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ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

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abstract

PURPOSE Acalabrutinib, a highly selective, potent, Bruton tyrosine kinase inhibitor, was evaluated in this global, multicenter, randomized, open-label, phase III study in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).

METHODS Eligible patients, aged ≥ 18 years with R/R CLL, were randomly assigned 1:1 centrally and stratified by del(17p) status, Eastern Cooperative Oncology Group performance status score, and number of prior lines of therapy. Patients received acalabrutinib monotherapy or investigator's choice (idelalisib plus rituximab [I-R] or bendamustine plus rituximab [B-R]). The primary end point was progression-free survival (PFS) assessed by an independent review committee (IRC) in the intent-to-treat population. Key secondary end points included IRC-assessed overall response rate, overall survival, and safety.

RESULTS From February 21, 2017, to January 17, 2018, a total of 398 patients were assessed for eligibility; 310 patients were randomly assigned to acalabrutinib monotherapy (n = 155) or investigator's choice (n = 155; I-R, n = 119; B-R, n = 36). Patients had received a median of two prior therapies (range, 1-10). After a median follow-up of 16.1 months (range, 0.03-22.4 months), median PFS was significantly longer with acalabrutinib monotherapy (PFS not reached) compared with investigator's choice (16.5 months [95% CI, 14.0 to 17.1 months]; hazard ratio, 0.31 [95% CI, 0.20 to 0.49]; $P < .0001$). Estimated 12-month PFS was 88% (95% CI, 81% to 92%) for acalabrutinib and 68% (95% CI, 59% to 75%) for investigator's choice. Serious adverse events occurred in 29% of patients (n = 44 of 154) treated with acalabrutinib monotherapy, 56% (n = 66 of 118) with I-R, and 26% (n = 9 of 35) with B-R. Deaths occurred in 10% (n = 15 of 154), 11% (n = 13 of 118), and 14% (n = 5 of 35) of patients receiving acalabrutinib monotherapy, I-R, and B-R, respectively.

CONCLUSION Acalabrutinib significantly improved PFS compared with I-R or B-R and has an acceptable safety profile in patients with R/R CLL.

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ASSOCIATED CONTENT

See accompanying article on page 2937

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Therapy for chronic lymphocytic leukemia (CLL) is undergoing a paradigm shift, with a change in the use of chemoimmunotherapy to targeted therapy with small-molecule inhibitors.[1] Therapeutic options for relapsed or refractory (R/R) CLL have included combination regimens such as bendamustine plus rituximab (B-R) and idelalisib plus rituximab (I-R).[2-6] B-R is still used in second-line therapy in many countries around the world,[7] and I-R is a viable option for patients intolerant to ibrutinib.[8,9] Studies with B-R showed a median progression-free survival (PFS) or event-free survival of 11-18 months.[4,10,11] The combination of I-R was associated with a median PFS of 19.4 months, but with characteristic treatment-limiting adverse events (AEs).[6,12]

Bruton tyrosine kinase (BTK) is a member of the B-cell receptor signaling pathway and a clinically validated target in B-cell malignancies.[13,14] The BTK inhibitor (BTKi) ibrutinib is approved in front-line and R/R CLL settings.[13,15]

Acalabrutinib is a selective, potent, covalent BTKi[16] that showed a tolerable safety profile and promising efficacy in a phase I/II study in patients with R/R CLL, with an overall response rate (ORR) of 94%, including in patients with high-risk disease characteristics,[16,17] and received US Food and Drug Administration approval in 2019 for the treatment of CLL.[18] In this phase

III ASCEND study, we compared the efficacy and safety of acalabrutinib monotherapy versus investigator's choice (I-R or B-R) in patients with R/R CLL (ClinicalTrials.gov identifier: NCT02970318; other study ID no. ACE-CL-309).

METHODS

Patients

Eligible patients were aged ≥ 18 years, had CLL,[19] and had previously received at least one systemic therapy. Patients were required to have an Eastern Cooperative Oncology Group performance status score of ≤ 2 and adequate hematologic, hepatic, and renal function (Data Supplement). Patients with significant cardiovascular disease and those who were previously treated with BTK, PI3K, SYK, or BCL-2 inhibitors were excluded. Concomitant treatment with warfarin or equivalent vitamin K antagonists was prohibited (Data Supplement). Patients who had previously received bendamustine treatment were eligible to receive bendamustine provided the duration of the prior response was ≥ 24 months.

Study Design and Treatments

ASCEND was a phase III, randomized, multicenter, open-label study; patients were enrolled at 102 community and clinic or hospital sites across 25 countries in North America, Europe, the Middle East, and the Asia-Pacific region (Data Supplement).

Acalabrutinib (100 mg twice daily) was administered orally until progressive disease (PD) or unacceptable toxicity occurred. In the investigator's choice group, idelalisib (150 mg twice daily) was administered orally until PD or unacceptable toxicity in combination with rituximab (375 mg/m^2 intravenously [IV] on day 1 of the first cycle, followed by 500 mg/m^2 IV every 2 weeks for four doses and then every 4 weeks for three doses for a total of eight infusions); alternatively, bendamustine was administered at 70 mg/m^2 IV on days 1 and 2 of each 28-day cycle in combination with rituximab (375 mg/m^2 IV on day 1 of the first cycle and 500 mg/m^2 IV thereafter on day 1 of cycles 2 through 6). Patients receiving investigator's choice who had confirmed disease progression were permitted to cross over to receive acalabrutinib monotherapy. Dose modifications were allowed for management of AEs (Data Supplement). Patients were withdrawn from the study due to withdrawal of consent, loss to follow-up, and death.

Patients were randomly assigned via a centralized procedure in a 1:1 ratio to receive acalabrutinib monotherapy or investigator's choice (I-R or B-R). Patients were stratified by del(17p) status (yes *v* no), Eastern Cooperative Oncology Group performance status score (0-1 *v* 2), and lines of prior therapy received (1-3 *v* ≥ 4).

The institutional review board or independent ethics committee at each site approved the protocol. The study was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice. All patients provided written informed consent. An independent data-monitoring committee periodically reviewed unblinded safety data and efficacy results of the planned interim analysis. Progression and responses were assessed centrally by the independent review committee (IRC), which was blinded to treatment-group assignments.

