SUPPLEMENTARY APPENDIX

Natural history of Waldenström macroglobulinemia following acquired resistance to ibrutinib monotherapy

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Table S1. Univariate logistic regression analysis for factors at T_0 predictive of IgM rebound.

Variable	OR (95% CI)	P-value
Age >65 years	1.97 (0.51-7.78)	0.36
>2 years from ibrutinib initiation	0.97 (0.26-3.57)	1.00
>10 years from WM diagnosis	1.38 (0.37-5.46)	0.77
Male sex	1.60 (0.41-6.31)	0.54
Hemoglobin level <10 g/dl	2.56 (0.65-11.6)	0.15
Platelet count <100 K/ul	3.44 (0.73-22.6)	0.11
Serum IgM level >4000 mg/dl	1.35 (0.17-16.5)	1.00
>4 prior therapies	2.18 (0.33-24.7)	0.45
Quadruple-class exposed	0.77 (0.37-5.46)	0.77
MYD88 mutation	3.24 (0.16-204.1)	0.55
CXCR4 mutation	0.99 (0.27-3.39)	1.00

Previous therapy includes ibrutinib monotherapy for all patients. Patients who had been previously treated with ibrutinib, rituximab, proteasome inhibitor, and alkylating agent were considered to be “quadruple-class exposed.” MYD88 and CXCR4 mutation status was available for 46 and 40 patients, respectively.

Table S2. Univariate logistic regression analysis for factors at T_0 predictive of an objective response to the first salvage regimen.

Variable	OR (95% CI)	P-value
Age >65 years	1.85 (0.51-6.96)	0.38
>2 years from ibrutinib initiation	1.23 (0.34-4.56)	0.78
>10 years from WM diagnosis	0.96 (0.25-3.67)	1.00
Male sex	0.59 (0.14-2.28)	0.54
Hemoglobin level <10 g/dl	0.27 (0.06-1.04)	0.06
Platelet count <100 K/ul	0.26 (0.05-1.07)	0.06
Serum IgM level >4000 mg/dl	1.70 (0.31-12.0)	0.71
>4 prior therapies	0.68 (0.07-3.64)	0.68
Quadruple-class exposed	0.22 (0.05-0.88)	0.02
MYD88 mutation	2.39 (0.12-150)	0.59
CXCR4 mutation	2.09 (0.55-6.93)	0.33

Previous therapy includes ibrutinib monotherapy for all patients. Patients who had been previously treated with ibrutinib, rituximab, proteasome inhibitor, and alkylating agent were considered to be “quadruple-class exposed.” MYD88 and CXCR4 mutation status was available for 46 and 40 patients, respectively.

Table S3. Comparison of clinical characteristics at T_0 between ibrutinib-resistant WM patients with BTK^{C481S} and BTK^{WT}.

Patient Characteristic	BTK C481S (n=7)	BTK WT (n=14)	P-value
Median age (range) – yrs			
WM diagnosis	63 (52-91)	60 (43-66)	0.15
Ibrutinib initiation	71 (61-93)	66 (43-79)	0.15
Ibrutinib discontinuation	73 (64-93)	68 (43-80)	0.16
Median time from WM dx (range) – yrs	9.4 (2.8-24)	9.7 (0.6-23)	0.69
Male sex – no. (%)	6 (86)	10 (71)	0.62
Median hemoglobin level (range) – g/dl	9.3 (7.7-11.2)	10.3 (7.3-15.3)	0.23
Median platelet count (range) – K/ul	148 (20-222)	189 (52-463)	0.25
Median serum IgM level	825 (407-3970)	1869 (314-6516)	0.17
Previous therapy			
Median no. of treatment (range)	3 (1-9)	3 (1-7)	0.13
Quadruple-class exposed – no. (%)	5 (71)	6 (43)	0.36
MYD88 mutation – no. (%)	7 (100)	14 (100)	UTC
CXCR4 mutation – no. (%)	5 (71)	7 (50)	0.64

Genotyping for BTK mutations was available for 21 WM patients with acquired ibrutinib resistance, and the characteristics of these patients are depicted in the table. Previous therapy includes ibrutinib monotherapy for all patients. Patients who had been previously treated with ibrutinib, rituximab, proteasome inhibitor, and alkylating agent were considered to be “quadruple-class exposed.” UTC: unable to calculate.

