

ORIGINAL ARTICLE

Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Bonnie Harrington, D.V.M., Susan O'Brien, M.D., Jeffrey A. Jones, M.D., M.P.H., Anna Schuh, M.D., Ph.D., Steve Devereux, M.D., Jorge Chaves, M.D., William G. Wierda, M.D., Ph.D., Farrukh T. Awan, M.D., Jennifer R. Brown, M.D., Ph.D., Peter Hillmen, M.B., Ch.B., Ph.D., Deborah M. Stephens, D.O., Paolo Ghia, M.D., Jacqueline C. Barrientos, M.D., John M. Pagel, M.D., Ph.D., Jennifer Woyach, M.D., Dave Johnson, B.S., Jane Huang, M.D., Xiaolin Wang, Sc.D., Allard Kaptein, Ph.D., Brian J. Lannutti, Ph.D., Todd Covey, B.A., Maria Fardis, Ph.D., Jesse McGreivy, M.D., Ahmed Hamdy, M.B., B.Ch., Wayne Rothbaum, M.A., Raquel Izumi, Ph.D., Thomas G. Diacovo, M.D., Amy J. Johnson, Ph.D., and Richard R. Furman, M.D.

ABSTRACT

BACKGROUND

Irreversible inhibition of Bruton's tyrosine kinase (BTK) by ibrutinib represents an important therapeutic advance for the treatment of chronic lymphocytic leukemia (CLL). However, ibrutinib also irreversibly inhibits alternative kinase targets, which potentially compromises its therapeutic index. Acalabrutinib (ACP-196) is a more selective, irreversible BTK inhibitor that is specifically designed to improve on the safety and efficacy of first-generation BTK inhibitors.

METHODS

In this uncontrolled, phase 1–2, multicenter study, we administered oral acalabrutinib to 61 patients who had relapsed CLL to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of acalabrutinib. Patients were treated with acalabrutinib at a dose of 100 to 400 mg once daily in the dose-escalation (phase 1) portion of the study and 100 mg twice daily in the expansion (phase 2) portion.

RESULTS

The median age of the patients was 62 years, and patients had received a median of three previous therapies for CLL; 31% had chromosome 17p13.1 deletion, and 75% had unmutated immunoglobulin heavy-chain variable genes. No dose-limiting toxic effects occurred during the dose-escalation portion of the study. The most common adverse events observed were headache (in 43% of the patients), diarrhea (in 39%), and increased weight (in 26%). Most adverse events were of grade 1 or 2. At a median follow-up of 14.3 months, the overall response rate was 95%, including 85% with a partial response and 10% with a partial response with lymphocytosis; the remaining 5% of patients had stable disease. Among patients with chromosome 17p13.1 deletion, the overall response rate was 100%. No cases of Richter's transformation (CLL that has evolved into large-cell lymphoma) and only one case of CLL progression have occurred.

CONCLUSIONS

In this study, the selective BTK inhibitor acalabrutinib had promising safety and efficacy profiles in patients with relapsed CLL, including those with chromosome 17p13.1 deletion. (Funded by the Acerta Pharma and others; ClinicalTrials.gov number, NCT02029443.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Byrd at B302 Starling Loving Hall, 320 W. 10th Ave., Columbus, OH 43210, or at john.byrd@osumc.edu.

Drs. Byrd, Harrington, and O'Brien, and Dr. Hamdy, Mr. Rothbaum, Dr. Izumi, Dr. Diacovo, Dr. Johnson, and Dr. Furman contributed equally to this article.

This article was published on December 7, 2015, at NEJM.org.

N Engl J Med 2016;374:323–32.

DOI: 10.1056/NEJMoa1509981

Copyright © 2015 Massachusetts Medical Society.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is the most prevalent leukemia among adults. Although chemoimmunotherapy prolongs the duration of remission and overall survival among most patients with CLL,^{1,2} relapse virtually always occurs. This has prompted aggressive discovery efforts for new therapies in CLL. Because B-cell receptor signaling is a driving factor for CLL tumor-cell survival,^{3,4} proximal kinases involved in this pathway have been therapeutic targets. Bruton's tyrosine kinase (BTK) is immediately downstream of the B-cell receptor and is essential for the activation of several tumor-cell survival pathways relevant to CLL.⁵ In addition, BTK is involved in chemokine-mediated homing and adhesion of CLL cells to the microenvironment, which contribute to their maintenance and proliferation.^{6,7}

In mice and humans, loss of BTK function results in a B-cell-dysfunction phenotype with decreased serum immunoglobulin levels and an increased predisposition to infections. Few other adverse effects have been reported.⁸⁻¹⁰ The unique structure of BTK, which is characterized by a cysteine (C481) within the ATP-binding pocket, makes it an attractive therapeutic target. Ibrutinib is a first-in-class, irreversible small-molecule inhibitor of BTK that has the ability to covalently bind to C481.¹¹ Ibrutinib has shown substantial single-agent activity in patients with relapsed CLL and in previously untreated patients.¹²⁻¹⁴ Progressive disease during ibrutinib treatment is uncommon in patients with previously untreated CLL and also in patients with low-risk genomic abnormalities.¹²⁻¹⁴

