Supplemental Figure Legends

Figure S1

Flow chart of the study.

Figure S2

Co-occurences and mutual exclusions in PRC2-altered (top) or WT (bottom) computed with the DISCOVER algorithm. The circos plots depict the co-occurences in genetic lesions.

Figure S3

A) Variant allelic fractions of PRC2 alterations in the GRAALL-2003-2005 cohort. Each dot represents one alteration. B) Variations of the variant allelic fraction of PRC2 alterations from diagnosis-relapse couples of 5 T-ALL samples. C) Acquisition, persistence and losses of PRC2 alterations from diagnosis-relapse couples of 5 T-ALL samples.

Figure S4

A) H3K27ac and H3K27me3 signals fold changes determined by ELISA in 6 PRC2 WT and 6 PRC2 ALT T-ALL PDX.

B) Distribution of the differential H3K27me3 and H3K27ac peaks in the genome.

C) Venn diagram showing the distribution of H3K27ac peaks in PRC2 WT or ALT samples.

D) Heatmap representing the unsupervised hierarchical clustering of 7 T-ALL primary samples based on the differential H3K27ac distribution at 4,151 loci in PRC2-altered T-ALL (n=7) vs WT samples (n=7).

E) H3K27ac and H3K27me3 signals fold changes determined by ELISA in 6 PRC2 WT PDX upon control or GSK343 treatment (3 µM, 24h).

Figure S5

A) Volcano plot of the differential H3K27ac distribution analysis in PRC2-altered T-ALL (n=7) vs WT samples (n=7).

B) Heatmap representing the unsupervised hierarchical clustering of 7 T-ALL primary samples based on the differential H3K27ac distribution at listed key hematopoietic TFs in PRC2-altered T-ALL (n=7) vs WT samples (n=7).

C) Bar plot indicating the enrichment in transcription factors signatures among the genes gaining H3K27ac signal at their promoters in PRC2 ALT samples.

D) TFs RNA expression from RNA-seq analysis of 47 T-ALL primary samples (33 PRC2 WT,14 PRC2 altered).

E) Visualization of the distribution of H3K27ac, H3K27me3 and H3K4me3 at the *HOXC* cluster in 1 PRC2 ALT and 1 PRC2 WT primary sample. The depicted box shows the *HOXC10* locus. These data are representative of the entire series.

F) Fold changes in HATs RNA expression in PRC2-altered T-ALL (n=14) vs WT samples (n=33) from RNA-seq analysis of 47 T-ALL primary samples.

Figure S6

A) Western blot indicating H3K27me3 and H3K27ac levels in the indicated T-ALL cell lines treated or not with GSK343 3 µM for 24h.

B) Cell viability of the indicated T-ALL cell lines treated with increased doses of GSK343 measured for 3 days.

C) Cell viability of the indicated T-ALL cell lines treated with JQ1 at the indicated doses alone or in combination with GSK343 3 µM for 3 days.

Figure S7

A) Viability of T-ALL PDX measured after 3 days of treatment with ruxolitinib at the indicated doses. Means and SEM are plotted (WT n=25, Altered n=11).

B) Isobolograms depicting survival rates of T-ALL PDX evaluated after 3 days of exposure to a combination of JQ1 and ruxolitinib doses (WT n=12, Altered n=12). 75% and 50% survival isoboles are represented as dashed lines.

C) Bar plot indicative of the JQ1/ruxolitinib combination indexes determined with Compusyn. Means and SEM are plotted. Each dot represents a replicate (WT n=12, Altered n=12).

