Supplemental Data

Supplemental Table 1: Baseline Demographics in Patients with a History of AF

	History of AF and recurrence (n=13)	History of AF without recurrence (n=21)
Age, median [range], years	74 [57->89]	68 [47-81]
Sex, male, n (%)	10 (76.9)	17 (81)
Race, n (%)		
White	13 (100)	20 (95.2)
Black	0	1 (4.8)
ECOG performance status, n (%)		
0-1	10 (76.9)	15 (75)
2	0	5 (25)
3-4	3 (23.1)	0
Primary Malignancy, n (%)		
CLL	9 (69.2)	14 (66.7)
MCL	1 (7.7)	4 (19)
WM	0	2 (9.5)
Others[1]	3 (23.1)	1 (4.8)
CLL, Rai stage (n=9 and 14, respectively), n (%)		
0 (Low risk)	0	0
1-2 (Intermediate risk)	4 (44.4)	3 (21.4)
3-4 (High risk)	5 (55.6)	11 (78.6)
CLL, risk stratification (n=9 and 14, respectively), n (%)		
Del11q22	0	8 (61.5)
Trisomy 12	0	0
Del13q14	7 (77.8)	5 (38.5)
Del17p13	3 (33.3)	2 (15.4)
IGHV mutated, >2%, n (%)	4 (50)	11 (91.7)
Cancer stage (MCL, WM, other), (n=4 and 7, respectively), n (%)		
3-4	4 (100)	7 (100)
Treatment History, n (%)		
Prior therapies, median [range]	2 (1-5)	2 [0-10]
Untreated	0	3 (14.3)
Prior anthracycline	2 (15.4)	6 (28.6)
Prior autologous HSCT	0	2 (9.5)
Prior allogeneic HSCT	0	0
Concomitant therapies with ibrutinib, n (%)		
Chemotherapy, n (%)	3 (23.1)	6 (28.6)
Anthracyclines, n (%)	0	0
MoAb therapy, n (%)	3 (23.1)	4 (19)

Baseline AF risk factors		
Hypertension, n (%)	6 (46.2)	13 (61.9)
Diabetes mellitus, n (%)	4 (30.8)	2 (9.5)
Myocardial infarction, n (%)	1 (7.7)	3 (14.3)
Coronary artery disease, n (%)	3 (23.1)	6 (28.6)
Congestive heart failure, n (%)	1 (7.7)	3 (14.3)
Obstructive sleep apnea, n (%)	0	5 (23.8)
Valvular heart disease, n (%)	2 (15.4)	1 (4.8)
Hyperthyroidism, n (%)	0	0
Coronary artery bypass graft, n (%)	1 (7.7)	1 (4.8)
Transient ischemic attack or stroke, n (%)	1 (7.7)	1 (4.8)
Cardiac Murmur, n (%)	4 (30.8)	7 (33.3)
Smoking, n (%)	7 (53.8)	10 (47.6)
Baseline systolic BP, median [range], mmHg	124 [104-164]	129 [95-178]
Baseline PR interval[2], median [range], msec	188 [142-262]	157 [112-210]
Predicted AF risk		
FHS AF risk[3], median [range], %	21.1 [3.3->30]	14.6 [2.1->30]
Low risk (<10%), n (%)	3 (33.3)	7 (43.8)
Intermediate risk (10-20%), n (%)	1 (11.1)	6 (37.5)
High risk (>20%), n (%)	5 (55.6)	3 (18.8)
Missing data, n (%)	4 (30.8)	5 (23.8)

ECOG = Eastern Cooperative Oncology Group; CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; WM = Waldenström's macroglobulinemia; HSCT = hematopoietic stem cell transplant; MoAb = Monoclonal antibody; [1] Diffuse large B cell lymphoma, graft-versus host disease, marginal zone lymphoma, hairy cell leukemia, follicular lymphoma; BP = blood pressure, normal considered < 120mmHg; [2]Normal range = 120-200msec; FHS = Framingham Heart Study [3]FHS 10-year risk of first AF, calculated according to Schnabel et al using the following variables: age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, significant murmur, prevalent heart failure

