

Expanded View Figures

Figure EV1. Apoptosis induction by the SM-drug combination is independent from TNF α and RIPK1.

- A–D LOUCY (A, B) or NALM-6 cells (C, D) cells were treated for 48 h with SM and/or VCR and/or TNF α in the presence of the TNF α -neutralizing antibody adalimumab (ADM). Apoptosis induction was determined by flow cytometry upon staining with Annexin-V/PI (A, C, D) and by analyzing active caspase-8 (B). Data are expressed as mean \pm SD of three independent experiments; *** P < 0.001 by unpaired Student's t -test.
- E Samples from two pediatric patients (ALL-3 and ALL-4; see Table EV1 for details) were treated for 24 h with DXR or VCR and/or LBW242 in combination with adalimumab. Apoptosis induction was determined by flow cytometry upon staining with Annexin-V/PI.
- F, G Ripoptosome inhibition does not inhibit apoptosis by the SM-drug combination. NALM-6 cells were treated for 48 h with SM and VCR (E) or SM and TNF α (F) in the presence of the RIPK1-inhibitor Necrostatin-1 (Nec). Apoptosis induction was determined by flow cytometry upon staining with Annexin-V/PI. Data are expressed as mean \pm SD of three independent experiments with * P < 0.05, ** P < 0.01 by unpaired Student's t -test.

