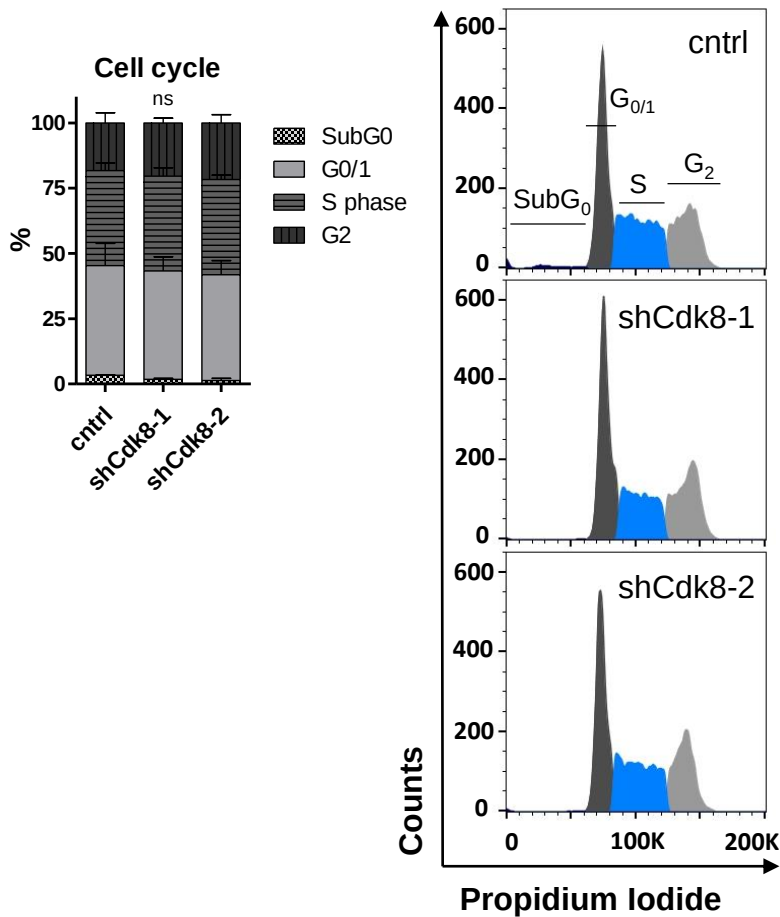
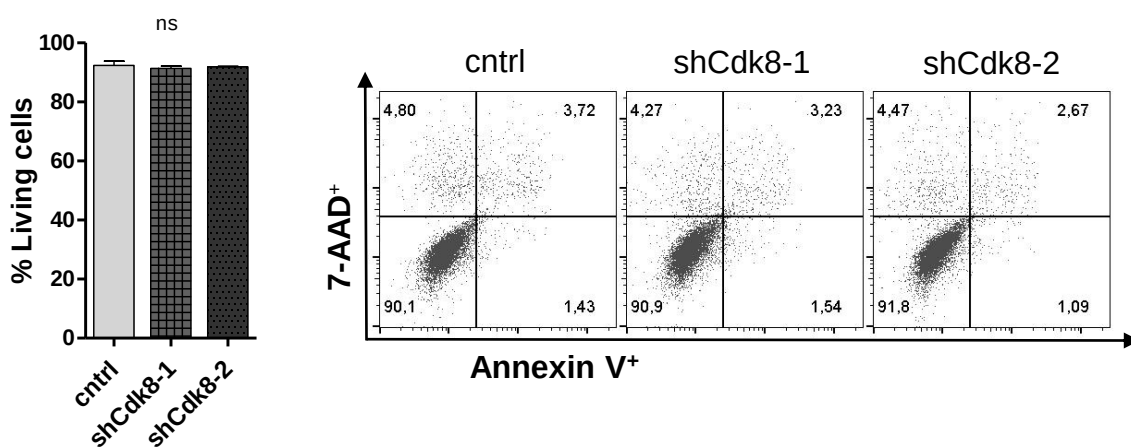


