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Author Contributions
RI provided substantial contributions to the design of the study, and all authors contributed to data collection and interpretation. Statistical analyses were performed by MHW and DJ. KAR developed the first draft of the manuscript, for which all authors reviewed and provided important intellectual contributions; all authors approved the final version for publication. All authors had full access to the data and vouch for the completeness and accuracy of the data.

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Data-Sharing Statement

Acerta Pharma, a member of the AstraZeneca Group, is committed to data transparency and will consider data-sharing requests on a case-by-case basis. Any requests for de-identified patient data can be submitted to Acerta Pharma 3 months post-publication and ending 5 years following article publication with the intent-to-achieve aims of the original proposal. In addition, Acerta Pharma will provide the study protocol, statistical analysis plan, and informed consent form, as well as post results on clinicaltrials.gov, as required.

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DJ has received research funding from Acerta Pharma and Pharmacyclics.

RI is an employee of Acerta Pharma, has equity ownership in AstraZeneca, and has patents for acalabrutinib.

MMF is an employee and stock shareholder of AstraZeneca.

CQ, RKR, and MHW are employees of Acerta Pharma.

TJK has received research funding from AbbVie and Hoffman-LaRoche.

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Acerta Pharma provided the study drug. The clinical study was designed by Raquel Izumi and Ahmed Hamdy (both of Acerta Pharma) in collaboration with John C Byrd (The Ohio State University Comprehensive Cancer Center). Data collection and interpretation were done by the authors, investigators, and study sponsor. Statistical analyses were performed by Min Hui Wang and Daniel Jones, who also oversaw mutation testing. Kerry A Rogers developed the first draft of the manuscript, which all authors reviewed and provided important intellectual contributions; all authors approved the final version for publication. All authors had full access to the data and vouch for the completeness and accuracy of the data. The study sponsor funded medical writing assistance under the direction of the authors.
Abstract

B-cell receptor signalling inhibition by targeting Bruton tyrosine kinase (BTK) is effective in treating chronic lymphocytic leukemia (CLL). The BTK inhibitor ibrutinib may be intolerable for some patients. Acalabrutinib is a more selective BTK inhibitor that may be better tolerated by patients who are intolerant to ibrutinib. A phase 2 study of acalabrutinib was conducted in patients with relapsed/refractory CLL who were ibrutinib-intolerant and had continued disease activity. Intolerance was defined as having discontinued ibrutinib due to persistent grade 3/4 adverse events (AEs) or persistent/recurrent grade 2 AEs despite dose modification/interruption. Patients received oral acalabrutinib 100 mg twice daily until disease progression or intolerance. Sixty patients were treated. Overall response rate to acalabrutinib was 73% and three patients (5%) achieved complete remission. At median follow-up of 35 months, the median progression-free and overall survival were not reached; 24-month estimates were 72% and 81%, respectively. The most frequent AEs with acalabrutinib were diarrhea (53%), headache (42%), contusion (40%), dizziness (33%), upper respiratory tract infection (33%), and cough (30%). Most common reasons for acalabrutinib discontinuation were progressive disease (23%) and AEs (17%). Most patients with baseline samples (49/52; 94%) and all with on-treatment samples (3/3; 100%) had no detectable BTK and/or PLCG2 mutations. Acalabrutinib is effective and tolerable in most patients with relapsed/refractory CLL who are intolerant of ibrutinib. Acalabrutinib may be useful for patients who may benefit from BTK inhibitor therapy but are ibrutinib intolerant.
Introduction

Targeted Bruton tyrosine kinase (BTK) inhibitors are highly effective for the treatment of chronic lymphocytic leukemia (CLL). These agents block signalling by inhibiting BTK, a key kinase in the B-cell receptor signalling pathway. The efficacy of BTK inhibition in CLL was demonstrated by ibrutinib, the first BTK inhibitor approved for treatment of CLL.

Ibrutinib is not always tolerated by patients with CLL. In a large, retrospective study of ibrutinib-treated CLL, toxicity was the most common reason for treatment discontinuation, accounting for 63.1% of discontinuations in the front-line setting and 50.2% of discontinuations among patients with relapsed/refractory CLL. The most common toxicities leading to discontinuation were arthralgia (41.6%), atrial fibrillation (25.0%), and rash (16.7%) in the front-line setting and atrial fibrillation (12.3%), infection (10.7%), and pneumonitis (9.9%) in relapsed/refractory CLL. These toxicities may be due to BTK inhibition or off-target effects of ibrutinib on other kinases. Some toxicities can be managed with supportive care and some require ibrutinib discontinuation, especially if more severe. For example, current guidelines recommend careful monitoring in the case of atrial fibrillation, and potential use of non-warfarin anticoagulation, though consideration should be given to alternate therapies if the atrial fibrillation is uncontrolled. Rates of ibrutinib discontinuation due to adverse events (AEs) during extended follow-up in a clinical trial population are approximately 20%. In CLL patients treated outside of clinical trials at academic and community sites, discontinuation rates due to AEs were as high as 50%, which may better capture tolerability in a general practice setting. This means that patients who cannot take ibrutinib due to toxicity may not be able to realise the potential benefit
of BTK inhibition on their disease, thereby reducing therapeutic options available for CLL
treatment.

Acalabrutinib is an oral covalent inhibitor of BTK approved for treatment of patients with
CLL.\textsuperscript{10} Acalabrutinib binds to BTK at the cysteine 481 residue, which is the same binding site
for ibrutinib.\textsuperscript{11} Compared with ibrutinib, acalabrutinib is a more selective BTK inhibitor.\textsuperscript{12,13}
Fewer off-target effects potentially provide an improved safety profile compared with
ibrutinib.\textsuperscript{5,14} A low frequency of AEs of interest, specifically atrial fibrillation and severe
bleeding, has been reported with acalabrutinib.\textsuperscript{11} In a phase 3 trial in patients with
relapsed/refractory CLL (ASCEND), atrial fibrillation events occurred in eight of 154 patients
(5\%) receiving acalabrutinib monotherapy, seven of whom had a history of ongoing
hypertension. Bleeding and infections (any grade), also events of clinical interest, occurred in 40
(26\%) and 87 (57\%) patients, respectively. In that trial, 11\% of patients receiving acalabrutinib
monotherapy discontinued due to AEs.\textsuperscript{15}

Given the improved selectivity of acalabrutinib relative to ibrutinib, we hypothesized that
acalabrutinib would be effective and tolerable in patients with CLL who discontinued ibrutinib
due to AEs. This hypothesis is supported by a previous study in which acalabrutinib
demonstrated an overall response rate (ORR; partial response [PR] or better) of 61\% in patients
with relapsed/refractory CLL who were previously unable to continue ibrutinib treatment
because of AEs.\textsuperscript{16} However, the previous study did not objectively define events classified as
ibrutinib-intolerant and analyzed a cohort of patients added to the open-label, phase 2, dose-
expansion portion of the phase 1/2 study.\textsuperscript{16} Therefore, we conducted a dedicated phase 2 study of
acalabrutinib in patients with relapsed/refractory CLL who were intolerant to ibrutinib treatment as defined by specific criteria, including event grade, persistence, and recurrence.

Methods

Study design and participants

This multicentre, single-agent, phase 2 study (clinicaltrials.gov identifier NCT02717611; ACE-CL-208) enrolled adults with CLL who had intolerance to ibrutinib and for whom purine analogue-based therapy was not an option. Ibrutinib intolerance was defined as A) having discontinued ibrutinib treatment due to grade 3 or 4 AEs that persisted despite optimal supportive care or B) having experienced grade 2 AEs related to ibrutinib treatment that persisted for at least 2 weeks or recurred at least twice, whether the dose of ibrutinib was reduced or interrupted, despite optimal supportive care. Patients must have had at least one prior ibrutinib treatment for CLL and not be appropriate for treatment or retreatment with purine analogue-based therapy (eg, fludarabine). After discontinuing ibrutinib, patients must have met the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria for progressive disease (PD) as a sign of continued disease activity and not have received other CLL therapy.

To meet eligibility, patients’ most recent systemic anticancer therapy was required to be ibrutinib; those who received an alternative anticancer therapy after ibrutinib discontinuation were excluded. Patients were excluded if they had an ongoing grade 3 or 4 AE attributed to ibrutinib. Also excluded were patients with evidence of active Richter transformation or any evidence of PD on ibrutinib; who had previously received a BCL-2 inhibitor; who had significant cardiovascular disease, such as uncontrolled or symptomatic untreated arrhythmias, congestive
heart failure, or myocardial infarction within 6 months of screening, or any class 3 or 4 cardiac
disease as defined by New York Heart Association Functional Classification or QTc >480 msec
at screening (except for controlled, asymptomatic atrial fibrillation during screening, which was
allowed); or were taking anticoagulation with warfarin or equivalent vitamin K antagonists
within 7 days of the first study drug dose (alternative anticoagulation therapy permitted). Patients
taking other anticoagulants were included.

All patients signed written informed consent before study enrolment. The study was approved by
the institutional review board/independent ethics committee of each participating institution and
conducted in accordance with the principles of the Declaration of Helsinki and International
Conference on Harmonisation Guidelines for Good Clinical Practice.

**Procedures**

Eligible patients were treated with acalabrutinib 100 mg orally twice a day on days 1 to 28 of 28-
day cycles until disease progression, as long as treatment was tolerated. Response was assessed
according to modified iwCLL 2008 criteria, with the first assessment occurring 3 months after
starting acalabrutinib. AEs were collected and graded according to Common Terminology
Criteria for Adverse Events version 4.03.

An exploratory analysis of molecular resistance to BTK inhibitors was performed retrospectively
using deep sequencing of *BTK* and *PLCG2* in patients with pretreatment samples (details in
Supplementary Methods).
Outcomes

The primary endpoint was investigator-assessed ORR according to iwCLL 2008 criteria. ORR was defined as the proportion of patients achieving a best overall response (BOR) of either CR, complete remission with incomplete bone marrow recovery (CRi), nodular partial remission (nPR), or PR at or before initiation of subsequent anticancer therapy. Secondary efficacy endpoints were duration of response (DOR; defined as the duration from time from initial response [CR, CRi, nPR, or PR] until documented PD), progression-free survival (PFS; defined as time from first dose to first documented PD or death), time to next treatment (TTNT; defined as time from first dose to institution of subsequent anticancer therapy for CLL or death), and overall survival (OS; defined as time from first dose to death). Safety was assessed via laboratory assessments and adverse events by frequency, and causal attribution of AEs.

Details of the statistical analysis can be found in the Supplemental Methods.