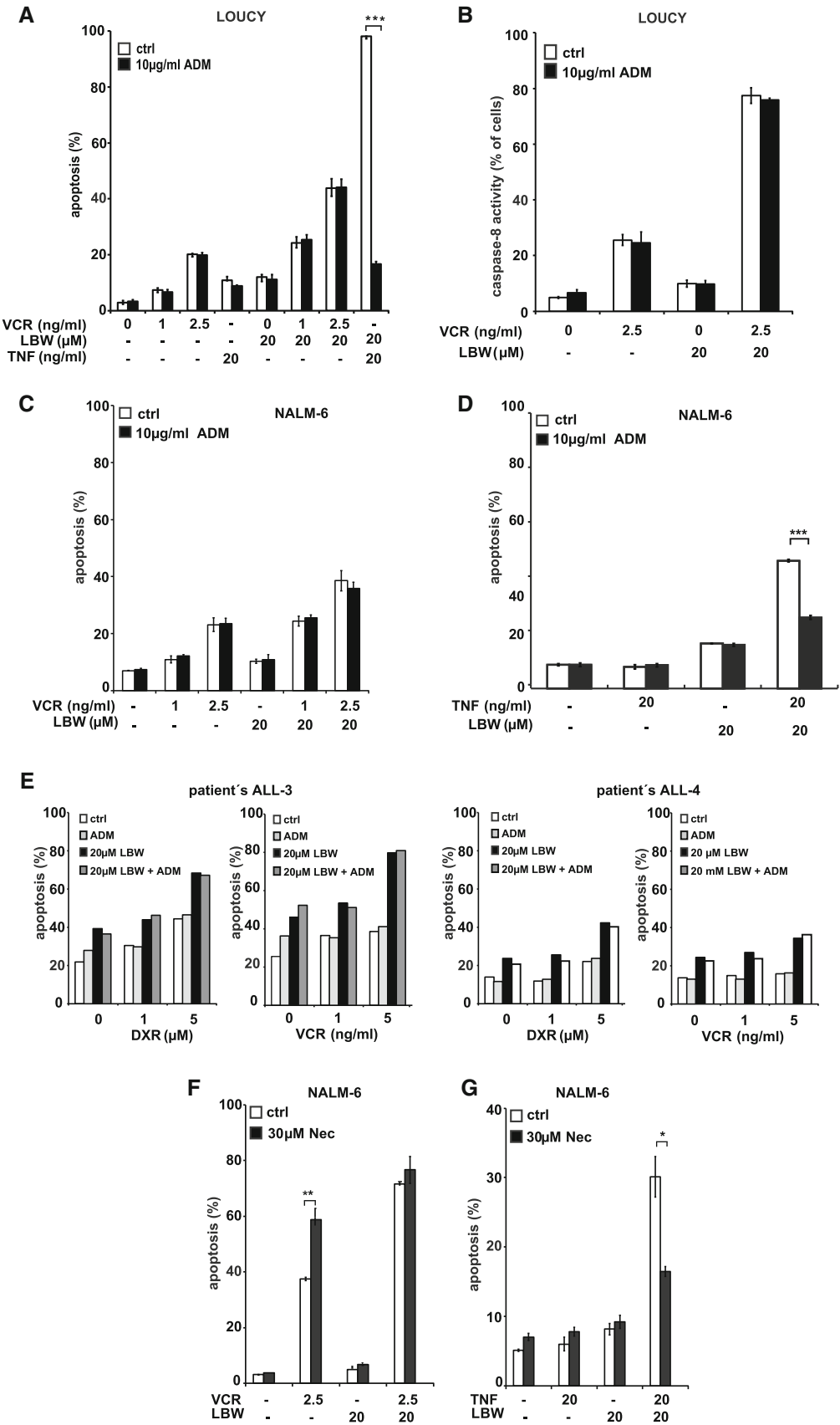


Figure EV1.

Figure EV2. IAP expression in acute leukemias.

A–E mRNA expression of XIAP (A) in different ALL subgroups and mRNA expression of cIAP-1 (B, C) and cIAP-2 (D, E) in samples shown in Fig 3A (B, D) and in distinct ALL subgroups (C, E). Subgroups of ALL significantly differed in their expression levels of all three genes with (A) XIAP: ANOVA $P = 3.74 \times 10^{-6}$; (C) cIAP-1: ANOVA $P = 4.45 \times 10^{-13}$ and (E) cIAP-2: ANOVA $P = 6.89 \times 10^{-14}$. Comparing pairs of two subgroups, statistically significant differences were detected by *post hoc* analysis for a P -value < 0.05 (A) for XIAP in B-other compared to ETV6-t and Ph-positive as well as Burkitt compared to ETV6-t, Hyperdiploidy, Ph-like, Ph-positive and T-ALL, (C) for cIAP-1 in T-ALL compared to B-other, KMT2A-t, Ph-like and Ph-positive (E) for cIAP-2 in Burkitt compared to B-other, KMT2A-t, Ph-positive and TCF3-t as well as for T-ALL compared to B-other, KMT2A-t and Ph-positive and Ph-positive compared to KMT2A-t. Each dot represents one patient sample (biological replicates). Data are expressed as median, 25th and 75th percentile, whiskers indicate min/max; ns (not significant) by Games-Howell *post hoc* test.