Supplementary Figures

A

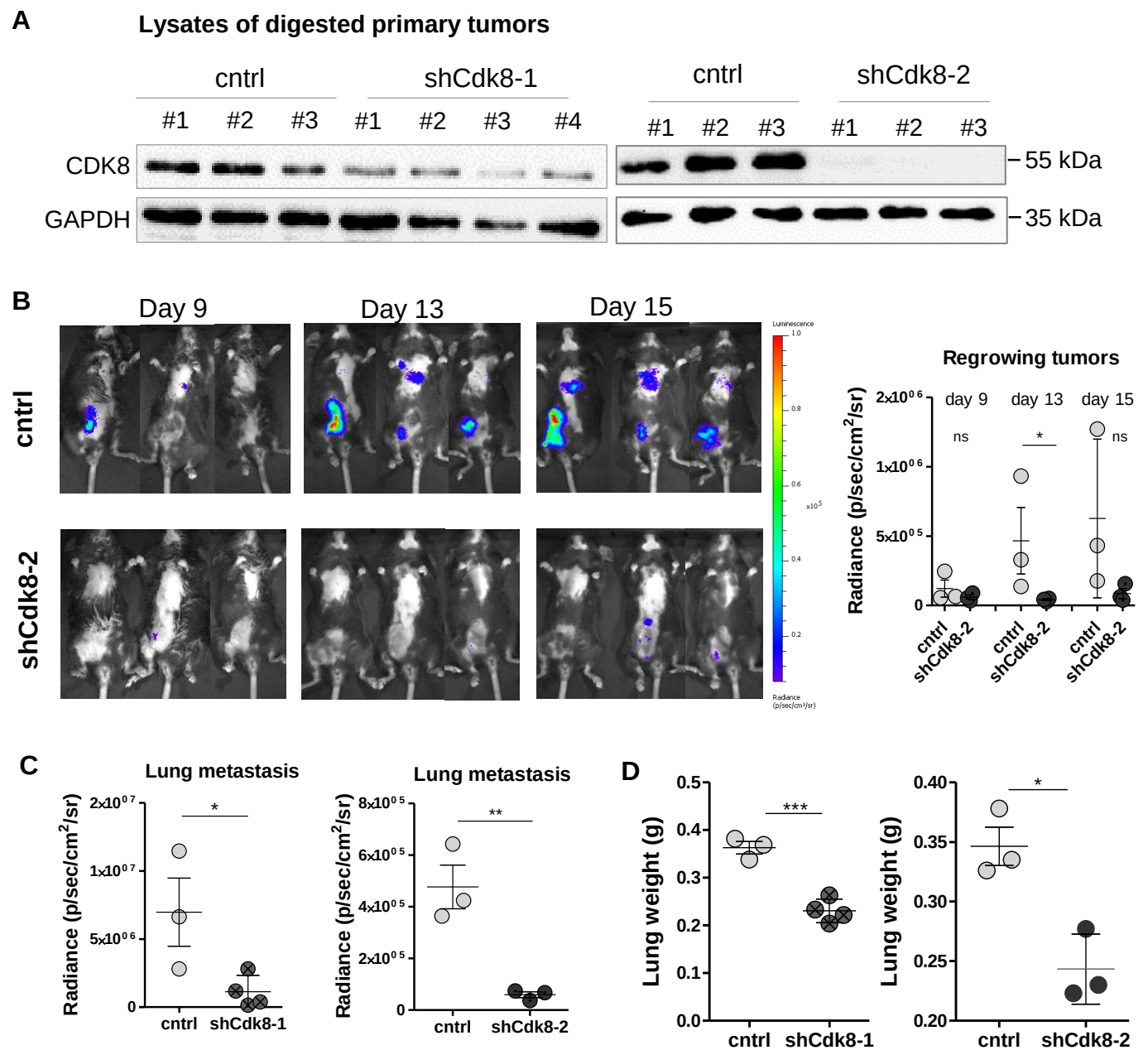


B



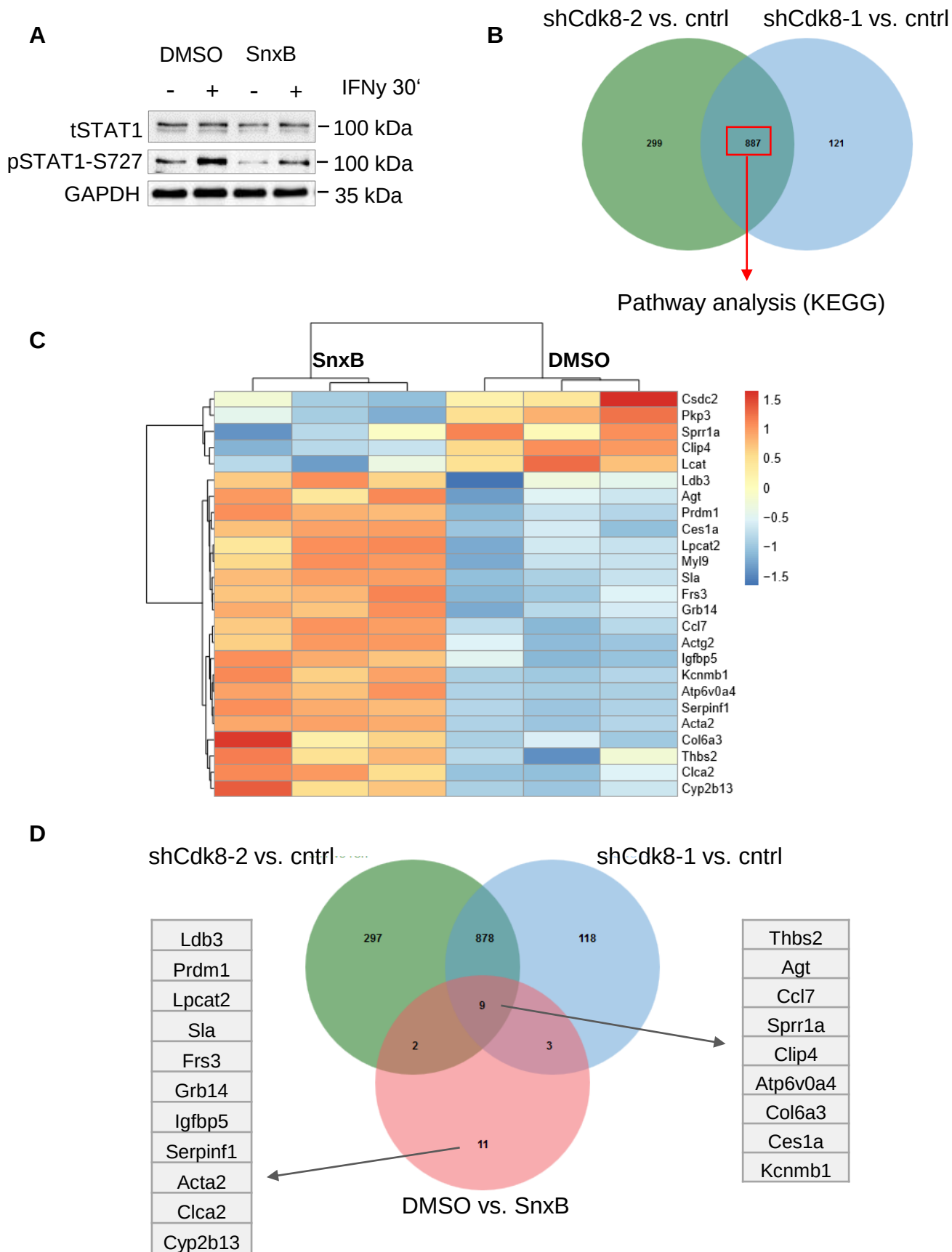
Supplementary Figure S1. Loss of CDK8 does not alter survival or cell cycle progression of murine TNBC cells.

(A) PI cell cycle staining and (B) Annexin V/ 7-AAD staining of control, shCdk8-1 and shCdk8-2 E0771 cells. Graphs show mean $\pm$ SEM of two pooled independent experiments. Representative histograms (A) and FACS blots (B) are shown.



