SUPPLEMENTAL MATERIAL

Supplemental Table 1. List of genetic alterations found in baseline samples.

Patient ID	Gene	Genetic alterations (depth, VAF)	Treatment arm
pts#1	*ARID1A*	p.Y470*,c.1410T>A(8095,0.0504)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#2	*NBN*	p.S53Cfs*9,c.156_157del(5036,0.4565)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#3	*ARID1A*	p.E2250Rfs*28,c.6747dup(7211,0.0062)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#3	*ATRX*	p.R2386*,c.7156C>T(2999,0.016)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#3	*TP53*	p.R282W,c.844C>T(7498,0.002)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#4	*CXCR4*	p.S338*,c.1013C>G(7335,0.0293)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#5	*TP53*	p.R248Q,c.743G>A(7740,0.0035)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#5	*TP53*	p.V272M,c.814G>A(7497,0.0027);	patients with *MYD88^{MUT}* treated with ibrutinib
pts#6	*KDM6A*	p.L1189*,c.3565del(2842,0.0046)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#7	*CXCR4*	p.T318Nfs*26,c.952dup(7085,0.1495)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#8	*PTEN*	p.K267Rfs*9,c.800del(6727,0.0025)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#9	*NF1*	p.N730*,c.2187dup(8250,0.1122)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#9	*TP53*	p.H178Pfs*3,c.532dup(9343,0.0764)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#10	*TP53*	p.R273H,c.818G>A(9104,0.0023);	patients with *MYD88^{MUT}* treated with ibrutinib
pts#10	*TP53*	p.Y220C,c.659A>G(9976,0.0012)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#11	*TP53*	p.R175L,c.524G>T(10153,0.1265)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#12	*TERT*	NA,c.-124C>T(10269,0.0316)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#12	*TP53*	p.R248P,c.743G>C(9014,0.0123)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#13	*ARID1A*	p.E1387Rfs*94,c.4159del(7748,0.0607)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#13	*ARID1A*	p.Q1327Afs*11,c.3977dup(8472,0.0146);	patients with *MYD88^{MUT}* treated with ibrutinib
pts#13	*CXCR4*	p.S338*,c.1013C>G(7422,0.1188)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#13	*TERT*	NA,c.-124C>T(8536,0.0056)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#13	*TP53*	p.N239Kfs*25,c.716dup(8016,0.0136)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#13	*TP53*	p.R280S,c.840A>C(8198,0.0101);	patients with *MYD88^{MUT}* treated with ibrutinib
pts#13	*TP53*	p.R306*,c.916C>T(8404,0.0138);	patients with *MYD88^{MUT}* treated with ibrutinib
pts#14	*TP53*	p.R273H,c.818G>A(8539,0.0015)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#15	*FGFR2*	p.R251Q,c.752G>A(8019,0.0175)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#16	*ARID1A*	p.K1047*,c.3139A>T(7221,0.0043);	patients with *MYD88^{MUT}* treated with ibrutinib
pts#16	*ARID1A*	p.R1446*,c.4336C>T(6892,0.0942)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#16	*CXCR4*	p.S341Ffs*3,c.1021dup(7112,0.0796)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#17	*TP53*	p.H179Y,c.535C>T(9911,0.0017)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#18	*CHEK2*	NA,c.1462-2A>G(6604,0.0033);	patients with *MYD88^{MUT}* treated with ibrutinib
pts#19	*ARID1A*	p.P225Afs*175,c.671dup(5992,0.0714)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#19	*CDKN2A*	Deletion(1.5)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#19	*CXCR4*	p.S338*,c.1013C>A(5004,0.1089)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#20	*CHEK2*	p.E122*,c.364G>T(7990,0.0125)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#20	*TP53*	p.D281E,c.843C>G(8705,0.0034);	patients with *MYD88^{MUT}* treated with ibrutinib
pts#20	*TP53*	p.R273H,c.818G>A(8598,0.0021)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#21	*ARID1A*	p.G314Afs*49,c.941del(11412,0.0067)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#21	*CXCR4*	p.S338*,c.1013C>G(8085,0.0105)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#21	*TERT*	NA,c.-124C>T(8750,0.0067)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#22	*TP53*	p.R273H,c.818G>A(7084,0.0032)	patients with *MYD88^{MUT}* treated with ibrutinib
pts#23	*CXCR4*	p.S341Pfs*25,c.1021del(7391,0.0077)	patients with *MYD88^{MUT}* treated with ibrutinib

pts#24	*ARID1A*	p.Y815Lfs*18,c.2444del(6547,0.2331)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#24	*ATM*	Deletion(1.58)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#24	*CXCR4*	p.L326Pfs*18,c.976dup(6240,0.2021)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#24	*PIK3CA*	p.H1047R,c.3140A>G(6478,0.0017)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#24	*SLC34A2*	Deletion(1.51)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#24	*TP53*	Deletion(1.57)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#24	*TP53*	p.R306*,c.916C>T(5305,0.2984);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#25	*CXCR4*	p.S338Ffs*3,c.1013_1020del(7523,0.0041)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#26	*TERT*	NA,c.-124C>T(9073,0.0385)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#27	*TERT*	NA,c.-124C>T(9112,0.0034)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#28	*TP53*	NA,c.673-1G>A(7150,0.0031);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#28	*TP53*	p.R158_A159del,c.472_477del(9201,0.0045)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#29	*ARID1A*	p.L2106Ffs*37,c.6315_6334del(7593,0.003)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#29	*CXCR4*	p.S338*,c.1013C>G(6497,0.0586)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#29	*TP53*	p.E258V,c.773A>T(7483,0.0055);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#29	*TP53*	p.R110H,c.329G>A(7839,0.0478)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*AKT2*	Amplification(2.65)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*ARID1A*	p.P146Qfs*86,c.437del(8825,0.3132)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*ATRX*	Deletion(1.34)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*CCNE1*	Amplification(2.68)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*CXCR4*	p.S338*,c.1013C>A(7442,0.3416)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*GNA11*	Amplification(2.77)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*KDM6A*	Deletion(1.29)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*KIT*	Amplification(2.54)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*MAP2K2*	Amplification(2.7)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*MAPK1*	Amplification(2.79)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*MYC*	Amplification(2.57)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*PDGFRA*	Amplification(2.54)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#30	*STAG2*	Deletion(1.32)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#31	*ARID1A*	p.G1610Dfs*37,c.4827_4828del(6495,0.0771)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#31	*CDKN2A*	Deletion(1.62)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#31	*CXCR4*	p.S338*,c.1013C>G(5764,0.0871)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#31	*TERT*	NA,c.-124C>T(6831,0.0829)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#32	*ARID1A*	p.A2097Mfs*38,c.6289_6290delinsA(5683,0.07)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#32	*ATRX*	p.Q2368*,c.7102C>T(1983,0.0111)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#33	*TP53*	p.V216M,c.646G>A(9972,0.005)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#34	*RB1*	p.L486Yfs*9,c.1457del(9092,0.0046)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#34	*TP53*	p.R273H,c.818G>A(10090,0.0062)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#35	*KDM6A*	p.L347*,c.1040T>A(4083,0.0073)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#36	*CHEK2*	p.T367Mfs*15,c.1100del(8143,0.5013)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#37	*ARID1A*	p.P1568Hfs*37,c.4703_4724del(6284,0.0126)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#37	*CXCR4*	p.S338*,c.1013C>G(6728,0.038)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#38	*ARID1A*	p.Y422*,c.1266C>A(8724,0.0454)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#38	*CXCR4*	p.S338Lfs*27,c.1012_1015del(7521,0.0158);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#38	*CXCR4*	p.G323Rfs*21,c.965dup(8082,0.0552)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#38	*PIK3CA*	p.E545G,c.1634A>G(7372,0.0012)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#38	*TP53*	NA,c.783-2A>G(8543,0.0057);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#38	*TP53*	p.R175H,c.524G>A(9587,0.0081)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#38	*TP53*	p.R273H,c.818G>A(8474,0.0077);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#38	*TP53*	p.Y205H,c.613T>C(9603,0.0409);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#39	*TP53*	NA,c.672+1G>A(10680,0.0033)	patients with *MYD88*^{MUT} treated with ibrutinib