Results

Patients, treatment, and disposition

In total, 60 patients were enrolled between March 23, 2016, and August 2, 2017. Median age was 69.5 years (range: 43-88 years) and median time from diagnosis to first dose of study drug was 103.2 months (range: 10.3-307.9 months). There were 17 (28%) patients with del(17p) and 31 (52%) with Rai stage III or IV disease. Baseline patient and disease characteristics are in Table 1.

Median number of prior therapies was two (range: 1-10). All patients had taken ibrutinib previously, with 50 (83%) receiving ibrutinib monotherapy and 10 (17%) receiving ibrutinib in
combination with another agent (Online Supplementary Table S1). Forty-three (72%) patients had been exposed to an anti-CD20 monoclonal antibody and 36 (60%) had received prior systemic chemotherapy (Online Supplementary Table S1).

Median duration of ibrutinib treatment was 5.7 months (range: <1-55.5). Out of 60 total patients, 15 (25%) received ibrutinib for <2 months. Of these 15 patients, only two discontinued acalabrutinib (due to squamous cell carcinoma of the lung and endometrial cancer [n=1 each]). As ibrutinib treatment occurred before study entry, treatment response to ibrutinib was not fully captured for the entire patient population (however, safety was captured). The most common AEs leading to ibrutinib discontinuation were atrial fibrillation (23%), diarrhea (12%), arthralgia (10%), and rash (10%) (Online Supplementary Table S2). After ibrutinib discontinuation, median time from taking the last dose of ibrutinib to starting acalabrutinib was 7.5 months (range: 0.8-31.1).

At a median follow-up of 34.6 months (range: 1.1-47.4), 29 (48%) patients remained on acalabrutinib; 45 patients (75%) had at least 1 year of treatment. Median acalabrutinib exposure was 32 months (range: 0.3-47.4). Of the 31 patients who discontinued acalabrutinib, the most common reason for discontinuation was disease progression (n=14, 23%) followed by AEs (n=10, 17%); other reasons were patient or physician decision (n=3 and n=3, respectively), and comorbid anorexia (n=1) (Figure 1). For the 14 patients who discontinued due to disease progression, 11 patients had an ECOG performance status of 1, 7 had Rai stage III-IV disease, and median age was 72 years. Four of these 15 patients had del(17p), 4 had del(11q) and 12 had unmutated IGHV.
Efficacy

The ORR to acalabrutinib treatment was 73% (n=44/60; 95% CI: 60-84%) (Figure 2). The ORR in patients with del(17p) was similar (71% [n=12/17]; 95% CI: 44-90%). The ORR including PR with lymphocytosis (PRL) patients was 78% (n=47/60; 95% CI: 66-88%), comprising three (5%) patients with a complete remission (CR), two (3%) with CRi, 39 (65%) with a PR, and three (5%) with a PRL. Of the 13 patients not achieving a response, four (7%) had stable disease (SD), one (2%) had progressive disease (PD); six (10%) patients were not evaluable for response due to discontinuing treatment before the first response assessment at 3 months, and two (3%) were not available for response assessment. For the six patients who were not evaluable, three discontinued due to AEs and three discontinued due to patient or physician decision (one and two patients, respectively) (Figure 1). Median DOR was not reached; estimated 24-month DOR was 81% (n=44, 95% CI: 66-90%) and 78% (n=47, 95% CI: 63-88%) when patients with PRL were included, and estimated 36-month DOR was 65% (95% CI: 46-79%) and 64% (95% CI: 45-77%) when patients with PRL were included (Figure 3; Panels A and B, respectively).

Median PFS was not reached; estimated 24-month and 36-month PFS were 72% (95% CI: 58-82%) and 58% (95% CI: 42-71%), respectively (Figure 4). Median OS was not reached. Estimated 24-month and 36-month OS were 81% (95% CI: 68-89%) and 78% (95% CI: 65-87%), respectively (Figure 4). Sixteen (27%) patients started a subsequent treatment for CLL, and median TTNT was 44 months (95% CI: 27-not estimable) (Online Supplementary Figure S1).
Efficacy (ORR, DOR, PFS) of acalabrutinib was also assessed by duration of previous ibrutinib treatment and by duration of treatment hold (time from ibrutinib discontinuation to start of acalabrutinib). These assessments were exploratory, and no statistical analyses were performed. The ORR was 64% (n=20/31; 95% CI: 45-81%) in patients who received prior ibrutinib treatment for ≥6 months and 83% (n=24/29; 95% CI: 64-94%) in those who received <6 months. DOR and PFS on acalabrutinib in patients who received prior ibrutinib treatment of ≥6 months trended towards being shorter (no statistical analyses were performed) (Online Supplementary Figure S2 A, C, and E). Duration of treatment hold did not appear to affect ORR, DOR, or PFS during acalabrutinib treatment (Online Supplementary Figure S2 B, D, and F).

Safety
The most frequent AEs of any grade occurring with acalabrutinib were diarrhea (n=32, 53%), headache (n=25, 42%), contusion (n=24, 40%), dizziness (n=20, 33%), upper respiratory tract infection (n=20, 33%), and cough (n=18, 30%) (Table 2 and Online Supplementary Table S3). The most frequent grade ≥3 AEs were pneumonia (n=9, 15%), neutropenia (n=7, 12%), lymphocyte count increased (including lymphocytosis and lymphocyte count increased; n=8, 13%), and thrombocytopenia (including platelet count decreased and thrombocytopenia; n=5, 8%) (Table 2). Serious adverse events (SAEs) of any grade were experienced by 31 (52%) patients. Treatment-related SAEs of any grade that were deemed related to acalabrutinib by the investigator were experienced by 10 (17%) patients. There were 5 dose reductions in 4 patients; one patient had 2 dose reductions due to vaginal yeast infection. All 4 patients had successful AE management with dose reduction and continued on study. However, one of these patients later discontinued acalabrutinib due to AEs.
Ten (16.7%) patients had an AE leading to acalabrutinib discontinuation, including pneumonia (n=2, one grade 3 event and one death), diarrhea (n=1, grade 2), headache (n=1, grade 1), endometrial cancer (n=1, grade 3), stomatitis (n=1, grade 2), subdural hematoma (n=1, grade 2), cerebrovascular accident (n=1, grade 2), transaminases increase (n=1, grade 4), and squamous cell carcinoma of lung (n=1, grade 2). Among these events, the investigator considered diarrhea, headache, stomatitis, and subdural hematoma, to be related to acalabrutinib treatment. Only one patient discontinued acalabrutinib due to the same AE (diarrhea) that resulted in prior ibrutinib discontinuation; grade 3 or 4 diarrhea led to ibrutinib discontinuation and grade 2 diarrhea led to acalabrutinib discontinuation.

To better understand acalabrutinib tolerability following ibrutinib discontinuation, the incidence of ibrutinib intolerance AEs was examined during acalabrutinib treatment. Among 60 enrolled patients, 27 ibrutinib-intolerance AEs occurred among 24 (40%) patients during acalabrutinib treatment. Of these, most events (67% [n=18/27 events in 18 patients]) were lower grade on acalabrutinib compared with prior ibrutinib treatment; 30% (n=8/27 events in six patients) were of an unchanged grade (Online Supplementary Table S4). Only one event (4% [n=1/27] events in 1 patient) was of a higher grade during acalabrutinib treatment compared with prior ibrutinib treatment. The event was increased liver function test (grade 2 on ibrutinib and grade 3 during acalabrutinib treatment). Two patients treated with acalabrutinib had recurrence of the same ibrutinib-intolerance AE of atrial fibrillation, both of whom had atrial fibrillation events with a lower severity grade on acalabrutinib treatment (grade 3/2 and grade 2/1 during ibrutinib/acalabrutinib treatment). One of the two patients had a medical history of atrial
fibrillation and hypertension and discontinued acalabrutinib treatment due to pneumonia that started the same day as atrial fibrillation. The second patient had a medical history of atrial fibrillation; at the time of data analysis, treatment with acalabrutinib was ongoing in the presence of ongoing atrial fibrillation (dose was not changed and no other action was taken).

Among 60 enrolled patients, during ibrutinib treatment, 41 patients had the following ibrutinib intolerance AEs: arthralgia, atrial fibrillation, bleeding, diarrhea, or rash (Table 3 and Online Supplementary Table S5). Of the 74 ibrutinib-intolerance AEs in the 60 enrolled patients, 42 (57%) did not recur during acalabrutinib treatment. Eighteen (30%) patients treated with acalabrutinib had recurrence of the same ibrutinib-intolerance AE. The most common ibrutinib intolerance AEs recurring with acalabrutinib were diarrhea (n=5) and bleeding events (n=5), all of which had the same or lower severity grade with acalabrutinib treatment. Among the five patients with recurrent bleeding events, only one patient had the same type of bleeding event reported with ibrutinib and acalabrutinib (recurrent hematuria); the other four patients had bleeding events with ibrutinib that were different from those reported on acalabrutinib (Online Supplementary Table S4).

Eleven deaths occurred during the study; causes included pneumonia (n=3), Richter transformation (n=2), bronchopulmonary aspergillosis, ventricular fibrillation, squamous cell carcinoma of lung, multiple organ dysfunction syndrome, disease progression, and death (n=1 each). Of the seven deaths due to AEs, two occurred while the patient was receiving study treatment (1 each, pneumonia and subdural hematoma), and the remainder occurred following acalabrutinib discontinuation. Of note, an 85-year-old male patient with multiple cardiac
morbidities died of ventricular fibrillation 27 days after acalabrutinib was discontinued due to stomatitis. The other event of interest which resulted in death occurred in a 76-year-old female patient with a medical history of herpes zoster who died of bronchopulmonary aspergillus 7 days after discontinuation of acalabrutinib due to pneumonia.

Analysis of mutations associated with resistance to BTK inhibitors

To determine if mutations associated with resistance to BTK inhibitors were present before acalabrutinib treatment, purified B-cell samples at the start of acalabrutinib treatment were tested for mutations in \(BTK\) and \(PLCG2\). Mutations in \(BTK\) and \(PLCG2\) have been associated with clinical disease progression during ibrutinib treatment and with resistance to acalabrutinib because both bind to BTK at the same site.\(^{18-22}\)

Samples were available for 55/60 (92%) patients. Pretreatment samples were available for 52 patients; three patients had later time points tested (cycle 1, day 28, n=1; cycle 6, day 28, n=2). Three (5%) were found to have a mutation in at least one gene. Two patients had multiple mutations associated with ibrutinib resistance in \(BTK\) or \(BTK\) and \(PLCG2\), while one patient had a \(PLCG2\) mutation of uncertain significance (Online Supplementary Table S6).\(^{18,19,23,24}\) All mutations were found in pretreatment samples.

