were incubated in 75 μM chloroquine solution for 1 h followed by exposure to the C12FDG substrate (5-dodecanoylaminofluorescein-di-β-D-galactopyranoside; ImaGene Green C12FDG *lacZ* Gene Expression Kit, Molecular Probes, I2904) for 20 min at 37 °C in PBS (pH 5.5, with 1 mM $MgCl_2$) and analysed on ImageStreamX Mark II Imaging Flow Cytometer. Cell viability was evaluated by annexin V (BD Pharmingen, 556419) and propidium iodide (5 μg ml^{-1}, Sigma-Aldrich) staining, analysed in a FACSCalibur flow cytometer (BD Biosciences). Viable cells were detected as annexin V/propidium iodide-double-negative. ABC transporter activity was analysed using the eFluxx-ID Gold multidrug resistance kit (Enzo Life Sciences), and ALDH activity using the ALDEFLUOR kit (StemCell Technologies)[46], according to the manufacturer's instructions. Colony-forming unit assays were performed by plating 10^2 or 10^3 cells in 1 ml of methylcellulose medium (MethoCult M3134 for mouse cells, or H4100 for human cells, Stem Cell Technologies). For mouse cells, the medium was supplemented with recombinant murine interleukin (IL)-3 (1 ng ml^{-1}, Miltenyi), recombinant murine IL-6 (10 ng ml^{-1}, Miltenyi), recombinant murine IL-7 (0.1 ng ml^{-1}, Peprotech), and recombinant murine stem-cell factor (SCF, 50 ng ml^{-1}, Peprotech). For the indicated assays, the medium was further supplemented with ADR (0.05 μg ml^{-1}), 4-OHT (1 μM), DOX (1 μg ml^{-1}), ICG-001 (10 μM), salinomycin (1 μM)[47,48], Wnt3a (10 ng ml^{-1}), Rspo2 (20 ng ml^{-1}) or GSK3β inhibitor CHIR99021 (1 μM). Clusters of greater than 50 cells were scored as colonies, using bright-field or fluorescence microscopy. For serial passaging, cells were washed out of methylcellulose with warm PBS after seven days (mouse B-cell lymphoma cells) or ten days (mouse T-ALL cells), counted and plated in fresh methylcellulose medium (10^2 or 10^3 cells per ml). Regarding luciferase-based Wnt reporter assays, cells stably transfected with TOPflash-$MSCV_{SIN}$ or FOPflash-$MSCV_{SIN}$ were ADR-exposed in a senescence-inducing schedule as described above. The luminescence signals were measured with the ONE-Glo kit (Promega) according to the manufacturer's instructions and normalized to viable cell counts. For depletion of Lin$^-$ cells from *Kras*^{G12D};shp53–GFP T-ALL samples or *Nras*^{G12D}/MLL-AF9 AML samples, cells were labelled with a cocktail of biotinylated lineage marker antibodies (BD Biosciences, 559971) followed by Streptavidin-PE (BD Biosciences, 554061). GFP$^+$PE$^+$ cells were flow-sorted in a FACS Aria II (BD Biosciences). For depletion of CD34$^+$ cells from *Bcl2*-transfected Molm-13 cell line, cells were stained with a directly conjugated anti-CD34-APC antibody (1:200, BD Biosciences, 560940), and CD34$^-$ cells were sorted in a FACS Aria II (BD Biosciences).

RNA-based expression analysis. For microarray-based gene expression profiling of untreated or five-day-ADR-exposed control;*Bcl2* or *Suv39h1*$^-$;*Bcl2* lymphomas, RNA was isolated and processed as previously reported[40].

The list of 5,401 probe sets differentially expressed between untreated and ADR-treated control;*Bcl2* lymphomas was determined by analysis of variance (ANOVA, cut-off at $q < 0.05$). The list of filtered genes was ranked according to expression fold changes, and the genes belonging to the ATSC[17] or core embryonic stem-cell signature[49] were marked in orange and blue, respectively.

