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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 28, 2020.

Supplement to: Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. *Lancet* 2020; **395:** 1278–91.

Supplementary Appendix

Supplement to: Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Flinn IW, et al. Acalabrutinib With or Without Obinutuzumab in CLL.

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Steven Dahlberg, M.S.	Statistical Consultant, Bellevue, WA, USA	Member
Michael Grever, M.D.	The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA	Member

Supplementary Methods

Patient Eligibility

Inclusion Criteria

1. Men and women:
    a. Aged ≥65 years, **OR**
    b. Aged >18 and < 65 years provided that they met at least one of the following criteria:
        i. Creatinine clearance 30 to 69 mL/min using the Cockcroft-Gault equation
        ii. A score higher than 6 on the Cumulative Illness Rating Scale-Geriatric

2. Eastern Cooperative Oncology Group performance status of 0, 1, or 2

3. Diagnosis of $CD20^+$ chronic lymphocytic leukaemia (CLL) that met published diagnostic criteria:[1]
    a. Monoclonal B cells (either kappa or lambda light chain restricted) that were clonally co-expressing ≥1 B-cell marker (CD19, CD20, or CD23) and CD5
    b. Prolymphocytes were allowed to comprise ≤55% of blood lymphocytes
    c. Presence of $\geq 5 \times 10^9$ B lymphocytes/L (5000/μL) in the peripheral blood (at any point since diagnosis)

4. Active disease that met ≥1 of the following International Workshop on CLL (iwCLL) 2008 criteria for requiring treatment:
    a. Evidence of progressive bone marrow failure as manifested by the development of, or worsening of, anaemia (haemoglobin <10 g/dL) and/or thrombocytopenia (platelets <100,000/μL)
    b. Massive (ie, ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly
    c. Massive nodes (ie, ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy
    d. Progressive lymphocytosis with an increase of >50% during a two-month period or a lymphocyte doubling time (LDT) of <6 months. LDT was obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of two weeks during an observation period of two to three months. In patients with initial blood lymphocyte counts of $<30 \times 10^9$/L (30,000/μL), LDT was not used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) were excluded
    e. Autoimmune anaemia and/or thrombocytopenia that was poorly responsive to standard therapy
    f. 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:
        i. Unintentional weight loss ≥10% within the previous six months before screening
        ii. Significant fatigue (ie, Eastern Cooperative Oncology Group performance status 2; inability to work or perform usual activities)
        iii. Fevers higher than 100·5°F or 38·0°C for two or more weeks before screening without evidence of infection
        iv. Night sweats for >1 month before screening without evidence of infection

5. Met the following laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥750 cells/μL ($0{\cdot}75 \times 10^9$/L) or ≥500 cells/μL ($0{\cdot}50 \times 10^9$/L) in subjects with documented bone marrow involvement and independent of growth factor support seven days before assessment.
    b. Platelet count ≥50,000 cells/μL (50×10^9/L), or ≥30,000 cells/μL (30×10^9/L) in patients with documented bone marrow involvement, and without transfusion support seven days before assessment. Patients with transfusion-dependent thrombocytopenia were excluded
    c. Serum aspartate aminotransferase and alanine aminotransferase ≤3·0 × upper limit of normal

   d. Total bilirubin ≤1·5 × upper limit of normal
   e. Estimated creatinine clearance (ie, estimated glomerular filtration rate using Cockcroft-Gault) ≥30 mL/min

6. Able to receive all outpatient treatment, all laboratory monitoring, and all radiologic evaluations

7. Sexually active women of reproductive age had to agree to use highly effective forms of contraception while on the study and for two days after the last dose of acalabrutinib or 18 months after the last dose of obinutuzumab in combination with chlorambucil, whichever was longer

8. Sexually active men capable of producing children had to agree to use highly effective forms of contraception during the study and for 90 days after the last dose of obinutuzumab or chlorambucil, whichever was later

9. Men agreed to refrain from sperm donation during the study and for 90 days after the last dose of obinutuzumab or chlorambucil, whichever was later

10. Were willing and able to adhere to the study visit schedule, understand and comply with other protocol requirements, and provide written informed consent and authorization to use protected health information. Note vulnerable patients, as defined in International Conference on Harmonisation's Good Clinical Practice guidelines, were not allowed on this protocol (eg, prisoners or institutionalised patients)

Exclusion Criteria

1. Any prior systemic treatment for CLL (note: Prior localised radiotherapy is allowed)

2. Known central nervous system lymphoma or leukaemia

3. Known prolymphocytic leukaemia or history of, or currently suspected, Richter's syndrome

4. Missing or incomplete documentation of fluorescence in situ hybridization (FISH) results reflecting the presence or absence of 17p deletion and the percentage of cells with the deletion in patient records before randomisation

5. Uncontrolled autoimmune haemolytic anaemia or idiopathic thrombocytopenic purpura, defined as decreasing haemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (>20 mg of prednisone daily or equivalent)

6. Corticosteroid use >20 mg within one 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 were administered steroids for leukaemia control or white blood cell count lowering were excluded

7. Major surgery within four weeks before first dose of study drug

8. History of prior malignancy except for the following:
   a. Malignancy treated with curative intent and with no evidence of active disease present for more than three years before screening and felt to be at low risk for recurrence by treating physician
   b. Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer
   c. Adequately treated cervical carcinoma in situ without current evidence of disease

9. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within six 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

10. Inability to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
11. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment
12. Known history of infection with HIV
13. Vaccinated with live, attenuated vaccines within four weeks of first dose of study drug
14. Serologic status reflecting active infection with hepatitis B or C. Patients who were positive for hepatitis B core antibody and negative for surface antigen or who were positive for hepatitis C antibody will need to have a negative polymerase chain reaction (PCR) result before randomisation. Those who were positive for hepatitis B surface antigen or positive for hepatitis B by PCR and those who were positive for hepatitis C by PCR were excluded
15. History of stroke or intracranial haemorrhage within six months before randomisation
16. History of a bleeding diathesis (eg, haemophilia, von Willebrand's disease)
17. Required or received anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within seven days of first dose of study drug
18. Required treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole)
19. Breast feeding or pregnant
20. Current life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety or put the study at risk
21. Concurrent participation in another therapeutic clinical trial
22. Required treatment with a strong cytochrome P450 3A inhibitor/inducer
23. Presence of a gastrointestinal ulcer diagnosed by endoscopy within three months before screening

Dose Modification Guidelines

Assessment of Toxicity
Dose modification decisions for haematologic toxicity were based on the grading scale in the Common Terminology Criteria for Adverse Events, version 4·03 or higher.

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

Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as few as seven days could cause a transient worsening of disease and/or of constitutional symptoms. In such

circumstances, and if medically appropriate, patients could resume therapy and relevant clinical, laboratory, and/or radiologic assessments were performed to document whether tumour control could be maintained or whether actual disease progression had occurred.

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

- Grade 4 absolute neutrophil count (<500/μL) for >7 days (neutrophil growth factors were permitted per ASCO [American Society of Clinical Oncology] guidelines [Smith 2015] and use had to be recorded on the case report form [CRF])
- Grade 3 platelet decreases in presence of significant bleeding
- Grade 4 platelet decreases
- Grade 3 or 4 nausea, vomiting, or diarrhoea, if persistent despite optimal antiemetic and/or antidiarrheal therapy
- Any other grade 4 toxicity or unmanageable grade 3 toxicity

For patients who received acalabrutinib and obinutuzumab: if acalabrutinib or obinutuzumab was discontinued, then the other study drug (obinutuzumab or acalabrutinib, respectively) could be continued at the discretion of the investigator (up to a total of six cycles of obinutuzumab).

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

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

Dose Modification and Discontinuation for Obinutuzumab and Chlorambucil
No reduction in the dose of obinutuzumab was allowed. Recommendations for chlorambucil dose reductions are described below. A dose delay of up to four weeks was permitted for obinutuzumab or chlorambucil to allow recovery of haematologic toxicities to grade ≤2 or nonhaematologic toxicities to grade 1 or baseline level. If the treatment was delayed for >4 weeks, chlorambucil was discontinued; obinutuzumab could be continued at the discretion of the investigator.

