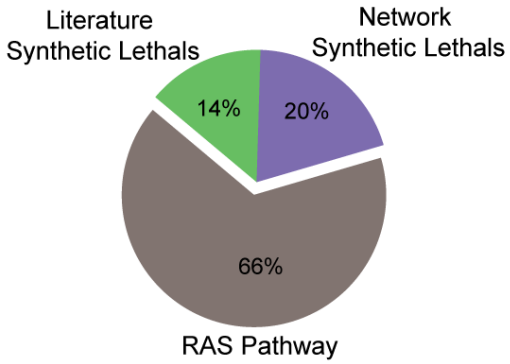
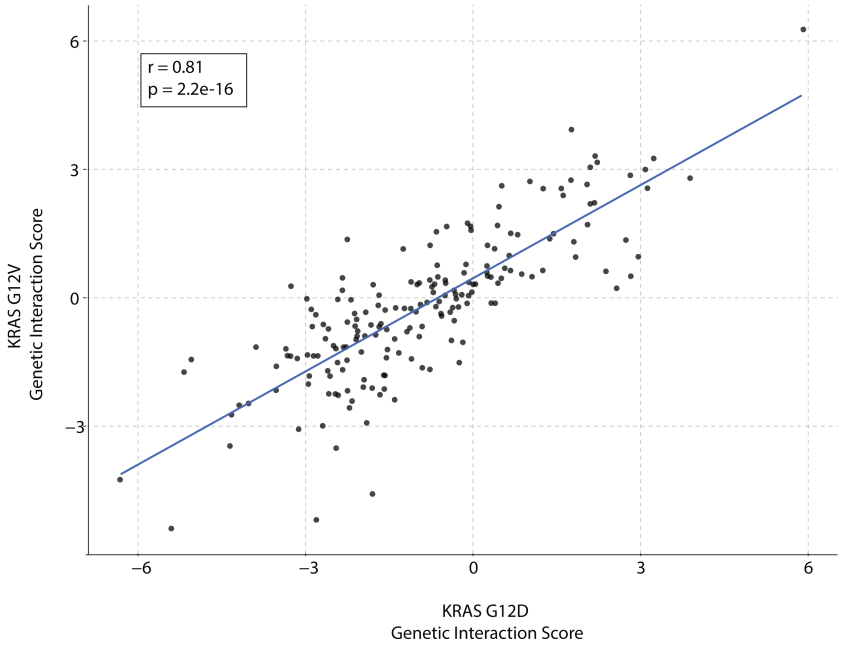
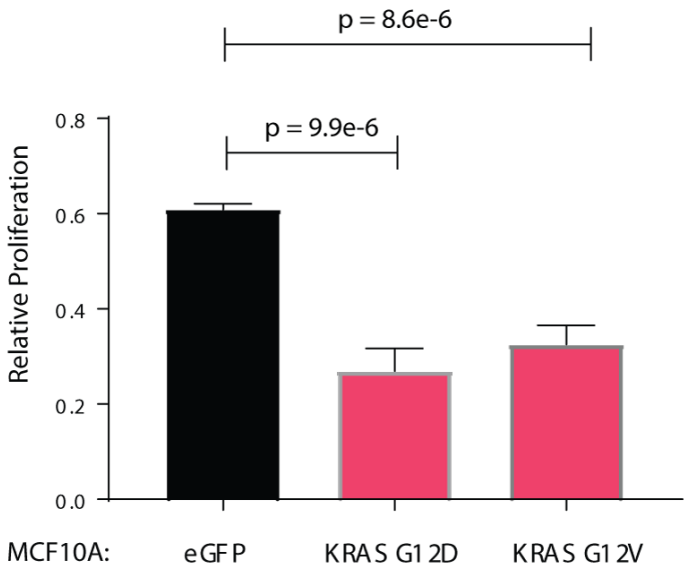
Supplementary Figures



