Supplementary Index

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"Randomized trial of ibrutinib versus ibrutinib plus rituximab (Ib+R) in patients with chronic lymphocytic leukemia (CLL)."

Table of Contents

Supplemental Tables

Supplemental Table 1. Time on Study Treatment and Time on Study. ITT Population

	Ibr (N=104)	Ibr+R (N=104)	Total (N=208)
Time on study treatment (months) [1]			
n	104	104	208
Mean (SD)	28.1 (13.62)	26.3 (14.08)	27.2 (13.85)
Median	29.7	27.4	27.9
Min, Max	0.7, 46.7	1.1, 47.8	0.7, 47.8
<3	2 (1.9%)	8 (7.7%)	10 (4.8%)
3-<6	7 (6.7%)	2 (1.9%)	9 (4.3%)
6-<12	8 (7.7%)	10 (9.6%)	18 (8.7%)
12-<24	19 (18.3%)	28 (26.9%)	47 (22.6%)
24-<36	31 (29.8%)	22 (21.2%)	53 (25.5%)
>=36	37 (35.6%)	34 (32.7%)	71 (34.1%)
Time on study (months) [2]			
n	104	104	208
Median (95% CI)	35.8 (32.3,38.9)	36.4 (32.3,39.1)	35.8 (33.4,38.9)
Min, Max	3.0,47.1	2.9+,47.8	2.9+,47.8

CI= confidence interval. + Indicates censored observation.
[1] Duration of time from the date of first dose of study treatment to the date of last dose of study treatment.
[2] Time on study is based on follow-up time of overall survival using reversed Kaplan-Meier estimates. Subjects who died were censored at death date.

Supplemental Table 2. Proportion of Subjects with CR/CRi. ITT Population

	Ibr (N=104) n(%)	Ibr+R (N=104) n(%)	Ibr vs. Ibr+R
All Subjects	21 (20.2)	27 (26.0)	
Rate difference (95% CI) [1]			-5.8 (-19.6, 8.3)
P value [1]			0.3234

N = number of subjects in the specified population. n = number of subjects with CR/CRi.
[1] Based on chi-square test.

Supplemental Table 3. Best Response by Subgroup. ITT Population

	Ibr n(%)				Ibr+R n(%)			
Subgroups	N	CR/CRi	PR/nPR	PRL	N	CR/CRi	PR/nPR	PRL
All subjects	104	21 (20.2)	64 (61.5)	11 (10.6)	104	27 (26.0)	65 (62.5)	4 (3.8)
Age, yrs.								
<65	51	9 (17.6)	34 (66.7)	6 (11.8)	48	14 (29.2)	30 (62.5)	1 (2.1)
≥65	53	12 (22.6)	30 (56.6)	5 (9.4)	56	13 (23.2)	35 (62.5)	3 (5.4)
Lines of prior treatment								
0	15	3 (20.0)	9 (60.0)	2 (13.3)	12	6 (50.0)	6 (50.0)	0
1-2	68	15 (22.1)	40 (58.8)	6 (8.8)	76	19 (25.0)	47 (61.8)	4 (5.3)
≥3	21	3 (14.3)	15 (71.4)	3 (14.3)	16	2 (12.5)	12 (75.0)	0
Del 17p/TP53 mutation (High risk)								
Yes	41	9 (22.0)	24 (58.5)	5 (12.2)	36	12 (33.3)	23 (63.9)	1 (2.8)
No	35	5 (14.3)	21 (60.0)	4 (11.4)	49	11 (22.4)	31 (63.3)	3 (6.1)
Del 11q								
Yes	27	4 (14.8)	20 (74.1)	1 (3.7)	15	3 (20.0)	10 (66.7)	1 (6.7)
No	75	16 (21.3)	43 (57.3)	10 (13.3)	86	24 (27.9)	53 (61.6)	3 (3.5)
IGVH status								
Mutated	26	4 (15.4)	17 (65.4)	2 (7.7)	22	5 (22.7)	14 (63.6)	2 (9.1)
Unmutated	61	14 (23.0)	36 (59.0)	6 (9.8)	62	18 (29.0)	38 (61.3)	2 (3.2)
β2 macroglobulin, mg/L								
≥4	43	10 (23.3)	28 (65.1)	1 (2.3)	45	12 (26.7)	26 (57.8)	2 (4.4)
<4	57	11 (19.3)	33 (57.9)	9 (15.8)	57	15 (26.3)	37 (64.9)	2 (3.5)
Rai stage								
0-2	66	14 (21.2)	45 (68.2)	5 (7.6)	62	18 (29.0)	38 (61.3)	1 (1.6)
3-4	38	7 (18.4)	19 (50.0)	6 (15.8)	42	9 (21.4)	27 (64.3)	3 (7.1)

N = number of subjects in each subgroup. n=number of subjects with response. % = n/N.

Supplemental Table 4. Progression Free Survival (PFS). ITT Population

Progression Free Survival (Months)	Ibr (N=104)	Ibr+R (N=104)	Comparison/Difference Ibr vs. Ibr+R
Events - n (%)	15 (14.4)	13 (12.5)	
Disease Progression - n	10	5	
Death - n	5	8	
Censored - n (%)	89 (85.6)	91 (87.5)	
Median (95% CI) [1]	NE (NE, NE)	NE (NE, NE)	
Min, Max	2.99+, 46.75+	2.92, 47.80+	
P value [2]			0.6917
Hazard Ratio (95% CI) [3]			1.162 (0.553, 2.443)
PFS at landmark times - % (95% CI) [1]			
6 months	99.0 (93.3, 99.9)	98.1 (92.5, 99.5)	1.0 (-2.3, 4.2)
12 months	97.0 (91.1, 99.0)	98.1 (92.5, 99.5)	-1.0 (-5.2, 3.2)
15 months	95.0 (88.4, 97.9)	95.0 (88.4, 97.9)	0.0 (-6.0, 6.1)
18 months	95.0 (88.4, 97.9)	95.0 (88.4, 97.9)	0.0 (-6.0, 6.1)
24 months	95.0 (88.4, 97.9)	92.5 (84.9, 96.4)	2.5 (-4.4, 9.3)
30 months	86.0 (76.6, 91.9)	89.8 (81.1, 94.6)	-3.7 (-13.5, 6.1)
36 months	86.0 (76.6, 91.9)	86.9 (77.3, 92.6)	-0.8 (-11.3, 9.6)

CI= confidence interval. + Indicates censored observation. NE = not estimable.
[1] Estimated by Kaplan-Meier method.
[2] P value is from unstratified log-rank test.
[3] Hazard ratio is estimated using unstratified Cox regression model.

Supplemental Table 5. Progression Free Survival (PFS) Analysis Results - High Risk Subjects (with 17p Deletion or TP53 Mutation)

ITT Population

Progression Free Survival (Months)	Ibr (N=41)	Ibr+R (N=36)	Comparison/Difference Ibr vs. Ibr+R
Events - n (%)	10 (24.4)	8 (22.2)	
Disease Progression - n	6	2	
Death - n	4	6	
Censored - n (%)	31 (75.6)	28 (77.8)	
Median (95% CI) [1]	NE (42.6, NE)	NE (NE, NE)	
Min, Max	5.36, 46.75+	13.34, 46.32+	
P value [2]			0.7788
Hazard Ratio (95% CI) [3]			1.143 (0.451, 2.897)
PFS at landmark times - % (95% CI) [1]			
6 months	97.6 (83.9, 99.7)	100.0 (NE, NE)	-2.4 (-7.2, 2.3)
12 months	92.7 (79.0, 97.6)	100.0 (NE, NE)	-7.3 (-15.3, 0.7)
15 months	90.1 (75.7, 96.2)	94.4 (79.3, 98.6)	-4.3 (-16.2, 7.7)
18 months	90.1 (75.7, 96.2)	94.4 (79.3, 98.6)	-4.3 (-16.2, 7.7)
24 months	90.1 (75.7, 96.2)	87.7 (70.3, 95.2)	2.4 (-12.2, 17.0)
30 months	77.7 (60.0, 88.3)	80.4 (61.2, 90.8)	-2.7 (-22.6, 17.2)
36 months	77.7 (60.0, 88.3)	73.1 (53.0, 85.6)	4.6 (-16.7, 25.9)

CI= confidence interval. + Indicates censored observation. NE = not estimable.
[1] Estimated by Kaplan-Meier method.
[2] P value is from unstratified log-rank test.
[3] Hazard ratio is estimated using unstratified Cox regression model.

Supplemental Table 6. Progression Free Survival (PFS) Analysis Results - Subjects with 11q Deletion

ITT Population

Progression Free Survival (Months)	Ibr (N=27)	Ibr+R (N=15)	Comparison/Difference Ibr vs. Ibr+R
Events - n (%)	3 (11.1)	0	
Disease Progression - n	2	0	
Death - n	1	0	
Censored - n (%)	24 (88.9)	15 (100.0)	
Median (95% CI) [1]	NE (42.6, NE)	NE (NE, NE)	
Min, Max	2.99+, 44.85+	11.33+, 45.77+	
P value [2]			0.2248
Hazard Ratio (95% CI) [3]			(0.374, 30.465)
PFS at landmark times - % (95% CI) [1]			
6 months	100.0 (NE, NE)	100.0 (NE, NE)	0.0 (0.0, 0.0)
12 months	100.0 (NE, NE)	100.0 (NE, NE)	0.0 (0.0, 0.0)
15 months	100.0 (NE, NE)	100.0 (NE, NE)	0.0 (0.0, 0.0)
18 months	100.0 (NE, NE)	100.0 (NE, NE)	0.0 (0.0, 0.0)
24 months	100.0 (NE, NE)	100.0 (NE, NE)	0.0 (0.0, 0.0)
30 months	94.7 (68.1, 99.2)	100.0 (NE, NE)	-5.3 (-15.3, 4.8)
36 months	94.7 (68.1, 99.2)	100.0 (NE, NE)	-5.3 (-15.3, 4.8)

CI= confidence interval. + Indicates censored observation. NE = not estimable.
[1] Estimated by Kaplan-Meier method.
[2] P value is from unstratified log-rank test.
[3] Hazard ratio is estimated using unstratified Cox regression model.

