Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials

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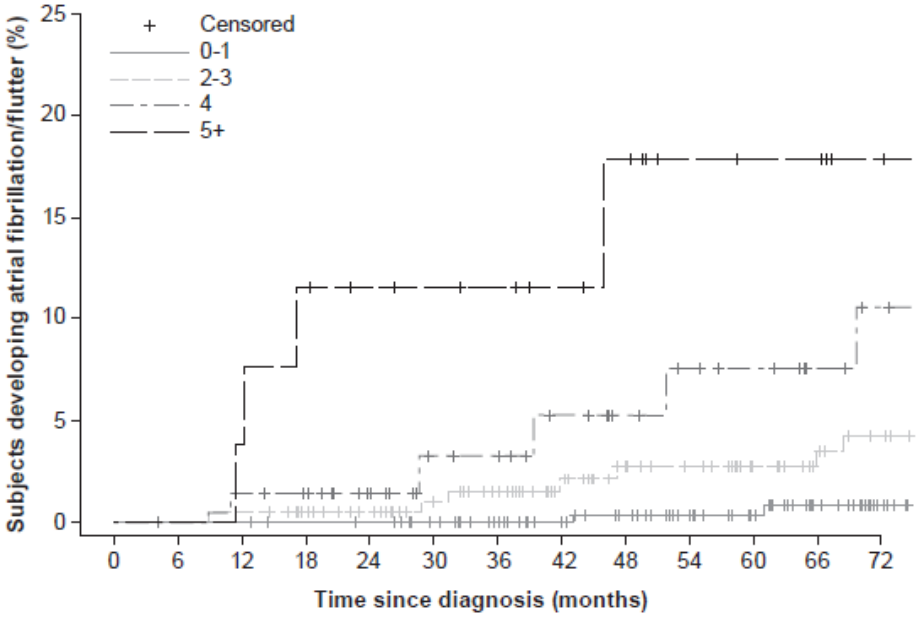
SUPPLEMENTARY MATERIAL: Figures, Information, and Tables

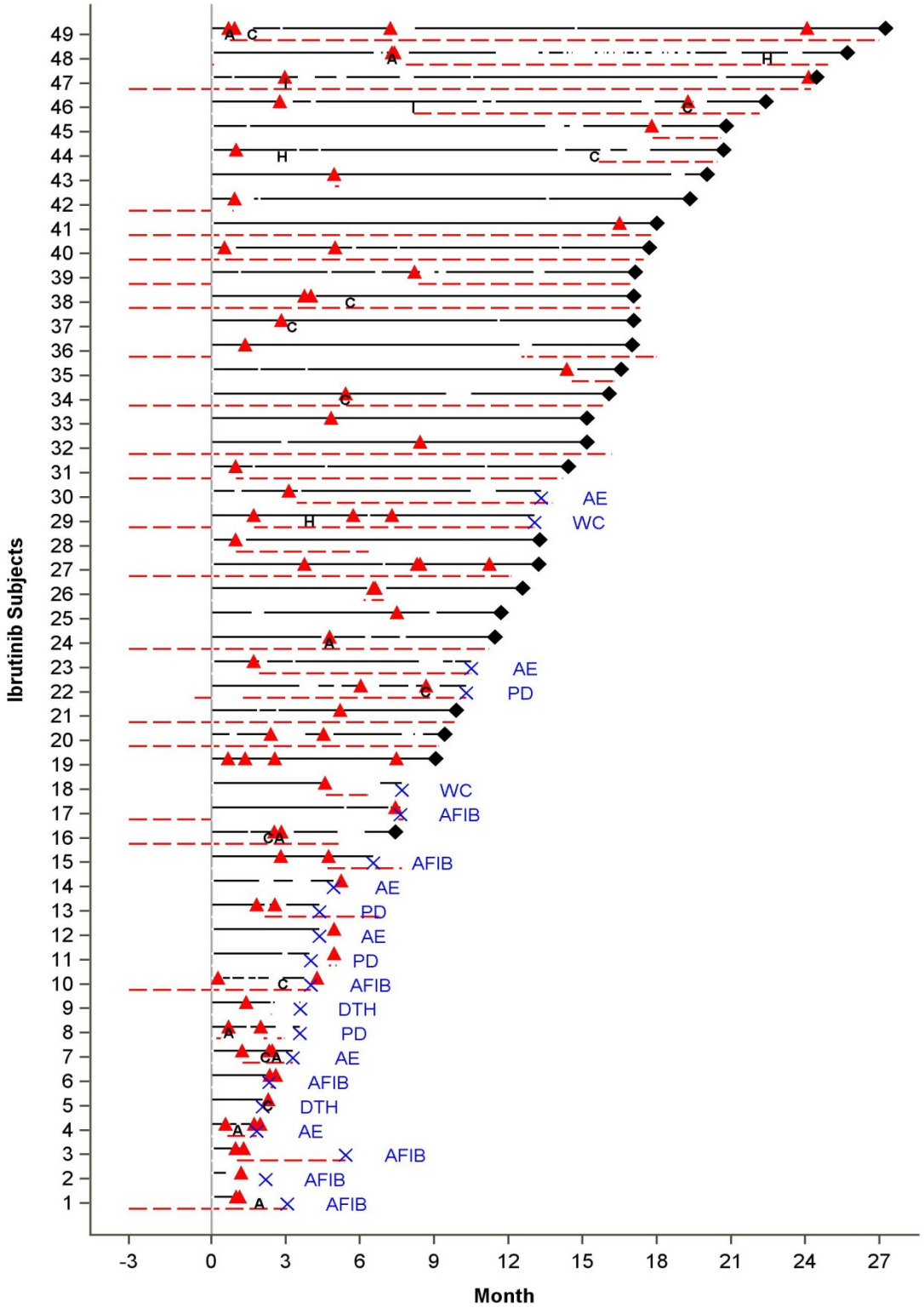
Supplementary Figure S1. Kaplan-Meier plot of time to AF by Shanafelt risk score category (CLL patients with no prior history of AF randomized to ibrutinib).