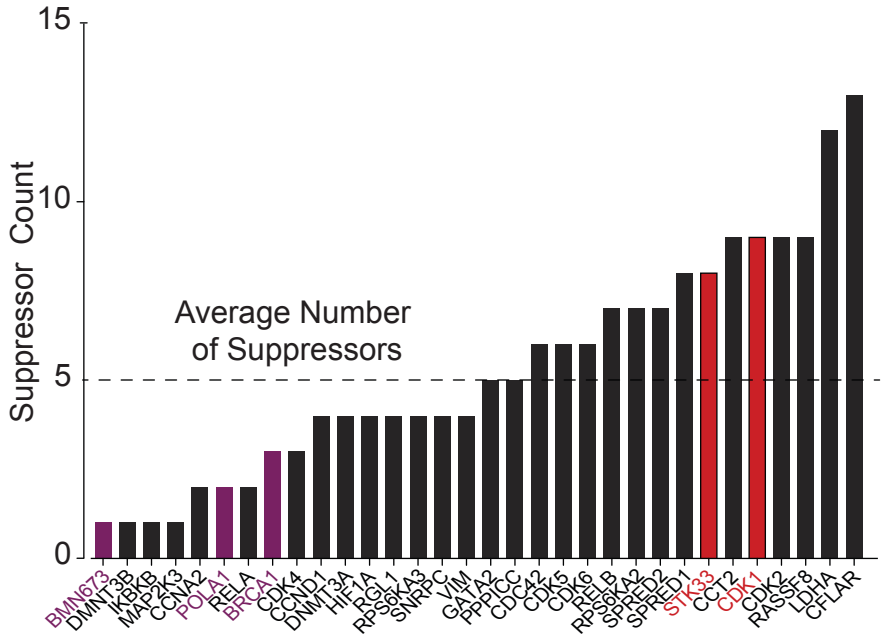
Supplementary Figure 1: Distribution of 196 genes tested in esiRNA screen. Individual genes are listed in Supplementary Table 4.



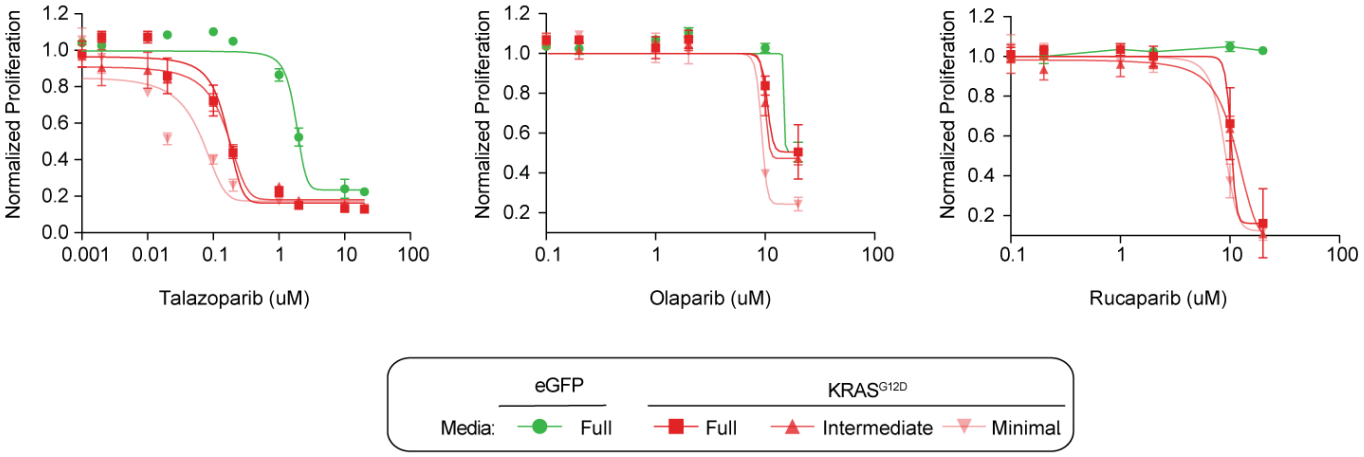
Supplementary Figure 2: Comparison of KRAS G12V and G12D screens. Isogenic KRAS G12V and KRAS G12D expressing MCF10A lines were screened using the same esiRNA library and scores for genes compared. P-value of Pearson's correlation (r) is shown.