For patients receiving obinutuzumab and chlorambucil: if obinutuzumab or chlorambucil was discontinued, then the other study drug (chlorambucil or obinutuzumab) could be continued at the discretion of the investigator (up to a total of six cycles of obinutuzumab or chlorambucil).

Obinutuzumab-chlorambucil administration on day 1 of the following cycle was given if the cytopenia had resolved to grade ≤2. If the cytopenia persisted, obinutuzumab-chlorambucil administration was delayed until the cytopenia had improved to grade ≤2. If a patient experiences grade 3 or 4 cytopenia, the guidelines for dose delay and dose reduction are outlined in the table below. Below are the recommended haematologic dose modifications for chlorambucil and obinutuzumab; investigators could also elect to follow appropriate dose modification guidelines in locally approved labelling for these drugs.

Cytopenia	Chlorambucil	Obinutuzumab
Grade 3 or 4	Delay dosing for a maximum of 4 weeks. Administer granulocyte colony-stimulating factor for neutropenia or platelets or red blood cells as required. First episode: if improvement to grade ≤2 (or baseline), decrease chlorambucil dose to 75% of initial dose for subsequent cycles. Second episode: if improvement to grade ≤2 (or baseline), decrease chlorambucil dose to 50% of initial dose for subsequent cycles. Third episode: discontinue chlorambucil.	Delay dose for a maximum of 4 weeks. If improvement to maximum of grade ≤2 (or baseline), administer full dose. If chlorambucil is discontinued, obinutuzumab may continue at the investigator's discretion.
Grade 1 or 2	No dose reduction or delay	No dose reduction or delay

Chlorambucil has been reported to exacerbate or precipitate autoimmune haemolytic anaemia and patients were monitored carefully for this condition. If a rapid decrease of haemoglobin occurred during therapy, the possibility of chlorambucil- or autoantibody induced haemolysis was considered and appropriate diagnostic tests (lactate dehydrogenase, bilirubin, haptoglobin, reticulocytes, Coombs-test) were performed. If haemolysis was suspected, a Coomb's test was performed. If, in the judgment of the treating physician, there was evidence of clinically significant haemolytic anaemia secondary to chlorambucil, study treatment was promptly discontinued. Full details of the haemolytic anaemia should be recorded on the adverse event pages of the CRF.

A patient had to discontinue obinutuzumab/chlorambucil if any of the following occur:

- Acute life-threatening respiratory symptoms
- Grade 4 infusion-related symptom – patient withdrawn immediately
- Grade 3 infusion-related symptom at rechallenge
- Grade 3 or 4 cytopenia (if not present at baseline) that had not resolved to grade ≤2 and delayed treatment by ≥4 weeks
- Grade ≥2 noncytopenia toxicity that did not resolve to ≤grade 1/baseline and delayed treatment by ≥4 weeks

Refer to local Summary of Product Characteristics or prescribing information for guidance on obinutuzumab/chlorambucil discontinuations.

Definition of Endpoints

Response Assessment Criteria (per iwCLL 2008, With Modification for Persistent Lymphocytosis[1, 2])

Response*	Lymphocytes	Bone Marrow	Physical Exam[a] (Nodes, Liver, Spleen)	Peripheral Blood
CR	Lymphocytes <4 × 10^9/L	Normocellular <30% lymphocytes No B-lymphoid nodules	Normal (eg, no lymph nodes >1·5 cm)	ANC > 1·5 × 10^9/L[b] Platelets > 100 × 10^9/L[b] Haemoglobin > 11·0 g/dL (untransfused)[b]

CRi	Lymphocytes <4 × 10^9/L	Hypocellular <30% lymphocytes No B-lymphoid nodules	Normal (eg, no lymph nodes >1·5 cm)	Persistent anaemia, 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 × 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 × 10^9/L or Platelets >100 × 10^9/L or 50% improvement over baseline[b] or Haemoglobin >11·0 g/dL or 50% improvement over baseline (untransfused)[b]
PRL	Lymphocytes ≥5 × 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 × 10^9/L or Platelets >100 × 10^9/L or 50% improvement over baseline[b] or Haemoglobin >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 Increase ≥50% in lymphadenopathy or Increase ≥50% in hepatomegaly or Increase ≥50% in splenomegaly	Platelets decrease of ≥50% from baseline secondary to CLL or Haemoglobin decrease of >2 g/dL from baseline secondary to CLL

ANC = absolute neutrophil count; CLL= chronic lymphocytic leukaemia; CR = complete remission (response); CRi = CR with incomplete bone marrow recovery; CT = computed tomography; 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 had to be met, and patients had to lack disease-related constitutional symptoms; PR: ≥2 of the above PR criteria for lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes plus one of the criteria for ANC, platelets, or haemoglobin had 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 haemoglobin had to be met; PD: ≥1 of the above PD criteria had 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 was required for confirmation. Note: Isolated elevation of treatment-related lymphocytosis by itself was not considered PD unless patient became symptomatic from this per Cheson 2012.

[a]CT scan of abdomen, pelvis, and thorax could 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.

Statistical Analysis

All tests for this interim analysis were performed at 2-sided significance level. The Lan-DeMets alpha-spending function based on the O'Brien-Fleming boundaries[3, 4] for superiority and futility (nonbinding) were used. Given the study assumptions, the minimum detectable treatment difference at the final analysis of PFS corresponded to an HR of approximately 0·735. Superiority for interim and final analyses were conducted at α levels of 0·012 (α1) and 0·046 (α2), respectively. Early stopping for futility was assessed at the interim analysis at a α-level of 0·396.

Statistical testing of secondary endpoints was planned in a fixed, sequential hierarchical manner for analyses on achieving statistical significance of the primary endpoint:
1) IRC-assessed PFS for acalabrutinib monotherapy vs obinutuzumab-chlorambucil; 2) IRC-assessed ORR for acalabturinib-obinutuzumab vs obinutuzumab-chlorambucil; 3) IRC-assessed ORR for acalabrutinib monotherapy vs obinutuzumab-chlorambucil; 4) OS for acalabturinib-obinutuzumab vs obinutuzumab-chlorambucil; and 5) OS for acalabrutinib monotherapy vs obinutuzumab-chlorambucil. The fixed sequence procedure performed tested for PFS between acalabrutinib-obinutuzumab and obinutuzumab-chlorambucil first and if the *P* value was ≤α1 for interim analysis, the procedure proceeded to test PFS between acalabrutinib monotherapy and obinutuzumab-chlorambucil and so on. Because this study did not achieve statistical significance for IRC-assessed ORR between acalabrutinib monotherapy and obinutuzumab-chlorambucil, all *P* values for subsequent tests, if displayed, are considered descriptive in nature. ORR was analysed using the Cochran–Mantel–Haenszel test adjusting for randomisation stratification factors. Exploratory prespecified subgroup analyses of efficacy outcomes by baseline and disease characteristics were also performed for the primary (acalabrutinib-obinutuzumab vs obinutuzumab-chlorambucil) and secondary (acalabrutinib monotherapy vs obinutuzumab-chlorambucil) comparisons. Comparisons between acalabrutinib-obinutuzumab and acalabrutinib monotherapy were *post hoc* analyses.

Supplementary Figures

Figure S1. Progression-Free Survival, and Overall Response Rate, as Assessed by Investigators.