Among those with high-risk genomic features, progression occurs more frequently, either shortly after the start of ibrutinib therapy, owing to Richter's transformation (CLL that has evolved into large-cell lymphoma), or later with progressive CLL.¹⁵ Ibrutinib also irreversibly binds to other kinases (e.g., epidermal growth factor receptor [EGFR], tyrosine kinase expressed in hepatocellular carcinoma [TEC], interleukin-2-inducible T-cell kinase [ITK], and T-cell X chromosome kinase [TXK]).¹¹ These pharmacodynamic features may be responsible for ibrutinib-related adverse events that are not typically observed in BTK-deficient patients, such as rash, diarrhea, arthralgias or myalgias, atrial fibrillation, ecchymosis, and major hemorrhage.¹²⁻¹⁴

Acalabrutinib (ACP-196) is a second-generation, selective, irreversible inhibitor of BTK that has improved pharmacologic features, including favorable plasma exposure, rapid oral absorption, a short half-life, and the absence of irreversible targeting to alternative kinases, such as EGFR, TEC, and ITK. Given the success of ibrutinib in the treatment of relapsed CLL,¹²⁻¹⁴ we sought to determine whether selective targeting of BTK by acalabrutinib would be effective, as measured by response and safety profile; side effects represent the most common reason that patients discontinue ibrutinib treatment.^{15,16}

Furthermore, we hypothesized that it might be possible to administer acalabrutinib twice daily, thus achieving a complete and continuous level of drug binding to BTK (>95% over a period of 24 hours), without increased toxic effects from inhibition of alternative kinases. Full target coverage may reduce drug resistance caused by mutations in the BTK enzyme and may also lower the rate of Richter's transformation.

METHODS

STUDY DESIGN

Preclinical studies with CLL cells and normal immune cells were performed according to methods outlined in the Supplementary Appendix (available with the full text of this article at NEJM.org) after written informed consent was obtained as part of an institutional review board–approved protocol at Ohio State University. The phase 1–2 multicenter study was designed to determine the recommended dose, safety, efficacy, pharmacokinetics, and pharmacodynamics of acalabrutinib in patients with relapsed CLL. All patients provided written informed consent. The institutional review board at each participating site approved the study protocol (available at NEJM.org). The study was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

PATIENTS

Eligibility criteria included the following: a diagnosis of relapsed CLL or small lymphocytic lymphoma, as defined by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL)¹⁷; a need for treatment, according to the

IWCLL guidelines; receipt of at least one previous therapy for CLL; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 (on a scale from 0 to 5, with higher numbers indicating greater disability); adequate organ function, defined by creatinine and bilirubin levels of no more than 1.5 times the upper limit of the normal range and an alanine aminotransferase level of no more than 2.5 times the upper limit of the normal range; and an absence of active infection. An absolute neutrophil count of at least 750 cells per cubic millimeter and a platelet count of at least 50,000 per cubic millimeter were required if no bone marrow involvement was present, but no restrictions for cytopenia were applied if bone marrow involvement was present. Exclusion criteria were any cancer that limited expected survival to less than 2 years, the need for warfarin therapy (other anticoagulation therapy was allowed), active gastrointestinal inflammation or malabsorption, and the use of medications associated with torsades des pointes, high-grade atrioventricular block, or a corrected QT interval of 480 msec or greater.

EVALUATION AND TREATMENT

All patients had a baseline assessment that included interphase cytogenetic analysis, mutational analysis of immunoglobulin heavy-chain variable (*IGHV*) genes, measurement of serum β_2 -microglobulin, and inquiry about B symptoms (i.e., weight loss, night sweats, and fever). Patients were successively enrolled in cohorts that were to receive oral acalabrutinib at a dose of 100 mg, 175 mg, 250 mg, or 400 mg once daily as part of the dose-escalation (phase 1) portion of the study or 100 mg twice daily as part of the expansion (phase 2) portion. The definition of dose-limiting toxic effects included grade 3 or greater nonhematologic toxic effects (except for alopecia or nausea, vomiting, or diarrhea that resolved with an intervention); grade 4 neutropenia lasting more than 5 days; grade 4 thrombocytopenia, or grade 3 thrombocytopenia with bleeding; grade 3 or greater febrile neutropenia; or a dosing delay due to toxic effects for more than 7 consecutive days. Escalation to the next cohort was allowed if fewer than two dose-limiting toxic effects were noted in six patients.

DISEASE EVALUATION

Patients were evaluated at screening, weekly for the first month, every 2 weeks for the second month, monthly for 4 months, and every 3 months thereafter. Assessments included history taking, physical examination, and laboratory studies for signs of toxic effects. Numbers of T cells, natural killer cells, and monocytes were measured at baseline and before cycles 3, 10, and 16 (each cycle lasted 28 days). Serum immunoglobulin levels were measured on the same schedule. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 4.03. Hematologic toxic effects were graded according to IWCLL criteria.¹⁷