Of the two patients with mutations associated with \(BTK\) and/or \(PLCG2\), one was electively taken off acalabrutinib after just over 2 months of exposure due to presence of these mutations and was not evaluable for response to acalabrutinib. The other patient received acalabrutinib and had PD after 15 months, having achieved a best response of SD during acalabrutinib treatment and at
CLL progression, the major BTK C481S clone identified at baseline expanded from 30.7% to 90.2% allele fraction (Online Supplementary Tables S6 and S7).

The patient with the D993N missense variant in *PLCG2* (which has been associated with ibrutinib resistance, but not shown to alter drug sensitivity in vitro to date), achieved a CR with acalabrutinib at treatment cycle 18 and had remained on therapy for 25 months at the time of data cutoff.

At the time of this analysis, five patients relapsed on acalabrutinib and peripheral blood mononuclear cell samples were collected at treatment termination. Three of five patients were confirmed to have no *BTK* or *PLCG2* mutations; one of these patients experienced a best overall response of PRL on acalabrutinib treatment (DOR, 11.53 months), the second patient had a best overall response of PR (DOR, 15.67 months), and a third patient had SD (Online Supplementary Table S7). The fourth patient who achieved a PR (DOR, 14.29 months) with low levels of BTK C481S and T474I mutations as well as a predominant *PLCG2* 1140N mutation at treatment termination, none of which were detectable at baseline. The fifth patient, described above, had a pre-existing clone with *BTK* C481S expand during treatment that was detectable at progression (Online Supplementary Table S7).

**Discussion**

This phase 2 study of acalabrutinib in patients who were ibrutinib intolerant demonstrated that acalabrutinib is effective and tolerable in a large proportion of this population. The ORR of 73% with median PFS that was not reached demonstrates durable disease control in this population of
relapsed/refractory CLL patients. A similar response rate was reported with ibrutinib in the front-line setting in a population of elderly patients with similar median age (71 years) and follow-up duration (22.1 months). In this study, 10% of patients were not evaluable for response because they discontinued treatment before the first response assessment. As responses to BTK inhibitors tend to improve with longer treatment duration, it is possible that with additional follow-up, the overall response rate will increase and additional CRs will be observed. It is not unexpected that acalabrutinib is effective in these patients, as the prior ibrutinib exposure was short for most patients (median, <6 months) and most were assumed to have a response to BTK inhibition (based on disease progressing after discontinuing ibrutinib due to AEs).

Acalabrutinib safety in this study is perhaps more helpful than the observed response rate in understanding the impact of this agent. At median follow-up of 35 months, 48% of patients remained on acalabrutinib. The most common reason for discontinuation was disease progression (23%) and the rate of acalabrutinib discontinuation due to AEs was 17%. This rate of discontinuation due to AEs is low considering that 100% of patients had discontinued ibrutinib due to AEs, suggesting that acalabrutinib is tolerable in a large proportion of patients who are intolerant of ibrutinib.

Comparing the full spectrum of AEs between ibrutinib and acalabrutinib in this study is difficult because the ibrutinib experience was not captured prospectively. The study’s intention was not to compare toxicity between two drugs, but rather to determine acalabrutinib tolerability in patients who discontinued ibrutinib due to toxicity. When reviewing events of arthralgia, atrial fibrillation, bleeding, diarrhea, and rash leading to ibrutinib intolerance, 24/41 patients
experienced recurrence during acalabrutinib treatment, and recurrence was at a similar (25%) or lower (75%) severity grade in all patients. Most AEs (64%) limiting ibrutinib treatment were not experienced during acalabrutinib treatment. Additionally, all AEs causing ibrutinib intolerance and recurring with acalabrutinib treatment (27 events in total) were reviewed to determine differences in maximal severity grade experienced. Of these AEs, only one occurred at a higher grade, while 18 occurred at a lower grade with acalabrutinib, demonstrating that the severity of intolerance AEs during acalabrutinib treatment may be decreased. This reduction in rate includes hemorrhage events, which have previously been observed as a BTKi class effect, but in this study were observed to occur at a lower grade with acalabrutinib than when patients were receiving ibrutinib. Only one patient discontinued acalabrutinib for the same AE (diarrhea) that was also the cause reported for ibrutinib discontinuation.

Clinical strategies for patients with ibrutinib intolerance, such as switching to alternative kinase inhibitors or combining different therapeutic agents, have been evaluated. Real-world data have suggested that ibrutinib-intolerant patients could be treated successfully with an alternative kinase inhibitor. Early phase clinical trial data have also demonstrated the efficacy and safety of an alternative kinase inhibitor, umbralisib, in ibrutinib-intolerant patients. There is a potential clinical benefit in switching patients with ibrutinib intolerance to another BTKi so that venetoclax remains a future treatment option. However, depending on AE type, severity, and potential for harm of recurrence, switching to another drug class such as venetoclax should be considered. The safety profile and efficacy of different therapeutic agents and combination strategies was evaluated in head-to-head trials. One such trial is ASCEND, a phase III study of acalabrutinib monotherapy versus rituximab plus idelalisib (I-R) or rituximab plus bendamustine.
(B-R), which demonstrated improved PFS for acalabrutinib compared with either rituximab combination; there were fewer SAEs and fewer AEs leading to discontinuation with acalabrutinib monotherapy compared with I-R.29 In that study, fatal AEs occurred in 6/154 (4%), 5/118 (4%), and 2/35 (6%) patients receiving acalabrutinib monotherapy, I-R, and B-R, respectively.

This study was not designed to test whether acalabrutinib is effective in patients with therapeutic resistance to ibrutinib and the analysis of mutations associated with resistance to ibrutinib was exploratory. Among patients with evaluable samples at baseline (92%), most (95%) had no mutation in \textit{BTK}/\textit{PLCG2} by deep sequencing of sorted B cells. One patient harboring a \textit{PLCG2} D993N mutation at baseline achieved a response to acalabrutinib. This is an uncommon \textit{PLCG2} potentially gain-of-function mutation and may not confer resistance to acalabrutinib or ibrutinib. However, acalabrutinib may not be effective in patients who develop progression on ibrutinib with typical resistance mutations.

Of the five patients with matched baseline and progression samples, only one acquired mutations in \textit{BTK} and \textit{PLCG2} after a best overall response of PR and DOR of 14.29 months. One patient had low levels of the \textit{BTK} C481S and the T4741 gatekeeper resistance mutation at baseline as well as the \textit{PLCG2} D1140N C2 domain mutation detected at progression. The \textit{PLCG2} D1140N mutation was predominant (indicating many CLL cells in the sample were without a \textit{BTK} mutation), whereas with ibrutinib, treatment resistance mutations in this \textit{PLCG2} domain were more commonly secondary mutations after \textit{BTK} C481X development.19
This study was designed to determine if acalabrutinib is effective in patients intolerant to ibrutinib or unable to continue ibrutinib treatment due to AEs. However, it is acknowledged that the study had a few limitations, the most significant being that the ibrutinib experience was not prospectively or rigorously captured. This not only means that a significant portion of these patients’ responses to ibrutinib were unknown, but also that every AE on ibrutinib was not captured in detail. In addition, subjective reporting of AEs by patients prior to enrollment who sought to have access to study drug could have influenced the patient enrollment. Therefore, it is possible that some AEs occurring at a low grade with ibrutinib may have occurred at a greater severity with acalabrutinib. To partially overcome this limitation, we applied two different approaches to assessing the occurrence of known AEs with ibrutinib during acalabrutinib treatment. However, only a prospective or randomized study could fully capture differences in toxicities between the two drugs. The other important limitation is in understanding differential CLL resistance to acalabrutinib. PD was the most common reason for acalabrutinib discontinuation, with a relatively high rate of 23%. The direct comparison of acalabrutinib with ibrutinib is ongoing via a phase 3 randomized non-inferiority clinical trial in patients with previously treated, high-risk CLL (NCT02477696).

In summary, the results of this study demonstrate that acalabrutinib is a safe and effective option for patients with relapsed/refractory CLL who were not able to tolerate ibrutinib. Acalabrutinib is an important therapeutic option in this population and will allow more CLL patients to benefit from BTK inhibitor treatment.
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| Characteristic                                                                 | N=60 |
|-------------------------------------------------------------------------------|------|
| Age, median (range), years                                                   | 69.5 (43-88) |
| Men, n (%)                                                                    | 38 (63) |
| ECOG PS ≤1, n (%)                                                             | 58 (97) |
| Number of prior systemic therapies, n (%)                                     |      |
| 1                                                                             | 14 (23) |
| 2                                                                             | 18 (30) |
| 3                                                                             | 11 (18) |
| ≥4                                                                            | 17 (28) |
| β₂-microglobulin >3 mg/L, n/N (%)                                            | 46/58 (79) |
| Genetic risk features, n/N (%)                                               |      |
| Unmutated IGHV                                                               | 46/58 (79) |
| del(11q)a                                                                    | 14/60 (23) |
| del(17p)a                                                                    | 17/60 (28) |
| Rai stage III-IV, n (%)                                                       | 31 (52) |
| Lymph nodes ≥5 cm, n (%)                                                      | 19 (32) |
| Laboratory values, median (range)                                            |      |
| Lymphocyte count, k/μL                                                        | 12.3 (0.9-172.4) |
| Neutrophil count, k/μL                                                        | 3.3 (0.4-20.1) |
| Hemoglobin, g/dL                                                              | 12.2 (7.5-17.3) |
| Platelet count, k/μL                                                          | 117.5 (37-350) |

*By fluorescence in situ hybridisation testing.