Study End Points and Assessments

The primary end point was IRC-assessed PFS, defined as the time from randomization until disease progression or death from any cause, using International Workshop on Chronic Lymphocytic Leukemia 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis.[20] Secondary end points included IRC-assessed ORR, overall survival (OS), and duration of response (DOR); investigator-assessed PFS, ORR, and DOR; and time to next CLL treatment (Data Supplement). Safety was assessed by AEs, laboratory measurements, and clinical evaluation. Treatment-emergent AEs were defined as any event with an onset date on or after the first dose date of study drug or any ongoing event that worsened in severity after the first dose date of study drug and prior to 30 days after the date of the last dose of study drug or the first date starting new anticancer therapy. All AEs and serious AEs (SAEs) are treatment emergent, unless otherwise specified. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

A sample size of 306 patients was planned on the basis of an assumption of the exponential model and a hazard ratio (HR) for PFS of 0.55; with 119 events at the final analysis, it provided approximately 90% power at the one-sided significance level of 0.025. A stratified log-rank test was used for the primary comparison of IRC-assessed PFS. A stratified Cox regression model was used to provide estimated PFS HRs and the two-sided 95% CIs. One prespecified interim analysis was planned when approximately 79 IRC-assessed PFS events (ie, 67% of the planned events for the final analysis) had occurred, using Lan and DeMets α-spending function with O'Brien-Fleming boundaries for efficacy.[21,22] For the primary analysis of IRC-assessed PFS, for patients who were alive and had not had disease progression, the data were censored on the date of the last disease assessment prior to subsequent anticancer therapy (including acalabrutinib monotherapy for patients who crossed over). On May 1, 2019, the independent data-monitoring committee reviewed the interim analysis and confirmed the prespecified statistical boundary for early efficacy was crossed. Therefore, formal statistical testing of selected secondary efficacy end points was subsequently performed per a prespecified hierarchical approach (Data Supplement). Sensitivity analyses and prespecified

subgroup analyses using prognostic variables were performed (Data Supplement).

Efficacy analyses, except OS, were performed for the intent-to-treat population and included the data from before initiation of new anticancer therapy or crossover treatment. OS was analyzed using the data throughout the study follow-up. Safety analyses were performed for the safety population, which consisted of all patients who received any amount of study drug.

RESULTS

Patient Characteristics and Treatment

Between February 21, 2017, and January 17, 2018, a total of 398 patients were assessed for eligibility; 310 patients were randomly assigned to treatment and included in the intent-to-treat population: 155 were assigned to receive acalabrutinib monotherapy and 155 to receive investigator's choice of treatment (I-R, n = 119; B-R, n = 36; Fig 1). The demographic and disease characteristics were generally well balanced at baseline (Table 1). Across treatment groups, the median age was 67 (range, 32-90) years; 243 patients (78%) had unmutated immunoglobulin heavy chain variable region (IGHV) genes, 49 (16%) had chromosome del(17p), and 73 (24%) had *TP53* mutations. The median number of prior therapies was one (range, 1-8) with acalabrutinib monotherapy and two (range, 1-10) with the investigator's choice.

Efficacy

At the time of data cutoff for the interim analysis (January 15, 2019), 124 of the 155 patients (80%) in the acalabrutinib monotherapy group continued receiving treatment (Data Supplement). In the B-R subgroup, 28 of 35 patients (80%) completed six cycles of treatment. In the I-R subgroup, 92 of the 118 patients (78%) completed eight doses of rituximab, and idelalisib treatment was ongoing in 38 patients (32%; Data Supplement). Of 155 patients randomly assigned to the investigator's choice group, 35 (23%) crossed over to receive subsequent acalabrutinib monotherapy.

After a median follow-up of 16.1 months (range, 0.03-22.4), 128 of the 155 patients (83%) in the acalabrutinib monotherapy group and 87 of the 155 patients (56%) in the investigator's choice group were progression free. Patients treated with acalabrutinib monotherapy had a significantly longer PFS than those receiving investigator's choice (median, not reached [NR] *v* 16.5 months [95% CI, 14.0 to 17.1 months]) as assessed by IRC. The relative reduction in the risk of progression or death was 69% with acalabrutinib monotherapy (HR, 0.31; 95% CI, 0.20 to 0.49; $P < .0001$; Fig 2A). In a post hoc analysis of investigator's choice therapy, median PFS was 15.8 and 16.9 months for patients receiving I-R and B-R, respectively (Fig 2B). The estimated PFS at 12 months was 88% (95% CI, 81% to 92%) with acalabrutinib monotherapy and 68% (95% CI, 58% to 76%) and 69% (95% CI, 50% to 82%) with I-R and B-R, respectively. When assessed by the investigator, PFS was similarly improved with acalabrutinib monotherapy (Data Supplement).

Acalabrutinib monotherapy treatment also resulted in improved median PFS in all prespecified subgroup analyses, including patients with high-risk genomic features, such as del(17p) plus *TP53* mutation (Fig 2C), del(11q) (Data Supplement), or unmutated IGHV (Fig 2D), as well as in prespecified analyses by baseline demographic and clinical characteristics (Fig 3; Data Supplement). Richter transformation occurred in four of the 155 patients in the acalabrutinib-monotherapy group and five of 155 patients receiving the investigator's choice of treatment (I-R, n = 4; B-R, n = 1).

IRC-assessed ORR was similar with acalabrutinib monotherapy (n = 126 of 155; 81%) and investigator's choice (n = 117 of 155 [75%]; Fig 4). Median DOR, per IRC, was NR with acalabrutinib monotherapy and 13.6 months (95% CI, 11.9 months to NR) with investigator's choice (HR, 0.33; 95% CI, 0.19 to 0.59; $P < .0001$). Efficacy results were similar when assessments were performed by the investigator (Data Supplement).

Data indicating improvements in absolute neutrophil counts, hemoglobin levels, and platelet counts are presented in the Data Supplement.

At the time of analysis, 10% of patients (n = 15) in the acalabrutinib-monotherapy group and 12% (n = 18; I-R, n = 13; B-R, n = 5) in the investigator's choice group had died (Data Supplement). Median OS was NR in either group (HR, 0.84; 95% CI, 0.42 to 1.66; Data Supplement); OS at 12 months was 94% (95% CI, 89% to 97%) in the acalabrutinib-monotherapy group and 91% (95% CI, 85% to 94%) in the investigator's choice group.

