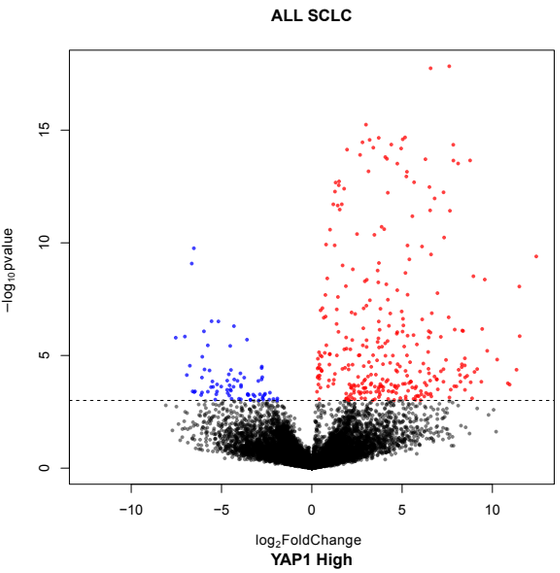
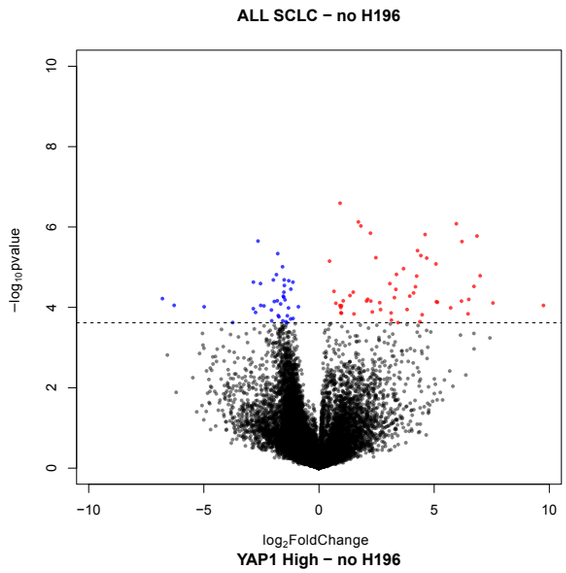
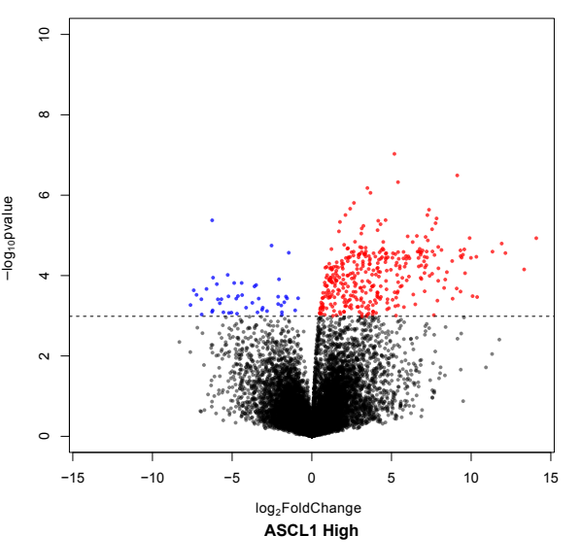
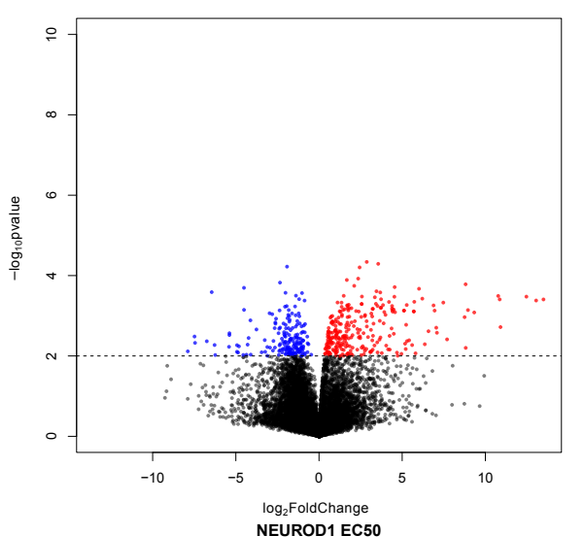
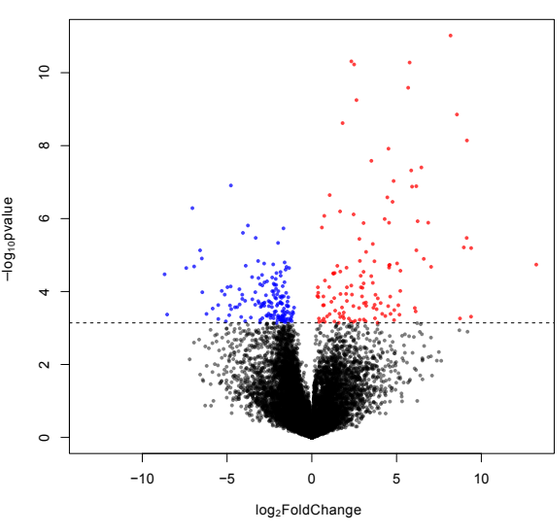
Supplementary Figure S1