Figure S1. Serial IgM measurements for patients with an IgM rebound who developed symptomatic hyperviscosity. Serial serum IgM measurements were available for 7 out of 10 patients (70%) who developed symptomatic hyperviscosity from an IgM rebound after discontinuing ibrutinib. Emergent plasmapheresis was administered at the last IgM level for each patient.

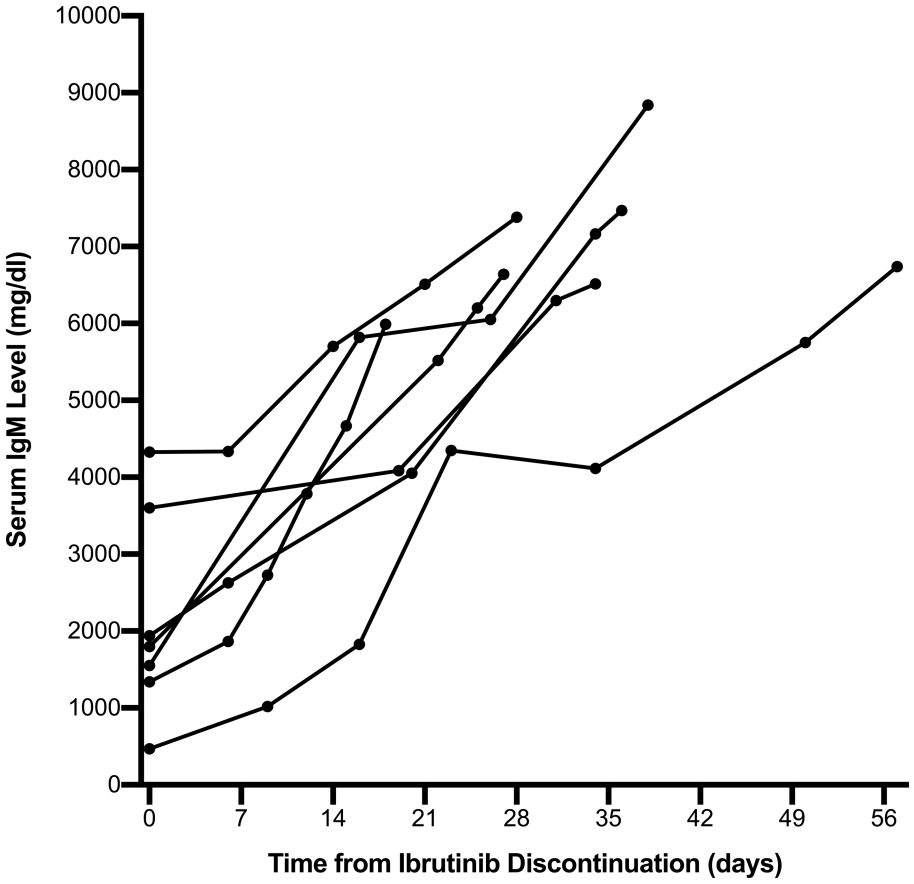

Figure S2. Overall survival from WM diagnosis. Kaplan-Meier curve for overall survival (OS) from the time of WM diagnosis for the entire cohort. The median OS was 20.4 years (95% CI 13.2-NR).

