tation of the recorded spectral data, the MaxQuant software version 1.2.2.5 (Max Planck Institute) was used, with a multiplicity of 2 for dimethyl labelling[53]. An FDR of 0.01 was applied on the peptide and the protein level, and an Andromeda-based search was performed using a mouse International Protein Index database (ipi.MOUSE.v3.84.fasta). Mass spectrometric measurement data were log-transformed regarding the heavy/light ratios using the R-statistical software (R Foundation for Statistical Computing). Three replicates were used to calculate mean values and significance levels using the Wilcoxon test. All identifications with a $-\log_{10}$-transformed P value >1 were considered significant.

Chromatin immunoprecipitation. Chromatin immunoprecipitation was performed according to Young and colleagues[54] with minor modifications. 1×10^7 cells were fixed for 20 min in a 1% formaldehyde solution. The fixation was stopped with 0.1 M glycine, the cell pellet was lysed and sonicated in 300 µl buffer LB3[54] (Bioruptor Sonicator, two cycles of 15 min each at high power in pulsed mode (30 s on, 30 s off)). 30 µl of 10% Triton X-100 was added and the sample was centrifuged at 13,000 rpm for 10 min at 4 °C. The supernatant was removed and an aliquot was retained as the input DNA sample. For immunoprecipitation, 140 µl of the supernatant was mixed with 50 µl of Dynabeads Protein G (Life Technologies/Invitrogen), pre-coated with 5 µg of an H3K4me3 antibody (A5051-001P, Diagenode) or an H3K27me3 antibody (39155, Active Motif) and incubated at 4 °C overnight. After incubation, the beads were magnetically separated from the supernatant, washed and eluted. After reverse-crosslinking, RNaseA and proteinase K digestion[54], the DNA was extracted with phenol/chloroform, and used as a template for qPCR. Sequence information of the specific primers used is available upon request. Enrichments were calculated according to the $\Delta\Delta C_t$ method, with Prame as endogenous control, and the input as calibrator. The values of the relative enrichments for the 4-OHT/ADR-treated samples were divided by the corresponding ADR sample values.

Statistical evaluation. On the basis of previous experience with the Eμ-*Myc* transgenic mouse lymphoma model, sample sizes typically reflect three to five individual primary tumours as independent biological replicates. All quantifications from staining reactions (for example, immunostainings or SA-β-gal assays) reflect at least three samples with at least 100 events counted (typically in three different areas) each. For assessing long-term outcome after *in vivo* treatments, six or more tumour-bearing animals per arm were used. No statistical method was used to predetermine sample size. No data were excluded, all probes/animals that met proper experimental conditions were included in the analysis. For purposes of tumour-initiation assays, a transplanted mouse scored positive if a palpable lymphadenopathy developed at any time point during the observation period of 100 days. The tumour initiation data were analysed using the ELDA (Extreme Limiting Dilution Analysis) software package at http://bioinf.wehi.edu.au/software/elda/ (ref. 55) with a confidence interval of 95%. Unless stated otherwise, data are presented as arithmetic means ± standard deviation (s.d.) and statistical analyses were based on paired or unpaired two-sided *t*-tests. The data not following a normal distribution (by Kolmogorov–Smirnov test) were analysed by unpaired *t*-test with Welch's correction. Similar variance between groups was not assumed. $P < 0.05$ was considered statistically significant. The whisker plot boxes indicate the first and third quartiles with median, and the upper and lower bars minimum and maximum values. For GSEA, the non-parametric Kolmogorov–Smirnov test was applied. Significant enrichment was accepted when $P < 0.05$ and FDR < 0.25, thus using the default significance levels for the method.

Data availability. Microarray datasets produced in our laboratory and analysed in this study are available at the Gene Expression Omnibus (GEO) repository of the National Center for Biotechnology Information, under the accession numbers GSE31099 and GSE44355, for control;*Bcl2* and *Suv39h1*$^{-}$;*Bcl2* lymphomas, respectively. Source Data for Figs 1–4 and Extended Data Figs 1–10 are provided with the online version of this paper. All other datasets generated during this study are available from the corresponding author on reasonable request.