Study end points for phase 1 included safety (maximum tolerated dose), pharmacodynamics, and pharmacokinetics; end points for phase 2 included the overall response rate, progression-free survival, and long-term side-effect profile. Response assessments, including radiologic examination, were performed at the end of cycles 2, 4, 6, 9, 12, 15, 18, and 21 for most patients. Bone marrow biopsy was performed in all patients at 12 months or when all other criteria for a complete response were met. Response was evaluated on the basis of the IWCLL criteria,¹⁷ but isolated lymphocytosis was not considered to indicate a relapse (a summary of the response criteria is available in Table S6 in the Supplementary Appendix). A partial response in the context of lymphocytosis was considered to be a partial response with lymphocytosis. Patients could be evaluated for efficacy if they had received at least one dose of acalabrutinib and had undergone at least one tumor-response assessment during treatment.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Detailed pharmacokinetic analyses were performed with the use of a validated assay during cycle 1 of therapy. BTK occupancy (the level of drug binding to BTK) by acalabrutinib was measured in peripheral-blood mononuclear cells with the aid of a biotin-tagged analogue probe at baseline, 4 hours after administration of acalabrutinib on days 1, 8, and 28, and before administration of acalabrutinib on days 2, 8, and 28. Phosphorylation of BTK was measured by means of intracellular flow cytometry. Immunoblot

analysis was performed with the use of methods described previously.¹⁸ The murine thrombosis model has been described previously.¹⁹ Additional details for laboratory studies are provided in the Supplementary Appendix.

STUDY OVERSIGHT

This study was designed by the first, third, and last authors together with the sponsor (Acerta Pharma). The clinical investigators and their research teams collected and evaluated all the data and assessed all the patients. The sponsor was responsible for analyzing the data. Investigators had open access to all data and analyses under standard confidentiality agreements. The first author wrote the initial draft of the manuscript. No professional medical-writing services were used. All the authors reviewed the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and analyses reported and the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

Results are presented through October 1, 2015. All the safety and efficacy analyses included patients who received acalabrutinib. One patient who discontinued treatment after 8 days was excluded from the analysis of the overall response rate, according to the protocol, because computed tomography had not been performed during treatment. However, laboratory assessments and physical examination showed that the patient had had a response and that the disease was not progressing when treatment was discontinued. Descriptive statistics were used to summarize the findings. The Wilcoxon signed-rank test was used to assess the change from baseline in immune-cell counts, cytokine levels, and immunoglobulin levels. Only patients with data at baseline and for each subsequent follow-up visit were included, and no adjustment for multiplicity was made. Because many exploratory tests were performed, P values of less than 0.05 should not be regarded as definitive, but rather as hypothesis-generating. Progression-free survival was defined as the time from the first dose of acalabrutinib to documented disease progression or death and was estimated with the use of the Kaplan–Meier method.²⁰ Data on progression-free survival for patients who discontinued treatment without documented disease progres-

sion were censored at the time of the last clinical assessment. Noncompartmental pharmacokinetic analyses were performed with the use of validated WinNonlin software (Certara USA).

RESULTS

MECHANISM OF ACTION

The chemical structures of acalabrutinib and ibrutinib are shown in Figure S1 in the Supplementary Appendix. Acalabrutinib showed dose-dependent inhibition of B-cell receptor signaling in primary CLL cells (Fig. S2A in the Supplementary Appendix). In kinase-inhibition assays, acalabrutinib was a more selective BTK inhibitor than ibrutinib (Table S1 in the Supplementary Appendix). These biochemical findings are physiologically relevant, because acalabrutinib did not inhibit EGFR, TEC, or ITK signaling (Fig. S2B through S2D in the Supplementary Appendix). The findings provide structural, biochemical, and in vitro differentiation of acalabrutinib from ibrutinib. These data, combined with objective clinical responses in a study of naturally occurring canine B-cell lymphomas, provided justification for the clinical development of acalabrutinib for the treatment of CLL.²¹

PATIENT DEMOGRAPHICS

A total of 61 patients were sequentially enrolled at six sites in the United States and the United Kingdom and received at least one dose of acalabrutinib. The baseline characteristics of the patients are listed in Table 1. At a median follow-up of 14.3 months (range, 0.5 to 20), 53 patients are still receiving treatment. The primary reasons for treatment discontinuation in 8 patients were the investigator's or patient's decision in the case of 2 patients; active autoimmune hemolytic anemia that required additional therapy in 1 patient; fatal pneumonia in 1 patient; adverse events of diarrhea, gastritis, and dyspnea in 1 patient each; and CLL progression in 1 patient.

PHARMACOKINETIC MEASUREMENTS

Acalabrutinib was rapidly absorbed and eliminated after oral administration (Fig. 1A). Pharmacokinetic results showed that exposure to acalabrutinib increased in a dose-proportional manner, with no drug accumulation. Mean peak plasma values occurred between 0.6 and 1.1 hours. The mean half-life was approximately 1 hour across

all cohorts. Additional pharmacokinetic measurements are summarized in Table S2 in the Supplementary Appendix.

PHARMACODYNAMIC MEASUREMENTS

The binding of acalabrutinib to the C481 residue was assessed in all treatment cohorts, with data summarized in Figure 1B. Starting with the dose of 100 mg once daily, BTK occupancy was complete (99 to 100%) 4 hours after dosing and ranged from 87 to 95% before dose administration with once-daily dosing. Because acalabrutinib has no plasma accumulation, we explored the feasibility and safety of a dosing regimen of 100 mg twice daily. Figure 1C shows improved BTK occupancy of 99% 4 hours after dose administration and 97% before dose administration on days 8 and 28. The interruption of B-cell receptor signaling was also assessed by measurement of phosphorylated BTK, as shown in Figure 1D. After treatment with acalabrutinib, complete loss of phosphorylated BTK was observed at the respective time points across all cohorts. Assessment of the *in vivo* function of platelets isolated from the blood of patients receiving acalabrutinib or ibrutinib (as a positive control) revealed a reduction in platelet–vessel wall interactions in the latter but not the former in a humanized mouse model of thrombosis (Fig. S4 in the Supplementary Appendix). Direct natural-killer-cell–mediated cytotoxicity was evaluated with the use of peripheral blood from the patients. Non–antibody-dependent cytotoxicity was not impaired with acalabrutinib treatment as compared with the pretreatment control (Fig. S3 in the Supplementary Appendix). Proinflammatory cytokines decreased significantly from baseline to day 28 of treatment (Fig. S5 in the Supplementary Appendix).