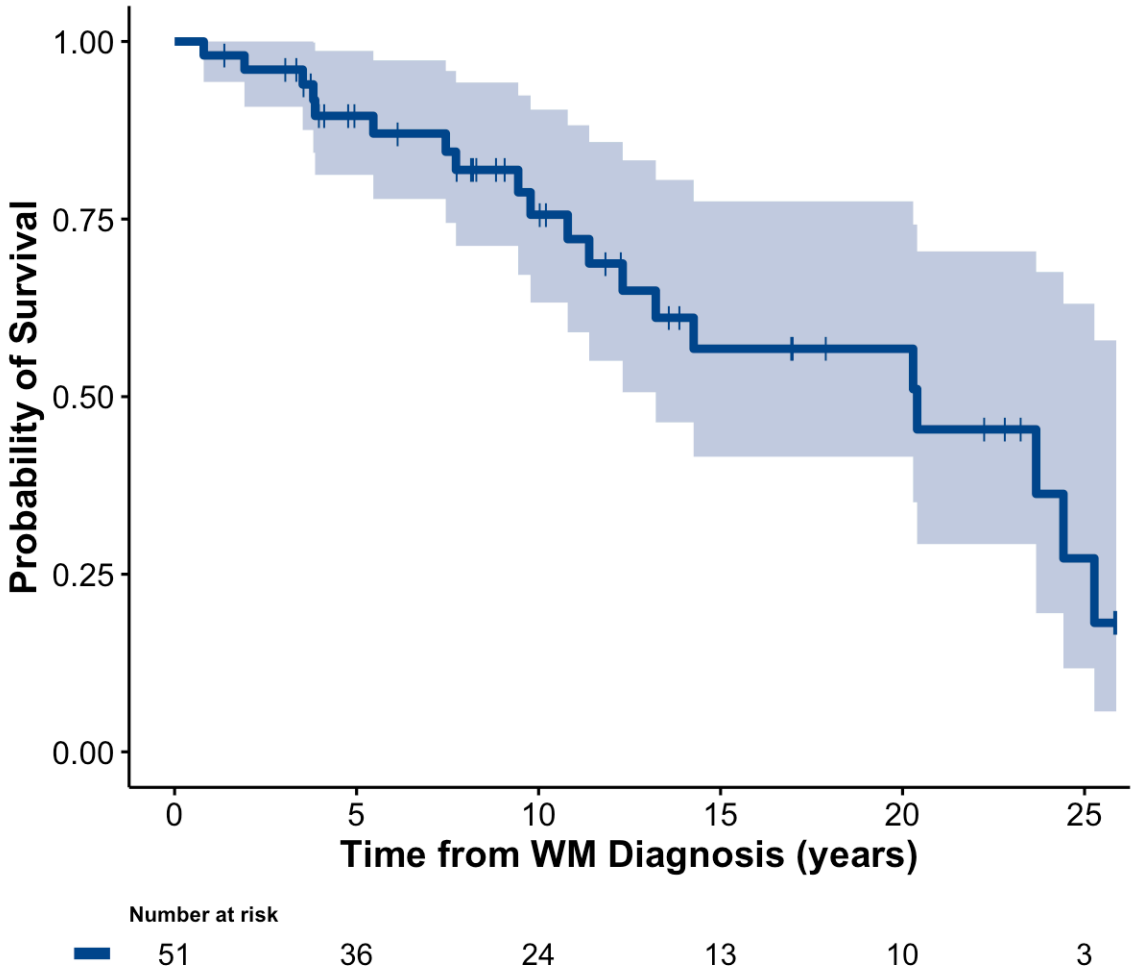

Figure S3. Overall survival following ibrutinib discontinuation stratified by quadruple-class exposed status. Kaplan-Meier curves for overall survival (OS) from the time of ibrutinib discontinuation (T_0). Previous therapy includes ibrutinib monotherapy for all patients. Patients who had been previously treated with ibrutinib, rituximab, proteasome inhibitor, and alkylating agent were considered to be "quadruple-class exposed." Patients with and without quadruple-class exposed disease had a median OS following T_0 of 13.2 months and NR, respectively ($p<0.001$). The 5-year OS for patients without quadruple-class exposed disease was 62% (95% CI 38-98%).