Figure S1

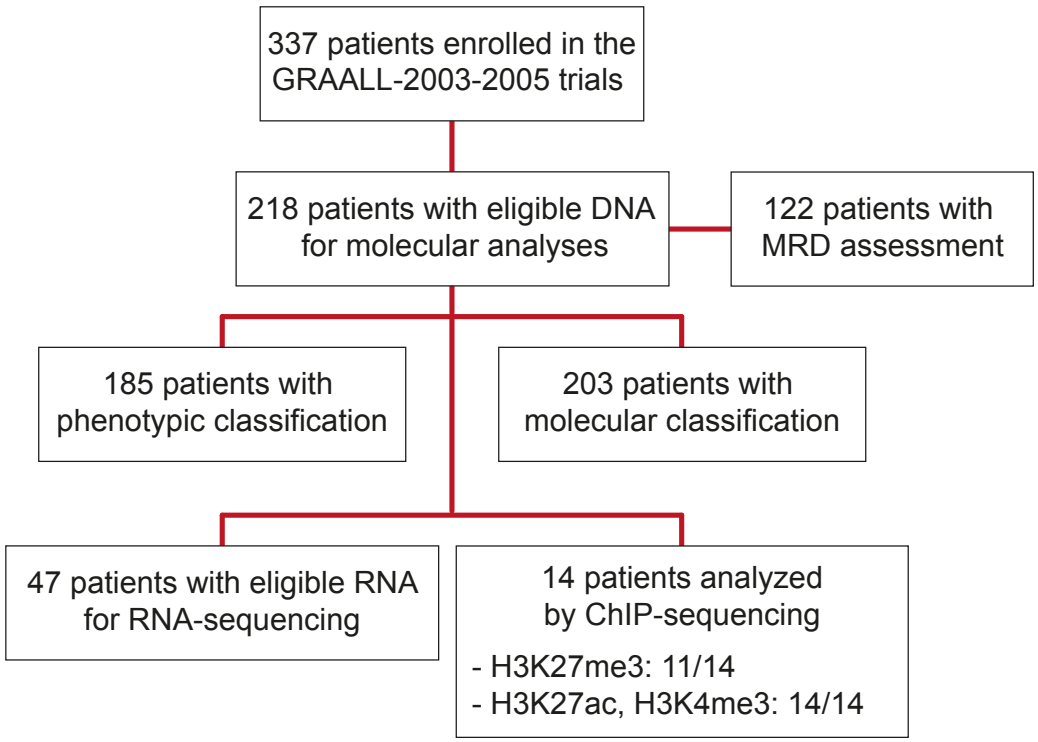

337 patients enrolled in the GRAALL-2003-2005 trials
218 patients with eligible DNA for molecular analyses
122 patients with MRD assessment
185 patients with phenotypic classification
203 patients with molecular classification
47 patients with eligible RNA for RNA-sequencing
14 patients analyzed by ChIP-sequencing
- H3K27me3: 11/14
- H3K27ac, H3K4me3: 14/14

Figure S2 (related to Figure 2)

