Supplemental Figures and Tables:

Supplemental Table 1. Long-term rates, time to development, and management of new or worsened hypertension (HTN) during ibrutinib therapy.

Final HTN status (n=562)	**n (%)**
New or worsened HTN	440 (78.3)
Months post-ibrutinib initiation	**Cumulative Incidence of new or worsened HTN, % (95% CI)**
1	39.9 (35.8 - 43.9)
3	57.9 (53.7 - 61.8)
6	64.0 (59.9 - 67.8)
12	70.2 (66.8 - 74.3)
Group	**Time to 50% cumulative incidence of HTN, months**
All patients (n=562)	1.8
New HTN (n=215)	4.2
Worsened HTN (n=347)	1.1
By baseline HTN status	
No baseline HTN (n=215)	
New HTN	154 (71.6)
Baseline HTN (n=347)	
Worsened HTN	286 (82.4)
Worsened CTCAE grade	268 (77.2)
New antihypertensive added	158 (45.5)
Increased antihypertensive dose(s)	28 (8.1)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.

Supplemental Table 2. Distribution of maximum SBP increase from baseline, %*

Maximum SBP Increase from Baseline, mmHg	**Total (n=562)**	**No baseline HTN (n=215)**	**Baseline HTN (n=347)**
≤ 0	6.2	5.2	6.8
>0 – 5	4.5	1.4	6.5
>5 – 10	8.3	7.5	8.9
>10 – 15	7.4	8.9	6.5
>15 – 20	7.3	6.1	8.0
>20 – 25	9.6	8.9	10.0
>25 – 30	11.6	15.5	9.1
>30 – 35	10.1	9.4	10.6
>35 – 40	9.1	8.5	9.4
>40 – 45	7.4	8.0	7.1

>45 – 50	7.6	8.0	7.4
>50	10.9	12.7	9.7

*Column totals = 100%

Supplemental Table 3A. Univariable predictors for the development of new or worsened hypertension (n=562).

Variable	Hazard Ratio	95% Confidence Interval	p-value
Age*	1.01	(1.00 – 1.02)	**0.01**
Age (ref: 23-49)			**0.03**†
50-59	0.86	(0.60 - 1.22)	0.40
60-69	1.20	(0.87 - 1.67)	0.26
≥70	1.20	(0.85 - 1.67)	0.30
BMI*	1.02	(1.00 – 1.04)	**0.04**
BMI (ref: <25)			**0.04**†
25-29.9	1.16	(0.94 - 1.44)	0.17
≥30	1.37	(1.07 - 1.74)	**0.01**
Male	1.21	(0.98 - 1.49)	0.07
Smoking (reference: Never)			0.22†
Previous	1.07	(0.89 - 1.30)	0.47
Current	1.48	(0.94 - 2.32)	0.09
Black/African-American	1.15	(0.71 - 1.86)	0.58
Primary malignancy			**0.04**†
CLL vs. MCL	1.03	(0.71 – 1.48)	0.89
CLL vs. Other‡	1.49	(1.09 – 2.02)	**0.01**
MCL vs. Other‡	1.45	(0.92 – 2.29)	0.11
RAI stage (ref: 0/1)			0.17†
2	1.14	(0.78 – 1.67)	0.51
3	0.82	(0.56 – 1.22)	0.33
4	0.60	(0.63 – 1.30)	0.28
Statin	1.08	(0.88 - 1.34)	0.47
ASA	1.09	(0.88 - 1.35)	0.40
Prior DM	1.44	(1.11 - 1.86)	**0.01**
Prior MI	0.94	(0.66 - 1.34)	0.73
Prior CAD	1.18	(0.96 - 1.44)	0.12
Prior CHF	1.24	(0.97 - 1.59)	0.09
Prior CKD	1.09	(0.87 - 1.38)	0.44
Prior CVA	1.02	(0.67 - 1.54)	0.93
Corticosteroid use	1.16	(0.84 - 1.61)	0.37
SNRI use	1.41	(0.93 - 2.14)	0.11
Estrogen and/or Progestin use	0.84	(0.60 - 1.17)	0.30
Bupropion use	0.72	(0.55 - 0.93)	**0.01**
ECOG (reference = 0)			0.94†
1	1.00	(0.82 - 1.20)	0.96
2 to 4	0.86	(0.55 - 1.36)	0.52
Unknown	0.96	(0.37 - 2.49)	0.94