Supplemental Table 7. Overall Survival (OS). ITT Population

Overall Survival (Months)	Ibr (N=104)	Ibr+R (N=104)	Comparison/Difference Ibr vs. Ibr+R
Death - n (%)	7 (6.7)	9 (8.7)	
Censored - n (%)	97 (93.3)	95 (91.3)	
Median (95% CI) [1]	NE (NE, NE)	NE (NE, NE)	
Min, Max	2.99+, 47.08+	2.92, 47.80+	
P value [2]			0.5722
Hazard Ratio (95% CI) [3]			0.753 (0.280, 2.022)
OS at landmark times - % (95% CI) [1]			
6 months	99.0 (93.3, 99.9)	98.1 (92.5, 99.5)	1.0 (-2.3, 4.2)
12 months	99.0 (93.3, 99.9)	98.1 (92.5, 99.5)	1.0 (-2.3, 4.2)
15 months	98.0 (92.3, 99.5)	97.0 (91.1, 99.0)	1.0 (-3.3, 5.3)
18 months	98.0 (92.3, 99.5)	97.0 (91.1, 99.0)	1.0 (-3.3, 5.3)
24 months	98.0 (92.3, 99.5)	93.4 (85.8, 97.0)	4.6 (-1.2, 10.4)
30 months	91.8 (83.5, 96.0)	90.7 (82.1, 95.3)	1.1 (-7.4, 9.7)
36 months	91.8 (83.5, 96.0)	89.2 (80.1, 94.3)	2.6 (-6.4, 11.5)

CI= confidence interval. + Indicates censored observation. NE = not estimable.
[1] Estimated by Kaplan-Meier method.
[2] P value is from unstratified log-rank test.
[3] Hazard ratio is estimated using unstratified Cox regression model.

Supplemental Table 8. Event Free Survival (EFS) Analysis Results Adjusting for Stratification Factors

ITT Population

Event Free Survival (Months)	Ibr (N=104)	Ibr+R (N=104)	Comparison/Difference Ibr vs. Ibr+R
Events - n (%)	15 (14.4)	13 (12.5)	
Disease Progression	10	5	
Death	5	8	
Censored - n (%)	89 (85.6)	91 (87.5)	
Median (95% CI) [1]	NE (NE, NE)	NE (NE, NE)	
Min, Max	2.99+, 46.75+	2.92, 47.80+	
P value [2]			0.9115
Hazard Ratio (95% CI) [3]			1.043 (0.494, 2.203)
EFS at landmark times - % (95% CI) [1]			
6 months	99.0 (93.3, 99.9)	98.1 (92.5, 99.5)	1.0 (-2.3, 4.2)
12 months	97.0 (91.1, 99.0)	98.1 (92.5, 99.5)	-1.0 (-5.2, 3.2)
15 months	95.0 (88.4, 97.9)	95.0 (88.4, 97.9)	0.0 (-6.0, 6.1)
18 months	95.0 (88.4, 97.9)	95.0 (88.4, 97.9)	0.0 (-6.0, 6.1)
24 months	95.0 (88.4, 97.9)	92.5 (84.9, 96.4)	2.5 (-4.4, 9.3)
30 months	86.0 (76.6, 91.9)	89.8 (81.1, 94.6)	-3.7 (-13.5, 6.1)
36 months	86.0 (76.6, 91.9)	86.9 (77.3, 92.6)	-0.8 (-11.3, 9.6)

CI= confidence interval. + Indicates censored observation. NE = not estimable.

[1] Estimated by Kaplan-Meier method.

[2] P value is from stratified log-rank test.

[3] Hazard ratio is estimated using stratified Cox regression model.

The randomization stratification factor used in both stratified log-rank test and Cox regression model is high-risk status based on del17p, del11q and TP53 mutation (yes, no). ECOG is not used because all subjects had ECOG

Supplemental Table 9. Time to Response (Month) Subgroup Analysis. Responders in ITT Population

	Ibr			Ibr+R		
Subgroups	n	Mean (SD)	Median (Min-Max)	n	Mean (SD)	Median (Min-Max)
All subjects	96	5.0 (1.14)	4.7 (4.2, 11.8)	96	5.1 (1.41)	4.8 (1.9, 11.3)
Age group, yrs.						
<65	49	5.1 (1.37)	4.7 (4.2, 11.8)	45	5.2 (1.64)	4.8 (1.9, 11.3)
≥65	47	4.9 (0.86)	4.7 (4.4, 10.3)	51	5.0 (1.19)	4.7 (2.9, 11.2)
Lines of prior treatment						
0	14	5.3 (1.48)	4.8 (4.4, 10.3)	12	5.0 (0.57)	4.8 (4.6, 6.7)
1-2	61	5.0 (1.24)	4.7 (4.2, 11.8)	70	5.2 (1.51)	4.7 (2.9, 11.3)
≥3	21	4.7 (0.24)	4.7 (4.4, 5.5)	14	5.0 (1.48)	4.9 (1.9, 9.2)
Del 17p/TP53 mutation (High risk)						
Yes	38	5.1 (1.45)	4.8 (4.2, 11.8)	36	5.4 (1.65)	4.8 (4.5, 11.2)
No	30	5.0 (1.20)	4.7 (4.5, 11.1)	45	4.9 (1.40)	4.7 (1.9, 11.3)
Del 11q						
Yes	25	4.9 (0.38)	4.8 (4.5, 6.0)	14	4.8 (0.24)	4.7 (4.5, 5.3)
No	69	5.1 (1.33)	4.7 (4.2, 11.8)	80	5.2 (1.54)	4.8 (1.9, 11.3)
IGHV status						
Mutated	23	5.0 (1.17)	4.8 (4.5, 10.3)	21	5.4 (1.96)	4.7 (4.6, 11.3)
Unmutated	56	5.1 (1.29)	4.7 (4.2, 11.8)	58	4.9 (1.02)	4.7 (1.9, 11.1)
Beta-2 macroglobulin, mg/L						
≥4	39	4.8 (0.32)	4.7 (4.2, 5.9)	40	5.0 (1.57)	4.7 (1.9, 11.2)
<4	53	5.0 (1.25)	4.7 (4.4, 11.8)	54	5.1 (1.20)	4.8 (4.4, 11.3)
Rai stage						
0-2	64	4.9 (0.75)	4.8 (4.4, 10.3)	57	5.1 (1.25)	4.8 (1.9, 11.1)
3-4	32	5.2 (1.68)	4.6 (4.2, 11.8)	39	5.2 (1.64)	4.8 (2.9, 11.3)

Time from start of treatment to initial response date of CR/CRi, PR/nPR or PRL.
Responder: subjects with best overall response of CR/CRi, PR/nPR or PRL.

Supplemental Table 10. Time to CR/CRi (Month). Subjects who had CR/CRi in ITT Population

Subgroups	Ibr n	Ibr Mean (SD)	Ibr Median (Min-Max)	Ibr+R n	Ibr+R Mean (SD)	Ibr+R Median (Min-Max)
All subjects	21	20.9 (8.02)	22.2 (10.5, 44.7)	27	15.2 (6.74)	11.5 (4.8, 35.5)
Age group, yrs.						
<65	9	22.5 (9.70)	22.6 (11.1, 44.7)	14	14.8 (5.74)	12.3 (4.8, 23.0)
≥65	12	19.7 (6.71)	21.5 (10.5, 33.1)	13	15.6 (7.89)	11.3 (10.3, 35.5)
Lines of prior treatment						
0	3	15.1 (6.18)	12.0 (11.1, 22.2)	6	14.9 (5.34)	11.6 (11.3, 21.9)
1-2	15	19.7 (5.15)	22.6 (10.5, 24.0)	19	16.0 (7.09)	11.4 (10.3, 35.5)
≥3	3	32.8 (12.01)	33.1 (20.7, 44.7)	2	8.1 (4.60)	8.1 (4.8, 11.3)
Del 17p/TP53 mutation (High risk)						
Yes	9	19.7 (4.72)	21.3 (11.1, 23.2)	12	15.7 (8.39)	11.6 (4.8, 35.5)
No	5	16.4 (6.17)	14.3 (10.5, 23.5)	11	15.2 (5.63)	11.4 (10.3, 23.0)
Del 11q						
Yes	4	18.1 (6.27)	18.6 (11.3, 24.0)	3	15.5 (6.64)	13.0 (10.4, 23.0)
No	16	22.3 (8.16)	22.4 (10.5, 44.7)	24	15.1 (6.89)	11.5 (4.8, 35.5)
IGHV status						
Mutated	4	25.5 (5.10)	23.3 (22.2, 33.1)	5	11.3 (1.02)	11.1 (10.3, 13.0)
Unmutated	14	19.9 (9.03)	20.9 (10.5, 44.7)	18	15.4 (7.50)	11.5 (4.8, 35.5)
β2 macroglobulin, mg/L						
≥4	10	19.0 (5.44)	21.8 (10.5, 23.2)	12	16.6 (8.56)	12.3 (4.8, 35.5)
<4	11	22.6 (9.75)	22.2 (10.5, 44.7)	15	14.0 (4.83)	11.3 (10.3, 22.8)
Rai stage						
0-2	14	18.2 (6.73)	20.7 (10.5, 33.1)	18	13.2 (4.93)	11.4 (4.8, 22.8)
3-4	7	26.2 (8.15)	23.5 (22.6, 44.7)	9	19.0 (8.39)	21.9 (11.0, 35.5)

Time from start of treatment to initial response date of CR/CRi.