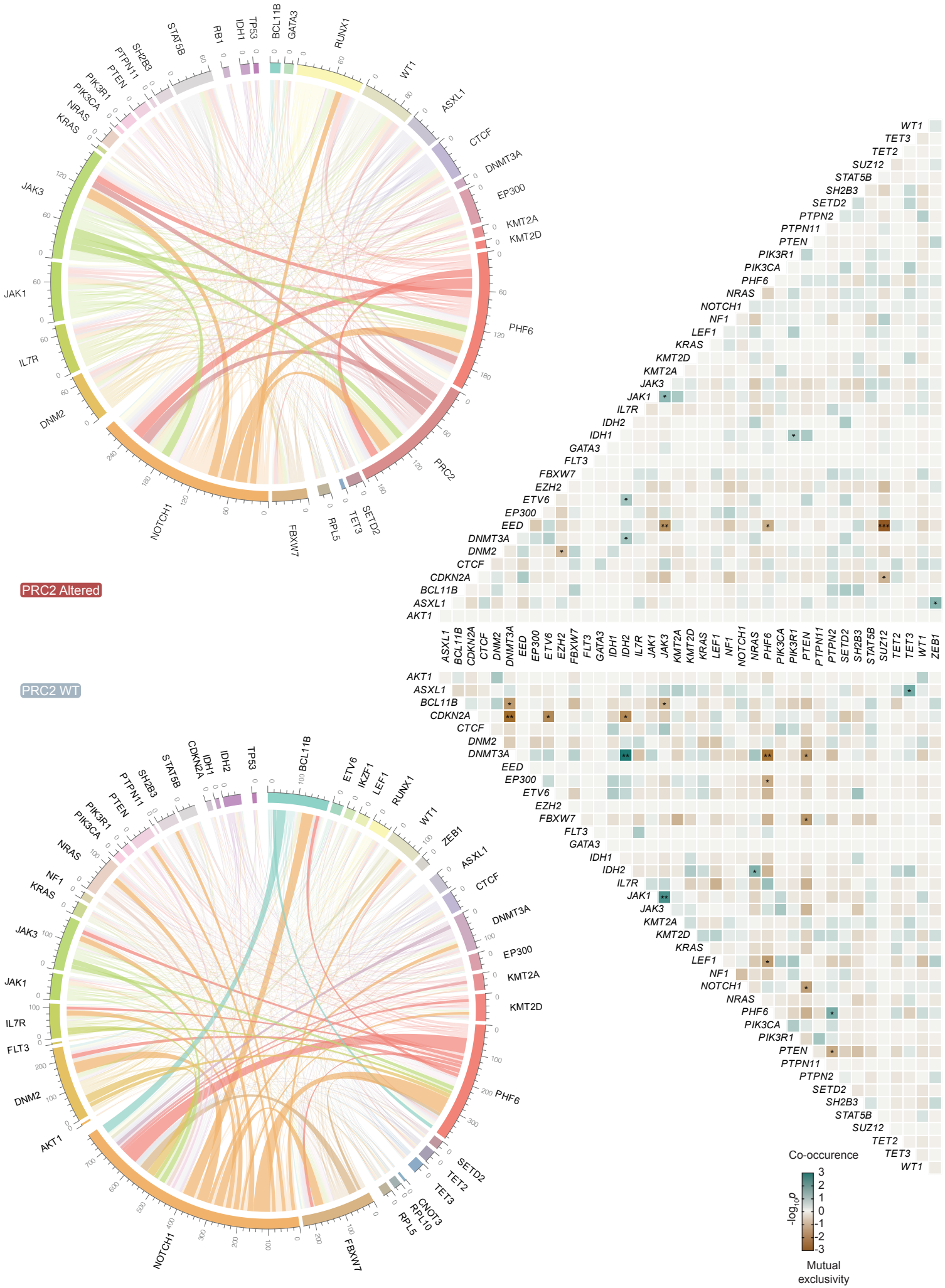


Figure S3 (related to Figure 2)