30. Adams, J. M. *et al.* The c-*myc* oncogene driven by immunoglobulin enhancers induces lymphoid malignancy in transgenic mice. *Nature* **318,** 533–538 (1985).
31. Peters, A. H. *et al.* Loss of the *Suv39h* histone methyltransferases impairs mammalian heterochromatin and genome stability. *Cell* **107,** 323–337 (2001).
32. Martins, C. P., Brown-Swigart, L. & Evan, G. I. Modeling the therapeutic efficacy of p53 restoration in tumors. *Cell* **127,** 1323–1334 (2006).
33. Reimann, M. *et al.* Tumor stroma-derived TGF-β limits myc-driven lymphomagenesis via Suv39h1-dependent senescence. *Cancer Cell* **17,** 262–272 (2010).
34. Schmitt, C. A. *et al.* Dissecting p53 tumor suppressor functions *in vivo*. *Cancer Cell* **1,** 289–298 (2002).
35. Premsrirut, P. K. *et al.* A rapid and scalable system for studying gene function in mice using conditional RNA interference. *Cell* **145,** 145–158 (2011).
36. Schmitt, C. A., McCurrach, M. E., de Stanchina, E., Wallace-Brodeur, R. R. & Lowe, S. W. *INK4a/ARF* mutations accelerate lymphomagenesis and promote chemoresistance by disabling p53. *Genes Dev.* **13,** 2670–2677 (1999).
37. Banchereau, J., de Paoli, P., Vallé, A., Garcia, E. & Rousset, F. Long-term human B cell lines dependent on interleukin-4 and antibody to CD40. *Science* **251,** 70–72 (1991).
38. Schmitt, C. A., Rosenthal, C. T. & Lowe, S. W. Genetic analysis of chemoresistance in primary murine lymphomas. *Nat. Med.* **6,** 1029–1035 (2000).
39. Feil, R., Wagner, J., Metzger, D. & Chambon, P. Regulation of Cre recombinase activity by mutated estrogen receptor ligand-binding domains. *Biochem. Biophys. Res. Commun.* **237,** 752–757 (1997).
40. Jing, H. *et al.* Opposing roles of NF-κB in anti-cancer treatment outcome unveiled by cross-species investigations. *Genes Dev.* **25,** 2137–2146 (2011).
41. Yang, D. H. *et al.* Wnt5a is required for endothelial differentiation of embryonic stem cells and vascularization via pathways involving both Wnt/β-catenin and protein kinase Cα. *Circ. Res.* **104,** 372–379 (2009).
42. Dickins, R. A. *et al.* Probing tumor phenotypes using stable and regulated synthetic microRNA precursors. *Nat. Genet.* **37,** 1289–1295 (2005).
43. Godar, S. *et al.* Growth-inhibitory and tumor- suppressive functions of p53 depend on its repression of *CD44* expression. *Cell* **134,** 62–73 (2008).
44. Dimri, G. P. *et al.* A biomarker that identifies senescent human cells in culture and in aging skin *in vivo*. *Proc. Natl Acad. Sci. USA* **92,** 9363–9367 (1995).
45. Reimann, M. *et al.* The Myc-evoked DNA damage response accounts for treatment resistance in primary lymphomas *in vivo*. *Blood* **110,** 2996–3004 (2007).
46. Greve, B., Kelsch, R., Spaniol, K., Eich, H. T. & Götte, M. Flow cytometry in cancer stem cell analysis and separation. *Cytometry A* **81A,** 284–293 (2012).
47. Gupta, P. B. *et al.* Identification of selective inhibitors of cancer stem cells by high-throughput screening. *Cell* **138,** 645–659 (2009).
48. Lu, D. *et al.* Salinomycin inhibits Wnt signaling and selectively induces apoptosis in chronic lymphocytic leukemia cells. *Proc. Natl Acad. Sci. USA* **108,** 13253–13257 (2011).
49. Kim, J. *et al.* A Myc network accounts for similarities between embryonic stem and cancer cell transcription programs. *Cell* **143,** 313–324 (2010).
50. Subramanian, A. *et al.* Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc. Natl Acad. Sci. USA* **102,** 15545–15550 (2005).
51. Rappsilber, J., Mann, M. & Ishihama, Y. Protocol for micro-purification, enrichment, pre-fractionation and storage of peptides for proteomics using StageTips. *Nat. Protocols* **2,** 1896–1906 (2007).
52. Boersema, P. J., Raijmakers, R., Lemeer, S., Mohammed, S. & Heck, A. J. Multiplex peptide stable isotope dimethyl labeling for quantitative proteomics. *Nat. Protocols* **4,** 484–494 (2009).
53. Cox, J. & Mann, M. MaxQuant enables high peptide identification rates, individualized p.p.b.-range mass accuracies and proteome-wide protein quantification. *Nat. Biotechnol.* **26,** 1367–1372 (2008).
54. Lee, T. I., Johnstone, S. E. & Young, R. A. Chromatin immunoprecipitation and microarray-based analysis of protein location. *Nat. Protocols* **1,** 729–748 (2006).
55. Hu, Y. & Smyth, G. K. ELDA: extreme limiting dilution analysis for comparing depleted and enriched populations in stem cell and other assays. *J. Immunol. Methods* **347,** 70–78 (2009).
56. Ivanova, N. B. *et al.* A stem cell molecular signature. *Science* **298,** 601–604 (2002).
57. Coppé, J. P., Desprez, P. Y., Krtolica, A. & Campisi, J. The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu. Rev. Pathol.* **5,** 99–118 (2010).
58. Whitfield, M. L. *et al.* Identification of genes periodically expressed in the human cell cycle and their expression in tumors. *Mol. Biol. Cell* **13,** 1977–2000 (2002).
59. Hu, Z. *et al.* The molecular portraits of breast tumors are conserved across microarray platforms. *BMC Genomics* **7,** 96 (2006).
60. Chambers, S. M. *et al.* Hematopoietic fingerprints: an expression database of stem cells and their progeny. *Cell Stem Cell* **1,** 578–591 (2007).