Supplemental Table 11. MRD by Subgroup. ITT Population

A. Time assessment: 12 months

	Ibr				Ibr+R			
Subgroups	N	n	Mean (SD)	Median (Min-Max)	N	n	Mean (SD)	Median (Min-Max)
All subjects	104	89	34.7 (26.26)	31.0 (0.0, 95.3)	104	88	18.2 (20.45)	10.8 (0.0, 77.0)
Age group, yrs.								
<65	51	47	37.3 (27.74)	32.0 (0.0, 95.3)	48	43	20.8 (22.25)	14.0 (0.0, 77.0)
≥65	53	42	31.7 (24.49)	28.0 (0.0, 93.0)	56	45	15.7 (18.47)	8.8 (0.0, 61.0)
Lines of prior treatment								
0	15	11	38.7 (24.75)	35.0 (0.2, 75.2)	12	11	18.2 (19.98)	15.0 (0.0, 61.0)
1-2	68	58	31.8 (25.01)	23.3 (0.1, 93.0)	76	66	19.3 (21.61)	9.7 (0.0, 77.0)
≥3	21	20	40.7 (30.35)	38.0 (0.0, 95.3)	16	11	11.6 (12.25)	9.1 (0.1, 35.8)
Del 17p/TP53 mutation (High risk)								
Yes	41	33	30.7 (24.25)	25.9 (0.2, 95.3)	36	34	19.7 (20.53)	15.0 (0.0, 73.0)
No	35	29	40.8 (25.03)	45.0 (0.0, 81.0)	49	42	20.3 (22.21)	9.7 (0.0, 77.0)
Del 11q								
Yes	27	24	33.2 (23.51)	27.3 (0.0, 71.0)	15	11	32.2 (29.54)	43.3 (1.6, 77.0)
No	75	63	35.1 (27.20)	32.0 (0.0, 95.3)	86	75	16.5 (18.39)	11.0 (0.0, 75.0)
IGHV								
Mutated	26	23	32.4 (21.51)	28.8 (0.5, 89.0)	22	19	16.2 (17.98)	8.8 (0.0, 59.3)
Unmutated	61	51	36.8 (27.71)	33.4 (0.0, 95.3)	62	55	19.9 (21.36)	12.0 (0.0, 77.0)
Beta-2 macroglobulin, mg/L								
≥4	43	37	35.1 (27.06)	25.9 (0.0, 95.3)	45	39	19.7 (20.98)	14.0 (0.0, 73.0)
<4	57	48	31.9 (24.04)	30.4 (0.0, 93.0)	57	48	16.5 (20.04)	8.7 (0.0, 77.0)
Rai stage								
0-2	66	60	29.9 (23.97)	23.0 (0.0, 79.2)	62	51	14.8 (19.67)	6.0 (0.0, 75.0)
3-4	38	29	44.5 (28.42)	41.0(1.9, 95.3)	42	37	22.9 (20.83)	15.0 (0.0, 77.0)

N = number of subjects in each subgroup. n=number of subjects with non-missing MRD value.

B. Time assessment: 24 months

Subgroups	Ibr N	Ibr n	Ibr Mean (SD)	Ibr Median (Min-Max)	Ibr+R N	Ibr+R n	Ibr+R Mean (SD)	Ibr+R Median (Min-Max)
All subjects	104	75	19.3 (20.83)	12.7 (0.0, 86.2)	104	64	12.4 (17.33)	4.8 (0.0, 84.8)
Age group, yrs.								
<65	51	39	21.8 (22.72)	14.1 (0.0, 85.5)	48	33	15.4 (21.43)	6.0 (0.0, 84.8)
≥65	53	36	16.5 (18.48)	10.8 (0.0, 86.2)	56	31	9.3 (10.99)	4.7 (0.0, 50.0)
Lines of prior treatment								
0	15	10	20.6 (18.30)	16.7 (0.0, 55.7)	12	9	13.0 (16.48)	8.3 (0.0, 50.0)
1-2	68	49	17.0 (18.76)	11.4 (0.0, 86.2)	76	48	13.3 (18.59)	4.8 (0.0, 84.8)
≥3	21	16	25.3 (27.49)	19.5 (0.0, 85.5)	16	7	5.9 (5.34)	3.5 (0.0, 12.3)
Del 17p/TP53 mutation (High risk)								
Yes	41	28	19.1 (19.97)	12.3 (0.0, 85.5)	36	23	17.2 (23.67)	9.7 (0.0, 84.8)
No	35	24	16.8 (16.51)	14.1 (0.0, 55.0)	49	33	10.8 (12.88)	4.7 (0.0, 57.2)
Del 11q								
Yes	27	20	15.2 (15.92)	8.0 (0.0, 55.0)	15	7	21.1 (24.48)	4.2 (0.7, 57.2)
No	75	54	21.1 (22.34)	13.9 (0.0, 86.2)	86	56	11.5 (16.33)	5.5 (0.0, 84.8)
IGHV status								
Mutated	26	20	16.9 (17.49)	12.1 (3.2, 79.4)	22	14	10.1 (9.70)	9.2 (0.0, 31.3)
Unmutated	61	42	20.1 (21.33)	13.9 (0.0, 85.5)	62	42	14.6 (20.19)	5.5 (0.0, 84.8)
Beta-2 macroglobulin, mg/L								
≥4	43	31	19.9 (22.53)	11.0 (0.0, 85.5)	45	28	8.2 (9.01)	4.6 (0.0, 31.3)
<4	57	41	17.2 (17.60)	13.7(0.0, 86.2)	57	35	15.8 (21.59)	7.4 (0.0, 84.8)
Rai stage								
0-2	66	51	13.6 (14.53)	10.0 (0.0, 55.7)	62	34	14.2 (22.06)	5.0 (0.0, 84.8)
3-4	38	24	31.2 (26.78)	24.1 (3.4, 86.2)	42	30	10.4 (9.52)	4.8 (0.0, 31.3)

N = number of subjects in each subgroup. n=number of subjects with non-missing MRD value.

Supplemental Table 12. Time to Normalization of Absolute Lymphocyte Count (ALC)

ITT Population

	Ibr (N=104)	Ibr+R (N=104)
Subjects with baseline ALC >= 4000/μL - N1	91	83
Normalized to < 4000/μL - n (%)	64 (70.3)	66 (79.5)
Time to Normalization (weeks) [1]		
n	64	66
Median	48	24
Min, Max	(2, 192)	(1, 144)

N = number of subjects in the specified treatment arm in the ITT population.
N1 = number of subjects with baseline ALC >= 4000/μL. % = n/N1.
Time from start of treatment to the first post-baseline ALC < 4000/μL.
Note: Actual date of ALC sampling is not available, nominal visit time is used (e.g. If the first post-baseline ALC < 4000/μL is at 3 months visit, then time to normalization is 12 weeks.

Supplemental Table 13. Descriptive Statistics for ALC (Absolute Lymphocyte Count, K/µL)

ITT Population

	Ibr (N=104)		Ibr+R (N=104)	
Time assessment	Absolute Value	Change from Baseline	Absolute Value	Change from Baseline
Baseline				
n	104		104	
Mean (SD)	56.8 (60.54)		46.5 (53.66)	
Median	29.6		29.9	
Min, Max	1, 351		0, 292	
1 week				
n	104	104	104	104
Mean (SD)	87.1 (90.50)	30.3 (51.17)	59.4 (63.26)	12.9 (35.46)
Median	56.8	15.9	39.1	4.6
Min, Max	1, 549	-120, 370	1, 327	-91, 145
2 weeks				
n	104	104	104	104
Mean (SD)	77.1 (80.15)	20.3 (50.38)	53.0 (60.12)	6.5 (40.27)
Median	44.6	15.4	33.7	3.4
Min, Max	1, 434	-165, 277	0, 306	-105, 185
3 weeks				
n	102	102	103	103
Mean (SD)	77.7 (77.07)	21.1 (50.67)	53.8 (67.01)	6.9 (51.91)
Median	50.3	14.6	30.4	2.6
Min, Max	0, 393	-171, 233	0, 334	-103, 256
1 month				
n	103	103	104	104
Mean (SD)	80.2 (81.44)	22.9 (57.01)	51.3 (64.13)	4.7 (54.97)
Median	51.8	14.2	32.1	0.3
Min, Max	1, 364	-175, 197	0, 342	-104, 297
2 months				
n	103	103	101	101
Mean (SD)	71.5 (73.43)	14.2 (56.46)	39.2 (56.40)	-8.0 (51.56)
Median	45.5	10.6	15.5	-0.7
Min, Max	1, 335	-172, 180	0, 350	-129, 247

Supplemental Table 13. Cont.

