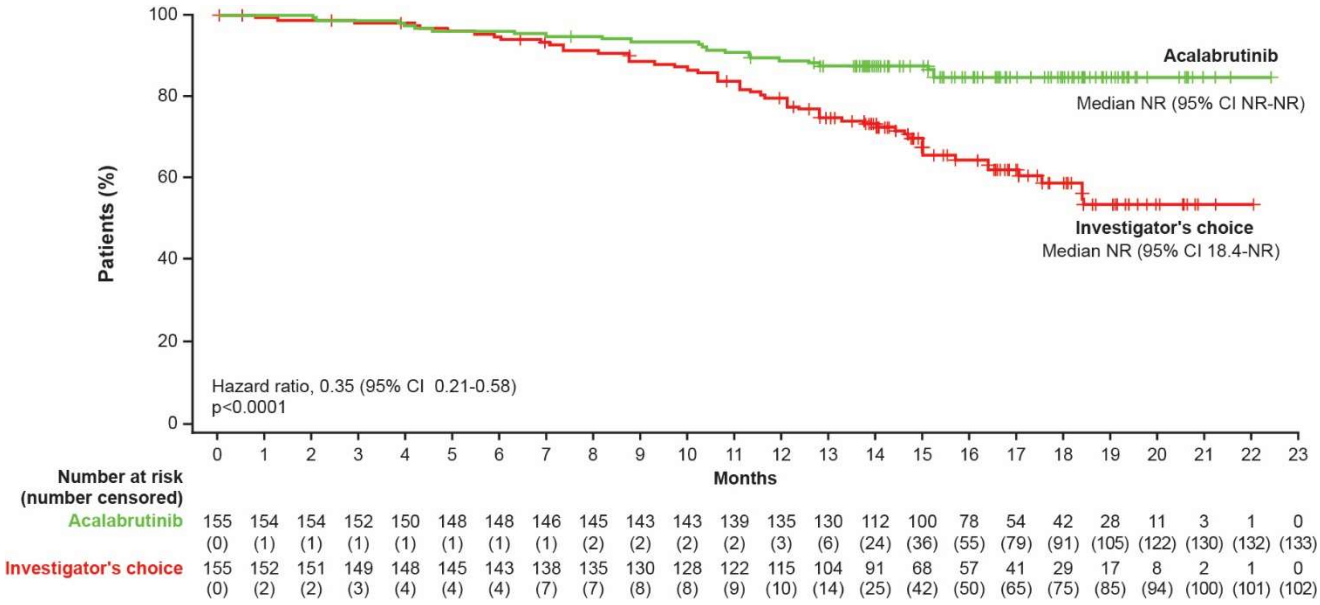
CI = confidence interval; NR = not reached.

Figure A8. Second primary malignancies. Second primary malignancies shown include treatment emergent and non-treatment emergent events from the time of randomization or cross-over.



The median time to onset of secondary primary malignancies was 204 days (range, 29-530) in the acalabrutinib group, 273 days (range, 92-548) in the I-R group and 182 days (range, 108-256) in the B-R group. Multiple occurrences of malignancies on the same day are denoted with a number next to the asterisk. Events of squamous cell carcinoma and metastatic squamous cell carcinoma were updated to "squamous cell carcinoma of the skin" following receipt of additional information after the interim database cut for this clinical study report. Three events were grade 5: malignant lung neoplasm, neuroendocrine carcinoma, and acute myeloid leukaemia. [a]Patient had squamous cell carcinoma on days 128, 170, and 330 after first dose. [b]Patient had malignant melanoma on day 29, and basal cell carcinoma and lip squamous cell carcinoma on day 289 after first dose. [c]Patient had myelodysplastic syndrome and acute myeloid leukaemia on days 345 and 349 after first dose, respectively. [d]Patient had basal cell carcinoma on day 273 after first dose and basal cell carcinoma and squamous cell carcinoma on day 412 after first dose. [e]Patient had lung adenocarcinoma on days 256 and 345 after first dose. "Ongoing" indicates that the patient was continuing acalabrutinib treatment at the time of the interim analysis.