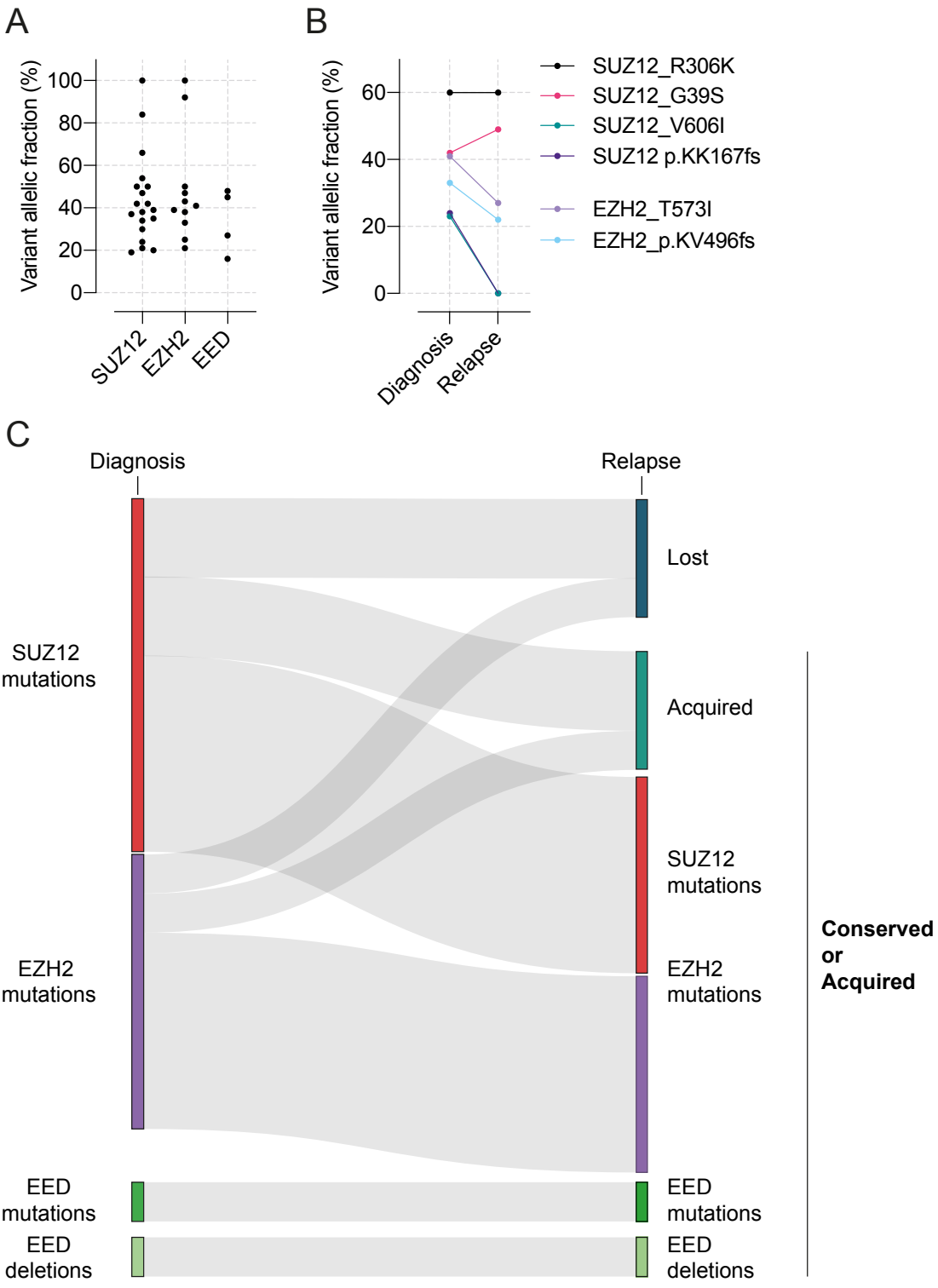


Figure S4 (related to Figure 5)