At 12 months, 89% (95% CI, 83% to 93%) of patients in the acalabrutinib-monotherapy group and 80% (95% CI, 72% to 85%) in the investigator's choice group had not received a next treatment for CLL (HR, 0.35; 95% CI, 0.21 to 0.58; $P < .0001$). In the acalabrutinib-monotherapy group, 13 of the 155 patients (8%) and 43 of the 155 (28%) in the investigator's choice group initiated subsequent CLL therapy (Data Supplement). The median time to next treatment was NR for acalabrutinib monotherapy or investigator's choice (95% CI, 18.4 to NR; HR, 0.35 [95% CI, 0.21 to 0.58]; $P < .0001$; Data Supplement).

Safety

The reporting period for treatment-emergent AEs was longer with acalabrutinib monotherapy and I-R versus B-R due to the longer duration of treatment in those groups (Data Supplement). Median duration of exposure was 15.7 months (range, 1.1-22.4 months) for acalabrutinib monotherapy, and 11.5 months (range, 0.1-21.1 months) for idelalisib in the I-R subgroup. Overall, 289 patients

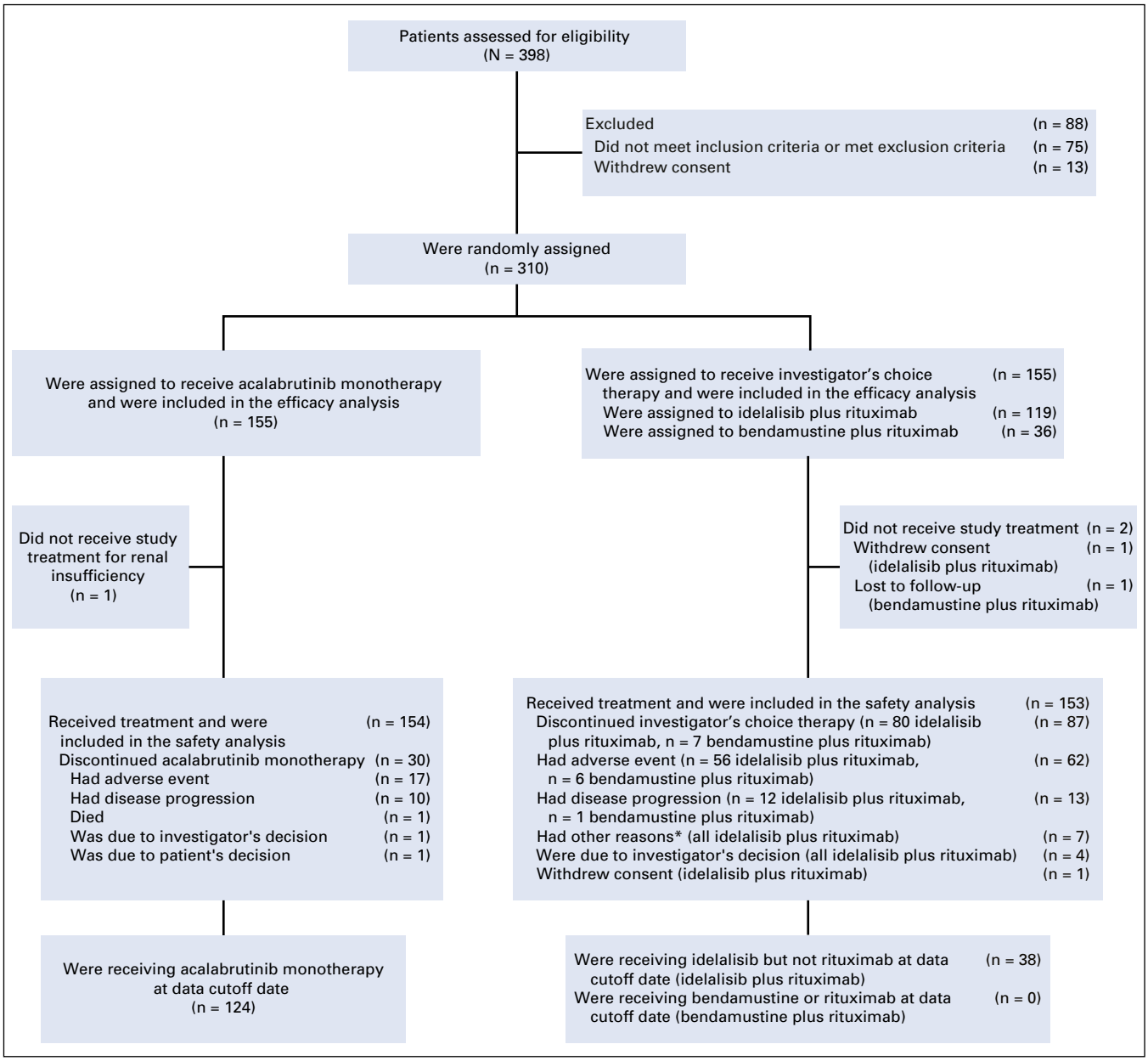

FIG 1. Random assignment, treatment, and follow-up of patients in the phase III ASCEND study. The 310 patients were randomly assigned to a treatment arm (n = 155 in the acalabrutinib-monotherapy group and n = 155 in the investigator's choice group [n = 119 in the idelalisib plus rituximab subgroup and n = 36 in the bendamustine plus rituximab subgroup). (*) Other reasons for discontinuation of idelalisib plus rituximab included adverse events preventing dosing (n = 2), and adverse events combined with disease progression preventing treatment administration, dose interruption for > 28 days, patient's decision, patient's death, and adverse events preventing treatment administration (n = 1 each).

(94%) had at least one AE: 144 of 154 patients (94%) who received acalabrutinib monotherapy, 117 of 118 (99%) who received I-R, and 28 of 35 (80%) who received B-R (Table 2). AEs of any grade occurring in ≥ 20% of patients given any treatment were: headache in patients receiving acalabrutinib monotherapy; diarrhea and neutropenia in patients receiving I-R; and neutropenia, infusion-related reaction, fatigue, and nausea in patients receiving B-R (Table 2).