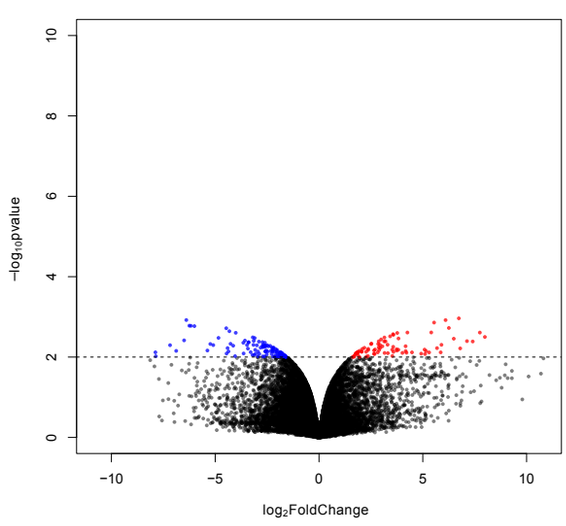


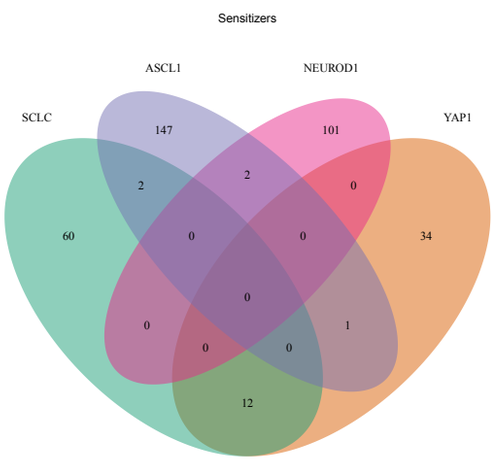


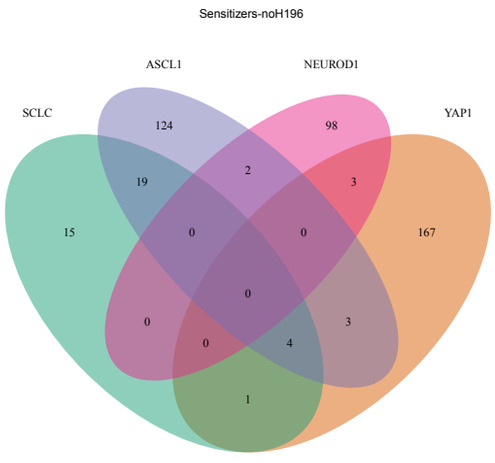


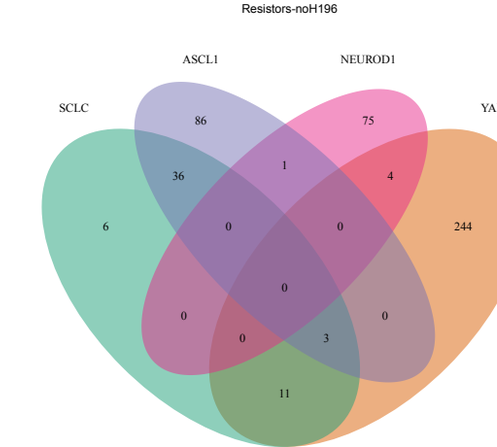




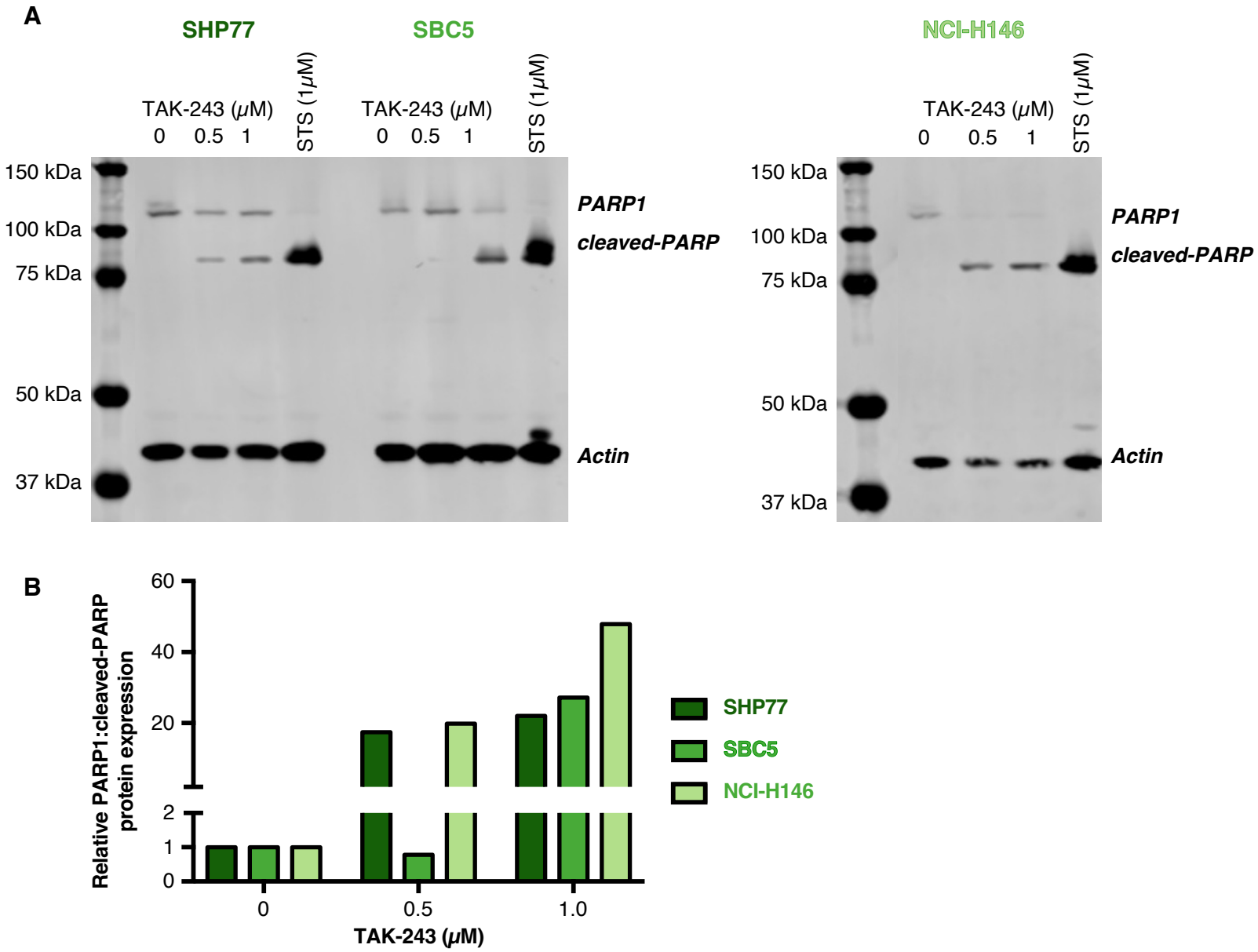




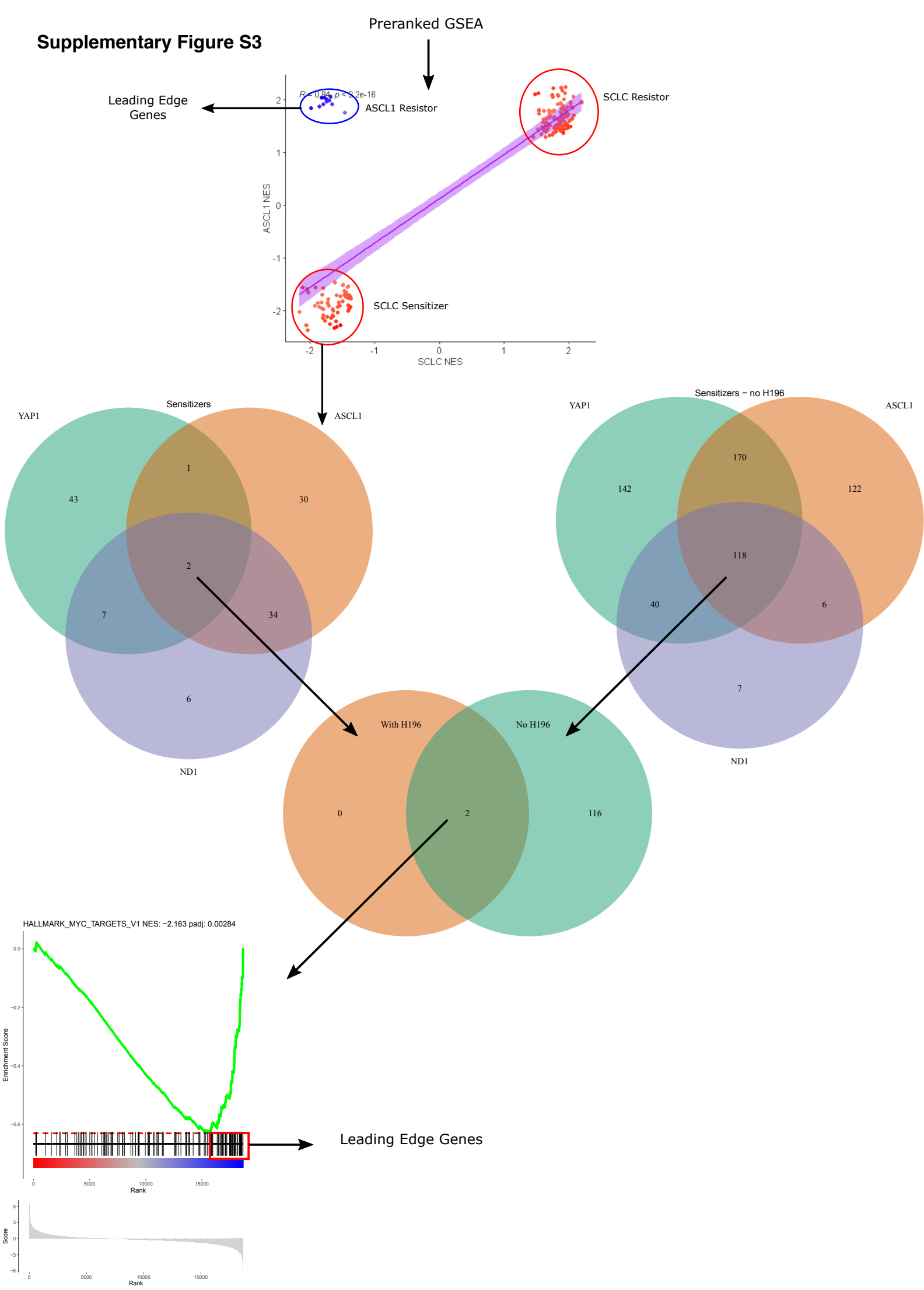




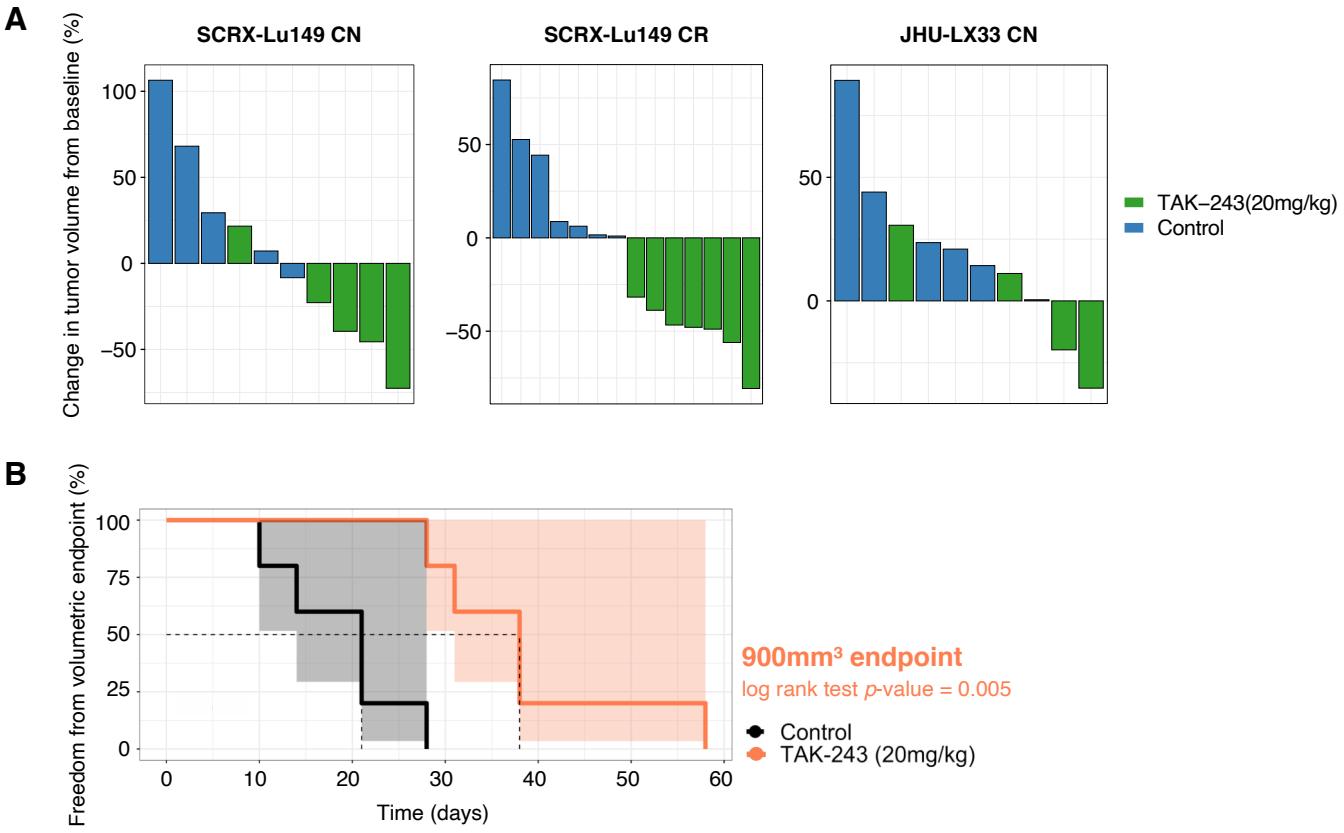
Supplementary Figure S2



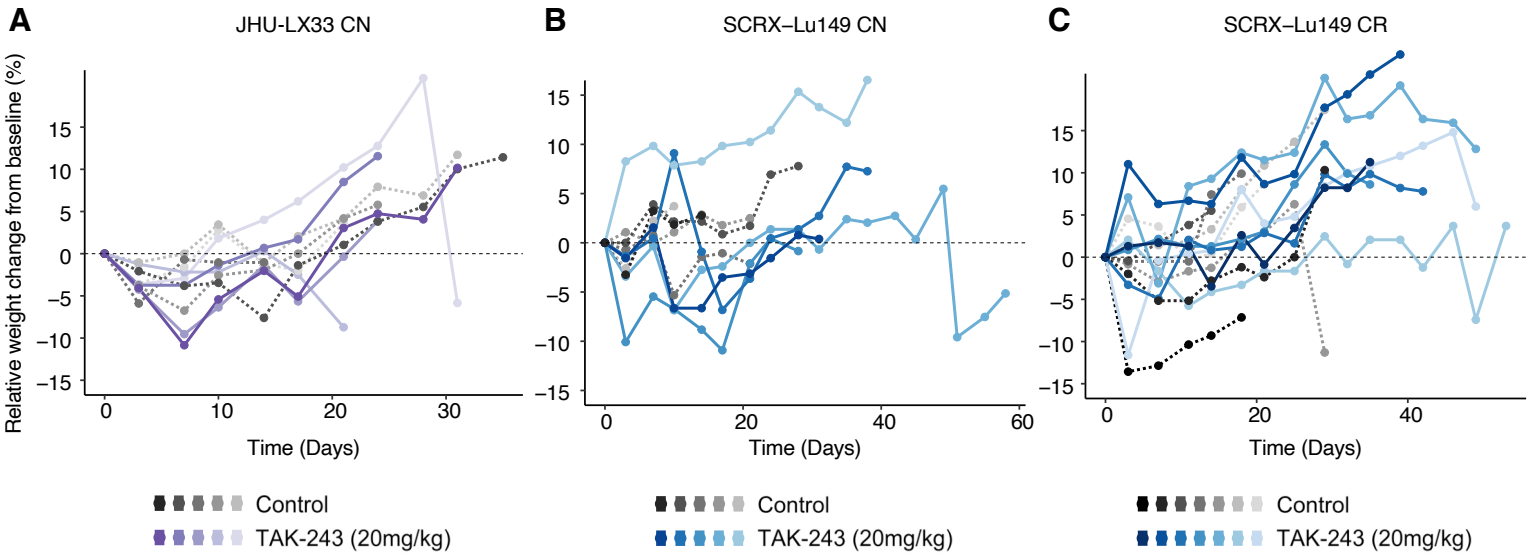
Supplementary Figure S3



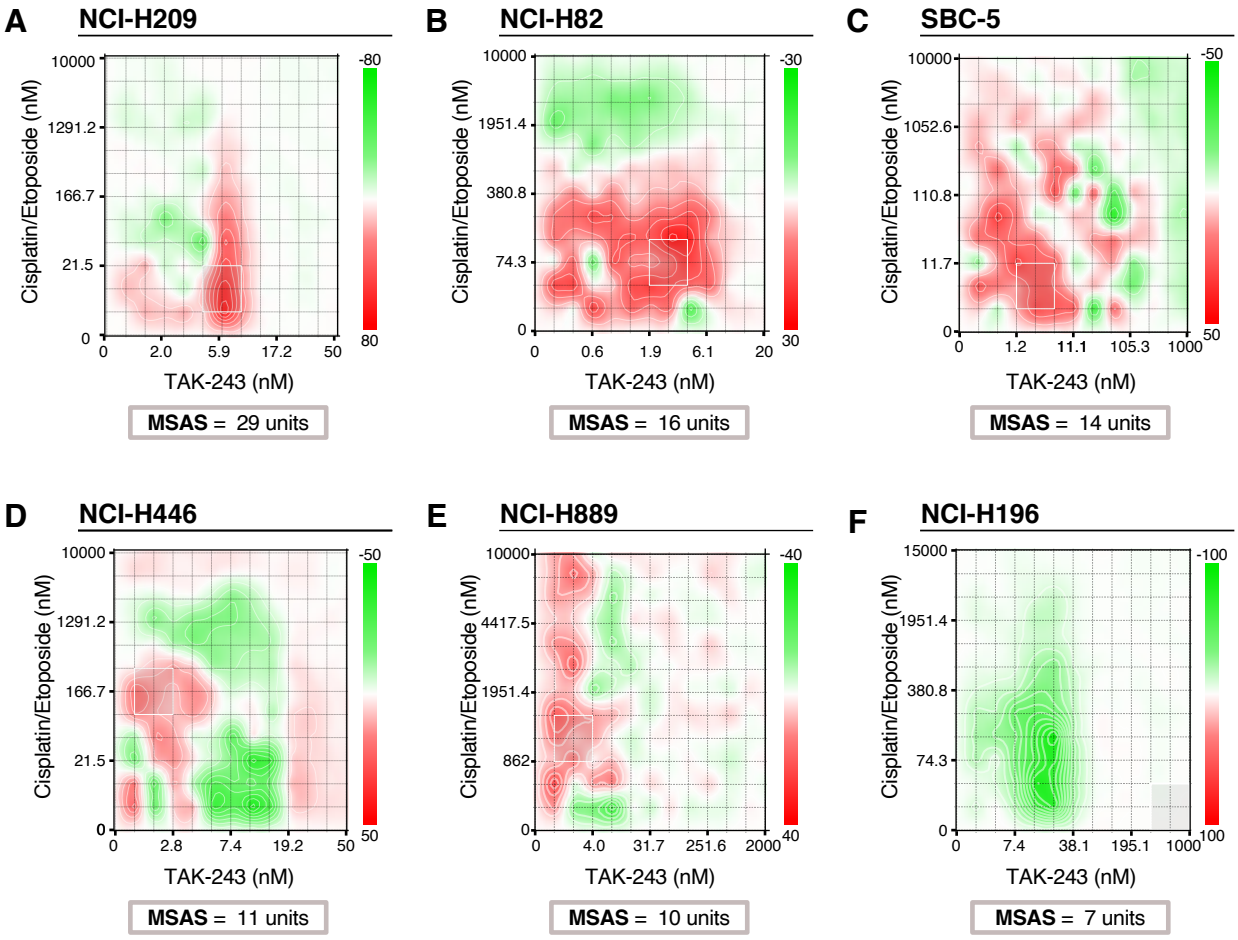
Supplementary Figure S4



Supplementary Figure S5

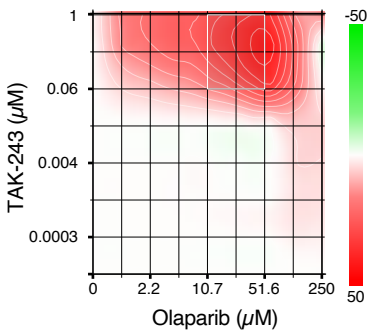


Supplementary Figure S6



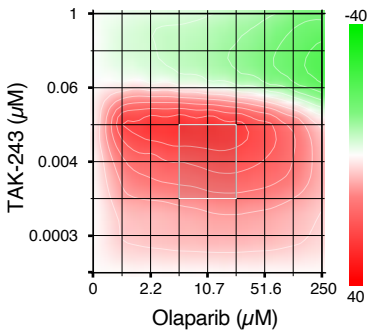
Supplementary Figure S7

A **NCI-H1092**



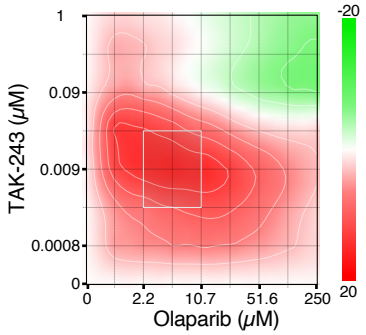
MSAS = 31 units

B **NCI-H446**