3 months				
n	101	101	98	98
Mean (SD)	56.0 (61.49)	-2.2 (52.14)	25.6 (36.79)	-22.1 (47.11)
Median	37.7	0.5	8.3	-4.9
Min, Max	0, 303	-175, 112	0, 229	-168, 126
4 months				
n	101	101	96	96
Mean (SD)	43.7 (50.96)	-14.6 (51.48)	18.3 (26.81)	-30.3 (46.50)
Median	26.6	-2.7	6.2	-11.4
Min, Max	1, 266	-211, 111	0, 128	-182, 53
6 months				
n	101	101	96	96
Mean (SD)	34.0 (43.04)	-24.4 (53.02)	12.5 (17.92)	-36.0 (46.72)
Median	17.6	-8.5	4.3	-20.5
Min, Max	0, 214	-259, 105	0, 103	-203, 42
9 months				
n	93	93	92	92
Mean (SD)	17.9 (24.05)	-40.6 (55.24)	6.6 (9.20)	-40.4 (46.92)
Median	8.6	-20.4	2.9	-25.2
Min, Max	0, 158	-311, 40	0, 53	-240, 15
12 months				
n	90	90	90	90
Mean (SD)	13.0 (20.92)	-47.1 (58.27)	5.0 (6.48)	-45.0 (53.54)
Median	5.3	-31.1	2.2	-26.7
Min, Max	0, 127	-342, 26	0, 34	-267, 7
15 months				
n	84	84	79	79
Mean (SD)	9.5 (13.84)	-50.5 (59.49)	4.2 (6.02)	-44.2 (51.19)
Median	4.1	-37.6	2.0	-28.6
Min, Max	0, 66	-341, 53	0, 37	-272, 5
18 months				
n	79	79	77	77
Mean (SD)	7.4 (11.81)	-50.2 (60.21)	3.5 (4.27)	-47.7 (57.46)
Median	4.1	-31.0	1.9	-26.0
Min, Max	1, 75	-341, 21	0, 22	-272, 0
21 months				
n	55	55	52	52
Mean (SD)	8.9 (18.53)	-53.6 (65.77)	4.8 (12.72)	-49.6 (58.92)
Median	3.3	-32.0	1.9	-26.6
Min, Max	1, 107	-347, 21	0, 92	-280, 33

Supplemental Table 13. Cont.

24 months				
n	75	75	65	65
Mean (SD)	5.7 (9.83)	-53.1 (61.75)	4.2 (9.11)	-49.3 (54.62)
Median	2.6	-31.0	2.1	-29.0
Min, Max	0, 70	-334, 16	0, 72	-243, 13
30 months				
n	67	67	57	57
Mean (SD)	4.5 (8.08)	-53.1 (63.59)	3.4 (4.77)	-50.0 (55.81)
Median	2.5	-26.6	2.0	-28.0
Min, Max	1, 65	-345, 4	1, 34	-244, 1
36 months				
n	51	51	45	45
Mean (SD)	7.9 (21.38)	-45.8 (57.46)	3.0 (3.57)	-49.3 (55.37)
Median	2.4	-18.8	1.8	-32.7
Min, Max	1, 120	-202, 98	1, 20	-248, 0
42 months				
n	35	35	34	34
Mean (SD)	7.0 (16.89)	-50.9 (60.05)	2.5 (2.96)	-42.9 (47.30)
Median	2.0	-29.0	1.6	-23.7
Min, Max	1, 86	-201, 39	0, 18	-144, 1
48 months				
n	22	22	17	17
Mean (SD)	8.1 (28.23)	-40.4 (50.42)	2.7 (1.87)	-50.1 (48.98)
Median	1.9	-16.4	2.0	-34.2
Min, Max	1, 134	-180, 4	1, 8	-126, 1

Supplemental Table 14. Descriptive Statistics β2 Macroglobulin (mg/L)

ITT Population

	Ibr (N=104)		Ibr+R (N=104)	
Time assessment	Absolute Value	Change from Baseline	Absolute Value	Change from Baseline
Baseline				
n	100		102	
Mean (SD)	4.1 (2.07)		4.1 (1.93)	
Median	3.7		3.7	
Min, Max	1, 13		1, 12	
1 week				
n	85	83	89	88
Mean (SD)	3.1 (1.46)	-1.1 (1.09)	3.0 (1.45)	-1.1 (1.00)
Median	2.8	-0.9	2.7	-1.0
Min, Max	2, 11	-5, 1	1, 10	-6, 1
2 weeks				
n	84	82	87	87
Mean (SD)	3.0 (1.28)	-1.2 (1.28)	2.9 (1.29)	-1.2 (1.07)
Median	2.7	-1.0	2.7	-0.9
Min, Max	1, 9	-5, 2	1, 9	-6, 0
3 weeks				
n	86	84	88	87
Mean (SD)	2.8 (1.29)	-1.3 (1.27)	2.8 (1.25)	-1.4 (1.19)
Median	2.4	-1.1	2.4	-1.1
Min, Max	1, 9	-6, 1	1, 9	-7, 0
1 month				
n	94	91	90	89
Mean (SD)	2.7 (1.25)	-1.4 (1.41)	2.8 (1.41)	-1.3 (1.30)
Median	2.4	-1.1	2.5	-1.0
Min, Max	1, 9	-7, 2	1, 11	-7, 2
2 months				
n	97	93	97	95
Mean (SD)	2.6 (1.08)	-1.3 (1.43)	2.7 (1.23)	-1.4 (1.45)
Median	2.3	-1.1	2.4	-1.1
Min, Max	1, 7	-6, 3	1, 9	-7, 3

Supplemental Table 14. Cont.

3 months				
n	97	93	95	93
Mean (SD)	2.6 (0.91)	-1.5 (1.57)	2.6 (0.99)	-1.5 (1.43)
Median	2.3	-1.0	2.4	-1.1
Min, Max	1, 7	-8, 1	1, 7	-7, 1
4 months				
n	100	96	95	94
Mean (SD)	2.6 (0.94)	-1.6 (1.59)	2.5 (0.91)	-1.6 (1.48)
Median	2.4	-1.4	2.2	-1.3
Min, Max	1, 6	-8, 2	1, 7	-7, 1
6 months				
n	98	94	93	92
Mean (SD)	2.6 (1.07)	-1.5 (1.55)	2.4 (0.89)	-1.7 (1.53)
Median	2.3	-1.3	2.2	-1.3
Min, Max	1, 8	-8, 1	1, 6	-8, 1
9 months				
n	89	85	91	89
Mean (SD)	2.5 (0.99)	-1.5 (1.59)	2.3 (0.83)	-1.7 (1.52)
Median	2.2	-1.2	2.1	-1.3
Min, Max	1, 7	-8, 1	1, 6	-8, 0
12 months				
n	86	82	84	84
Mean (SD)	2.4 (0.89)	-1.7 (1.60)	2.3 (0.90)	-1.8 (1.64)
Median	2.2	-1.4	2.2	-1.5
Min, Max	1, 6	-9, 1	1, 7	-10, 1
15 months				
n	79	75	74	73
Mean (SD)	2.4 (0.91)	-1.7 (1.57)	2.3 (1.00)	-1.7 (1.39)
Median	2.1	-1.3	2.2	-1.6
Min, Max	1, 5	-9, 0	1, 7	-7, 1
18 months				
n	77	74	74	73
Mean (SD)	2.3 (0.80)	-1.8 (1.68)	2.3 (1.37)	-1.8 (1.95)
Median	2.2	-1.5	2.1	-1.5
Min, Max	1, 5	-9, 2	1, 12	-10, 6
21 months				
n	53	50	51	51
Mean (SD)	2.4 (0.80)	-1.7 (1.90)	2.3 (0.85)	-1.9 (1.70)
Median	2.3	-1.3	2.1	-1.7
Min, Max	1, 5	-9, 0	1, 7	-6, 5

Supplemental Table 14. Cont.

24 months				
n	74	71	63	62
Mean (SD)	2.3 (0.79)	-1.9 (1.80)	2.1 (0.62)	-2.0 (1.78)
Median	2.1	-1.8	2.0	-1.5
Min, Max	1, 5	-9, 1	1, 5	-9, 1
30 months				
n	64	62	55	54
Mean (SD)	2.4 (0.73)	-1.8 (1.81)	2.2 (0.57)	-1.8 (1.43)
Median	2.2	-1.4	2.1	-1.5
Min, Max	1, 4	-10, 1	1, 4	-6, -0
36 months				
n	47	44	42	41
Mean (SD)	2.4 (0.81)	-1.9 (1.63)	2.0 (0.48)	-1.9 (1.47)
Median	2.2	-1.7	2.0	-1.8
Min, Max	1, 5	-8, 0	1, 3	-6, -0
42 months				
n	31	30	31	31
Mean (SD)	2.6 (0.81)	-1.9 (2.39)	2.4 (0.71)	-1.7 (1.63)
Median	2.3	-1.5	2.2	-1.4
Min, Max	2, 5	-10, 1	1, 4	-6, 2
48 months				
n	21	21	16	16
Mean (SD)	2.7 (0.68)	-1.7 (2.27)	2.5 (0.71)	-1.6 (1.25)
Median	2.7	-1.1	2.3	-1.6
Min, Max	2, 4	-9, 0	1, 3	-5, 0

Supplemental Table 15. Descriptive Statistics for Igs (mg/dL)