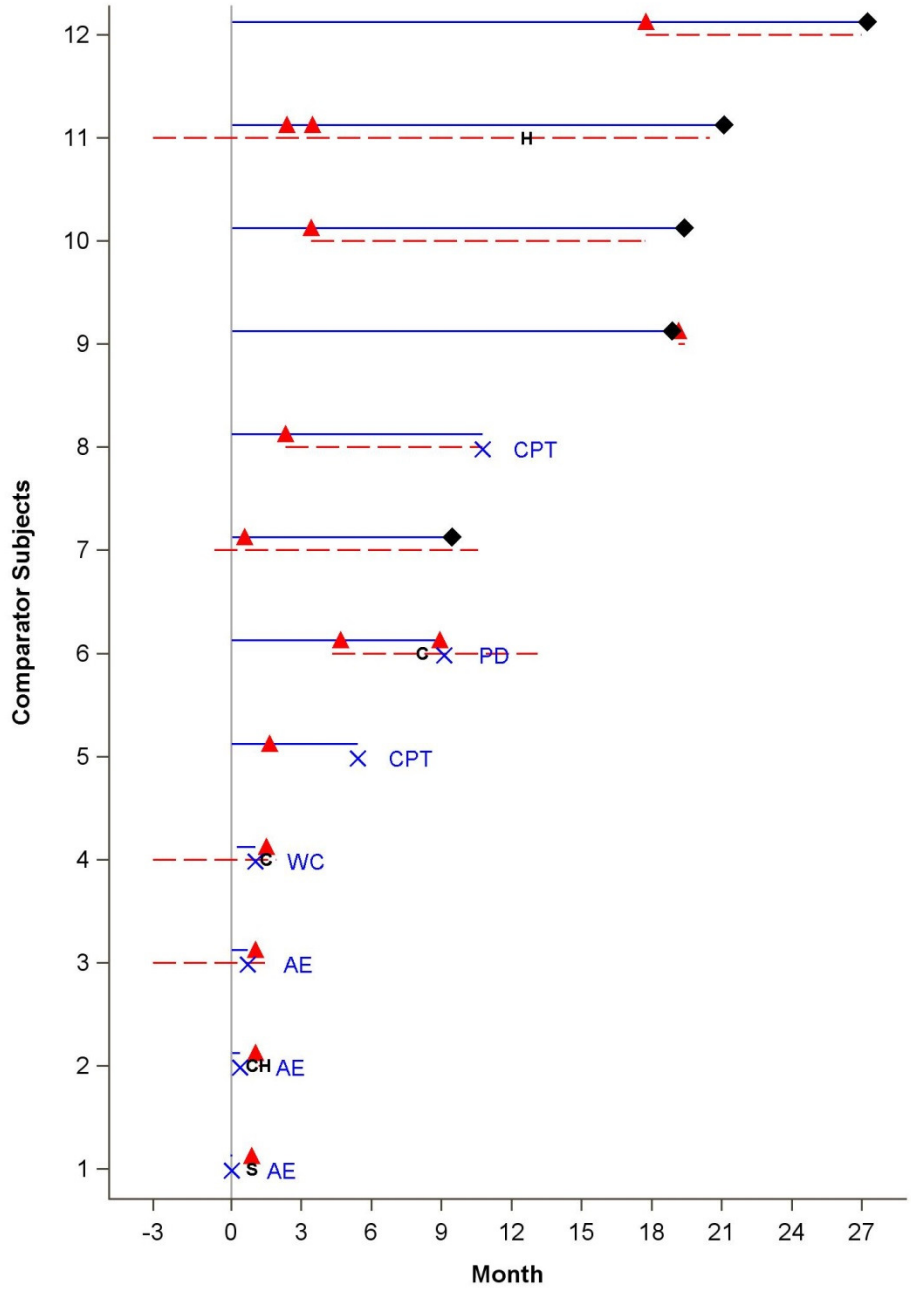


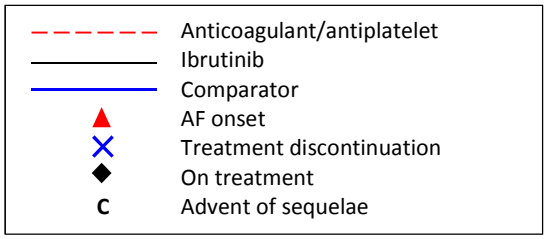
Patients at risk by Shananfelt Risk Category

0-1	282	282	282	281	280	274	265	257	251	242	231	217	203
2-3	209	209	209	203	197	187	180	166	155	151	139	131	125
4	71	71	70	68	62	53	52	47	43	40	38	34	28
5+	26	26	26	24	20	19	18	16	14	9	8	8	5

Supplementary Figure 2. Swimmer's plot of individual course of study treatment, concomitant medications, and clinical sequelae for patients with AF.