SAFETY

Long-term therapy with acalabrutinib has not been associated with any high-grade cumulative toxic effects. Most of the events that were observed were grade 1 or 2 and resolved over time (Table 2). The most common adverse events were headache (with overall events occurring in 43% of the patients and grade 3 or 4 events in 0%), diarrhea (overall in 39% and grade 3 or 4 in 2%), increased weight (overall in 26% and grade 3 or 4 in 2%), pyrexia (overall in 23% and grade 3 or 4 in 3%), and upper respiratory tract infection

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.

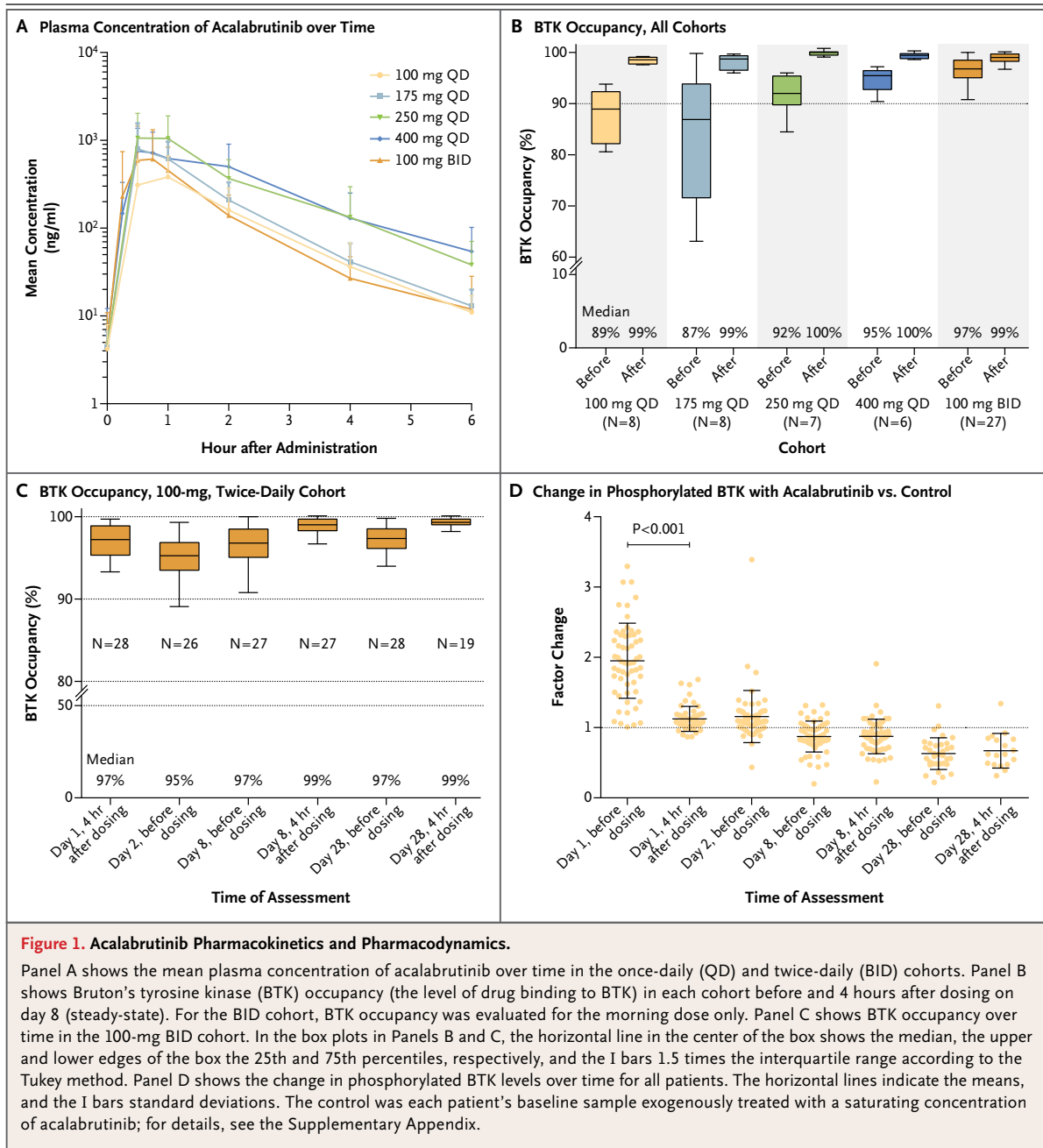
Characteristic	Value (N = 61)
Age	
Median — yr	62
Range — yr	44–84
≥65 yr — no. (%)	27 (44)
≥70 yr — no. (%)	15 (25)
Diagnosis of chronic lymphocytic leukemia — no. (%)	61 (100)
ECOG performance status — no. (%) [*]	
0	22 (36)
1	36 (59)
2	3 (5)
Bulky lymph nodes — no. (%)	
≥5 cm in diameter	28 (46)
≥10 cm in diameter	3 (5)
Rai risk classification — no. (%) [†]	
Low	1 (2)
Intermediate	19 (31)
High	41 (67)
No. of previous therapies	
Median	3
Range	1–13
Cytopenia at baseline — no. (%)	
Absolute neutrophil count ≤1500/μl	15 (25)
Hemoglobin ≤11.0 g/dl	21 (34)
Platelet count ≤100,000/μl	32 (52)
Prognostic factors — no./total no. (%)	
Unmutated immunoglobulin variable-region heavy-chain gene	38/51 (75)
Chromosome 17p13.1 deletion [‡]	18/59 (31)
Chromosome 11q22.3 deletion [‡]	17/59 (29)
β ₂ -microglobulin >3.5 mg/liter	47/58 (81)