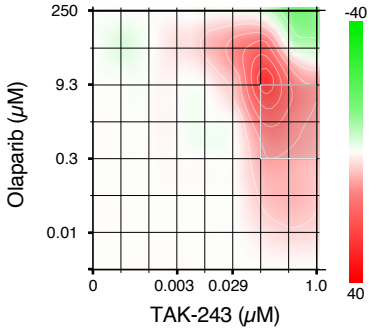
MSAS = 21 units

C **NCI-H1048**



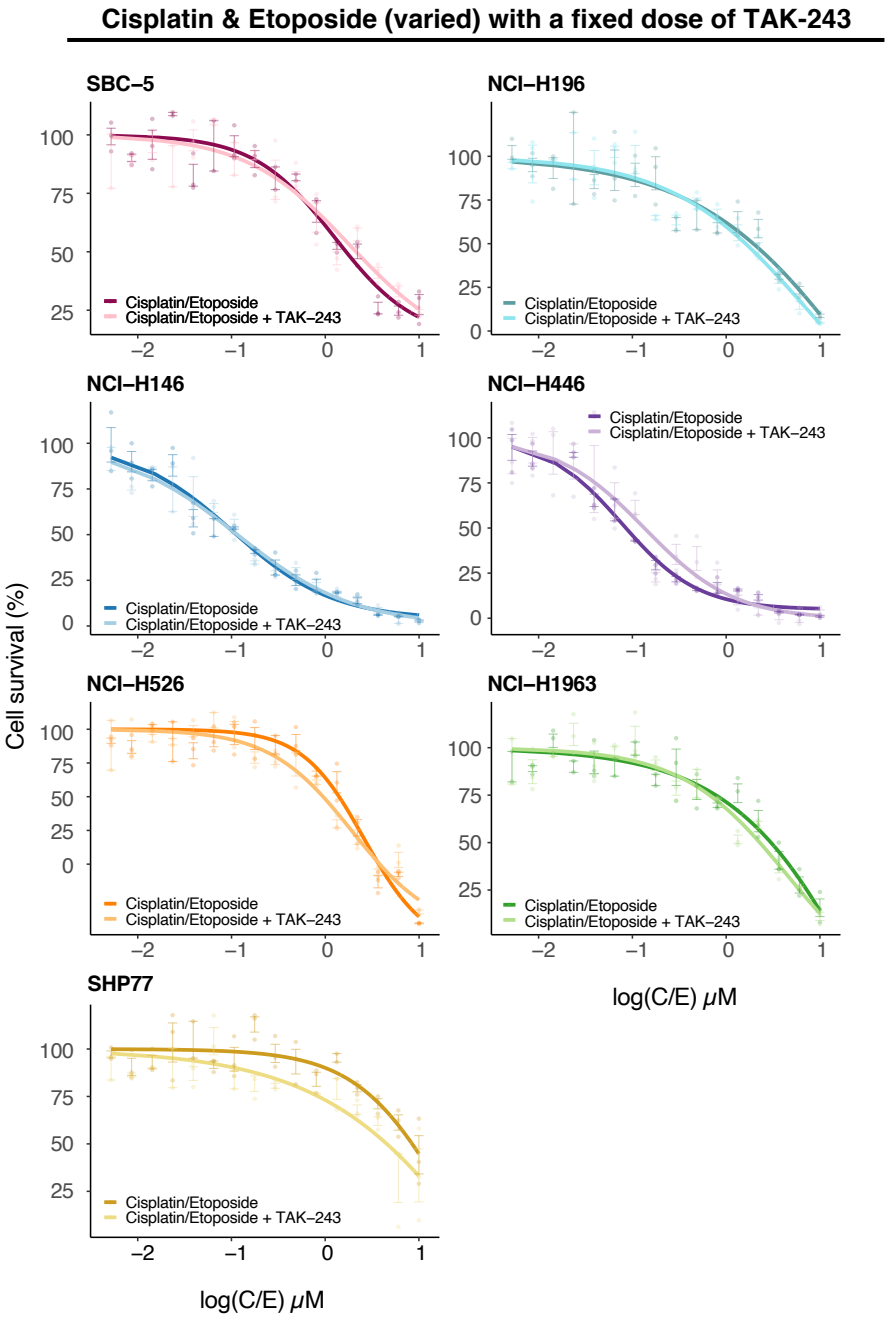
MSAS = 18 units

D **SHP77**

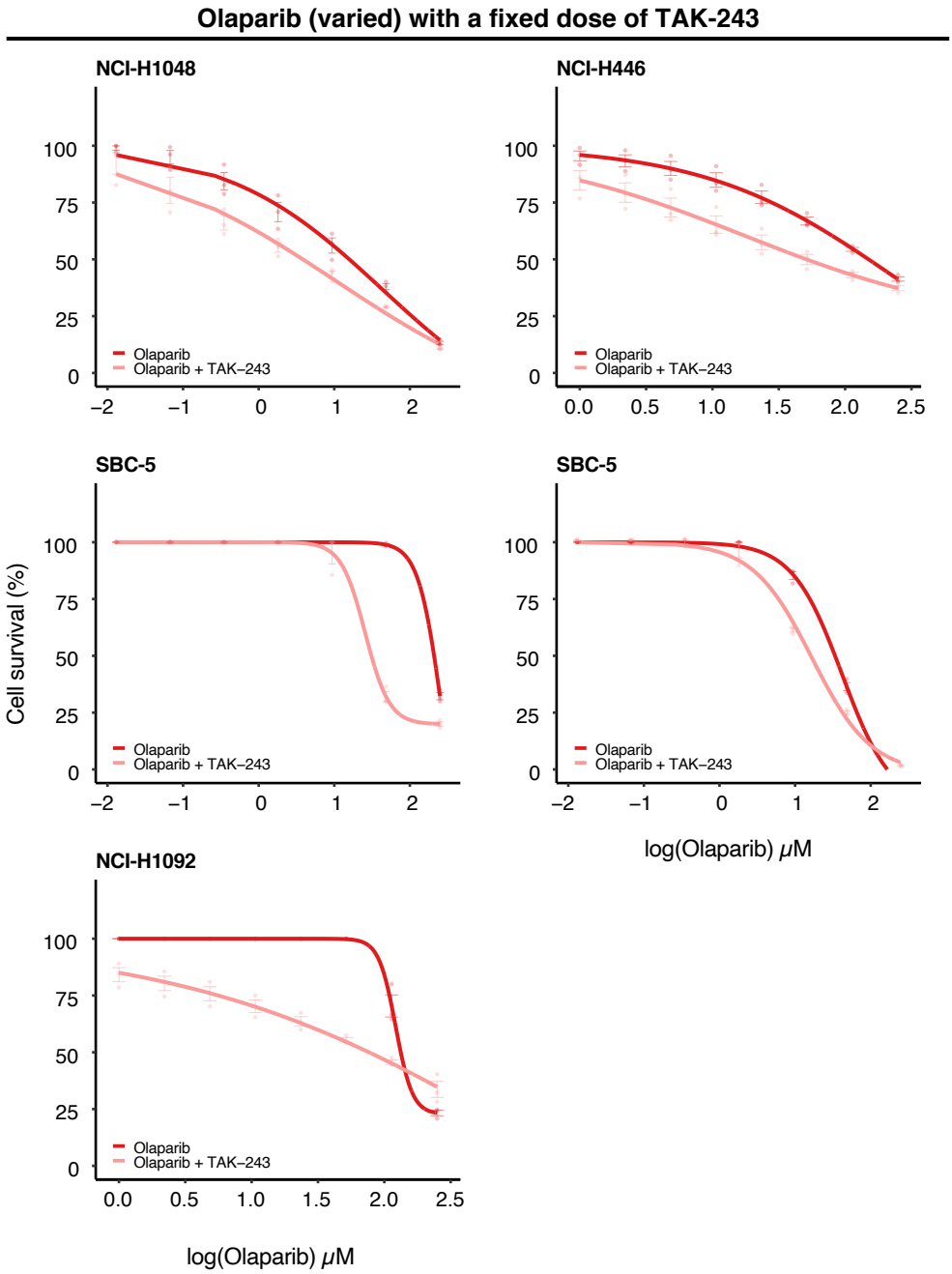


MSAS = 13 units

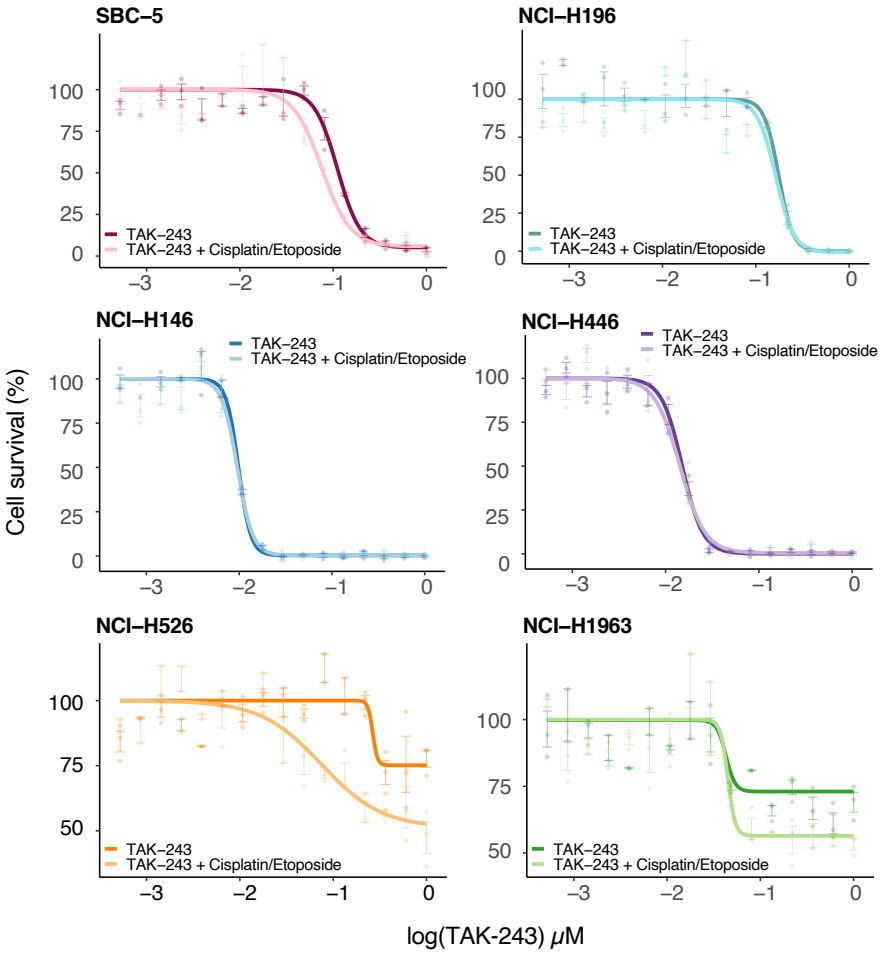
Supplementary Figure S8



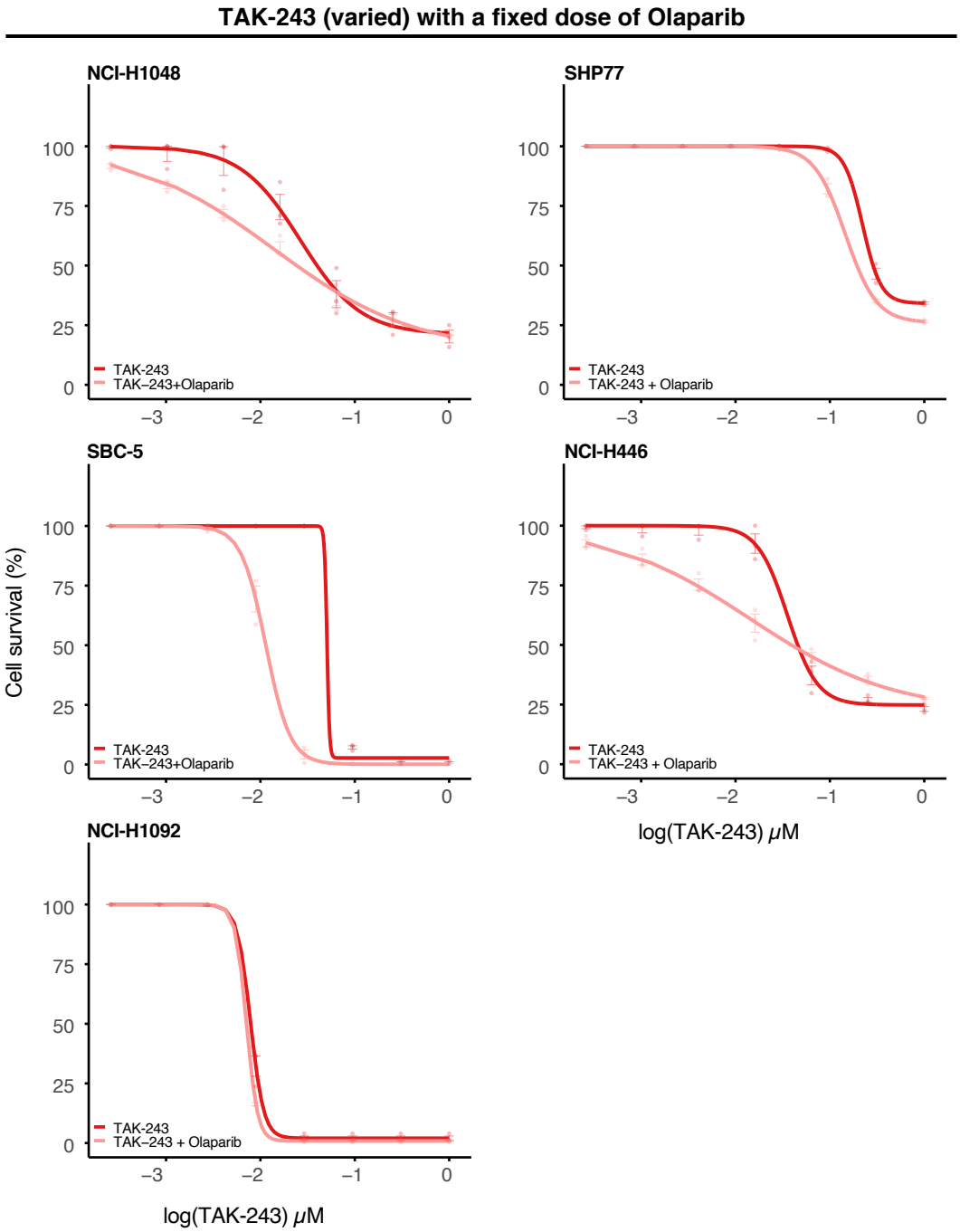
Supplementary Figure S9



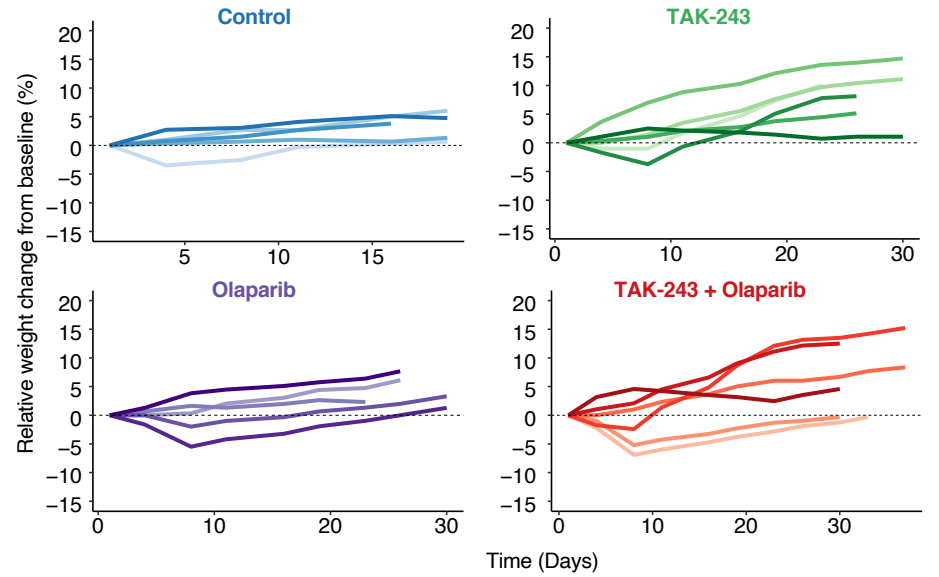
Supplementary Figure S10



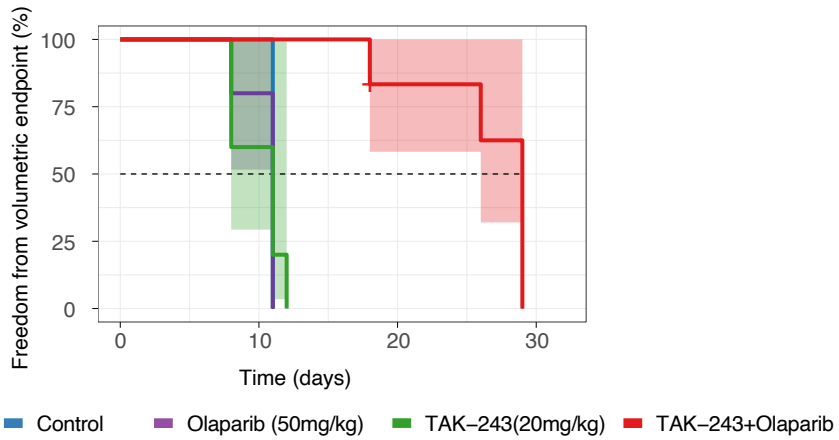
Supplementary Figure S11



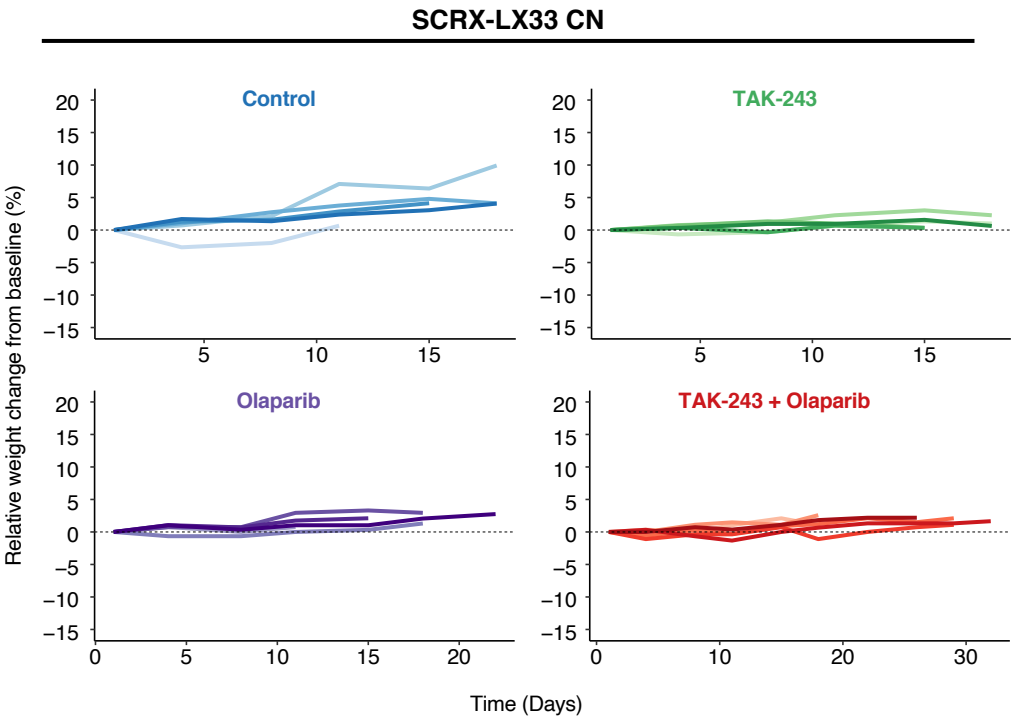
Supplementary Figure S12



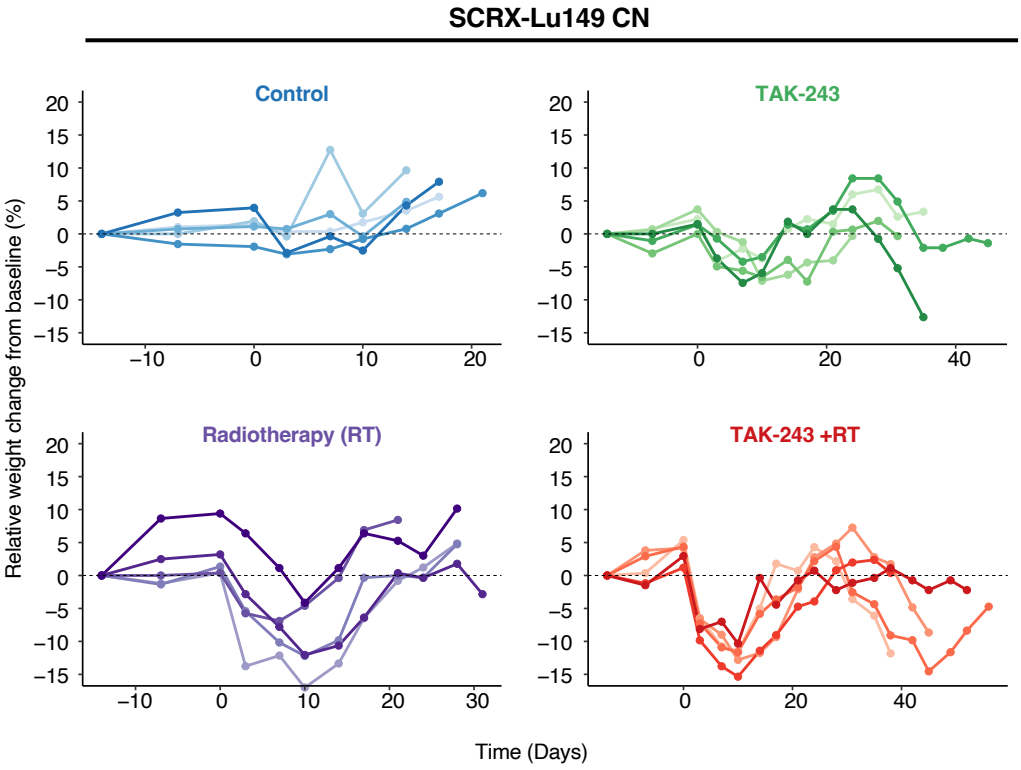
Supplementary Figure S13



Supplementary Figure S14



Supplementary Figure S15



Supplementary Figure S1. Linear-regression biomarker analysis of TAK-243 response in SCLC cell-lines.