Figure A9. Time to next treatment. Kaplan-Meier curve of time to next CLL treatment in patients receiving acalabrutinib or investigator's choice therapy in the intention-to-treat population.



Median time of onset was 185.5 (range, 29.0-530.0) and 100.5 (range 92.0-273.0) days, respectively.

NR=not reached.

Table A1. Patient disposition

Variable	Acalabrutinib (n=155)	Idelalisib plus rituximab (n=119)	Bendamustine plus rituximab (n=36)
Treatment status — n (%)			
Did not receive treatment	1 (1)	1 (1)	1 (3)
Ongoing	124 (80)	38 (32)	0
Completed	NA	NA	28 (78)
Discontinued	30 (19)	80 (67)	7 (19)
Primary reason for treatment discontinuation* — n (%)			
Adverse event	17 (11)	56 (47)	6 (17)
Death	1 (1)	0	0
Investigator decision	1 (1)	4 (3)	0
Disease progression	10 (6)	12 (10)	1 (3)
Withdrawal of consent	0	1 (1)	0
Other†	1 (1)	7 (6)	0

NA=not applicable.

*Based on the earlier drug of the regimen that was discontinued; if drugs were discontinued on the same date, the discontinuation reason provided is for idelalisib (in the idelalisib plus rituximab subgroup) or bendamustine (bendamustine plus rituximab subgroup).
†The other reason for discontinuation of acalabrutinib was patient decision; other reasons for discontinuation of idelalisib plus rituximab included adverse events preventing dosing (n=2); adverse events combined with disease progression preventing treatment administration, dose interruption for more than 28 days, patient decision, patient death, and adverse events preventing treatment administration (n=1 each).

Table A2. Subsequent therapies

	Acalabrutinib (N=155)	Investigator's Choice Therapy (N=155)
Median (range) number of subsequent therapies, n (%)	1 (1-2)	1 (1-3)
Median (range) time from first dose to subsequent anticancer therapy, months	10.2 (2-15)	11.1 (1-19)
Subsequent therapy, n (%)		
Alkylators other than bendamustine	5 (3)	6 (4)
Bendamustine	2 (1)	1 (1)
Anti-CD20 monoclonal antibodies	7 (5)	4 (3)
Ibrutinib	2 (1)	4 (3)
Venetoclax	5 (3)	2 (1)
Other*	1 (1)	2 (1)

*One patient received azacitidine and cytarabine + idarubicin, 1 patient received cytarabine + methotrexate, and 1 patient received dexamethasone monotherapy.

Table A3. Treatment exposure and dose modification

Variable	Acalabrutinb (N=154)	Idelalisib Plus Rituximab (n=118)		Bendamustine Plus Rituximab (n=35)	
		Idelalisib	Rituximab	Bendamustine	Rituximab
Received ≥6 intravenous treatment cycles, n (%)	–	–	92 (78)	29 (83)	28 (80)
Median (range) duration of treatment, months	15.7 (1.1-22.4)	11.5 (0.1-21.1)	5.5 (0.9-8.5)	5.6 (1.0-7.1)	5.5 (0.9-7.1)
Median (range) relative dose intensity, %	99.5 (52.0-100.0)	91.2 (47.0-100.0)	98.2 (9.0-104.0)	96.4 (15.0-103.0)	97.9 (2.0-102.0)
Patients with dose withholding,* n (%)	35 (23)	68 (58)	23 (19)	4 (11)	6 (17)
Adverse event	29 (19)	67 (57)	21 (18)	3 (9)	4 (11)
Investigator decision	1 (1)	1 (1)	6 (5)	1 (3)	1 (3)
Patient error	0	1 (1)	0	0	0
Procedure	8 (5)	0	0	0	0
Other	1 (1)	7 (6)	2 (2)	1 (3)	2 (6)
Patients with dose reduction, n (%)	12 (8)	55 (47)	NA	6 (17)	NA
Adverse event	5 (3)	28 (24)	NA	6 (17)	NA
Investigator decision	1 (1)	7 (6)	NA	0	NA
Patient error	6 (4)	8 (7)	NA	0	NA
Procedure	0	2 (2)	NA	0	NA
Other	1 (1)	9 (8)	NA	0	NA
Missing	2 (1)	30 (25)	NA	6 (17)	NA
Patients with infusion interruption, n (%)	NA	NA	23 (19)	0	11 (31)
Adverse event	NA	NA	20 (17)	0	11 (31)
Other	NA	NA	3 (3)	0	0
Length of treatment†					
<3	3 (2)	10 (8)	6 (5)	3 (9)	4 (11)
≥3 and <6	6 (4)	23 (19)	20 (17)	3 (9)	3 (9)
≥6 and <9	3 (2)	11 (9)	92 (78)	29 (83)	28 (80)
≥9 and <12	10 (6)	18 (15)	0	0	0