* Values for Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with higher numbers indicating greater disability.

† The Rai stage (which ranges from 0 [low risk] to I or II [intermediate risk] to III or IV [high risk]) was derived at the time of screening for this trial.

‡ Deletion of chromosome 17p13.1 or chromosome 11q22.3 was determined at a local laboratory or by a review of the patient's medical history.

(overall in 23% and grade 3 or 4 in 0%). Severe diarrhea, rash, arthralgia or myalgia, bruising, and bleeding events each occurred in no more than 2% of patients. No major hemorrhage or atrial fibrillation was noted. Serious adverse events are listed in Table S3 in the Supplementary Appendix. Only one death (due to pneumo-



nia) has occurred during the study. Serum IgG, IgA, and IgM levels were measured over time, and the results did not show a clinically significant change over time, except among patients receiving intravenous immune globulin (Fig. S6 in the Supplementary Appendix). Numbers of T cells (CD4+ and CD8+), natural killer cells,

and monocytes also showed no clinically significant change over time (Fig. S7 in the Supplementary Appendix).

CLINICAL RESPONSE

The clinical activity of acalabrutinib was robust, with 98% of the patients having a reduction in

Table 2. Adverse Events.*

Table 2. Adverse Events.			
Adverse Event	All Grades†	Grades 1–2	Grades 3–4
	number of patients (percent)		
Headache	26 (43)	26 (43)	0
Diarrhea	24 (39)	23 (38)	1 (2)
Increased weight	16 (26)	15 (25)	1 (2)
Pyrexia	14 (23)	12 (20)	2 (3)
Upper respiratory tract infection	14 (23)	14 (23)	0
Fatigue	13 (21)	11 (18)	2 (3)
Peripheral edema	13 (21)	13 (21)	0
Hypertension	12 (20)	8 (13)	4 (7)
Nausea	12 (20)	12 (20)	0
Contusion	11 (18)	11 (18)	0
Arthralgia	10 (16)	9 (15)	1 (2)
Petechiae	10 (16)	10 (16)	0
Decreased weight	10 (16)	10 (16)	0

* Listed are adverse events that were reported in at least 15% of the 61 patients, on or before the data cutoff date of October 1, 2015, regardless of the cause.

† One grade 5 event of pneumonia was reported.