Supplemental Table 2: Baseline Demographics in Patients Treated on a Clinical Trial versus. Commercial Ibrutinib

	Clinical Trial (n=472)	Commercial (n=110)	p-value
Age, median [range], years	65 [23->89]	65 [29->89]	0.23
Sex, male, n (%)	336 (71.2)	70 (63.6)	0.12
Race, n (%)			
White	444 (94.1)	96 (87.3)	0.03
Black	18 (3.8)	13 (11.8)	
ECOG performance status, n (%)			
0-1	447 (94.7)	83 (75.4)	<0.01
2	23 (4.9)	16 (15.7)	
3-4	1 (0.2)	3 (3)	
Primary Malignancy, n (%)			
CLL	354 (75)	79 (71.8)	<0.01
MCL	43 (9.1)	14 (12.7)	
WM	2 (0.4)	10 (9.1)	
Others[1]	73 (15.5)	7 (6.4)	
CLL, Rai stage (n=354 and 79, respectively), n (%)			
0 (Low risk)	3 (0.8)	0	<0.01
1-2 (Intermediate risk)	96 (27.1)	22 (27.8)	
3-4 (High risk)	255 (72)	52 (65.8)	
CLL, risk stratification (n=354 and 79, respectively), n (%)			
Del11q22	111 (31.9)	27 (36.5)	0.44
Trisomy 12	68 (19.5)	20 (27.8)	0.12
Del13q14	185 (53.2)	34 (45.9)	0.26
Del17p13	144 (41.3)	16 (21.9)	<0.01
IGHV mutated, >2%, n (%)	67 (21.6)	11 (20)	0.79
Cancer stage (MCL, WM, other), (n=118 and 31, respectively), n (%)			
3-4	83 (70.3)	31 (100)	0.08
Treatment History, n (%)			
Prior therapies, median [range]	3 [0-18]	2 [0-9]	<0.01
Untreated	32 (6.8)	4 (4.5)	0.39
Prior anthracycline	112 (23.7)	22 (20)	0.40
Prior autologous HSCT	31 (6.6)	7 (6.4)	0.74
Prior allogeneic HSCT	19 (4)	2 (1.8)	
Concomitant therapies with ibrutinib, n (%)			
Chemotherapy, n (%)	159 (33.7)	16 (14.5)	<0.01
Anthracyclines, n (%)	6 (1.3)	3 (2.7)	0.38
MoAb therapy, n (%)	131 (27.8)	12 (10.9)	<0.01
Baseline AF risk factors			
Hypertension, n (%)	200 (42.4)	62 (56.4)	0.01
Diabetes mellitus, n (%)	57 (12.1)	19 (17.3)	0.15

Myocardial infarction, n (%)	27 (5.7)	9 (8.2)	0.33
Coronary artery disease, n (%)	47 (10)	19 (17.3)	0.03
Congestive heart failure, n (%)	9 (1.9)	5 (4.5)	0.10
Obstructive sleep apnea, n (%)	31 (6.6)	15 (13.6)	0.01
Valvular heart disease, n (%)	16 (3.4)	6 (5.5)	0.31
Hyperthyroidism, n (%)	4 (0.8)	1 (0.9)	0.95
Coronary artery bypass graft, n (%)	11 (2.3)	1 (0.9)	0.34
Transient ischemic attack or stroke, n (%)	18 (3.8)	4 (3.6)	0.93
Cardiac Murmur, n (%)	49 (10.4)	18 (16.4)	0.08
Smoking, n (%)	216 (45.9)	46 (41.8)	0.44
Baseline systolic BP, median [range], mmHg	130 [86-186]	127 [95-178]	0.38
Baseline PR interval[2], median [range], msec	156 [80-302]	153 [116-220]	0.24
Predicted AF risk			
FHS AF risk[3], median [range], %	6.7 [0.2->30]	8.7 [0.4->30]	0.26
Low risk (<10%), n (%)	232 (64.1)	25 (56.8)	0.50
Intermediate risk (10-20%), n (%)	83 (22.9)	11 (25)	
High risk (>20%), n (%)	47 (13.0)	8 (18.2)	
Missing data, n (%)	110 (23.3)	66 (60)	