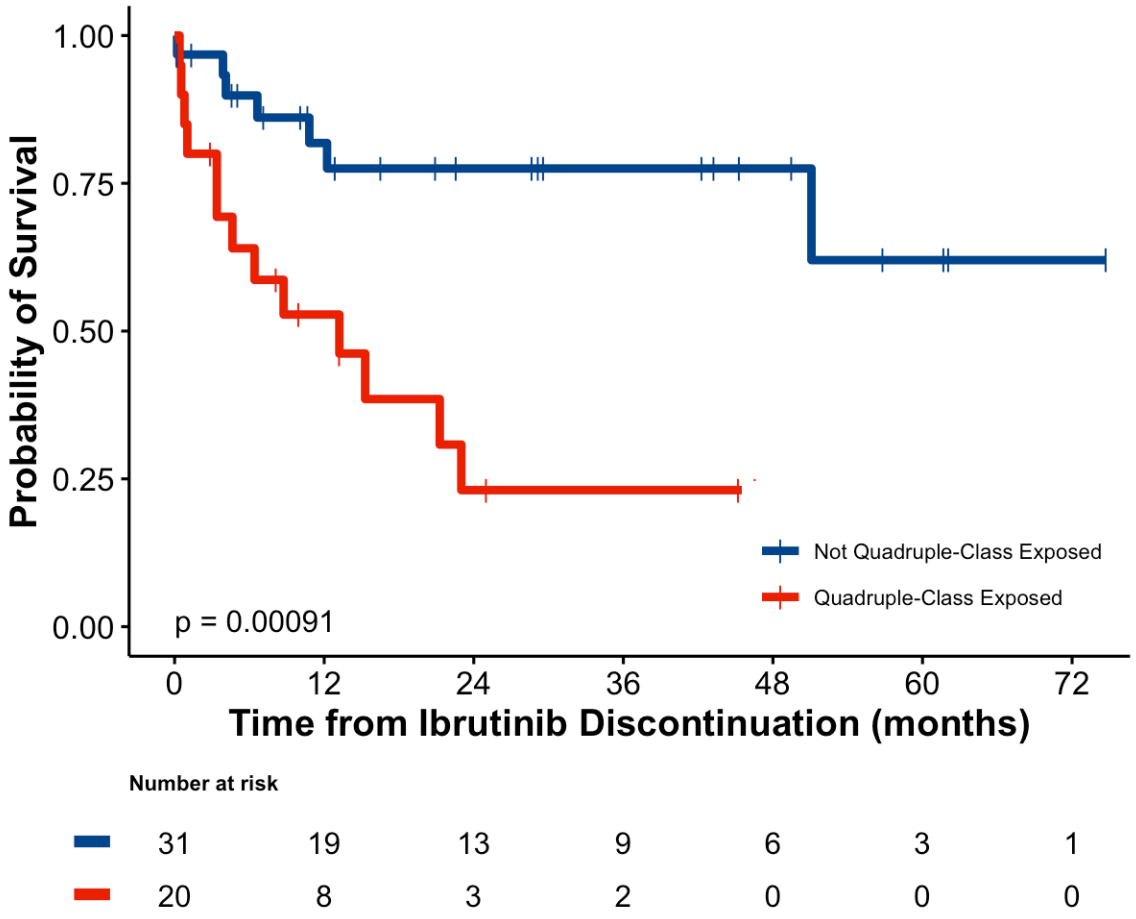

Figure S4. Cumulative incidence of ibrutinib discontinuation stratified by BTK mutation status. Kaplan-Meier curves for the duration of time between ibrutinib initiation and discontinuation. There was no difference in the time to ibrutinib discontinuation between patients with BTK^{C481S} and BTK^{WT} (1.9 vs. 1.8 years; p=0.50).