pts#40	*ARID1A*	p.A162Cfs*240,c.477_483dup(10892,0.0063)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#40	*TP53*	p.S241C,c.722C>G(9167,0.061)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#41	*KRAS*	p.Q61R,c.182A>G(6941,0.0012)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#42	*RAD51B*	p.Q371*,c.1111C>T(5806,0.0079)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#43	*CDKN2A*	p.R80*,c.238C>T(8448,0.0014)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#43	*CXCR4*	p.S338*,c.1013C>G(7735,0.0804)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*ARID1A*	Deletion(1.48)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*CXCR4*	Amplification(2.86)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*CXCR4*	p.S338*,c.1013C>A(10290,0.43);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TERT*	NA,c.-124C>T(10692,0.0039)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TERT*	NA,c.-124C>T(10954,0.0032);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	NA,c.673-2A>G(6897,0.0042);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	NA,c.673-2A>T(6897,0.0071);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	NA,c.769_782+4del(6729,0.0202);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	NA,c.782+1G>A(6754,0.0036);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.A138P,c.412G>C(7444,0.3434)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.H179R,c.536A>G(7895,0.0018);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.I195F,c.583A>T(8145,0.0133);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.L188_P190del,c.563_571del(8204,0.0048);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.Q167*,c.499C>T(7844,0.0119);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.R175H,c.524G>A(7875,0.0076);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.R273H,c.818G>A(7046,0.0051);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.S240R,c.718A>C(7015,0.0038);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#44	*TP53*	p.Y220C,c.659A>G(7832,0.1099);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#45	*ATM*	p.R2443*,c.7327C>T(5789,0.4662)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#45	*CXCR4*	p.S338*,c.1013C>G(6476,0.0188)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#46	*MSH6*	p.L60*,c.179T>A(11998,0.0057)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#47	*EZH2*	p.L77*,c.230T>A(5562,0.0117)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#48	*CHEK2*	p.C243Lfs*4,c.728del(5682,0.0086)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#48	*KDM6A*	p.T588Yfs*9,c.1761dup(4061,0.0172)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#48	*TERT*	NA,c.-124C>T(6964,0.0045)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#49	*CXCR4*	p.S338*,c.1013C>A(6053,0.0302)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#49	*TERT*	NA,c.-124C>T(6285,0.0056)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#49	*TERT*	NA,c.-57A>C(7094,0.0234);	patients with *MYD88*^{MUT} treated with ibrutinib
pts#50	*ARID1A*	p.G925Dfs*14,c.2774_2780del(7922,0.0139)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#50	*CXCR4*	p.T318Nfs*26,c.952dup(8529,0.019)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#51	*TP53*	p.V216M,c.646G>A(8011,0.0027)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#52	*CCNE1*	p.Q277*,c.829C>T(5373,0.0065)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#52	*CXCR4*	p.S338*,c.1013C>G(6794,0.0071)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#52	*TP53*	p.Y220C,c.659A>G(7833,0.006)	patients with *MYD88*^{MUT} treated with ibrutinib
pts#53	*FANCL*	p.T367Nfs*13,c.1096_1099dup(5947,0.4286)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#54	*ATM*	p.R337C,c.1009C>T(6068,0.0313)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#54	*CXCR4*	p.S338*,c.1013C>A(6580,0.0462)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#55	*ARID1A*	p.R1276*,c.3826C>T(6224,0.2281)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#55	*CXCR4*	p.R334*,c.1000C>T(5565,0.2165)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#55	*MYC*	Amplification(2.88)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#55	*TP53*	Deletion(1.62)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*ARID1A*	p.Q467*,c.1399C>T(6362,0.4516)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*CXCR4*	p.S338*,c.1013C>G(2718,0.4636)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*FGFR3*	Amplification(3.24)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*KMT2D*	p.P647Hfs*283,c.1940del(11642,0.006)	patients with *MYD88*^{MUT} treated with zanubrutinib

pts#56	*MLH1*	Deletion(1.1)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*PIK3CA*	Amplification(2.87)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*PTPN11*	p.G503E,c.1508G>A(3114,0.0071)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*RAD50*	p.K583Rfs*14,c.1748del(3258,0.0218)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*RAD51B*	p.Q371*,c.1111C>T(12354,0.0552)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*TERT*	NA,c.-124C>T(33744,0.3868)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*TP53*	Deletion(1.28)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#56	*TP53*	p.C135F,c.404G>T(8776,0.8714);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#57	*ATM*	p.W488*,c.1464G>A(7758,0.0032);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#57	*NBN*	p.N141Kfs*12,c.423_432del(6546,0.0063)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#58	*TP53*	p.I251N,c.752T>A(6959,0.005);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#58	*TP53*	p.R175H,c.524G>A(8134,0.0118)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#59	*ARID1A*	p.Q799*,c.2395C>T(9962,0.0169)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#60	*CXCR4*	p.T318Cfs*24,c.952_956del(7713,0.0054)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#60	*TP53*	p.H179R,c.536A>G(7759,0.034)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#61	*CXCR4*	p.S319Lfs*2,c.954del(7631,0.0206)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#61	*TERT*	NA,c.-124C>T(9302,0.0114)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#62	*ARID1A*	NA,c.3867-1G>A(8591,0.0101);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#62	*ARID1A*	p.L2053Ffs*38,c.6159_6181del(7967,0.0126)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#62	*NBN*	p.S42Afs*7,c.123del(5638,0.5035)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#63	*CXCR4*	p.S330Qfs*13,c.988_989del(8513,0.263)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#64	*PAX5*	fusion_JAK2-PAX5(14)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#64	*TERT*	NA,c.-146C>T(8109,0.007)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#65	*KRAS*	p.A59G,c.176C>G(8969,0.0016)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#66	*TP53*	p.C135G,c.403T>G(9518,0.004)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#66	*TP53*	p.C176F,c.527G>T(9837,0.0114);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#67	*TP53*	p.C238S,c.713G>C(7676,0.0167)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#68	*ARID1A*	p.A1687Ifs*14,c.5059_5065del(4645,0.0222)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#68	*CXCR4*	p.S338Ffs*6,c.1012dup(4786,0.0244)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#69	*VHL*	p.R167Q,c.500G>A(8625,0.003)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#70	*CXCR4*	p.S338*,c.1013C>A(6137,0.0473)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#70	*TP53*	p.G226Lfs*11,c.675_682del(6241,0.0215);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#70	*TP53*	p.R175H,c.524G>A(6454,0.0626)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#71	*CHEK2*	p.R346H,c.1037G>A(8420,0.0059)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#71	*CXCR4*	p.R334*,c.1000C>T(8886,0.0479)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#71	*TERT*	NA,c.-124C>T(9674,0.0326)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#71	*TP53*	p.H193R,c.578A>G(10219,0.0515)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#72	*CXCR4*	p.S341Hfs*2,c.1021_1022del(8437,0.0036)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#72	*KDM6A*	p.S1274Pfs*18,c.3820del(3872,0.0039)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#73	*ARID1A*	p.P225Afs*175,c.671dup(9040,0.0827);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#73	*ARID1A*	p.P977Qfs*5,c.2930del(8375,0.1226);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#73	*CXCR4*	p.S338*,c.1013C>G(7660,0.1449)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#73	*MSH6*	p.G54Wfs*36,c.158_159insA(10748,0.0108)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#73	*TERT*	NA,c.-57A>C(9596,0.0987)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#73	*TP53*	p.D281Y,c.841G>T(8216,0.004);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#73	*TP53*	p.V272M,c.814G>A(8327,0.006)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#74	*ARID1A*	p.Q1127*,c.3379C>T(7190,0.1917)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#74	*CXCR4*	p.S319Cfs*24,c.956_957del(7464,0.1573)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#74	*MAPK3*	Amplification(2.62)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#74	*TERT*	NA,c.-124C>T(8333,0.1457)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#74	*TP53*	p.Y220H,c.658T>C(9330,0.3539)	patients with *MYD88*^{MUT} treated with zanubrutinib