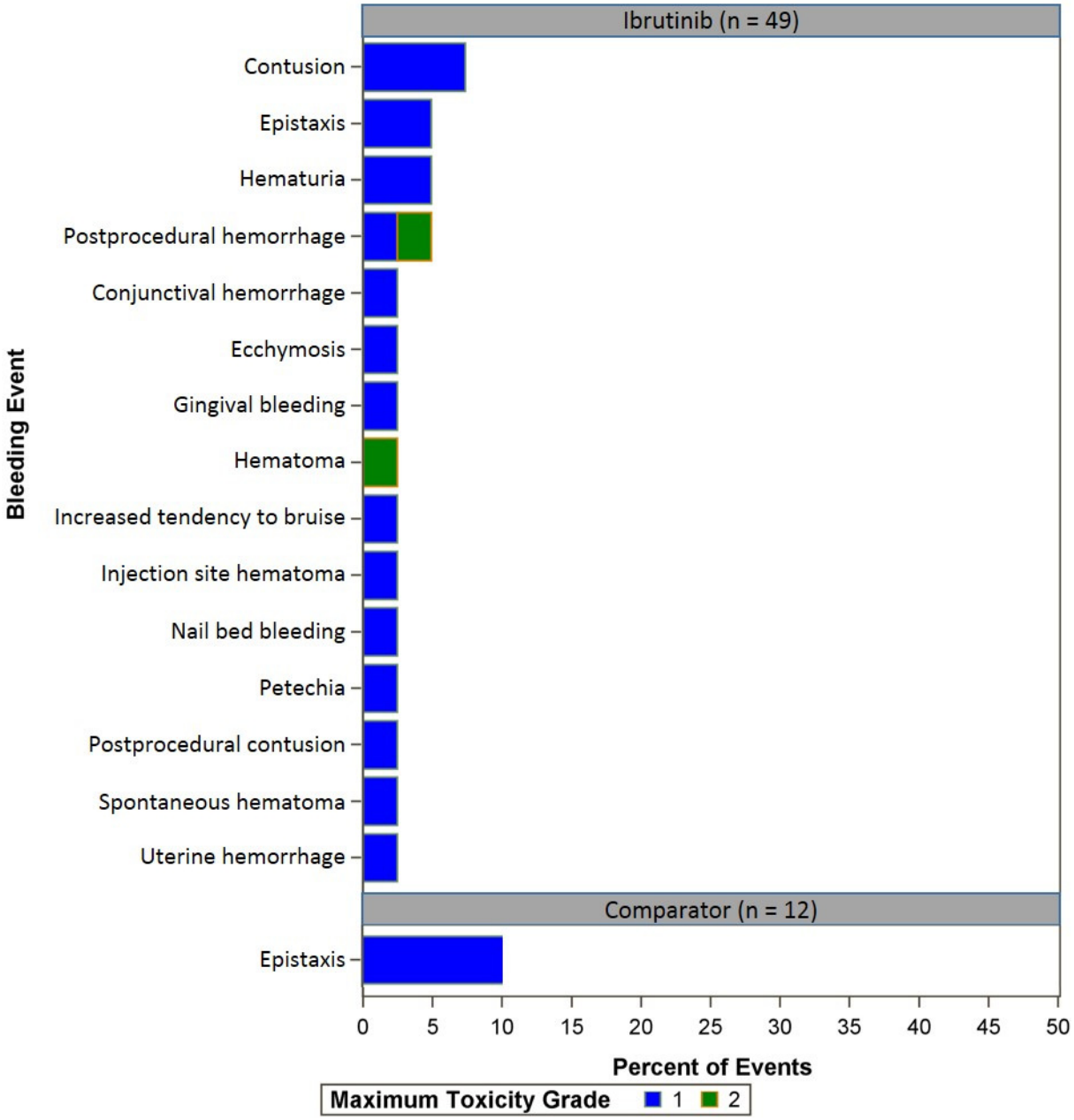






A, other arrhythmias; AE, adverse event; AF, atrial fibrillation; AFIB, atrial fibrillation/atrial flutter; C, congestive heart failure; CH, CHF and hypertension; CPT, completed study; DTH, death; H, hypertension; I, ischemic cardiac disease; PD, progressive disease; S, stroke; WC, withdrew consent.

Supplementary Figure 3. Incidence and highest toxicity grade bleeding events while on anticoagulation or antiplatelet medication in patients who had AF.



AF, atrial fibrillation.

Supplementary Information 1

Briefly, the RESONATE study enrolled 391 patients with previously treated CLL/SLL who were randomly assigned, in a 1:1 ratio, to receive either oral ibrutinib (420 mg once daily) until disease progression or occurrence of unacceptable toxic effects, or intravenous ofatumumab for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks, consistent with local labeling. The randomization was stratified according to resistance to purine analog chemoimmunotherapy and chromosome 17p13.1 deletion.[1]

The RESONATE-2 study enrolled 269 patients with treatment-naïve CLL/SLL without 17p deletion who were randomly assigned, in a 1:1 ratio, to either oral ibrutinib (420 mg once daily) or up to 12 cycles of chlorambucil (at a dose of 0.5 mg/kg of body weight on days 1 and 15 of each 28-day cycle, which was increased to a maximum of 0.8 mg/kg, if tolerable).[2]

In the HELIOS study, 578 patients with previously treated CLL/SLL without 17p deletion were randomly assigned, in a double-blinded 1:1 ratio, to receive either ibrutinib (420 mg once daily) or placebo, in combination with BR. Ibrutinib or placebo were initiated in cycle 1 with BR and were continued until disease progression or unacceptable toxicity. BR was given for a maximum of 6 cycles (1 cycle was 28 days; bendamustine: 70 mg/m² intravenously on days 2-3 in cycle 1, and days 1-2 in cycles 2-6; rituximab: 375 mg/m² on day 1 of cycle 1, and 500 mg/m² on day 1 of cycles 2-6).