Variable	Hazard Ratio	95% Confidence Interval	p-value
CY3PA4 Inhibitor	1.46	(0.98 - 2.18)	0.06
Concomitant Therapy, any	1.06	(0.87 - 1.31)	0.55
Concomitant Anthracycline	2.24	(1.29 - 3.92)	**0.004**
Concomitant Cytotoxic Chemotherapy	1.06	(0.87 - 1.31)	0.55
Concomitant Monoclonal Antibody	1.20	(0.96 - 1.49)	0.11
Concomitant Targeted Therapy	1.06	(0.67 - 1.69)	0.81
Concomitant Immunomodulatory	0.73	(0.44 - 1.24)	0.25
Baseline SBP, mmHg (reference: <100)			**0.002**†
100-119	3.29	(1.60 - 6.76)	**0.001**
120-129	3.15	(1.52 - 6.52)	**0.002**
>129	3.76	(1.85 - 7.63)	**<0.001**
Baseline DBP, mmHg (reference: <70)			0.14†
70-79	1.26	(1.03 - 1.55)	**0.03**
80-89	1.18	(0.91 - 1.54)	0.21
90-119	1.31	(0.78 - 2.18)	0.31
Ibrutinib dose, mg (560/840 vs 280/480)	0.84	(0.63 - 1.12)	0.24

Abbreviations: ASA, aspirin; BMI, body-mass-index; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CLL, chronic lymphocytic lymphoma; CVA, cerebrovascular accident; CV, cardiovascular; CY3PA4, cytochrome P450, family 3, subfamily A; DBP, diastolic blood pressure; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group; MI, myocardial infarction; MCL, mantle cell lymphoma; N/A, not available; SNRI, serotonin and norepinephrine reuptake inhibitors; WM, Waldenström's macroglobulemia. *Considered as a continuous variable. †Omnibus p-value (reflects overall variable effect). ‡Diffuse large B-Cell lymphoma, follicular lymphoma, hairy cell leukemia, graft-versus-host disease, marginal zone lymphoma, and Waldenström's macroglobulemia.

Supplemental Table 3B. Multivariable predictors for new hypertension alone (n=215).*

Variable	Hazard Ratio	95% Confidence Interval	p-value
Age**	1.00	(0.98 – 1.02)	0.90
BMI**	1.00	(0.97 – 1.04)	0.88
Male	1.17	(0.81 – 1.68)	0.41
Black/African-American	1.36	(0.33 – 5.67)	0.67
History of DM	1.73	(1.03 – 2.93)	**0.04**
History of CKD	0.86	(0.52 – 1.42)	0.56
Smoking Status: Current/Previous vs. Never	0.94	(0.65 – 1.34)	0.72
Baseline SBP, mmHg			**0.02**†
<100	reference	reference	
100-119	3.05	(1.41 – 6.58)	**0.004**
120-129	3.24	(1.46 – 7.17)	**0.004**
>129‡	3.98	(1.54 – 10.26)	**0.004**

Abbreviations: BMI, body-mass-index; CKD, chronic kidney disease; DM, diabetes mellitus; SBP, systolic blood pressure. *Reflects inclusion of variables with univariable association with new hypertension during ibrutinib use and/or established traditional hypertension risk factors. **Considered as continuous variables. †Omnibus p-value (reflects overall variable effect). ‡Subjects without a formal diagnosis of hypertension and not on antihypertensive therapy.