ECOG PS: Eastern Cooperative Oncology Group performance status; IGHV: immunoglobulin heavy chain gene.
Table 2. Adverse events occurring in ≥10% of patients (all grades) or ≥5% of patients (grade ≥3 in severity).

| Adverse event                         | All Grades | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---------------------------------------|------------|---------|---------|---------|---------|---------|
| Diarrhea                              | 32 (53)    | 18 (30) | 11 (18) | 3 (5)   | 0       | 0       |
| Headache                              | 25 (42)    | 20 (33) | 4 (7)   | 1 (2)   | 0       | 0       |
| Contusion                              | 24 (40)    | 20 (33) | 4 (7)   | 0       | 0       | 0       |
| Dizziness                              | 20 (33)    | 18 (30) | 1 (2)   | 1 (2)   | 0       | 0       |
| Upper respiratory tract infection     | 20 (33)    | 3 (5)   | 17 (28) | 0       | 0       | 0       |
| Cough                                 | 18 (30)    | 9 (15)  | 9 (15)  | 0       | 0       | 0       |
| Nausea                                | 15 (25)    | 10 (17) | 5 (8)   | 0       | 0       | 0       |
| Neutropenia\(^a\)                     | 15 (25)    | 0       | 3 (5)   | 7 (12)  | 5 (8)   | 0       |
| Arthralgia                            | 14 (23)    | 8 (13)  | 5 (8)   | 1 (2)   | 0       | 0       |
| Fatigue                               | 14 (23)    | 6 (10)  | 7 (12)  | 1 (2)   | 0       | 0       |
| Pneumonia                             | 13 (22)    | 0       | 4 (7)   | 7 (12)  | 0       | 2 (3)   |
| Pyrexia                               | 12 (20)    | 7 (12)  | 5 (8)   | 0       | 0       | 0       |
| Lymphocyte count increased\(^b\)     | 10 (17)    | 0       | 2 (3)   | 8 (13)  | 0       | 0       |
| Thrombocytopenia\(^c\)                | 10 (17)    | 3 (5)   | 2 (3)   | 3 (5)   | 2 (3)   | 0       |
| Back pain                             | 10 (17)    | 4 (7)   | 5 (8)   | 1 (2)   | 0       | 0       |
| Constipation                          | 10 (17)    | 9 (15)  | 0       | 1 (2)   | 0       | 0       |
| Dyspnea                               | 10 (17)    | 7 (12)  | 3 (5)   | 0       | 0       | 0       |
| Rash                                  | 10 (17)    | 6 (10)  | 4 (7)   | 0       | 0       | 0       |
| Sinusitis                             | 10 (17)    | 0       | 10 (17) | 0       | 0       | 0       |
| Anemia                                | 9 (15)     | 3 (5)   | 3 (5)   | 3 (5)   | 0       | 0       |
| Upper-airway cough syndrome           | 9 (15)     | 6 (10)  | 3 (5)   | 0       | 0       | 0       |
| Fall                                  | 8 (13)     | 4 (7)   | 2 (3)   | 2 (3)   | 0       | 0       |
| Hematuria                             | 8 (13)     | 5 (8)   | 2 (3)   | 1 (2)   | 0       | 0       |
| Hypertension                          | 8 (13)     | 2 (3)   | 4 (7)   | 2 (3)   | 0       | 0       |
| Night sweats                          | 8 (13)     | 4 (7)   | 4 (7)   | 0       | 0       | 0       |
| Edema peripheral                      | 8 (13)     | 6 (10)  | 2 (3)   | 0       | 0       | 0       |
| Condition                        | n  | (%) | n  | (%) | n  | (%) | n  | (%) | n  | (%) | n  | (%) |
|---------------------------------|----|-----|----|-----|----|-----|----|-----|----|-----|----|-----|
| Urinary tract infection         | 8  | (13)| 7  | (12)| 1  | (2 )| 0  |     | 0  |     | 0  |     |
| Weight increased                | 8  | (13)| 3  | (5 )| 5  | (8 )| 0  |     | 0  |     | 0  |     |
| Abdominal pain                  | 7  | (12)| 2  | (3 )| 4  | (7 )| 1  | (2 )| 0  |     | 0  |     |
| Influenza-like illness          | 7  | (12)| 4  | (7 )| 2  | (3 )| 1  | (2 )| 0  |     | 0  |     |
| Chills                          | 6  | (10)| 6  | (10)| 0  |     | 0  |     | 0  |     | 0  |     |
| Depression                      | 6  | (10)| 3  | (5 )| 3  | (5 )| 0  |     | 0  |     | 0  |     |
| Hyperhidrosis                   | 6  | (10)| 6  | (10)| 0  |     | 0  |     | 0  |     | 0  |     |
| Insomnia                        | 6  | (10)| 4  | (7 )| 2  | (3 )| 0  |     | 0  |     | 0  |     |
| Nasal congestion                | 6  | (10)| 3  | (5 )| 3  | (5 )| 0  |     | 0  |     | 0  |     |

All data presented as n (%).

*Includes events of neutropenia and neutrophil count decreased.
*Includes events of lymphocytosis and lymphocyte count increased.
*Includes events of platelet count decreased and thrombocytopenia.
Table 3. Ibrutinib-intolerance adverse events and recurrence after acalabrutinib treatment.

| Adverse event     | Number of patients with ibrutinib intolerance<sup>a</sup> | Acalabrutinib experience for same patients |
|-------------------|----------------------------------------------------------|------------------------------------------|
|                   |                                                          | Total  | Lower grade | Same grade | Higher grade |
| Atrial fibrillation | 16<sup>b</sup>                                           | 2      | 2           | 0          | 0            |
| Diarrhea          | 7                                                        | 5      | 3           | 2          | 0            |
| Rash              | 7                                                        | 3      | 3           | 0          | 0            |
| Bleeding<sup>c,d</sup> | 6                                                      | 5      | 3           | 2          | 0            |
| Arthralgia        | 7<sup>e</sup>                                            | 2      | 1           | 1          | 0            |
| Total             | 41                                                       | 24     | 18          | 6          | 1            |

<sup>a</sup>Among 60 patients meeting the study enrolment criteria, 41 patients had a medical history of one or more (43 events in total) of the following categories of ibrutinib-intolerance events: atrial fibrillation, diarrhea, rash, bleeding, or arthralgia.

<sup>b</sup>Includes patients with atrial flutter (n=2).

<sup>c</sup>Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma.

<sup>d</sup>All but 1 patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment.

<sup>e</sup>Includes one patient with arthritis.
Figure Legends

**Figure 1. Trial profile.** AE: adverse event.

**Figure 2. Response to acalabrutinib.** Patients who discontinued study treatment before evaluation for response (n=6) or who were not available for response assessment (n=2) were classified as not evaluable. CR: complete remission; Cri: CR with incomplete bone marrow recovery; ORR: overall response rate; PD: progressive disease; PR: partial remission; PRL: partial remission with lymphocytosis; SD: stable disease.

**Figure 3: Duration of response to acalabrutinib.** The median was not reached when patients with PRL were excluded (A) and when they were included (B). CI: confidence interval; DOR: duration of response; PR: partial remission; PRL: partial remission with lymphocytosis.

**Figure 4. Progression-free survival and overall survival with acalabrutinib.** The medians were not reached for PFS (A) and OS (B). CI: confidence interval; OS: overall survival; PFS: progression-free survival.
Enrolment

Assessed for eligibility (n=60)

Excluded (n=0)
- Not meeting inclusion criteria (n=0)
- Declined to participate (n=0)
- Other reasons (n=0)

No randomisation

Allocation

Allocated to intervention (n=60)
- Received allocated intervention (n=60)
- Did not receive allocated intervention (n=0)

Follow-Up

Lost to follow-up (n=0)

Discontinued intervention (n=31)
- Progression (n=14)
- Adverse events (n=10)
- Patient decision (n=3)
- Physician decision (n=2)
- Anorexia (n=1)

Analysis

Analysed (n=60)
- Efficacy-evaluable population (n=60)
- Safety-evaluable population (n=60)
- Excluded from response evaluation (n=8)
  - Not available (n=2)
  - Not evaluable (n=6)
    - Discontinued due to AEs (n=3)
    - Physician decision (n=2)
    - Patient decision (n=1)
A. Median DOR (≥PR): not reached
   24-mo DOR rate: 81.2% (95% CI: 65.9, 90.2%)
   36-mo DOR rate: 65.3% (95% CI: 45.6, 79.3%)

B. Median DOR (≥PRL): not reached
   24-mo DOR rate: 78.2% (95% CI: 63.2, 87.6%)
   36-mo DOR rate: 63.6% (95% CI: 45.1, 77.3%)
A. 

- Median PFS: not reached
- 24-mo PFS rate: 71.9% (95% CI: 57.8, 82.1%)
- 36-mo PFS rate: 58.3% (95% CI: 42.2, 71.3%)

B. 

- Median OS: not reached
- 24-mo OS rate: 81.1% (95% CI: 68.4, 89.0%)
- 36-mo OS rate: 78.3% (95% CI: 64.7, 87.2%)

Number at risk:

| Months From Initiation of Study Treatment | Number at Risk |
|------------------------------------------|----------------|
| 0                                        | 60             |
| 3                                        | 53             |
| 6                                        | 51             |
| 9                                        | 50             |
| 12                                       | 44             |
| 15                                       | 38             |
| 18                                       | 38             |
| 21                                       | 37             |
| 24                                       | 34             |
| 27                                       | 25             |
| 30                                       | 8              |
| 33                                       | 3              |
| 36                                       | 1              |
| 39                                       | 0              |
Supplement to: Phase 2 Study of Acalabrutinib in Ibrutinib-Intolerant Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia

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Supplemental Methods

Eligibility criteria

Inclusion criteria

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

1. Men and women ≥18 years of age
2. Prior diagnosis of chronic lymphocytic leukemia (CLL) that meets published diagnostic criteria\(^1\) as follows:
   a. Monoclonal B cells (either kappa or lambda light chain restricted) that are clonally co-expressing ≥1 B-cell marker (CD19, CD20, or CD23) and CD5
   b. Prolymphocytes may comprise ≤55% of blood lymphocytes
   c. No evidence of cyclin D1 rearrangement or BCL-1 overexpression
   d. Presence of \(\geq 5 \times 10^9\) B lymphocytes/L (≥5000/µL) in the peripheral blood (at any point since diagnosis)
3. Must have received ≥1 prior therapy for CLL and not be appropriate for treatment or retreatment with purine analogue–based therapy as defined by ≥1 of the following criteria:
   a. Failure to respond (stable disease or disease progression on treatment) or progression-free interval of <3 years from treatment with a purine analogue–based therapy and anti-CD20 antibody–containing chemoimmunotherapy regimen after ≥2 cycles
   b. Age ≥70 years
   c. Age ≥65 years with the presence of 1 of the following comorbidities that might
place the subject at an unacceptable risk for treatment-related toxicity with purine analogue–based therapy, provided they have received ≥1 prior treatment including ≥2 cycles of an alkylating agent–based (or purine analogue–based) anti-CD20 antibody–containing chemoimmunotherapy regimen:

i. Cumulative Illness Rating Scale–Geriatric score ≥6

ii. Creatinine clearance <70 mL/min

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

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

4. Intolerant of ibrutinib, defined as:

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

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

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

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

7. Eastern Cooperative Oncology Group performance status of ≤2
8. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 3.9.10

9. Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 2 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 3.9.10