ECOG = Eastern Cooperative Oncology Group; CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; WM = Waldenström's macroglobulinemia; HSCT = hematopoietic stem cell transplant; MoAb = Monoclonal antibody; [1] Diffuse large B cell lymphoma, graft-versus host disease, marginal zone lymphoma, hairy cell leukemia, follicular lymphoma; BP = blood pressure, normal considered < 120mmHg; [2]Normal range = 120-200msec; FHS = Framingham Heart Study [3]FHS 10-year risk of first AF, calculated according to Schnabel et al using the following variables: age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, significant murmur, prevalent heart failure

Supplemental Table 3: Baseline Population Demographics Based on AF Status

	AF (n=76)	No AF (n=506)
Age, median [range], years	70 [48->89]	64 [23->89]
Sex, male, **n (%)**	64 (84.2)	342 (67.6)
Race, n (%)		
White	71 (93.4)	469 (92.7)
Black	2 (2.6)	29 (5.7)
Others	3 (3.9)	8 (1.6)
ECOG performance status, n (%)		
0-1	68 (89.5)	462 (92.9)
2	5 (6.6)	34 (6.8)
3-4	3 (3.9)	1 (0.2)
Primary Malignancy, n (%)		
CLL	61 (80.3)	372 (73.5)
MCL	6 (7.9)	51 (10.1)
WM	1 (1.3)	11 (2.2)
Others[1]	8 (10.5)	72 (14.2)
CLL, Rai stage (n=433), n (%)		
0 (Low risk)	1 (1.6)	2 (0.5)
1-2 (Intermediate risk)	15 (24.6)	103 (27.7)
3-4 (High risk)	45 (73.7)	262 (70.4)
Unknown	0	5 (1.3)
CLL, risk stratification (n=433), n (%)		
Del11q22	17 (28.3)	121 (33.4)
Trisomy 12	17 (28.3)	71 (19.7)
Del13q14	37 (61.7)	182 (50.3)
Del17p13	19 (31.7)	141 (39)
IGHV mutated, >2%, n (%)	16 (29.6)	62 (19.9)
Cancer stage (MCL, WM, other), (n=149), n (%)		
1-2	0	8 (5.9)
3-4	13 (86.6)	101 (75.3)
Not applicable, unknown	2 (13.3)	25 (18.7)
Treatment History, n (%)		
Prior therapies, median [range]	3 [0-18]	3 [0-13]
Untreated	5 (6.6)	32 (6.3)
Prior anthracycline	11 (14.5)	123 (24.3)
Prior autologous HSCT	3 (3.9)	35 (6.9)
Prior allogeneic HSCT	1 (1.3)	20 (4)
Concomitant therapies with ibrutinib, n (%)		
Chemotherapy, n (%)	22 (28.9)	153 (30.2)
Anthracyclines, n (%)	2 (2.6)	7 (1.4)
Baseline AF risk factors		

Hypertension, n (%)	36 (47.4)	226 (44.7)
Diabetes mellitus, n (%)	16 (21.1)	60 (11.9)
Myocardial infarction, n (%)	8 (10.5)	28 (5.5)
Coronary artery disease, n (%)	13 (17.1)	53 (10.5)
Congestive heart failure, n (%)	3 (3.9)	11 (2.2)
Obstructive sleep apnea, n (%)	7 (9.2)	39 (7.7)
Valvular heart disease, n (%)	3 (3.9)	19 (3.8)
Hyperthyroidism, n (%)	0	5 (1)
Coronary artery bypass graft, n (%)	4 (5.3)	8 (1.6)
Transient ischemic attack or stroke, n (%)	2 (2.6)	20 (4)
Cardiac Murmur, n (%)	15 (19.7)	52 (10.3)
Smoking, n (%)	38 (50)	224 (44.4)
Baseline systolic BP, median [range], mmHg	133 [90-168]	128 [86-186]
Baseline PR interval[2], median [range], msec	158 [114-262]	156 [80-302]
Predicted AF risk		
FHS AF risk[3], median [range], %	13.5 [2.2->30]	6.4 [0.02->30]
Low risk (<10%), n (%)	17 (35.4)	240 (67.0)
Intermediate risk (10-20%), n (%)	14 (29.2)	80 (22.4)
High risk (>20%), n (%)	17 (35.4)	38 (10.6)
Missing data, n (%)	28 (36.8)	148 (29.2)