Supplemental Table 3C. Multivariable predictors for worsened hypertension alone (n=347).*

Variable	Hazard Ratio	95% Confidence Interval	p-value
Age**	1.02	(1.00 – 1.03)	**0.01**
BMI**	1.03	(1.00 – 1.05)	**0.04**
Male	0.92	(0.71 – 1.20)	0.55
Black/African-American	0.73	(0.42 – 1.28)	0.28
History of DM	1.07	(0.77 – 1.49)	0.68
History of CKD	0.95	(0.71 – 1.27)	0.72
Smoking Status: Current/Previous vs. Never	1.12	(0.88 – 1.42)	0.37
Primary malignancy			**0.01**†
CLL vs. MCL	0.97	(0.63 – 1.53)	0.93
CLL vs. Other‡	1.84	(1.23 – 2.75)	**0.003**
MCL vs. Other‡	1.20	(1.06 – 3.31)	**0.03**
CY3PA4 Inhibitor	2.83	(1.80 – 4.45)	**<0.001**
Baseline SBP			**<0.001**†
<120	reference	reference	
120-129	0.61	(0.38 – 0.99)	**0.04**
130-139	0.97	(0.65 – 1.46)	0.89
>139	0.43	(0.29 – 0.63)	**<0.001**

Abbreviations: BMI, body-mass-index; CKD, chronic kidney disease; CLL, chronic lymphocytic lymphoma; CY3PA4, cytochrome P450, family 3, subfamily A; DM, diabetes mellitus; MCL, mantle cell lymphoma; SBP, systolic blood pressure; WM, Waldenström's macroglobulemia. *Reflects variables with univariate association with new hypertension during ibrutinib use and/or established traditional hypertension risk factors. **Considered as continuous variables. †Omnibus p-value (reflects overall variable effect). ‡Diffuse large B-Cell lymphoma, follicular lymphoma, hairy cell leukemia, graft-versus-host disease, marginal zone lymphoma, and Waldenström's macroglobulemia.

Supplemental Table 4A. Prevention of worsening hypertension (HTN) among ibrutinib users, by antihypertensive therapeutic class (n=347).*

Variable	Hazard Ratio	95% CI (lower - upper)	p-value
Beta-blocker	1.12	(0.88 - 1.43)	0.36
ACE inhibitor/ARB	0.90	(0.66 - 1.23)	0.50
Calcium channel blocker	1.20	(0.94 - 1.53)	0.14
Diuretic†	0.88	(0.67 - 1.15)	0.34
Other anti-HTN medication‡	1.18	(0.81 - 1.70)	0.39

Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval. *Univariate analyses, as no significant associations were noted. †Includes loop, thiazide, and potassium-sparing diuretics. ‡Clonidine, hydralazine, nitrates, and alpha-1 antagonists.

Supplemental Table 4B. Change in blood pressure during the 1st year of ibrutinib therapy, among subjects requiring the addition of only a single new or additional antihypertensive class. No class significantly lowered pressures. [From the 209 patients started on a new or additional antihypertensive, 101 patients saw the addition within 12 months of ibrutinib initiation, of which 64 were treated with the addition of a single antihypertension drug, 37 had pre and post antihypertensive blood pressure measures; another 24 (out of 34) required initiation of ≥ 2 antihypertensives, and had available blood pressure measures pre and 12 months post initiation of the first antihypertensive added during ibrutinib use].

Medication Class	No. with single-class therapy added (n = 37, %)	Change in SBP, mmHg (Post – Pre), mean (SD)
ACE/ARB	9 (24.3)	+1.2 (16.8)
Beta Blocker	9 (24.3)	+1.5 (13.4)
Calcium Channel Blocker	9 (24.3)	+2.0 (19.3)
Diuretic*	10 (27.0)	-0.3 (21.2)
Other†	0	n/a
Overall	37 (100)	+1.0 (17.3)
Combination‡	24 (n/a)	-6.0 (17.0)

Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HTN, hypertension; SBP, systolic blood pressure. *Includes loop, thiazide, and potassium-sparing diuretics. †Clonidine, hydralazine, nitrates, and alpha-1 antagonists. ‡Subjects requiring ≥ 2 antihypertensives to be initiated during ibrutinib use.