10. Men must agree to refrain from sperm donation during the study and for 2 days after the last dose of study drug

11. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty

12. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorisation to use protected health information (in accordance with national and local patient privacy regulations)

Exclusion criteria

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

1. Ongoing grade 3 or 4 AE attributed to ibrutinib therapy. Note: Patients may be eligible for enrolment once the ibrutinib-related AE improves to grade ≤2

2. Treatment with systemic anticancer therapy for CLL is prohibited between discontinuation of ibrutinib and enrolment in this trial

3. Prior exposure to a BCL-2 inhibitor (eg, venetoclax/ABT-199)

4. Prior malignancy (other than CLL), except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease-
free for ≥2 years

5. Significant cardiovascular disease such as uncontrolled or symptomatic untreated arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec at screening. Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enrol in the study

6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass

7. Evidence of active Richter transformation or any evidence of disease progression on ibrutinib therapy or any Bruton tyrosine kinase inhibitor

8. Central nervous system involvement by CLL or related Richter transformation

9. Known history of HIV, serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection
   a. Subjects who are hepatitis B core antibody–positive and who are surface antigen–negative will need to have a negative polymerase chain reaction (PCR) result before enrolment. Those who are hepatitis B surface antigen–positive or hepatitis B PCR–positive will be excluded
   b. Subjects who are hepatitis C antibody–positive will need to have a negative PCR result before enrolment. Those who are hepatitis C PCR–positive will be excluded

10. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura
defined as declining hemoglobin or platelet count secondary to autoimmune destruction
within the screening period or requirement for high doses of steroids (>20 mg daily of
prednisone or equivalent for >2 weeks)

11. History of stroke or intracranial hemorrhage within 2 months before the first dose of
study drug

12. History of bleeding diathesis (eg, hemophilia or von Willebrand disease)

13. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before
screening

14. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had
major surgery, they must have recovered adequately from any toxicity and/or
complications from the intervention before the first dose of study drug

15. Requires treatment with a strong CYP3A inhibitor/inducer

16. Requires treatment with proton-pump inhibitors (eg, omeprazole, esomeprazole,
lansoprazole, dlexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-
pump inhibitors who switch to H2 receptor antagonists or antacids are eligible for
enrolment in this study

17. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists
(eg, phenprocoumon) within 7 days of first dose of study drug. Alternative
anticoagulation therapy is permitted

18. Absolute neutrophil count <0.75 x 10⁹/L or platelet count <50 x 10⁹/L, unless there is
bone marrow involvement

19. Total bilirubin >1.5 x upper limit of normal (ULN); or aspartate aminotransferase or
alanine aminotransferase >3.0 x ULN
20. Estimated creatinine clearance of <30 mL/min, calculated using the formula of Cockcroft and Gault ([140 – age] • mass [kg]/[72 • creatinine mg/dL] • multiply by 0.85 if female)

21. Breastfeeding or pregnant

22. Concurrent participation in another therapeutic clinical trial

**Exploratory analysis of molecular resistance to BTK inhibitors**

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

**Statistical analysis**

Data as of March 6, 2020, were included in the analysis. All safety and efficacy analyses included enrolled patients who received at least one dose of acalabrutinib. No formal tests of hypotheses were performed. Continuous variables were reported using descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized as the number and percentage of patients in a given
category; confidence intervals (CI) were provided as appropriate. For the primary endpoint, the ORR and the associated 95% exact (Clopper-Pearson) CI were reported. Time-to-event endpoints (DOR, PFS, OS, and TTNT) were analyzed using the Kaplan-Meier method; median time to event (months) was reported, and estimated event-free rates and 95% CIs were reported for selected landmarks.

References

1. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-5456.

2. Woyach JA, Ruppert AS, Guinn D, et al. BTK(C481S)-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol. 2017;35(13):1437-1443.

3. Jones D, Woyach JA, Zhao W, et al. PLCG2 C2 domain mutations co-occur with BTK and PLCG2 resistance mutations in chronic lymphocytic leukemia undergoing ibrutinib treatment. Leukemia. 2017;31(7):1645-1647.
### Table S1. Prior systemic CLL therapies.

| Prior therapy                        | N=60  |
|--------------------------------------|-------|
| Ibrutinib                            | 60 (100) |
| Monotherapy                          | 50 (83) |
| Combination therapy<sup>a</sup>      | 10 (17) |
| Anti-CD20 monoclonal antibody        |       |
| Rituximab                            | 40 (67) |
| Ofatumumab                           | 9 (15)  |
| Systemic chemotherapy                |       |
| Alkylator                            | 32 (53) |
| Bendamustine                         | 18 (30) |
| Nucleoside analog                    |       |
| Fludarabine                          | 24 (40) |
| Steroid                              | 7 (12)  |
| Alemtuzumab                          | 6 (10)  |
| Lenalidomide                         | 6 (10)  |
| Investigational drug<sup>c</sup>     | 6 (10)  |
| Idelalisib                           | 2 (3)   |

Data presented are n (%).

CLL, chronic lymphocytic leukemia.

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

<sup>b</sup>Some patients received both agents.

<sup>c</sup>Investigational drugs included: antineoplastic agents, entospletinib, gossypol acetic acid, monalizumab, spebrutinib, and ublituximab.
Table S2. Adverse events leading to ibrutinib discontinuation.

| Preferred term                                      | All treated subjects (N=60) |
|-----------------------------------------------------|-----------------------------|
|                                                     | All grades b n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) |
| Patients with ≥1 event a                          | 60 (100)               | 20 (33.3)     | 36 (60.0)     | 4 (6.7)       |
| Atrial fibrillation                                | 14 (23.3)              | 5 (8.3)       | 8 (13.3)      | 1 (1.7)       |
| Diarrhea                                           | 7 (11.7)               | 4 (6.7)       | 3 (5.0)       | 0             |
| Arthralgia                                         | 6 (10.0)               | 2 (3.3)       | 4 (6.7)       | 0             |
| Rash                                               | 6 (10.0)               | 2 (3.3)       | 4 (6.7)       | 0             |
| Asthenia                                           | 2 (3.3)                | 2 (3.3)       | 0             | 0             |
| Atrial flutter                                     | 2 (3.3)                | 0             | 2 (3.3)       | 0             |
| Fatigue                                            | 2 (3.3)                | 0             | 2 (3.3)       | 0             |
| Neutropenia                                        | 2 (3.3)                | 0             | 1 (1.7)       | 1 (1.7)       |
| Arthritis                                          | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Aspartate aminotransférase increased               | 1 (1.7)                | 0             | 1 (1.7)       | 0             |
| Cellulitis                                         | 1 (1.7)                | 0             | 1 (1.7)       | 0             |
| Cough                                              | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Dizziness                                          | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Ecchymosis                                         | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Edema                                              | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Epistaxis                                          | 1 (1.7)                | 0             | 1 (1.7)       | 0             |
| Febrile neutropenia                                | 1 (1.7)                | 0             | 0             | 1 (1.7)       |
| Gastritis                                          | 1 (1.7)                | 0             | 1 (1.7)       | 0             |
| Gastrointestinal disorder                          | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Glaucoma                                           | 1 (1.7)                | 0             | 0             | 1 (1.7)       |
| Guillain-Barré syndrome                            | 1 (1.7)                | 0             | 1 (1.7)       | 0             |
| Hematuria                                          | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Hemorrhage                                         | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Headache                                           | 1 (1.7)                | 1 (1.7)       | 0             | 0             |
| Hypersensitivity                                   | 1 (1.7)                | 0             | 1 (1.7)       | 0             |
| Hypertension                                       | 1 (1.7)                | 0             | 1 (1.7)       | 0             |
Liver function test increased | 1 (1.7) | 1 (1.7) | 0 | 0
Macular edema | 1 (1.7) | 0 | 1 (1.7) | 0
Myalgia | 1 (1.7) | 0 | 1 (1.7) | 0
Neutrophil count decreased | 1 (1.7) | 0 | 1 (1.7) | 0
Pneumonia | 1 (1.7) | 0 | 1 (1.7) | 0
Pulmonary hemorrhage | 1 (1.7) | 0 | 1 (1.7) | 0
Rash, maculopapular | 1 (1.7) | 1 (1.7) | 0 | 0
Retinal hemorrhage | 1 (1.7) | 1 (1.7) | 0 | 0
Retinal vein occlusion | 1 (1.7) | 1 (1.7) | 0 | 0
Stent-graft endoleak | 1 (1.7) | 0 | 1 (1.7) | 0
Stomatitis | 1 (1.7) | 1 (1.7) | 0 | 0
Thrombocytopenia | 1 (1.7) | 0 | 1 (1.7) | 0
Uveitis | 1 (1.7) | 0 | 1 (1.7) | 0

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

*Adverse events are not mutually exclusive; several patients experienced ≥1 adverse event.

Grade 1 adverse events were not cause for ibrutinib discontinuation and were, therefore, not captured.
Table S3. Treatment-emergent adverse events with acalabrutinib.