Volcano plots showing genes significantly correlated to TAK-243 response across *(top)* all SCLC cell-lines with (n = 24) and without NCI-H196 (n=23), *(middle)* T.N./YAP1-high cell-lines with (n = 6) and without NCI-H196 (n=5), *(bottom)* ASCL1-high cell-lines (n=13), and NEUROD1-high cell-lines (n=3). Blue dots represent negative correlations (FDR<0.05) while red represent positive correlations (FDR<0.05) and black represent no correlation with TAK-243 response. *(right)* Venn diagrams showing overlap of significant negatively correlated genes (sensitizers) and positively correlated genes (resistors) for analyses with and without NCI-H196. Eight gene sets of potential biomarkers specific to each group were identified from the genes in each analysis not overlapping with any other genes. SCLC, small cell lung cancer; T.N., triple negative.

Supplementary Figure S2. Dose-dependent increases in cellular apoptosis following 24-hours of TAK-243 treatment across three SCLC cell-lines.
SCLC cell-lines were treated with increasing doses of TAK-243 and immunoblotting for PARP1 and cleaved-PARP was performed. Blots represent SHP77, SBC-5 and NCI-H196 SCLC cell-lines *(left to right)*. Color gradient (dark to light green) indicated TAK-243 sensitivity in descending order (resistant to sensitive). Actin was used a loading control. Staurosporine was included as a positive control. SCLC, small cell lung cancer; STS, staurosporine.

