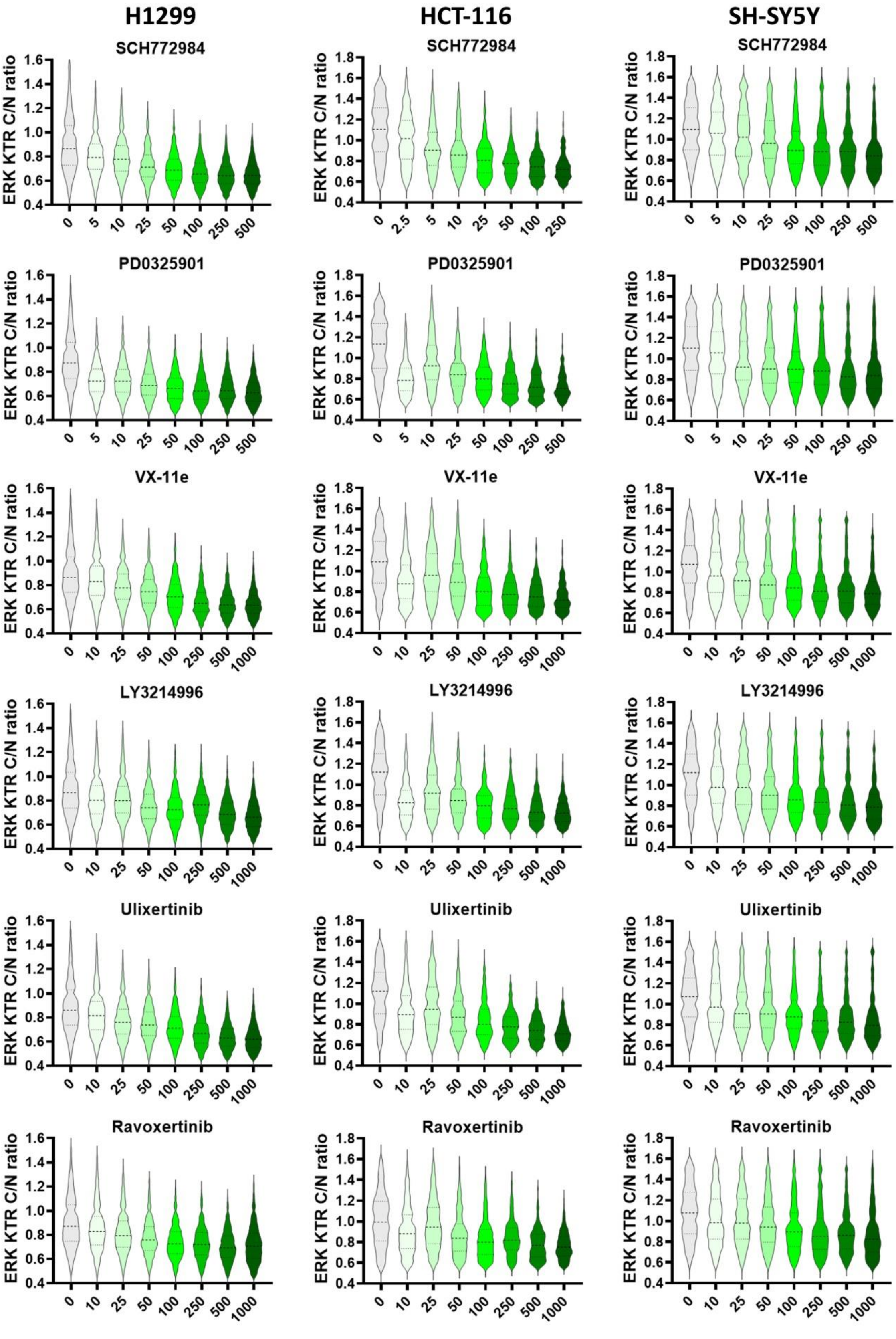
H1299
HCT-116
SH-SY5Y
SCH772984
PD0325901
VX-11e
LY3214996
Ulixertinib
Ravoxertinib
ERK KTR C/N ratio
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
0
2.5
5
10
25
50
100
250
500
1000

Figure S1. ERK KTR median intensity ratios for cytoplasm to nucleus (C/N ratio) are shown by violin plots for cells treated with ERK inhibitors for 24 hours. Median values and 25th to 75th percentiles are shown.