| Adverse event                                      | All treated subjects (N=60) | All grades n (%) | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Grade 5 n (%) |
|----------------------------------------------------|-----------------------------|------------------|---------------|---------------|---------------|---------------|---------------|
| Diarrhea                                           |                             | 32 (53.3)        | 18 (30.0)     | 11 (18.3)     | 3 (5.0)       | 0             | 0             |
| Headache                                           |                             | 25 (41.7)        | 20 (33.3)     | 4 (6.7)       | 1 (1.7)       | 0             | 0             |
| Contusion                                           |                             | 24 (40.0)        | 20 (33.3)     | 4 (6.7)       | 0             | 0             | 0             |
| Dizziness                                          |                             | 20 (33.3)        | 18 (30.0)     | 1 (1.7)       | 1 (1.7)       | 0             | 0             |
| Upper respiratory tract infection                   |                             | 20 (33.3)        | 3 (5.0)       | 17 (28.3)     | 0             | 0             | 0             |
| Cough                                              |                             | 18 (30.0)        | 9 (15.0)      | 9 (15.0)      | 0             | 0             | 0             |
| Nausea                                             |                             | 15 (25.0)        | 10 (16.7)     | 5 (8.3)       | 0             | 0             | 0             |
| Neutropenia\textsuperscript{a}                     |                             | 15 (25.0)        | 0             | 3 (5.0)       | 7 (11.7)      | 5 (8.3)       | 0             |
| Arthralgia                                          |                             | 14 (23.3)        | 8 (13.3)      | 5 (8.3)       | 1 (1.7)       | 0             | 0             |
| Fatigue                                            |                             | 14 (23.3)        | 6 (10.0)      | 7 (11.7)      | 1 (1.7)       | 0             | 0             |
| Pneumonia                                          |                             | 13 (21.7)        | 0             | 4 (6.7)       | 7 (11.7)      | 0             | 2 (3.3)       |
| Pyrexia                                            |                             | 12 (20.0)        | 7 (11.7)      | 5 (8.3)       | 0             | 0             | 0             |
| Back pain                                           |                             | 10 (16.7)        | 4 (6.7)       | 5 (8.3)       | 1 (1.7)       | 0             | 0             |
| Constipation                                        |                             | 10 (16.7)        | 9 (15.0)      | 0             | 1 (1.7)       | 0             | 0             |
| Dyspnea                                            |                             | 10 (16.7)        | 7 (11.7)      | 3 (5.0)       | 0             | 0             | 0             |
| Lymphocytosis\textsuperscript{b}                   |                             | 10 (16.7)        | 0             | 2 (3.3)       | 8 (13.3)      | 0             | 0             |
| Rash                                               |                             | 10 (16.7)        | 6 (10.0)      | 4 (6.7)       | 0             | 0             | 0             |
| Sinusitis                                           |                             | 10 (16.7)        | 0             | 10 (16.7)     | 0             | 0             | 0             |
| Thrombocytopenia\textsuperscript{c}                |                             | 10 (16.7)        | 3 (5.0)       | 2 (3.3)       | 3 (5.0)       | 2 (3.3)       | 0             |
| Anemia                                             |                             | 9 (15.0)         | 3 (5.0)       | 3 (5.0)       | 3 (5.0)       | 0             | 0             |
| Cough syndrome, upper airway                        |                             | 9 (15.0)         | 6 (10.0)      | 3 (5.0)       | 0             | 0             | 0             |
| Fall                                               |                             | 8 (13.3)         | 4 (6.7)       | 2 (3.3)       | 2 (3.3)       | 0             | 0             |
| Hematuria                                           |                             | 8 (13.3)         | 5 (8.3)       | 2 (3.3)       | 1 (1.7)       | 0             | 0             |
| Hypertension                                        |                             | 8 (13.3)         | 2 (3.3)       | 4 (6.7)       | 2 (3.3)       | 0             | 0             |
| Night sweats                                        |                             | 8 (13.3)         | 4 (6.7)       | 4 (6.7)       | 0             | 0             | 0             |
| Edema, peripheral                                   |                             | 8 (13.3)         | 6 (10.0)      | 2 (3.3)       | 0             | 0             | 0             |
| Urinary tract infection                             |                             | 8 (13.3)         | 0             | 7 (11.7)      | 1 (1.7)       | 0             | 0             |
| Condition                     | 8 (13.3) | 3 (5.0) | 5 (8.3) | 0 | 0 | 0 |
|-------------------------------|----------|---------|---------|---|---|---|
| Weight increased             | 7 (11.7) | 2 (3.3) | 4 (6.7) | 1 (1.7) | 0 | 0 |
| Abdominal pain                | 7 (11.7) | 4 (6.7) | 2 (3.3) | 1 (1.7) | 0 | 0 |
| Influenza-like illness        | 6 (10.0) | 6 (10.0) | 0 | 0 | 0 | 0 |
| Chills                        | 6 (10.0) | 6 (10.0) | 0 | 0 | 0 | 0 |
| Depression                    | 6 (10.0) | 3 (5.0) | 3 (5.0) | 0 | 0 | 0 |
| Hyperhidrosis                 | 6 (10.0) | 6 (10.0) | 0 | 0 | 0 | 0 |
| Insomnia                      | 6 (10.0) | 4 (6.7) | 2 (3.3) | 0 | 0 | 0 |
| Nasal congestion              | 6 (10.0) | 3 (5.0) | 3 (5.0) | 0 | 0 | 0 |
| Basal cell carcinoma          | 5 (8.3) | 0 | 3 (5.0) | 2 (3.3) | 0 | 0 |
| Decreased appetite            | 5 (8.3) | 2 (3.3) | 2 (3.3) | 1 (1.7) | 0 | 0 |
| Dry mouth                     | 5 (8.3) | 5 (8.3) | 0 | 0 | 0 | 0 |
| Hypoesthesia                  | 5 (8.3) | 5 (8.3) | 0 | 0 | 0 | 0 |
| Hypotension                   | 5 (8.3) | 4 (6.7) | 1 (1.7) | 0 | 0 | 0 |
| Localized edema               | 5 (8.3) | 3 (5.0) | 2 (3.3) | 0 | 0 | 0 |
| Muscle spasms                 | 5 (8.3) | 3 (5.0) | 1 (1.7) | 1 (1.7) | 0 | 0 |
| Myalgia                       | 5 (8.3) | 5 (8.3) | 0 | 0 | 0 | 0 |
| Pain in extremity             | 5 (8.3) | 4 (6.7) | 0 | 1 (1.7) | 0 | 0 |
| Petechia                      | 5 (8.3) | 4 (6.7) | 1 (1.7) | 0 | 0 | 0 |
| Pollakiuria                   | 5 (8.3) | 4 (6.7) | 1 (1.7) | 0 | 0 | 0 |
| Pruritus                      | 5 (8.3) | 5 (8.3) | 0 | 0 | 0 | 0 |
| Skin lesion                   | 5 (8.3) | 3 (5.0) | 2 (3.3) | 0 | 0 | 0 |
| Vomiting                      | 5 (8.3) | 3 (5.0) | 2 (3.3) | 0 | 0 | 0 |
| Abdominal discomfort          | 4 (6.7) | 2 (3.3) | 2 (3.3) | 0 | 0 | 0 |
| Arthritis                     | 4 (6.7) | 3 (5.0) | 1 (1.7) | 0 | 0 | 0 |
| Bronchitis                    | 4 (6.7) | 1 (1.7) | 3 (5.0) | 0 | 0 | 0 |
| Dry skin                      | 4 (6.7) | 3 (5.0) | 1 (1.7) | 0 | 0 | 0 |
| Ecchymosis                    | 4 (6.7) | 4 (6.7) | 0 | 0 | 0 | 0 |
| Epistaxis                     | 4 (6.7) | 4 (6.7) | 0 | 0 | 0 | 0 |
| Gastro-esophageal reflux disease | 4 (6.7) | 2 (3.3) | 2 (3.3) | 0 | 0 | 0 |
| Hyperkalemia                  | 4 (6.7) | 3 (5.0) | 1 (1.7) | 0 | 0 | 0 |
| Hyponatremia                  | 4 (6.7) | 0 | 1 (1.7) | 3 (5.0) | 0 | 0 |
| Condition                                      | Severity 1 | Severity 2 | Severity 3 | Severity 4 | Severity 5 | Severity 6 |
|-----------------------------------------------|------------|------------|------------|------------|------------|------------|
| Musculoskeletal pain                          | 4 (6.7)    | 1 (1.7)    | 3 (5.0)    | 0          | 0          | 0          |
| Nocturia                                       | 4 (6.7)    | 2 (3.3)    | 2 (3.3)    | 0          | 0          | 0          |
| Noncardiac chest pain                         | 4 (6.7)    | 2 (3.3)    | 2 (3.3)    | 0          | 0          | 0          |
| Rhinitis, allergic                             | 4 (6.7)    | 3 (5.0)    | 1 (1.7)    | 0          | 0          | 0          |
| Stomatitis                                     | 4 (6.7)    | 2 (3.3)    | 2 (3.3)    | 0          | 0          | 0          |
| Tinnitus                                       | 4 (6.7)    | 3 (5.0)    | 1 (1.7)    | 0          | 0          | 0          |
| Tremor                                        | 4 (6.7)    | 3 (5.0)    | 1 (1.7)    | 0          | 0          | 0          |
| Alanine aminotransferase increased             | 3 (5.0)    | 1 (1.7)    | 1 (1.7)    | 1 (1.7)    | 0          | 0          |
| Cardiac failure, congestive                    | 3 (5.0)    | 0          | 0          | 3 (5.0)    | 0          | 0          |
| Chest pain                                     | 3 (5.0)    | 1 (1.7)    | 0          | 2 (3.3)    | 0          | 0          |
| Clostridium difficile infection                | 3 (5.0)    | 0          | 3 (5.0)    | 0          | 0          | 0          |
| Hemoptysis                                     | 3 (5.0)    | 2 (3.3)    | 1 (1.7)    | 0          | 0          | 0          |
| Hypokalemia                                    | 3 (5.0)    | 1 (1.7)    | 0          | 2 (3.3)    | 0          | 0          |
| Large intestine polyp                         | 3 (5.0)    | 2 (3.3)    | 1 (1.7)    | 0          | 0          | 0          |
| Lower respiratory tract infection              | 3 (5.0)    | 0          | 2 (3.3)    | 1 (1.7)    | 0          | 0          |
| Malaise                                        | 3 (5.0)    | 2 (3.3)    | 1 (1.7)    | 0          | 0          | 0          |
| Oropharyngeal pain                             | 3 (5.0)    | 2 (3.3)    | 1 (1.7)    | 0          | 0          | 0          |
| Otitis media                                   | 3 (5.0)    | 0          | 2 (3.3)    | 1 (1.7)    | 0          | 0          |
| Pain                                           | 3 (5.0)    | 3 (5.0)    | 0          | 0          | 0          | 0          |
| Paresthesia                                    | 3 (5.0)    | 3 (5.0)    | 0          | 0          | 0          | 0          |
| Peripheral swelling                            | 3 (5.0)    | 3 (5.0)    | 0          | 0          | 0          | 0          |
| Productive cough                               | 3 (5.0)    | 3 (5.0)    | 0          | 0          | 0          | 0          |
| Purpura                                        | 3 (5.0)    | 3 (5.0)    | 0          | 0          | 0          | 0          |
| Rash, maculopapular                            | 3 (5.0)    | 2 (3.3)    | 1 (1.7)    | 0          | 0          | 0          |
| Sepsis                                         | 3 (5.0)    | 0          | 0          | 0          | 3 (5.0)    | 0          |
| Skin infection                                 | 3 (5.0)    | 1 (1.7)    | 2 (3.3)    | 0          | 0          | 0          |
| Skin laceration                                | 3 (5.0)    | 3 (5.0)    | 0          | 0          | 0          | 0          |
| Squamous cell carcinoma of skin                | 3 (5.0)    | 0          | 3 (5.0)    | 0          | 0          | 0          |
| Condition                          | Count | (5.0) | (1.7) | (3.3) | Count | (5.0) |
|-----------------------------------|-------|-------|-------|-------|-------|-------|
| Syncope                           | 3     | 0     | 0     | 3     | 0     | 0     |
| Urinary retention                 | 3     | 1     | 2     | 0     | 0     | 0     |
| Vertigo                           | 3     | 3     | 0     | 0     | 0     | 0     |
| Weight decreased                  | 3     | 0     | 3     | 0     | 0     | 0     |
| Abdominal distension              | 2     | 2     | 0     | 0     | 0     | 0     |
| Actinic keratosis                 | 2     | 0     | 2     | 0     | 0     | 0     |
| Alopecia                          | 2     | 2     | 0     | 0     | 0     | 0     |
| Anxiety                           | 2     | 1     | 1     | 0     | 0     | 0     |
| Arthropod bite                    | 2     | 1     | 1     | 0     | 0     | 0     |
| Asthenia                          | 2     | 2     | 0     | 0     | 0     | 0     |
| Atrial fibrillation               | 2     | 1     | 1     | 0     | 0     | 0     |
| Blood creatinine increased        | 2     | 1     | 1     | 0     | 0     | 0     |
| Bone pain                         | 2     | 2     | 0     | 0     | 0     | 0     |
| Bronchopulmonary aspergillosis    | 2     | 0     | 0     | 0     | 1     | 1     |
| Cardiac murmur                    | 2     | 2     | 0     | 0     | 0     | 0     |
| Cataract                          | 2     | 1     | 1     | 0     | 0     | 0     |
| Cellulitis                        | 2     | 0     | 1     | 1     | 0     | 0     |
| *Clostridium difficile* colitis   | 2     | 0     | 1     | 1     | 0     | 0     |
| Conjunctivitis                    | 2     | 0     | 2     | 0     | 0     | 0     |
| Dyspnea, exertional               | 2     | 1     | 1     | 0     | 0     | 0     |
| Dysuria                           | 2     | 1     | 1     | 0     | 0     | 0     |
| Ear discomfort                    | 2     | 2     | 0     | 0     | 0     | 0     |
| Ear pain                          | 2     | 2     | 0     | 0     | 0     | 0     |
| Edema                             | 2     | 2     | 0     | 0     | 0     | 0     |
| Folliculitis                      | 2     | 0     | 2     | 0     | 0     | 0     |
| Gait disturbance                  | 2     | 1     | 1     | 0     | 0     | 0     |
| Hemorrhoids                       | 2     | 2     | 0     | 0     | 0     | 0     |
| Herpes zoster                      | 2     | 1     | 1     | 0     | 0     | 0     |
| Hiatus hernia                     | 2     | 1     | 1     | 0     | 0     | 0     |
| Hyperkeratosis                    | 2     | 1     | 1     | 0     | 0     | 0     |
| Condition                  | Count 3.3 | Count 1.7 | Count 1.7 | Count 0 | Count 0 | Count 0 |
|----------------------------|-----------|-----------|-----------|---------|---------|---------|
| Hypersensitivity           | 2         | 1         | 1         | 0       | 0       | 0       |
| Hyperuricemia              | 2         | 2         | 0         | 0       | 0       | 0       |
| Hypogammaglobulinemia      | 2         | 0         | 2         | 0       | 0       | 0       |
| Hypomagnesemia             | 2         | 2         | 0         | 0       | 0       | 0       |
| Hypophosphatemia           | 2         | 0         | 0         | 2       | 0       | 0       |
| Influenza                  | 2         | 1         | 1         | 0       | 0       | 0       |
| Lethargy                   | 2         | 2         | 0         | 0       | 0       | 0       |
| Leukocytosis               | 2         | 0         | 0         | 2       | 0       | 0       |
| Ligament sprain            | 2         | 1         | 1         | 0       | 0       | 0       |
| Lymph node pain            | 2         | 2         | 0         | 0       | 0       | 0       |
| Lymphedema                 | 2         | 0         | 2         | 0       | 0       | 0       |
| Memory impairment          | 2         | 1         | 1         | 0       | 0       | 0       |
| Micturition urgency        | 2         | 1         | 1         | 0       | 0       | 0       |
| Migraine with aura         | 2         | 2         | 0         | 0       | 0       | 0       |
| Neck pain                  | 2         | 1         | 1         | 0       | 0       | 0       |
| Nephrolithiasis            | 2         | 1         | 0         | 1       | 0       | 0       |
| Onychoclasis               | 2         | 2         | 0         | 0       | 0       | 0       |
| Oral herpes                | 2         | 2         | 0         | 0       | 0       | 0       |
| Palpitations               | 2         | 2         | 0         | 0       | 0       | 0       |
| Pleural effusion           | 2         | 1         | 1         | 0       | 0       | 0       |
| Postprocedural hemorrhage  | 2         | 2         | 0         | 0       | 0       | 0       |
| Respiratory failure        | 2         | 0         | 0         | 2       | 0       | 0       |
| Rhinorrhea                 | 2         | 2         | 0         | 0       | 0       | 0       |
| Sinus bradycardia          | 2         | 2         | 0         | 0       | 0       | 0       |
| Sleep apnea syndrome       | 2         | 1         | 1         | 0       | 0       | 0       |
| Squamous cell carcinoma    | 2         | 0         | 2         | 0       | 0       | 0       |
| Tooth infection            | 2         | 0         | 2         | 0       | 0       | 0       |
| Transaminases increased    | 2         | 1         | 0         | 0       | 1       | 0       |
| Vitamin D deficiency       | 2         | 1         | 1         | 0       | 0       | 0       |
| Vulvovaginal mycotic       | 2         | 1         | 1         | 0       | 0       | 0       |
| Condition                                      | Category 1 | Category 2 | Category 3 | Category 4 | Category 5 | Category 6 |
|-----------------------------------------------|------------|------------|------------|------------|------------|------------|
| Abdominal pain, lower                         | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Acanthoma                                      | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Acne                                          | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Acute kidney injury                            | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Adjustment disorder with depressed mood       | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Adnexa uteri cyst                             | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Ankle fracture                                | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Anticonvulsant drug level increased           | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Aortic stenosis                               | 1 (1.7)    | 0          | 0          | 1 (1.7)    | 0          | 0          |
| Apnea                                         | 1 (1.7)    | 0          | 0          | 1 (1.7)    | 0          | 0          |
| Arachnoid cyst                                | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Arrhythmia                                    | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Ascites                                       | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Asthma                                        | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Barrett esophagus                             | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Blister                                       | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Blood blister                                 | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Blood phosphorus decreased                    | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Bone lesion                                   | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Bronchiectasis                                | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Bronchiolitis                                 | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Bronchitis, chronic                           | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Cardiomyopathy                                | 1 (1.7)    | 0          | 0          | 1 (1.7)    | 0          | 0          |