The primary endpoint of all three CLL/SLL studies was the duration of PFS, as assessed by an independent review committee (IRC), according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL).[3] Key secondary end points included the duration of OS, response rate and safety.[4]

The RAY study enrolled 280 patients with previously treated MCL who had received one or more prior rituximab-containing chemotherapy regimens. Patients were randomly assigned, in a 1:1 ratio, to

ibrutinib (560 mg once daily) or intravenous temsirolimus (175 mg for a 3-week cycle followed by 75 mg). The primary endpoint was PFS. Complete response, partial response, and progressive disease were assessed by an IRC per revised Cheson criteria.[5] Secondary end points included overall response rate, OS, 1-year survival rate, duration of response, time to next treatment, safety, pre-specified patient-reported outcomes, biomarkers, and pharmacokinetics.[6]

Supplementary Information 2

CV events captured using MedDRA SMQ were grouped into five CVD categories: arrhythmia, congestive heart failure, ischemic heart disease, hypertension, and ischemic CNS vascular conditions

Arrhythmia (modified MedDRA SMQ v16.0): Accelerated idioventricular rhythm, Accessory cardiac pathway, Acute coronary syndrome, Adams-Stokes syndrome, Agonal rhythm, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia supraventricular, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial parasystole, Atrial tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Bifascicular block, Bradyarrhythmia, Bradycardia, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac arrest, Cardiac death, Cardiac fibrillation, Cardiac flutter, Cardiac telemetry abnormal, Cardio-respiratory arrest, Chronotropic incompetence, Conduction disorder, ECG P wave inverted, Echocardiogram abnormal, Electrocardiogram abnormal, Electrocardiogram ambulatory abnormal, Electrocardiogram change, Electrocardiogram delta waves abnormal, Electrocardiogram P wave abnormal, Electrocardiogram PQ interval prolonged, Electrocardiogram PR prolongation, Electrocardiogram PR shortened, Electrocardiogram Q wave abnormal, Electrocardiogram QRS complex prolonged, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Electrocardiogram repolarization abnormality, Electrocardiogram RR interval prolonged, Electrocardiogram U-wave abnormality, Extrasystoles, Heart alternation, Heart rate abnormal, Heart rate decreased, Heart rate increased, Heart rate irregular, Lenegre's disease, Long QT syndrome, Loss of consciousness, Nodal arrhythmia, Nodal rhythm, Pacemaker generated arrhythmia, Pacemaker syndrome, Palpitations, Parasystole, Paroxysmal arrhythmia, Pulseless electrical activity, Rebound tachycardia, Reduction ventriculoplasty, Reperfusion arrhythmia, Retrograde p-waves, Rhythm idioventricular, Sick sinus syndrome, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia,

Sinus tachycardia, Sudden cardiac death, Sudden death, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Syncope, Tachyarrhythmia, Tachycardia, Tachycardia paroxysmal, Torsade de pointes, Trifascicular block, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular parasystole, Ventricular preexcitation, Ventricular tachyarrhythmia, Ventricular tachycardia, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome.

Congestive heart failure (modified MedDRA SMQ v16.0): Acute left ventricular failure, Acute pulmonary edema, Acute right ventricular failure, Artificial heart implant, Atrial natriuretic peptide abnormal, Atrial natriuretic peptide increased, Brain natriuretic peptide abnormal, Brain natriuretic peptide increased, Cardiac asthma, Cardiac cirrhosis, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Cardiac failure high output, Cardiac index decreased, Cardiac output decreased, Cardiac resynchronization therapy, Cardiac ventriculogram abnormal, Cardiac ventriculogram left abnormal, Cardiac ventriculogram right abnormal, Cardiogenic shock, Cardiomegaly, Cardiopulmonary failure, Cardiorenal syndrome, Cardio-respiratory distress, Cardiothoracic ratio increased, Central venous pressure increased, Chronic left ventricular failure, Chronic right ventricular failure, Cor pulmonale, Cor pulmonale acute, Cor pulmonale chronic, Diastolic dysfunction, Dilatation ventricular, Dyspnea, Dyspnea paroxysmal nocturnal, Ejection fraction decreased, Heart transplant, Hepatic congestion, Hepatic vein dilatation, Hepatojugular reflux, Jugular vein distension, Left ventricular dysfunction, Left ventricular failure, Low cardiac output syndrome, Myocardial depression, Neonatal cardiac failure, Nocturnal dyspnea, N-terminal prohormone brain natriuretic peptide abnormal, N-terminal prohormone brain natriuretic peptide increased, Edema, Edema due to cardiac disease, Edema neonatal, Edema peripheral, Orthopnea, Peripheral edema neonatal, Pulmonary congestion, Pulmonary edema, Pulmonary edema neonatal, Right ventricular dysfunction, Right ventricular dysfunction, Right ventricular failure, Scan myocardial perfusion abnormal, Systolic

dysfunction, Venous pressure increased, Venous pressure jugular abnormal, Venous pressure jugular increased, Ventricular assist device insertion, Ventricular dysfunction, Ventricular dyssynchrony, Ventricular failure.