Grade 3/4 AEs occurred more often with I-R (n = 101 of 118; 86%) versus acalabrutinib monotherapy (n = 70 of 154; 45%) or B-R (n = 15 of 35; 43%) (Table 2). The most common grade 3/4 AEs in the 154 patients receiving acalabrutinib monotherapy were neutropenia (n = 24; 16%), anemia (n = 18; 12%), and pneumonia (n = 8; 5%). The most common grade 3/4 AEs in the 118 patients receiving I-R were neutropenia (n = 47; 40%), diarrhea (n = 28; 24%), pneumonia and alanine aminotransferase increased

TABLE 1. Baseline Characteristics

Characteristic	Acalabrutinib Monotherapy (n = 155)	Investigator's Choice Therapy (n = 155)
Age		
Median, years (range)	68 (32-89)	67 (34-90)
75 years or older	34 (22)	31 (20)
Male sex, No. (%)	108 (70)	100 (65)
ECOG performance status score		
0	58 (37)	55 (35)
1	78 (50)	79 (51)
2	19 (12)	21 (14)
Rai stage 3 or 4	65 (42)	64 (41)
Bulky disease of at least 10 cm	22 (14)	24 (15)
Cytogenetic subgroup, No./N (%)		
del(17p)	28/155 (18)	21/154 (14)
del(11q)	39/155 (25)	44/154 (29)
Complex karyotype[a]	50/154 (32)	46/153 (30)
TP53 mutational status, No./N (%)		
Mutated	39/152 (26)	34/153 (22)
Unmutated	113/152 (74)	119/153 (78)
IGHV mutational status, No./N (%)		
Mutated	33/154 (21)	26/153 (17)
Unmutated	118/154 (77)	125/153 (82)
Undetermined	3/154 (2)	2/153 (1)
Creatinine clearance < 60 mL/min	41 (26)	37 (24)
Absolute lymphocyte count, $\times 10^9$ cells/L, median (range)	48.9 (0.6-461.2)	37.4 (0.5-479.1)
Absolute neutrophil count, $\times 10^9$ cells/L, median (range)	3.8 (0.1-24.5)	4.3 (0.2-16.4)
Platelet count, $\times 10^9$ cells/L, median (range)	119.5 (17.0-357.0)	116.0 (23.0-454.0)
Number of prior therapies		
1	82 (53)	67 (43)
2	40 (26)	46 (30)
3	17 (11)	24 (15)
≥ 4	16 (10)	18 (12)
Median (range)	1 (1-8)	2 (1-10)
Previous therapy		
Purine analogues	109 (70)	104 (67)
Alkylators other than bendamustine	133 (86)	131 (85)
Bendamustine	47 (30)	48 (31)
Anti-CD20 monoclonal antibodies	130 (84)	119 (77)
Stem cell transplant	1 (1)	1 (1)
Other[b]	9 (6)	6 (4)

NOTE. Data are No. (%) unless otherwise noted.

Abbreviation: CD, clusters of differentiation; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death ligand-1; TP53, tumor protein p53.

[a]Patients with ≥ 3 abnormalities.

[b]Anti-CD52 antibody (n = 6); anti-CD19 antibody (n = 3); immunomodulatory agent (n = 2); anti-PD-L1 antibody (n = 1); anti-CD23 antibody (n = 1); autologous dendritic cell vaccine (n = 1); hydroxycarbamide (n = 1).

(n = 10; 9% each), thrombocytopenia and neutrophil count decreased (n = 9; 8% each), anemia and pyrexia (n = 8; 7% each), and AST increased and transaminases increased (n = 6; 5% each). The most common grade 3/4 events in the 35 patients receiving B-R were neutropenia (n = 11; 31%), anemia (n = 3; 9%), and constipation (n = 2; 6%).

SAEs were reported more frequently with I-R treatment (n = 66 of 118 patients; 56%) than with acalabrutinib monotherapy (n = 44 of 154; 29%) or B-R (n = 9 of 35; 26%). SAEs occurring in two or more of 154 patients receiving acalabrutinib monotherapy were pneumonia (n = 8) and atrial fibrillation (n = 3). SAEs occurring in patients receiving I-R were diarrhea (n = 16), pneumonia (n = 10), pyrexia (n = 8), anemia (n = 4), colitis (n = 3), and pneumococcal pneumonia (n = 3). No SAEs occurred in more than one of the 35 patients receiving B-R (Data Supplement).

AEs led to dose reduction in five of 154 patients (3%) who received acalabrutinib monotherapy, 28 of 118 patients (24%) who received I-R, and six of 35 patients (17%) who received B-R. There were no dose reductions of rituximab (Data Supplement). AEs led to discontinuation less frequently in patients receiving acalabrutinib monotherapy (n = 17 of 155; 11%) compared with I-R (n = 56 of 119 [47%]; Data

