Supplemental Appendix

Supplemental Methods

Cardiovascular risk factors were identified based on preexisting cardiovascular risk factors or past medical history of a cardiac disorder, including the preferred terms and/or system organ class terms of hypercoagulation, cardiac disorders, cardiac septal defect, hypothyroidism, hyperthyroidism, Addison's disease, Basedow's disease, Cushing's syndrome, hypoparathyroidism, toxic goitre, blood cholesterol increased, cardiac murmur, heart rate irregular, hyperlipidemia, diabetes mellitus, hypercholesterolemia, type 2 diabetes mellitus, obesity, hyperglycemia, hyperkalemia, dyslipidemia, glucose tolerance impaired, hypercalcemia, type 1 diabetes mellitus, hypertriglyceridemia, hypocalcemia, metabolic syndrome, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, transient ischemic attack, cerebrovascular accident, cerebral hemorrhage, cerebral ischemia, hemorrhage intracranial, hypertonia, ischemic stroke, chronic kidney disease, renal failure, renal impairment, glomerulonephritis chronic, respiratory thoracic and mediastinal disorders, tobacco use, cardiac-related surgical and medical procedures, and vascular disorders.

Hypertension risk factors were identified based on preexisting history of hypertension or presence of underlying conditions, including the preferred terms coronary artery disease, cardiac failure (chronic and congestive), hypertensive heart disease, left ventricular dysfunction, left ventricular failure, myocardial fibrosis, myocardial ischemia, myocarditis, hypertrophic cardiomyopathy, Cushing's syndrome, blood cholesterol increased, hyperlipidemia, hypercholesterolemia, (type 2) diabetes mellitus, obesity, overweight, transient ischemic attack, cerebellar stroke, cerebrovascular accident, chronic kidney disease, chronic

obstructive pulmonary disease, pulmonary hypertension, pulmonary edema, coronary artery bypass, coronary arterial stent insertion, cardiac pacemaker insertion, stent placement, hypertension, essential hypertension, and aortic stenosis.

Supplemental Table S1. Patient Demographics and Baseline Characteristics for the Pooled Acalabrutinib Monotherapy and Comparator Arms From ASCEND and ELEVATE-TN

Demographic/Baseline Characteristic	Pooled Patients From ASCEND and ELEVATE-TN		Pooled Patients From ASCEND and ELEVATE-TN With Cardiac Events	
	Acalabrutinib Monotherapy (N=333)	Pooled Comparator Arms (n=322)	Acalabrutinib Monotherapy (N=45)	Pooled Comparator Arms (n=25)
Age, median (range), years	69.0 (32–89)	69.0 (34–91)	72.0 (54–84)	70.0 (55–91)
Male, n (%)	217 (65.2)	202 (62.7)	26 (57.8)	16 (64.0)
Race, n (%)				
White	314 (94.3)	296 (91.9)	42 (93.3)	24 (96.0)
Black or African American	4 (1.2)	4 (1.2)	2 (4.4)	1 (4.0)
Asian	7 (2.1)	7 (2.2)	1 (2.2)	0
American Indian or Alaska Native	0	1 (0.3)	0	0
Native Hawaiian or Other Pacific Islander	0	2 (0.6)	0	0
Missing	8 (2.4)	12 (3.7)	0	0
BMI (kg/m^2), median (range)	27.1 (18–49)[a]	26.7 (16–46)[b]	26.9 (18–47)[c]	29.0 (22–38)[d]
ECOG PS score, n (%)				
0	148 (44.4)	136 (42.2)	17 (37.8)	7 (28.0)
1	152 (45.6)	155 (48.1)	23 (51.1)	17 (68.0)
2	33 (9.9)	31 (9.6)	5 (11.1)	1 (4.0)

3	0	0	0	0
Number of prior regimens, median (range)	0 (0–8)	0 (0–10)	0 (0–5)	0 (0–5)
Treatment-naïve disease, n (%)	179 (53.8)	169 (52.5)	25 (55.6)	13 (52.0)
Relapsed/refractory disease, n (%)	154 (46.2)	153 (47.5)	20 (44.4)	12 (48.0)

[a]n=328.

[b]n=318.

[c]n=44.

[d]n=24.

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status.