| Cardiorenal syndrome                          | 1 (1.7)    | 0          | 0          | 1 (1.7)    | 0          | 0          |
| Carpal tunnel syndrome                        | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Cerebrovascular accident                      | 1 (1.7)    | 0          | 1 (1.7)    | 0          | 0          | 0          |
| Cheilitis                                     | 1 (1.7)    | 1 (1.7)    | 0          | 0          | 0          | 0          |
| Cholangitis                                   | 1 (1.7)    | 0          | 0          | 1 (1.7)    | 0          | 0          |
| Condition                                      | Code 1 (1.7) | Code 0 | Code 0 | Code 1 (1.7) | Code 0 | Code 0 | Code 1 (1.7) | Code 0 | Code 0 |
|-----------------------------------------------|--------------|--------|--------|--------------|--------|--------|--------------|--------|--------|
| Cholelithiasis                                | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Chronic kidney disease                        | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Chronic myelomonocytic leukemia               | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Chronic obstructive pulmonary disease         | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Chronic sinusitis                             | 1 (1.7)      | 0      | 1 (1.7)| 0            | 0      | 0      | 0            | 0      | 0      |
| Cold sweat                                    | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Colitis                                       | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Confusional state                             | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Conjunctival hemorrhage                       | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Cyst                                          | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Deep vein thrombosis                          | 1 (1.7)      | 0      | 1 (1.7)| 0            | 0      | 0      | 0            | 0      | 0      |
| Dental caries                                 | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Dermal cyst                                   | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Dermatitis acneiform                          | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Diastasis recti abdominis                     | 1 (1.7)      | 0      | 1 (1.7)| 0            | 0      | 0      | 0            | 0      | 0      |
| Disturbance in attention                      | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Diverticulitis                                | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Drug hypersensitivity                         | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Dry eye                                       | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Dysarthria                                    | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Dyspepsia                                     | 1 (1.7)      | 0      | 1 (1.7)| 0            | 0      | 0      | 0            | 0      | 0      |
| Dysphagia                                     | 1 (1.7)      | 0      | 1 (1.7)| 0            | 0      | 0      | 0            | 0      | 0      |
| Ear infection                                 | 1 (1.7)      | 0      | 1 (1.7)| 0            | 0      | 0      | 0            | 0      | 0      |
| Encephalopathy                                | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Endometrial cancer                            | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Enterocolitis                                 | 1 (1.7)      | 0      | 0      | 1 (1.7)      | 0      | 0      | 0            | 0      | 0      |
| Enterocolitis, infectious                     | 1 (1.7)      | 0      | 1 (1.7)| 0            | 0      | 0      | 0            | 0      | 0      |
| Eosinophilia                                  | 1 (1.7)      | 1 (1.7)| 0      | 0            | 0      | 0      | 0            | 0      | 0      |
| Diagnosis                                      | Count | 1 (1.7) | 0 | 0 | 1 (1.7) | 0 | 0 | 0 |
|-----------------------------------------------|-------|---------|---|---|---------|---|---|---|
| *Escherichia* bacteremia                      | 1 (1.7)|         |   |   | 1 (1.7) |   |   |   |
| Esophagitis                                   | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Eye contusion                                 | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Face injury                                   | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Feeling cold                                  | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Fluid overload                                | 1 (1.7)| 0       | 1 (1.7)| 0 | 0       |   |   |   |
| Folate deficiency                             | 1 (1.7)| 0       | 1 (1.7)| 0 | 0       |   |   |   |
| Gastric polyps                                | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Gastritis                                     | 1 (1.7)| 0       | 1 (1.7)| 0 | 0       |   |   |   |
| Gastroenteritis                               | 1 (1.7)| 0       | 1 (1.7)| 0 | 0       |   |   |   |
| Gastrointestinal adenocarcinoma               | 1 (1.7)|         |   |   | 1 (1.7) |   |   |   |
| Gastrointestinal hemorrhage                   | 1 (1.7)|         |   |   | 1 (1.7) |   |   |   |
| Gingivitis                                    | 1 (1.7)|         |   |   | 1 (1.7) |   |   |   |
| Glomerulosclerosis                            | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Goitre                                        | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Groin pain                                    | 1 (1.7)|         |   |   | 1 (1.7) |   |   |   |
| Hemangioma of bone                            | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hemangioma of skin                            | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hematochezia                                  | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hematoma                                      | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hemoglobin decreased                          | 1 (1.7)|         |   |   | 1 (1.7) |   |   |   |
| *Helicobacter* infection                      | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hiccups                                       | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hip fracture                                  | 1 (1.7)|         |   |   | 1 (1.7) |   |   |   |
| Hordeolum                                     | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hot flush                                     | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hyperglycemia                                 | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hyperlipidemia                                | 1 (1.7)|         |   |   | 1 (1.7) |   |   |   |
| Hyperparathyroidism                           | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Hypersomnia                                   | 1 (1.7)| 1 (1.7) | 0 | 0 | 0       |   |   |   |
| Condition                        | 1 (1.7) | 1 (1.7) | 0  | 0  | 0  | 0  | 0  |
|---------------------------------|---------|---------|----|----|----|----|----|
| Hypertrichosis                  |         |         |    |    |    |    |    |
| Hypoacusis                      |         |         |    |    |    |    |    |
| Hypocalcemia                    |         |         |    |    |    |    |    |
| Hypoglycemia                    |         |         |    |    |    |    |    |
| Hypothermia                     |         |         |    |    |    |    |    |
| Hypovolemia                     |         |         |    |    |    |    |    |
| Immunodeficiency                |         |         |    |    |    |    |    |
| Increased appetite              |         |         |    |    |    |    |    |
| Increased tendency to bruise    |         |         |    |    |    |    |    |
| Infected bite                   |         |         |    |    |    |    |    |
| Inflammation                    |         |         |    |    |    |    |    |
| Inguinal hernia                 |         |         |    |    |    |    |    |
| Injection-site hemorrhage       |         |         |    |    |    |    |    |
| Intermittent claudication       |         |         |    |    |    |    |    |
| Iron deficiency                 |         |         |    |    |    |    |    |
| Iron deficiency anemia          |         |         |    |    |    |    |    |
| Joint range of motion decreased |         |         |    |    |    |    |    |
| Joint swelling                  |         |         |    |    |    |    |    |
| Kidney infection                |         |         |    |    |    |    |    |
| Laryngeal inflammation          |         |         |    |    |    |    |    |
| Left ventricular dysfunction    |         |         |    |    |    |    |    |
| Lentigo maligna                 |         |         |    |    |    |    |    |
| Limb injury                     |         |         |    |    |    |    |    |
| Liver function test abnormal    |         |         |    |    |    |    |    |
| Liver function test increased   |         |         |    |    |    |    |    |
| Localized infection             |         |         |    |    |    |    |    |
| Lumbar spinal stenosis          |         |         |    |    |    |    |    |
| Condition                                           | Count | 1 (1.7) | 0 | 1 (1.7) | 0 | 0 | 0 |
|-----------------------------------------------------|-------|---------|---|---------|---|---|---|
| Malignant melanoma in situ                         | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Melanocytic nevus                                   | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Middle ear effusion                                 | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Migraine                                            | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Mitral valve incompetence                           | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Musculoskeletal chest pain                          | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Musculoskeletal stiffness                           | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Nail infection                                      | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Nasopharyngitis                                     | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Neuralgia                                           | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Neuropathy, peripheral                              | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Nightmare                                           | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Ocular hyperemia                                    | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Onychomycosis                                       | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Oral blood blister                                  | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Oral fungal infection                               | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Oral pain                                           | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Osteoarthritis                                      | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Osteoporosis                                        | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Osteosclerosis                                      | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Pancytopenia                                        | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Patella fracture                                    | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Peripheral coldness                                 | 1 (1.7)| 1 (1.7)| 0 | 0 | 0 | 0 |
| Plantar fasciitis                                   | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Pneumonia aspiration                                | 1 (1.7)| 0       | 0 | 1 (1.7)| 0 | 0 |
| Pneumonia, mycoplasmal                              | 1 (1.7)| 0       | 0 | 1 (1.7)| 0 | 0 |
| Pneumonia, respiratory syncytial viral              | 1 (1.7)| 0       | 0 | 1 (1.7)| 0 | 0 |
| Pneumonia, viral                                    | 1 (1.7)| 0       | 1 (1.7)| 0 | 0 | 0 |
| Condition                               | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Value 6 | Value 7 |
|-----------------------------------------|---------|---------|---------|---------|---------|---------|---------|
| Polycythemia                            | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Portal hypertension                     | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Postoperative hypertension              | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Precancerous skin lesion                | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Procedural pain                         | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Prostatic obstruction                   | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Prostatic-specific antigen increased    | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Pseudomonas infection                   | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Pulmonary mass                          | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Pulmonary edema                         | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Pulmonary sepsis                        | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Pyelitis                                | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Pyelonephritis                          | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Pyuria                                  | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Rash, erythematous                      | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Renal tubular necrosis                  | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Respiratory fume inhalation disorder    | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Respiratory tract infection             | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Retinal tear                            | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Retinopathy                             | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Rhinitis                                | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Rhinovirus infection                    | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Rib fracture                            | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Sciatica                                | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Scoliosis                               | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Scratch                                 | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Seborrheic keratosis                    | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Sensory loss                            | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Sinus headache                          | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Condition                                      | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Value 6 | Value 7 |
|-----------------------------------------------|---------|---------|---------|---------|---------|---------|---------|
| Sinus tachycardia                             | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Skin abrasion                                 | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Skin burning sensation                        | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Skin discoloration                            | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Skin exfoliation                              | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Skin hemorrhage                               | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Skin hyperpigmentation                        | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Skin mass                                     | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Skin papilloma                                | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Sleep disorder                                | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Spinal fracture                               | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Spinal osteoarthritis                         | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Spinal pain                                   | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Splenic rupture                               | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Spontaneous hemorrhage                        | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Sputum discolored                             | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Squamous cell carcinoma of lung                | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Stress urinary incontinence                   | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Subdural hematoma                             | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Synovial cyst                                 | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Tachycardia                                   | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Tendon disorder                               | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Thermal burn                                  | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Thrombophlebitis, superficial                 | 1 (1.7) | 0       | 1 (1.7) | 0       | 0       | 0       | 0       |
| Thyroid mass                                  | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Tinea infection                               | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Toothache                                     | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Transfusion reaction                          | 1 (1.7) | 0       | 0       | 1 (1.7) | 0       | 0       | 0       |
| Transient acantholytic                        | 1 (1.7) | 1 (1.7) | 0       | 0       | 0       | 0       | 0       |
| Condition                          | Row 1 | Row 2 | Row 3 | Row 4 | Row 5 | Row 6 |
|-----------------------------------|-------|-------|-------|-------|-------|-------|
| dermatosis                        | 1 (1.7) | 0 | 1 (1.7) | 0 | 0 | 0 |
| Tumor flare                       | 1 (1.7) | 0 | 1 (1.7) | 0 | 0 | 0 |
| Umbilical hernia                  | 1 (1.7) | 0 | 1 (1.7) | 0 | 0 | 0 |
| Urinary incontinence              | 1 (1.7) | 1 (1.7) | 0 | 0 | 0 | 0 |
| Vaginal hemorrhage                | 1 (1.7) | 0 | 1 (1.7) | 0 | 0 | 0 |
| Varices, esophageal               | 1 (1.7) | 0 | 1 (1.7) | 0 | 0 | 0 |
| Ventricular arrhythmia            | 1 (1.7) | 0 | 1 (1.7) | 0 | 0 | 0 |
| Ventricular fibrillation          | 1 (1.7) | 0 | 0 | 0 | 0 | 1 (1.7) |
| Vision blurred                    | 1 (1.7) | 1 (1.7) | 0 | 0 | 0 | 0 |
| Vitreous floaters                 | 1 (1.7) | 1 (1.7) | 0 | 0 | 0 | 0 |
| Vitreous hemorrhage               | 1 (1.7) | 1 (1.7) | 0 | 0 | 0 | 0 |
| Wheezing                          | 1 (1.7) | 0 | 1 (1.7) | 0 | 0 | 0 |
| Wrist fracture                    | 1 (1.7) | 1 (1.7) | 0 | 0 | 0 | 0 |