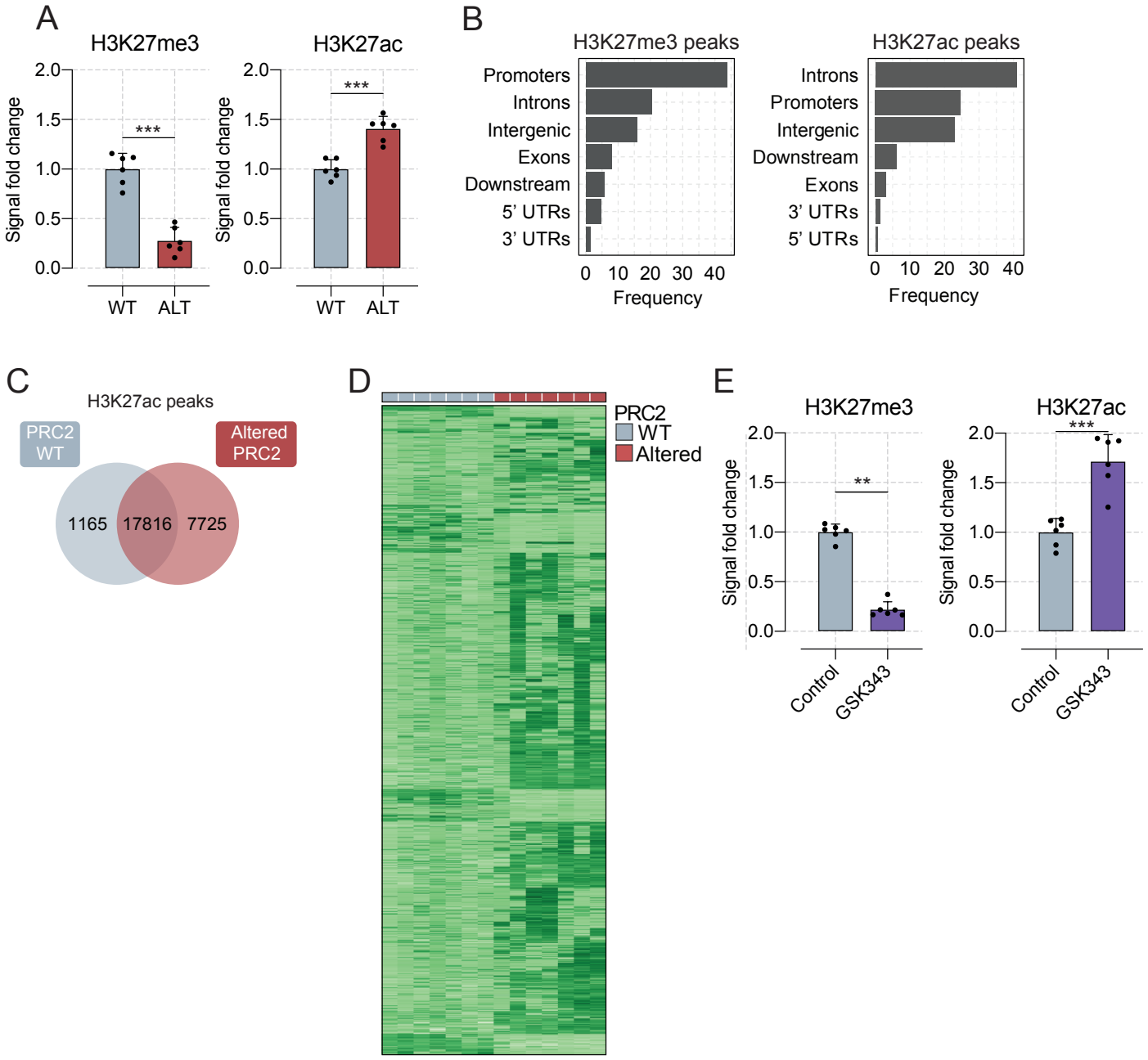


Figure S5

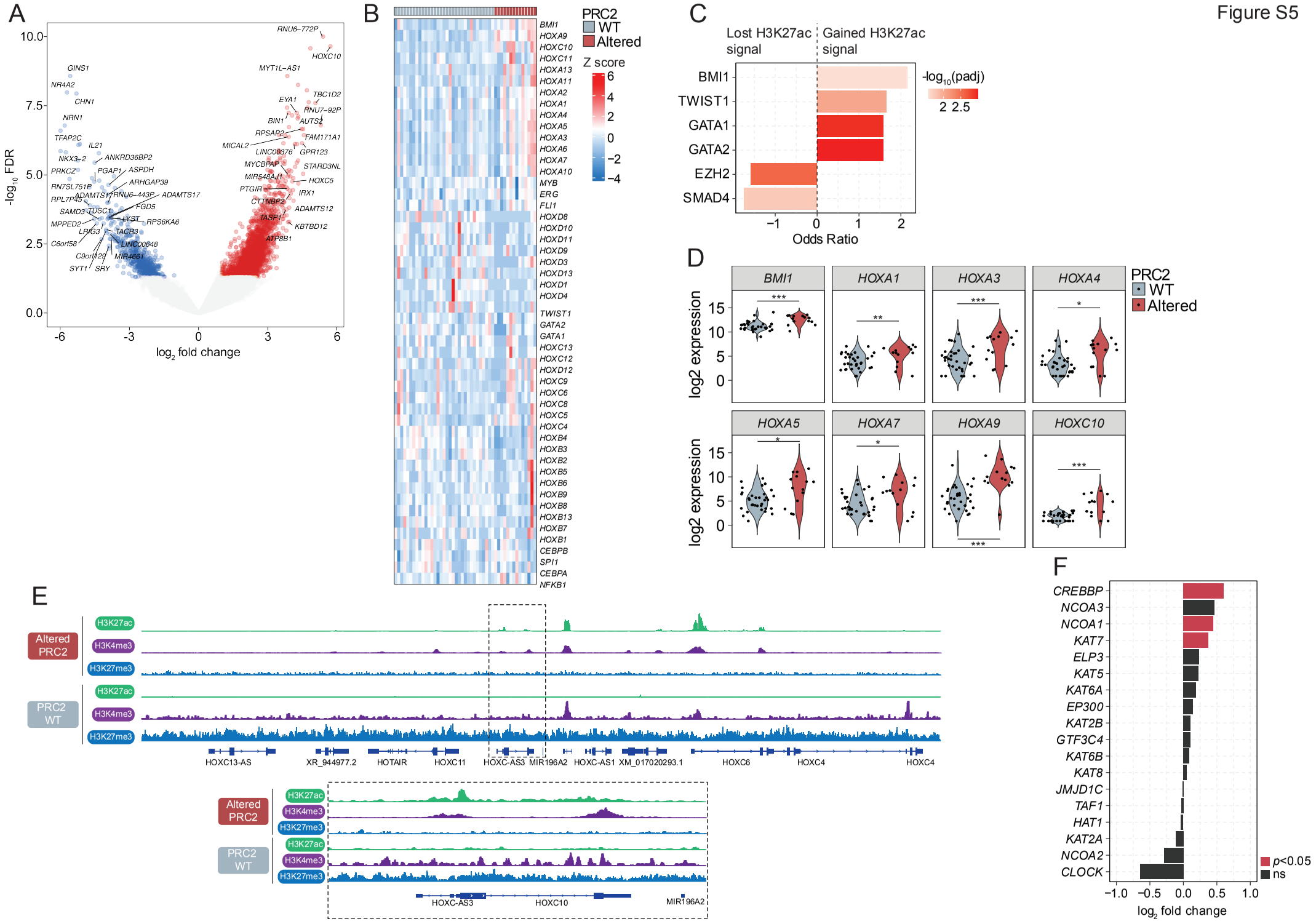

A
B
C
D
E
F
PRC2
WT
Altered
Z score
Lost H3K27ac signal
Gained H3K27ac signal
-log10(padj)
Odds Ratio
log2 expression
H3K27ac
H3K4me3
H3K27me3
Altered PRC2
PRC2 WT
p<0.05
ns
log2 fold change
-log10 FDR

Figure S6 (related to Figure 6)