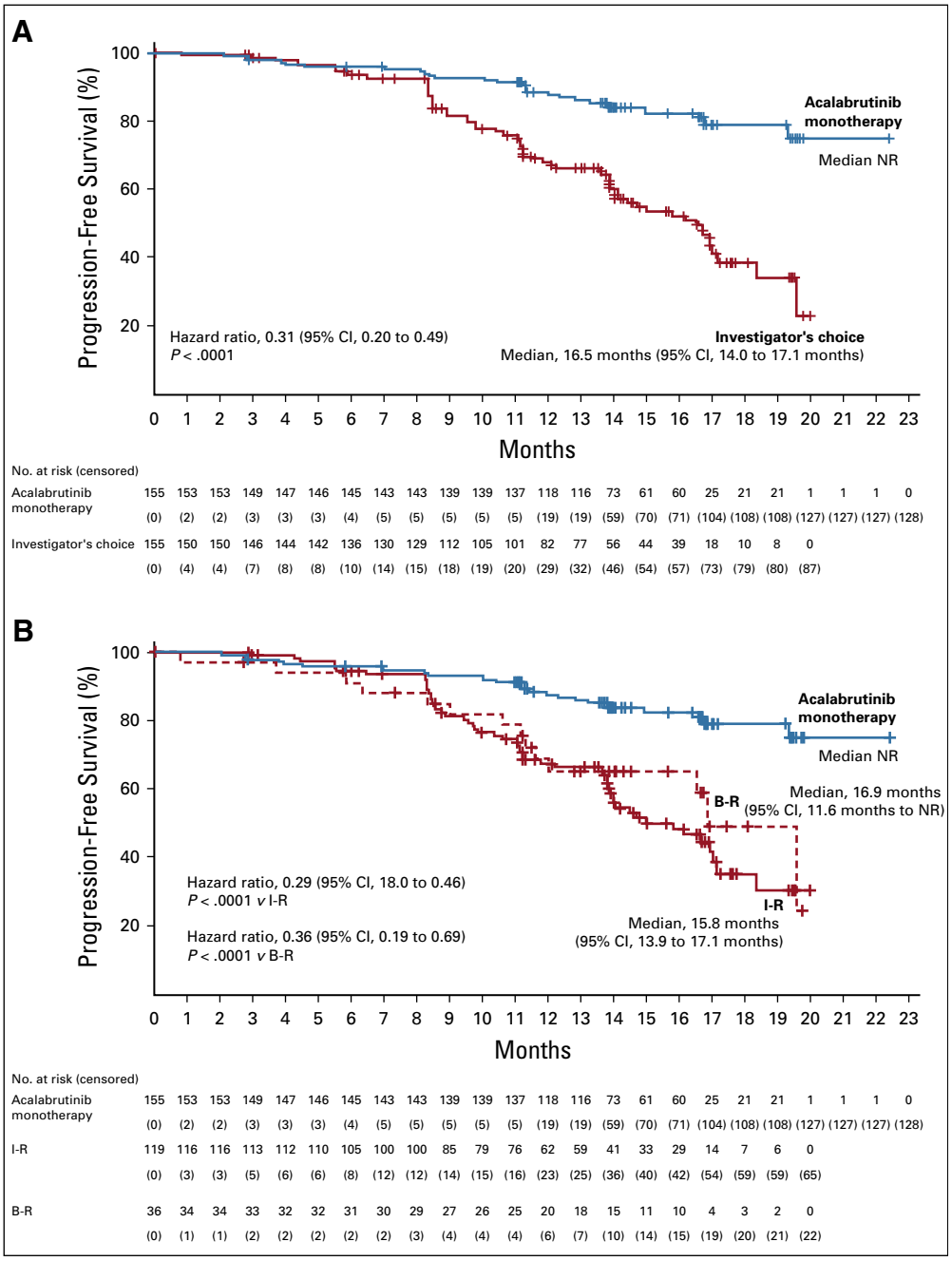

FIG 2. Progression-free survival. The primary end point of progression-free survival is shown for (A) all patients, (B) for all patients by therapy received, and (C) for patients by del(17p) plus *TP53* mutation status and (D) IGHV mutation status in the intent-to-treat population. B-R, bendamustine plus rituximab; I-R, idelalisib plus rituximab; IGHV, immunoglobulin heavy chain variable region; NR, not reached; *TP53*, tumor protein p53.

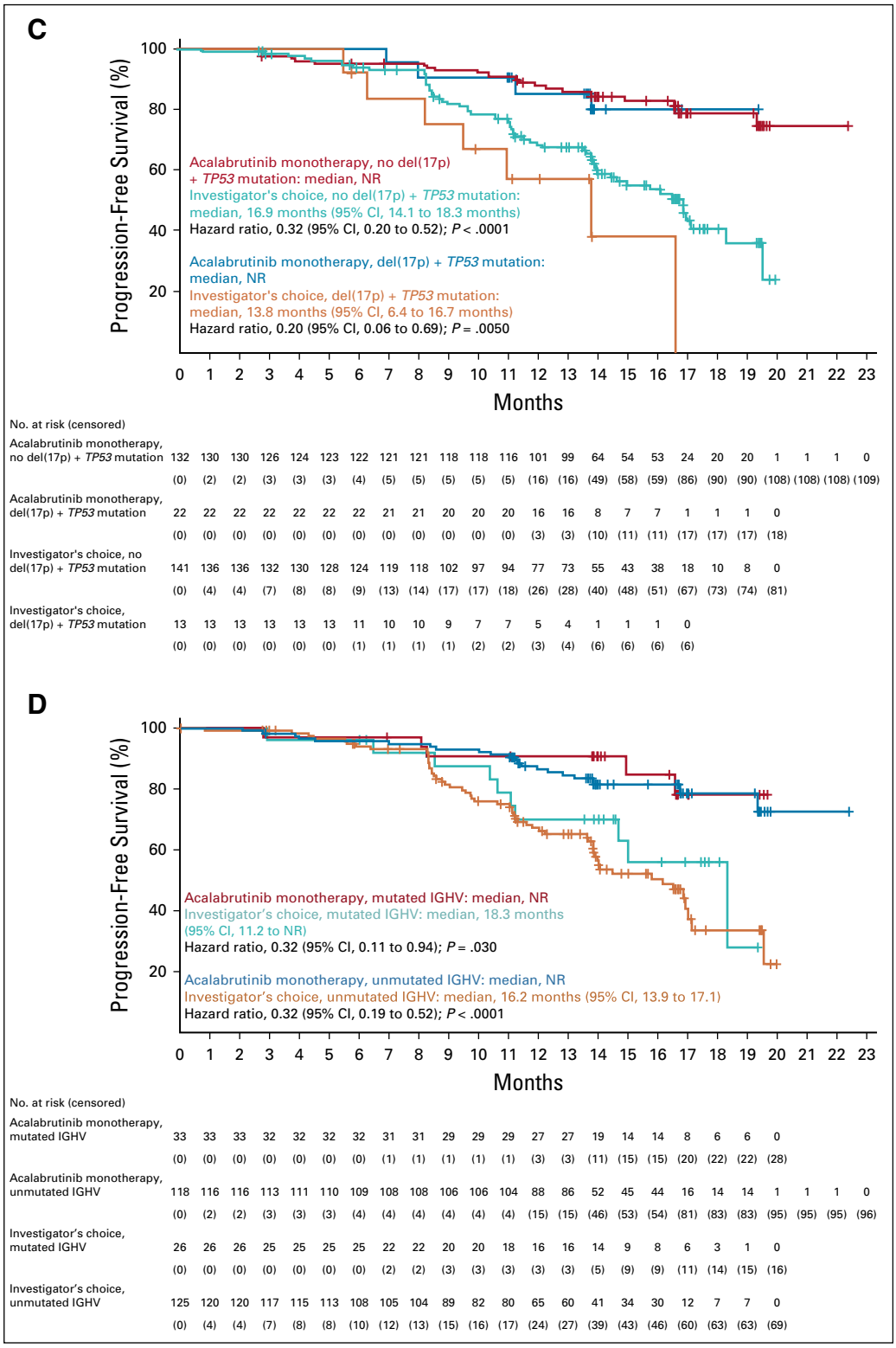

FIG 2. (Continued).