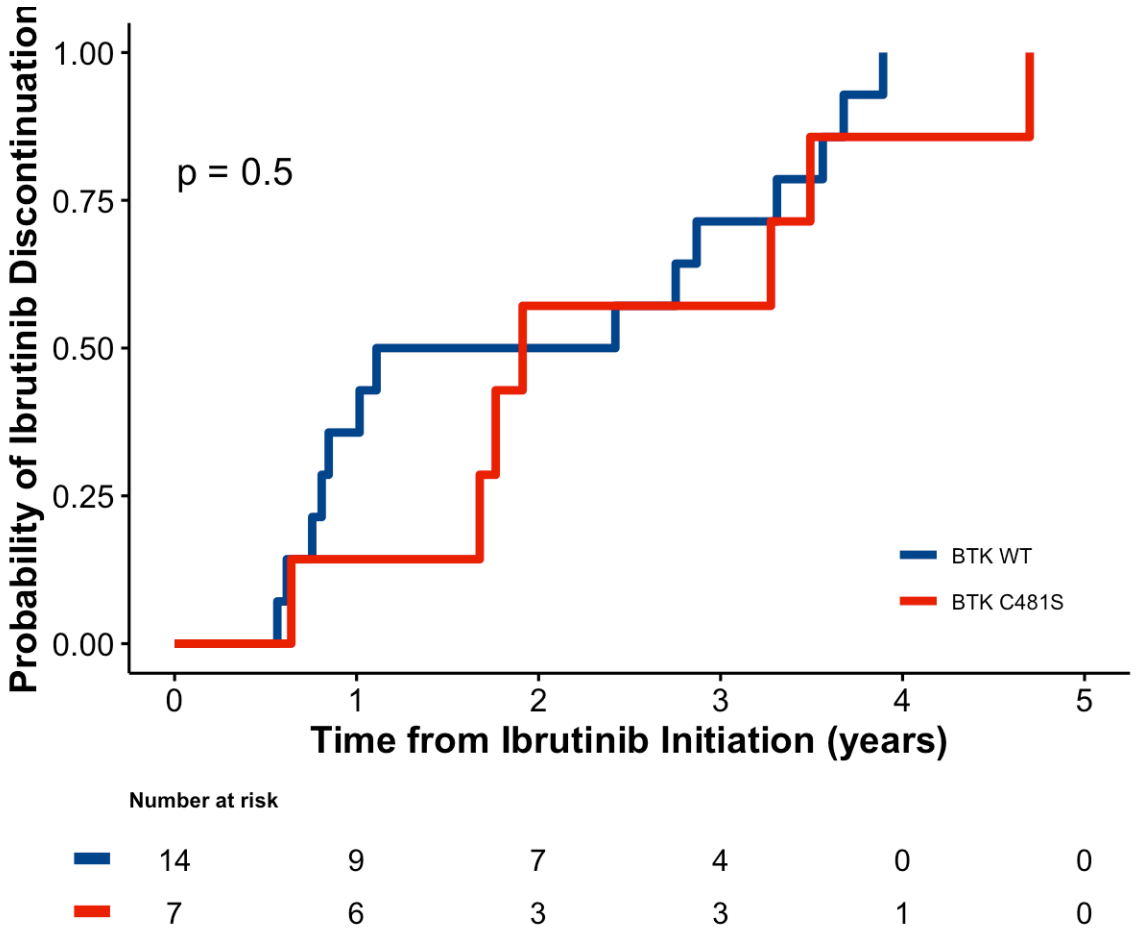

Figure S5. Overall survival following ibrutinib discontinuation stratified by BTK mutation status. Kaplan-Meier curves for overall survival (OS) from the time of ibrutinib discontinuation (T_0). Twenty-one patients had genotyping for BTK mutations performed; 7 patients had BTK^{C481S}, and 14 patients had BTK^{WT}. By univariate analysis, patients with BTK^{C481S} had a significantly shorter median OS following T_0 versus BTK^{WT} (6.4 months vs. NR; p=0.026). In an exploratory analysis, we evaluated the presence of BTK^{C481S} against quadruple-class exposed disease for OS after T_0. In this model, only quadruple-class exposed disease was significantly associated with worse OS (HR 5.50, 95% CI 1.15-26.2; p=0.03). BTK^{C481S} was not independently associated with OS after adjusting for quadruple-class exposed disease (p=0.09).

