nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The DepMap portal (https://depmap.org/portal/) in open source was used to collect dependency score of myeloma cell lines for PIM1, PIM2, PIM3 MCL1, BCL2 and BCLXL gene.
Data analysis	Prism GraphPad software 10.2.2), was used for figure production and data/statistical analysis. CytExpert software (2.4) was used for cytometric data and flowJo software (10.4.0) was used for cytometric data analysis. GeneSys (1.6.1) was used for immunoblotting imaging. NDPview Plus was used for histo-immunofluorescence staining analysis. QuPath (0.5.0-x64) was used for histological image analysis and quantification. ImageJ (2.14.0/1.54f) was used for immunofluorescence staining analysis. Bioinformatic analysis were performed using iDEP 2.01 software (http://bioinformatics.sdstate.edu/idep/)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The RNA data that support the finfings of this study have been submitted to the GEO repository and are assigned with the access number GSE266112.
The authors declare that all other data supporting the findings of this study are available within the paper in the Source Data File.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Our results are not related to or did not take into account sex and/or gender. This information was not collected and available for the primary B cells used in our culture model of cell differentiation.
Reporting on race, ethnicity, or other socially relevant groupings	Our results are not related to or did not take into account socially constructed or socially relevant categorization variables in our manuscript. This information was not collected and available for the primary B cells used in our culture model of cell differentiation.
Population characteristics	Not applicable
Recruitment	Not applicable
Ethics oversight	Peripheral blood samples for B cell isolation were obtained from healthy blood donors. The collection was performed according to ethical guidelines and with the approval from of the relevant authorities, such as the French Ministry of Higher Education and Research.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No samples-size calculation was performed.
Data exclusions	No data were excluded from analysis.
Replication	When possible, experiments were run at least in triplicate to confirm reproducibility. For flow cytometry experiments, All in vitro cell line and primary B cells drug treatments were performed at least in triplicate to confirm reproducibility. In vitro drug sensitivity cell line experiments were completed at least in triplicate except for BCLXLi treatment, in duplicate, and replicate results were highly similar. In vitro drug sensitivity in primary B cells experiments were performed once due to limited sample avaibility. Western blots of cell lines and of primary B cells were replicated twice. Immunoprecipitation were replicated once, but performed in two differents cell lines and sometimes also in primary cells. To optimise the xenograft model and to test inhibitor doses, xenograft experiments were performed with only three mice in each treatment group. Xenograft experiments to assess the synergy between the 2 inhibitors were performed with at least n=5 mice in each treatment group. Premature deaths with no obvious cause have sometimes hampered the size of the groups.
Randomization	In the xenograft experiments, mice were randomly assigned to each treatment group using the Ig level of each mouse to ensure homogeneous groups (mean Ig levels of mice in each group identical between groups) in terms of tumour uptake.
Blinding	Not applicable

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Primary antibodies used for Immunoblotting and Immunoprecipitation:
All primary antibodies were used at 1/1000e except the β actin used at 1/2000e.
β actin (AC-15) Sigma-Aldrich A1978
BAD (D24A9) Cell Signaling #9239
BAD Cell Signaling 9292
phospho-BAD (Ser112) (40A9) Cell Signaling #5284
Caspase 3 Cell Signaling #9662
PIM2 (D1D2) Cell Signaling #4730
PIM3 (D17C9) Cell signaling #4165
PIM1 (D8D7Y) Cell Signaling #54523
phospho-eIF2a (Ser51) (D9G8) Cell Signaling #3398
eIF2a (D7D3) Cell Signaling #5324
ATF4 (W16016A) Biolegend #693902
CHOP Cell Signaling #2895
NOXA (D8L7U) Cell Signaling #14766
BCLXL Cell Signaling #2762`
BCLXL (2H12) BD Bioscience #551022
MCL1 (D5V5L) Cell Signaling #39224
BCL2 (4D7) BD Biosciences #551098
BAX Cell Signaling #2772
BAK (D4E4) Cell Signaling #12105
BAX (6A7) Biolegend #633802
BIM (C34C5) Cell Signaling #2933
Isotype Rabbit IgG (DA1E) Cell Signaling #3900 (for immunoprecipitation only)

Secondary antibodies used for immunoblotting:
Clean blot Thermo Fisher 21230
HRP-Donkey anti-Rat IgG (Poly4054) BioLegend 405405
HRP-Donkey anti-Rabbit IgG (Poly4064) BioLegend 406401
HRP-Donkey anti-Mouse IgG (Poly4053) BioLegend 405306
Ubiquitine-HRP antibody (P4D1) Cytoskeleton AUB01
All secondary antibodies were used at 1/5000e except for the Clean blot reagent used at 1/500e.

