SUPPLEMENTAL MATERIAL

Plain language summary

Why was this study done?

Acalabrutinib and ibrutinib are effective targeted therapies that act by inhibiting the activity of a protein call Bruton tyrosine kinase, or BTK, which plays a key role in chronic lymphocytic leukemia, or CLL. However, ibrutinib also inhibits the activity of other proteins similar to BTK, which may result in additional side effects. The phase 3 ELEVATE-RR study that compared acalabrutinib with ibrutinib previously showed that acalabrutinib is no less effective than ibrutinib in patients with CLL who have received previous treatment for their disease but results in fewer side effects than ibrutinib, particularly certain types of cardiovascular side effects, with long-term treatment. The analysis presented here uses several additional methods to compare the safety of the two therapies, including a relatively new scoring method.

How were the data collected?

Assessments measuring the side effects that patients experienced were collected while patients were being treated. In-depth event-based analyses, including an adverse event (AE) burden score, which was based on all side effects patients experienced during treatment and took into consideration how many times a patient experienced the same side effect, how long each occurrence of a side effect lasted, and how severe it was.

What were the results?

After approximately 3 years of treatment, side effects such as atrial fibrillation (an irregular and often rapid heart rhythm), hypertension (high blood pressure), bleeding events, diarrhea, and arthralgia (joint pain) were less commonly observed with acalabrutinib versus ibrutinib, even when adjusting for the length of time each patient was on treatment. In ibrutinib-treated patients, heart-related side effects (atrial fibrillation and hypertension) occurred earlier in treatment compared with patients receiving acalabrutinib, regardless of whether they had a prior history of these events before starting treatment. AE burden was also lower with acalabrutinib compared with ibrutinib overall (considering all side effects) and for the side effects of atrial fibrillation, hypertension, and bleeding. In addition, the overall AE burden score was lower for acalabrutinib vs ibrutinib during each of the first 4 years of treatment.

Why do the results matter to patients and physicians?

In addition to results previously published for this study, this analysis further shows that acalabrutinib is associated with lower impact of important side effects like atrial fibrillation, hypertension, bleeding events, diarrhea, and arthralgia compared with ibrutinib in patients with previously treated CLL. These findings may help patients and physicians in deciding which treatment options may be most appropriate.

Table S1. Patient demographics and baseline characteristics

Characteristic	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
Age, mean (SD), years	65.5 (9.3)	65.3 (9.6)
<65 years	124 (46.3)	122 (46.0)
≥65 years	144 (53.7)	143 (54.0)
Female sex	83 (31.0)	71 (26.8)
Race		
White	257 (95.9)	245 (92.5)
Black or African American	5 (1.9)	8 (3.0)
Asian	1 (0.4)	2 (0.8)
Not reported	5 (1.9)	10 (3.8)
ECOG PS score		
0	116 (43.3)	126 (47.5)
1	131 (48.9)	117 (44.2)
2	20 (7.5)	22 (8.3)
Missing	1 (0.4)	0
Bulky disease		
≥5 cm	128 (47.8)	136 (51.3)
≥10 cm	33 (12.3)	34 (12.8)
Rai stage		
3	40 (14.9)	46 (17.4)

4	91 (34.0)	88 (33.2)
Cytogenetic abnormalities		
del(17p) and/or *TP53* mutated	136 (50.7)	135 (50.9)
del(17p)	121 (45.1)	120 (45.3)
TP53 mutated	100 (37.3)	112 (42.3)
del(11q)	167 (62.3)	175 (66.0)
Complex karyotype*	124 (46.3)	125 (47.2)
IGHV unmutated	220 (82.1)	237 (89.4)
No. prior therapies, median (range)	2 (1–9)	2 (1–12)
1	132 (49.3)	126 (47.5)
2	67 (25.0)	74 (27.9)
3	35 (13.1)	37 (14.0)
≥4	33 (12.3)	28 (10.6)
Missing	1 (0.4)	0

Data are n (%) unless otherwise specified.

ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region genes; SD, standard deviation; *TP53*, tumor protein 53.

*Patients with ≥3 chromosomal abnormalities.