Gene set enrichment analysis (GSEA) was performed with the GSEA v2.0 software (Broad Institute of MIT (Massachusetts Institute of Technology) and Harvard, http://www.broad.mit.edu/gsea)[50] on transcriptome data produced in our laboratory (GSE31099 and GSE44355) or on publicly available transcriptome datasets downloaded from the Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/): normal colon epithelium and colon adenomas from *Apc*$^{Min/+}$ mice (GSE422, samples GSM6191–GSM6201), Braf-V600E-infected human melanocytes (GSE46801), human mammary epithelial cells in p16^{INK4a}-dependent stasis or telomere shortening-induced agonescence (GSE16058), normal human foreskin BJ fibroblasts in replicative senescence (GSE13330, samples GSM336385–GSM336628) and normal human mesenchymal stem cells in replicative senescence (GSE9593, samples GSM242185, GSM242668, GSM242669 and GSM242672–GSM242674). Probed gene sets were taken without further change from the indicated publications, downloaded from the Molecular Signature Database (MsigDB) of the Broad Institute (http://software.broadinstitute.org/gsea/msigdb/collections.jsp) or from the Gene Ontology (GO) browser AmiGO ('GO Cell cycle process' (GO:0022402), GO 'Wnt signaling pathway' (GO0016055), GO 'Canonical Wnt receptor signaling' (GO:0060070), GO 'Noncanonical Wnt signaling' (GO0035567), GO 'Notch signaling pathway' (GO0007219), GO 'Smoothened signaling pathway' (GO0007224)), or generated from the gene list reflecting the Mouse Wnt Signalling Pathway PCR Array (SA Biosciences; genes from this list annotated to have a role in cell growth and proliferation were used as a separate gene set, http://www.sabiosciences.com/rt_pcr_product/HTML/PAMM-043A.html#function). Normalized enrichment scores (NES) with P values <0.05 and false discovery rates (FDR) <0.25 were considered statistically significant.

For quantitative reverse-transcriptase PCR analyses of stem-cell-related genes in lymphoma cells, RNA extracted with Trizol (Invitrogen) was transcribed into cDNA using SuperScript II reverse transcriptase (Invitrogen). A panel of established stem-cell-related markers consisting of mouse *Abcg2*, *Cebpb*, *Kit*, *Cd34*, *Cd44*, *Prom1* (also known as *Cd133*), *Slamf1* (also known as *Cd150*), *Klf4*, *Ly6a* (also known as *Sca1*) or human *ABCG2*, *CD34*, *CD44*, *PROM1* (also known as *CD133*), *SLAMF1* (also known as *CD150*), *LGR5*, a panel of Wnt signalling targets: *Ccnd1*, *Fosl1*, *Fzd3*, *Id2*, *Met*, as well as a panel of established mouse SASP factors: *Igfbp6*, *Ccl2*, *Ccl20*, *Cxcl1*, *Ctgf*, *Il6*, *Kitl* and *Tnfa* were analysed by qPCR using commercially available Taqman assays (Applied Biosystems). Transcript quantification was calculated as $2^{(-\Delta Ct)}$ based on $\Delta C_t = \Delta C_{t(treated)} - \Delta C_{t(untreated)}$, with *GAPDH* transcript levels as an internal control.

Protein-based expression analyses. Immunophenotyping by flow cytometry was carried out as described previously[8,45], using the primary antibodies directed against human CD34 (BD Biosciences, 560940, 1:200), human CD33 (BD Biosciences, 555450 1:200), or against mouse antigens: H3K9me3 (Abcam, ab8898, 1:2,000), β-catenin (eBiosciences, 50-2567, 1:20), Thy1.2 (BD Biosciences, 553005, 1:200), TdT (Miltenyi, 130-100-749, 1:10), Kit (BD Biosciences, 553355, 1:200), Sca1 (BD Biosciences, 557404, 1:200), followed by secondary antibodies: anti-rabbit AlexaFluor 594 (Invitrogen A21207, 1:200) and Streptavidin-APC (BD Biosciences, 554067, 1:2,000).

For immunoblotting analyses, whole-cell pellets were lysed in Laemmli sample buffer (60 mM Tris-HCl at pH 6.8, 10% glycerol, 2% SDS, 5% 2-mercaptoethanol) supplemented with protease and phosphatase inhibitors, resolved by electrophoresis on a 12% SDS polyacrylamide gel (SDS–PAGE), transferred onto an Immobilon-P membrane (Millipore) and probed using antibodies against total β-catenin (BD Biosciences, 610153, 1:200), active β-catenin (dephosphorylated at serine 37 (Ser37) and threonine 41 (Thr41); Millipore, 05-665, 1:1,000), H3K9me3 (Abcam, ab8898, 1:2,000), total Erk (Cell Signaling Technology (CST), 9102, 1:1,000), phospho-Erk1/2 (that is, Erk1/2 phosphorylated at Thr202 and Tyr204; CST, 4376, 1:1,000), total Akt (CST, 9272, 1:1,000), phospho-Akt (that is, Akt-P-Ser473; CST, 4060, 1:2,000), total GSK3β (CST, 12456, 1:1,000), phospho-GSK3β (that is, GSK3β-P-Ser9; CST, 5558, 1:1,000) and α-tubulin (Sigma, T5168, 1:500) as a loading control.