pts#75	*CXCR4*	p.E345*,c.1032dup(5873,0.0043)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#75	*MSH6*	p.L60Sfs*23,c.177_178insAGCCC(8846,0.0032)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#76	*NF1*	p.R1947*,c.5839C>T(7942,0.0089)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#77	*CXCR4*	p.G336Dfs*28,c.1007_1013del(7984,0.0089)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#78	*KRAS*	p.A146V,c.437C>T(6746,0.0064)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#79	*CXCR4*	p.S341Ffs*3,c.1021dup(11373,0.0127)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#79	*FANCL*	p.M1?,c.2T>C(10901,0.4921)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#79	*KRAS*	p.A146V,c.437C>T(9709,0.0038)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#79	*MAPK3*	Amplification(3.33)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#79	*TERT*	NA,c.-124C>T(15065,0.0042)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#80	*CXCR4*	p.H337Lfs*6,c.1010_1011del(6857,0.006)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#81	*KRAS*	p.Q61H,c.183A>C(5345,0.0011)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#81	*STAG2*	p.M163Wfs*20,c.486del(2835,0.0078);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#81	*TERT*	NA,c.-124C>T(6972,0.0086)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#82	*ARID1A*	p.P225Afs*175,c.671dup(8064,0.0537)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#82	*CXCR4*	p.V340Hfs*2,c.1018_1022del(8117,0.0793)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#83	*BRAF*	p.K601N,c.1803A>T(7378,0.0034)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#83	*RAD51B*	p.Q371*,c.1111C>T(6739,0.0062)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#84	*TP53*	p.Y220C,c.659A>G(9127,0.0057)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	Deletion(1.2)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	NA,c.559+1G>T(3815,0.01);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	NA,c.782+1G>A(3293,0.0055);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.A138P,c.412G>C(3854,0.0029);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.C176F,c.527G>T(3778,0.0082);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.D259V,c.776A>T(3278,0.0104);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.K132M,c.395A>T(3810,0.0026);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.L264Yfs*81,c.790del(3632,0.0033);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.P278R,c.833C>G(3732,0.0032);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.R110L,c.329G>T(4006,0.0057);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.R175H,c.524G>A(3751,0.0032);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.R249S,c.747G>T(3461,0.0061);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.R273L,c.818G>T(3625,0.5004);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.W53*,c.159G>A(3601,0.0069);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.W91*,c.273G>A(4026,0.0055);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#85	*TP53*	p.Y205D,c.613T>G(3972,0.0358);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#86	*ARID1A*	p.T300Nfs*100,c.898dup(8669,0.0077)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#86	*TP53*	p.V157I,c.469G>A(6965,0.4923)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#87	*CXCR4*	p.S338*,c.1013C>G(4238,0.2017)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#87	*HNF1A*	p.G292Rfs*25,c.872dup(5266,0.0199)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#88	*ATM*	p.L1541*,c.4622T>A(5429,0.0494)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#88	*CXCR4*	p.T318Nfs*26,c.952dup(7675,0.0179)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#88	*TERT*	NA,c.-124C>T(8534,0.0179)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#88	*TP53*	p.G266E,c.797G>A(8009,0.0397)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#89	*ARID1A*	p.E1647Dfs*5,c.4941_4947del(9126,0.0083)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#89	*ARID1A*	p.G945Pfs*64,c.2825_2831dup(8623,0.0111);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#89	*ARID1A*	p.Q1364Nfs*116,c.4090_4093del(8213,0.0622);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#89	*ARID1A*	p.Q372*,c.1114C>T(8569,0.0327);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#89	*ARID1A*	p.S558Pfs*62,c.1671_1678del(8861,0.0037);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#89	*ARID1A*	p.Y1233*,c.3699del(8268,0.0083);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#89	*CXCR4*	p.S338*,c.1013C>A(7694,0.3765)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#89	*TERT*	NA,c.-124C>T(9758,0.0399)	patients with *MYD88*^{MUT} treated with zanubrutinib

pts#89	*TP53*	p.C275R,c.823T>C(8892,0.3065)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#90	*CHEK2*	p.T367Mfs*15,c.1100del(8442,0.4831)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#90	*CXCR4*	p.H337Tfs*7,c.1007dup(8496,0.312)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#90	*MYCN*	Amplification(2.61)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#90	*PIK3CA*	Amplification(2.66)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#91	*ATM*	p.I2223Sfs*12,c.6666del(6699,0.0043)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#92	*ARID1A*	p.Y1555*,c.4664dup(6404,0.0787)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#92	*CXCR4*	p.V340Cfs*4,c.1017dup(7233,0.0896)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#92	*IDH2*	p.R140Q,c.419G>A(7737,0.133)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#92	*TP53*	p.M246K,c.737T>A(6316,0.0982)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#92	*TP53*	p.R273H,c.818G>A(6581,0.007);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#93	*ARID1A*	p.Q2128*,c.6382C>T(8549,0.1627)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#94	*TP53*	NA,c.375+1G>A(8337,0.0042)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#95	*TP53*	p.R110L,c.329G>T(8035,0.0031)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#95	*TP53*	p.T256P,c.766A>C(7112,0.0506);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#96	*CXCR4*	p.H337Pfs*31,c.1009_1010insCTCCA(6815,0.0172)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#97	*CXCR4*	p.S339Ffs*3,c.1014_1018del(8875,0.0325)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#98	*CXCR4*	p.S338*,c.1013C>A(6880,0.1709)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*ARID1A*	p.Q748*,c.2242C>T(8100,0.019)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*CXCR4*	p.R322Qfs*22,c.963dup(7375,0.0157)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*PIK3CA*	p.H1047R,c.3140A>G(7789,0.0015)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*TP53*	NA,c.673-2A>C(7750,0.0045);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*TP53*	NA,c.673-2A>T(7750,0.0053);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*TP53*	NA,c.783-2A>T(7824,0.0038);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*TP53*	p.C141S,c.422G>C(8146,0.0033)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*TP53*	p.R175H,c.524G>A(8616,0.0036);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#99	*TP53*	p.Y234C,c.701A>G(7531,0.0086);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#100	*KDM6A*	p.G557Vfs*34,c.1668_1674del(4738,0.0281)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#101	*TP53*	p.Y236C,c.707A>G(6904,0.0043)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#102	*RB1*	p.V654M,c.1960G>A(6179,0.0123)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#102	*TP53*	p.R280G,c.838A>G(8026,0.0082)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#103	*TP53*	p.C242S,c.725_726delinsCA(7116,0.1766);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#103	*TP53*	p.G266E,c.797G>A(6934,0.0055);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#103	*TP53*	p.H193R,c.578A>G(7707,0.0016)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#104	*CXCR4*	p.S338*,c.1013C>A(7322,0.0097)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#105	*TP53*	p.V173M,c.517G>A(7779,0.0094)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#105	*TSC1*	p.P196Lfs*14,c.587del(7587,0.0032)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#106	*TP53*	p.E285K,c.853G>A(10317,0.0018)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#107	*CXCR4*	p.S338*,c.1013C>G(5808,0.38)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#107	*RB1*	NA,c.1215+1G>A(3852,0.0047)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#107	*TP53*	NA,c.560-3T>G(8717,0.0037)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#107	*TP53*	p.P219S,c.655C>T(8303,0.0031);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#108	*CXCR4*	p.S338Ffs*6,c.1012dup(8602,0.0548)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#109	*ARID1A*	p.Q456Hfs*163,c.1368del(6225,0.0178)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#109	*CXCR4*	p.S338*,c.1013C>G(6804,0.0332)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#110	*BARD1*	p.N18Tfs*40,c.51del(9449,0.0047)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#110	*MSH6*	p.G54Wfs*36,c.158_159insA(12644,0.0102)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#111	*ARID1A*	p.P1296Lfs*5,c.3887del(8302,0.0037)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#111	*ARID1A*	p.Q537*,c.1609C>T(7997,0.0104);	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#111	*CXCR4*	p.T318Cfs*24,c.952_956del(7437,0.0176)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#111	*NRAS*	p.Q61K,c.181C>A(6878,0.0145)	patients with *MYD88*^{MUT} treated with zanubrutinib