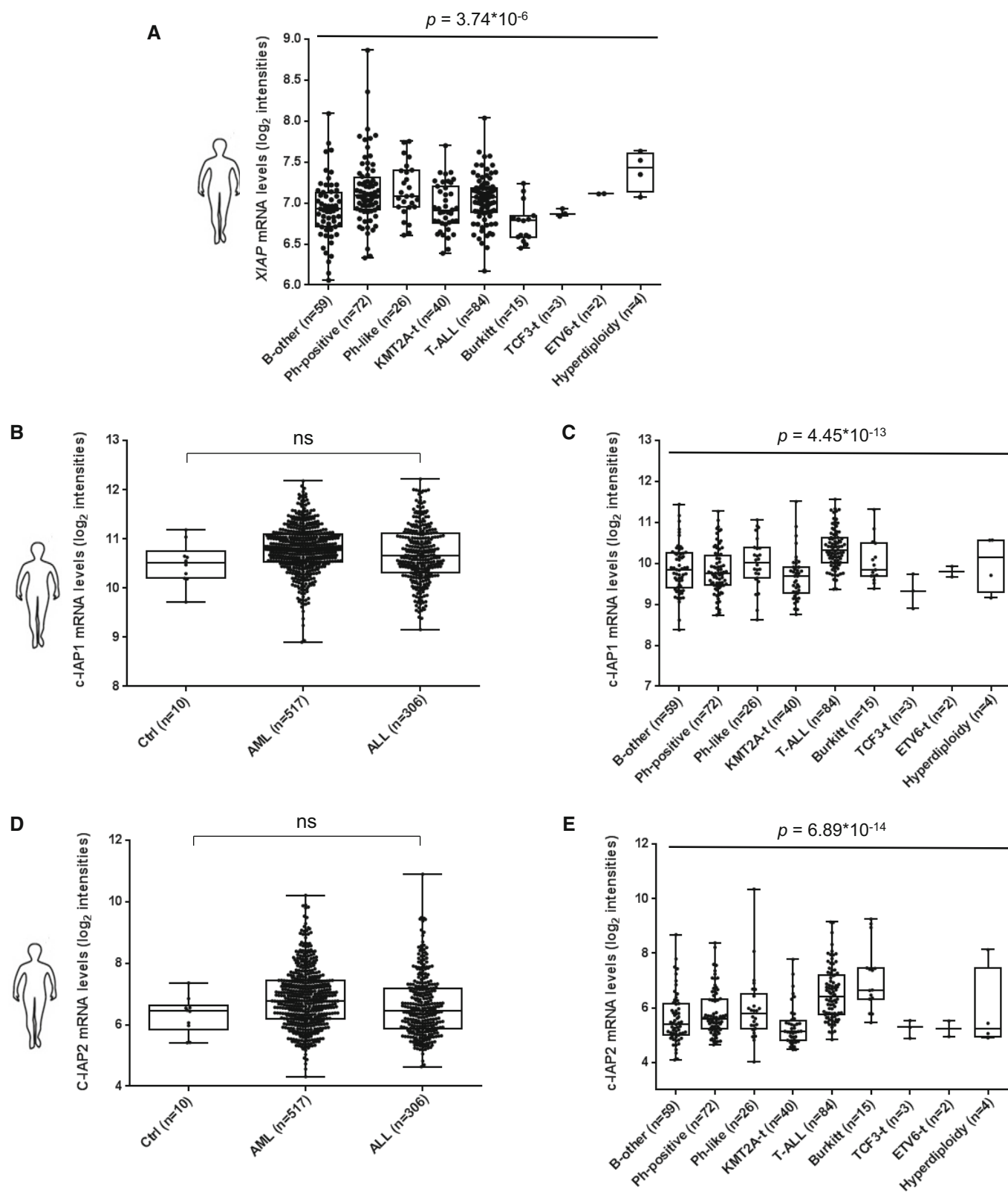


Figure EV2.

Figure EV3. XIAP plays an essential role for patients' r/r ALL cells growing in mice.

- A Control and XIAP-targeting shRNAs are expressed in similar amounts in PDX cells. Experiments were performed as described in Fig 5A, and expression levels of dsRED in the sh-CTRL/mTagBFP and sh-XIAP/eGFP subpopulation were analyzed by FACS.
- B Expression of transgenes and control shRNA sequences does not affect proliferation of PDX ALL cells *in vivo*. Competitive *in vivo* assays with different combinations of colors and control shRNA sequences for up to four passages in ALL-265 *in vivo*. Each mouse is considered as one independent experiment (P0, $n = 16$; P1, $n = 16$; P2, $n = 16$; P3, $n = 14$). Data are expressed as mean \pm SEM, ns, not significant by unpaired Student's *t*-test.
- C, D Experiments were performed and are depicted exactly as described in Fig 5C and D, except that PDX ALL-199 was studied. In (C) each mouse analyzed ($n = 8$) is considered as one independent experiment. Data are expressed as mean \pm SEM of all mice analyzed; **** $P < 0.0001$ by unpaired Student's *t*-test. (D) ALL-199 PDX cells of a representative mouse were analyzed separately for dsRED/shRNA high- and low-expressing cells.