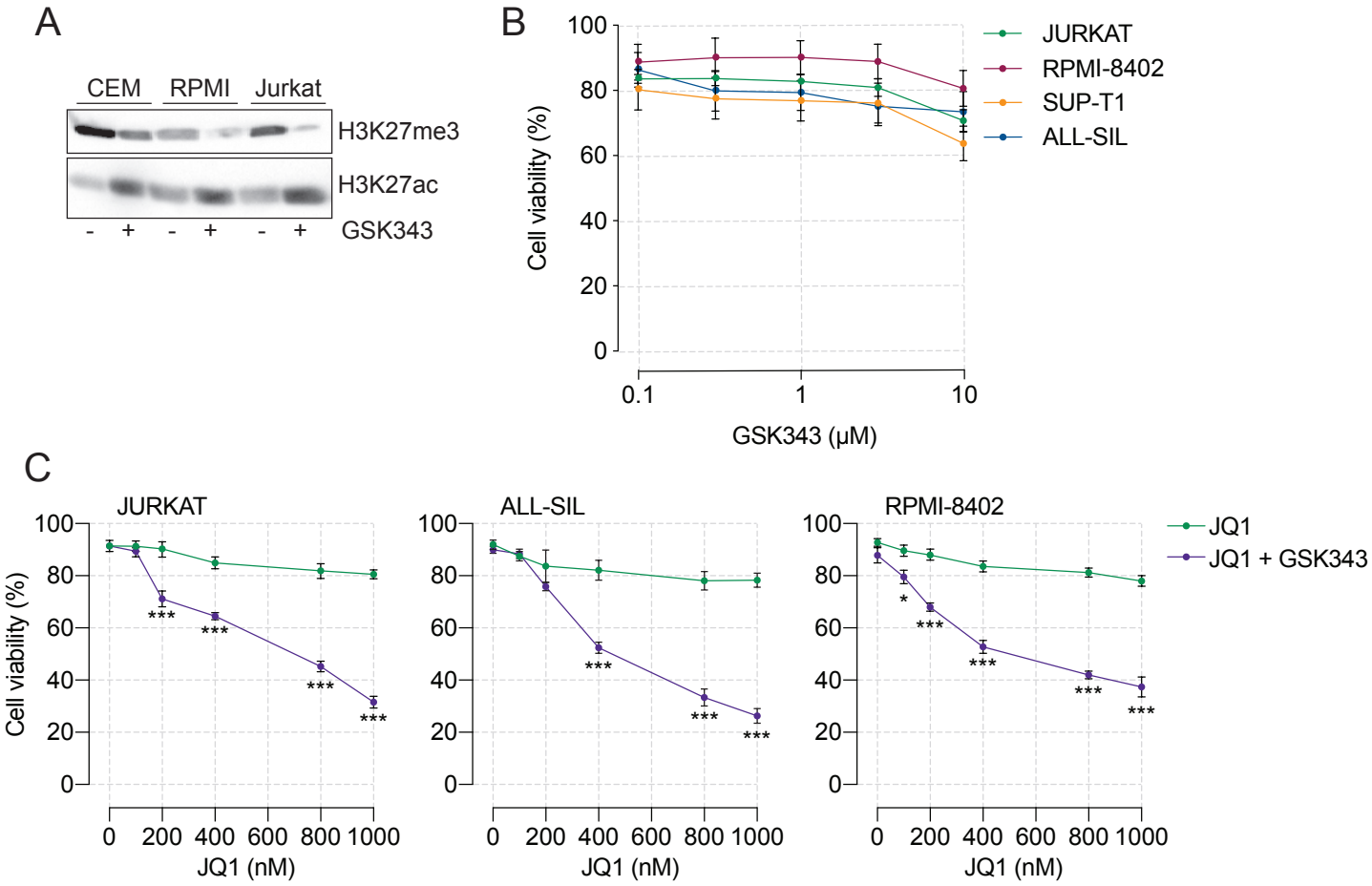
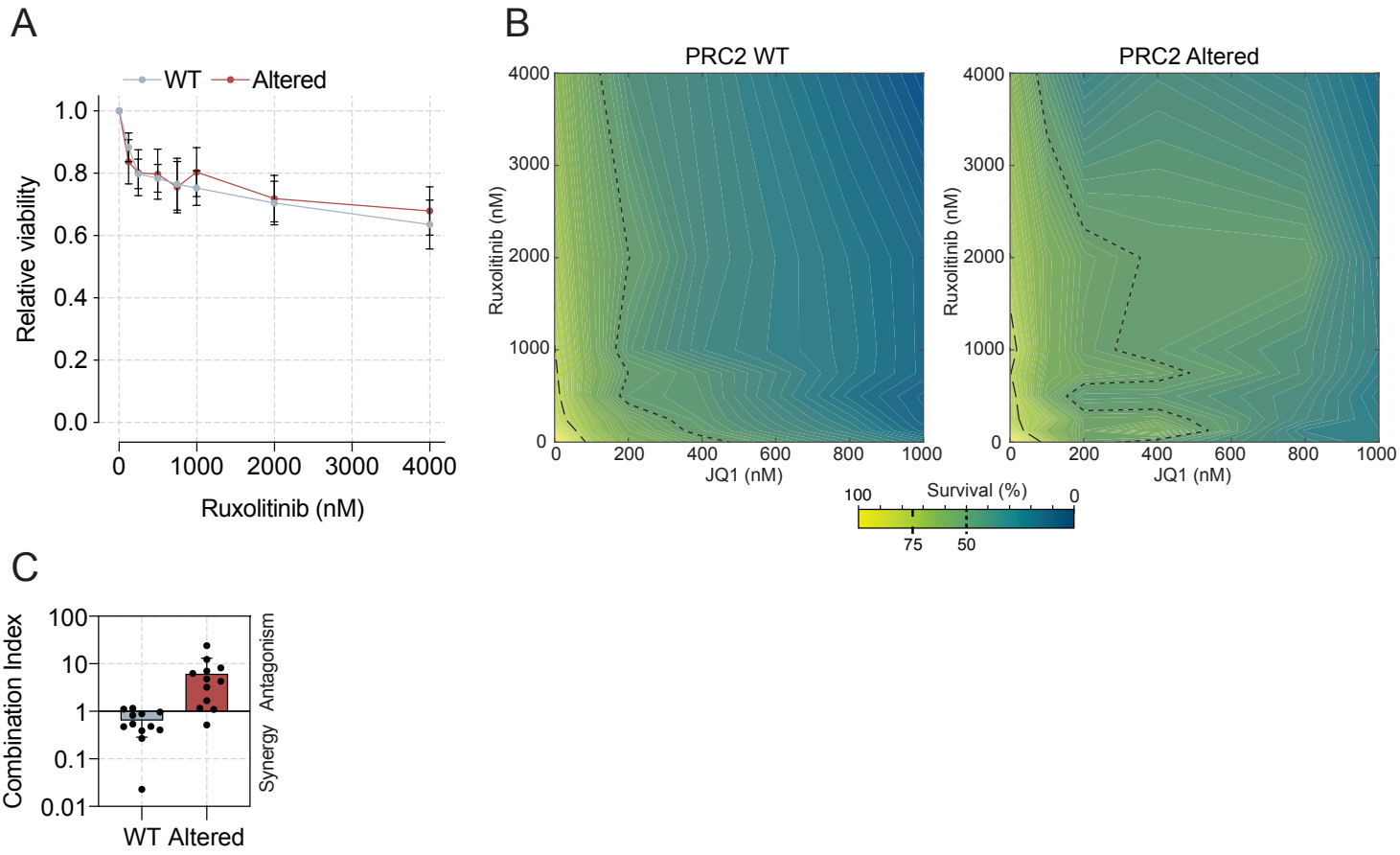


Figure S7


A
WT
Altered
Relative viability
1.0
0.8
0.6
0.4
0.2
0.0
0
1000
2000
3000
4000
Ruxolitinib (nM)
B
PRC2 WT
PRC2 Altered
Ruxolitinib (nM)
JQ1 (nM)
Survival (%)
100
75
50
0
C
Combination Index
100
10
1
0.1
0.01
Synergy
Antagonism
WT
Altered