pts#112	*CXCR4*	p.G335*,c.1003_1025del(6479,0.0145)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#113	*ARID1A*	p.R1335*,c.4003C>T(6537,0.0387)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#113	*CHEK2*	NA,c.684-1G>A(4017,0.007)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#113	*CXCR4*	p.S341Pfs*25,c.1021del(5827,0.0395)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#113	*STAG2*	p.K584Rfs*2,c.1751del(2764,0.0033)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#113	*TP53*	p.R273C,c.817C>T(6214,0.0459)	patients with *MYD88*^{MUT} treated with zanubrutinib
pts#114	*CCND3*	p.T283I,c.848C>T(6441,0.2469)	patients with *MYD88*^{WT}
pts#114	*CXCR4*	p.V320Efs*23,c.959_960del(7231,0.2466)	patients with *MYD88*^{WT}
pts#114	*PIK3CA*	Amplification(2.57)	patients with *MYD88*^{WT}
pts#115	*NRAS*	p.G12D,c.35G>A(6525,0.0032)	patients with *MYD88*^{WT}
pts#116	*ERBB3*	Amplification(2.89)	patients with *MYD88*^{WT}
pts#117	*KDM6A*	p.L1119Rfs*33,c.3355_3356insGAAG(3644,0.0129)	patients with *MYD88*^{WT}
pts#117	*TP53*	p.H214R,c.641A>G(10196,0.0036)	patients with *MYD88*^{WT}
pts#118	*CCND2*	Amplification(2.79)	patients with *MYD88*^{WT}
pts#118	*CDK4*	Amplification(3.09)	patients with *MYD88*^{WT}
pts#118	*ERBB3*	Amplification(2.91)	patients with *MYD88*^{WT}
pts#118	*KRAS*	Amplification(2.78)	patients with *MYD88*^{WT}
pts#118	*PIK3CA*	Amplification(2.91)	patients with *MYD88*^{WT}
pts#118	*PIK3CB*	Amplification(2.86)	patients with *MYD88*^{WT}
pts#118	*PTPN11*	Amplification(2.79)	patients with *MYD88*^{WT}
pts#118	*RAD52*	Amplification(2.78)	patients with *MYD88*^{WT}
pts#118	*RAF1*	Amplification(2.76)	patients with *MYD88*^{WT}
pts#118	*RB1*	p.L448Rfs*13,c.1343_1347del(10601,0.0395)	patients with *MYD88*^{WT}
pts#119	*TP53*	p.R175H,c.524G>A(10670,0.0035)	patients with *MYD88*^{WT}
pts#120	*ARID1A*	p.A162Cfs*240,c.477_483dup(10767,0.0081)	patients with *MYD88*^{WT}
pts#120	*TP53*	p.S241C,c.722C>G(9649,0.0652)	patients with *MYD88*^{WT}
pts#121	*ATM*	p.Q2297*,c.6889C>T(8721,0.0036);	patients with *MYD88*^{WT}
pts#121	*NBN*	NA,c.702+1G>C(8063,0.0098)	patients with *MYD88*^{WT}
pts#122	*TP53*	NA,c.782+1G>T(9310,0.0091)	patients with *MYD88*^{WT}
pts#123	*CDK4*	Amplification(2.69)	patients with *MYD88*^{WT}
pts#124	*BARD1*	p.A23Rfs*35,c.67del(8691,0.0037)	patients with *MYD88*^{WT}

Supplemental Table 2. Summary of numbers of patients with specific mutated genes in patients with *MYD88^{MUT}* or *MYD88^{WT}* treated by zanubrutinib or ibrutinib.

Gene	Patients with *MYD88^{MUT}* treated with ibrutinib (n=92)	Patients with *MYD88^{MUT}* treated with zanubrutinib (n=98)	Patients with *MYD88^{MUT}* (n=190)	Patients with *MYD88^{WT}* (n=20)
CXCR4	20	33	53	1
CXCR4 (NS)	13	14	27	0
CXCR4 (FS)	7	19	26	1
TP53	22	26	48	4
ARID1A	16	16	32	1
TERT	9	10	19	0
ATM	2	4	6	1
PIK3CA	2	3	5	2
CHEK2	4	3	7	0
KDM6A	4	2	6	1
KRAS	1	4	5	1
RB1	1	2	3	1
MSH6	1	3	4	0
NBN	1	2	3	1
RAD51B	1	2	3	0
STAG2	1	2	3	0
ATRX	3	0	3	0
CDKN2A	3	0	3	0
FANCL	0	2	2	0
MAPK3	0	2	2	0
MYC	1	1	2	0
NF1	1	1	2	0
NRAS	0	1	1	1
PTPN11	0	1	1	1
BARD1	0	1	1	1
CCNE1	2	0	2	0
CDK4	0	0	0	2
ERBB3	0	0	0	2
MLH1	0	1	1	0
BRAF	0	1	1	0
FGFR3	0	1	1	0
HNF1A	0	1	1	0
IDH2	0	1	1	0
KMT2D	0	1	1	0
MYCN	0	1	1	0
PAX5-JAK2 fusion	0	1	1	0

RAD50	0	1	1	0
TSC1	0	1	1	0
VHL	0	1	1	0
AKT2	1	0	1	0
CCND2	0	0	0	1
CCND3	0	0	0	1
EZH2	1	0	1	0
FGFR2	1	0	1	0
GNA11	1	0	1	0
MAP2K2	1	0	1	0
MAPK1	1	0	1	0
PDGFRA	1	0	1	0
PIK3CB	0	0	0	1
PTEN	1	0	1	0
RAD52	0	0	0	1
RAF1	0	0	0	1
SLC34A2	1	0	1	0
KIT	1	0	1	0

Supplemental Table 3. *TP53*, *TERT*, and *ARID1A* mutation rate by *CXCR4* or *MYD88* status. Mutation rate comparison of *TP53, TERT,* and *ARID1A* by *CXCR4* or *MYD88* status in 210 next-generation sequencing–evaluable WM patients. $TP53^{MUT}$, $ARID1A^{MUT}$, and $TERT^{MUT}$ were associated with a higher rate of $CXCR4^{MUT}$. $TP53^{MUT}$ rates were similar between patients with $MYD88^{MUT}$ and $MYD88^{WT}$, $TERT^{MUT}$, and $ARID1A^{MUT}$ were more often detected in patients with $MYD88^{MUT}$. *P* value was calculated by Fisher's exact test. *MYD88* status was assessed by PCR-based assay, and *CXCR4* status was evaluated by next-generation sequencing. FS, frameshift; MUT, mutated; NS, nonsense; WM, Waldenström macroglobulinemia; WT, wild-type.