Source data are available online for this figure.

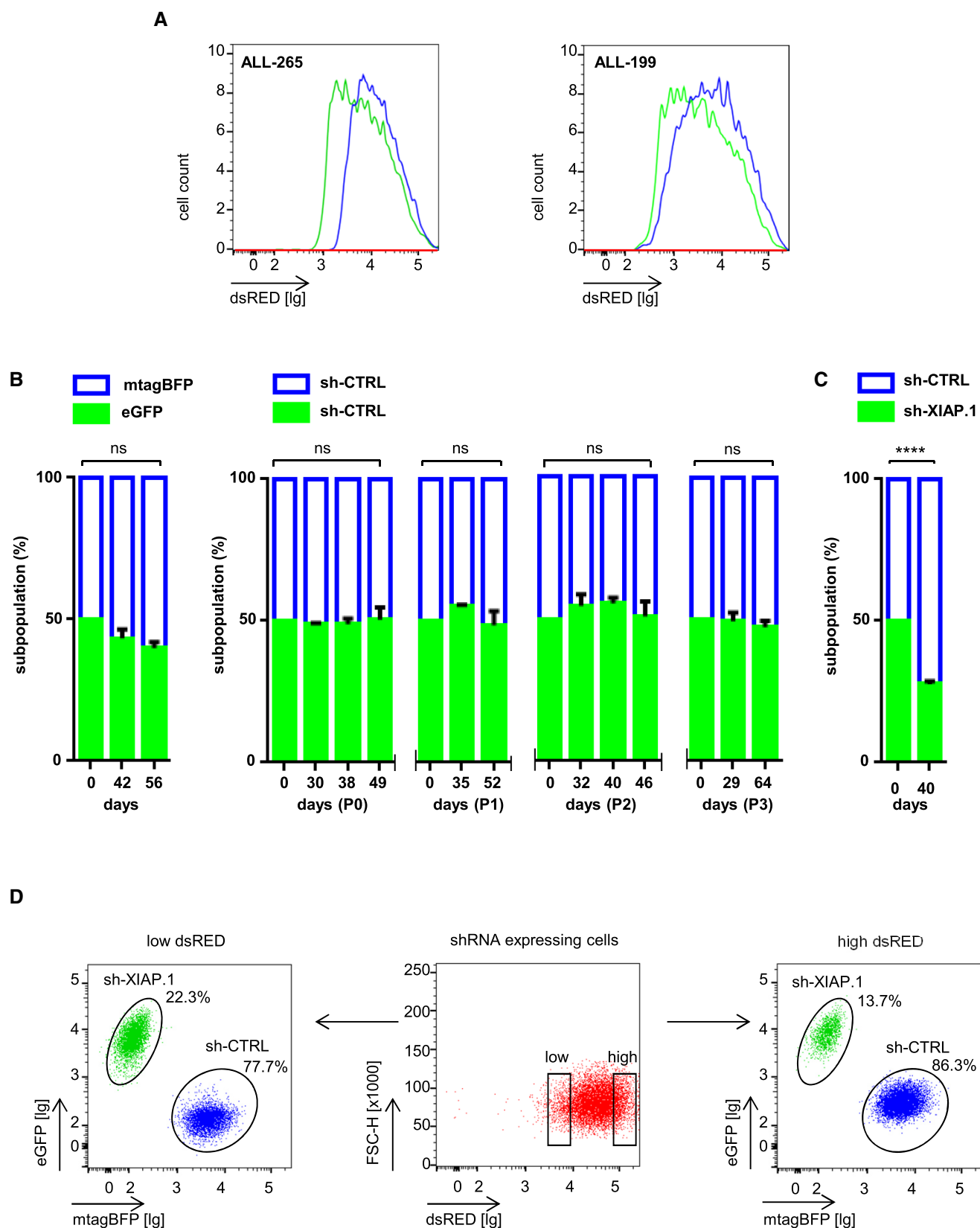


Figure EV3.