Table S2. Characteristics of any-grade atrial fibrillation/flutter and hypertension

	Any-Grade Afib/flutter		Any-Grade HTN	
	Acalabrutinib (n = 266)	**Ibrutinib (n = 263)**	**Acalabrutinib (n = 266)**	**Ibrutinib (n = 263)**
Median (range) time to onset, months*	28.8 (0.4, 52.0)	16.0 (0.5, 48.3)	8.1 (0.0, 44.0)	7.0 (0.0, 39.8)
Leading to treatment discontinuation, n (%)	0	7 (2.7)	0	0
Leading to dose reduction, n (%)	1 (0.4)	0	0	0
Concomitant medication use,† n (%)	22 (8.3)	36 (13.7)	13 (4.9)	50 (19.0)
Antithrombotic agents	14 (5.3)	24 (9.1)	–	–
Beta-blocking agents	13 (4.9)	16 (6.1)	–	–
Renin-angiotensin system–acting agents	–	–	9 (3.4)	36 (13.7)
Calcium channel blockers	–	–	8 (3.0)	19 (7.2)
Subsequent AEs w/in 30 days after event, n/N (%)				
HTN	1/25 (4.0)	1/42 (2.4)	–	–
Hemorrhage	7/25 (28.0)	12/42 (28.6)	7/25 (28.0)	23/61 (37.7)
Major hemorrhage	2/25 (8.0)	2/42 (4.8)	1/25 (4.0)	2/61 (3.3)
Atrial fibrillation	–	–	3/25 (12.0)	6/61 (9.8)

AE, adverse event; Afib/flutter, atrial fibrillation/flutter; HTN, hypertension.

*Median and range calculated only among patients with the event.

†Includes concomitant medication used to treat the event occurring in ≥5% of patients in each arm.

Table S3. Characteristics of any-grade hemorrhage

	Acalabrutinib (n = 266)	**Ibrutinib (n = 263)**
Median (range) time to onset, months*	1.2 (0.0–36.1)	1.2 (0.0–41.2)
Incidence by patient subgroup, n/N (%)		
Age		
<65 years	32/124 (25.8)	57/121 (47.1)
≥65 years	69/142 (48.6)	78/142 (54.9)
Prior line of therapy		
1–3	92/238 (38.7)	127/236 (53.8)
≥4	9/28 (32.1)	8/27 (29.6)
Leading to treatment discontinuation, n (%)	2 (0.8)	4 (1.5)
Leading to dose reduction, n (%)	3 (1.1)	2 (0.8)
Concomitant antithrombotic use†, n (%)	119 (44.4)	139 (52.5)
Major hemorrhage within 14 days of antithrombotic	6 (2.3)	8 (3.0)
Prior treatment-emergent thrombocytopenia in patients with hemorrhage events, n/N (%)	9/101 (8.9)	7/135 (5.2)

*Median and range calculated only among patients with the event.

†Concomitant antithrombotic use among all patients at any time.

Table S4. Characteristics of any-grade infections

	Acalabrutinib (n = 266)	**Ibrutinib (n = 263)**
Median (range) time to onset, months*	3.9 (0.0–54.4)	2.5 (0.1–46.7)
Incidence by patient subgroup, n/N (%)		
Age		
<65 years	98/124 (79.0)	91/121 (75.2)
≥65 years	110/142 (77.5)	123/142 (86.6)
Prior line of therapy		
1–3	185/238 (77.7)	189/236 (80.1)
≥4	23/28 (82.1)	25/27 (92.6)
Leading to treatment discontinuation, n (%)	16 (6.0)	17 (6.5)
Leading to dose reduction, n (%)	1 (0.4)	2 (0.8)
Type of infection, n (%)		
Upper respiratory tract infections	126 (47.4)	110 (41.8)
Urinary tract infections	25 (9.4)	44 (16.7)
Pneumonia†	58 (21.8)	48 (18.3)
Sepsis‡	12 (4.5)	12 (4.6)
Opportunistic infections§	13 (4.9)	11 (4.2)

MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardised MedDRA Query. *Median and range calculated only among patients with the event.

†Includes all preferred terms that contain the term “pneumonia.”

‡Includes all preferred terms that contain the term “sepsis.”

§Opportunistic infections were identified based on MedDRA SMQ (narrow).

Table S5. Incidence of any-grade cardiac arrhythmias, any-grade hypertension, and grade ≥3 infection by baseline characteristics

Baseline Characteristic	Patients With Baseline Characteristic, n (%)		Event Incidence, n (%)					
			Any-Grade Cardiac Arrhythmias		Any-Grade Hypertension		Grade ≥3 Infection	
	Acala (n = 266)	Ibru (n = 263)	Acala (n = 266)	Ibru (n = 263)	Acala (n = 266)	Ibru (n = 263)	Acala (n = 266)	Ibru (n = 263)
Age								
< median	129 (48.5)	134 (51.0)	12 (9.3)	16 (11.9)	13 (10.1)	32 (23.9)	38 (29.5)	34 (25.4)
≥ median	137 (51.5)	129 (49.0)	30 (21.9)	38 (29.5)	14 (10.2)	30 (23.3)	45 (32.8)	51 (39.5)
Male	184 (69.2)	192 (73.0)	34 (18.5)	43 (22.4)	22 (12.0)	45 (23.4)	60 (32.6)	65 (33.9)
Female	82 (30.8)	71 (27.0)	8 (9.8)	11 (15.5)	5 (6.1)	17 (23.9)	23 (28.0)	20 (28.2)