Panel A shows Kaplan–Meier estimates of progression-free survival (primary endpoint) and Panel B shows best overall response rates. [a]One patient (1%) had PR-L, one (1%) patient had PD, and four patients (2%) were not evaluable. [b]Five patients (3%) had PR-L, three patients (2%) had PD, six patients (3%) were not evaluable, and one patient (1%) had an unknown response. [c]Three patients (2%) had PD, and 12 patients (7%) were not evaluable. Acala, acalabrutinib; Chlb, chlorambucil; CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; NE, not evaluable; nPR, nodular partial remission; NR, not reached; Obin, obinutuzumab; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

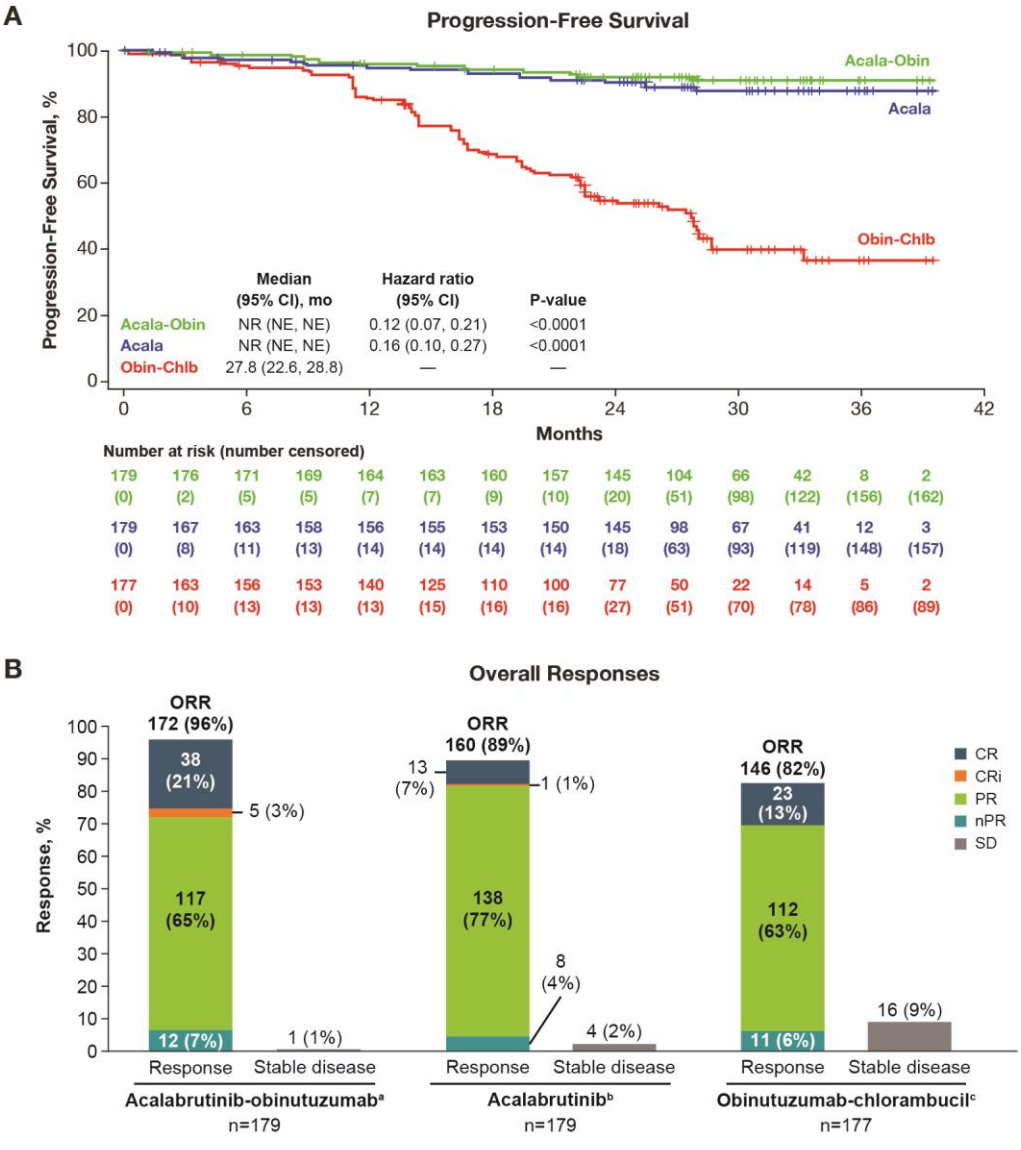


Figure S2. Minimal Residual Disease in Patients With Complete Response or Complete Response With Incomplete Bone Marrow Recovery by Investigator Assessment.

CR/CRi, complete response/CR with incomplete marrow recovery; MRD, minimal residual disease. Data presented is from peripheral blood or bone marrow.

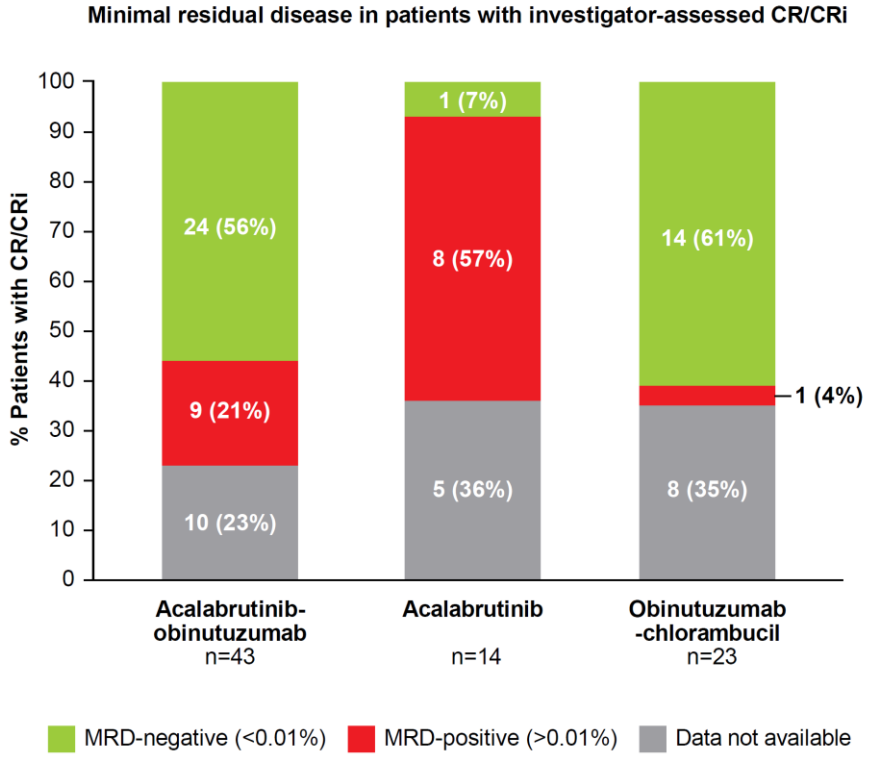


Figure S3. Sustained Haematologic Improvement.

Left panel shows improvement in neutrophil count in patients with baseline neutropenia, middle panel shows haemoglobin in patients with baseline anaemia, and right panel shows platelet count in patients with baseline thrombocytopenia.