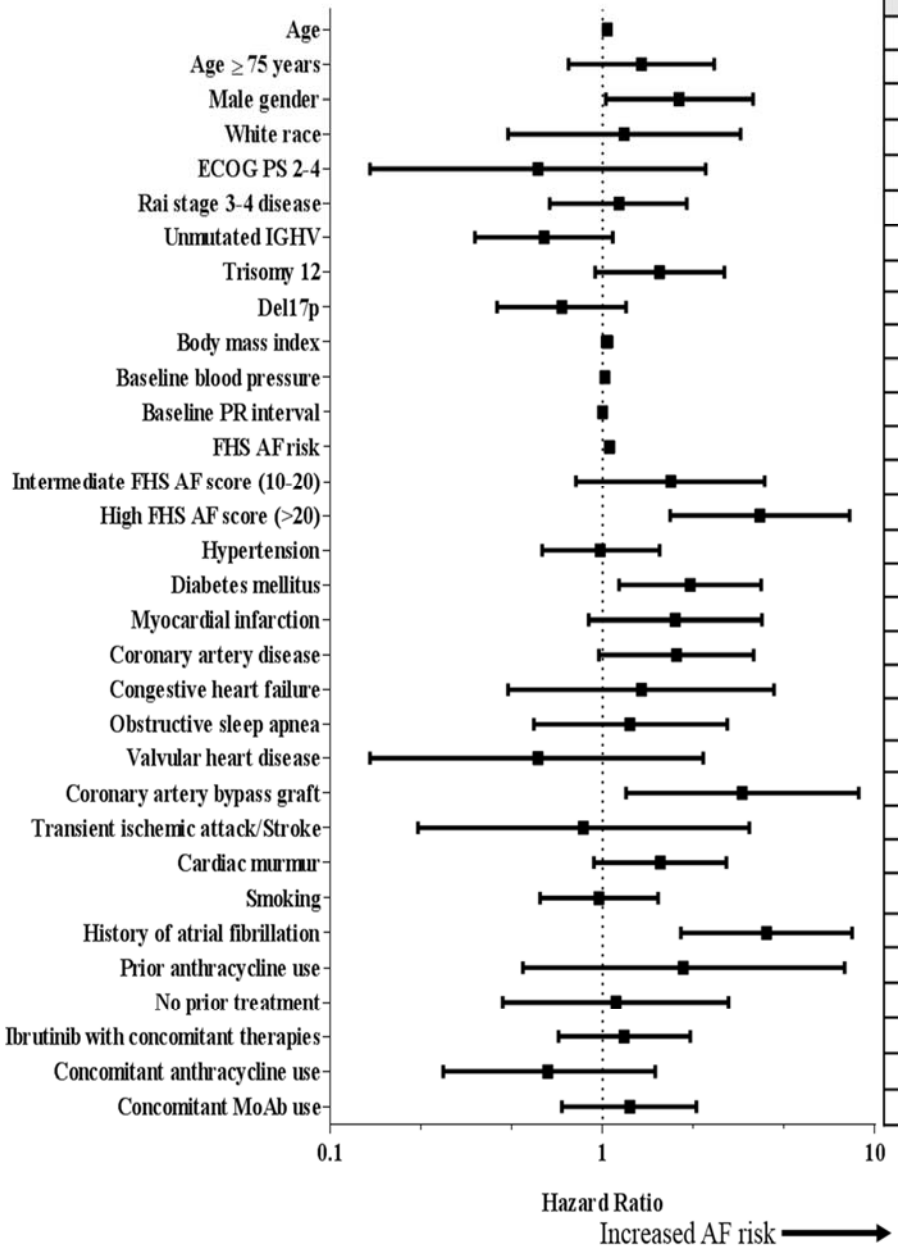
ECOG = Eastern Cooperative Oncology Group; CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; WM = Waldenström's macroglobulinemia; HSCT = hematopoietic stem cell transplant; MoAb = Monoclonal antibody; [1] Diffuse large B cell lymphoma, graft-versus host disease, marginal zone lymphoma, hairy cell leukemia, follicular lymphoma; BP = blood pressure, normal considered < 120mmHg; [2]Normal range = 120-200msec; FHS = Framingham Heart Study [3]FHS 10-year risk of first AF, calculated according to Schnabel et al using the following variables: age, sex, body mass index, systolic blood pressure, treatment for hypertension, PR interval, significant murmur, prevalent heart failure