Number of prior lines of therapy								
1	133 (50.0)	124 (47.1)	20 (15.0)	26 (21.0)	12 (9.0)	39 (31.5)	37 (27.8)	31 (25.0)
>1	133 (50.0)	139 (52.9)	22 (16.5)	28 (20.1)	15 (11.3)	23 (16.5)	46 (34.6)	54 (38.8)
Medical history								
Coronary artery disease	32 (12.0)	36 (13.7)	9 (28.1)	11 (30.6)	2 (6.3)	7 (19.4)	13 (40.6)	9 (25.0)
Supraventricular arrhythmias	26 (9.8)	16 (6.1)	14 (53.8)	5 (31.3)	2 (7.7)	1 (6.3)	11 (42.3)	7 (43.8)
Ventricular arrhythmias	5 (1.9)	8 (3.0)	1 (20.0)	3 (37.5)	0	5 (62.5)	2 (40.0)	1 (12.5)
Heart valve disease	6 (2.3)	9 (3.4)	0	1 (11.1)	0	2 (22.2)	6 (100.0)	3 (33.3)
Diabetes	51 (19.2)	44 (16.7)	13 (25.5)	6 (13.6)	3 (5.9)	7 (15.9)	23 (45.1)	22 (50.0)

Obesity	15 (5.6)	10 (3.8)	2 (13.3)	3 (30.0)	3 (20.0)	1 (10.0)	3 (20.0)	4 (40.0)
Ischemic stroke	9 (3.4)	9 (3.4)	1 (11.1)	3 (33.3)	1 (11.1)	2 (22.2)	3 (33.3)	6 (66.7)
Chronic kidney disease	20 (7.5)	21 (8.0)	3 (15.0)	6 (28.6)	1 (5.0)	5 (23.8)	8 (40.0)	13 (61.9)
Hypertension	128 (48.1)	127 (48.3)	26 (20.3)	31 (24.4)	17 (13.3)	30 (23.6)	39 (30.5)	43 (33.9)
Heart failure	12 (4.5)	10 (3.8)	2 (16.7)	2 (20.0)	1 (8.3)	1 (10.0)	3 (25.0)	3 (30.0)
Prior medication								
Renin-angiotensin system–acting agents	78 (29.3)	70 (26.6)	17 (21.8)	16 (22.9)	8 (10.3)	8 (11.4)	25 (32.1)	29 (41.4)
Antihypertensives	9 (3.4)	3 (1.1)	1 (11.1)	1 (33.3)	0	0	3 (33.3)	2 (66.7)
Antithrombotic agents	67 (25.2)	68 (25.9)	18 (26.9)	21 (30.9)	8 (11.9)	18 (26.5)	23 (34.3)	21 (30.9)

Beta blockers	69 (25.9)	67 (25.5)	19 (27.5)	21 (31.3)	5 (7.2)	10 (14.9)	26 (37.7)	22 (32.8)
Calcium channel blockers	35 (13.2)	34 (12.9)	7 (20.0)	10 (29.4)	3 (8.6)	6 (17.6)	13 (37.1)	12 (35.3)
Lymphocyte count								
< median	138 (51.9)	126 (47.9)	22 (15.9)	27 (21.4)	13 (9.4)	24 (19.0)	37 (26.8)	44 (34.9)
≥ median	128 (48.1)	137 (52.1)	20 (15.6)	27 (19.7)	14 (10.9)	38 (27.7)	46 (35.9)	41 (29.9)
Absolute neutrophil count								
<500 /mm^3	1 (0.4)	2 (0.8)	1 (100.0)	0	0	0	0	2 (100.0)
<1000 /mm^3	11 (4.1)	10 (3.8)	2 (18.2)	1 (10.0)	1 (9.1)	1 (10.0)	4 (36.4)	4 (40.0)
<2500 /mm^3	57 (21.4)	58 (22.1)	11 (19.3)	15 (25.9)	4 (7.0)	8 (13.8)	18 (31.6)	26 (44.8)
Hemoglobin								
<12 g/dL	141 (53.0)	139 (52.9)	25 (17.7)	27 (19.4)	13 (9.2)	26 (18.7)	51 (36.2)	55 (39.6)

<10 g/dL	59 (22.2)	57 (21.7)	10 (16.9)	13 (22.8)	4 (6.8)	10 (17.5)	19 (32.2)	25 (43.9)
<8 g/dL	12 (4.5)	10 (3.8)	0	2 (20.0)	1 (8.3)	3 (30.0)	5 (41.7)	6 (60.0)

Table S6. AE burden score for common symptomatic AEs

	AE Burden Score, Mean (SD)			
	Grade 1–4		Grade 1–5	
	Acalabrutinib	Ibrutinib	Acalabrutinib	Ibrutinib
Fatigue	0.09 (0.268)	0.10 (0.401)	0.09 (0.268)	0.10 (0.401)
Diarrhea	0.11* (0.537)	0.11 (0.325)	0.11* (0.537)	0.11 (0.325)
Headache	0.08* (0.296)	0.08 (0.440)	0.08* (0.296)	0.08 (0.440)
Musculoskeletal events†	0.14 (0.373)	0.35* (1.103)	0.14 (0.373)	0.35* (1.103)

AE, adverse event; SD, standard deviation.