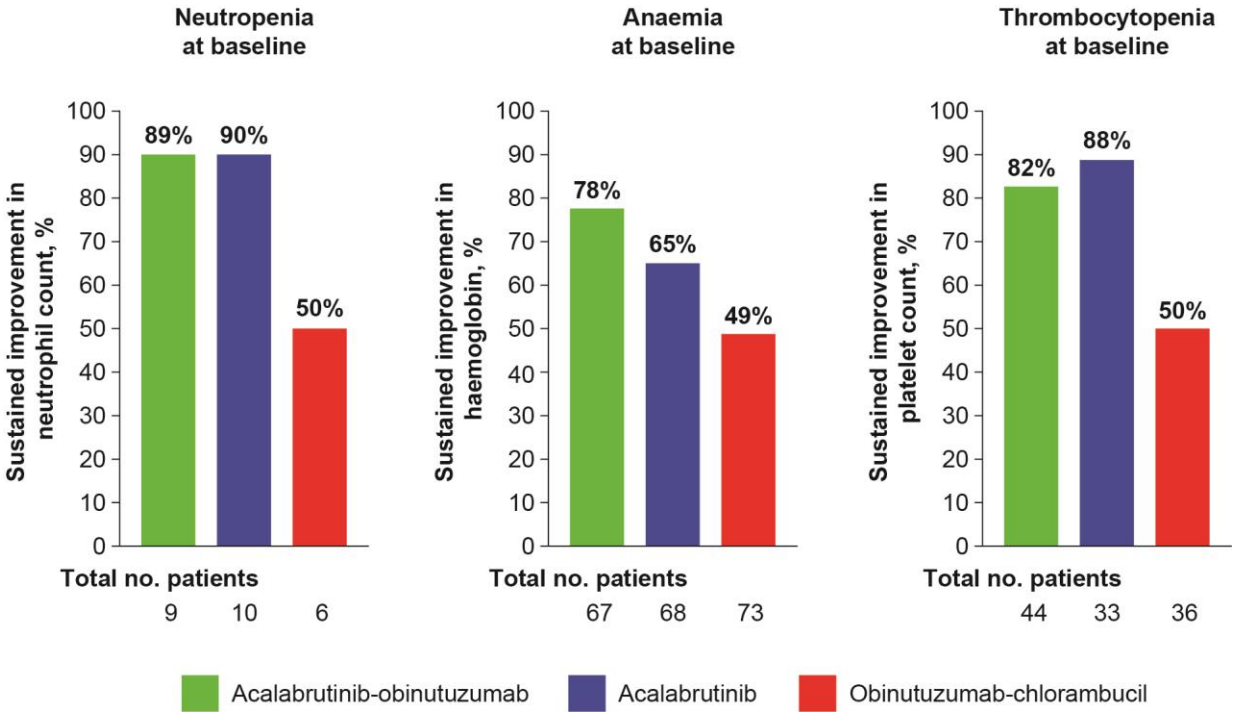


Figure S4. Kaplan–Meier Assessments of Time to Next Treatment.

Acala, acalabrutinib; Chlb,chlorambucil; Obin, obinutuzumab.

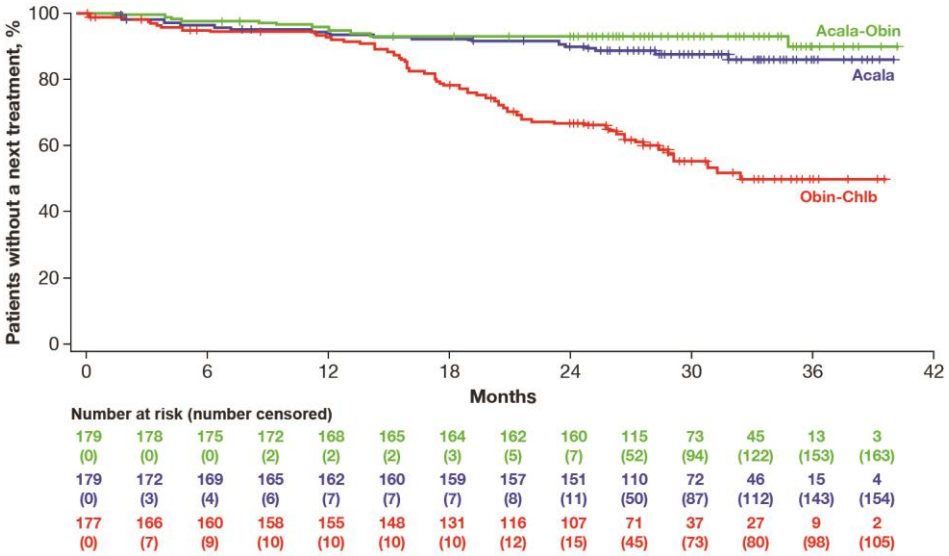
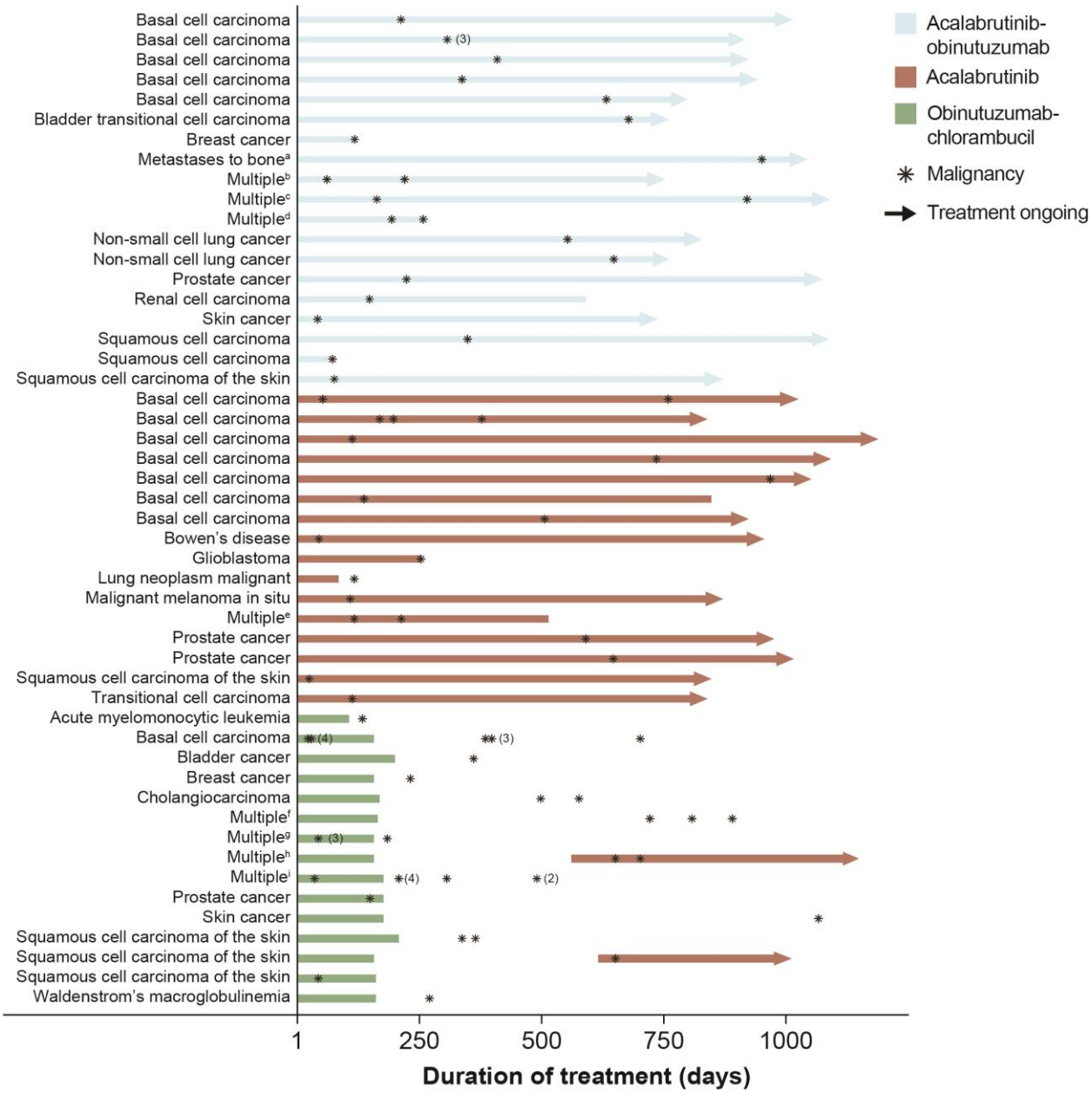


Figure S5. Second Primary Malignancies.

Shown are treatment-emergent and non-treatment–emergent second primary malignancies from the time of randomisation or crossover. The median time to onset of second primary malignancies was 226 days (interquartile range, 117–553) in the acalabrutinib-obinutuzumab arm, 127 days (interquartile range, 110–547) in the acalabrutinib monotherapy arm, and 271 days (interquartile range 42–648) in the obinutuzumab-chlorambucil arm. Multiple occurrences of malignancies on the same day are denoted with a number next to the asterisk. [a]Metastases were from prostate cancer. [b]Basal cell carcinoma (day 62) and squamous cell carcinoma of the skin (day 219). [c]Basal cell carcinoma (day 163) and skin cancer (day 920). [d]Basosquamous carcinoma (day 194) and stage IV gastric cancer (day 257). [e]Basal cell carcinoma (day 118) and squamous cell carcinoma of the skin (day 211). [f]Transitional cell carcinoma (day 721), basal cell carcinoma (day 806), and metastatic transitional cell carcinoma (day 889). [g]Basal cell carcinoma (day 41), Bowen's disease (day 41), squamous cell carcinoma of the skin (day 41), and lung adenocarcinoma (day 183). [h]Nodular melanoma (day 648), and malignant melanoma (day 702). [i]Bowen's disease (day 33 and four events on day 206), basal cell carcinoma (day 303), malignant melanoma (day 489), and squamous cell carcinoma of the skin (day 489).


