Supplemental Table 1. Cases of Ventricular Arrhythmias and Sudden Death on Ibrutinib

FAERS Case ID	Event	Age (yrs)	Sex	Indication	Dose (mg)	Time To Event (days)	Concomitant Medications	Prior Cardiac History	Post Event Cardiac Work-up	Summary
N/A (Case #1 in text)	VT	60	M	CLL	420	86	cholecalciferol	None	Exercise stress test was negative for ischemic changes but notable for a 20 beat run of polymorphic VT (Figure 1B). Coronary angiography showed no significant CAD. Cardiac MRI showed LVEF of 58% with no RWMA and no late gadolinium enhancement to suggest prior infarct, inflammation, or infiltration. EP studies induced PVCs that mapped to the moderator band, but the focus could not be ablated.	The patient had a month of palpitations and then a syncopal episode. His troponin I peaked at 0.226 ng/mL (normal range, 0.000-0.041ng/mL) approximately 6 hours after presentation. Work-up was notable for polymorphic VT that occurred shortly before beginning an exercise stress test. When RFA was unsuccessful at suppressing PVCs, quinidine was initiated and ibrutinib was restarted at discharge, ten days after the event. Attempted downtitration of his quinidine six months later resulted in a dramatic increase in PVCs. He has since been maintained on ibrutinib, quinidine, and metoprolol for 28 months and continues to have short runs of asymptomatic nonsustained VT captured by his ICD. Family history included a father with HTN, AAA, and carotid stenosis, and a mother with HTN.
10287309 (Case #2 in text)	VT and VF	55	M	CLL	420	366	valacyclovir, ursodiol	None	Coronary angiography without significant CAD, a normal echocardiogram with an LVEF of 65% and no valvular abnormalities, a normal cardiac MRI without late gadolinium enhancement, and negative genetic testing for inherited sodium channelopathies.	His wife witnessed his collapse. He was resuscitated by paramedics and subsequently had polymorphic VT and VF while undergoing a neuroprotective cooling protocol. An ICD was implanted. He had complete neurologic recovery and was discharged on bisoprolol. Ibrutinib was resumed fifty days after the event and he has since been maintained on ibrutinib and bisoprolol for two years without any additional documented episodes of VT. Family history is notable for a father who had a fatal MI at age 56.
10922721 (Case #3 in text)	VT	58	M	CLL	420	28	fenofibrate, allopurinol, TMP/SMX valacyclovir, temazepam, aspirin	afib, MI (chest pain and posi-tive stress test one year prior resulting in stent placement)	Echo with preserved LVEF and aortic valve sclerosis. Coronary angiography showed no lesions outside of a known prior lesion in the distal segment of the LAD. An exercise stress test showed no ischemic changes and an EP study showed no inducible arrhythmias. Cardiac MRI showed no RWMA and no abnormal enhancement.	He had symptomatic polymorphic VT. He was admitted and ibrutinib was stopped. He was discharged off ibrutinib and on nadolol 40mg daily. Ibrutinib was resumed 57 days after the initial event, but 25 days later, he developed frequent PVCs during a lower respiratory tract infection, and ibrutinib was permanently discontinued. There was no family history of cardiac disease.
N/A (Case #4 in text)	VF	85	M	CLL	140	698	apixaban	Afib developed while on ibrutinib	Cardiac MRI showed a minor subendocardial infarction in the inferior wall of the left ventricle with reversible ischemia in the surrounding area, supplied by the dominant right coronary artery (RCA). Angiogram show chronic occlusion of the RCA with moderate disease in the LCX and LAD arteries (with an iFR of 0.78 in the LAD).	Subject first developed atrial fibrillation on ibrutinib. He then had a witnessed cardiac arrest while riding a bike. Paramedics documented VF and he was shocked x 3 with ROSC. He had an elevated troponin at time of admission. ICD was implanted and bisoprolol was started. Two stents were eventually placed. One month later, he was restarted on ibrutinib at 140mg daily without subsequent cardiac events. Ibrutinib was discontinued seven months later, after disease progression. Family history was negative for any cardiac issues.