Antibodies used for immunohisto-fluorescence:
All primary antibodies were used at 1/200e. All secondary antibodies were used at 1/500e.
CD138 (B-A38) R&D Systems NB100-64980
Cytochrome c (6H2.B4) BD Biosciences 556432
BAX R&D Systems NBP2 67285
BAX (6A7) Biolegend 633802
Alexa Fluor 594 Donkey anti-Rabbit Jackson ImmunoResearch Laboratories, 711-586-152
Alexa Fluor 594 Donkey anti-Mouse Jackson ImmunoResearch Laboratories, 715-586-152
Alexa Fluor 488 Donkey anti-Rabbit Jackson ImmunoResearch Laboratories, 711-546-152
Alexa Fluor 488 Donkey anti-Mouse Jackson ImmunoResearch Laboratories, 715-546-152
MitoTraker Deep red FM, Thermo Fisher Scientific, M46753

Antibodies used for flow cytometry and cell sorting:
CD38-APC BD Biosciences 555462
CD23-PE.Cy7 BD Biosciences 561167
CD44-APC BD Biosciences 559942
CD27-PE BD Biosciences 566944

CD19-FITC BD Biosciences 555412
CD45-PE.Cy7 Biolegend 157206
CD20-FITC BioLegend 302304
CD38-APC Miltenyi Biotech 130-113-429
CD138-PE Miltenyi Biotech 130-119-840
Cytochrome c (6H2.B4)-AF647 Biolegend 612310
CaspGLOW Fluorescein Active Caspase-3 Staining Kit ThermoFisher Scientific 88-7004-42
MitoPROBE TMRM Kit ThermoFisher Scientific M20036

Validation

All antibodies used in this study were commercial and validated by the manufacturer for use to detect human species targets. Species, application validations and citations for primary antibodies can be found from the manufacturer's websites.

Antibodies for immunoblotting and Immunoprecipitation:

-β actin (AC-15) Mouse mAb (Sigma-Aldrich A1978) detects endogenous levels of β actin protein. Species Reactivity: sheep, carp, feline, chicken, rat, mouse, Hirudo medicinalis, rabbit, canine, pig, human, bovine, guinea pig. Application: WB, IF, IHC, ARR, ICC. Dilution used for WB 1/2000.

-BAD Rabbit mAb (9292, Cell Signaling Technology) detects endogenous levels of total Bad protein. The antibody does not cross-react with other Bcl-2 family members.Species Reactivity: Human, Mouse, Rat, Monkey. Application: WB, IP. Used for immunoprecipitation (1/50).

-BAD (D24A9) Rabbit mAb (9239, Cell Signaling Technology) detects endogenous levels of total Bad protein. The antibody does not cross-react with other Bcl-2 family members. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues surrounding Pro102 of human Bad. Reactivity: Human, Mouse, Rat, Monkey. Application: WB. Dilution used for WB 1/1000.

-Phospho-Bad (Ser112) (40A9) Rabbit mAb detects endogenous levels of Bad only when phosphorylated at Ser112. The Ser112 nomenclature is based upon the mouse sequence. The analogous phosphorylation site is Ser75 in human and Ser113 in rat. This antibody does not detect Bad phosphorylated at other sites, nor does it detect related family members. Monoclonal antibody is produced by immunizing animals with a synthetic phosphopeptide corresponding to residues surrounding Ser112 of mouse Bad. Reactivity: Human, Mouse, Rat, Monkey. Application: WB, IF, FC. Dilution used for WB 1/1000.

-Caspase3 Rabbit mAb (9662, Cell Signaling Technology) detects endogenous levels of full length caspase-3 (35 kDa) and the large fragment of caspase-3 resulting from cleavage (17 kDa). Species Reactivity: Human, Mouse, Rat, Monkey. Application: WB, IP, IHC. Dilution used for WB 1/1000.

-PIM2 (D1D2) Rabbit mAb (4730, Cell Signaling Technology) detects endogenous levels of total Pim-2 protein. The antibody does not cross-react with other Pim family members. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues surrounding Cys266 of human Pim-2. Species Reactivity: Human. Application: WB, IP. Dilution used for WB 1/1000.