Supplemental Table 5. Occurrence of major adverse cardiovascular events (MACE), by post-ibrutinib initiation hypertension (HTN) status.

Final status	No or Stable HTN (n=122), %	New or Worsened HTN (n=440), %
MACE	9 (7.4)	84 (19.1)
Cumulative incidence of MACE (95% CI)		
Months post-ibrutinib initiation	**No or Stable HTN (n=122), %**	**New or Worsened HTN (n=440), %**
3	4.1 (1.5 - 8.7)	4.8 (3.1 - 7.1)
6	5.8 (2.6 - 11.0)	6.4 (4.3 - 8.9)
12	5.8 (2.6 - 11.0)	8.0 (5.7 - 10.7)

Final status	No or Stable HTN (n=122), %	New or Worsened HTN (n=440), %
24	6.7 (3.1 - 12.1)	12.2 (9.3 - 15.4)
36	6.7 (3.1 - 12.1)	14.2 (11.1 - 17.6)
Median (IQR) follow-up time, months*		
Group	**No or Stable HTN (n=122), %**	**New or Worsened HTN (n=440), %**
All patients	4.9 (1.5 - 24.1)	27.8 (10.2 - 46.9)
No MACE	5.7 (1.6 - 25.2)	30.9 (12.0 - 49.0)

Abbreviations: CI, confidence interval; IQR, interquartile range. *Reflects censoring at the time of MACE, death, or ibrutinib discontinuation for any reason.

Supplemental Table 6A. Multivariable analysis for the development of atrial fibrillation (AF) or ventricular arrhythmias (VA) during ibrutinib use (competing risks: death or ibrutinib discontinuation), considering new or worsened HTN at any time point.

Variable	Hazard Ratio	95% CI (lower - upper)	p-value
New/Worsened HTN versus No/Stable HTN	3.18	(1.37, 7.37)	**0.01**
Age†	1.05	(1.02-1.07)	**<0.001**
BMI†	1.01	(0.97-1.05)	0.69
Male	2.09	(1.17-3.75)	**0.01**
Prior AF	0.79	(0.26-2.45)	0.68
Prior DM	1.17	(0.61-2.23)	0.64
Prior MI	1.43	(0.66-3.11)	0.36
Prior CHF	1.96	(0.87-4.42)	0.10

Abbreviations: AF, atrial fibrillation; BMI, body-mass-index; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction. *Time varying covariate, where new/worsened HTN was considered only from the date/time of the initial new/worsened HTN event through the end of follow-up. †Considered as a continuous variable.

Supplemental Table 6B. Multivariable analysis for the development of atrial fibrillation (AF) or ventricular arrhythmias (VA) during ibrutinib use (competing risks: death or ibrutinib discontinuation), considering patients as having new/worsened HTN only from the time of reaching clinical HTN thresholds.

Variable	Hazard Ratio	95% CI (lower - upper)	p-value
New/Worsened HTN versus No/Stable HTN*	5.35	(2.94-9.73)	**<0.001**
Age†	1.05	(1.02-1.07)	**<0.001**
BMI†	1.01	(0.96-1.05)	0.79
Male	2.12	(1.19-3.76)	**0.01**
Prior AF	1.02	(0.34-3.09)	0.97
Prior DM	1.13	(0.59-2.15)	0.72
Prior MI	1.65	(0.77-3.53)	0.20
Prior CHF	2.01	(0.89-4.53)	0.09

Abbreviations: AF, atrial fibrillation; BMI, body-mass-index; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction. *Time varying covariate, where new/worsened HTN was considered only from the date/time of the initial new/worsened HTN event through the end of follow-up. †Considered as a continuous variable.