≥12 and <18	94 (61)	46 (39)	0	0	0
≥18 and <24	38 (25)	10 (8)	0	0	0

NA=not applicable.

*Defined as missing dose for ≥7 consecutive days for acalabrutinib and idelalisib, and ≥1 dose not administered in the prescheduled visit for bendamustine and rituximab. Regardless of drug, patients were only counted once for each reason for dose withholding.

†Unit is months for acalabrutinib and idelalisib and cycles for bendamustine and rituximab.

Table A4. Serious adverse events occurring in >1 patient in any group

	Acalabrutinib (n=154)		Idelalisib plus rituximab (n=118)		Bendamustine plus rituximab (n=35)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any serious adverse event, n (%)	44 (29)	41 (27)	66 (56)	60 (51)	9 (26)	9 (26)
Pneumonia	8 (5)	8 (5)	10 (8)	9 (8)	1 (3)	1 (3)
Atrial fibrillation	3 (2)	1 (1)	0	0	1 (3)	1 (3)
Dyspnea	2 (1)	2 (1)	1 (1)	1 (1)	0	0
Gastrointestinal hemorrhage	2 (1)	2 (1)	1 (1)	1 (1)	0	0
Pneumonitis	2 (1)	2 (1)	2 (2)	2 (2)	0	0
Respiratory tract infection	2 (1)	2 (1)	0	0	0	0
Skin ulcer	2 (1)	2 (1)	0	0	0	0
Spinal compression fracture	2 (1)	2 (1)	1 (1)	1 (1)	0	0
Squamous cell carcinoma of skin	2 (1)	1 (1)	0	0	0	0
Urinary tract infection	2 (1)	2 (1)	1 (1)	1 (1)	0	0
Anemia	1 (1)	1 (1)	4 (3)	4 (3)	1 (3)	1 (3)
Chest pain	1 (1)	1 (1)	2 (2)	1 (1)	0	0
Diarrhea	1 (1)	1 (1)	16 (14)	16 (14)	0	0
Femur fracture	1 (1)	1 (1)	2 (2)	2 (2)	0	0
Influenza	1 (1)	1 (1)	2 (2)	2 (2)	1 (3)	1 (3)
Pyrexia	1 (1)	0	8 (7)	6 (5)	1 (3)	1(3)
Clostridium difficile colitis	0	0	2 (2)	1 (1)	0	0
Colitis	0	0	3 (3)	2 (2)	0	0
Cytomegalovirus infection	0	0	2 (2)	1 (1)	0	0
Enterocolitis	0	0	2 (2)	1 (1)	0	0
Interstitial lung disease	0	0	2 (2)	2 (2)	0	0
Lower respiratory tract infection	0	0	2 (2)	2 (2)	0	0
Pneumonocystis jirovecii pneumonia	0	0	2 (2)	2 (2)	0	0
Pneumonia pneumococcal	0	0	3 (3)	3 (3)	0	0