Incidence and exposure-adjusted incidence of fatigue, diarrhea, and headache can be found in Table 1; for musculoskeletal events, any-grade and grade ≥3 incidence was 79 (29.7%) vs 98 (37.3%) and 3 (1.1%) vs 4 (1.5%) for acalabrutinib vs ibrutinib, respectively; any-grade and grade ≥3 exposure-adjusted incidence was 0.9 vs 1.2 and 0.03 vs 0.05, respectively.

*Two-sided *P*-value < .05 without multiplicity adjustment based on Wilcoxon rank-sum test. *P*-value compares difference in overall distribution rather than mean score.

†Includes preferred terms arthralgia, myalgia, muscle spasms, and musculoskeletal pain.

Table S7. Least squares mean change from baseline in PROs (MMRM)

	EORTC QLQ-C30 GHS			EQ-5D-3L VAS		
	Acalabrutinib	**Ibrutinib**	**Difference (95% CI)**	**Acalabrutinib**	**Ibrutinib**	**Difference (95% CI)**
Baseline score, mean (SD) [completion rate, n (%)*]	60.7 (21.91) [239 (90.2)]	60.5 (21.25) [232 (87.9)]	–	64.8 (19.96) [238 (89.8)]	65.0 (19.37) [234 (88.6)]	–
LS mean (SE) change from baseline [completion rate, n (%)*]						
Average	5.39 (1.74)	4.26 (1.75)	1.12 (−1.26, 3.51)	4.08 (1.68)	2.42 (1.68)	1.66 (−0.58, 3.90)
Week 12	5.35 (1.76) [219 (86.2)]	3.55 (1.77) [215 (87.4)]	1.79 (−0.77, 4.36)	3.60 (1.69) [215 (84.6)]	1.81 (1.70) [210 (85.4)]	1.79 (−0.56, 4.14)
Week 16	5.35 (1.76) [207 (83.5)]	3.60 (1.77) [195 (81.3)]	1.75 (−0.79, 4.29)	3.63 (1.69) [206 (83.1)]	1.85 (1.69) [192 (80.0)]	1.78 (−0.55, 4.11)
Week 20	5.35 (1.75) [206 (83.7)]	3.65 (1.76) [197 (82.8)]	1.71 (−0.81, 4.22)	3.66 (1.69) [202 (82.1)]	1.89 (1.69) [192 (80.7)]	1.77 (−0.54, 4.08)
Week 24	5.36 (1.75) [215 (88.8)]	3.69 (1.76) [198 (85.3)]	1.66 (−0.82, 4.15)	3.69 (1.68) [209 (86.4)]	1.93 (1.69) [195 (84.1)]	1.76 (−0.53, 4.06)
Week 36	5.37 (1.74) [207 (88.1)]	3.83 (1.75) [187 (85.4)]	1.53 (−0.90, 3.96)	3.78 (1.68) [203 (86.4)]	2.05 (1.68) [186 (84.9)]	1.74 (−0.52, 4.00)
Week 48	5.37 (1.74) [198 (85.3)]	3.97 (1.75) [180 (84.9)]	1.40 (−0.99, 3.79)	3.88 (1.68) [197 (84.9)]	2.17 (1.68) [178 (84.0)]	1.71 (−0.52, 3.95)