Basal cell carcinoma
Basal cell carcinoma
Basal cell carcinoma
Basal cell carcinoma
Basal cell carcinoma
Bladder transitional cell carcinoma
Breast cancer
Metastases to bone[a]
Multiple[b]
Multiple[c]
Multiple[d]
Non-small cell lung cancer
Non-small cell lung cancer
Prostate cancer
Renal cell carcinoma
Skin cancer
Squamous cell carcinoma
Squamous cell carcinoma
Squamous cell carcinoma of the skin
Basal cell carcinoma
Basal cell carcinoma
Basal cell carcinoma
Basal cell carcinoma
Basal cell carcinoma
Basal cell carcinoma
Basal cell carcinoma
Bowen's disease
Glioblastoma
Lung neoplasm malignant
Malignant melanoma in situ
Multiple[e]
Prostate cancer
Prostate cancer
Squamous cell carcinoma of the skin
Transitional cell carcinoma
Acute myelomonocytic leukemia
Basal cell carcinoma
Bladder cancer
Breast cancer
Cholangiocarcinoma
Multiple[f]
Multiple[g]
Multiple[h]
Multiple[i]
Prostate cancer
Skin cancer
Squamous cell carcinoma of the skin
Squamous cell carcinoma of the skin
Squamous cell carcinoma of the skin
Waldenstrom's macroglobulinemia
(3)
(4)
(3)
(3)
(4)
(2)
1
250
500
750
1000
Duration of treatment (days)
Acalabrutinib-obinutuzumab
Acalabrutinib
Obinutuzumab-chlorambucil
Malignancy
Treatment ongoing

Supplementary Tables

Table S1. Patient Baseline Characteristics and Demographics.

	Acalabrutinib-Obinutuzumab (n = 179)	Acalabrutinib (n = 179)	Obinutuzumab-Chlorambucil (n = 177)
Ethnicity—no. (%)			
Hispanic or Latino	2 (1)	11 (6)	11 (6)
Not Hispanic or Latino	169 (94)	156 (87)	156 (88)
Not Reported	8 (5)	12 (7)	10 (6)
Region—no. (%)			
North America	64 (36)	70 (39)	61 (35)
South America	5 (3)	8 (5)	7 (4)
Western Europe	49 (27)	42 (24)	52 (29)
Central and Eastern Europe	48 (27)	46 (26)	40 (23)
Australia and New Zealand	13 (7)	13 (7)	17 (10)
High-risk features—no. (%)			
Del(17)(p13·1), *TP53* mutation, del(11)(q22·3), or unmutated IGHV	117 (65)	129 (72)	129 (73)
Del(17)(p13·1), *TP53* mutation, or del(11)(q22·3)	53 (30)	52 (29)	55 (31)
Del(17)(p13·1) and/or *TP53* mutation	25 (14)	23 (13)	25 (14)
Del(17)(p13·1) and *TP53* mutation	13 (7)	12 (7)	12 (7)
β_2-Microglobulin >3·5 mg/L—no. (%)	132 (74)	140 (78)	132 (75)
Median absolute neutrophil count (range)—$\times 10^9$ cells/L	6·2 (0·6–120·5)	5·5 (0·0–102·1)	5·9 (0·3–95·6)
Median platelet count (range) —$\times 10^9$ cells/L	140·0 (25·0–480·0)	140·5 (16·0–370·0)	149·0 (25·0–554·0)
Median haemoglobin—g/dL	11·8 (5·5–15·7)	11·5 (6·5–17·2)	11·6 (7·1–15·5)

Del, deletion; IGHV, immunoglobulin heavy-chain variable; *TP53*, tumour protein 53.

Table S2. Treatment Exposure and Dose Modifications by Study Drug.

Variable	Acalabrutinib-Obinutuzumab (n = 179)		Acalabrutinib (n = 179)	Obinutuzumab-Chlorambucil (n = 177)	
	Acalabrutinib	Obinutuzumab		Obinutuzumab	Chlorambucil
Treatment status—no. (%)					
Did not receive study treatment	0	0	1 (0·6)	8 (4·5)	8 (4·5)
Ongoing	146 (82)[a]	0	142 (79)	1 (1)[b]	0
Completed	–	163 (91)	–	152 (86)	137 (77)
Discontinued	33 (18)	179 (100)	36 (20)	168 (95)	169 (95)
Duration of treatment—mo					
Median	27·7	5·5	27·7	5·6	5·5
Interquartile range	25·0–32·8	5·5–5·6	24·8–33·0	5·5–5·9	5·5–5·7
Relative dose intensity—%					
Median	98·3	100	99·2	100	95·2
Interquartile range	95·8–99·7	100·0–100·0	96·5–99·9	100·0–100·0	76·0–100·0
Patients with dose withholding[c]—no. (%)	82 (46·1)	19 (10·7)	55 (30·7)	22 (13·0)	40 (23·7)
Adverse event	60 (33·7)	18 (10·1)	28 (15·6)	21 (12·4)	37 (21·9)
Patient error	17 (9·6)	0	13 (7·3)	0	0
Investigator decision	3 (1·7)	2 (1·1)	0	0	5 (3·0)
Procedure	26 (14·6)	0	21 (11·7)	0	0
Other[d]	0	1 (0·6)	0	1 (0·6)	2 (1·2)
Patients with dose reduction—no. (%)	35 (19·7)	–	24 (13·4)	–	52 (30·8)
Adverse event	14 (7·9)	–	5 (2·8)	–	48 (28·4)
Patient error	18 (10·1)	–	13 (7·3)	–	0
Investigator decision	4 (2·2)	–	5 (2·8)	–	6 (3·6)
Procedure	0	–	0	–	0
Other[e]	2 (1·1)	–	2 (1·1)	–	2 (1·2)
Unknown	8 (4·5)	–	3 (1·7)	–	1 (0·6)

[a]Includes patients with ongoing acalabrutinib treatment regardless of completion of obinutuzumab.
[b]A data error at the time of interim analysis showed that 1 patient was still on obinutuzumab treatment.
[c]Treatment with acalabrutinib was held up to 28 days for any unmanageable, potentially study drug-related toxicity that is grade ≥3 in severity; treatment with obinutuzumab or chlorambucil was held up to 4 weeks to allow recovery of haematologic toxicities to grade ≤2 or nonhaematologic toxicities to grade 1 or baseline level.
[d]Other reasons included treatment was stopped (n = 1), pharmacy error (n = 1), grade 4 thrombocytopenia (n = 1), and discontinued (n = 1).
[e]Other reasons included site error (n = 3), and grade 3 neutropenia (n = 1).

Table S3. MRD in Patients With CR/CRi by Investigator Assessment.

Patients With CR/CRi by Investigator Assessment[a]— No. (%)	Acalabrutinib-Obinutuzumab (n = 43)	Acalabrutinib (n = 14)	Obinutuzumab-Chlorambucil (n = 23)
MRD assessments			
Flow cytometry[b]			
Peripheral blood			
Patients evaluable	31 (72)	9 (64)	15 (65)
MRD-negative	21 (49)	1 (7)	14 (61)
Bone marrow			
Patients evaluable	18 (42)	7 (50)	8 (35)
MRD-negative	11 (26)	0	5 (22)
Peripheral blood or bone marrow			
Patients evaluable	33 (77)	9 (64)	15 (65)
MRD-negative	24 (56)	1 (7)	14 (61)

CR, complete response; CRi, CR with incomplete marrow recovery; MRD, minimal residual disease.
[a]First available MRD data point presented after first investigator-assessed CR/CRi.