Supplemental Table 4: Stroke prevention strategy by CHADS2 score[1]

CHADS2 Score[1]	n	Anticoagulant[2] + antiplatelet[3], n (%)	Anticoagulant[2] only, n (%)	Antiplatelet[3] only, n (%)	None, n (%)
All AF patients (n=76)					
0	22	1 (5)	3 (14)	11 (50)	7 (32)
1	28	0	13 (46)	12 (43)	3 (11)
2	15	1 (7)	3 (20)	9 (60)	2 (13)
3	8	0	0	4 (50)	4 (50)
4	3	0	1 (33)	2 (67)	0
p-value (trend)[4]		0.76	0.68	0.53	0.84
Incident AF patients (n=63)					
0	18	1 (6)	3 (17)	8 (44)	6 (33)
1	26	0 (0)	13 (50)	10 (38)	3 (12)
2	12	0 (0)	3 (25)	7 (58)	2 (17)
3	5	0 (0)	0 (0)	3 (60)	2 (40)
4	2	0 (0)	1 (50)	1(50)	0 (0)
p-value (trend)		0.26	0.96	0.40	0.53
Recurrent AF patients (n=13)					
0	4	0 (0)	0 (0)	3 (75)	1 (25)
1	2	0 (0)	0 (0)	2 (100)	0 (0)
2	3	1 (33)	0 (0)	2 (67)	0 (0)
3	3	0 (0)	0 (0)	1 (33)	2 (67)
4	1	0 (0)	0 (0)	1 (100)	0 (0)
p-value (trend)		0.76	-	0.49	0.57