Supplemental Table 6C. Multivariable predictors of major adverse cardiovascular events (MACE) during ibrutinib use, with HTN considered as a time varying covariate (n=562).*

Variable	Hazard Ratio	95% CI (lower - upper)	p-value
New/Worsened HTN versus No/Stable HTN**	5.40	(3.13-9.32)	**<0.001**
Age†	1.05	(1.03-1.07)	**<0.001**
BMI†	1.03	(0.99-1.07)	0.18
Male	1.80	(1.06-3.05)	**0.03**
Prior AF	0.77	(0.25-2.38)	0.65
Prior CAD	1.38	(0.78-2.43)	0.27
Prior CHF	2.73	(1.44-5.19)	**0.002**
Prior CVE	0.98	(0.39-2.47)	0.96
Prior DM	1.17	(0.67-2.06)	0.58
Prior CKD	1.07	(0.65-1.77)	0.79

Abbreviations: AF, atrial fibrillation; BMI, body-mass-index; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CVE, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension. *MACE includes the combined outcome of AF, CHF, CVA, MI (myocardial infarction), VF/VT (ventricular fibrillation/ventricular tachycardia), and cardiovascular death during ibrutinib use. **Patients considered no/stable HTN until the date/time of new/worsened HTN event, and then were considered as new/worsened HTN from the date of HTN development or worsening for the remainder of time at risk for MACE. †Considered as a continuous variable.

Supplemental Table 7A. Effect of antihypertensive therapy initiation on the subsequent risk of major adverse cardiovascular events (MACE) during ibrutinib use, among patients with new or worsened HTN alone (n=440).*

Variable	Hazard Ratio	95% CI (lower - upper)	p-value
New anti-HTN medication versus No (new) anti-HTN medication	0.40	(0.24-0.66)	**<0.001**
Age†	1.04	(1.02-1.06)	**<0.001**
BMI†	1.03	(0.99-1.07)	0.08
Male	1.66	(0.91-3.03)	0.10
History of AF	0.62	(0.18-2.11)	0.45
Prior CAD	1.07	(0.55-2.11)	0.84
Prior CHF	2.78	(1.40-5.53)	**0.004**
Prior CVE	0.76	(0.23-2.44)	0.64
Prior DM	1.46	(0.81-2.64)	0.21
Prior CKD	1.17	(0.68-2.01)	0.58

Abbreviations: AF, atrial fibrillation; BMI, body-mass-index; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CVE, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension. *MACE includes the combined outcome of AF, CHF, CVA, MI (myocardial infarction), VF/VT (ventricular fibrillation/ventricular tachycardia), and cardiovascular death during ibrutinib use. **Patients considered as having a new antihypertensive initiated only if treatment was started prior to an arrhythmic event; those starting antihypertensives only after MACE [40 (19.8%) of the 202 subjects started on a new antihypertensive in this cohort] were included among the "no antihypertensive" group for this analysis. †Considered as a continuous variable.

Supplemental Table 7B. Effect of antihypertensive therapy initiation on the subsequent risk of major adverse cardiovascular events (MACE) during ibrutinib use, among patients with new or worsened HTN, excluding those with new beta-blocker or calcium channel inhibitor use (ie. atrioventricular node blockers; n=349).*

Variable	Hazard Ratio	95% CI (lower - upper)	p-value
New anti-HTN medication versus No (new) anti-HTN medication	0.52	(0.27-1.01)	0.052
Age†	1.05	(1.02-1.07)	**<0.001**
BMI†	1.03	(0.99-1.07)	0.11
Male	1.82	(0.92-3.59)	0.09
History of AF	0.56	(0.14-2.20)	0.40
Prior CAD	0.98	(0.48-2.03)	0.97
Prior CHF	2.52	(1.16-5.49)	**0.02**
Prior CVE	0.95	(0.29-3.16)	0.94
Prior DM	1.35	(0.71-2.56)	0.36