Table S4. Subsequent Therapies.

	Acalabrutinib-Obinutuzumab (n = 179)	Acalabrutinib (n =179)	Obinutuzumab-Chlorambucil (n = 177)
Patients who received ≥1 subsequent therapy—no. (%)	5 (2·8)	11 (6·1)	10 (5·6)[c]
Subsequent therapy—no. (%)			
Bendamustine	1 (0·6)	2 (1·1)	3 (1·7)
Anti-CD20 monoclonal antibodies	4 (2·2)	5 (2·8)	5 (2·8)
Ibrutinib	0	1 (0·6)	6 (3·4)
Venetoclax	0	2 (1·1)	0
Cyclosporine	0	1 (0·6)	0
RCHOP[a]	0	4 (2·2)	0
FCR	0	1 (0·6)	0
CVP	1 (0·6)	1 (0·6)	0
Steroids	0	1 (0·6)	1 (0·6)
Obinutuzumab and chlorambucil	0	2 (1·1)	0
PI3K	1 (0·6)	1 (0·6)	0
Other[b]	0	3 (1·7)	0

CVP, cyclophosphamide/vincristine sulfate/prednisone; FCR, fludarabine/cyclophosphamide/rituximab; PI3K, phosphoinositide-3-kinase; RCHOP, rituximab/cyclophosphamide/hydroxyaunomycine/oncovin/prednisone.

[a]In patients with Richter's transformation

[b]Other includes methotrexate (n = 1), radiotherapy (n = 1), and vindesine (n = 1).

[c]An additional 45 patients in the obinutuzumab-chlorambucil arm crossed over to acalabrutinib monotherapy.

Table S5. AEs in ≥10% of Patients in Any Treatment Arm During the First Six Months.

AE—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)			Acalabrutinib (n = 179)			Obinutuzumab-Chlorambucil (n = 169)		
	Any Grade	Grade 1–2	Grade ≥3	Any Grade	Grade 1–2	Grade ≥3	Any Grade	Grade 1–2	Grade ≥3
Patients with ≥1 AE	163 (91·6)	74 (41·6)	89 (50·0)	162 (90·5)	112 (62·6)	50 (27·9)	167 (98·8)	50 (29·6)	117 (69·2)
Headache	65 (36·5)	64 (36·0)	1 (0·6)	61 (34·1)	60 (33·5)	1 (0·6)	20 (11·8)	20 (11·8)	0
Diarrhoea	52 (29·2)	46 (25·8)	6 (3·4)	45 (25·1)	45 (25·1)	0	36 (21·3)	33 (19·5)	3 (1·8)
Neutropenia	44 (24·7)	4 (2·2)	40 (22·5)	12 (6·7)	0	12 (6·7)	76 (45·0)	6 (3·6)	70 (41·4)
Fatigue	42 (23·6)	40 (22·5)	2 (1·1)	25 (14·0)	24 (13·4)	1 (0·6)	29 (17·2)	28 (16·6)	1 (0·6)
Contusion	36 (20·2)	36 (20·2)	0	23 (12·8)	23 (12·8)	0	6 (3·6)	6 (3·6)	0
Nausea	31 (17·4)	31 (17·4)	0	29 (16·2)	29 (16·2)	0	53 (31·4)	53 (31·4)	0
Dizziness	26 (14·6)	26 (14·6)	0	13 (7·3)	13 (7·3)	0	10 (5·9)	10 (5·9)	0
Infusion-related reaction	24 (13·5)	20 (11·2)	4 (2·2)	0	0	0	67 (39·6)	58 (34·3)	9 (5·3)
Cough	22 (12·4)	22 (12·4)	0	20 (11·2)	19 (10·6)	1 (0·6)	15 (8·9)	15 (8·9)	0
Thrombocytopenia	21 (11·8)	6 (3·4)	15 (8·4)	8 (4·5)	5 (2·8)	3 (1·7)	24 (14·2)	4 (2·4)	20 (11·8)
Arthralgia	20 (11·2)	20 (11·2)	0	17 (9·5)	16 (8·9)	1 (0·6)	8 (4·7)	6 (3·6)	2 (1·2)
Pyrexia	18 (10·1)	18 (10·1)	0	7 (3·9)	6 (3·4)	1 (0·6)	34 (20·1)	33 (19·5)	1 (0·6)
Constipation	17 (9·6)	17 (9·6)	0	11 (6·1)	11 (6·1)	0	17 (10·1)	16 (9·5)	1 (0·6)
Anaemia	16 (9·0)	8 (4·5)	8 (4·5)	20 (11·2)	9 (5·0)	11 (6·1)	20 (11·8)	8 (4·7)	12 (7·1)
Chills	16 (9·0)	16 (9·0)	0	5 (2·8)	5 (2·8)	0	14 (8·3)	13 (7·7)	1 (0·6)
Upper respiratory tract infection	14 (7·9)	14 (7·9)	0	19 (10·6)	19 (10·6)	0	14 (8·3)	13 (7·7)	1 (0·6)
Vomiting	14 (7·9)	13 (7·3)	1 (0·6)	16 (8·9)	15 (8·4)	1 (0·6)	19 (11·2)	18 (10·7)	1 (0·6)
Back pain	13 (7·3)	13 (7·3)	0	19 (10·6)	17 (9·5)	2 (1·1)	14 (8·3)	13 (7·7)	1 (0·6)
Rash	13 (7·3)	12 (6·7)	1 (0·6)	18 (10·1)	17 (9·5)	1 (0·6)	7 (4·1)	7 (4·1)	0

Shown are AEs irrespective of whether the event was considered related or unrelated to treatment by the investigators.
AE, adverse event.

Table S6. SAEs Occurring in ≥2 Patients in Any Treatment Group.

SAE—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)		Acalabrutinib (n = 179)		Obinutuzumab-Chlorambucil (n = 169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
SAE—no. (%)						
Pneumonia	12 (6·7)	8 (4·5)	5 (2·8)	4 (2·2)	3 (1·8)	3 (1·8)
Infusion-related reaction	4 (2·2)	3 (1·7)	0	0	2 (1·2)	2 (1·2)
Anaemia	3 (1·7)	3 (1·7)	4 (2·2)	4 (2·2)	0	0
Febrile neutropenia	3 (1·7)	3 (1·7)	2 (1·1)	2 (1·1)	7 (4·1)	7 (4·1)
Urosepsis	3 (1·7)	3 (1·7)	0	0	0	0
Acute kidney injury	2 (1·1)	2 (1·1)	0	0	1 (0·6)	1 (0·6)
Basal cell carcinoma	2 (1·1)	1 (0·6)	1 (0·6)	0	0	0
Cellulitis	2 (1·1)	2 (1·1)	2 (1·1)	2 (1·1)	0	0
Chronic obstructive pulmonary disease	2 (1·1)	1 (0·6)	0	0	0	0
Fall	2 (1·1)	2 (1·1)	2 (1·1)	2 (1·1)	1 (0·6)	1 (0·6)
Herpes zoster	2 (1·1)	2 (1·1)	0	0	0	0
Lower respiratory tract infection	2 (1·1)	2 (1·1)	0	0	0	0
Rhinovirus infection	2 (1·1)	0	0	0	0	0
Sepsis	2 (1·1)	2 (1·1)	0	0	2 (1·2)	2 (1·2)
Squamous cell carcinoma	2 (1·1)	1 (0·6)	0	0	0	0
Urinary tract infection	2 (1·1)	1 (0·6)	3 (1·7)	3 (1·7)	0	0
Acute myocardial infarction	1 (0·6)	1 (0·6)	3 (1·7)	3 (1·7)	1 (0·6)	0
Asthenia	1 (0·6)	1 (0·6)	0	0	2 (1·2)	1 (0·6)
Pyrexia	1 (0·6)	0	1 (0·6)	0	2 (1·2)	0
Respiratory tract infection	1 (0·6)	1 (0·6)	2 (1·1)	2 (1·1)	1 (0·6)	1 (0·6)
Tumour lysis syndrome	1 (0·6)	1 (0·6)	0	0	8 (4·7)	8 (4·7)
Autoimmune haemolytic anaemia	0	0	2 (1·1)	2 (1·1)	0	0
Cardiac failure	0	0	2 (1·1)	2 (1·1)	0	0
Dyspnoea	0	0	3 (1·7)	3 (1·7)	1 (0·6)	1 (0·6)
Hypoxia	0	0	0	0	2 (1·2)	1 (0·6)
Pleural effusion	0	0	0	0	2 (1·2)	0

SAE, serious adverse event.