-PIM1 (D8D7Y) Rabbit mAb (54523, Cell Signaling Technology) detects endogenous levels of total Pim-1 protein. The antibody does not cross-react with other Pim family members. Monoclonal antibody is produced by immunizing animals with recombinant protein specific to a central region of human Pim-1 protein. Species Reactivity: Human, Mouse, Rat. Application: WB, IP. Dilution used for WB 1/1000.

-phospho-eIF2a (Ser51) (D9G8) Rabbit mAb (3398, Cell Signaling Technology) detects endogenous eIF2α only when phosphorylated at Ser51. The antibody does not recognize eIF2α phosphorylated at other sites. Human eIF2alpha residue Ser52 historically has been referenced as Ser51. Monoclonal antibody is produced by immunizing animals with a synthetic phosphopeptide corresponding to residues surrounding Ser51 of human eIF2α. Species Reactivity: Human, Mouse, Rat, Monkey, D. melanogaster. Application: WB, IP, IHC. Dilution used for WB 1/1000.

-eIF2a (D7D3) Rabbit mAb (5324, Cell Signaling Technology) detects endogenous levels of total eIF2a protein. Monoclonal antibody is produced by immunizing animals with a purified recombinant protein fragment representing sequence in the central region of human eIF2α. Species Reactivity: Human, Mouse, Rat, Monkey. Application: WB, IP, IHC. Dilution used for WB 1/1000.

-ATF4 (W16016A) Rat mAb (693902, Biolegend) detects endogenous levels of Atf4 protein. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues surrounding 1102-351 aa of human Atf4. Species Reactivity: Human, Mouse. Application: WB. Dilution used for WB 1/1000.

-CHOP (L63F7) Mouse mAb (2895, Cell Signaling Technology) detects endogenous levels of total CHOP protein. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to the sequence of human CHOP. Species Reactivity: Human, Mouse, Rat. Applications: WB, IP, IF, FC, ChIP. Dilution used for WB 1/1000.

-NOXA (D8L7U) Rabbit mAb (14766, Cell Signaling Technology) detects endogenous levels of total Noxa protein. This antibody also cross-reacts with multiple unidentified proteins, most notably at 35, 50, and 80 kDa. Noxa protein is identified at 10 kDa. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues near the amino terminus of human Noxa protein. Species Reactivity: Human. Applications: WB, IP. Dilution used for WB 1/1000.

-BCL-XL Rabbit mAb (2762, Cell Signaling Technology) detects endogenous levels of total Bcl-xL protein. The antibody does not cross-react with other Bcl-2 family members. Species Reactivity: Human, Mouse, Rat, Monkey. Application: WB, IP. Dilution used for WB 1/1000. Used for immunopreicipation at 1/50.

-BCL-XL (2H12) Mouse mAb (551022, BD Biosciences) has been reported to recognize human, mouse and rat Bcl-xL (long) protein. An N-terminal peptide (amino acids 3-14) common to human and mouse Bcl-xL and Bcl-xS (short) proteins was used as the immunogen. Thus the antibody is also predicted to recognize the Bcl-xS protein as the sequence used for the immunogen is common to both Bcl-xL and Bcl-xS proteins. Reports from development, however, have indicated that Bcl-xS has not been observable. The antibody does not cross-react with other Bcl-2 family members. Species Reactivity: Human, Mouse, Rat. Application: WB. Dilution used for WB 1/1000.

-MCL-1 (D5V5L) Rabbit mAb (39224, Cell Signaling Technology) recognizes endogenous levels of total Mcl-1 protein. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues surrounding Leu35 of human Mcl-1 protein. Species Reactivity: Human. Applications: WB, IHC, IF. Dilution used for WB 1/1000. Used for immunopreicipation at 1/50.

-BCL2 (4D7) Mouse mAb (551098, BD Biosciences) detects endogenous levels of human Bcl2 protein. A synthetic peptide containing amino acids 61-76 of the human Bcl-2 protein was used as immunogen. This peptide sequence differs from that of mouse Bcl-2 and hence 4D7 does not cross-react with mouse. 4D7 recognizes Bcl-2 as a 26 kDa band; however, additional higher molecular weight

bands have been observed in some cell types. These bands may represent oligomers of Bcl-2, which have been reported to occur with members of the Bcl-2 family during the preparation of nonionic detergent extracts. Species Reactivity: Human. Applications: WB, IP. Dilution used for WB 1/1000.

-BAX Rabbit mAb (2772, Cell Signaling Technology) detects endogenous levels of total Bax protein. The antibody does not cross-react with other Bcl-2 family members. Species Reactivity: Human, Mouse, Rat, Monkey. Application: WB, IP. Dilution used for WB 1/1000.