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FAERS Case ID	Event	Age (yrs)	Sex	Indication	Dose (mg)	Time To Event (days)	Concomitant Medications	Prior Cardiac History	Post Event Cardiac Work-up	Summary
10440611	VT and VF	73	M	CLL	420	31	metoprolol, digoxin, allopurinol, calcitriol, hydralazine, isosorbide, simvastatin, spironolactone, levothyroxine, torsemide, warfarin	CAD s/p CABG, STEMI, iCMP with LVEF 15%	None	Asymptomatic VT discovered on ICD interrogation, one week later admitted with seven fires of ICD. Ibrutinib stopped.
10701100	VF	59	M	CLL	Unk	150	acyclovir, fluticasone	None	Coronary angiography with “normal coronary arteries”, normal LVEF by echo.	Found in bed breathing abnormally, diagnosed with VF by EMS, resuscitated. Ibrutinib stopped.
10587102	VT	76	M	CLL	420	19	metoprolol, diazepam, fluticasone	None	Unk	Patient reports that he had palpitations that were eventually diagnosed as atrial fibrillation and VT
10659798	VT	61	M	CLL	420	25	rituximab	None	Echo with LVEF 65% and mild concentric LVH. Arrhythmia monitoring on ibrutinib showed PVCs were 44% of beats. MPI with no reversible or irreversible defects.	Bigeminy noted on clinic visit after starting ibrutinib, then found to have frequent PVCs. He experienced VT during a stress test. Ibrutinib stopped.
10705365	VT	68	M	MCL	560	33	sotalol, zolpidem, paracetamol, allopurinol, dabigatran, bumetanide, pantoprazole, fluvastatin, candesartan, lormetazepam	MI s/p CABG, CMP s/p ICD, afib	Unk	Subject had VT evoked during an EP test 3yrs prior to ibrutinib, but no other history of ventricular arrhythmias. Admitted with VT storm, amiodarone normalized the heart rhythm.
11116365	VT	66	F	CLL	420	73	perazine	None	Echo with new reduced LVEF 25%. Coronary angiography “excluded coronary heart disease.” MRI “excluded an acute myocarditis."	Presented with vertigo and found to have monomorphic VT. ICD placed due to identified low LVEF. Ibrutinib stopped.
10704793	VT and VF	61	M	CLL	420	65	losartan, amlodipine, aspirin, marijuana	None	Echo with concentric LVH and no segmental wall motion abnormalities. Coronary angiography with no hemodynamically significant stenosis, LVEF 65%.	Wife found patient unresponsive at home. EMS found him in VT/VF and restored sinus with defibrillation. Potassium was 2.2. He suffered anoxic brain injury and died.
10250309	SD	49	M	CLL	420	235	acetaminophen	None	Autopsy with no abnormalities in coronary arteries and no evidence for cardiac infarct or ischemia. AV nodal artery with dysplasia of unclear significance.	Patient had palpitations prior to starting ibrutinib with negative Holter monitor. Found collapsed in bathroom and could not be resuscitated.
10470277	SD	57	F	CLL	Unk	57	Unk	None	Unk	Developed dizziness after starting ibrutinib and was evaluated by a cardiologist who felt “there was a possibility she had Brugada syndrome.” Found dead at home.
10416800	SD	57	M	WM	Unk	62	mesalamine, prochlorperazine	None	None	Patient suddenly found dead in his bed.
10813661	SD	56	M	MCL	560	296	valacyclovir, TMP/SMX, dexlansoprazole, testosterone, acyclovir, IVIg	None	None	The patient was on ibrutinib with no evidence of disease and was well at last clinic visit, then suddenly died.
10983628	SD	71	M	CLL	Unk	169	labetalol, nifedipine, pramipexole, albuterol, beclomethasone, benzonatate, lisinopril, hydrochlorothiazide, bumetanide, clindamycin	None	None	Patient suddenly expired; an autopsy was not performed.
11131286	SD	62	F	DLBCL	560	6	R-CHOP, valsartan, insulin, metformin, glibenclamide, acetaminophen	CAD	Autopsy revealed no significant coronary artery stenosis, coronary thrombosis, myocardial infarction or valve disease.	Started ibrutinib + R-CHOP on a trial for DLBCL and suddenly died shortly thereafter. Autopsy showed severe hepatic steatosis and cirrhosis but was unrevealing for cause of death.

AAA = abdominal aortic aneurysm, CABG = coronary artery bypass graft, CAD = coronary artery disease, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B cell lymphoma, EMS = emergency medical services, EP = electrophysiology, FAERS = FDA Adverse Event Reporting System, HTN = hypertension, ICD = implantable cardioverter defibrillator, iCMP = ischemic cardiomyopathy, iFR = instant wave-free ratio, ILR = implantable loop recorder, LAD = left anterior descending, LCX = left circumflex, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy, MCL = mantle cell lymphoma, MPI = myocardial perfusion imaging, PVC = premature ventricular contractions, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, RFA = radiofrequency ablation, ROSC = return of spontaneous circulation, RWMA = regional wall motion abnormalities, SD = sudden death, STEMI = ST segment elevation myocardial infarction, TMP/SMX = trimethoprim/sulfamethoxazole, Unk = unknown, VT = ventricular tachycardia, VF = ventricular fibrillation, SD = sudden death, MCL = mantle cell lymphoma, WM = Waldenstrom Macroglobulinemia

Supplemental Table 2. Summarized Data from the HELIOS Trial (Ref. 12)

	Ibrutinib+BR	Placebo + BR
Characteristic		
Median drug exposure (months)	14.7 (0.2-27.1)	12.8 (0.2-27.3)
Number of patients	287	287
Event[1]		
Ventricular fibrillation (Grade 4)	1	0
Ventricular flutter (Grade 5)	1	0
Ventricular tachycardia (Grade 3)	1	0
Cardiac Arrest (Grade 4 and Grade 5)	2	0
Cardio-respiratory arrest (Grade 4)	1	0
Sudden Death	1	0

[1]: For calculation of incidence rates, all events are presumed to have occurred in separate subjects.