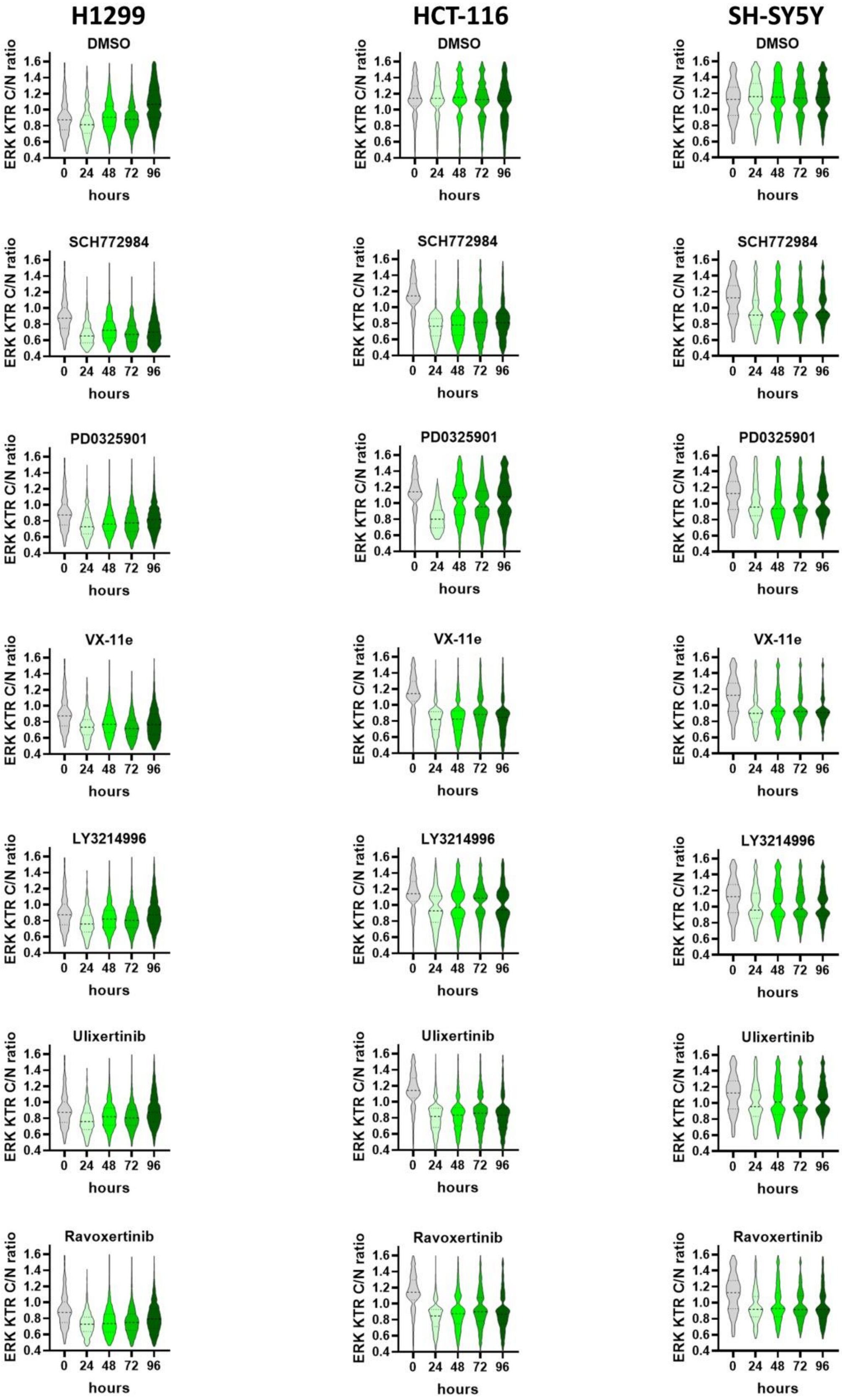
H1299
HCT-116
SH-SY5Y
DMSO
SCH772984
PD0325901
VX-11e
LY3214996
Ulixertinib
Ravoxertinib
ERK KTR C/N ratio
0.4
0.6
0.8
1.0
1.2
1.4
1.6
0
24
48
72
96
hours