For immunofluorescence, cells were fixed in 4% paraformaldehyde, permeabilized with 0.1% Triton X-100/PBS, blocked in 1% bovine serum albumin supplemented with the anti-mouse Cd32/Cd16 antibody (BD Biosciences, 53142, 1:50) and incubated with a primary antibody against total β-catenin (1:200), followed by 0.01% Tween 20 as detergent buffer and Alexa Fluor 594 (Invitrogen A11008, 1:5,000) as a secondary anti-mouse IgG antibody. The slides were stained with 4,6-diamidino-2-phenylindole (DAPI, Biolegend, 422801, 1:1,000 in PBS) as a nuclear counterstain, and mounted with Mowiol 4-88 (Calbiochem). Immunohistochemistry was performed on formalin-fixed, paraffin-embedded lymph-node sections as described previously[33]. Cryo-sections of mouse lymph-nodes were stained with an fluorescein isothiocyanate-conjugated antibody against total β-catenin (BD Biosciences, 562505, 1:200), and human DLBCL sections were stained with a primary antibody against total β-catenin (BD Biosciences, 610153, 1:200), followed by a secondary anti-mouse IgG antibody (1:1,000, Dako REAL Detection System (labelled streptavidin–biotin), Dako, K5005).

Global proteome analysis. *Suv39h1*$^-$;*Bcl2*;*Suv39h1*-ER^{T2} cells were sampled in ice-cold methanol after five days of ADR ± 4-OHT treatment. 50 μg of the protein extracts were digested using an xt-PAL (CTC Analytics) pipetting robot with the Chronos software package (Axel Semrau), reduced with 1 mM tris(2-carboxyethyl) phosphine. Free sulfhydryl groups were carbamidomethylated using 5.5 mM chloroacetamide. The proteins were digested using 0.5 μg sequencing-grade endopeptidase LysC (Wako) for 3 h at room temperature, and subsequently diluted with four volumes of 50 mM ammonium bicarbonate. Tryptic digestion occurred over 10 h at room temperature using 1 μg of sequencing-grade trypsin (Promega). The reaction was stopped by adding trifluoroacetic acid to a final pH of 2. The peptides were purified using C18-stage tips (3M)[51]. By applying the dimethyl labelling technique, the untreated lymphoma samples, serving as the reference, were 'light'-labelled, whereas others (ADR ± 4-OHT-treated) were 'heavy'-labelled, on the xt-PAL machine by automatically adding 4 μl light (+28 Da) or heavy (+32 Da) formaldehyde and 4 μl cyanoborohydride to a final concentration of 0.8%[52]. The reaction was carried out overnight, quenched by 16 μl of 50 mM ammonium bicarbonate buffer and acidified by 8 μl 50% trifluoroacetic acid. The 'heavy'- and 'light'-labelled samples were mixed in a 1:1 ratio and measured as technical duplicates on a Q-Exactive mass spectrometer (Thermo Fisher) coupled to a Proxeon nano-LC system (Thermo Fisher) in data-dependent acquisition mode, selecting the top ten peaks for higher-energy collisional dissociation fragmentation. A three-hour gradient (solvent A: 5% acetonitrile, 0.1% formic acid; solvent B: 80% acetonitrile, 0.1% formic acid) was applied to the samples using a custom-made nano-LC column (0.075 mm × 250 mm, 3 μm Reprosil C18, Dr. Maisch GmbH). The peptides were eluted in gradients of 4 to 76% acetonitrile and 0.1% formic acid in water at flow rates of 0.25 μl min^{-1}. Mass spectrometric acquisition was performed at a resolution of 70,000 in the scan range of 300 to 1,700 m/z. Dynamic exclusion was set to 30 s and the normalized collision energy to 26 eV. For the automatic interpre-