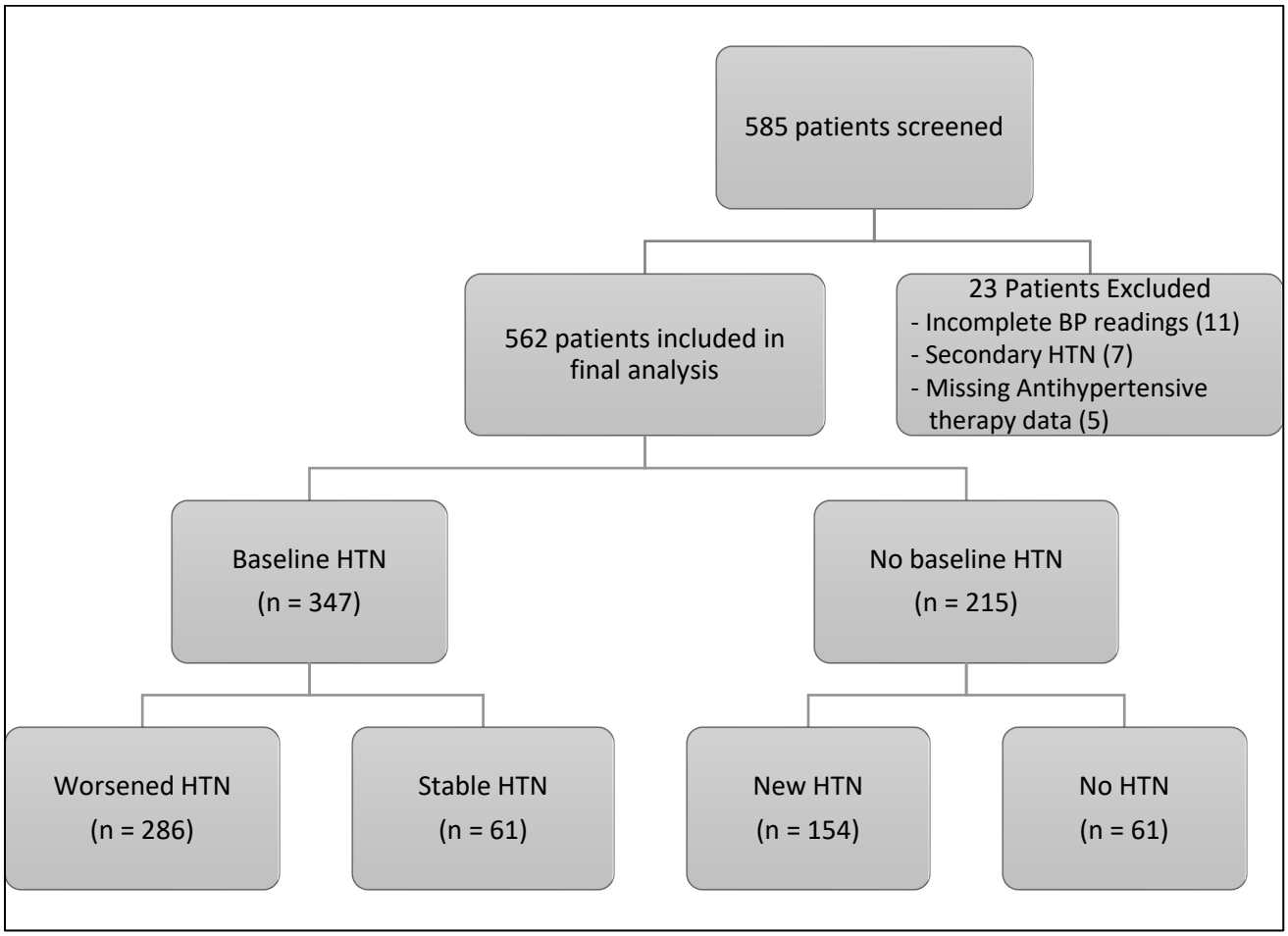
Variable	Hazard Ratio	95% CI (lower - upper)	p-value
Prior CKD	1.05	(0.57-1.94)	0.87

