SUPPLEMENTARY FIGURE LEGENDS

Figure S1: Analysis of IC50 value of LBH589 in 6 ALL derived cell lines involving different genetic subtypes of this disease.

Figure S2: *In vitro* efficacy of LBH589 in ALL cell lines

Acetylation of H3 and H4 was measured by western blot in ALL cell lines after treatment with 50nM LBH589 for 48 hours. Cell survival was analyzed by MTT at 24, 48, 72 and 96 hours after treatment with 50nM LBH589. Apoptosis of ALL cells was measured (presence of oligonucleosomal fragments study, FACS analysis of activated caspase-3 and PARP cleavage of 85 Kda by western blot) after 48 hours of treatment with 50nM of LBH589. Results are the mean ± SD of at least 3 independent experiments or a representative experiment for western blot. Total H3 was used as loading control.

Figure S3: Toxicity of LBH589 in healthy BALB/cA-RAG2$^{-/-}$γc$^{-/-}$ mice

BALB/cA-RAG2$^{-/-}$γc$^{-/-}$ mice (n = 6 per group) were treated with LBH589 i.p. at doses between 1 and 20 mg/kg for 3 cycles as described in the Materials and Methods. (A) Weight changes relative to day 0 according to the dose of LBH589 received. (B) Increase in spleen weight after treatment with LBH589. (C) H&E staining and histological analysis of brain and spleen injuries after treatment with different doses of LBH589. A remarkable splenitis and meningoencephalitis are observed in the group treated with 20 mg/kg with spongiosis of the central nervous system.

Figure S4: Scheme of set-up and development of the human xenograft ALL mice models

Figure S5: Characterization of ALL-T1 model

(A) Peripheral blood smear of a healthy mouse and a mouse engrafted with ALL-T1 in which human blasts are detected (arrows). (B) Percentage of human leukemic cells in peripheral blood, bone marrow and spleen of ALL-T1 mice 1 and 19 days after transplant, as detected with a specific antibody against human CD45. (C) Time course of human leukemic cells in peripheral blood, bone marrow and spleen of ALL-T1 mice from day 1 to 19 after transplant, and liver and spleen weight gain. (D) Histological and immunohistochemical analysis of spleen, kidney, liver and brain from mice transplanted with ALL-T1 cells. H&E staining and immunohistochemistry with antibodies against Ki67 (cell proliferation) and human CD45 (leukemic cells) are shown. Results are the

mean ± SD of at least 3 independent experiments for C, and a representative analysis for A, B and D.

Figure S6: Characterization of ALL-T1 model

(A) Peripheral blood smear of a healthy mouse and a mouse engrafted with ALL-T1 in which human blasts are detected. (B) Percentage of human leukemic cells in peripheral blood, bone marrow and spleen of ALL-B1 mice 21 and 36 days after transplant, as detected with a specific antibody against human CD22. (C) Time course of human leukemic cells in peripheral blood, bone marrow and spleen of ALL-T1 mice from day 21 to 36 after transplant, and liver and spleen weight gain. (D) Histological and immunohistochemical analysis of spleen, kidney, liver and brain from mice transplanted with ALL-B1 cells. H&E staining and immunohistochemistry with antibodies against Ki67 (cell proliferation) and human CD19 (leukemic cells) are shown. Results are the mean ± SD of at least 3 independent experiments for C, and a representative analysis for A, B and D.

Figure S7: Molecular characterization of the human xenograft ALL mice model after multiple generations

Heatmaps and clusterings of the primary ALL samples and ALL cells from spleens of transplanted mice. The heatmaps show a coherent clustering of the samples corresponding to ALL-T1 and ALL-B1 classes using Pearson distance: (A) clustering of microarray SNP RMA signals; (B) clustering of genome-wide methylation beta average signals; (C) clustering of genome-wide expression microarray RMA signals. In the heatmaps dark-red corresponds to maximum correlation and dark-green to minimum correlation. PS: primary samples obtained from patients with ALL; S2: samples of splenocyte counterparts without freezing; S3: samples of splenocyte counterparts after freezing and transplant.

Figure S8: Toxicity of the combination of LBH589, Dexamethasone and Vincristine

Healthy BALB/cA-RAG2-/-γc-/- mice were treated with LBH589 at 5 mg/kg or a combination of LBH589 and Dexamethasone and Vincristine at three different doses: 0.025, 0.25 and 0.50 mg/kg, for three cycles. Each cycle consisted of 5 consecutive days of treatment with LBH589, 7 consecutive days of Dexamethasone and 1 day of Vincristine. The weight loss of each mouse was monitored daily. Five mice were included in each group.

Figure S9: Effect of the combination of LBH589, Dexamethasone and Vincristine in normal hematopoietic cells. A) Effect of combination of LBH589, Vincristine and Dexametasone in hematopoietic cells of immunodeficient BALB/c-RAG2$^{-/-}$γc$^{-/-}$mice. White blood cell or leukocyte count (WBC) red blood cell or erythrocyte count (RBC) haemoglobin (Hb) hematocrit or relative volume of erythrocytes (HCT) and platelet or thrombocyte count (PLT) cells were analyzed by HEMAVET in control mice, mice treated with Vincristine plus Dexamethasone and mice treated with combination of three drugs, LBH589, Vincristine and Dexamethasone. K/μl: Thousands of leukocytes per microliter of whole blood; M/μl: Millions of leukocytes per microliter of whole blood; g/dL: Grams of hemoglobin per deciliter of whole blood B) Apoptosis induced by LBH589, Vincristine plus Dexamethasone combination or with LBH589, Vincristine and Dexamethasone combination in human CD34+ cells and ALL-T1 human acute lymphoblastic leukemia mice model cells by the activation of caspase-3 by FACS. C) Cell survival of in human CD34+ cells and ALL-T1 mouse model cells proliferation after 24 hours of treatment with LBH589, Vincristine plus Dexamethasone combination or with LBH589, Vincristine and Dexamethasone combination. All experiments were repeated three times.