**A close-up of a barcode

Description automatically generated**

**A diagram of a graph

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**Supplementary Figure 1. Gene set enrichment analysis (GSEA) on pediatric LLA patients (40 poor x 40 good responders to MTX).** **a**,Cancer Hallmarks most enriched in poor responders compared to good responders; “*TNF-α signaling via NF-κB*” is highlighted. **b**, Enrichment plot of the pathway. (**c – e**) Expression of the respective NF-κB genes in poor and good responders (*p*-values for unpaired t-test). Size = number of genes that compose the Hallmark; ES = enrichment score; NES = normalized enrichment score; NOM p-val = nominal *p*-value; FRD q-val = false discovery rate (*q*-value); FWER p-val = familywise error rate *p*-value. Analysis made on data from Sorich *et al*.23.

**A diagram of different types of data

Description automatically generated with medium confidenceSu****pplementary Figure 2. NF-κB activity induced by MTX or TNF-α in transduced ALL cell lines at 16 and 24 h.** NF-κB signal in cell lines treated with MTX (100 nmol/l, in blue), TNF-α (100 ng/ml, in red) or vehicle (Ctrl, white bars) for (**a**) 16 h or (**b**) 24 h. One-way ANOVA followed by Tukey’s post-test was performed for each cell line. Symbols: ns: non-significant difference across conditions; ^: MTX differed from both TNF-α and Ctrl, which did not differ between each other; ⊕: TNF-α differed from Ctrl and MTX, which did not differ between each other; #: all three groups differed from one another. **c** and **d**, Ratio between averages in **a** and **b**, respectively, depicting fold change of NF-κB modulation by MTX (blue dots) or TNF-α (red dots) in relation to control (dashed line, normalized per cell line).

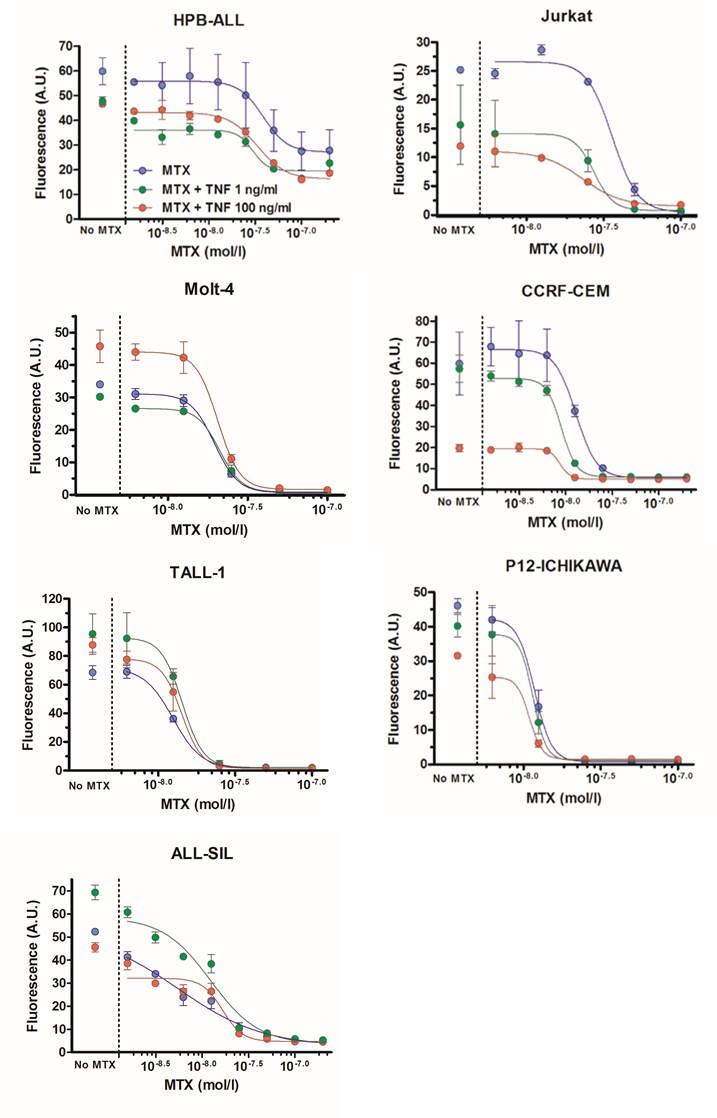
**Supplementary Figure 3. Survival curves to MTX and NF-κB inhibitors (48 h).** **a,** T-ALL cell lines treated with BAY 11 70-82. **b**, BCP-ALL cell lines treated with BAY 11 70-82. **c**, T-ALL cell lines treated with parthenolide. **d**, BCP-ALL cell lines treated with parthenolide. HPB-ALL, Nalm16 and Nalm30 received a constant dose of MTX (100 μmol/l), either alone or combined with increasing doses of the NF-κB inhibitor. Survival is expressed in relation to control (vehicle).

**a**

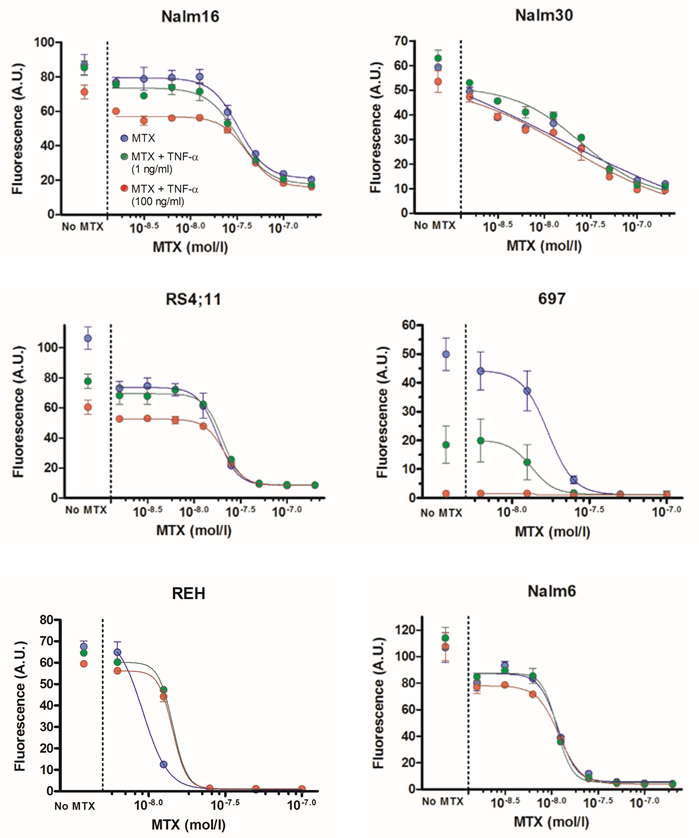
**b**

**c**

**d**



**a**



**b**

**Supplementary Figure 4.** **Survival curves to MTX in the presence or not of TNF-α.** The cytokine was added daily over the course of 96 h (green:1 ng/mL; red: 100 ng/mL; blue: only media). A.U., arbitrary units of fluorescence.