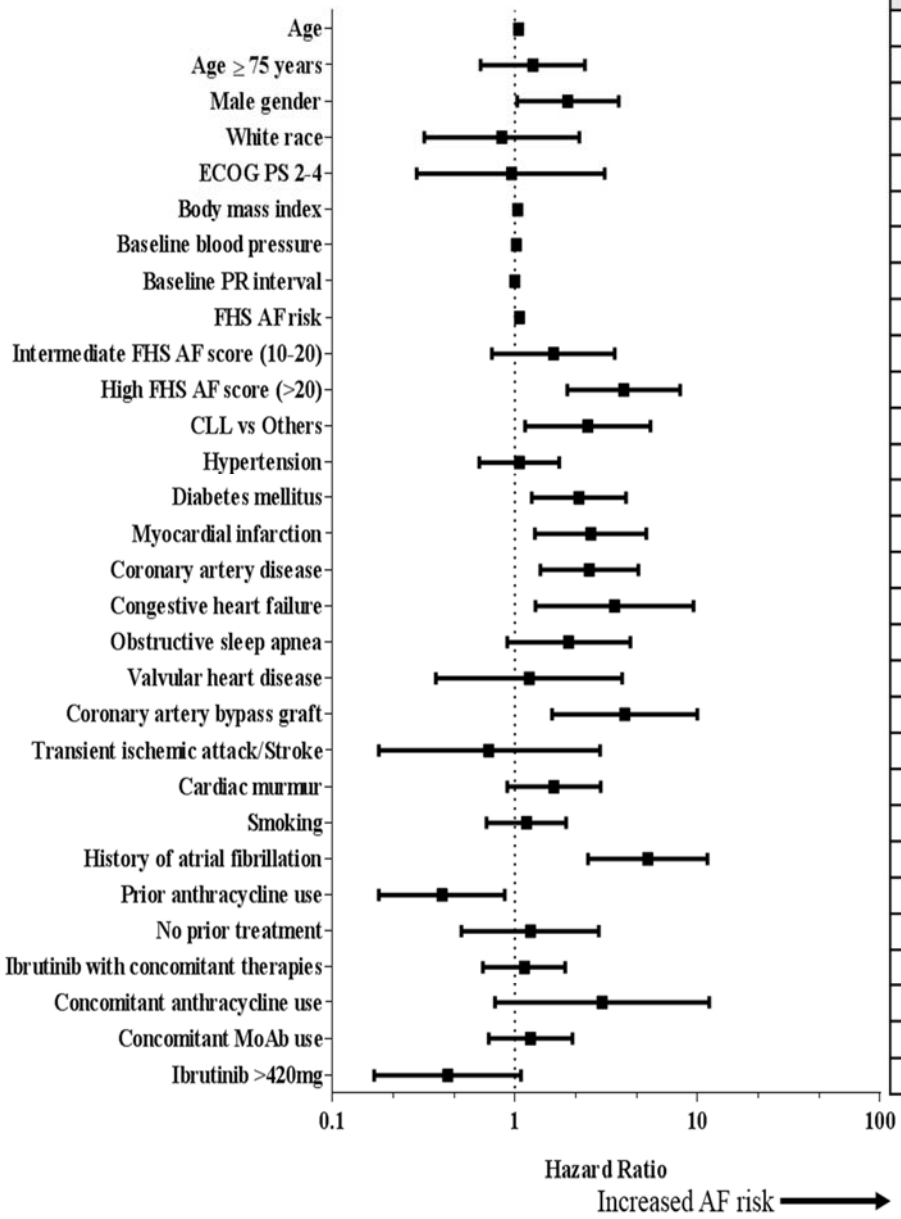
[1]CHADS2 scoring system: heart failure = 1 point, hypertension requiring treatment = 1 point, age $\geq$ 75 years = 1 point, diabetes mellitus = 1 point, history of stroke or transient ischemic attack = 2 points; add points to determine score. CHADS2 score stroke prevention recommendations: 0 = aspirin 81-325mg; 1 = either aspirin 81-325mg or therapeutic anticoagulation depending on patient preference; 2 or higher = therapeutic anticoagulation.
[2]Anticoagulants prescribed = enoxaparin, rivaroxaban, apixaban, dabigatran, warfarin, heparin
[3]Antiplatelets prescribed = aspirin 81-325mg
[4]p-value is from chi-square test for the trend in the proportions of patients receiving the treatment associated with CHADS2 score

Supplemental Figure 1: Univariable Analysis for AF Risk factors for CLL patient population (n= 433)