Mutation rate, n (%)	***MYD88*^{WT} (n=20)**	***MYD88*^{MUT} (n=190)**	***P* value**	***CXCR4*^{WT} (n=156)**	***CXCR4*^{MUT} (n=54)**	***P* value**	***CXCR4*^{FS} (n=27)**	***P* value**	***CXCR4*^{NS} (n=27)**	***P* value**
TP53 status										
Wild-type	16 (80.0)	142 (74.7)		123 (78.8)	35 (64.8)		19 (70.3)		16 (59.3)	
Mutated	4 (20.0)	48 (25.3)	0.787	33 (21.2)	19 (35.2)	0.046	8 (29.6)	0.633	11 (40.7)	0.055
ARID1A status										
Wild-type	19 (95.0)	158 (83.2)		147 (94.2)	30 (55.6)		16 (59.3)		14 (51.9)	
Mutated	1 (5.0)	32 (16.8)	0.212	9 (5.8)	24 (44.4)	<0.001	11 (40.7)	<0.001	13 (48.2)	<0.001
TERT status										
Wild-type	20 (100.0)	171 (90.0)		150 (96.1)	41 (75.9)		23 (85.2)		18 (66.7)	
Mutated	0 (0.0)	19 (10.0)	0.227	6 (3.9)	13 (24.1)	<0.001	4 (14.8)	0.278	9 (33.3)	<0.001

Supplemental Table 4. Mutation rate of *CXCR4, TP53, TERT, ARID1A* by treatment arms in *MYD88^{MUT}* WM patients.

The mutation rate of *CXCR4, TP53, ARID1A,* and *TERT* was compared between zanubrutinib-treated and ibrutinib-treated *MYD88^{MUT}* WM patients. Zanubrutinib-treated *MYD88^{MUT}* had higher *CXCR4^{FS}* rate than ibrutinib-treated *MYD88^{MUT}*. Comparison analysis was conducted in 190 next-generation sequencing–evaluable *MYD88^{MUT}* WM patients. *P* value was calculated by Fisher's exact test. FS, frameshift; MUT, mutated; NS, nonsense; WM, Waldenström macroglobulinemia; WT, wild-type.

Mutation rate, n (%)	**Patients with *MYD88*^{MUT} treated with zanubrutinib (n=98)**	**Patients with *MYD88*^{MUT} treated with ibrutinib (n=92)**	***P* value**
CXCR4 status			
Wild-type	65 (66.3)	72 (78.3)	-
Mutated	33 (33.7)	20 (21.7)	0.076
FS	19 (19.4)	7 (7.6)	0.021
NS	14 (14.3)	13 (14.2)	1.000
TP53 status			
Wild-type	72 (73.5)	70 (76.1)	-
Mutated	26 (26.5)	22 (23.9)	0.740
ARID1A status			
Wild-type	82 (83.7)	76 (82.6)	-
Mutated	16 (16.3)	16 (17.4)	0.849
TERT status			
Wild-type	88 (89.8)	83 (90.2)	-
Mutated	10 (10.2)	9 (9.8)	1.000

Supplemental Table 5. *TP53* alterations by *CXCR4* status and by treatment arms in patients with *MYD88^{MUT}* WM.

MYD88^{MUT} WM patients treated with ibrutinib or zanubrutinib were separately classified into four subgroups based on *TP53* VAF and deletion status, including: *TP53* mutation/deletion not detected (*TP53^{WT}*), *TP53^{MUT}* with VAF between 0.25% and <1% (*TP53$^{VAF<1\%}$*), *TP53^{MUT}* with 1%≤ VAF <10% (*TP53$^{1\%\leq VAF<10\%}$*), *TP53^{MUT}* with VAF ≥10% or deletion (*TP53$^{VAF\geq 10\% \text{ or deletion}}$*). For patients with multiple *TP53* mutations, the maximum VAF was used for classification. Correlation analysis of TP53 alteration and CXCR4 status show that *TP53* mutations with VAF ≥1% or deletion is associated with higher rate of *CXCR4^{NS}*. More patients with TP53 VAF ≥1% or deletion were randomized in the zanubrutinib arm compared to ibrutinib arm. Difference was compared between patients with *TP53* VAF ≥1% or deletion and *TP53* VAF <1% or wildtype, the *P* value was calculated by Fisher's exact test. FS, frameshift; MUT, mutated; NS, nonsense; VAF, variant allele frequency; WM, Waldenström macroglobulinemia; WT, wild-type.

Subgroups	***TP53^{WT}*** **(N=142)**	***TP53$^{VAF<1\%}$*** **(N=22)**	***TP53$^{1\%\leq VAF<10\%}$*** **(N=16)**	***TP53$^{VAF\geq 10\% \text{ or deletion}}$*** **(N=10)**	**P-value**
CXCR4 mutational status					
CXCR4^{WT} (n=137)	108 (76.1)	18 (81.8)	7 (43.8)	4 (40.0)	-
CXCR4^{MUT} (n=53)	34 (23.9)	4 (18.2)	9 (56.3)	6 (60.0)	<0.001
CXCR4^{FS} (n=26)	18 (12.7)	1 (4.6)	5 (31.3)	2 (20.0)	0.059
CXCR4^{NS} (n=27)	16 (11.3)	3 (13.6)	4 (25.0)	4 (40.0)	0.016
Treatment arm					
patients with *MYD88^{MUT}* treated with ibrutinib (n=92)	70 (49.3)	13 (59.1)	6 (37.5)	3 (30.0)	-
patients with *MYD88^{MUT}* treated with zanubrutinib (n=98)	72 (50.7)	9 (40.9)	10 (62.5)	7 (70.0)	0.144

Supplemental Table 6. Response assessment by *TP53* alterations status and by treatment in patients with *MYD88^{MUT}* WM.

Response rate (VGPR+CR or major response), time to response, and PFS were compared within four subgroups based on TP53 VAF and deletion status including *TP53^{WT}*, *TP53$^{VAF<1\%}$*, *TP53$^{1\%\leq VAF<10\%}$*, *TP53$^{VAF\geq 10\% \text{ or deletion}}$*. CR, complete response; MUT, mutated; NE, not estimable; PFS, progression-free survival; VAF, variant allele frequency; VGPR, very good partial response; WM, Waldenström macroglobulinemia; WT, wildtype.