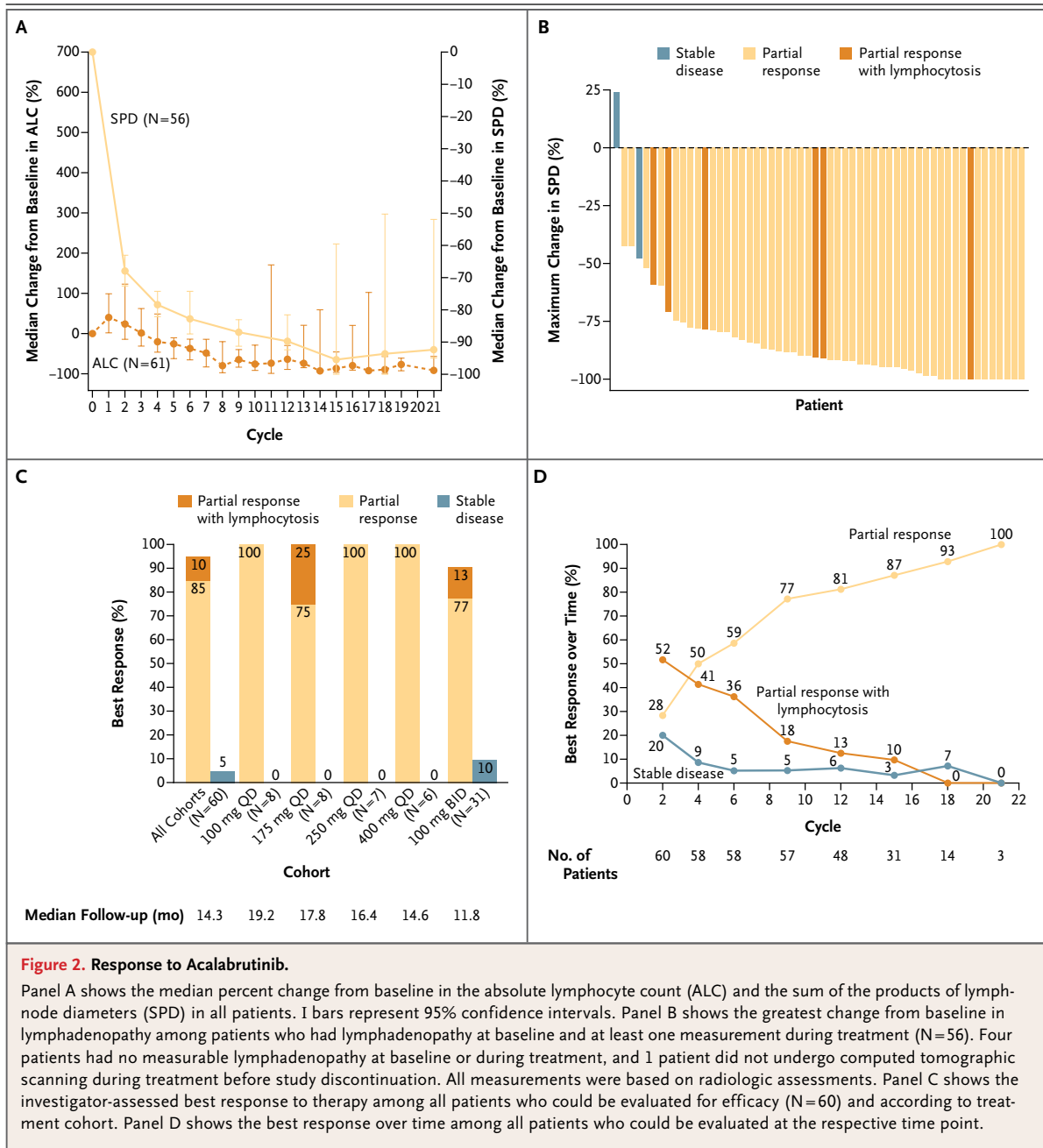
lymphadenopathy and 61% having concomitant treatment-related lymphocytosis (defined as an absolute lymphocyte count >5000 cells per microliter and an increase of ≥50% from baseline) (Fig. 2A and 2B). The absolute lymphocyte count increased by a median of only 40% from baseline, despite substantial reductions in lymphadenopathy (Fig. 2A and 2B). Among patients who had cytopenia at baseline, improvements in platelet count, hemoglobin levels, and absolute neutrophil count were noted in 62%, 76%, and 80% of the patients, respectively (Table S4 in the Supplementary Appendix). Among the 16 patients who had B symptoms at baseline, resolution of symptoms occurred in 88% of the patients by the end of cycle 3 and in 100% of patients by the end of cycle 9 (Table S5 in the Supplementary Appendix).

At a median follow-up of 14.3 months, the overall response rate among the 60 patients who could be evaluated was 95% (partial response in 85% and partial response with lymphocytosis in 10%), and the rate of stable disease was 5%. Responses were observed across all cohorts (Fig. 2C), and the response rate increased over time (Fig. 2D). Among the 18 patients with chromosome 17p13.1 deletion, the response rate was 100% (partial response in 89% and partial re-

sponse with lymphocytosis in 11%). Among the 4 patients who had received previous idelalisib therapy, the response rate was 100% (partial response in 75% and partial response with lymphocytosis in 25%). At the time of the analysis, only 1 patient with chromosome 17p13.1 deletion had disease progression during therapy. At progression, this patient had a C481S (major clone) mutation in *BTK* and an L845F (minor clone) mutation in *PLCγ2*, as has been reported in some patients who had disease progression during ibrutinib therapy.²² No cases of Richter's transformation have been reported. A Kaplan-Meier plot of progression-free survival is shown in Figure 3. Only two events of progression or death have been noted thus far: one death from pneumonia (at 13 months) and a single case of CLL progression (at 16 months).

DISCUSSION

The introduction of irreversible BTK inhibitors such as ibrutinib for the treatment of CLL and other related B-cell lymphoproliferative disorders represented a major therapeutic advance.¹²⁻¹⁴ Concurrent with ibrutinib clinical development, another irreversible BTK inhibitor, CC-292, was studied in CLL. CC-292 had an acceptable side-



effect profile, but the clinical results were inferior to those observed in previous phase 1 studies of ibrutinib.^{23,24} At the time, it was suggested that CC-292 may be a more selective inhibitor of BTK than ibrutinib. This introduced the question of whether irreversible BTK inhibitors need to inhibit alternative targets, as ibrutinib does, to ensure efficacy. In the current study, we