-BAX (6A7) Mouse mAb (633802, Biolegend) detects endogenous levels of Bax protein. The antibody does not cross-react with other Bcl-2 family members. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues surrounding aminoacid 12-24 of human Bak protein and associated to the active form of Bax. Species Reactivity: Human, Mouse, Rat, Monkey. Application: IP. Used for IP at 1/200.

-BAK (D4E4) Rabbit mAb (12105, Cell Signaling Technology) detects endogenous levels of total Bak protein. The antibody does not cross-react with other Bcl-2 family members. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues surrounding Gly75 of human Bak protein.Species Reactivity: Human, Mouse, Rat, Monkey. Application: WB, IP, IHC, IF, FC. Dilution used for WB 1/1000.

-BIM (C34C5) Rabbit mAb (2933, Cell Signaling Technology) detects endogenous levels of total Bim (EL, L and S isoforms) protein. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues surrounding Pro25 of Bim. Species Reactivity: Human, Mouse, Rat. Application: WB, IP, IHC, IF, FC. Dilution used for WB 1/1000. Used for immunopreicipation at 1/50.

Antibodies for immunohisto-fluorescence:

-CD138 (B-A38) Mouse mAb (R&D Systems NB100-64980) recognizes a heparan sulfate rich membrane glycoprotein of 200kD known as Syndecan-1 (CD138). Syndecan functions as a receptor for collagen, fibronectin and thrombospondin. NB100-64980 stains all plasma cells and plasma cell lines. No staining of other leucocytes is seen in peripheral blood or bone marrow, although some ALL cell lines express the antigen weakly. Some staining of epithelial and endothelial cells may be seen in immunohistology. Species Reactivity: Human. Application: WB, IP, IHC, IF, FC. Dilution used for immunohisto-fluoresence 1/250.

-BAX Rabbit polyclonal mAb (R&D Systems NBP2 67285) : detects endogenous levels of Bax protein. This Polyclonal antibody is produced by immunizing animals with a synthetic peptide within Human Bax aa 1-50 / 192. Dilution used for immunohisto-fluoresence 1/250.

-BAX (6A7) mouse mAb (Biolegend 633802) : detects endogenous levels of Bax protein. The antibody does not cross-react with other Bcl-2 family members. Monoclonal antibody is produced by immunizing animals with a synthetic peptide corresponding to residues surrounding aminoacid 12-24 of human Bak protein and associated to the active form of Bax. Species Reactivity: Human, Mouse, Rat, Monkey. Application: IP. Used for immunofluorescence at 1/250.

-Cytochrome c (6H2.B4) (BD Biosciences 556432) : The 6H2.B4 monoclonal antibody has been reported to recognize the native and not the denatured form of rat, mouse, and human cytochrome c.

-Alexa Fluor 594 Donkey anti-Mouse Jackson ImmunoResearch Laboratories, 715-586-151

-Alexa Fluor 594 Donkey anti-Rabbit Jackson ImmunoResearch Laboratories, 711-586-152

-Alexa Fluor 488 Donkey anti-Mouse Jackson ImmunoResearch Laboratories, 715-546-151

-Alexa Fluor 488 Donkey anti-Rabbit Jackson ImmunoResearch Laboratories, 711-546-152

Antibodies for cytometry:

For antibodies from BD biosciences (CD38-APC 555462 ; CD23-PE.Cy7 561167 ; CD44-APC 559942; CD27-PE 566944; CD19-FITC 555412) see : https://www.bdbiosciences.com/en-us

For antibodies from Biolegend (CD45-PE.Cy7 157206; CD20-FITC 302304) see : https://www.biolegend.com/

For antibodies from Miltenyo Biotech (CD38-APC 130-113-429; CD138-PE 130-119-840) see:

For CaspGLOW Kit from ThermoFischer Scientific : this kit was actually discontinuated. See Method for protocol used.

For MitoPROBE TMRM Kit from ThermoFischer Scientific see: https://www.thermofisher.com/order/catalog/product/M20036?SID=srch-srp-M20036

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	OPM2 (ACC 50) and SKMM2 (ACC 430) were obtained from DSMZ. U266 (TIB-196) and RPMI8226 (CCL-155) were obtained from ATCC. XG6, XG7 and XG21 cell lines were shared by the laboratory of Dr Jerome Moreaux, IGH UMR CNRS 9002, Montpellier, France.
Authentication	The cell lines were authenticated by HLA typing.
Mycoplasma contamination	Cell lines were tested for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in this study.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	NSG (NOD.Cg-Prkdc<scid>Il2rg<tm1Wjl>/SzJ) female mice (Charles River) with ages ranging from 6-9 weeks , were used for myeloma cell line xenograft implantation by intrafemoral injection.