Table A5. Treatment-emergent adverse events leading to treatment discontinuation

Adverse events leading to discontinuation, n (%)	Acalabrutinib (N=154)	Idelalisib Plus Rituximab (n=118)		Bendamustine Plus Rituximab (n=35)	
		Idelalisib	Rituximab	Bendamustine	Rituximab
Any adverse event	16 (10)	59 (50)	15 (13)	4 (11)	6 (17)
Abdominal pain	1 (1)*	–	–	–	–
ALT increased	1 (1)	5 (4)	1 (1)	–	–
Bladder transitional cell carcinoma	1 (1)	–	–	–	–
Brain neoplasm	1 (1)	–	–	–	–
Malignant brain neoplasm	1 (1)	–	–	–	–
Congestive cardiac failure	1 (1)	–	–	–	–
Cerebral ischemia	1 (1)	–	–	–	–
Cytopenia	1 (1)	–	–	–	–
Headache	1 (1)	–	–	–	–
Hepatitis B	1 (1)	–	–	–	–
Immune thrombocytopenic purpura	1 (1)	–	–	–	–
Malignant lung neoplasm	1 (1)	–	–	–	–
Peritonitis	1 (1)	–	–	–	–
Prostate cancer	1 (1)	–	–	–	–
Respiratory tract infection	1 (1)	–	–	–	–
Squamous cell carcinoma of skin	1 (1)	–	–	–	–
Diarrhea	–	14 (12)	–	–	–
Pneumonia	–	4 (3)	3 (3)	–	–
Transaminases increased	–	4 (3)	1 (1)	–	–
AST increased	–	3 (3)	–	–	–
Colitis	–	3 (3)	–	–	–
Interstitial lung disease	–	3 (3)	1 (1)	–	–
Pneumonitis	–	3 (3)	1 (1)	–	–
Hepatotoxicity	–	2 (2)	–	–	–
Neutrophil count decreased	–	2 (2)	–	–	–
Infusion-related reaction	–	–	1 (1)	–	1 (3)
Chronic cardiac failure	–	1 (1)	1 (1)	–	–

Cardiopulmonary failure	–	1 (1)	–	–	–
Cytomegalovirus infection	–	1 (1)	–	–	–
Dyspepsia	–	1 (1)	–	–	–
Epstein-Barr virus-positive mucocutaneous ulcer	–	1 (1)	–	–	–
Hepatitis E	–	1 (1)	–	–	–
Hepatocellular injury	–	1 (1)	–	–	–
Liver injury	–	1 (1)	–	–	–
Myocardial infarction	–	1 (1)	–	–	–
Neutropenia	–	1 (1)	–	–	–
Oesophagitis	–	1 (1)	–	–	–
Organizing pneumonia	–	1 (1)	1 (1)	–	–
Pneumocystis jirovecii pneumonia	–	1 (1)	–	–	–
Pneumonia legionella	–	1 (1)	1 (1)	–	–
Pseudomonal pneumonia	–	1 (1)	–	–	–
Pruritus	–	1 (1)	–	–	–
Maculopapular rash	–	1 (1)	–	–	–
Septic shock	–	1 (1)	1 (1)	–	–
Thrombocytopenia	–	1 (1)	–	–	–
Vertigo	–	1 (1)	1 (1)	–	–
Gastroenteritis	–	–	1 (1)	–	–
Pustular rash	–	–	1 (1)	–	–
Urosepsis	–	–	1 (1)	–	–
Acute cardiac failure	–	–	–	–	1 (3)
Bronchitis	–	–	–	1 (3)	1 (3)
Gastric neoplasm	–	–	–	1 (3)	1 (3)
Hemolytic anemia	–	–	–	1 (3)	–
Hepatitis B reactivation	–	–	–	1 (3)	1 (3)
Urticaria	–	–	–	–	1 (3)

*****Event resulted from a grade 4 hemorrhage associated with pancreatic cancer diagnosed 1-2 days subsequent to the abdominal pain.