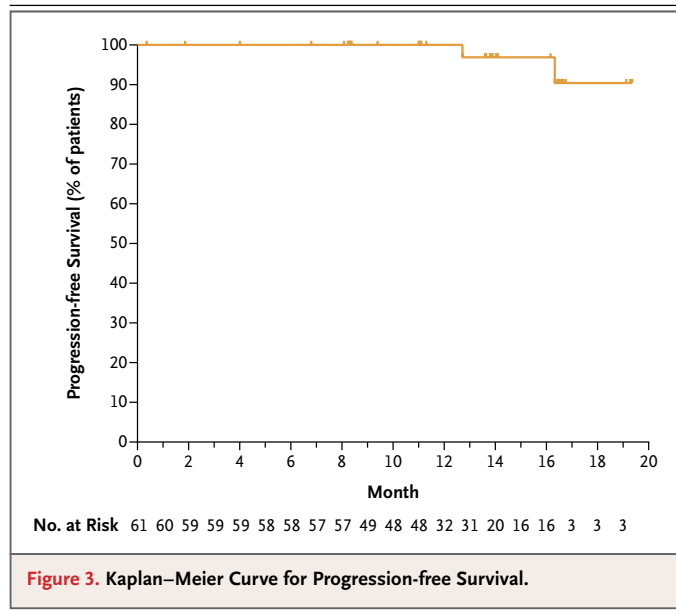
showed that acalabrutinib has structural, biochemical, in vitro, pharmacokinetic, and pharmacodynamic properties that are different from those of ibrutinib. These preclinical findings prompted initiation of this study involving patients with relapsed CLL; in this ongoing study, acalabrutinib therapy has been associated with a high response rate and durable remissions. No

cases of Richter's transformation and only one case of late CLL progression have occurred, even though this trial included high-risk patients with relapsed CLL. These results suggest that BTK is a highly active and important target in CLL.

Along with this clinical activity, the safety profile of acalabrutinib was also favorable, despite prolonged, continuous administration. Adverse events were mostly grade 1 or 2 and self-limiting, and most resolved over time. With a median follow-up of 14.3 months, only 8 of 61 patients (13%) have discontinued the study treatment. Our preclinical work with acalabrutinib showed that many of the alternative kinase targets of ibrutinib were not influenced at pharmacologic concentrations of acalabrutinib. These biochemical findings may be clinically relevant, because acalabrutinib does not inhibit EGFR signaling (drugs that inhibit such signaling are associated with adverse events such as rash and severe diarrhea)²⁵ or ITK signaling (a critical modulator of natural killer cell function). Furthermore, TEC kinase, which is expressed in platelets and whose phosphorylation is highly dependent on platelet aggregation,^{26,27} is also not inhibited by acalabrutinib. In patients receiving ibrutinib, we observed diminished platelet reactivity at sites of vascular injury in humanized mice, which was not the case with acalabrutinib. The latter finding may help explain why major bleeding events with acalabrutinib have, thus far, not occurred.

In addition, no cases of atrial fibrillation have been reported to date, despite 14 months of follow-up; during the same time frame, cases were noted in patients treated with ibrutinib.¹³ In contrast, transient headaches were observed with acalabrutinib more frequently than they have been seen historically with ibrutinib; the headaches that occur during acalabrutinib therapy occur early in treatment and generally resolve with time. Randomized studies will be required to fully appreciate differences in adverse events between acalabrutinib and ibrutinib.

Having an alternative BTK inhibitor with more selective pharmacodynamic features for clinical use may be attractive and offers the potential opportunity to improve on the efficacy and safety observed with ibrutinib. In particular, genetic studies of two CLL mouse models^{28,29} and several types of lymphoma^{22,30,31} suggest that a selective and potent pharmacologic inhibitor of BTK offers a potential advance for treating



this disease. The short half-life and selective properties of acalabrutinib allow twice-daily dosing with virtually complete and continuous BTK inhibition without increased toxic effects. Thus far, twice-daily dosing of ibrutinib has not been pursued and may not be possible owing to the potential for drug accumulation given the ibrutinib half-life of 4 to 13 hours.³²

In summary, data on a selective BTK inhibitor, acalabrutinib, provide strong justification for further clinical investigation of the efficacy and safety of this drug as compared with those of ibrutinib and other CLL therapies. On the basis of these data and to meet these goals, a phase 3 study (ClinicalTrials.gov number, NCT02477696) has commenced in which acalabrutinib is being compared with ibrutinib in high-risk patients with relapsed CLL.

Supported by Acerta Pharma, which funded the clinical performance of this trial and the monitoring associated with it; also supported by the National Cancer Institute (P01 CA095426, T32 CA09338, K23 CA178183, R35 CA197734, R01 CA169162, R01HD081281, and R01 CA177292), Leukemia and Lymphoma Society, Four Winds Foundation, Sullivan Chronic Lymphocytic Leukemia Research Fund, Mr. and Mrs. Michael Thomas, Al and Midge Lipkin, and the D. Warren Brown Foundation.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the investigators and coordinators at each of the clinical sites, the patients who participated in this trial and their families, and employees of Acerta Pharma who contributed to this trial, including Tasheda Navarro, Fanny Krantz, Greg Slatter, Tjeerd Barf, Diana Mittag, Bart van Lith, Maaike Emmelot-van Hoek, and Michael Gulrajani. Earlier versions of the figures were created by David Ehlert (Cognition Studios).