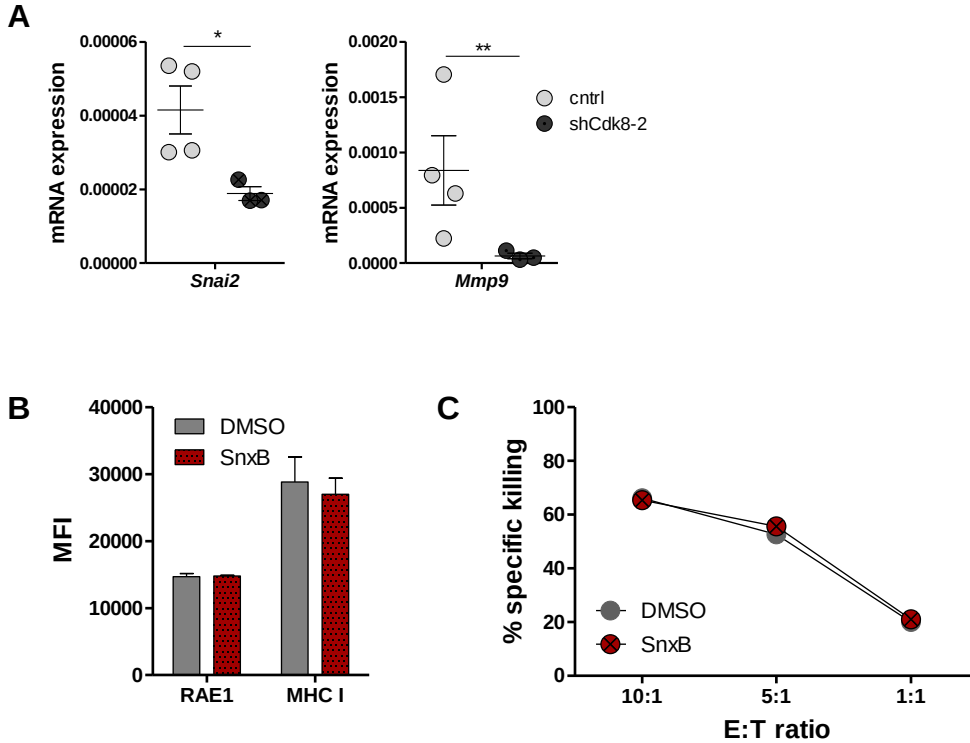
Supplementary Figure S2. CDK8 supports the re-growth of tumors and distant metastasis formation.

(A) Lysates of digested primary tumors were analyzed for CDK8 expression by western blotting. GAPDH was used as a loading control. (B) Representative *in vivo* imaging pictures of mice (left) and evaluation of measured radiance signals $\pm$ SEM (right) of mice implanted with E0771 control versus shCdk8-2 cells. *In vivo* imaging was performed on day 9, day 13 and day 15 post-surgery (endpoint of the experiment). (C) Radiance signals of *ex vivo* lung metastasis and (D) lung weight $\pm$ SEM of two independent experiments, at day 15 post-surgery.



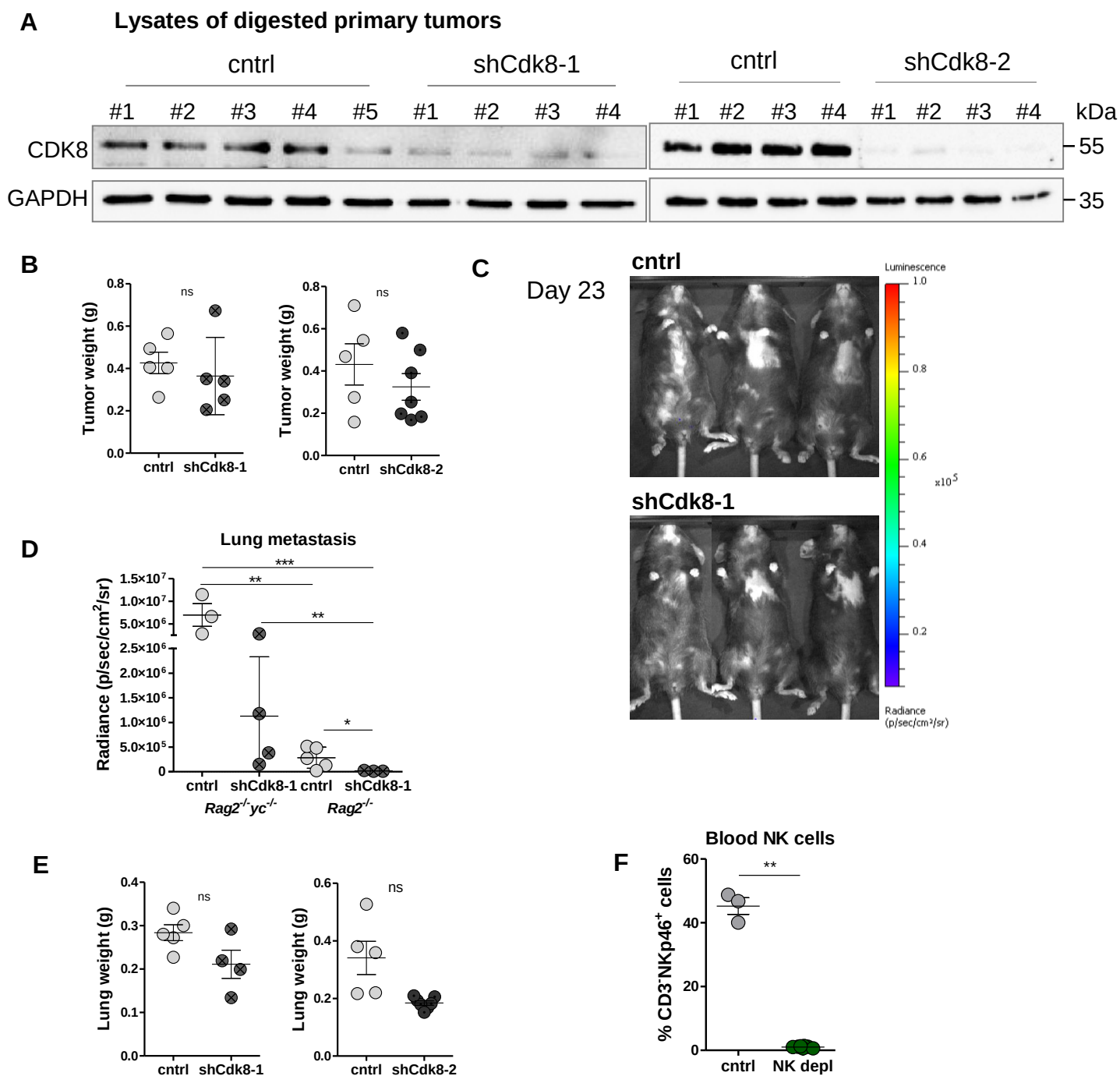
Supplementary Figure S3. CDK8/CDK19 inhibitor treatment does not mimic genetic knockdowns of CDK8.