Table A6. Treatment-emergent events of clinical interest

	Acalabrutinib (n=154)		Idelalisib plus rituximab (n=118)		Bendamustine plus rituximab (n=35)	
Adverse event, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with ≥1 AE of clinical interest	127 (82)	64 (42)	113 (96)	95 (81)	26 (74)	17 (49)
Cardiac events	20 (13)	5 (3)	9 (8)	4 (3)	3 (9)	3 (9)
Atrial fibrillation	8 (5)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
Ventricular tachyarrhythmias	0	0	0	0	0	0
Bleeding	40 (26)	3 (2)	9 (8)	3 (3)	2 (6)	1 (3)
Major bleeding*	3 (2)	3 (2)	3 (3)	3 (3)	1 (3)	1 (3)
Hepatotoxicity†	7 (5)	3 (2)	33 (28)	26 (22)	3 (9)	2 (6)
Hypertension	5 (3)	3 (2)	5 (4)	1 (1)	0	0
Infections	87 (57)	23 (15)	77 (65)	33 (28)	17 (49)	4 (11)

*Defined as any serious or grade ≥3 bleeding or central nervous system bleeding of any grade. In the acalabrutinib group, events were gastrointestinal hemorrhage (n=2) and immune thrombocytopenic purpura (n=1); for idelalisib plus rituximab, gastrointestinal hemorrhage, immune thrombocytopenic purpura, and hematuria (n=1 each); and for bendamustine plus rituximab, hemorrhagic anemia and tumor hemorrhage (both in 1 patient).

[†]Defined as a select group of hepatic events including hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions, liver-related investigations, abnormalities, and noninfectious hepatitis.

Table A7. Treatment-emergent cardiac events

	Acalabrutinib (n=154)		Idelalisib plus rituximab (n=118)		Bendamustine plus rituximab (n=35)	
Adverse event, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Cardiac events	20 (13)	5 (3)	9 (8)	4 (3)	3 (9)	3 (9)
Atrial fibrillation	8 (5)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
Atrial fibrillation	8 (5)	2 (1)	3 (3)	0	1 (3)	1 (3)
Atrial flutter	0	0	1 (1)	1 (1)	0	0
Ventricular tachyarrhythmias	0	0	0	0	0	0
Other cardiac events	15 (10)	4 (3)	7 (6)	4 (3)	2 (6)	2 (6)
Cardiac failure	3 (2)	1 (1)	1 (1)	1 (1)	0	0
Acute myocardial infection	0	0	1 (1)	1 (1)	1 (3)	1 (3)
Angina pectoris	0	0	1 (1)	0	1 (3)	1 (3)
Chronic cardiac failure	0	0	1 (1)	1 (1)	0	0
Cardiomyopathy	0	0	1 (1)	1 (1)	0	0
Cardiopulmonary failure	0	0	1 (1)	1 (1)	0	0
Myocardial infarction	0	0	1 (1)	1 (1)	1 (3)	1 (3)
Sinus arrhythmia	0	0	1 (1)	0	0	0
Palpitations	4 (3)	0	0	0	0	0
Supraventricular extrasystoles	2 (1)	0	0	0	0	0
Acute coronary syndrome	1 (1)	1 (1)	0	0	0	0
Unstable angina	1 (1)	1 (1)	0	0	0	0
Arrhythmia	1 (1)	0	0	0	0	0
Bradycardia	1 (1)	0	0	0	0	0
Cardiac arrest	1 (1)	1 (1)	0	0	0	0
Congestive cardiac failure	1 (1)	1 (1)	0	0	0	0
Sinus bradycardia	1 (1)	0	0	0	0	0
Tachycardia	1 (1)	0	0	0	0	0
Acute cardiac failure	0	0	0	0	1 (3)	1 (3)