ITT Population

	Ibr (N=104)			Ibr+R (N=104)		
Time assessment	IgG	IgA	IgM	IgG	IgA	IgM
Baseline						
n	101			104		
Mean (SEM)	754.4 (56.4)	74 (6.4)	56.5 (11.5)	652.3 (33.3)	91.7 (27.4)	55.3 (13)
Median	653	60	30.5	600.5	44.5	22
Min, Max	60, 4829	5, 333	11, 1051	105, 1769	3, 2836	11, 1019
3 months						
n	99			95		
Mean (SEM)	712 (42.3)	91.9 (7.9)	47 (8)	635.4 (30.6)	102.5 (23.9)	55.3 (19.9)
Median	606	71	25.5	605	59	17
Min, Max	56, 2860	7, 497	11, 741	130, 1486	3, 2232	11, 1710
6 months						
n	95			87		
Mean (SEM)	685.3 (42.6)	94.4 (9.6)	49.3 (8.2)	622.3 (31.2)	100.9 (24.6)	59.8 (24.9)
Median	577	67	28	582	50	16
Min, Max	58, 2791	5, 747	11, 702	146, 1406	3, 2104	11, 1970
12 months						
n	88			86		
Mean (SEM)	635.4 (36)	89.1 (8.2)	44.9 (6.7)	600 (29.5)	103.2 (23.8)	36.4 (9.1)
Median	589.5	68	27.5	565	51.5	16.5
Min, Max	53, 2380	7, 495	10, 492	147, 1224	3, 1951	10, 750
24 months						
n	75			62		
Mean (SEM)	656.4 (38.3)	89.6 (8.5)	40 (6.5)	563.1 (30.4)	105.3 (28.6)	25.8 (4.6)
Median	599	77	24	575	45	15
Min, Max	33, 2158	7, 379	10, 418	117, 1140	3, 1696	10, 260
36 months						
n	21			19		
Mean (SEM)	600 (72.1)	77.5 (18.4)	51.5 (28.6)	431.5 (35.4)	66.1 (14.7)	18.4 (2.2)
Median	627	33.5	13	439	50	13
Min, Max	30, 1125	6, 309	11, 590	157, 673	3, 256	11, 44

Supplemental Table 16. Descriptive Statistics for T cells (cells/µL)

ITT Population

	Ibr (N=104)			Ibr+R (N=104)		
Time assessment	CD3+	CD4+	CD8+	CD3+	CD4+	CD8+
Baseline						
n	74			76		
Mean (SEM)	3469 (322)	1592 (141)	1670 (183)	3496 (473)	1539 (178)	1502 (188)
Median	2437	1179	1034	2530	1088	880
Min, Max	217, 12607	141, 5278	95, 7222	140, 26330	61, 9474	28, 9843
6 months						
n	63			57		
Mean (SEM)	2945 (364)	1324 (126)	1524 (214)	1910 (200)	918 (115)	987 (106)
Median	2208	1022	868	1449	636	714
Min, Max	117, 17467	159, 4747	146, 9234	137, 7727	91, 5118	40, 3626
12 months						
n	48			44		
Mean (SEM)	1549 (155)	763 (66)	718 (106)	1629 (185)	799 (90)	808 (104)
Median	1317	658	551	1266	581	587
Min, Max	275, 5957	125, 3018	116, 4370	361, 6307	178, 2886	67, 3709
24 months						
n	12			8		
Mean (SEM)	941 (136)	498 (73)	426 (74)	1793 (451)	900 (233)	893 (257)
Median	890	482	399	1631	838	858
Min, Max	149, 1876	86, 971	64, 981	284, 4560	165, 2267	109, 2406

Supplemental Table 17. Grade 3 or higher Treatment Emergent Adverse Events (TEAE) by Preferred Term

Safety Population

	Ibr (N=104)			Ibr+R (N=104)		
MedDRA Preferred Term	Grade 3-5 n(%)	Grade 3+4 n(%)	Grade 5 n(%)	Grade 3-5 n(%)	Grade 3+4 n(%)	Grade 5 n(%)
Subjects with any TEAE	69 (66.3)	67 (64.4)	2 (1.9)	71 (68.3)	68 (65.4)	3 (2.9)
Hypertension	32 (30.8)	32 (30.8)	0	33 (31.7)	33 (31.7)	0
Neutrophil Count Decreased	10 (9.6)	10 (9.6)	0	14 (13.5)	14 (13.5)	0
Atrial Fibrillation	8 (7.7)	8 (7.7)	0	6 (5.8)	6 (5.8)	0
Infections And Infestations	6 (5.8)	6 (5.8)	0	3 (2.9)	3 (2.9)	0
Respiratory, Thoracic And Mediastinal Disorders	6 (5.8)	6 (5.8)	0	6 (5.8)	6 (5.8)	0
Lung Infection	5 (4.8)	5 (4.8)	0	5 (4.8)	4 (3.8)	1 (1.0)
Platelet Count Decreased	5 (4.8)	5 (4.8)	0	7 (6.7)	7 (6.7)	0
Diarrhea	4 (3.8)	4 (3.8)	0	1 (1.0)	1 (1.0)	0
Fatigue	4 (3.8)	4 (3.8)	0	0	0	0
Gastrointestinal Disorders	4 (3.8)	4 (3.8)	0	2 (1.9)	2 (1.9)	0
Cough	3 (2.9)	3 (2.9)	0	0	0	0
Leukocytosis	3 (2.9)	3 (2.9)	0	8 (7.7)	8 (7.7)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	3 (2.9)	3 (2.9)	0	4 (3.8)	4 (3.8)	0
Upper Respiratory Infection	3 (2.9)	3 (2.9)	0	1 (1.0)	1 (1.0)	0
Wound Infection	3 (2.9)	3 (2.9)	0	2 (1.9)	2 (1.9)	0
Abdominal Pain	2 (1.9)	2 (1.9)	0	0	0	0
Anemia	2 (1.9)	2 (1.9)	0	3 (2.9)	3 (2.9)	0
Dyspnea	2 (1.9)	2 (1.9)	0	3 (2.9)	3 (2.9)	0
Febrile Neutropenia	2 (1.9)	2 (1.9)	0	6 (5.8)	6 (5.8)	0
Headache	2 (1.9)	2 (1.9)	0	1 (1.0)	1 (1.0)	0
Hyperglycemia	2 (1.9)	2 (1.9)	0	1 (1.0)	1 (1.0)	0
Treatment Related Secondary Malignancy	2 (1.9)	2 (1.9)	0	2 (1.9)	2 (1.9)	0
Urinary Tract Infection	2 (1.9)	2 (1.9)	0	0	0	0
Vascular Disorders	2 (1.9)	2 (1.9)	0	2 (1.9)	1 (1.0)	1 (1.0)
Appendicitis	1 (1.0)	1 (1.0)	0	0	0	0
Blood And Lymphatic System Disorders	1 (1.0)	1 (1.0)	0	1 (1.0)	1 (1.0)	0
Bronchial Infection	1 (1.0)	1 (1.0)	0	0	0	0
Cardiac Disorders	1 (1.0)	1 (1.0)	0	3 (2.9)	3 (2.9)	0
Chest Pain Cardiac	1 (1.0)	1 (1.0)	0	0	0	0
Death Nos	1 (1.0)	0	1 (1.0)	0	0	0
Depression	1 (1.0)	1 (1.0)	0	1 (1.0)	1 (1.0)	0

Supplemental Table 17. Cont.

Dizziness	1 (1.0)	1 (1.0)	0	1 (1.0)	1 (1.0)	0
Ejection Fraction Decreased	1 (1.0)	1 (1.0)	0	0	0	0
Eye Disorders	1 (1.0)	1 (1.0)	0	0	0	0
Hematoma	1 (1.0)	1 (1.0)	0	0	0	0
Hypocalcemia	1 (1.0)	1 (1.0)	0	0	0	0
Insomnia	1 (1.0)	1 (1.0)	0	0	0	0
Nausea	1 (1.0)	1 (1.0)	0	2 (1.9)	2 (1.9)	0
Neck Pain	1 (1.0)	1 (1.0)	0	0	0	0
Pain	1 (1.0)	1 (1.0)	0	0	0	0
Pancreatitis	1 (1.0)	1 (1.0)	0	0	0	0
Postoperative Hemorrhage	1 (1.0)	1 (1.0)	0	0	0	0
Rash Maculo Papular	1 (1.0)	1 (1.0)	0	0	0	0
Rectal Hemorrhage	1 (1.0)	1 (1.0)	0	0	0	0
Renal And Urinary Disorders	1 (1.0)	1 (1.0)	0	1 (1.0)	1 (1.0)	0
Respiratory Failure	1 (1.0)	0	1 (1.0)	1 (1.0)	1 (1.0)	0
Skin And Subcutaneous Tissue Disorders	1 (1.0)	1 (1.0)	0	1 (1.0)	1 (1.0)	0
Skin Infection	1 (1.0)	1 (1.0)	0	1 (1.0)	1 (1.0)	0
Stroke	1 (1.0)	1 (1.0)	0	0	0	0
Surgical And Medical Procedures	1 (1.0)	1 (1.0)	0	0	0	0
Syncope	1 (1.0)	1 (1.0)	0	0	0	0
Upper Gastrointestinal Hemorrhage	1 (1.0)	1 (1.0)	0	0	0	0
Vertigo	1 (1.0)	1 (1.0)	0	0	0	0
Back Pain	0	0	0	1 (1.0)	1 (1.0)	0
Bladder Infection	0	0	0	1 (1.0)	1 (1.0)	0
Bone Pain	0	0	0	1 (1.0)	1 (1.0)	0
Cataract	0	0	0	1 (1.0)	1 (1.0)	0
Chronic Kidney Disease	0	0	0	1 (1.0)	1 (1.0)	0
Enterocolitis Infectious	0	0	0	1 (1.0)	1 (1.0)	0
Fever	0	0	0	1 (1.0)	1 (1.0)	0
Hallucinations	0	0	0	1 (1.0)	1 (1.0)	0
Hypokalemia	0	0	0	2 (1.9)	2 (1.9)	0
Hyponatremia	0	0	0	1 (1.0)	1 (1.0)	0
Kidney Infection	0	0	0	1 (1.0)	1 (1.0)	0
Obstruction Gastric	0	0	0	1 (1.0)	0	1 (1.0)
Oral Pain	0	0	0	1 (1.0)	1 (1.0)	0
Otitis Media	0	0	0	1 (1.0)	1 (1.0)	0
Pericardial Effusion	0	0	0	1 (1.0)	1 (1.0)	0
Pleural Effusion	0	0	0	1 (1.0)	1 (1.0)	0
Pleuritic Pain	0	0	0	1 (1.0)	1 (1.0)	0
Rash Acneiform	0	0	0	1 (1.0)	1 (1.0)	0
Seizure	0	0	0	1 (1.0)	1 (1.0)	0
Sepsis	0	0	0	1 (1.0)	1 (1.0)	0
Sinusitis	0	0	0	2 (1.9)	2 (1.9)	0
Vomiting	0	0	0	1 (1.0)	1 (1.0)	0
White Blood Cell Decreased	0	0	0	1 (1.0)	1 (1.0)	0

Subjects with multiple events for a given preferred term are counted once only using maximum severity for each preferred term.
Events are sorted by decreasing frequency of preferred term by Grade 3-5 column in the ibrutinib group.
TEAEs are defined as: (1) events with onset dates on or after the first dose of study drug, and within 30 days following the last dose of study drug; (2) events that are considered study drug-related regardless of the start date of the event; (3) events present at baseline that worsen in severity or are subsequently considered drug-related by the investigator.