Patients with *MYD88^{MUT}* treated with ibrutinib (n=92)				
	TP53^{WT} **(N=70)**	***TP53$^{VAF<1\%}$*** **(N=13)**	***TP53$^{1\%\leq VAF<10\%}$*** **(N=6)**	***TP53$^{VAF\geq 10\% \text{ or deletion}}$*** **(N=3)**
VGPR or better, n (%)	21 (30.0)	3 (23.1)	0 (0.0)	0 (0.0)
Major response, n (%)	60 (85.7)	9 (69.2)	4 (66.7)	1 (33.3)
Time to VGPR or better, median (min, max), months	11.4 (2.0, 49.9)	24.9 (5.6, 46.9)	NE	NE
Time to major response, median (min, max), months	2.9 (0.9, 49.8)	3.0 (1.0, 8.5)	4.8 (1.0, 13.8)	1.9 (1.9, 1.9)
PFS Event-free rate at 42 months, % Median, months	 72.2 NE	 72.7 NE	 41.7 21.7	 33.3 38.6
Patients with *MYD88^{MUT}* treated with zanubrutinib (n=98)				
	TP53^{WT} **(n=72)**	***TP53$^{VAF<1\%}$*** **(n=9)**	***TP53$^{1\%\leq VAF<10\%}$*** **(n=10)**	***TP53$^{VAF\geq 10\% \text{ or deletion}}$*** **(n=7)**
VGPR or better, n (%)	27 (37.5)	3 (33.3)	3 (30.0)	3 (42.9)
Major response, n (%)	59 (81.9)	7 (77.8)	8 (80.0)	6 (85.7)
Time to VGPR or better, median (min, max), months	6.5 (1.9, 42.0)	4.7 (3.0, 25.7)	11.1 (11.1, 26.0)	6.7 (4.7, 22.1)
Time to major response, median (min, max), months	2.8 (0.9, 49.8)	2.9 (1.8, 4.6)	2.8 (1.0, 5.6)	2.8 (1.0, 3.7)

PFS Event-free rate at 42 months, % Median, months	84.6 NE	75 NE	53.3 NE	57.1 NE
All patients with *MYD88^{MUT}* (n=190)				
	TP53^{WT} **(n=142)**	***TP53$^{VAF<1\%}$*** **(n=22)**	***TP53$^{1\%\leq VAF<10\%}$*** **(n=16)**	***TP53$^{VAF\geq 10\%}$ or deletion*** **(n=10)**
VGPR or better, n (%)	48 (33.8)	6 (27.3)	3 (18.8)	3 (30.0)
Major response, n (%)	119 (83.8)	16 (72.7)	12 (75.0)	7 (70.0)
Time to VGPR or better, median (min, max), months	9.3 (1.9, 49.9)	15.2 (3.0, 46.9)	11.1 (11.1, 26.0)	6.7 (4.7, 22.1)
Time to major response, median (min, max), months	2.9 (0.9, 49.8)	2.9 (1.0, 8.5)	2.9 (1.0, 13.8)	2.8 (1.0, 3.7)
PFS Event-free rate at 42 months, % Median, months	78.4 NE	74.1 NE	49.2 33.2	48 38.6

Supplementary Table 7. Co-occurrences of *CXCR4* and *TP53* mutations in patients with *TERT*^{MUT}.

A total of 19 patients with *MYD88*^{MUT} detected *TERT*^{MUT}, including nine treated with ibrutinib and 10 treated with zanubrutinib. Patients with *TERT*^{MUT}, especially those with PFS events, had high rates of *CXCR4* or *TP53* co-mutations in both ibrutinib-treated and zanubrutinib-treated groups. Zanubrutinib treatment group had more patients with co-mutations of *TERT*, *CXCR4*, *TP53* than ibrutinib treatment group (60% vs 22.2%). MUT, mutated; PFS, progression-free survival; WT, wildtype.

Patients with *TERT*^{MUT} treated with ibrutinib (n=9)			
Co-mutation with	**Total (N=9)**	**With PFS events (n=3)**	**Without PFS events (n=6)**
***CXCR4*^{MUT}, n (%)**	**5 (55.6)**	**2 (66.7)**	**3 (50.0)**
***TP53*^{MUT}, n (%)**	**3 (33.3)**	**3 (100.0)**	**0 (0.0)**
Both *CXCR4*^{MUT} and *TP53*^{MUT}, n (%)	**2 (22.2)**	**2 (66.7)**	**0 (0.0)**
Patients with *TERT*^{MUT} treated with zanubrutinib (n=10)			
Co-mutation with	**Total (N=10)**	**With PFS events (n=6)**	**Without PFS events (n=4)**
***CXCR4*^{MUT}, n (%)**	**8 (80.0)**	**5 (83.3)**	**3 (75.0)**
***TP53*^{MUT}, n (%)**	**6 (60.0)**	**5 (83.3)**	**1 (25.0)**
Both *CXCR4*^{MUT} and *TP53*^{MUT}, n (%)	**6 (60.0)**	**5 (83.3)**	**1 (25.0)**

Supplemental Table 8. Genetic variants and paired analysis of five WM patients at the time of progressive disease.

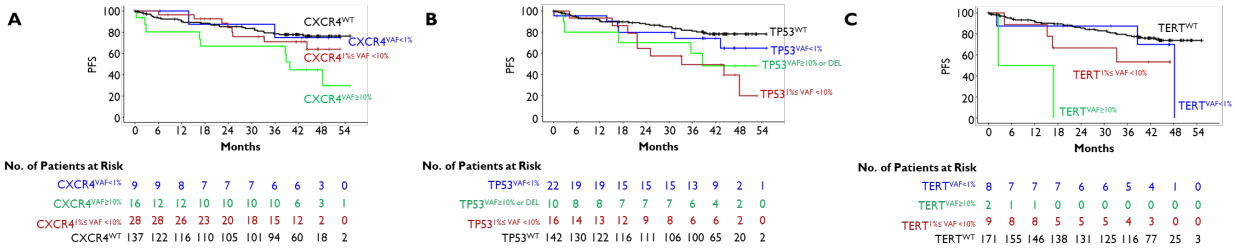
PD samples and baseline samples from five patients who progressed after achieving a response on zanubrutinib (three *MYD88*^{MUT}, two *MYD88*^{WT}) were tested by NGS panels covering 106 genes and 152 genes, respectively. Variants not covered by NGS panel were marked as unknown. Baseline data were not available for patient #1 and genetic variants were marked as unknown. Patient #3 had VGPR when collecting post-treatment samples, but disease progression occurred 14 months after sampling. BOR, best overall response; MR, minor response; MUT, mutated; NGS, next-generation sequencing; PD, progressive disease; PR, partial response; RR, relapsed/refractory; TN, treatment naïve; VAF, variant allele frequency; VGPR, very good partial response.

Patient ID	TN/RR status	Treatment (*MYD88* status)	BOR	On-treatment duration, months	Gene	At PD		At Screening	
						Mutation	VAF (%)	Mutation	VAF (%)
PD #1	RR	Zanubrutinib (*MYD88*^{MUT})	PR	34.5	*BTK*	C481S	8.16	Unknown	
					TP53	R248G	19.76	Unknown	
					TP53	Deletion		Unknown	
					MYC	Amplification		Unknown	
					NOTCH1	Amplification		Unknown	
					BIRC3	R549Afs*10	22.31	Unknown	
PD #2	RR	Zanubrutinib (*MYD88*^{MUT})	PR	33.4	*CXCR4*	T318Nfs*26	4.13	T318Nfs*26	1.78
					TP53	G266E	7.68	G266E	3.97
					TERT	-124C>T	3.85	-124C>T	1.79
					ATM	L1541*	3.32	L1541*	4.93
					EP300	M2106Cfs*28	1.57	Unknown	