Supplement). AEs leading to discontinuation are presented in the Data Supplement.

In the acalabrutinib-monotherapy group, atrial fibrillation events occurred in eight of 154 patients (5%), seven of whom had a history of ongoing hypertension (including one patient with concomitant ischemic heart disease; Data Supplement). In the investigator's choice group, four of 153 patients (3%) had atrial fibrillation (Data Supplement).

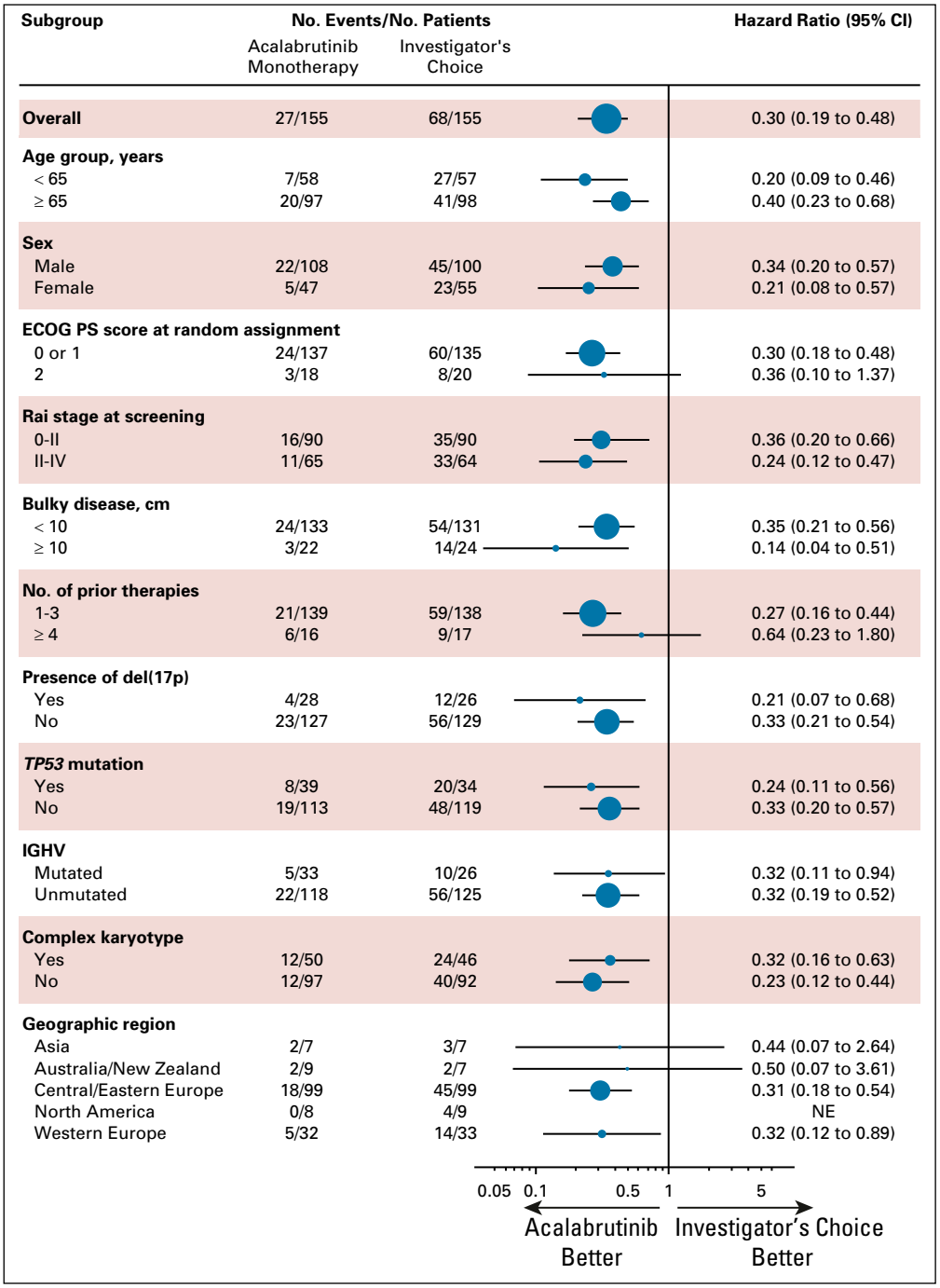

FIG 3. Subgroup analysis of progression-free survival. Forest plot showing progression-free survival analyzed by prespecified subgroups according to baseline demographic and clinical characteristics. The 95% CI was based on unstratified Cox-regression model. ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; NE, not estimable; *TP53*, tumor protein p53.

Bleeding AEs of any grade (most commonly, contusion and hematoma) were more common with acalabrutinib monotherapy than investigator's choice (40 of 154 [26%] *v* 11 of 153 [7%], respectively; Data Supplement). Major hemorrhage, defined as any serious or grade ≥ 3 hemorrhage or CNS hemorrhage of any grade, excluding immune thrombocytopenic purpura, occurred in two patients (1%) treated with acalabrutinib monotherapy (grade 3 GI hemorrhage and grade 4 GI hemorrhage) and three patients (2%) treated with investigator's choice (I-R: grade 3 GI hemorrhage, grade 3 hematuria; B-R: grade 3 hemorrhagic anemia and grade 3 tumor hemorrhage [both in 1 patient]). No grade 5 bleeding events occurred. There were no intracranial hemorrhages.