Supplemental Table 18. Treatment Emergent Adverse Events (TEAE) by Preferred Term and Maximum Severity

Safety Population

MedDRA Preferred Term	Ibr (N=104) Any Grade n(%)	Ibr (N=104) Grade 3+4 n(%)	Ibr (N=104) Grade 5 n(%)	Ibr+R (N=104) Any Grade n(%)	Ibr+R (N=104) Grade 3+4 n(%)	Ibr+R (N=104) Grade 5 n(%)
Subjects with any TEAE	104 (100.0)	67 (64.4)	2 (1.9)	104 (100.0)	68 (65.4)	3 (2.9)
Hypertension	50 (48.1)	32 (30.8)	0	45 (43.3)	33 (31.7)	0
Upper Respiratory Infection	36 (34.6)	3 (2.9)	0	25 (24.0)	1 (1.0)	0
Arthralgia	34 (32.7)	0	0	27 (26.0)	0	0
Skin And Subcutaneous Tissue Disorders	33 (31.7)	1 (1.0)	0	31 (29.8)	1 (1.0)	0
Diarrhea	29 (27.9)	4 (3.8)	0	28 (26.9)	1 (1.0)	0
Bruising	26 (25.0)	0	0	25 (24.0)	0	0
Fatigue	23 (22.1)	4 (3.8)	0	13 (12.5)	0	0
Cough	22 (21.2)	3 (2.9)	0	13 (12.5)	0	0
Headache	19 (18.3)	2 (1.9)	0	16 (15.4)	1 (1.0)	0
Skin Infection	15 (14.4)	1 (1.0)	0	11 (10.6)	1 (1.0)	0
Nausea	14 (13.5)	1 (1.0)	0	8 (7.7)	2 (1.9)	0
Atrial Fibrillation	13 (12.5)	8 (7.7)	0	10 (9.6)	6 (5.8)	0
Myalgia	13 (12.5)	0	0	16 (15.4)	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	13 (12.5)	3 (2.9)	0	14 (13.5)	4 (3.8)	0
Sinusitis	13 (12.5)	0	0	12 (11.5)	2 (1.9)	0
Infections And Infestations	12 (11.5)	6 (5.8)	0	10 (9.6)	3 (2.9)	0
Gastrointestinal Disorders	11 (10.6)	4 (3.8)	0	6 (5.8)	2 (1.9)	0
Lung Infection	11 (10.6)	5 (4.8)	0	7 (6.7)	4 (3.8)	1 (1.0)
Dizziness	10 (9.6)	1 (1.0)	0	6 (5.8)	1 (1.0)	0
Edema Limbs	10 (9.6)	0	0	12 (11.5)	0	0
Neutrophil Count Decreased	10 (9.6)	10 (9.6)	0	14 (13.5)	14 (13.5)	0
Musculoskeletal And Connective Tissue Disorder	9 (8.7)	0	0	7 (6.7)	0	0
Abdominal Pain	8 (7.7)	2 (1.9)	0	5 (4.8)	0	0
Insomnia	8 (7.7)	1 (1.0)	0	2 (1.9)	0	0
Pain In Extremity	8 (7.7)	0	0	12 (11.5)	0	0
Respiratory, Thoracic And Mediastinal Disorders	8 (7.7)	6 (5.8)	0	9 (8.7)	6 (5.8)	0
Back Pain	7 (6.7)	0	0	12 (11.5)	1 (1.0)	0
Fall	7 (6.7)	0	0	1 (1.0)	0	0
Palpitations	7 (6.7)	0	0	8 (7.7)	0	0
Urinary Tract Infection	7 (6.7)	2 (1.9)	0	8 (7.7)	0	0
Cardiac Disorders	6 (5.8)	1 (1.0)	0	5 (4.8)	3 (2.9)	0

Supplemental Table 18. Cont.

Hyperhidrosis	6 (5.8)	0	0	1 (1.0)	0	0
Platelet Count Decreased	6 (5.8)	5 (4.8)	0	7 (6.7)	7 (6.7)	0
Rash Maculo Papular	6 (5.8)	1 (1.0)	0	6 (5.8)	0	0
Sinus Bradycardia	6 (5.8)	0	0	8 (7.7)	0	0
Vomiting	6 (5.8)	0	0	4 (3.8)	1 (1.0)	0
Bronchial Infection	5 (4.8)	1 (1.0)	0	4 (3.8)	0	0
Dyspnea	5 (4.8)	2 (1.9)	0	4 (3.8)	3 (2.9)	0
Otitis Media	5 (4.8)	0	0	1 (1.0)	1 (1.0)	0
Paresthesia	5 (4.8)	0	0	4 (3.8)	0	0
Surgical And Medical Procedures	5 (4.8)	1 (1.0)	0	0	0	0
Arthritis	4 (3.8)	0	0	1 (1.0)	0	0
Fever	4 (3.8)	0	0	9 (8.7)	1 (1.0)	0
Gastroesophageal Reflux Disease	4 (3.8)	0	0	7 (6.7)	0	0
Hematuria	4 (3.8)	0	0	2 (1.9)	0	0
Hyperglycemia	4 (3.8)	2 (1.9)	0	4 (3.8)	1 (1.0)	0
Pain	4 (3.8)	1 (1.0)	0	3 (2.9)	0	0
Postnasal Drip	4 (3.8)	0	0	1 (1.0)	0	0
Sore Throat	4 (3.8)	0	0	6 (5.8)	0	0
Allergic Rhinitis	3 (2.9)	0	0	4 (3.8)	0	0
Anxiety	3 (2.9)	0	0	5 (4.8)	0	0
Bloating	3 (2.9)	0	0	1 (1.0)	0	0
Chest Pain Cardiac	3 (2.9)	1 (1.0)	0	3 (2.9)	0	0
Depression	3 (2.9)	1 (1.0)	0	2 (1.9)	1 (1.0)	0
Ear Pain	3 (2.9)	0	0	0	0	0
Enterocolitis Infectious	3 (2.9)	0	0	1 (1.0)	1 (1.0)	0
Eye Disorders	3 (2.9)	1 (1.0)	0	4 (3.8)	0	0
Hemorrhoids	3 (2.9)	0	0	0	0	0
Leukocytosis	3 (2.9)	3 (2.9)	0	8 (7.7)	8 (7.7)	0
Malaise	3 (2.9)	0	0	1 (1.0)	0	0
Mucositis Oral	3 (2.9)	0	0	8 (7.7)	0	0
Neck Pain	3 (2.9)	1 (1.0)	0	2 (1.9)	0	0
Peripheral Sensory Neuropathy	3 (2.9)	0	0	3 (2.9)	0	0
Pruritus	3 (2.9)	0	0	1 (1.0)	0	0
Rectal Hemorrhage	3 (2.9)	1 (1.0)	0	0	0	0
Renal And Urinary Disorders	3 (2.9)	1 (1.0)	0	2 (1.9)	1 (1.0)	0
Sinus Tachycardia	3 (2.9)	0	0	3 (2.9)	0	0
Tinnitus	3 (2.9)	0	0	2 (1.9)	0	0
Vertigo	3 (2.9)	1 (1.0)	0	2 (1.9)	0	0
Wound Infection	3 (2.9)	3 (2.9)	0	2 (1.9)	2 (1.9)	0
Abdominal Distension	2 (1.9)	0	0	0	0	0
Alopecia	2 (1.9)	0	0	0	0	0
Anemia	2 (1.9)	2 (1.9)	0	3 (2.9)	3 (2.9)	0
Constipation	2 (1.9)	0	0	0	0	0
Dysesthesia	2 (1.9)	0	0	1 (1.0)	0	0
Epistaxis	2 (1.9)	0	0	1 (1.0)	0	0
Esophagitis	2 (1.9)	0	0	1 (1.0)	0	0

Supplemental Table 18. Cont.