Supplemental Table S2. Most Common (>5% of Patients) Types of Concomitant Medications in Patients with Cardiac Events

Medication Classification[a], n (%)	Patients With Cardiac AEs N=129
Antithrombotic agents[b,c]	36 (27.9)
Beta blocking agents[c]	30 (23.3)
Other analgesics and antipyretics	18 (14.0)
Other beta-lactam antibacterials	18 (14.0)
Drugs for peptic ulcer and GERD	16 (12.4)
Intravenous solution additives	15 (11.6)
Opioids	15 (11.6)
Hypnotics and sedatives	14 (10.9)
Beta-lactam antibacterials, penicillins	13 (10.1)
High-ceiling diuretics	13 (10.1)
Lipid-modifying agents, plain	12 (9.3)
Antiarrhythmics, class I and III	11 (8.5)
Antiemetics and antinauseants	11 (8.5)
Other antibacterials	11 (8.5)
Vasodilators used in cardiac diseases	11 (8.5)
Corticosteroids for systemic use, plain	10 (7.8)
Adrenergics, inhalants	9 (7.0)
Anesthetics, general	9 (7.0)
Drugs for constipation	8 (6.2)
Potassium	8 (6.2)
Quinolone antibacterial	8 (6.2)
Cardiac glycosides	7 (5.4)
Direct-acting antivirals	7 (5.4)
Iron preparations	7 (5.4)

[a]Classification by ATC level 3.

[b]Includes antiplatelet, anticoagulant, and thrombolytic medications. Among patients on antithrombotic agents, 17 (13.2%) received aspirin, including 13 patients (10.1%) who received aspirin with other antithrombotic agents and 4 (3.1%) who received aspirin as the only antithrombotic agent.

[c]Sixteen patients (12.4%) received both antithrombotic and beta-blocking agents.

ATC, anatomical-therapeutic-chemical; GERD, gastroesophageal reflux disease.

Supplemental Table S3. Event Management and Resolution of Grade ≥3 Cardiac AEs in the First 6 Months

Patient Number	Event[b]	Grade	Dose Modification/ Discontinuation	Outcome
1	Coronary artery stenosis	4	Dose delay	Resolved
2	Cardiac tamponade	4	Dose not changed	Resolved
3	Cardiac failure	4	Dose not changed	Ongoing
4	Acute myocardial infarction	3	Dose delay	Resolved
	Atrial fibrillation	3	Dose delay	Resolved
5	Acute coronary syndrome	3	Dose delay	Resolved
	Angina unstable	3	Dose not changed	Resolved
6	Atrial fibrillation	3	Dose not changed	Resolved
7	Atrial fibrillation	3	Dose not changed	Resolved
	Cardiac failure congestive	3	Acalabrutinib discontinued	Resolved
8	Cardiac failure	3	Acalabrutinib discontinued	Resolved
9	Cardiac failure congestive	3	Dose not changed	Resolved
	Pericarditis constrictive	3	Dose delay	Resolved

[a]All but 1 AE (grade 4 cardiac tamponade) were managed with concomitant medications; grade 4 cardiac tamponade was managed by hospitalization.

Supplemental Table S4. Atrial Fibrillation Events Stratified by Shanafelt Risk Score Categories

Shanafelt Risk Score[a] Category	Patients With No History of Atrial Fibrillation (with or without AF events) (n=706), n (%)	Patients With No History of Atrial Fibrillation (subset With Treatment-emergent AF)[b] (n=29), n (%)
0–1	171 (24.2)	3/171 (1.8)
2–3	297 (42.1)	14/297 (4.7)
4	190 (26.9)	6/190 (3.2)
≥5	48 (6.8)	6/48 (12.5)

[a]Classification methodology: older age (2 points for age 65–74 years; 3 points for age ≥75 years), male gender (1 point), valvular heart disease (2 points), and hypertension (1 point).[1-3]

[b]Percentages calculated using the number of patients in each Shanafelt risk score category as the denominator.

AF, atrial fibrillation.

References

1. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102(10):1796-1805.
2. Archibald WJ, Rabe KG, Kabat BF, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib: risk prediction, management, and clinical outcomes. Ann Hematol. 2021;100:143-155.
3. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). Leuk Lymphoma. 2017;58(7):1630-1639.