Hypertension (modified MedDRA SMQ v16.0): Accelerated hypertension, Aldosterone urine abnormal, Aldosterone urine increased, Angiotensin converting enzyme increased, Angiotensin I increased, Angiotensin II increased, Blood aldosterone abnormal, Blood aldosterone increased, Blood catecholamines abnormal, Blood catecholamines increased, Blood pressure abnormal, Blood pressure ambulatory abnormal, Blood pressure ambulatory increased, Blood pressure diastolic abnormal, Blood pressure diastolic decreased, Blood pressure diastolic increased, Blood pressure fluctuation, Blood pressure fluctuation, Blood pressure inadequately controlled, Blood pressure inadequately controlled, Blood pressure increased, Blood pressure management, Blood pressure orthostatic abnormal, Blood pressure orthostatic increased, Blood pressure systolic abnormal, Blood pressure systolic decreased, Blood pressure systolic increased, Catecholamines urine abnormal, Catecholamines urine increased, Diastolic hypertension, Diuretic therapy, Eclampsia, Ectopic aldosterone secretion, Ectopic renin secretion, Endocrine hypertension, Epinephrine abnormal, Epinephrine increased, Essential hypertension, Gestational hypertension, HELLP syndrome, Hyperaldosteronism, Hypertension, Hypertension neonatal, Hypertensive angiopathy, Hypertensive cardiomegaly, Hypertensive cardiomyopathy, Hypertensive crisis, Hypertensive emergency, Hypertensive encephalopathy, Hypertensive heart disease, Hypertensive nephropathy, Hypertrophic cardiomyopathy, Labile blood pressure, Labile blood pressure, Labile hypertension, Malignant hypertension, Malignant hypertensive heart disease, Malignant renal hypertension, Maternal hypertension affecting fetus, Mean arterial pressure increased, Metabolic syndrome, Metanephrine urine abnormal, Metanephrine urine increased, Neurogenic hypertension, Non-dipping, Norepinephrine abnormal, Norepinephrine increased, Normetanephrine urine increased, Orthostatic hypertension, Pre-eclampsia, Prehypertension,

Procedural hypertension, Pseudoaldosteronism, Renal artery ablation, Renal hypertension, Renin abnormal, Renin increased, Renin-angiotensin system inhibition, Renovascular hypertension, Retinopathy hypertensive, Secondary aldosteronism, Secondary hypertension, Systolic hypertension, Tyramine reaction, Withdrawal hypertension.

Ischemic heart disease (modified MedDRA SMQ v16.0): Acquired cardiac septal defect, Acute myocardial infarction, Angina pectoris, Angina unstable, Arteriogram coronary abnormal, Arteriosclerosis coronary artery, Arteriospasm coronary, Blood creatine phosphokinase abnormal, Blood creatine phosphokinase increased, Blood creatine phosphokinase MB, abnormal, Blood creatine phosphokinase MB increased, Cardiac enzymes increased, Cardiac stress test abnormal, Computerized tomogram coronary artery abnormal, Coronary artery aneurysm, Coronary angioplasty, Coronary arterial stent insertion, Coronary artery bypass, Coronary artery disease, Coronary artery dissection, Coronary artery embolism, Coronary artery insufficiency, Coronary artery occlusion, Coronary artery reocclusion, Coronary artery restenosis, Coronary artery stenosis, Coronary artery thrombosis, Coronary bypass thrombosis, Coronary endarterectomy, Coronary no-reflow phenomenon, Coronary ostial stenosis, Coronary revascularization, Dissecting coronary artery aneurysm, ECG electrically inactive area, ECG signs of myocardial ischemia, Electrocardiogram ST segment abnormal, Electrocardiogram ST segment depression, Electrocardiogram ST segment elevation, Electrocardiogram ST-T segment abnormal, Electrocardiogram ST-T segment depression, Electrocardiogram ST-T segment elevation, Electrocardiogram T wave abnormal, Electrocardiogram T wave inversion, Exercise electrocardiogram abnormal, Exercise test abnormal, External counterpulsation, Hemorrhage coronary artery, Infarction, Ischemic cardiomyopathy, Kounis syndrome, Microvascular coronary artery disease, Multiple gated acquisition scan abnormal, Myocardial infarction, Myocardial ischemia, Myocardial reperfusion injury, Myocardial stunning, Papillary muscle infarction, Percutaneous coronary intervention, Postprocedural myocardial infarction, Postinfarction angina, Prinzmetal angina, Silent myocardial infarction, Stress

cardiomyopathy, Stress echocardiogram abnormal, Subclavian coronary steal syndrome, Subendocardial ischemia, Troponin I increased, Troponin increased, Troponin T increased, Vascular graft occlusion.