Eye Infection	2 (1.9)	0	0	1 (1.0)	0	0
Febrile Neutropenia	2 (1.9)	2 (1.9)	0	6 (5.8)	6 (5.8)	0
Flank Pain	2 (1.9)	0	0	0	0	0
Fracture	2 (1.9)	0	0	2 (1.9)	0	0
Gastrointestinal Pain	2 (1.9)	0	0	1 (1.0)	0	0
Hematoma	2 (1.9)	1 (1.0)	0	0	0	0
Lip Infection	2 (1.9)	0	0	0	0	0
Muscle Weakness Lower Limb	2 (1.9)	0	0	2 (1.9)	0	0
Nasal Congestion	2 (1.9)	0	0	2 (1.9)	0	0
Osteoporosis	2 (1.9)	0	0	1 (1.0)	0	0
Paronychia	2 (1.9)	0	0	2 (1.9)	0	0
Periodontal Disease	2 (1.9)	0	0	0	0	0
Rash Acneiform	2 (1.9)	0	0	4 (3.8)	1 (1.0)	0
Reproductive System And Breast Disorders	2 (1.9)	0	0	3 (2.9)	0	0
Skin Ulceration	2 (1.9)	0	0	0	0	0
Stroke	2 (1.9)	1 (1.0)	0	0	0	0
Thromboembolic Event	2 (1.9)	0	0	0	0	0
Treatment Related Secondary Malignancy	2 (1.9)	2 (1.9)	0	2 (1.9)	2 (1.9)	0
Urinary Frequency	2 (1.9)	0	0	1 (1.0)	0	0
Vascular Disorders	2 (1.9)	2 (1.9)	0	2 (1.9)	1 (1.0)	1 (1.0)
Weight Gain	2 (1.9)	0	0	1 (1.0)	0	0
Weight Loss	2 (1.9)	0	0	0	0	0
Wheezing	2 (1.9)	0	0	0	0	0
Ankle Fracture	1 (1.0)	0	0	0	0	0
Anorexia	1 (1.0)	0	0	0	0	0
Appendicitis	1 (1.0)	1 (1.0)	0	0	0	0
Ascites	1 (1.0)	0	0	0	0	0
Blood And Lymphatic System Disorders	1 (1.0)	1 (1.0)	0	1 (1.0)	1 (1.0)	0
Bone Pain	1 (1.0)	0	0	1 (1.0)	1 (1.0)	0
Chest Pain Cardiac	1 (1.0)	1 (1.0)	0	0	0	0
Chills	1 (1.0)	0	0	4 (3.8)	0	0
Creatinine Increased	1 (1.0)	0	0	1 (1.0)	0	0
Death Nos	1 (1.0)	0	1 (1.0)	0	0	0
Dehydration	1 (1.0)	0	0	0	0	0
Dry Mouth	1 (1.0)	0	0	1 (1.0)	0	0
Dysgeusia	1 (1.0)	0	0	1 (1.0)	0	0
Dyspepsia	1 (1.0)	0	0	5 (4.8)	0	0
Dysphagia	1 (1.0)	0	0	1 (1.0)	0	0
Ear And Labyrinth Disorders	1 (1.0)	0	0	2 (1.9)	0	0
Ejection Fraction Decreased	1 (1.0)	1 (1.0)	0	0	0	0
Erythema Multiforme	1 (1.0)	0	0	0	0	0
Esophageal Pain	1 (1.0)	0	0	1 (1.0)	0	0
Flu Like Symptoms	1 (1.0)	0	0	1 (1.0)	0	0
Gastritis	1 (1.0)	0	0	0	0	0
Hearing Impaired	1 (1.0)	0	0	1 (1.0)	0	0

Supplemental Table 18. Cont.

Hoarseness	1 (1.0)	0	0	1 (1.0)	0	0
Hypocalcemia	1 (1.0)	1 (1.0)	0	0	0	0
Hypoglycemia	1 (1.0)	0	0	0	0	0
Hypohidrosis	1 (1.0)	0	0	0	0	0
Injury, Poisoning And Procedural Complications	1 (1.0)	0	0	0	0	0
Investigations	1 (1.0)	0	0	0	0	0
Irritability	1 (1.0)	0	0	0	0	0
Joint Range Of Motion Decreased	1 (1.0)	0	0	0	0	0
Keratitis	1 (1.0)	0	0	0	0	0
Laryngospasm	1 (1.0)	0	0	0	0	0
Lethargy	1 (1.0)	0	0	0	0	0
Localized Edema	1 (1.0)	0	0	1 (1.0)	0	0
Lower Gastrointestinal Hemorrhage	1 (1.0)	0	0	0	0	0
Metabolism And Nutrition Disorders	1 (1.0)	0	0	0	0	0
Nail Infection	1 (1.0)	0	0	2 (1.9)	0	0
Nail Loss	1 (1.0)	0	0	1 (1.0)	0	0
Non Cardiac Chest Pain	1 (1.0)	0	0	2 (1.9)	0	0
Oral Pain	1 (1.0)	0	0	3 (2.9)	1 (1.0)	0
Pain Of Skin	1 (1.0)	0	0	0	0	0
Pancreatitis	1 (1.0)	1 (1.0)	0	0	0	0
Penile Infection	1 (1.0)	0	0	0	0	0
Pharyngitis	1 (1.0)	0	0	0	0	0
Photosensitivity	1 (1.0)	0	0	0	0	0
Pleural Effusion	1 (1.0)	0	0	1 (1.0)	1 (1.0)	0
Postoperative Hemorrhage	1 (1.0)	1 (1.0)	0	1 (1.0)	0	0
Productive Cough	1 (1.0)	0	0	5 (4.8)	0	0
Prostate Infection	1 (1.0)	0	0	0	0	0
Prostatic Pain	1 (1.0)	0	0	0	0	0
Purpura	1 (1.0)	0	0	0	0	0
Radiculitis	1 (1.0)	0	0	0	0	0
Respiratory Failure	1 (1.0)	0	1 (1.0)	1 (1.0)	1 (1.0)	0
Sleep Apnea	1 (1.0)	0	0	2 (1.9)	0	0
Sneezing	1 (1.0)	0	0	0	0	0
Syncope	1 (1.0)	1 (1.0)	0	0	0	0
Toothache	1 (1.0)	0	0	1 (1.0)	0	0
Upper Gastrointestinal Hemorrhage	1 (1.0)	1 (1.0)	0	0	0	0
Urinary Retention	1 (1.0)	0	0	2 (1.9)	0	0
Urinary Tract Pain	1 (1.0)	0	0	0	0	0
Urine Discoloration	1 (1.0)	0	0	0	0	0
Urticaria	1 (1.0)	0	0	0	0	0
Allergic Reaction	0	0	0	1 (1.0)	0	0
Aortic Valve Disease	0	0	0	1 (1.0)	0	0
Bladder Infection	0	0	0	1 (1.0)	1 (1.0)	0

Supplemental Table 18. Cont.

Blurred Vision	0	0	0	4 (3.8)	0	0
Cataract	0	0	0	1 (1.0)	1 (1.0)	0
Cheilitis	0	0	0	1 (1.0)	0	0
Chest Wall Pain	0	0	0	3 (2.9)	0	0
Chronic Kidney Disease	0	0	0	1 (1.0)	1 (1.0)	0
Confusion	0	0	0	1 (1.0)	0	0
Conjunctivitis	0	0	0	1 (1.0)	0	0
Dry Skin	0	0	0	3 (2.9)	0	0
Edema Face	0	0	0	1 (1.0)	0	0
Erectile Dysfunction	0	0	0	1 (1.0)	0	0
Flatulence	0	0	0	2 (1.9)	0	0
Flushing	0	0	0	1 (1.0)	0	0
General Disorders And Administration Site Conditions	0	0	0	1 (1.0)	0	0
Generalized Muscle Weakness	0	0	0	1 (1.0)	0	0
Gingival Pain	0	0	0	2 (1.9)	0	0
Gum Infection	0	0	0	1 (1.0)	0	0
Hallucinations	0	0	0	1 (1.0)	1 (1.0)	0
Hypokalemia	0	0	0	2 (1.9)	2 (1.9)	0
Hyponatremia	0	0	0	1 (1.0)	1 (1.0)	0
Hypothyroidism	0	0	0	2 (1.9)	0	0
Infusion Related Reaction	0	0	0	5 (4.8)	0	0
Intracranial Hemorrhage	0	0	0	1 (1.0)	0	0
Joint Infection	0	0	0	1 (1.0)	0	0
Kidney Infection	0	0	0	1 (1.0)	1 (1.0)	0
Laryngeal Hemorrhage	0	0	0	1 (1.0)	0	0
Memory Impairment	0	0	0	2 (1.9)	0	0
Mucosal Infection	0	0	0	2 (1.9)	0	0
Nail Discoloration	0	0	0	2 (1.9)	0	0
Nervous System Disorders	0	0	0	1 (1.0)	0	0
Obstruction Gastric	0	0	0	1 (1.0)	0	1 (1.0)
Papulopustular Rash	0	0	0	3 (2.9)	0	0
Pericardial Effusion	0	0	0	1 (1.0)	1 (1.0)	0
Pericarditis	0	0	0	1 (1.0)	0	0
Periorbital Edema	0	0	0	1 (1.0)	0	0
Pleuritic Pain	0	0	0	1 (1.0)	1 (1.0)	0
Rash Pustular	0	0	0	3 (2.9)	0	0
Restlessness	0	0	0	1 (1.0)	0	0
Retinopathy	0	0	0	2 (1.9)	0	0
Seizure	0	0	0	1 (1.0)	1 (1.0)	0
Sepsis	0	0	0	1 (1.0)	1 (1.0)	0
Sinus Disorder	0	0	0	2 (1.9)	0	0
Skin Hyperpigmentation	0	0	0	1 (1.0)	0	0
Stomach Pain	0	0	0	2 (1.9)	0	0
Supraventricular Tachycardia	0	0	0	1 (1.0)	0	0
Urinary Tract Obstruction	0	0	0	1 (1.0)	0	0
Urinary Urgency	0	0	0	1 (1.0)	0	0

Supplemental Table 18. Cont.

