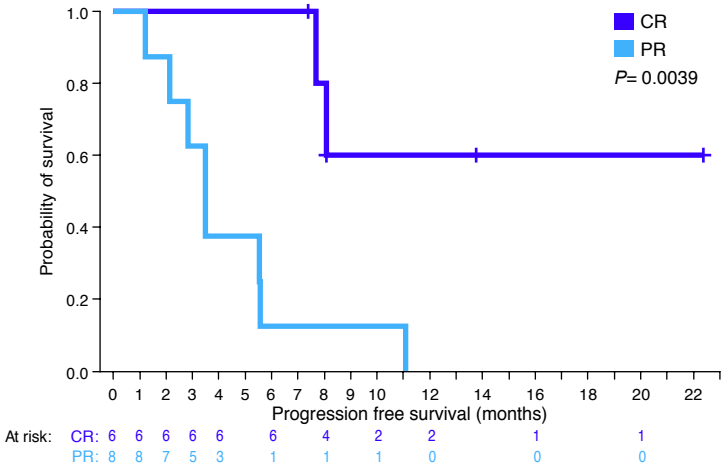
Supplementary Table

Supplementary Table 1. Treatment-emergent adverse events that occurred in ≥10% of subjects (N=80)

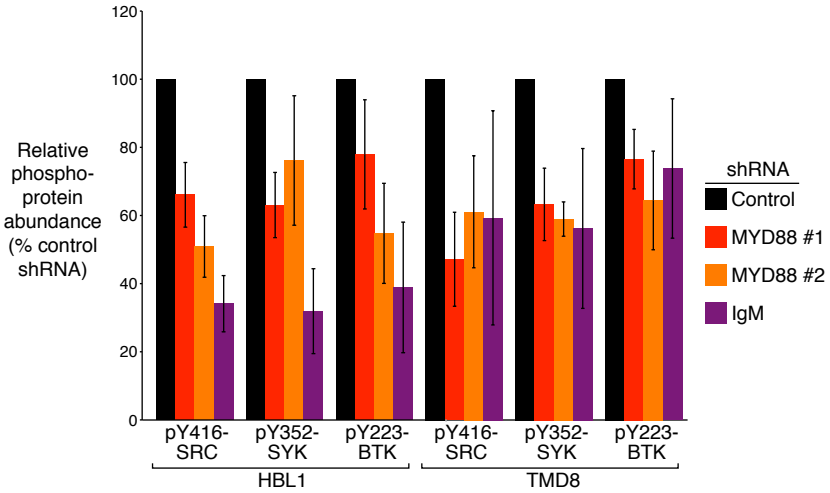
Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Overall
Nonhematological						
Fatigue	16 (20)	10 (13)	6 (8)	0	0	32 (40)
Diarrhea	25 (31)	3 (4)	2 (3)	0	0	30 (38)
Nausea	17 (21)	5 (6)	2 (3)	0	0	24 (30)
Cough	10 (13)	5 (6)	0	0	0	15 (19)
Pyrexia	10 (13)	2 (3)	2 (3)	0	0	14 (18)
Hypomagnesemia	8 (10)	4 (5)	1 (1)	0	0	13 (16)
Constipation	9 (11)	3 (4)	0	0	0	12 (15)
Edema peripheral	7 (9)	3 (4)	1 (1)	0	0	11 (14)
Dyspepsia	8 (10)	2 (3)	0	0	0	10 (13)
Myalgia	7 (9)	3 (4)	0	0	0	10 (13)
Vomiting	6 (8)	2 (3)	2 (3)	0	0	10 (13)
Arthralgia	8 (10)	1 (1)	0	0	0	9 (11)
Dyspnea	5 (6)	3 (4)	1 (1)	0	0	9 (11)
Hyperglycemia	7 (9)	0	2 (3)	0	0	9 (11)
Hypoalbuminemia	4 (5)	4 (5)	1 (1)	0	0	9 (11)
Hyponatremia	3 (4)	0	5 (6)	1 (1)	0	9 (11)
Abdominal pain	2 (3)	6 (8)	1 (1)	0	0	9 (11)
Decreased appetite	5 (6)	2 (3)	1 (1)	0	0	8 (10)
Dizziness	8 (10)	0	0	0	0	8 (10)
Hematological						
Anemia	8 (10)	7 (9)	4 (5)	0	0	19 (24)
Thrombocytopenia	7 (9)	3 (4)	4 (5)	1 (1)	0	15 (19)
Platelet count decreased	5 (6)	2 (3)	1 (1)	1 (1)	0	9 (11)

All data presented as n (%). Adverse events listed per Medical Dictionary for Regulatory Activities preferred term.

Supplementary Figures



Supplementary Fig. 1. Progression-free survival in subjects with ABC DLBCL who had a CR or PR induced by ibrutinib, as indicated.



Supplementary Fig. 2. Knockdown of MYD88 decreases proximal BCR signaling. Shown are relative levels of the indicated phosphorylated species of Src-family kinases, SYK, and BTK as quantified by immunoblotting of extracts of the indicated ABC DLBCL lines following induction of the indicated sgRNAs. Levels were quantified by densitometric analysis of immunoblots. Data are means ± S.E.M from independent experiments performed using HBL1 (n=7) and TMD8 (n=10) cells.