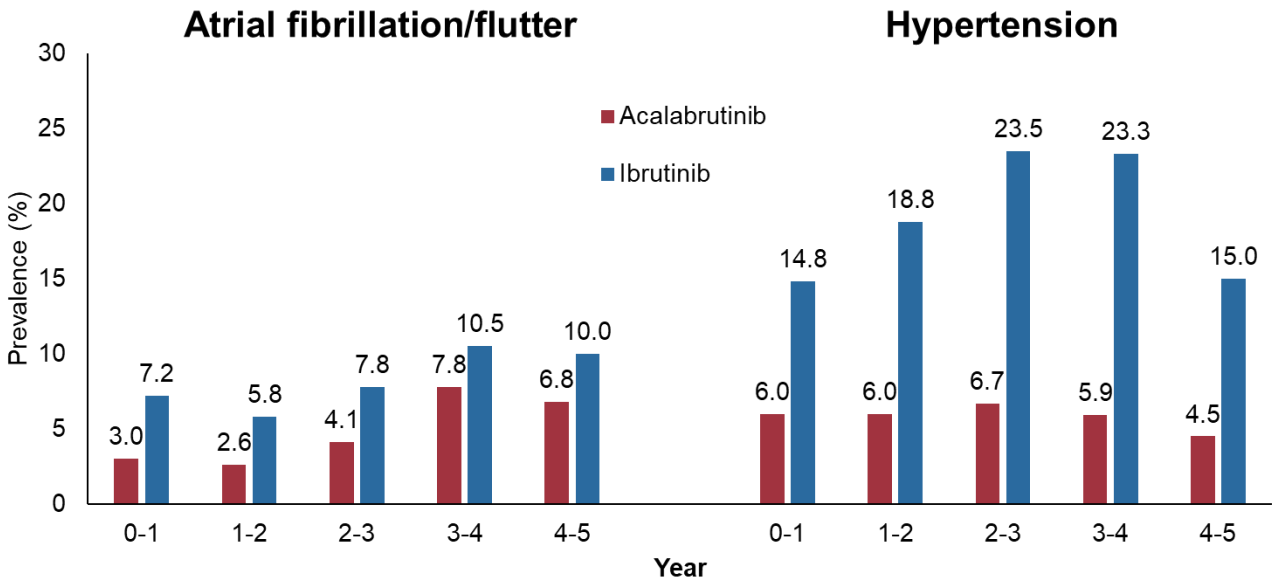
Week 60	5.38 (1.74) [195 (86.3)]	4.11 (1.75) [162 (82.7)]	1.27 (−1.11, 3.65)	3.97 (1.67) [193 (85.4)]	2.29 (1.68) [163 (83.2)]	1.69 (−0.54, 3.92)
Week 72	5.39 (1.74) [190 (87.6)]	4.25 (1.75) [165 (87.8)]	1.14 (−1.24, 3.52)	4.07 (1.68) [187 (86.2)]	2.41 (1.68) [165 (87.8)]	1.66 (−0.58, 3.90)
Week 84	5.40 (1.74) [178 (85.6)]	4.39 (1.76) [158 (87.8)]	1.01 (−1.41, 3.43)	4.16 (1.68) [179 (86.1)]	2.52 (1.69) [157 (87.2)]	1.64 (−0.62, 3.90)
Week 96	5.41 (1.75) [172 (86.0)]	4.53 (1.77) [151 (86.8)]	0.88 (−1.59, 3.35)	4.26 (1.69) [170 (85.0)]	2.64 (1.70) [151 (86.8)]	1.61 (−0.69, 3.91)
Week 108	5.42 (1.77) [174 (89.7)]	4.67 (1.79) [140 (85.9)]	0.75 (−1.80, 3.29)	4.35 (1.70) [176 (90.7)]	2.76 (1.71) [139 (85.3)]	1.59 (−0.76, 3.94)
Week 120	5.43 (1.79) [165 (87.3)]	4.81 (1.81) [137 (87.8)]	0.62 (−2.02, 3.25)	4.44 (1.71) [162 (85.7)]	2.88 (1.72) [137 (87.8)]	1.56 (−0.86, 3.98)
Week 132	5.44 (1.81) [153 (87.9)]	4.95 (1.84) [127 (85.8)]	0.49 (−2.26, 3.23)	4.54 (1.72) [152 (87.4)]	3.00 (1.74) [126 (85.1)]	1.54 (−0.96, 4.03)
Week 144	5.45 (1.83) [141 (82.0)]	5.09 (1.87) [121 (84.6)]	0.35 (−2.52, 3.23)	4.63 (1.74) [141 (82.0)]	3.12 (1.76) [118 (82.5)]	1.51 (−1.07, 4.10)
Week 156	5.46 (1.86) [123 (81.5)]	5.23 (1.90) [113 (86.3)]	0.22 (−2.79, 3.24)	4.73 (1.76) [127 (84.1)]	3.24 (1.78) [112 (85.5)]	1.49 (−1.20, 4.17)
Week 168	5.46 (1.89) [97 (71.9)]	5.37 (1.94) [82 (71.3)]	0.09 (−3.07, 3.26)	4.82 (1.78) [93 (68.9)]	3.36 (1.81) [83 (72.2)]	1.46 (−1.33, 4.26)
Week 180	5.47 (1.92) [74 (71.8)]	5.51 (1.98) [66 (73.3)]	−0.04 (−3.36, 3.29)	4.92 (1.80) [77 (74.8)]	3.48 (1.83) [69 (76.7)]	1.44 (−1.47, 4.35)

Meaningful improvements in EORTC QLQ-C30 GHS and EQ-5D-3L VAS were defined as a change in score greater than +8 and a change in score of +7 or greater, respectively.