Abbreviations: AF, atrial fibrillation; BMI, body-mass-index; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CVE, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension. *MACE includes the combined outcome of AF, CHF, CVA, MI (myocardial infarction), VF/VT (ventricular fibrillation/ventricular tachycardia), and cardiovascular death during ibrutinib use. **Patients considered as having a new antihypertensive initiated only if treatment was started prior to an arrhythmic event; those starting antihypertensives only after MACE [37 (33.3%) of the 111 subjects started on a new antihypertensive in this cohort] were included among the "no antihypertensive" group for this analysis. †Considered as a continuous variable.

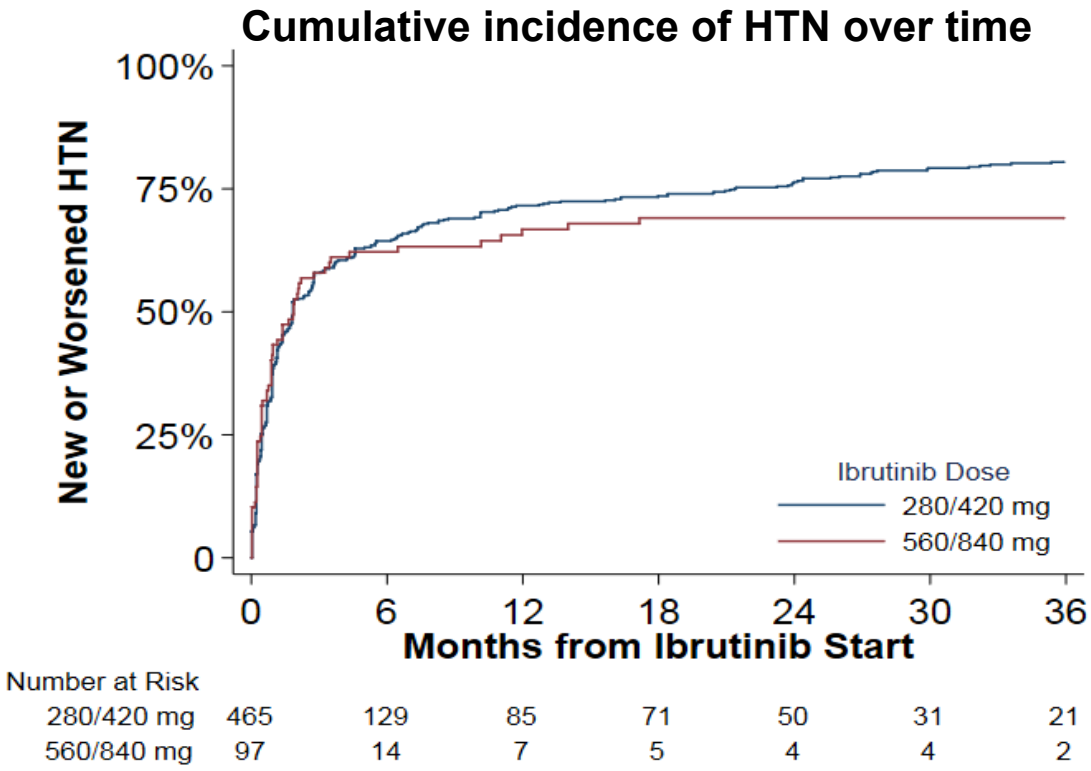
Supplemental Table 8. Cumulative incidence of new, predicted, and grade 3 or more HTN over time.