Hypertension occurred in five of 154 patients (3%) receiving acalabrutinib monotherapy (grade 3 in three patients; 2%); there were no grade 4 or 5 events. Grade ≥ 3 infections occurred in 23 of 154 patients (15%) receiving acalabrutinib monotherapy and 37 of 153 patients (24%) treated with investigator's choice (Data Supplement). Fungal infections occurring during acalabrutinib monotherapy included mycotic pneumonia (n = 1) and bronchopulmonary aspergillosis (n = 1). Second primary malignancies (SPMs) occurred in 21 of 154 patients (14%) treated with

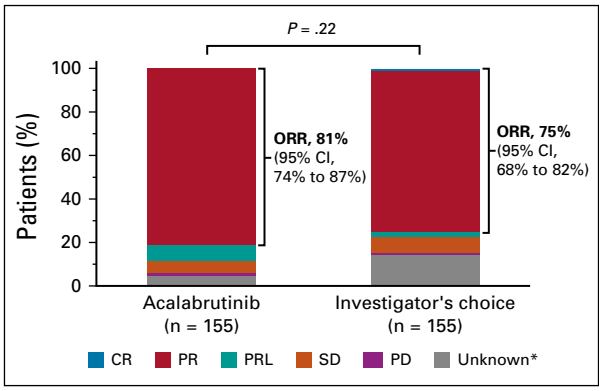

FIG 4. Overall response rate (ORR). (*) Twenty patients had an independent review committee global assessment as "not applicable" but also an independent review committee time-point assessment that included partial response (PR) at either a single point or at nonconsecutive points. Six other patients had no postbaseline independent review committee response assessment. CR, complete response; PD, progressive disease; PRL, partial response with lymphocytosis; SD, stable disease.

acalabrutinib monotherapy and seven of 153 patients (5%) treated with investigator's choice (Data Supplement). Notably, nine and three of the malignancies in the acalabrutinib-monotherapy and investigator's choice groups, respectively, were nonmelanoma skin cancers. AEs that resulted in death occurred in six of 154 (4%), five of 118 (4%), and two of 35 (6%) patients receiving acalabrutinib monotherapy, I-R, and B-R, respectively (Data Supplement).

DISCUSSION

This study demonstrates that acalabrutinib monotherapy significantly improved PFS compared with investigator's choice of combination regimens (I-R or B-R) after a median follow-up of 16.1 months. Prespecified subgroup analyses showed a consistent PFS benefit with acalabrutinib monotherapy, including in patients with high-risk features. In addition, acalabrutinib monotherapy was associated with improved PFS regardless of age, Rai stage, or bulky disease. At 12 months, PFS significantly favored the acalabrutinib-monotherapy group, with an estimated IRC-assessed rate of 88%; however, median PFS was NR because of the low number of events.

Recent trials demonstrated that ibrutinib with or without an anti-CD20 antibody (rituximab or obinutuzumab) and venetoclax plus obinutuzumab provided superior PFS compared with chemoimmunotherapy for front-line CLL treatment.[23-25] These findings are leading to a shift in the CLL treatment paradigm away from traditional chemoimmunotherapies to targeted therapies. Our study further supports this change in the standard of care for patients with CLL, and also their use in the salvage setting, because not all patients worldwide may have the same access to novel therapies.

In additional support of the ongoing shift toward chemotherapy-free treatments, at least in an academic setting, most patients in the control arm were treated with I-R, facilitating for the first time, to our knowledge, a direct comparison between two B-cell receptor inhibitors. The median PFS observed herein with I-R was 15.8 months, which is somewhat shorter than the 19.4 months reported for patients who were censored upon entry into the extension phase of the phase III idelalisib trial.[12] This correlates with a median treatment duration in this study with I-R of 11.5 months, compared with 18.4 months in a previous study.[26] The lower exposure to I-R in the current study was mainly due to a high discontinuation rate because of AEs, including grade ≥ 3 diarrhea, which had a higher incidence compared with other reports.[12,26] We speculate that more clinical experience with idelalisib and awareness of the possibility of characteristic AEs may have facilitated earlier identification of these events and discontinuations in ASCEND to prevent clinical deterioration. In addition, the possibility exists that because this population was younger and less heavily pretreated compared with the patients in the pivotal idelalisib study, a more intact immune system may result in more immunologic dysfunction from PI3K inhibition, thus leading to more severe AEs.[6] The median PFS observed with B-R (16.9 months) was consistent with prior studies in patients with R/R CLL (range, 14.3-17.0 months).[10,27]

Current guidelines recommend the use of I-R as first-line therapy for CLL in patients with del(17p)/*TP53* mutation if they are not eligible for other targeted therapies, and as second-line therapy in patients without del(17p)/*TP53* mutation in whom first-line treatment did not work.[28,29] Although ibrutinib was approved in the United States for patients with del(17p) during the recruitment period, it should be noted that most patients were enrolled outside the United States, where ibrutinib was not globally available and I-R was, indeed, a viable option for this subgroup of patients. ORR was similar for both the acalabrutinib-monotherapy and investigator's choice groups in our study. Prior studies with I-R also reported a high ORR of 81%[6]; however, the median DOR with acalabrutinib monotherapy was significantly longer compared with investigator's choice in our study. A phase III clinical trial previously reported an ORR of 85.5% (n = 94 of 110 patients) in patients treated with I-R in the primary and extension studies.[12] Although this regimen is now used less frequently in daily clinical practice because of a poor toxicity profile, it remains a viable alternative for patients who discontinue ibrutinib because of AEs.[8,9]

The nature and frequency of the AEs associated with acalabrutinib are consistent with data in previous reports,[17,30] with no new safety events observed. Patients receiving acalabrutinib monotherapy had fewer SAEs and

TABLE 2. Treatment-emergent AEs observed in ≥10% of patients in any treatment group or grade ≥3 in ≥5% in any treatment group