Table S7. AEs of Any Grade Leading to Treatment Discontinuation.

AE Leading to Discontinuation—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)		Acalabrutinib (n = 179)	Obinutuzumab-Chlorambucil (n = 169)	
	Acalabrutinib	Obinutuzumab		Obinutuzumab	Chlorambucil
Any AE	19 (10·7)	11 (6·2)	17 (9·5)	10 (5·9)	24 (14)
Specific AEs	–	–	–	–	–
Abdominal distension	1 (0·6)	–	–	–	–
Acute kidney injury	1 (0·6)	–	–	–	–
Acute myelomonocytic leukaemia	–	–	–	–	1 (0·6)
Acute myocardial infarction	–	–	1 (0·6)	–	–
Anaphylactic reaction	–	–	–	1 (0·6)	–
Bacteraemia	–	–	–	–	1 (0·6)
Brain injury	–	–	1 (0·6)	–	–
Brain neoplasm	–	–	1 (0·6)	–	–
Bronchopulmonary aspergillosis	–	–	1 (0·6)	–	–
Cardiac failure	–	–	1 (0·6)	–	–
Cardiac tamponade	–	–	1 (0·6)	–	–
Delirium	–	–	1 (0·6)	–	–
Disseminated cryptococcosis	–	–	1 (0·6)	–	–
Dizziness	1 (0·6)	–	–	–	–
Dyspnoea	–	–	–	1 (0·6)	1 (0·6)
Encephalitis	1 (0·6)	–	–	–	–
Fatigue	1 (0·6)	–	1 (0·6)	–	–
Febrile neutropenia	1 (0·6)	–	–	–	–
Gastrointestinal haemorrhage	1 (0·6)	1 (0·6)	–	–	–
Glioblastoma	–	–	1 (0·6)	–	–
Haemophagocytic lymphohistiocytosis	–	–	1 (0·6)	–	–
Hepatitis B reactivation	2 (1·1)	1 (0·6)	–	–	–
Infusion-related reaction	–	2 (1·1)	–	2 (1·2)	–
Ischemic stroke	1 (0·6)	–	–	–	–
Lung disorder	–	–	1 (0·6)	–	–
Muscle spasms	–	–	–	–	1 (0·6)
Musculoskeletal pain	–	–	–	1 (0·6)	1 (0·6)

Myocardial infarction	1 (0·6)	1 (0·6)	–	–	–
Myositis	–	–	1 (0·6)	–	–
Neck mass[a]	1 (0·6)	1 (0·6)	–	–	–
Neutropenia	–	2 (1·1)	–	3 (1·8)	11 (6·5)
Neutrophil count decreased	–	–	–	1 (0·6)	1 (0·6)
Odynophagia	–	–	1 (0·6)	–	–
Pericardial effusion	1 (0·6)	–	–	–	–
Platelet count decreased	–	–	–	–	1 (0·6)
Pneumonia bacterial	–	–	1 (0·6)	–	–
Progressive multifocal leukoencephalopathy	1 (0·6)	–	–	–	–
Pyrexia	1 (0·6)	–	–	–	–
Rash	1 (0·6)	–	–	–	–
Rash maculopapular		–	–	–	1 (0·6)
Sepsis	2 (1·1)	1 (0·6)	–	–	1 (0·6)
Squamous cell carcinoma	1 (0·6)	1 (0·6)	–	–	–
Thrombocytopenia	–	1 (0·6)	1 (0·6)	–	2 (1·2)
Transient ischemic attack	1 (0·6)	–		–	–
Tumour ulceration	–	–	1 (0·6)	–	–
Upper respiratory tract infection	–	–	–	1 (0·6)	2 (1·2)
Visual impairment	1 (0·6)	–	–	–	–
Weight increased	1 (0·6)	–	–	–	–

AE, adverse event.

[a]Left parotid squamous cell carcinoma.

Table S8. Events of Clinical Interest.

Events—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)		Acalabrutinib (n = 179)		Obinutuzumab-Chlorambucil (n = 169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	25 (14·0)	8 (4·5)	25 (14·0)	9 (5·0)	13 (7·7)	3 (1·8)
Atrial fibrillation	6 (3·4)	1 (0·6)	7 (3·9)	0	1 (0·6)	0
Ventricular tachyarrhythmias	0	0	0	0	0	0
Bleeding	76 (42·7)	3 (1·7)	70 (39·1)	3 (1·7)	20 (11·8)	0
Hypertension	13 (7·3)	5 (2·8)	8 (4·5)	4 (2·2)	6 (3·6)	5 (3·0)
Infections	123 (69·1)	37 (20·8)	117 (65·4)	25 (14·0)	74 (43·8)	14 (8·3)
Tumour lysis syndrome	3 (1·7)	2 (1·1)	0	0	15 (8·9)	13 (7·7)

Table S9. Summary of Cardiac Events.

Events—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)		Acalabrutinib (n = 179)		Obinutuzumab-Chlorambucil (n = 169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	25 (14·0)	8 (4·5)	25 (14·0)	9 (5·0)	13 (7·7)	3 (1·8)
Atrial fibrillation	6 (3·4)	1 (0·6)	7 (3·9)	0	1 (0·6)	0
Atrial fibrillation	5 (2·8)	1 (0·6)	6 (3·4)	0	1 (0·6)	0
Atrial flutter	1 (0·6)	0	1 (0·6)	0	0	0
Other cardiac events	21 (11·8)	7 (3·9)	23 (12·8)	9 (5·0)	13 (7·7)	3 (1·8)
Angina pectoris	5 (2·8)	1 (0·6)	4 (2·2)	0	1 (0·6)	0
Palpitations	3 (1·7)	0	3 (1·7)	0	1 (0·6)	0
Tachycardia	3 (1·7)	0	1 (0·6)	0	3 (1·8)	0
Myocardial ischemia	2 (1·1)	1 (0·6)	1 (0·6)	0	0	0
Acute coronary syndrome	1 (0·6)	1 (0·6)	0	0	0	0
Acute myocardial infarction	1 (0·6)	1 (0·6)	3 (1·7)	3 (1·7)	1 (0·6)	0
Angina unstable	1 (0·6)	1 (0·6)	0	0	0	0
Atrioventricular block complete	1 (0·6)	1 (0·6)	0	0	0	0
Cardiac disorder	1 (0·6)	0	0	0	0	0
Cardiac failure	1 (0·6)	0	2 (1·1)	2 (1·1)	0	0
Cardiac failure chronic	1 (0·6)	0	0	0	1 (0·6)	1 (0·6)
Cardiomegaly	1 (0·6)	0	0	0	0	0
Hypertensive heart disease	1 (0·6)	0	0	0	0	0
Left ventricular failure	1 (0·6)	0	0	0	0	0
Myocardial infarction	1 (0·6)	1 (0·6)	1 (0·6)	1 (0·6)	0	0
Pericardial effusion	1 (0·6)	1 (0·6)	0	0	0	0
Pericarditis	1 (0·6)	1 (0·6)	0	0	1 (0·6)	0
Sinus tachycardia	1 (0·6)	0	0	0	0	0
Supraventricular tachycardia	1 (0·6)	0	1 (0·6)	0	0	0
Ventricular extrasystoles	1 (0·6)	0	1 (0·6)	0	0	0
Aortic valve disease	0	0	1 (0·6)	1 (0·6)	0	0
Arrhythmia	0	0	1 (0·6)	0	1 (0·6)	0
Arrhythmia supraventricular	0	0	0	0	1 (0·6)	0
Arteriosclerosis coronary artery	0	0	1 (0·6)	0	0	0
Bradycardia	0	0	1 (0·6)	0	2 (1·2)	1 (0·6)

Bundle branch block right	0	0	0	0	1 (0·6)	0
Cardiac arrest	0	0	0	0	1 (0·6)	1 (0·6)
Cardiac failure congestive	0	0	1 (0·6)	1 (0·6)	0	0
Cardiac tamponade	0	0	1 (0·6)	1 (0·6)	0	0
Cardiac ventricular thrombosis	0	0	0	0	1 (0·6)	0
Extrasystoles	0	0	1 (0·6)	0	0	0
Pericardial cyst	0	0	1 (0·6)	0	0	0
Pericarditis constrictive	0	0	1 (0·6)	1 (0·6)	0	0
Tricuspid valve incompetence	0	0	1 (0·6)	0	0	0

Table S10. Summary of Major Bleeding Events.