Figure S2. ERK KTR median intensity ratios for cytoplasm to nucleus (C/N ratio) are shown by violin plots for cells treated with drugs for 24, 48, and 96 h, as well as prior treatment (0 h). Median values and 25th to 75th percentiles are shown.

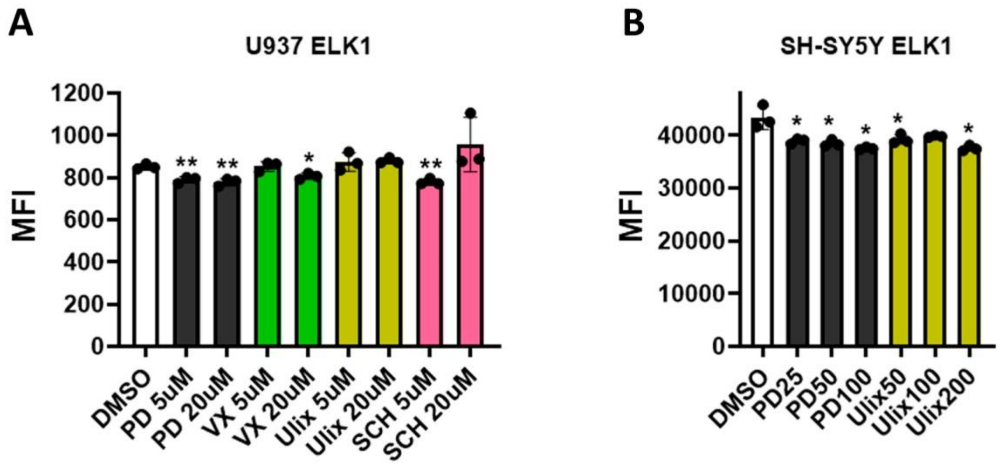

Figure S3. Measurement of ELK1 activity in U937 and SH-SY5Y cells. Mean fluorescence intensities (MFI) measured in U937 and SH-SY5Y cells with stable expression of FuGW-S(Elk1)p-mKate2 system. Measurements were taken 24 hours after drug treatment.

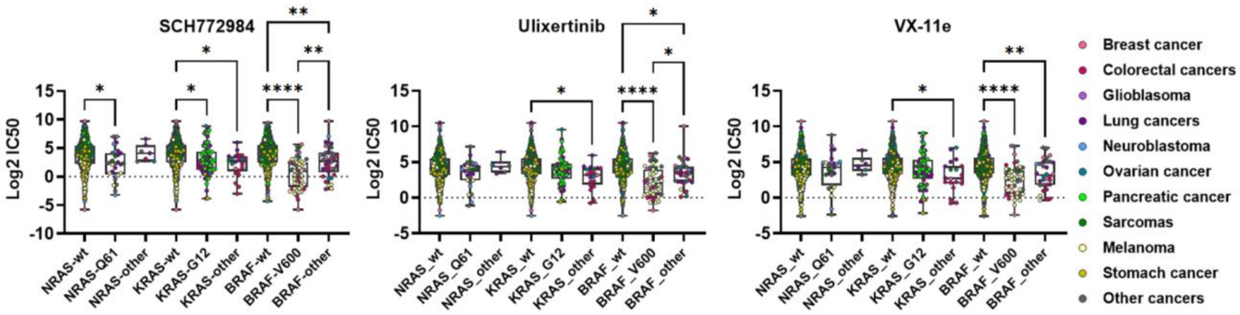

Figure S4. Impact of codon mutation on sensitivity to ERK1/2 inhibitors. IC50 values for SCH772984, ulixertinib, and VX-11e were compared for cells with wild type genes (wt) and with mutations in certain codons. Only mutated codons which represented by 10 or more cell lines are shown. *- $p < 0.05$, **- $p < 0.01$, ***- $p < 0.001$ as analyzed by one-way ANOVA.