Wild animals	No wild animals were used in this study
Reporting on sex	Only female mice were used in this study. Our data (not shown) showed considerable variability in cell engraftment depending on the sex of the mice. Transplants performed in females showed a more rapid and efficient engraftment, in contrast to those performed in males. The use of both sexes would have led to considerable variability in our results. It was therefore decided to use only female mice in order to obtain the most reproducible data possible.
Field-collected samples	No field collected samples were used in this study
Ethics oversight	Mice were maintained in specific pathogen-free conditions in Rennes animal facility. All procedures were carried out with the approval of the Committee on the Ethics of Animal Experiments under the French Ministry of Higher Education and Research (permission#: 8556– 2017011613335049_v8) and in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals, EEC Council Directive 2010/63/EU. Mice were housed with full access to water and chow and monitored daily after initial injection, taking daily body weight measurements. Monitoring of immunoglobulin (Ig) level in mice sera each week was used to assess tumour progression. Treatment began two weeks after transplant (after confirmation of the increased in Ig level in mice sera) and mice were euthanized as soon as tumor progression impacts on the animals' health.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Plants

Seed stocks	Not applicable
Novel plant genotypes	Not applicable
Authentication	Not applicable

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	For cell lines experiments, 5x10^5 cells were plated in 24-well plate in culture media and drug treatment were added successively. Viability and mitochondrial depolarization (TMRM signal) in response to drug treatments was measured the following day. For primary cells experiments, peripheral blood samples were obtained from healthy volunteers, Blood samples were processed to isolate peripheral blood mononuclear cells (PBMCs) following Ficoll density centrifugation. B cells were enriched by depleting unwanted cell types using specific antibodies coupled to magnetic beads (Naive B Cell Isolation Kit II or B Cell Isolation Kit II). The AutoMACS depletion sensitive program from Miltenyi Biotech was used for this purpose. The isolated CD19+/CD27- NBCs or CD19+ total B cells were routinely checked for purity. This is a critical step to ensure that the isolated cells are of the desired type. A purity level greater than 99% indicates that the isolated cells are highly enriched for the specific B cell subset of interest. The general process of stimulation and differentiation for B cells is describe in methods. At day 0 , 8x10^5 cells were plated in 24-well plate in culture media and drug treatment were added at day 0 or day 3. Viability in response to drug treatments was measured the following day. At day 4, 5x10^5. cells were plated in 24-well plate in culture media and drug treatment were added at day 5. Viability of PBs and the TMRM signal in response to drug treatments was measured the following day. At day 7, 5x10^5 cells were plated in 24-well plate in culture media and drug treatment were added at day 8. Viability of PCs in response to drug treatments was measured the following day. For mice experiments, after mice euthanasia, the femurs are flushed with PBS and the cells are then rapidly lysed with a homemade lysis solution (ACK buffer). Two millions of cells were then isolated and labelled with murine CD45 (mCD45), human CD38 (hCD38) and human CD138 (hCD138) antibodies.
Instrument	CytoFLEX S (Beckman Coulter)
Software	CytExpert (2.4) (CytoFLEX sofware)

Cell population abundance	Not applicable
Gating strategy	Events above baseline FSC/SSC were labeled as cells, then discriminated by FSC-H/FSC-A to identify single cells for all experiment. DAPI negative cells were identified as alive cells. For somes experiment, to identified apoptotic cells, a caspase3 staining (CaspGLOW FITC kit) was used to exclude caspase 3 active positive cells. The mitochondrial depolarization was assessed by using the TMRM signal (MitoPROBE TMRM kit) : a left shift of the TMRM signal indicated the depolarization. For primary cells drug treatment experiments, CD38+/CD23- cells were assigned as plasmablasts (PBs) at day 6-7; CD138+/ CD38+/CD20- cells were assigned as early plasma cells (ePCs) at day 9-10. For cell lines experiments, the TMRM signal was analysed in alive cells. For primary cells, the TMRM signal was analysed in DAPI-negative PBs or ePCs. For mice experiment, human tumor cells were were identified as mCD45-negative hCD138-positive cells.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.