	Acalabrutinib-Obinutuzumab (n = 178)		Acalabrutinib (n = 179)		Obinutuzumab-Chlorambucil (n = 169)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any major bleeding[a]—no. (%)	5 (2·8)	3 (1·7)	3 (1·7)	3 (1·7)	2 (1·2)	0
Gastric ulcer haemorrhage	1 (0·6)	1 (0·6)	0	0	0	0
Gastrointestinal haemorrhage	1 (0·6)	1 (0·6)	0	0	0	0
Haematemesis	1 (0·6)	1 (0·6)	0	0	0	0
Post procedural haemorrhage	1 (0·6)	0	0	0	0	0
Subdural haemorrhage	1 (0·6)	0	0	0	1 (0·6)[b]	0
Haemarthrosis	0	0	1 (0·6)	1 (0·6)	0	0
Haemoptysis	0	0	0	0	1 (0·6)	0
Postprocedural haematoma	0	0	1 (0·6)	1 (0·6)	0	0
Retinal haemorrhage	0	0	1 (0·6)	1 (0·6)	0	0

[a]Defined as any serious or grade ≥3 haemorrhagic event, or any grade haemorrhagic event in the central nervous system.

[b]Patient had a grade 5 subarachnoid haemorrhage >30 days after the last dose.

Table S11. Summary of Grade ≥3 Infections.

Type of Infection—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)	Acalabrutinib (n = 179)	Obinutuzumab-Chlorambucil (n = 169)
Any grade ≥3 infection	37 (20·8)	25 (14·0)	14 (8·3)
Pneumonia, upper respiratory, and respiratory			
Upper respiratory tract infection	4 (2·2)	0	1 (0·6)
Rhinovirus	0	0	0
Bronchitis	0	0	0
Pneumonia	10 (5·6)	4 (2·2)	3 (1·8)
Influenza	1 (0·6)	0	0
Lower respiratory tract infection	3 (1·7)	0	0
Respiratory tract infection	1 (0·6)	2 (1·1)	1 (0·6)
Lung infection	0	1 (0·6)	0
Pneumonia streptococcal	1 (0·6)	1 (0·6)	0
Pneumonia bacterial	0	1 (0·6)	0
Respiratory syncytial virus infection	1 (0·6)	0	0
Fungal infections			
Aspergillus infection	0	1 (0·6)	0
Bronchopulmonary aspergillosis	0	1 (0·6)	0
Candida infection	0	0	1 (0·6)
Disseminated cryptococcosis	0	1 (0·6)	0
Fungal infection	0	1 (0·6)	0
Sinusitis fungal	0	0	1 (0·6)
Sepsis			
Klebsiella sepsis	0	1 (0·6)	0
Septic shock	0	1 (0·6)	0
Bacteraemia	0	0	1 (0·6)
Bacterial sepsis	1 (0·6)	0	1 (0·6)
Neutropenic sepsis	1 (0·6)	0	0
Escherichia sepsis	1 (0·6)	0	0
Pseudomonal sepsis	1 (0·6)	0	0
Sepsis	3 (1·7)	0	2 (1·2)
Urosepsis	3 (1·7)	0	1 (0·6)
Gastrointestinal			
Gastroenteritis	0	1 (0·6)	1 (0·6)
Clostridium difficile infection	1 (0·6)	0	0
Diverticulitis	0	0	1 (0·6)
Peritonitis bacterial	1 (0·6)	0	0
Kidney and bladder			
Urinary tract infection	1 (0·6)	3 (1·7)	0
Cystitis	1 (0·6)	0	0
Kidney infection	0	1 (0·6)	0
Pyelonephritis	0	1 (0·6)	0
Ear, eye, and mouth			
Otitis externa	0	1 (0·6)	0
Vestibular neuronitis	0	1 (0·6)	0

	Conjunctivitis viral	1 (0·6)	0	0
	Dacryocystitis	0	0	1 (0·6)
	Otitis media chronic	1 (0·6)	0	0
Other				
	Cellulitis	2 (1·1)	3 (1·7)	1 (0·6)
	Herpes zoster	3 (1·7)	0	0
	Epstein-Barr virus infection	0	1 (0·6)	0
	Tooth abscess	0	1 (0·6)	0
	Viral infection	1 (0·6)	0	0
	Bursitis infective	0	1 (0·6)	0
	Infection	0	1 (0·6)	0
	Encephalitis	1 (0·6)	0	0
	Progressive multifocal leukoencephalopathy	1 (0·6)	0	0
	Vascular access site infection	1 (0·6)	0	0
	Wound infection	1 (0·6)	0	0

Table S12. Summary of Deaths.

Event—No. (%)	Acalabrutinib-Obinutuzumab (n = 178)	Acalabrutinib (n = 179)	Obinutuzumab-Chlorambucil (n = 169)
Death	8 (5)	12 (7)	15 (9)
Primary cause of death			
CLL disease progression	2 (1)	1 (1)	1 (1)
Richter's transformation	0	1 (1)	1 (1)
Other[a]	0	3 (2)	0
Unknown[b]	2 (1)	1 (1)	2 (1)
Adverse event	4 (2)[c]	6 (3)[d]	11 (7)
Within 30 days of last dose			
Acute myelomonocytic leukaemia	0	0	1 (1)
Bacterial sepsis	0	0	1 (1)
Bronchopulmonary aspergillosis	0	1 (1)	0
Cardiac arrest	0	0	1 (1)
Febrile neutropenia	0	1 (1)	0
Gastric cancer stage IV	1 (1)	0	0
Goitre	0	1 (1)[d]	0
Lung adenocarcinoma	0	0	1 (1)
Myositis	0	1 (1)	0
Parkinson's disease	0	1 (1)	0
Pneumonia	1 (1)	0	0
Metastases to bone	1 (1)[c]	0	0
Sepsis	2 (1)	0	0
Septic shock	0	1 (1)	0
Beyond 30 days after last dose			
Acute myocardial infarction	0	0	1 (1)[e]
Brain neoplasm	0	0	1 (1)
Cardiac failure	0	1 (1)	0
Cholangiocarcinoma	0	0	1 (1)
Duodenal ulcer haemorrhage	0	0	1 (1)
Pneumonia pneumococcal	0	0	1 (1)
Progressive multifocal leukoencephalopathy	0	0	1 (1)
Sepsis	0	0	1 (1)
Subarachnoid haemorrhage	0	0	1 (1)

CLL, chronic lymphocytic leukaemia.

[a]Other reasons for death included cerebrovascular accident (n = 1), glioblastoma (n = 1), and respiratory insufficiency (n = 1).

[b]Four patients died of unknown causes, and one patient died at home with a possible cause of cardiac arrest.

[c]Bone metastases were from recurrence of prostate cancer. Death occurred after data cutoff.

[d]Complications from surgery for a multinodular goitre led to tracheostomy, cardiopulmonary arrest, shock, and respiratory failure, and the cause of death was reported as "other."

[e]Patient died after crossover to the acalabrutinib monotherapy arm.

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