Month:	0	3	6	9	12
Observed	0%	29.4%	35.2%	40.0%	44.2%
Predicted	0%	0.8%	1.7%	2.5%	3.4%
Grade ≥3	0%	1.3%	1.9%	2.6%	3.9%

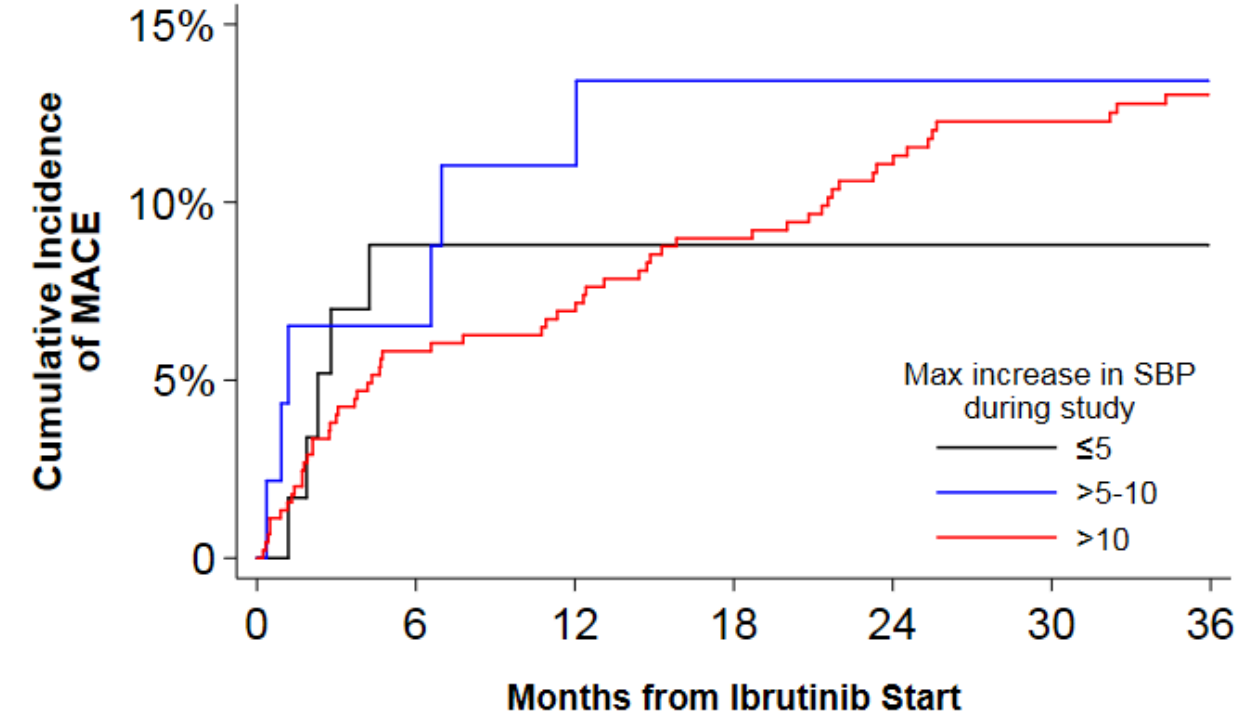
Supplemental Figure 1: Study consort diagram. From a registry of all patients with hematologic malignancies treated with ibrutinib at a large comprehensive cancer center over a 7-year period, those with available blood pressure measures were included.



Supplemental Figure 2. Cumulative incidence of new or worsened hypertension (HTN), stratified by ibrutinib dose.



Supplemental Figure 3. Cumulative incidence of major adverse cardiovascular events (MACE), stratified by the degree of increase systolic blood pressure (SBP).



Number at Risk

≤5	59	16	11	11	8	6	6
>5-10	46	25	25	25	13	9	8
>10	447	375	332	296	253	220	179

Supplemental Figure 4. Cumulative incidence of progression or death after the 12 month timepoint (ie. landmark) alone.