APPENDIX

The authors' affiliations are as follows: the Division of Hematology, Department of Internal Medicine, Ohio State University (J.C. Byrd, J.A.J., F.T.A., J.W., A.J.J.), and the Department of Veterinary Biosciences, College of Veterinary Medicine (B.H.) — both in Columbus; UC Irvine Health Chao Family Comprehensive Cancer Center, University of California, Irvine, Orange (S.O.); University of Oxford, Oxford (A.S.), NHS Foundation Trust, King's College Hospital, London (S.D.), and the Department of Haematology, St. James's University Hospital, Leeds (P.H.) — all in the United Kingdom; Northwest Medical Specialties, Tacoma (J.C.), and the Swedish Cancer Institute, Seattle (J.M.P.) — both in Washington; the Department of Leukemia, Division of Cancer Medicine, University of Texas, and M.D. Anderson Cancer Center — both in Houston (W.G.W.); the Department of Medical Oncology, Dana-Farber Cancer Institute, Boston (J.R.B.); Huntsman Cancer Institute, University of Utah, Salt Lake City (D.M.S.); Università Vita-Salute San Raffaele and Istituto Scientifico San Raffaele, Milan (P.G.); Hofstra North Shore-LIJ School of Medicine, Chronic Lymphocytic Leukemia Research and Treatment Center, Lake Success (J.C. Barrientos), and the Department of Pathology and Cell Biology, Columbia University Medical Center (T.G.D.), and New York-Presbyterian/Weill Cornell Medical Center, New York (R.R.F.) — all in New York; and Acerta Pharma, Oss, the Netherlands (D.J., J.H., X.W., A.K., B.J.L., T.C., M.F., J.M., A.H., W.R., R.L.).

REFERENCES

- Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014;370:1101-10.
- Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet* 2010;376:1164-74.
- Quiroga MP, Balakrishnan K, Kurtova AV, et al. B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: specific targeting with a novel spleen tyrosine kinase inhibitor, R406. *Blood* 2009;114:1029-37.
- Herishanu Y, Pérez-Galán P, Liu D, et al. The lymph node microenvironment promotes B-cell receptor signaling, NF- κ B activation, and tumor proliferation in chronic lymphocytic leukemia. *Blood* 2011;117:563-74.
- Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. *Blood* 2011;117:6287-96.
- Ponader S, Chen S-S, Buggy JJ, et al. The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. *Blood* 2012;119:1182-9.
- de Rooij MFM, Kuil A, Geest CR, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. *Blood* 2012;119:2590-4.
- Rawlings DJ, Saffran DC, Tsukada S, et al. Mutation of unique region of Bruton's tyrosine kinase in immunodeficient XID mice. *Science* 1993;261:358-61.
- Zhu Q, Zhang M, Winkelstein J, Chen SH, Ochs HD. Unique mutations of Bruton's tyrosine kinase in fourteen unrelated X-linked agammaglobulinemia families. *Hum Mol Genet* 1994;3:1899-900.
- Saffran DC, Parolini O, Fitch-Hilgenberg ME, et al. A point mutation in the SH2 domain of Bruton's tyrosine kinase in atypical X-linked agammaglobulinemia. *N Engl J Med* 1994;330:1488-91.
- Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A* 2010;107:13075-80.
- Byrd JC, O'Brien S, James DF. Ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2013;369:1278-9.
- Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014;371:213-23.
- O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol* 2014;15:48-58.
- Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol* 2015;1:80-7.
- Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood* 2015;125:2062-7.
- 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;111:5446-56.
- Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. *Blood* 2013;122:2539-49.
- Chen JTK, Tan K, Zhou H, et al. Modifying murine von Willebrand factor A1 domain for in vivo assessment of human platelet therapies. *Nat Biotechnol* 2008;26:114-9.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1957;53:457-81.
- Gardner HL, Harrington BK, Izumi R, et al. ACP-196: a second generation Btk inhibitor demonstrates biologic activity in a canine model of B-cell non-Hodgkin lymphoma. Presented at the American Association for Cancer Research Annual Meeting, San Diego, CA, April 5-9, 2014. abstract.
- Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med* 2014;370:2286-94.
- Evans EK, Tester R, Aslanian S, et al. Inhibition of Btk with CC-292 provides early pharmacodynamic assessment of activity in mice and humans. *J Pharmacol Exp Ther* 2013;346:219-28.
- Brown J, Harb WA, Hill BT, et al. Phase 1 study of single agent CC-292, a highly selective Bruton's tyrosine kinase (BTK) inhibitor, in relapsed/refractory chronic lymphocytic leukemia (CLL). Presented at the 55th Annual Meeting of the American Society of Hematology, New Orleans, December 7-10, 2013. abstract.
- Lynch TJ Jr, Kim ES, Eaby B, Garey J, West DP, Lacouture ME. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist* 2007;12:610-21.
- Atkinson BT, Ellmeier W, Watson SP. Tec regulates platelet activation by GPVI in the absence of Btk. *Blood* 2003;102:3592-9.
- Hamazaki Y, Kojima H, Mano H, et al. Tec is involved in G protein-coupled receptor- and integrin-mediated signalings in human blood platelets. *Oncogene* 1998;16:2773-9.
- Kil LP, de Bruijn MJ, van Hulst JA, Langerak AW, Yuvaraj S, Hendriks RW. Bruton's tyrosine kinase mediated signaling enhances leukemogenesis in a mouse model for chronic lymphocytic leukemia. *Am J Blood Res* 2013;3:71-83.
- Woyach JA, Bojnik E, Ruppert AS, et al. Bruton's tyrosine kinase (BTK) function is important to the development and expansion of chronic lymphocytic leukemia (CLL). *Blood* 2014;123:1207-13.
- Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med* 2015;21:922-6.
- Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013;369:507-16.
- de Jong J, Skee D, Murphy J, et al. Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. *Pharmacol Res Perspect* 2015;3(4):e00156.

Copyright © 2015 Massachusetts Medical Society.