Table A8. Summary of treatment-emergent Grade ≥3 infections

Type of Infection, N (%)	Acalabrutinib (n=154)	Idelalisib plus rituximab (n=118)	Bendamustine plus rituximab (n=35)
Any grade ≥3 infection	23 (14.9)	33 (28.0)	4 (11.4)
Pneumonia, upper respiratory, and respiratory			
Upper respiratory tract infection	3 (1.9)	4 (3.4)	1 (2.9)
Pneumonia	8 (5.2)	10 (8.5)	1 (2.9)
Respiratory tract infection	2 (1.3)	1 (0.8)	0
Bronchitis	0	1 (0.8)	1 (2.9)
Influenza	1 (0.6)	2 (1.7)	1 (2.9)
Pneumonia pneumococcal	0	4 (3.4)	0
Lower respiratory tract infection	0	2 (1.7)	0
Pneumonia hemophilus	0	1 (0.8)	0
Pneumonia legionella	0	1 (0.8)	0
Pneumonia pseudomonal	0	1 (0.8)	0
Lung infection	1 (0.6)	0	0
Pneumonia klebsiella	1 (0.6)	0	0
Fungal infections			
Pneumocystitis jirovecii pneumonia	0	2 (1.7)	0
Pneumonia fungal	1 (0.6)	0	0
Sepsis			
Pseudomonal sepsis	0	1 (0.8)	0
Urosepsis	0	1 (0.8)	0
Sepsis	1 (0.6)	0	0
Gastrointestinal			
Gastroenteritis	1 (0.6)	1 (0.8)	0
Clostridium difficile colitis	0	1 (0.8)	0
Peritonitis	1 (0.6)	0	0
Diverticulitis	0	0	1 (2.9)
Gastroenteritis viral	0	0	1 (2.9)
Kidney and bladder			
Urinary tract infection	2 (1.3)	2 (1.7)	0
Escherichia urinary tract infection	1 (0.6)	0	0
Ear, eye, and mouth			
Otitis media	1 (0.6)	0	0
Ophthalmic herpes zoster	1 (0.6)	0	0
Other			
Cytomegalovirus infection	0	2 (1.7)	0
Herpes zoster	0	2 (1.7)	0
Cytomegalovirus viremia	0	1 (0.8)	0
Hepatitis E	0	1 (0.8)	0
Herpes virus infection	0	1 (0.8)	0
Pseudomonas infection	0	1 (0.8)	0
Epididymitis	1 (0.6)	0	0
Cellulitis	1 (0.6)	0	0

Device related infection	1 (0.6)	0	0
Hepatitis B	1 (0.6)	0	0
Postoperative wound infection	1 (0.6)	0	0

Table A9. Summary of deaths

Adverse event, n (%)	Acalabrutinib (n=154)	Idelalisib plus rituximab (n=118)	Bendamustine plus rituximab (n=35)
Deaths	15 (10)	13 (11)	5 (14)
Causes of death			
Disease progression	5 (3)	0	0
Unknown	1 (1)	1 (1)	0
Richter transformation	1 (1)	3 (3)	1 (3)
Adverse events	8 (5)	9 (8)	4 (11)
Within 30 days of last dose	5 (3)	3 (3)	1 (3)
Brain neoplasm	1 (1)	0	0
Cachexia due to spinalioma	1 (1)	0	0
Cerebral ischemia*	1 (1)	0	0
Neuroendocrine carcinoma	1 (1)	0	0
Sepsis	1 (1)	0	0
Acute cardiac failure	0	0	1 (3)
Cardiopulmonary failure	0	1 (1)	0
Neutropenic sepsis	1 (1)	0	0
Interstitial pneumonitis	0	1 (1)	0
Acute myocardial infarction	0	1 (1)	0
After 30 days of last dose	3 (2)	6 (5)	3 (9)
Bronchopneumonia	0	0	1 (3)
Heart failure	0	1 (1)	0
Septic shock	0	2 (2)	0
Multiorgan failure†	1 (1)	0	0
Malignant lung neoplasm	1 (1)	0	0
Chronic cardiac failure	0	1 (1)	0
Gastric neoplasm	0		1 (3)
Pseudomonal pneumonia	0	1 (1)	0
Cardiac arrest	0	0	1 (1)
Infectious complications‡	0	1 (1)	0
Acute myeloid leukemia	1 (1)	0	0

Data includes all treatment emergent and non-treatment emergent deaths occurring during both the randomization and crossover periods.

*Event began before data cutoff, but death occurred after data cutoff.

†Due to complications from pancreatic neoplasm.

‡Patient had legionella sepsis

References

Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical endpoints in chronic lymphocytic leukemia. *J Clin Oncol* 2012;**30**(23): 2820–2

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):5446–56

Smith TJ, Bohlke KB, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015; **33**:3199–3212

Treanda (bendamustine hydrochloride) [prescribing information]. North Wales, PA, USA: Teva Pharmaceuticals USA, Inc; 2017