PD #3	**RR**	**Zanubrutinib (*MYD88^{MUT}*)**	**VGPR**	**21.2**	***CXCR4***	**S338***	**4.62**	**S341Hfs*2**	**0.35**
					TP53	**R248Q**	**0.58**	**Not detected**	
						D281Y	**0.24**	**Not detected**	
					TERT	**-57A>C**	**5.18**	**Not detected**	
					ARID1A	**P225Afs*175**	**3.09**	**Not detected**	
						P977Qfs*5	**5.28**	**Not detected**	
					KDM6A	**Unknown**		**S1274Pfs*18**	**0.38**
PD #4	**TN**	**Zanubrutinib (*MYD88^{WT}*)**	**PR**	**10.2**	***TP53***	**H214R**	**0.21**	**H214R**	**0.36**
					KDM6A	**Unknown**		**L1119Rfs*33**	**1.28**
PD #5	**RR**	**Zanubrutinib (*MYD88^{WT}*)**	**VGPR**	**27.9**	***CXCR4***	**V320Efs*23**	**1.14**	**V320Efs*23**	**24.65**
					CCND3	**T283I**	**1.37**	**T283I**	**24.68**
					CDKN2A	**Deletion**		**Not detected**	
					PIK3CA	**Unknown**		**Amplification**	

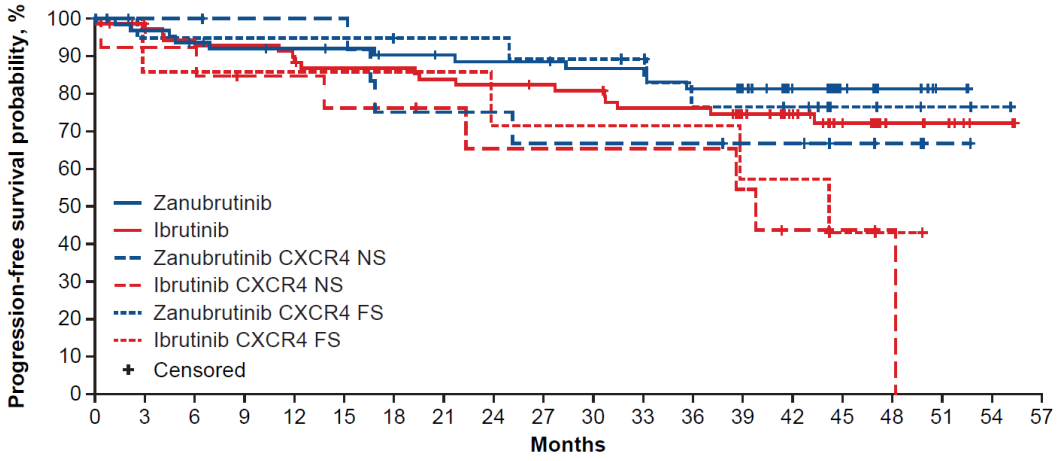
Supplemental Figure 1. PFS by *CXCR4*, *TP53*, *TERT* VAF status in patients with *MYD88*^{MUT} WM.

Pooled analysis of patients with *MYD88*^{MUT} including 98 treated with zanubrutinib and 92 treated with ibrutinib. PFS was plotted based on the VAF status of *CXCR4* (A), *TP53* (B), and *TERT* (C). Worse PFS was seen in patients harboring these mutations with VAF≥1%. DEL, deletion; MUT, mutated; PFS, progression-free survival; VAF, variant allele frequency; WM, Waldenström macroglobulinemia; WT, wild-type.



Supplemental Figure 2. PFS by *CXCR4* mutational status and by treatment in patients with *MYD88*^{MUT} WM.

PFS comparison by *CXCR4* mutational status (WT, NS, FS) in patients treated by zanubrutinib or ibrutinib. A Cox regression model with treatment group, *TERT* (WT, MUT), and *TP53* (WT, MUT) mutational status as covariates was used to compare PFS between zanubrutinib and ibrutinib in patients with *CXCR4*^{NS}, *CXCR4*^{FS}, and *CXCR4*^{WT}. FS, frameshift; HR, hazard ratio; MUT, mutated; NS, nonsense; PFS, progression-free survival; WM, Waldenström macroglobulinemia; WT, wild-type.



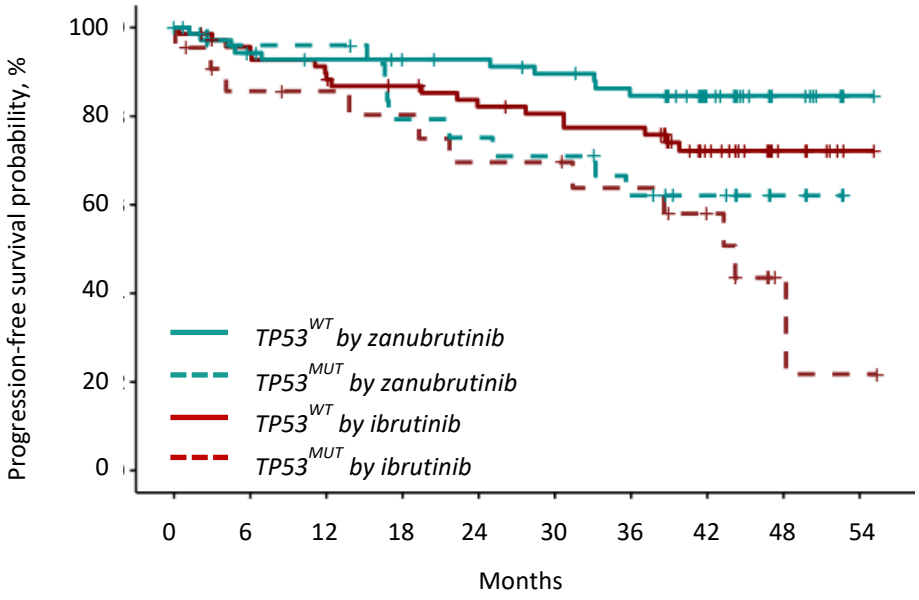
No. of Patients at Risk																			
Zanubrutinib	65	61	58	56	55	54	52	51	50	50	48	48	45	38	26	15	9	5	0
Ibrutinib	72	68	64	63	61	58	58	56	55	54	53	49	49	40	34	23	9	6	2	0
Zanubrutinib CXCR4 NS	14	13	13	12	12	12	9	9	9	8	8	8	8	7	7	5	3	1	0
Ibrutinib CXCR4 NS	13	12	12	10	10	9	8	7	6	6	6	6	6	5	3	2	1	0	
Zanubrutinib CXCR4 FS	19	18	18	18	18	18	17	17	17	16	16	15	12	12	10	5	3	2	1	0
Ibrutinib CXCR4 FS	7	6	6	6	6	6	6	6	5	5	5	5	5	4	4	2	1	0		

	Zanubrutinib vs Ibrutinib in different subgroups		
	CXCR4^{NS}	CXCR4^{FS}	CXCR4^{WT}
HR (95%CI)	0.30 (0.07, 1.22)	0.21 (0.04, 1.16)	0.68 (0.32, 1.45)
P-value	0.093	0.074	0.322

Supplemental Figure 3. PFS by *TP53* alteration and by treatment in patients with *MYD88*^{MUT} WM.