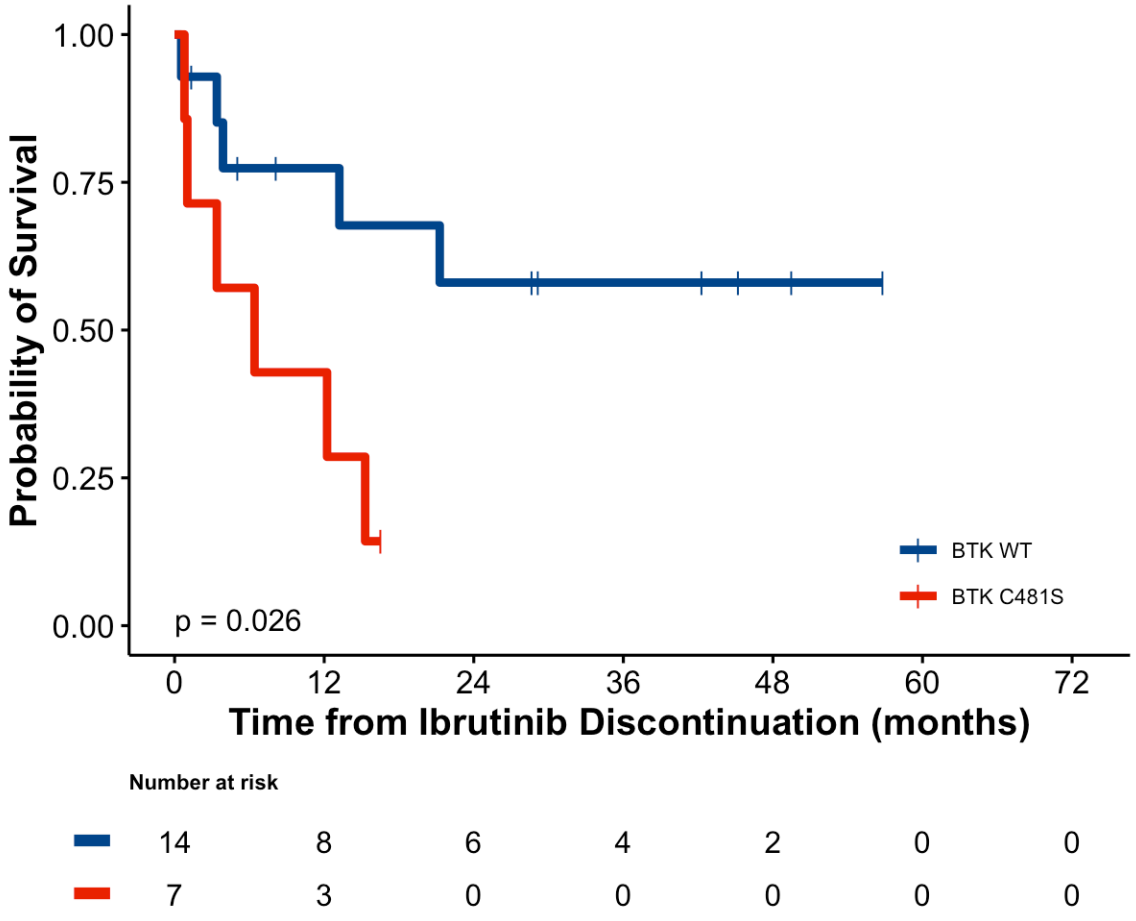

Figure S6. Overall survival following ibrutinib discontinuation stratified by TP53 mutation status. Kaplan-Meier curves for overall survival (OS) from the time of ibrutinib discontinuation (T_0). Twenty patients had genotyping for TP53 mutations performed; 3 patients had $TP53^{MUT}$, and 17 patients had $TP53^{WT}$. Patients with $TP53^{MUT}$ had a significantly shorter median OS following T_0 versus $TP53^{WT}$ (0.5 vs. 21.3 months; p=0.023).