(A) E0771 control cells were treated with 1 μ M Senexin B (SnxB) or DMSO for 48 hours and incubated $\pm$ IFN γ for 30min and blotted for STAT1, pSTAT1-S727 and GAPDH expression. (B) Venn diagram depicting overlap of genes regulated by two different CDK8-targeting shRNAs (shCdk8-1 and -2). (C) Heatmap of 25 differentially expressed genes between E0771 control cells treated with 1 μ M Senexin B (SnxB) or DMSO for 48 hours (RNA-seq data; n=3 replicates). (D) Venn diagram depicting overlaps of genes regulated upon Senexin B treatment with genes regulated by two different CDK8-targeting shRNAs (shCdk8-1 and -2). Left table shows 11 genes solely regulated by Senexin B treatment and right table depicts 9 genes regulated upon Senexin B treatment and genetic CDK8 knockdowns.



Supplementary Figure S4. CDK8/CDK19 inhibitor treatment of E0771 does not alter their killing by NK cells.

(A) Real-time quantitative PCR of RNA extracted from digested primary tumors of control versus shCdk8-2 implanted *Rag2^{-/-}γc^{-/-}* mice $\pm$ SEM. Expression levels of *Snai2* and *Mmp9* were normalized to the house keeping gene *Rplp0*. (B) MFI of RAE1 and MHC I (H-2K+ H-2D) expression of E0771 cells treated with 1 μ M Senexin B (SnxB) or DMSO as a cntrl; expression levels of NK ligands were analyzed by flow cytometry. Bar graphs represent technical triplicates (mean $\pm$ SEM). (C) IL2-expanded C57BL/6 NK cells were incubated for 4 hours with CFSE-labelled E0771 control tumor cells pretreated with 1 μ M Senexin B (SnxB) or DMSO for 44 hours in effector:target (E:T) ratio of 10:1, 5:1 and 1:1. The specific killing was assessed by flow cytometry. One representative experiment out of two independent experiments is shown.



Supplementary Figure S5. Loss of CDK8 in TNBC increases NK-cell mediated tumor surveillance.

(A) Lysates of digested primary tumors were analyzed for CDK8 expression by western blotting. GAPDH was used as a loading control. (B) Tumor weight (g) $\pm$ SEM of *Rag2*^{-/-} mice shown in Figure 4B. (C) Representative *in vivo* imaging pictures of *Rag2*^{-/-} mice on day 23 post surgery. (D) Comparison of radiance signals of lung metastasis $\pm$ SEM of *Rag2*^{-/-}*yc*^{-/-} (on day 15 post-surgery) and *Rag2*^{-/-} mice (on day 23 post-surgery) implanted with control versus shCdk8-1 TNBC cells. (E) Lung weight (g) of *Rag2*^{-/-} mice $\pm$ SEM. (F) Percentage of CD3⁺NKp46⁺ NK cells $\pm$ SEM in blood of control and NK-cell depleted mice, after three injections of α NK1.1 antibody and prior to tumor cell implantation; percentage of NK cell numbers were analyzed by flow cytometry.