Ischemic CNS vascular conditions (MedDRA SMQ v17.1): Amaurosis fugax, Basal ganglia infarction, Basal ganglia stroke, Basilar artery occlusion, Basilar artery stenosis, Basilar artery thrombosis, Brachiocephalic arteriosclerosis, Brachiocephalic artery occlusion, Brachiocephalic artery stenosis, Brain hypoxia, Brain stem embolism, Brain stem infarction, Brain stem ischaemia, Brain stem stroke, Brain stem thrombosis, Capsular warning syndrome, Carotid angioplasty, Carotid arterial embolus, Carotid arteriosclerosis, Carotid artery bypass, Carotid artery disease, Carotid artery insufficiency, Carotid artery occlusion, Carotid artery restenosis, Carotid artery stenosis, Carotid artery stent insertion, Carotid artery stent removal, Carotid artery thrombosis, Carotid endarterectomy, Carotid revascularisation, Cerebellar artery occlusion, Cerebellar artery thrombosis, Cerebellar embolism, Cerebellar infarction, Cerebellar ischaemia, Cerebral arteriosclerosis, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery restenosis, Cerebral artery stenosis, Cerebral artery thrombosis, Cerebral gas embolism, Cerebral infarction, Cerebral infarction foetal, Cerebral ischaemia, Cerebral revascularisation, Cerebral septic infarct, Cerebral small vessel ischaemic disease, Cerebral thrombosis, Cerebral vasoconstriction, Cerebral venous thrombosis, Cerebrovascular accident, Cerebrovascular disorder, Cerebrovascular insufficiency, Cerebrovascular stenosis, Embolic cerebral infarction, Embolic hypoxic-ischaemic encephalopathy, Embolic stroke, Hypoxic-ischaemic encephalopathy, In-stent cerebral artery stenosis, Inner ear infarction, Ischaemic cerebral infarction, Ischaemic stroke, lacunar infarction, Lateral medullary syndrome, Migrainous infarction, Millard-Gubler syndrome, Moyamoya disease, Perinatal stroke , Post procedural stroke, Precerebral artery occlusion, Retinal artery occlusion, Reversible ischaemic neurological deficit, Spinal artery embolism, Spinal artery thrombosis, Stroke in evolution, Subclavian steal syndrome, Thalamic infarction, Thrombotic cerebral infarction, Thrombotic stroke,

Transient ischaemic attack, Vascular encephalopathy, Vertebral artery occlusion, Vertebral artery stenosis, Vertebral artery thrombosis, Vertebrobasilar insufficiency.

Supplementary Information 3

CATEGORY: Cardiac disorders
Adverse Event: Atrial fibrillation
Short Name: Atrial fibrillation
MedDRA Code: 10003658

Grade	Description
1	Asymptomatic, intervention not indicated
2	Non-urgent medical intervention indicated
3	Symptomatic and incompletely controlled medically, or controlled with device (e.g. pacemaker), or ablation
4	Life-threatening consequences; urgent intervention indicated
5	Death

Supplementary Information 4

Ibrutinib dose modification for adverse events

Interrupt ibrutinib therapy for any grade 3 or greater non-hematological adverse event, grade 3 or greater neutropenia with infection or fever or grade 4 hematological toxicities. Once the symptoms of the event have resolved to grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose. If the event reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these adverse events persist or recur following two dose reductions, discontinue ibrutinib. Recommended dose modifications are described below[7]:

Toxicity occurrence	CLL/SLL dose modification after recovery Starting dose = 420 mg	MCL dose modification after recovery Starting dose = 560 mg
First	Restart at 420 mg daily	Restart at 560 mg daily
Second	Restart at 280 mg daily	Restart at 420 mg daily
Third	Restart at 140 mg daily	Restart at 280 mg daily
Fourth	Discontinue ibrutinib	Discontinue ibrutinib

Supplementary Table S1. Median duration of therapy by study (safety population).

Study		Median duration of therapy
PCYC-1112 (RESONATE, NCT01578707)	Ibrutinib (N=195)	8.6 months (range: 0.2-16.1 months)
	Ofatumumab (N=191)	5.3 months (range: 0.0-7.4 months)
PCYC-1115 (RESONATE-2, NCT01722487)	Ibrutinib (N=135)	17.4 months (range: 0.7-24.7 months)
	Chlorambucil (N=132)	7.1 months (range: 0.5-11.7 months)
CLL3001 (HELIOS, NCT01611090)	Ibrutinib + BR (N=287)	14.7 months (range: 0.2-27.1 months)
	Placebo + BR (N=287)	12.8 months (range: 0.2-27.3 months)
MCL3001 (RAY, NCT01646021)	Ibrutinib (N=139)	14.4 months (range: 0.0-28.2 months)
	Temsirolimus (N=139)	3.0 months (range: 0.0-27.0 months)
Total	Ibrutinib (N=756)	13.3 months (range: 0.0, 28.2 months)
	Comparator (N=749)	5.8 months (range: 0.0, 27.4)

BR, bendamustine and rituximab.

Supplementary Table S2. Patients experiencing 1 or more AF episodes.

Number of AF episodes	Ibrutinib (n=49)	Comparator (n=12)
1	27 (55.1)	10 (83.3)
2	16 (32.7)	2 (16.7)
3	3 (6.1)	0
4	3 (6.1)	0

AF, atrial fibrillation.

Supplementary Table S3. Patients with multiple AF events.

	Ibrutinib (n=22)	Comparator (n=2)
Clinical characteristics		
Median age, years (range)	72.0 (59-84)	64.5 8 (58-71)
<65, n (%)	2 (9.1)	1 (50.0)
Male, n (%)	16 (72.7)	2 (100)
Race (White), n (%)	21 (95.5)	2 (100)
BMI, n (%)[a]		
>18-24.9	8 (36.4)	0
25-29.9	11 (50.0)	1 (50.0)
≥30	2 (9.1)	1 (50.0)
Prior history for patients, n (%)		
AF/abnormal heart rhythm	7 (31.8)	2 (100)
Comorbid cardiac condition	8 (36.4)	2 (100)
Diabetes	3 (13.6)	0
Hyperlipidemia	4 (18.2)	0
Hypertension	14 (63.6)	2 (100)
Infection	10 (45.5)	1 (50.0)
Study drug management after AF		
No dose modification	7 (31.8)	1 (50.0)
Drug interrupted	10 (45.5)	1 (50.0)
Discontinued	5 (22.7)	0
Concomitant medications after AF		
Antiplatelets		
Aspirin	14 (63.6)	0
Antiplatelets other than aspirin	4 (18.2)	0
Anticoagulants		
Low-molecular-weight heparin	12 (54.5)	1 (50.0)
Novel oral anticoagulants	4 (18.2)	1 (50.0)
Vitamin K antagonists	3 (13.6)	0
Other	1 (4.5)	0

AF, atrial fibrillation; BMI, body mass index.