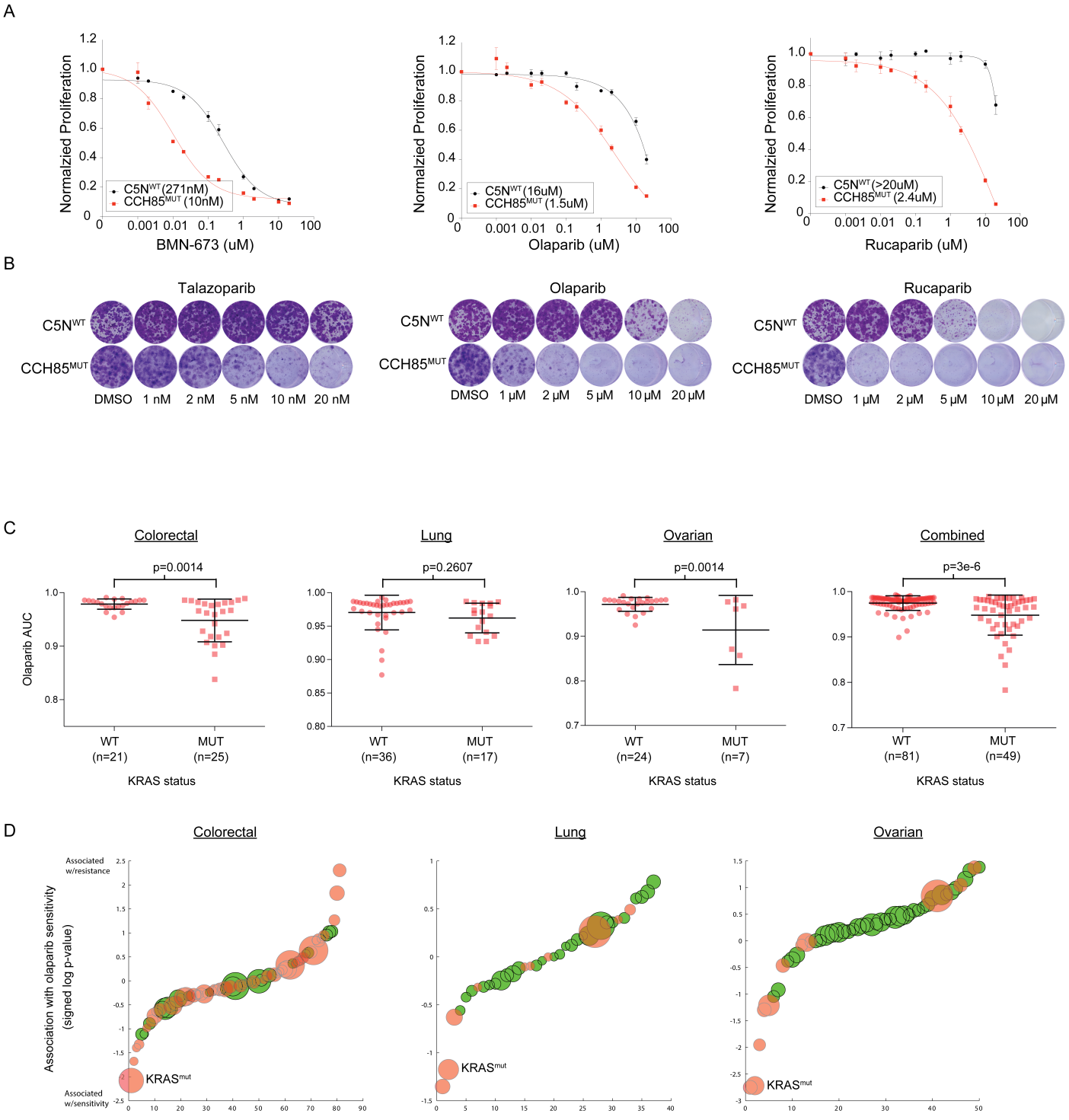
Supplementary Figure 3: siRNA mediated validation of BRCA1 dependency in mutant KRAS cells. The indicated MCF10A isogenic cell lines were transfected with BRCA1 siRNA and proliferation measured over 72 hours. Data are proliferation relative to control non-targeting knockdown. P-values based on two-sided t-test. Error bars are s.d.



Supplementary Figure 4: Suppressors of synthetic lethal genes. Histogram of the number of suppressor genes identified for KRAS synthetic lethal genes and talazoparib. Suppressors defined as genes with a *Z*-score > 2. Purple gene highlight network genes from the cell cycle/replication cluster, red genes highlight two published KRAS synthetic lethal genes with suppressor counts greater than average.



Supplementary Figure 5: PARP inhibitor sensitivity is independent of media conditions. Relative proliferation of control eGFP and KRAS G12D MCF10A lines after treatment with PARP inhibitors talazoparib, rucaparib or olaparib for 96 hours in full, intermediate or minimal media conditions. Error bars, s.d.



Supplementary Figure 6: Olaparib drug response analysis in cancer cell lines collections. (A) Relative proliferation of RAS wild-type C5N skin keratinocyte cells or carcinogen induced CCH85 HRAS-mutant skin carcinoma cells in the presence of PARP inhibitors for 72 hours. IC50s are indicated. (B) Long-term clonogenic growth of the same cell lines treated with PARP inhibitors for 9 days. (C) Cell lines from the three different tumor types that harbor >5 KRAS mutant and >5 wild-type cell lines were

analyzed with respect to olaparaib sensitivity in the genomics of drug sensitivity database (GDSC) (Yang et al., 2013). Responses were compared based on drug area under the dose response curve (AUC) analysis (Yang et al., 2013) with lower values indicating more drug sensitivity. Shown are responses for each tumor type individually as well as all three combined. The number of cell lines in each category are shown. P-values based on a two-sided t-test. (D) Associations of genomic features with olaparib sensitivity downloaded from the GDSC database. P-values of association were converted into a signed score by taking the log of the p-value and adding a sign to indicate association with sensitivity (negative values) and association with resistance (positive values). Mutation based features in red and copy-number based features in green. Error bars, s.d.. Not significant, n.s.