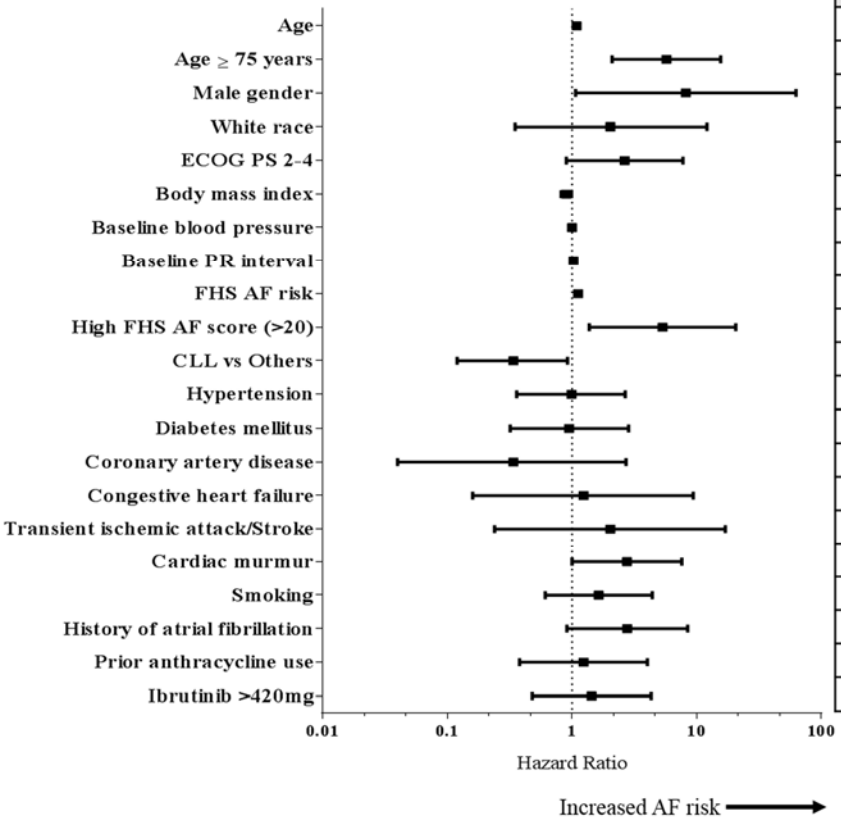
	Hazard Ratio	95% CI		p-value
Age	1.04	1.02	1.07	<0.01
Age ≥ 75 years	1.39	0.75	2.57	0.29
Male gender	1.91	1.03	3.57	0.04
White race	1.2	0.45	3.21	0.71
ECOG PS 2-4	0.58	0.14	2.39	0.45
Rai stage 3-4 disease	1.15	0.64	2.04	0.65
Unmutated IGHV	0.61	0.34	1.09	0.09
Trisomy 12	1.62	0.94	2.80	0.082
Del17p	0.71	0.41	1.22	0.22
Body mass index	1.04	1.00	1.08	0.07
Baseline blood pressure	1.02	1.00	1.04	0.03
Baseline PR interval	1.00	0.99	1.01	0.40
FHS AF risk	1.06	1.03	1.10	<0.01
Intermediate FHS AF score (10-20)	1.78	0.80	3.94	0.16
High FHS AF score (>20)	3.78	1.77	8.08	<0.001
Hypertension	0.98	0.60	1.62	0.95
Diabetes mellitus	2.10	1.15	3.82	0.02
Myocardial infarction	1.85	0.89	3.85	0.10
Coronary artery disease	1.87	0.97	3.59	0.06
Congestive heart failure	1.39	0.45	4.26	0.57
Obstructive sleep apnea	1.26	0.56	2.87	0.58
Valvular heart disease	0.58	0.14	2.34	0.44
Coronary artery bypass graft	3.26	1.22	8.73	0.02
Transient ischemic attack/Stroke	0.85	0.21	3.46	0.82
Cardiac murmur	1.63	0.93	2.85	0.09
Smoking	0.97	0.59	1.60	0.90
History of atrial fibrillation	4.00	1.94	8.25	<0.01
Prior anthracycline use	0.63	0.26	1.56	0.32
No prior treatment	1.12	0.43	2.90	0.82
Ibrutinib with concomitant therapies	1.20	0.69	2.10	0.51
Concomitant anthracycline use	1.98	0.51	7.74	0.32
Concomitant MoAb use	1.26	0.71	2.21	0.43

Supplemental Figure 2: Univariable Analysis for AF Risk factors for entire patient population treated on a clinical trial (n= 472)