CI, confidence interval; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-3L, EuroQoL 5-Dimension 3-Levels; GHS, Global Health Status; LS, least squares; MMRM, mixed model for repeated measures; PROs, patient-reported outcomes; SD, standard deviation; SE, standard error; VAS, visual analogue scale.

*Completion rate for all questions. Completion percentages calculated as (# subjects who completed all questions at the visit) / (# subjects expected to complete at that visit); a subject is expected to complete if they are alive and have not discontinued treatment at the visit, and if the subject's target date for the visit falls on or before the data cutoff date.

Figure S1. Prevalence of any-grade atrial fibrillation/flutter and hypertension by yearly interval



No. at risk										
Acalabrutinib	266	232	195	153	44	266	232	195	153	44
Ibrutinib	263	207	166	133	40	263	207	166	133	40

Figure S2. Cumulative incidence of any-grade atrial fibrillation/flutter and hypertension

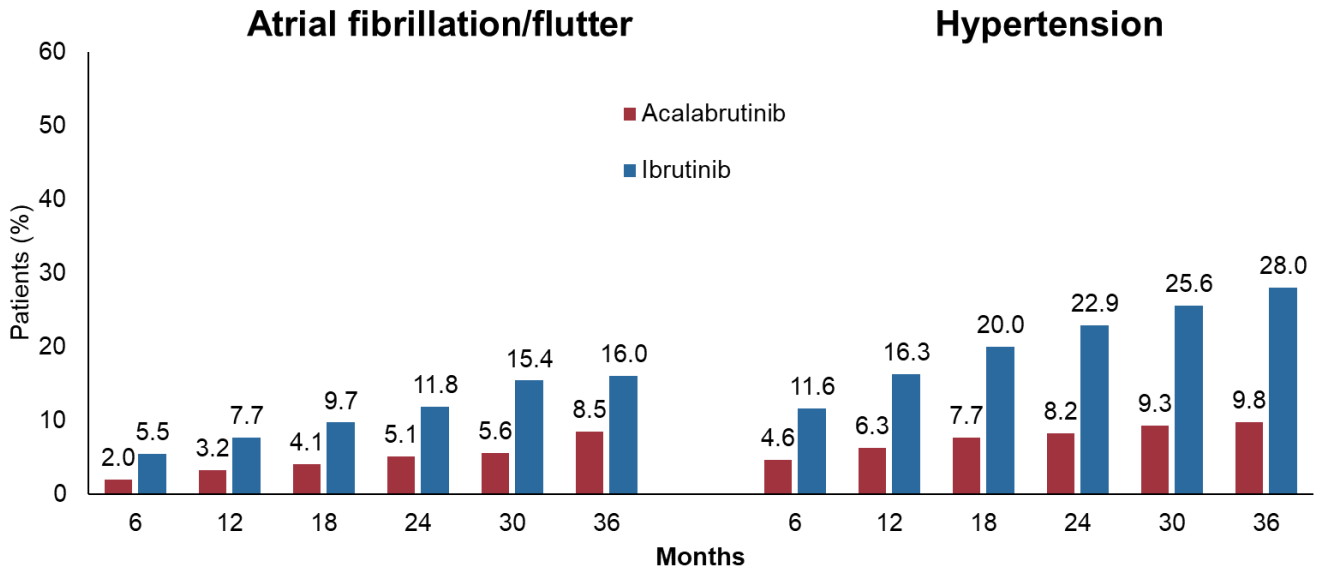


Figure S3. Cumulative incidence of any-grade bleeding

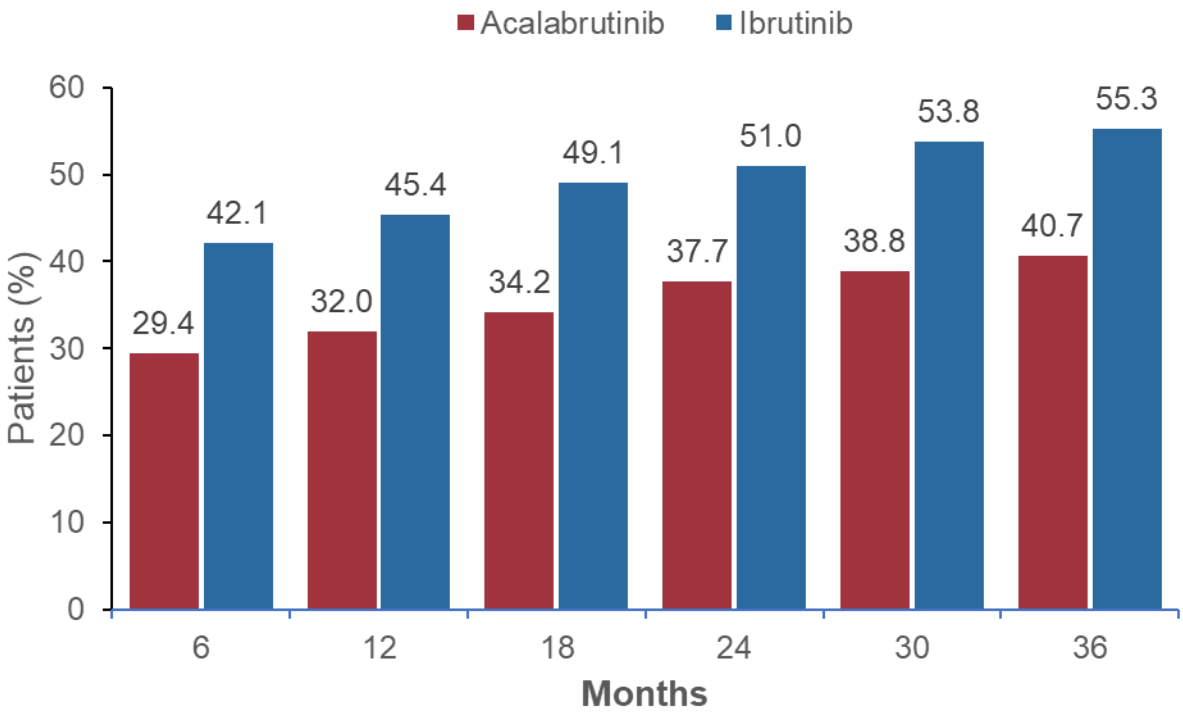
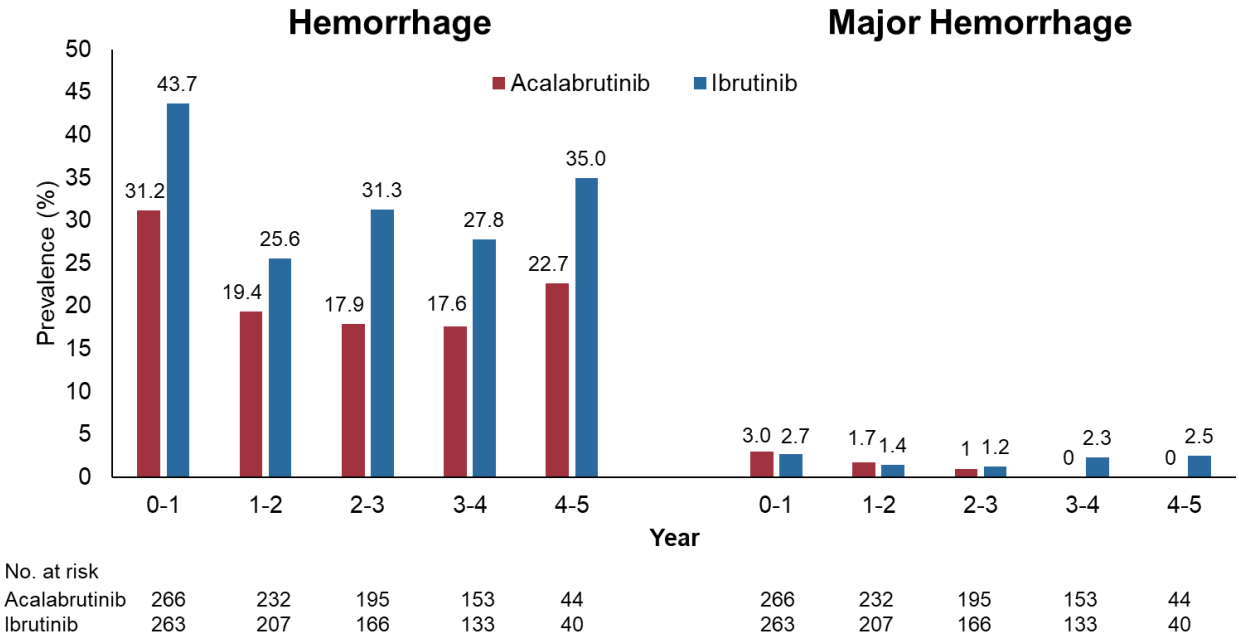


Figure S4. Prevalence of any-grade hemorrhage and major hemorrhage by yearly interval



No. at risk										
Acalabrutinib	266	232	195	153	44	266	232	195	153	44
Ibrutinib	263	207	166	133	40	263	207	166	133	40