MYD88^{MUT} WM patients treated with ibrutinib or zanubrutinib were separately classified into different subgroups based on *TP53* VAF and deletion status. The PFS Kaplan-Meier curves were compared A) between patients with *TP53*^{WT} and patients with *TP53*^{MUT}, B) between patients with *TP53*^{WT}, *TP53*$^{VAF<1\%}$, and *TP53*$^{VAF \geq 1\% \text{ or deletion}}$, and C) in patients with *TP53*$^{\text{WT or VAF<1\%}}$ and *TP53*$^{\text{VAF}\geq 1\% \text{ or deletion}}$. Patients with *TP53*$^{\text{VAF}\geq 1\% \text{ or deletion}}$ had worse PFS compared to patients with *TP53*$^{\text{WT or VAF<1\%}}$ independent of treatment. Zanubrutinib showed more favorable PFS than ibrutinib regardless of *TP53* alteration status. HR[1] and *P*-values[1] were estimated using a Cox regression model with *CXCR4* (WT, MUT), *TP53* (WT or VAF <1% vs VAF ≥1% or deletion), and *TERT* (WT, MUT) mutational status as covariates. In addition, a Cox regression model with treatment group, *CXCR4* (WT, MUT), and *TERT* (WT, MUT) mutational status as covariates was used to compare PFS between zanubrutinib and ibrutinib in patients with *TP53*$^{\text{WT or VAF<1\%}}$ and *TP53*$^{\text{VAF}\geq 1\% \text{ or deletion}}$. The HR[2] and *P*-value[2] are shown. MUT, mutated; VAF, variant allele frequency; WM, Waldenström macroglobulinemia; WT, wild-type.

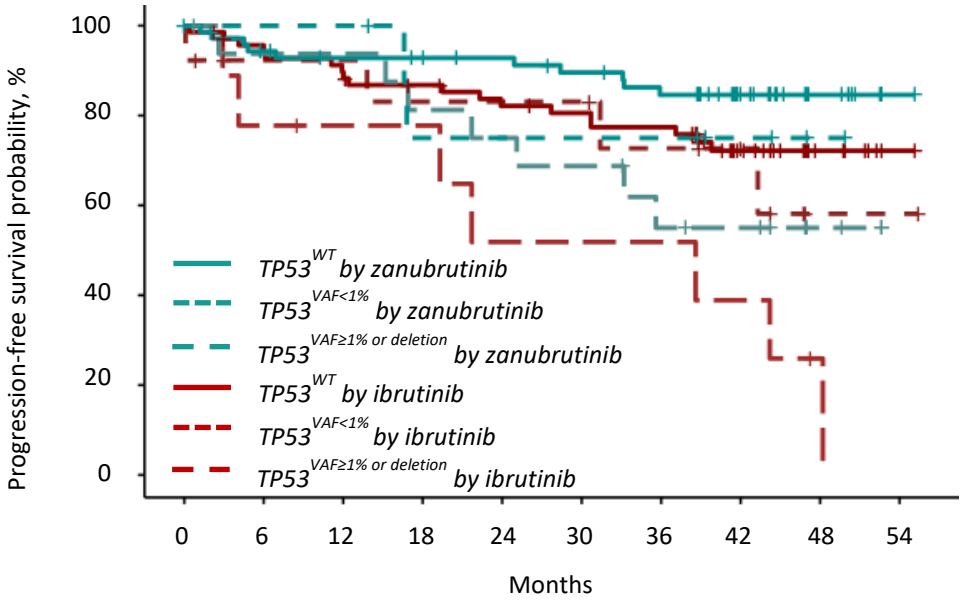
A)



No. of Patients at Risk

TP53^{WT} *by zanubrutinib*	72	65	61	60	58	55	51	34	11	1
TP53^{MUT} *by zanubrutinib*	26	24	24	19	18	17	14	10	4	0
TP53^{WT} *by ibrutinib*	70	65	61	57	53	51	49	32	9	1
TP53^{MUT} *by ibrutinib*	22	17	16	15	13	13	11	9	2	1

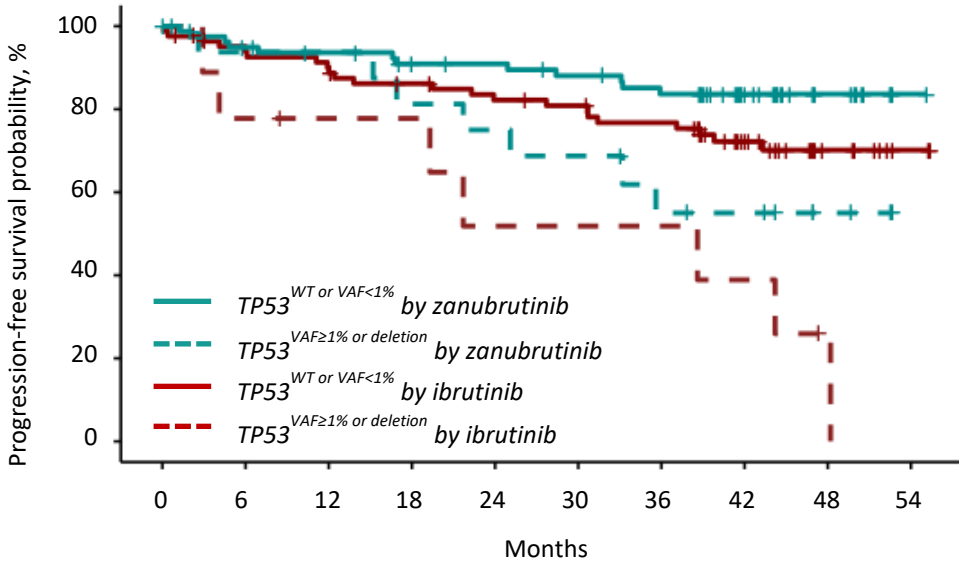
B)



No. of Patients at Risk

TP53^{WT} *by zanubrutinib*	72	65	61	60	58	55	51	34	11	1
TP53$^{VAF<1\%}$ *by zanubrutinib*	9	9	9	6	6	6	6	3	1	0
TP53$^{VAF\geq1\% \text{ or deletion}}$ *by zanubrutinib*	17	15	15	13	12	11	8	7	3	0
TP53^{WT} *by ibrutinib*	70	65	61	57	53	51	49	32	9	1
TP53$^{VAF<1\%}$ *by ibrutinib*	13	10	10	9	9	9	7	6	1	1
TP53$^{VAF\geq1\% \text{ or deletion}}$ *by ibrutinib*	9	7	6	6	4	4	4	3	1	0

C)



No. of Patients at Risk

TP53$^{WT\ or\ VAF<1\%}$ *by zanubrutinib*	81	74	70	66	64	61	57	37	12	1
TP53$^{VAF\geq1\%\ or\ deletion}$ *by zanubrutinib*	17	15	15	13	12	11	8	7	3	0
TP53$^{WT\ or\ VAF<1\%}$ *by ibrutinib*	83	75	71	66	62	60	56	38	10	2
TP53$^{VAF\geq1\%\ or\ deletion}$ *by ibrutinib*	9	7	6	6	4	4	4	3	1	0

	TP53$^{VAF\geq1\%\ or\ deletion}$ vs *TP53*$^{WT\ or\ VAF<1\%}$ in different treatment arms			Zanubrutinib vs ibrutinib in different subgroups	
	Patients with *MYD88*^{MUT} treated with ibrutinib (n=92)	Patients with *MYD88*^{MUT} treated with zanubrutinib (n=98)		*TP53*$^{WT\ or\ VAF<1\%}$ (n=164)	*TP53*$^{VAF\geq1\%\ or\ deletion}$ (n=26)
HR (95% CI)[1]	3.792 (1.422, 10.114)	2.239 (0.767, 6.534)	HR (95% CI)[2]	0.515 (0.251, 1.056)	0.491 (0.158, 1.529)
P-value[1]	0.008	0.140	*P*-value[2]	0.070	0.220

Supplemental Figure 4. PFS by *TP53* mutation status in patients with *MYD88*^{WT} WM treated by zanubrutinib.

Patients with *MYD88*^{WT} and *TP53*^{MUT} have less favorable PFS than *TP53*^{WT} patients. HR, hazard ratio; MUT, mutated; PFS, progression-free survival; WM, Waldenström macroglobulinemia; WT, wild-type.