SUPPLEMENTAL NOTES

Supplementary Note 1

Guidelines for Dose Modifications. For any unmanageable toxicity ≥Grade 3, study drug was withheld for ≤28 consecutive days, or discontinued if the event lasted for ≥28 days. After the first occurrence of Grade 4 ANC (<500/μL), ≥Grade 3 platelets (<50,000/μL) or, in the presence of baseline thrombocytopenia, either a drop in platelets of 50% to 75% from baseline in the presence of Grade ≥2 bleeding or a decrease of >75% from baseline or <20,000/μL, whichever is higher, Grade ≥3 persistent nausea, vomiting, or diarrhea despite use of antiemetic or antidiarrheal therapy, or any other Grade 4 toxicity or unmanageable nonhematologic Grade 3 toxicity ibrutinib treatment was halted until recovery to grade ≤1 or baseline, and then treatment with ibrutinib 560 mg resumed. If a second or third occurrence of the above mentioned events, treatment with study drug was halted until recovery to grade ≤1 or baseline, then treatment resumed with a reduced dose: 420 mg after second occurrence and 280 mg after the third occurrence. After the fourth occurrence, treatment was discontinued.

Supplementary Note 2

Molecular Analysis. Gene expression profiling of formalin-fixed, paraffin-embedded DLBCL biopsies was performed using U133plus2.0 arrays (Affymetrix, Santa Clara, CA) and a Sensation kit (Genisphere, Hatfield, PA). Assignment of tumors as ABC, GCB or unclassified DLBCL utilized a 200-gene linear predictor model based on a previously described algorithm,[1] adjusted to include only those Affymetrix probes that produced well correlated values between frozen and FFPE biopsies from the same patient in a

training set of 21 DLBCL cases. Linear predictor model scores of paired FFPE and frozen samples were highly correlated (r = 0.96). DLBCL subtype assignment was performed in a blinded fashion prior to analysis of clinical trial outcome data.

CD79B, *CD79A*, *CARD11*, and *MYD88* mutations were detected by Sanger sequencing of PCR-amplified exons from genomic DNA. Next-generation DNA sequencing of these genes and *TNFAIP3* was performed by Foundation Medicine, Cambridge, MA.

Supplementary Note 3

Cell lines. Cell lines were engineered to express an ecotropic retroviral receptor and Tet repressor, and were retrovirally transduced as described.[2] Cell lines were obtained from: Martin Dyer (University of Leicester, Leicester, United Kingdom; HBL1[3]), Hans Messner (University of Toronto, Toronto, Canada; OCI-Ly10 [LY10][4]), Shuji Tohda (Tokyo Medical and Dental University, Tokyo, Japan; TMD8[5]), Momoko Nishikori (Kyoto University, Kyoto, Japan; DLBCL2[6]), DMSZ (U2932, BJAB; http://www.dsmz.de). All cell line identities were confirmed by SNP fingerprinting and were confirmed to be negative for mycoplasma using the MycoAlert detection kit (Lonza). shRNA targeting sequences: MYD88#1:GGCATATGCCTGAGCGTTTCG; MYD88#2:GGTGGTTGTCTCTGATGATTA; IgM:ACCAGAGAGAGGAACTCAAAG; Control:CTCTCAACCCTTTAAATCTGA. Wild type CD79A and a CD79A deletion mutant (Fig. 2c) were inserted into the BamHI site of pBMN-LYT2 using G-blocks (IDT) and Gibson cloning (NEB).

Supplementary Note 4

Immunoblot analysis. ABC DLBCL lines were treated with the MYD88 dimerization inhibitor IMG2005 (100 μM; Imgenex) for 16hr, or were induced for shRNA expression with doxycycline for 48hr. Lysates (10^6 cells) were boiled in Laemmli sample buffer, electrophoresed through a 10% Tris-glycine polyacrylamide gel, and transferred to a PVDF membrane. Immunoblotting antibodies included: anti-phosphotyrosine clone 4G10 (Millipore), rabbit anti-pY416-Src family kinases, anti-pY352-Syk, anti-pY223-Btk (Cell Signaling Technologies), anti-β-actin-HRP and anti-IgM-HRP (Santa Cruz Biotechnologies). Semi-quantitative analysis of band intensity on western blots was performed using Image J software.

Supplementary Note 5

Fluorescence-activated cell sorting analysis. Cell lines were co-transduced with a doxycycline-inducible shRNA vector targeting the endogenous *CD79A* 3' UTR and a vector expressing WT or mutant CD79A coding regions along with the Lyt2 surface marker, as described.[7] Following doxycycline-inducible knockdown of endogenous CD79A, cells were stained on ice with anti-human IgM-PE (BD) and the Lyt2 marker with anti-Lyt2-Alexa647 (Biolegend). Surface IgM expression was measured in transduced subpopulations gated by FACS have equivalent Lyt2 expression.

Supplementary References

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7. Davis, R.E. *et al.* Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature* **463**, 88-92 (2010).