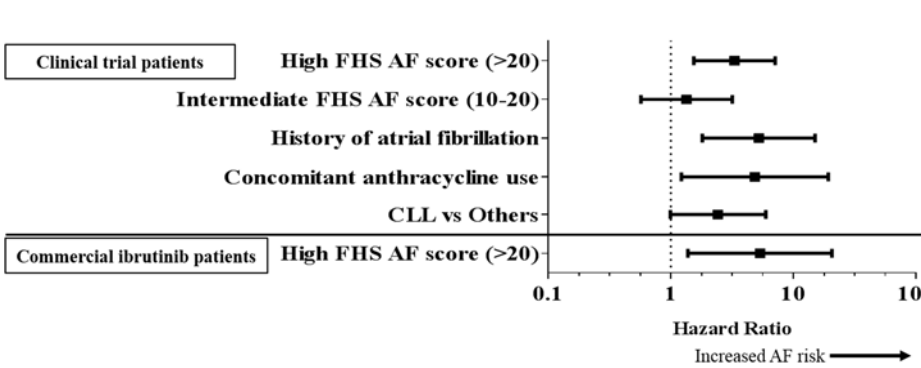
Hazard Ratio	95% CI		p-value
1.05	1.03	1.08	<0.01
1.26	0.65	2.42	0.50
1.95	1.03	3.71	0.04
0.85	0.32	2.26	0.74
1.95	1.03	3.71	0.04
1.04	1.00	1.08	0.07
1.02	1.00	1.04	0.04
1.00	0.99	1.01	0.43
1.06	1.03	1.10	<0.01
1.63	0.75	3.53	0.22
3.95	1.94	8.05	<0.01
2.51	1.14	5.53	0.02
1.06	0.64	1.75	0.82
2.25	1.24	4.07	0.01
2.61	1.29	5.25	0.01
2.56	1.38	4.75	<0.01
3.52	1.30	9.53	0.01
1.97	0.91	4.30	0.09
1.20	0.37	3.87	0.77
4.00	1.60	9.99	<0.01
0.72	0.18	2.93	0.64
1.64	0.91	2.96	0.10
1.16	0.70	1.91	0.56
5.35	2.52	11.36	<0.01
0.40	0.18	0.88	0.02
1.22	0.51	2.89	0.66
1.13	0.67	1.89	0.65
3.01	0.78	11.59	0.11
1.22	0.72	2.07	0.47
0.43	0.17	1.08	0.07

Supplemental Figure 3: Univariable Analysis for AF Risk factors for patients treated with commercial ibrutinib (n=110)



Hazard Ratio	95% CI		p-value
1.09	1.04	1.15	<0.01
5.72	2.10	15.59	<0.01
8.19	1.07	62.73	0.04
2.04	0.35	12.07	0.43
2.65	0.90	7.76	0.07
0.90	0.82	0.99	0.03
1.00	0.97	1.03	0.96
1.03	1.01	1.05	<0.01
1.12	1.06	1.19	<0.01
5.34	1.38	20.61	0.01
0.34	0.12	0.92	0.03
0.99	0.36	2.68	0.97
0.95	0.32	2.84	0.92
0.34	0.04	2.72	0.31
1.24	0.16	9.38	0.83
2.04	0.24	16.97	0.51
2.76	1.00	7.61	0.05
1.64	0.61	4.41	0.33
2.77	0.91	8.47	0.07
1.24	0.38	4.02	0.72
1.44	0.48	4.32	0.51

Supplemental Figure 4: Multivariable Analysis for AF Risk factors for patients treated on a clinical trial (n=472), and with commercial ibrutinib (n=110)



	Hazard Ratio	95% CI		p-value
High FHS AF score (>20)	1.34	0.57	3.16	0.51
Intermediate FHS AF score (10-20)	3.30	1.54	7.08	<0.01
History of atrial fibrillation	5.22	1.81	15.01	<0.01
Concomitant anthracycline use	4.84	1.22	19.23	0.03
CLL vs Others	2.42	0.99	5.95	0.05
High FHS AF score (>20)	5.34	1.38	20.61	0.01