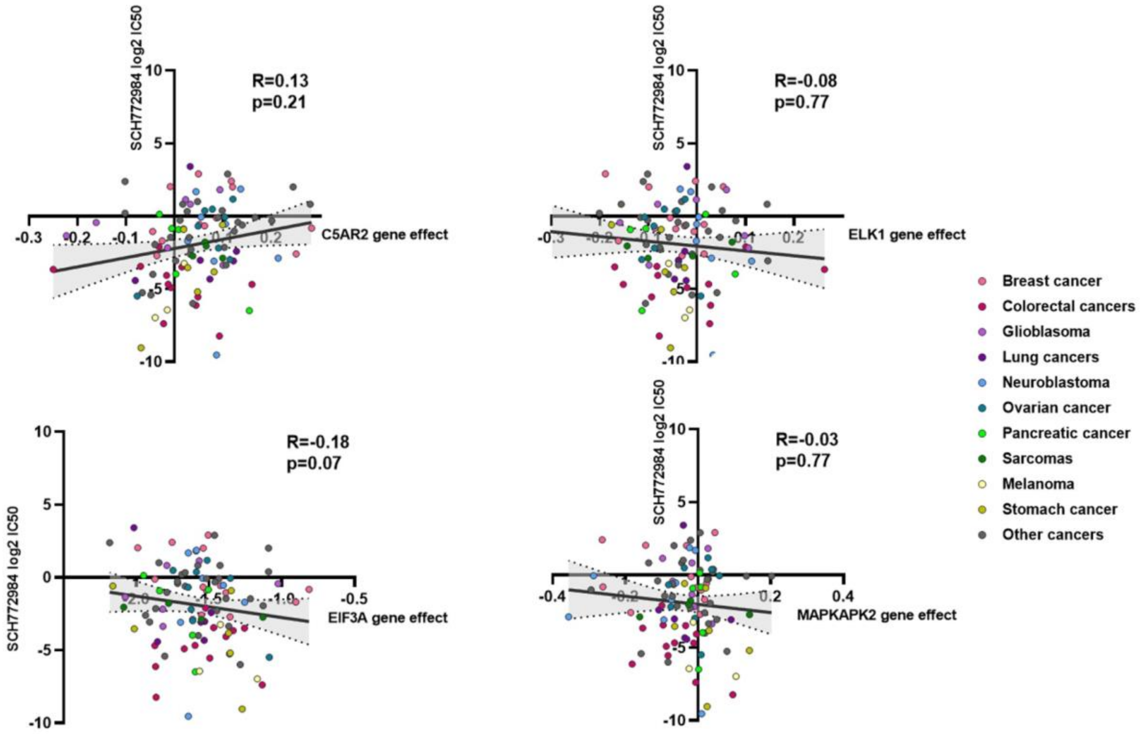

Figure S5. Correlation of gene effect and SCH772984 IC50 values for solid cancer cell lines. Pearson correlations were calculated for *C5AR2*, *ELK1*, *EIF3A*, *MAPKAPK2* gene effects from DepMap 21Q4 Chronos database and IC50 values from Genomics of Drug Sensitivity in Cancer database. Gene effect values >0 correspond to increased cell proliferation and survival after CRISPR gene knockout, and <0 to decreased cell proliferation and survival (dependency).

Table S1. Differential analysis of genetic features impact on sensitivity to ERK inhibitors. Each list contains data for particular drug IC50 ratio between cells with particular mutation vs. wild type cells. p-values were calculated using non-parametric Mann-Whitney t-test, p-adj- p-values adjusted by FDR.

Table S2. List of 478 ERK-related genes. For each gene the source (Gene Ontology or REACTOME) is indicated.

Table S3. Elastic net results. Table contains elastic net coefficients for each gene and z-scores based on first 100 rounds of elastic net.

Table S4. Cell lines and compounds used in the study. First list contains description for cell lines used in the study, and second for drugs.