*Includes events of neutropenia and decreased neutrophil count.
*Includes events of lymphocytosis and increased lymphocyte count.
*Includes events of thrombocytopenia and decreased platelet count.
Table S4. Ibrutinib-intolerance adverse events recurring with acalabrutinib.

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

Two patients experienced >1 adverse event defined as intolerance.
Table S5. Recurrence of intolerance AEs in patients previously treated with ibrutinib in combination with other agents.

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

Benda, bendamustine; GI, gastrointestinal; IBR, ibrutinib; LEN, lenalidomide; Mona, monalizumab; NE, not evaluable; OBIN, obinutuzumab; OFA, ofatumumab; PR, partial response; R, rituximab; SD, stable disease; UTX, ublituximab.
Table S6. *BTK* and *PLCG2* mutations at baseline.

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

<sup>a</sup>Due to local testing confirming a C481 mutation, the patient was removed from the trial before any tumor assessment was performed.

*BTK*, Bruton tyrosine kinase gene; *CR*, complete response; *PLCG2*, phospholipase C gamma 2 gene; *PR*, partial response; *SD*, stable disease; *VAF*, variant allele frequency.
Table S7. *BTK* and *PLCG2* status at treatment termination (n=5)

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

*BTK*, Bruton tyrosine kinase gene; CR, complete response; ND, no mutations detected with deep sequencing of sorted B cells; *PLCG2*, phospholipase C gamma 2 gene; PR, partial response; PRL, partial response with treatment-induced lymphocytosis; SD, stable disease; VAF, variant allele frequency.
Figure S1. Time to next treatment (TTNT) after acalabrutinib. The median time to next treatment was not reached.
Figure S2. Objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS) by duration of ibrutinib treatment (A, C, and E) and by duration of treatment hold after ibrutinib discontinuation (B, D, and F). Duration of treatment hold after ibrutinib is calculated as first date of acalabrutinib dosing to last dose date of ibrutinib dosing + 1. CR, complete remission; CRi, complete remission with incomplete bone marrow recovery; PD, progressive disease; PR, partial remission; PRL, partial remission with lymphocytosis; SD, stable disease.

A.
F.

![Graph showing PFS (Proportion) vs. Months From Initiation of Study Treatment]

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

Legend:
- Duration of treatment hold <6 months
- Duration of treatment hold ≥6 months
+ Censored