[a]One ibrutinib patient was missing BMI at baseline.

Supplementary Table S4. Incidence and characterization of AF events in patients on ibrutinib with extended follow-up.

	Patients with AF (n=78)
Time to onset of initial event (months)	
Median (range)	5.7 (0.3-40.2)
Mean (SD)	11.5 (11.10)
Number of AF episodes	
1	49 (62.8)
>1	29 (37.2)
2	20 (25.6)
3	5 (6.4)
4	2 (2.6)
6	2 (2.6)
Treatment-emergent AF	
Grade 1/2	43 (55.1)
SAEs	38 (48.7)
Action taken with ibrutinib	
Dose reduction	5 (6.4)
Dose interruption	25 (32.1)
Treatment discontinuation	7 (9.0)

AF, atrial fibrillation; SAEs, serious adverse events.

Supplementary Table S5. Baseline demographic and clinical characteristics of patients with AF events without and with treatment interruption

	Ibrutinib (n=756)		Comparator (n=749)	
	Patients with AF events without treatment interruption (n=25)	Patients with AF events with treatment interruption (n=24)	Patients with AF events without treatment interruption (n=8)	Patients with AF events with treatment interruption (n=4)
Median age, years (range)	69.0 (59-78)	73.0 (62-84)	70.0 (58-80)	72.5 (67-88)
<65, n (%)	7 (0.9)	2 (0.3)	1 (0.1)	0
≥65, n (%)	18 (2.4)	14 (1.9)	7 (0.9)	4 (0.5)
Male, n (%)	18 (2.4)	15 (2.0)	5 (0.7)	4 (0.5)
Race (White), n (%)	24 (3.2)	23 (3.0)	8 (1.1)	4 (0.5)
BMI, n (%)[a]				
>18-24.9	9 (1.2)	8 (1.1)	1 (0.1)	1 (0.1)
25-29.9	10 (1.3)	11 (1.5)	1 (0.1)	2 (0.3)
≥30	6 (0.8)	3 (0.4)	6 (0.8)	1 (0.1)
Initial diagnosis, n (%)				
CLL/SLL	21 (2.8)	22 (2.9)	5 (0.7)	4 (0.5)
MCL	4 (0.5)	2 (0.3)	3 (0.4)	0
Anticoagulant at baseline, n (%)	2 (0.3)	2 (0.3)	0	2 (0.3)
Antiplatelet at baseline, n (%)	7 (0.9)	10 (1.3)	2 (0.3)	0
Prior history for patients, n (%)				
AF/abnormal heart rhythm	7 (0.9)	6 (0.8)	1 (0.1)	2 (0.3)
Coronary artery disease	1 (0.1)	2 (0.3)	0	0
Diabetes	5 (0.7)	2 (0.3)	4 (0.5)	1 (0.1)
Hyperlipidemia	9 (1.2)	7 (0.9)	2 (0.3)	0
Hypertension	14 (1.9)	17 (2.2)	7 (0.9)	3 (0.4)
Infection	17 (2.2)	9 (1.2)	3 (0.4)	2 (0.3)

AF, atrial fibrillation; BMI, body mass index; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; SLL; small lymphocytic lymphoma.

[a]Two patients with ibrutinib had missing BMI at baseline.

Supplementary Table S6A. Concomitant use of ibrutinib with other medications in patients, during AF event.

	Ibrutinib (n=49)		Comparator (n=12)	
	Management during AF event		Management during AF event	
	n (%)	Median duration (range), weeks	n (%)	Median duration (range), weeks
Beta blockers or alpha blockers	40 (81.6)	4.4 (0.1-20.6)	8 (66.7)	4.4 (0.4-10.0)
Diuretics	18 (36.7)	4.4 (0.1-22.6)	8 (66.7)	2.4 (0.1-5.4)
ACE inhibitors	19 (38.8)	4.6 (3.4-18.0)	4 (33.3)	3.1 (0.1-4.4)
Calcium channel blockers	12 (24.5)	4.4 (0.1-15.3)	3 (25.0)	0.3 (0.1-4.4)
Antiarrhythmic	18 (36.7)	3.9 (0.1-18.0)	7 (58.3)	3.9 (0.1-8.6)
Digoxin	11 (22.4)	1.6 (0.1-9.9)	1 (8.3)	0.1 (0.1-0.1)
Lipid-lowering medications, statins, and antidiabetics	21 (42.9)	4.7 (0.1-19.6)	4 (33.3)	3.0 (0.6-4.7)
Antiplatelets				
Aspirin	23 (46.9)	4.4 (0.1-15.9)	3 (25.0)	2.0 (2.0-4.3)
Antiplatelets other than aspirin	8 (16.3)	4.2 (0.6-9.9)	0	0
Anticoagulants				
Low-molecular-weight heparin	20 (40.8)	3.3 (0.1-15.3)	7 (58.3)	2.0 (0.9-4.4)
Novel oral anticoagulants	10 (20.4)	4.4 (2.0-9.9)	1 (8.3)	9.1 (9.1-9.1)
Vitamin K antagonists	5 (10.2)	4.0 (0.3-4.4)	2 (16.7)	3.3 (2.1-4.4)
Other	4 (8.2)	0.6 (0.1-4.4)	1 (8.3)	4.4 (4.4-4.4)

ACE, angiotensin-converting-enzyme; AF, atrial fibrillation.