Figure S5. Cumulative incidence of any-grade infections

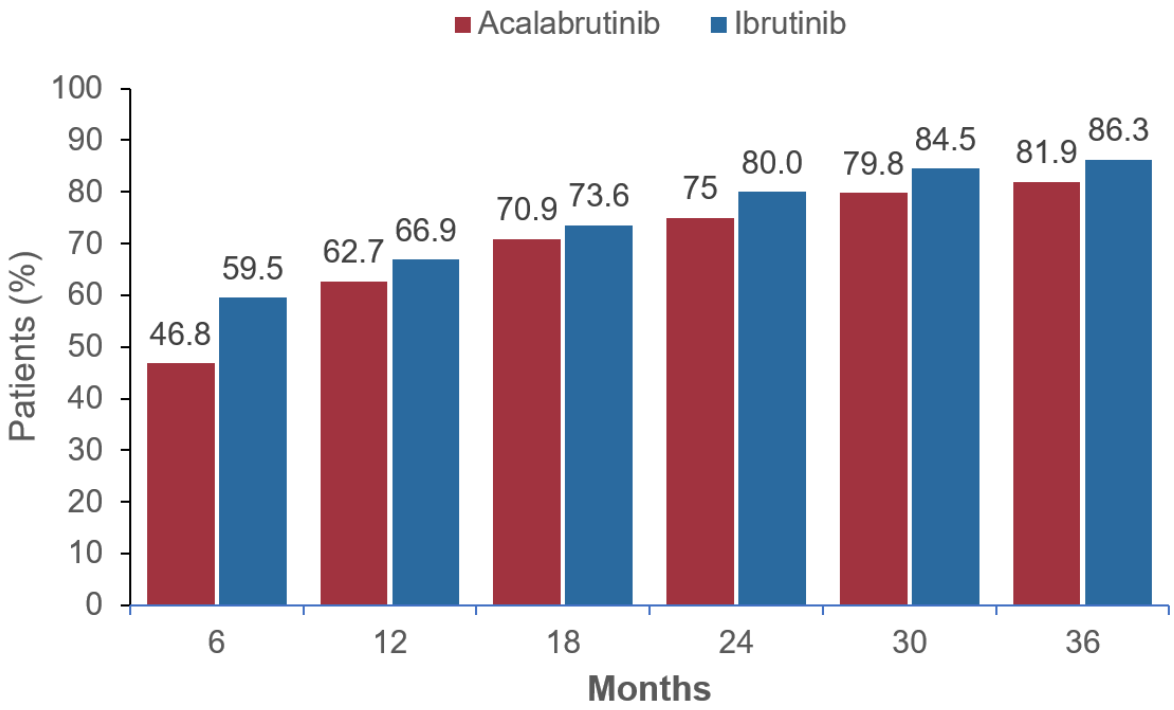
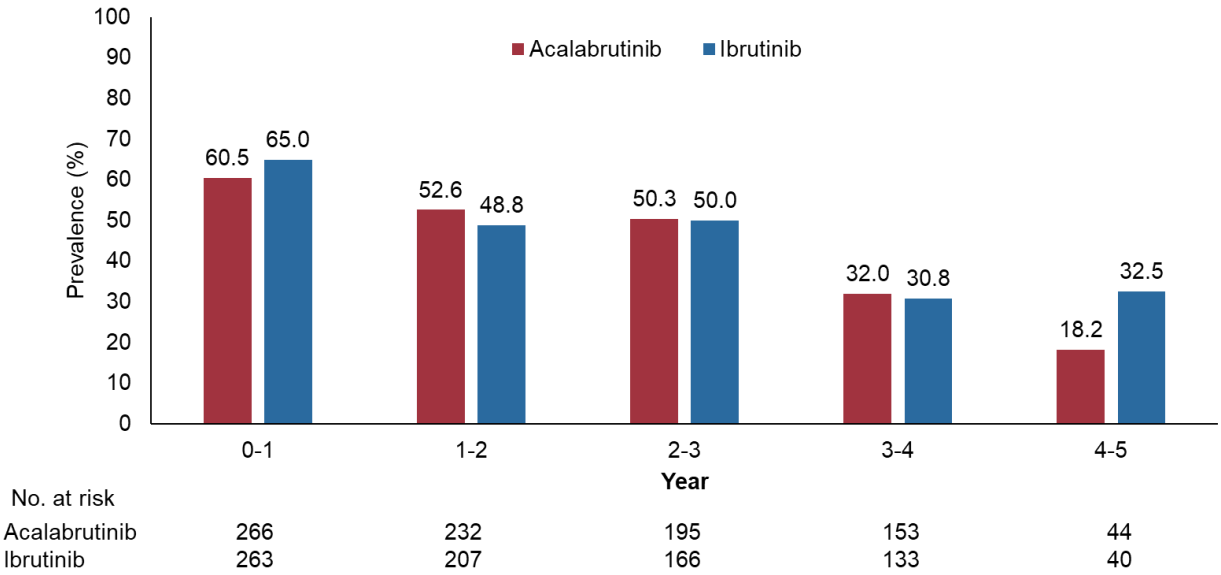


Figure S6. Prevalence of any-grade infections by yearly interval



No. at risk					
Acalabrutinib	266	232	195	153	44
Ibrutinib	263	207	166	133	40