Uveitis	0	0	0	1 (1.0)	0	0
Ventricular Arrhythmia	0	0	0	1 (1.0)	0	0
Watering Eyes	0	0	0	1 (1.0)	0	0
White Blood Cell Decreased	0	0	0	1 (1.0)	1 (1.0)	0

Subjects with multiple events for a given preferred term are counted once only using maximum severity for each preferred term.
Events are sorted by decreasing frequency of preferred term by Any Grade column in the ibrutinib group.
TEAEs are defined as: (1) events with onset dates on or after the first dose of study drug, and within 30 days following the last dose of study drug; (2) events that are considered study drug-related regardless of the start date of the event; (3) events present at baseline that worsen in severity or are subsequently considered drug-related by the investigator.

Supplemental Table 19. Annualized Discontinuation Rate

	Ibr (N = 104)			Ibr+R (N = 104)		
	n	Patient-years at Risk	ADR	n	Patient-years at Risk	ADR
Overall	33	243.9	13.5	37	228.2	16.2
Within the 1st year of treatment	15	95.42	15.7	20	93.87	21.3
Within the 2nd year of treatment	7	76.70	9.1	12	70.36	17.1
Within the 3rd year of treatment	6	52.52	11.4	3	45.73	6.6

N = number of subjects randomized in specified treatment group. n = number of subjects who discontinued treatment.
Patient-years at risk is the sum of treatment duration in year for all subjects in the specified treatment group.
ADR = 100 * n / Patient-years at risk.

Supplemental Table 20. Event Free Survival (EFS) Analysis Results Adjusting for Stratification Factors

Event Free Survival (Months)	Ibr (N=104)	Ibr+R (N=104)	Comparison/Difference Ibr vs. Ibr+R
Events - n (%)	15 (14.4)	13 (12.5)	
Disease Progression	10	5	
Death	5	8	
Censored - n (%)	89 (85.6)	91 (87.5)	
Median (95% CI) [1]	NE (NE, NE)	NE (NE, NE)	
Min, Max	2.99+, 46.75+	2.92, 47.80+	
P value [2]			0.9115
Hazard Ratio (95% CI) [3]			1.043 (0.494, 2.203)
EFS at landmark times - % (95% CI) [1]			
6 months	99.0 (93.3, 99.9)	98.1 (92.5, 99.5)	1.0 (-2.3, 4.2)
12 months	97.0 (91.1, 99.0)	98.1 (92.5, 99.5)	-1.0 (-5.2, 3.2)
15 months	95.0 (88.4, 97.9)	95.0 (88.4, 97.9)	0.0 (-6.0, 6.1)
18 months	95.0 (88.4, 97.9)	95.0 (88.4, 97.9)	0.0 (-6.0, 6.1)
24 months	95.0 (88.4, 97.9)	92.5 (84.9, 96.4)	2.5 (-4.4, 9.3)
30 months	86.0 (76.6, 91.9)	89.8 (81.1, 94.6)	-3.7 (-13.5, 6.1)
36 months	86.0 (76.6, 91.9)	86.9 (77.3, 92.6)	-0.8 (-11.3, 9.6)

CI= confidence interval. + Indicates censored observation. NE = not estimable.
[1] Estimated by Kaplan-Meier method.
[2] P value is from stratified log-rank test.
[3] Hazard ratio is estimated using stratified Cox regression model.
The randomization stratification factor used in both stratified log-rank test and Cox regression model is high-risk status based on del17p, del11q and TP53 mutation (yes, no). ECOG is not used because all subjects had ECOG 0-1.

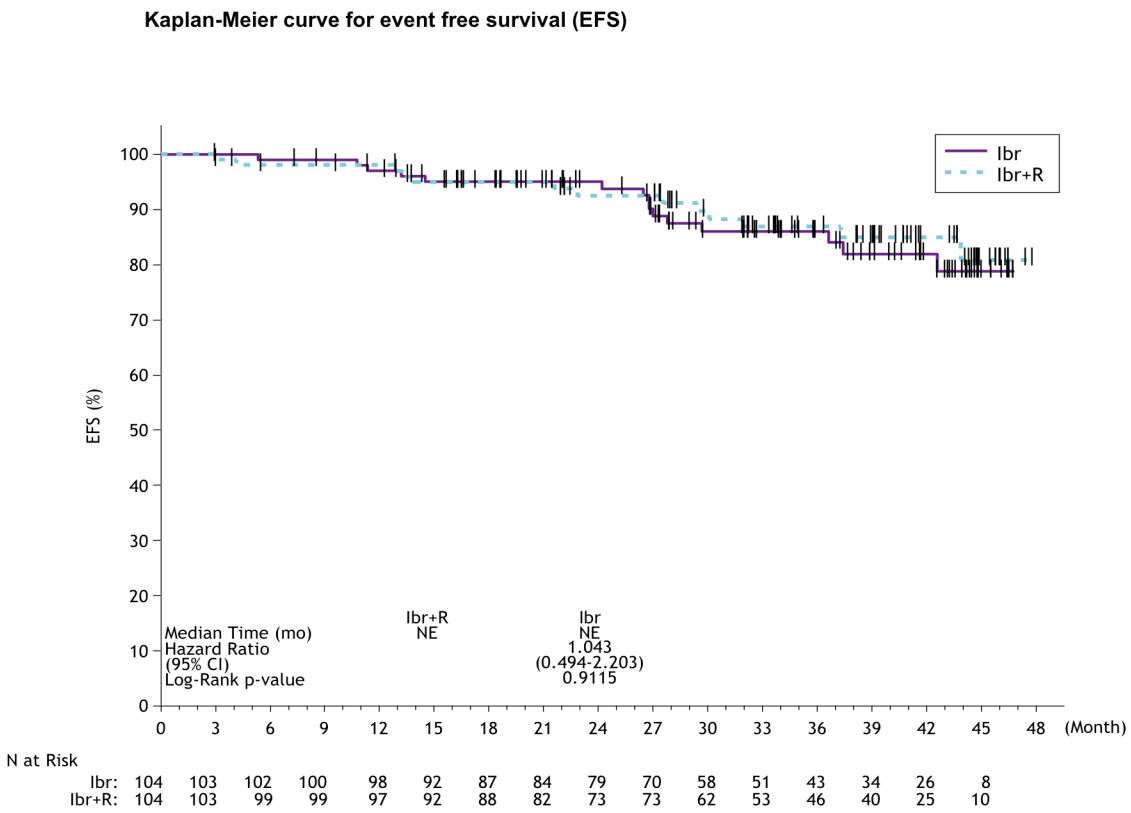
Supplemental Table 21. Best Response by Month 12 and Month 24

	Ibr (N = 104) n (%)				Ibr+R (N = 104) n (%)			
	ORR	CR/CRi	PR/PRn	PRL	ORR	CR/CRi	PR/PRn	PRL
By Month 12	96 (92.3)	6 (5.8)	71 (68.3)	19 (18.3)	96 (92.3)	18 (17.3)	71 (68.3)	7 (6.7)
By Month 24	96 (92.3)	19 (18.3)	66 (63.5)	11 (10.6)	96 (92.3)	26 (25.0)	66 (63.5)	4 (3.8)

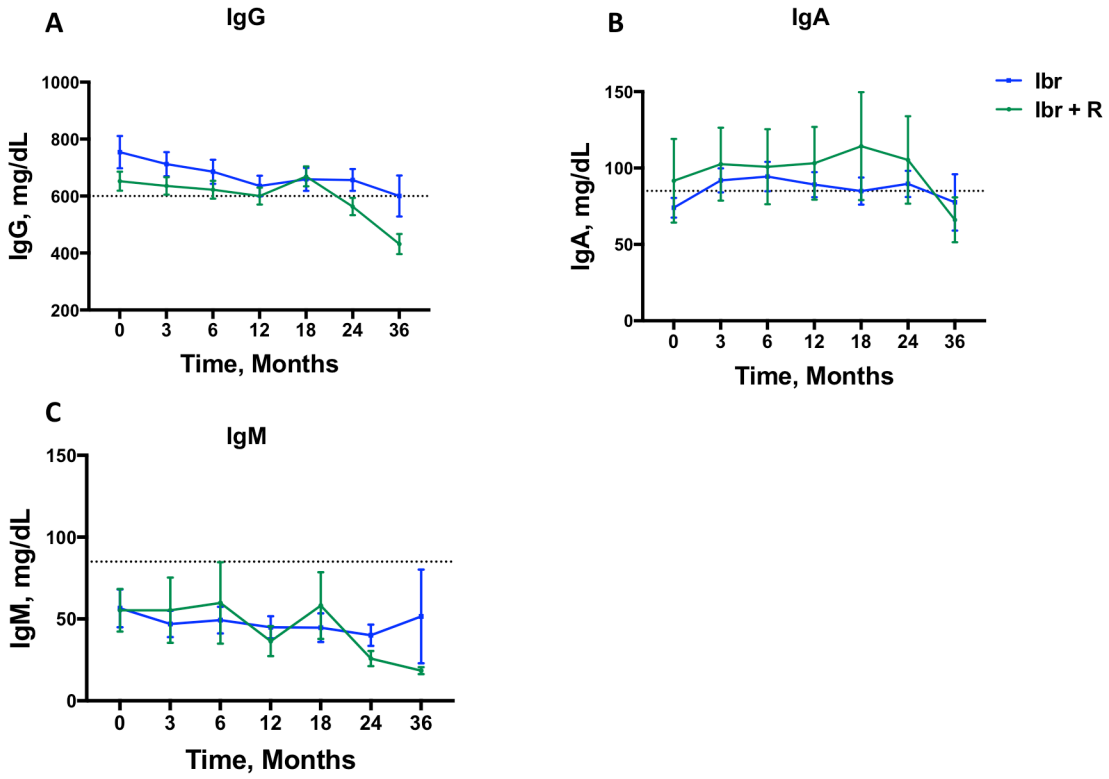
N = number of subjects in each subgroup. n=number of subjects with response. % = n/N.

Supplemental Figures

Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3