	Acalabrutinib Monotherapy (n = 154)			Idelalisib Plus Rituximab (n = 118)			Bendamustine Plus Rituximab (n = 35)		
AE	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Entire study									
All	68 (44)	48 (31)	22 (14)	11 (9)	59 (50)	42 (36)	11 (31)	8 (23)	7 (20)
Neutropenia	6 (4)	14 (9)	10 (6)	6 (5)	24 (20)	23 (19)	1 (3)	5 (14)	6 (17)
Diarrhea	26 (17)	2 (1)	0	27 (23)	26 (22)	2 (2)	5 (14)	0	0
Pyrexia	18 (12)	1 (1)	0	13 (11)	7 (6)	1 (1)	5 (14)	1 (3)	0
Cough	23 (15)	0	0	17 (14)	1 (1)	0	2 (6)	0	0
Upper respiratory tract infection	19 (12)	3 (2)	0	13 (11)	4 (3)	0	3 (9)	1 (3)	0
Headache	33 (21)	1 (1)	0	7 (6)	0	0	0	0	0
Thrombocytopenia	11 (7)	2 (1)	4 (3)	7 (6)	7 (6)	2 (2)	4 (11)	0	1 (3)
Anemia	5 (3)	16 (10)	2 (1)	2 (2)	8 (7)	0	1 (3)	3 (9)	0
Fatigue	13 (8)	2 (1)	0	10 (8)	0	0	7 (20)	1 (3)	0
Nausea	11 (7)	0	0	14 (12)	1 (1)	0	7 (20)	0	0
Pneumonia	8 (5)	8 (5)	0	4 (3)	10 (8)	0	1 (3)	1 (3)	0
Rash	10 (6)	0	0	12 (10)	4 (3)	0	2 (6)	0	0
Constipation	10 (6)	0	0	9 (8)	0	0	3 (9)	2 (6)	0
Respiratory tract infection	14 (9)	1 (1)	1 (1)	7 (6)	1 (1)	0	0	0	0
ALT increased	1 (1)	2 (1)	0	4 (3)	9 (8)	1 (1)	2 (6)	1 (3)	0
Infusion-related reaction	0	0	0	7 (6)	2 (2)	0	7 (20)	1 (3)	0
AST increased	2 (1)	1 (1)	0	5 (4)	6 (5)	0	1 (3)	1 (3)	0
Neutrophil count decreased	1 (1)	1 (1)	1 (1)	0	3 (3)	6 (5)	0	0	1 (3)
Transaminases increased	0	0	0	1 (1)	6 (5)	0	0	0	0
First 6 months									
All	74 (48)	41 (27)	14 (9)	21 (18)	57 (48)	32 (27)	10 (29)	9 (26)	7 (20)
Neutropenia	5 (3)	9 (6)	7 (5)	6 (5)	24 (20)	18 (15)	2 (6)	5 (14)	6 (17)
Diarrhea	17 (11)	1 (1)	0	19 (16)	10 (8)	1 (1)	5 (14)	0	0
Pyrexia	14 (9)	0	0	12 (10)	6 (5)	1 (1)	5 (14)	1 (3)	0
Headache	32 (21)	1 (1)	0	5 (4)	0	0	0	0	0
Thrombocytopenia	8 (5)	3 (2)	3 (2)	6 (5)	7 (6)	2 (2)	4 (11)	0	1 (3)
Cough	16 (10)	0	0	15 (13)	0	0	2 (6)	0	0
Anemia	5 (3)	13 (8)	2 (1)	2 (2)	7 (6)	0	1 (3)	3 (9)	0
Fatigue	10 (6)	2 (1)	0	7 (6)	0	0	7 (20)	1 (3)	0
Nausea	9 (6)	0	0	10 (8)	0	0	7 (20)	0	0
Constipation	9 (6)	0	0	8 (7)	0	0	3 (9)	2 (6)	0
Pneumonia	1 (1)	4 (3)	0	1 (1)	4 (3)	0	1 (3)	1 (3)	0
ALT increased	1 (1)	1 (1)	0	3 (3)	8 (7)	1 (1)	1 (3)	1 (3)	0
Infusion-related reaction	0	0	0	6 (5)	2 (2)	0	7 (20)	1 (3)	0
AST increased	1 (1)	1 (1)	0	4 (3)	5 (4)	0	1 (3)	1 (3)	0
Neutrophil count decreased	0	0	1 (1)	1 (1)	3 (3)	4 (3)	0	0	1 (3)

NOTE. Data are No. (%). AEs are listed in order of descending frequency in the total study population (patients who had at least one study drug dose) in each period.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

grade ≥ 3 AEs and fewer AEs leading to discontinuation compared with I-R (the preferred investigator's choice therapy). Events of atrial fibrillation and grade ≥ 3 hypertension and bleeding occurred infrequently in patients with acalabrutinib monotherapy, with no intracranial hemorrhages reported.[17,30] The incidence of SPMs was higher with acalabrutinib monotherapy compared with investigator's choice; however, half of the malignancies with acalabrutinib monotherapy were nonmelanoma skin cancers. The high incidence of SPMs observed here with acalabrutinib monotherapy is consistent with previous reports in patients receiving BTKi therapy.[31,32] Furthermore, SPMs are common in patients with CLL.[33]

The benefits of BTKi therapy have been evaluated in treatment-to-progression settings. Long-term tolerability is paramount, particularly because CLL commonly occurs in elderly patients who often have comorbidities.[12] AEs associated with ibrutinib can be therapeutically limiting,[34] (eg, 11%-67% of patients discontinued ibrutinib because of AEs after a median of 6 months)[35-38] and are suggested to relate to the binding of non-BTK targets,[17,39] although this is not definitively established. The tolerability profile of acalabrutinib suggests the decreased off-target activity observed in preclinical studies[17,40] may translate to a clinical setting. A phase III study directly comparing acalabrutinib with ibrutinib in high-risk patients with R/R CLL (ClinicalTrials.gov identifier: NCT02477696; other study no. CL-006) is ongoing.

This was a randomized, controlled trial with blinded efficacy assessments (by IRC); however, some limitations exist, including patients and investigators not being masked to treatment assignment, and there was no specific quota for each of the investigator's choice arms, with allocation purely determined by the investigator. The median OS was not reached in either group in this interim analysis. Given the limited follow-up period and the low number of events that occurred in this study, extended follow-up will be needed to detect any differences in OS; however, the ability of patients to cross over to receive acalabrutinib may preclude detection. Furthermore, the absence of an ibrutinib monotherapy arm, which would have facilitated a direct comparison with acalabrutinib, limits interpretation of the study given the current treatment landscape.

In conclusion, this phase III study demonstrated a statistically significant and clinically meaningful PFS with acalabrutinib compared with I-R or B-R treatment, together with a tolerable safety profile, in patients with R/R CLL. These findings suggest the use of acalabrutinib as an effective treatment for patients with R/R CLL (including patients with high-risk disease characteristics), and support the recent approval of acalabrutinib in this setting.

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DATA AVAILABILITY STATEMENT

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

ASCEND: Phase III, Randomized Trial of Acalabrutinib Versus Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

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