Supplementary Table S6B. Use of other medications during the course of study participation, in patients who experienced AF.

	Ibrutinib (n=49)		Comparator (n=12)	
	n (%)	Median duration while on study (range), weeks	n (%)	Median duration while on study (range), weeks
Beta blockers or alpha blockers	41 (83.7)	54.4 (0.1-194.4)	9 (75.0)	57.9 (0.4-114.4)
Diuretics	23 (46.9)	39.9 (0.1-148.6)	8 (66.7)	3.1 (0.3-21.6)
ACE inhibitors	19 (38.8)	56.7 (4.6-143.0)	5 (41.7)	6.3 (0.6-104.0)
Calcium channel blockers	16 (32.7)	28.7 (0.1-80.3)	3 (25.0)	6.0 (0.1-10.4)
Antiarrhythmic	25 (51.0)	9.1 (0.1-66.1)	7 (58.3)	20.9 (0.1-77.1)
Digoxin	13 (26.5)	1.3 (0.1-19.7)	1 (8.3)	0.1 (0.1-0.1)
Lipid-lowering medications, statins, and antidiabetics	22 (44.9)	59.5 (0.1-114.3)	5 (41.7)	10.0 (4.1-152.1)
Antiplatelets				
Aspirin	23 (46.9)	50.3 (2.1-103.9)	4 (33.3)	4.4 (2.0-61.0)
Antiplatelets other than aspirin	10 (20.4)	18.1 (0.1-74.9)	0	0
Anticoagulants				
Low-molecular-weight heparin	25 (51.0)	4.3 (0.1-50.4)	7 (58.3)	2.4 (0.9-45.1)
Novel oral anticoagulants	12 (24.5)	40.9 (2.3-99.1)	1 (8.3)	87.3 (87.3-87.3)
Vitamin K antagonists	7 (14.3)	13.0 (0.3-55.0)	2 (16.7)	4.1 (2.1-6.0)
Other	8 (16.3)	0.4 (0.1-76.1)	1 (8.3)	67.6 (67.6-67.6)

ACE, angiotensin-converting-enzyme; AF, atrial fibrillation.

Supplementary Table S7. CHA_2DS_2-VASc scores for patients in the pooled analysis.

CHA_2DS_2-VASc score	Ibrutinib (N=756)		Comparator (N=749)	
	Patients with AF (n=49)	Patients without AF (n=707)	Patients with AF (n=12)	Patients without AF (n=737)
0	6.1%	15.1%	0	16.0%
1	22.4%	27.2%	16.7%	28.5%
2	20.4%	27.7%	25.0%	23.3%
3	32.7%	17.4%	16.7%	19.3%
4	12.2%	10.5%	41.7%	9.2%
5	4.1%	2.0%	0	3.1%
6	2.0%	0.1%	0	0.5%

Supplementary Table S8. Brief narrative of patients randomized to ibrutinib with bleeding events leading to death.

Patient 1, ruptured abdominal aortic aneurism	A 75-year-old white man with CLL entered the study with an ongoing history of arterial hypertension, hyperlipidemia, and an abdominal aortic aneurysm. At study entry, the aneurysm was 7.8 cm in diameter. On study day 40 it ruptured and the subject died during an endovascular procedure to repair the aneurysm.
Patient 2, post-procedural hemorrhage	A 72-year-old white man with CLL who had an SAE of hematochezia on study day 128. Ibrutinib was held and then restarted at a reduced dose of 280 mg/day on study day 140. On study day 170 a colonoscopy to remove a grade 3 villous adenoma (which was a cause of hematochezia) was performed; drug was not held as per the protocol guidance; grade 5 post-procedural hemorrhage occurred concurrently with a grade 5 event of colon perforation on study day 170 at the location of an abdominal drain site.
Patient 3, subdural hematoma	A 74-year-old white man with MCL with a grade 1 AE of head injury (date not specified); no action was taken with the study drug and no treatment was reported. On study day 501, a grade 4 SAE of subdural hematoma and a non-serious AE of grade 1 confusional state were reported. Treatment with the study drug was discontinued on study day 501 due to the event of subdural hematoma, with the last dose received on the same day. On study day 523, the subject died due to subdural hematoma.

AE, adverse event; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; SAE, serious adverse event.

Supplementary Table S9. Clinical sequelae for patients with AF.

Patients with AF	Ibrutinib (n=49)	Comparator (n=12)
Single AF event	**27 (55.1)**	**10 (83.3)**
Sequelae[a]	5 (10.2)	2 (16.7)
Medical history[b]	3 (6.1)	2 (16.7)
No medical history	2 (4.1)	0
No sequelae	22 (44.9)	8 (66.7)
Medical history[b]	16 (32.7)	6 (50.0)
No medical history	6 (12.2)	2 (16.7)
Multiple AF events	**22 (44.9)**	**2 (16.7)**
Sequelae[a]	13 (26.5)	2 (16.7)
Medical history[b]	9 (18.4)	2 (16.7)
No medical history	4 (8.2)	0
No sequelae	9 (18.4)	0
Medical history[b]	7 (14.3)	
No medical history	2 (4.1)	

AF, atrial fibrillation.

[a]Sequelae include chronic heart failure, ischemic cardiac events, arrhythmias and/or hypertension.

[b]Medical history includes history of chronic heart failure, ischemic cardiac events, arrhythmias and/or hypertension.

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