Supplementary Figure S3. Representative diagram of methods used to identify potential biomarker gene-sets using GSEA.
First, a pre-ranked GSEA was performed for each of the six analyses in Supplementary Figure S2. Pairwise comparisons were performed such that significantly enriched pathways (FDR<0.05) in both the 'all SCLC cell-line' analysis and in a SCLC subtype analysis were correlated. Pathways that were negatively correlated with the SCLC analysis were considered unique to the subtype and gene-sets were selected using leading-edge genes. Pathways that were positively correlated with the SCLC analysis were compared with other positively correlated pathways from the other pairwise comparisons and pathways shared between all three pairwise comparisons were considered specific to 'all SCLC cell-lines' *(middle Venn diagrams)*. This was performed for analyses both with and without NCI-H196. Pathways that survived the removal of NCI-H196 (overlap of bottom Venn diagram) were selected as potential biomarkers and leading-edge genes were used to generated gene-sets. GSEA, gene-set enrichment analysis; SCLC, small cell lung cancer.

Supplementary Figure S4. TAK-243 is effective in the SCRX-Lu149 PDX model.
A. Waterfall plot depicting the best response of individual mice treated with either the vehicle control (10% HP-β-CD[2-hydroxypropyl-β-cyclodextrin] diluted in sterile water) or 20mg/kg of TAK-243 (biweekly X 3 weeks, IV) in SCRX-LU149 CN *(left)*, SCRX-LU149 CR *(middle)* and JHU-LX33 CN *(right)* SCLC PDX models. Best response was considered as the smallest tumor volume (compared to baseline) over the course of the study. **B.** Kaplan-Meier survival of SCRX-LU149 CN at a 900mm^3 volumetric endpoint. Animals were treated with either vehicle control or 20mg/kg of TAK-243 (BIW X 3

weeks, IV) alone. Freedom from volumetric endpoint was determined. Shaded areas represent the 95% confidence intervals around each curve, and the dotted line represents the median freedom from volumetric endpoint. The Log Rank test was used to evaluate statistical significance, with adjusted *p*-values to account for multiple tests. SCLC, small cell lung cancer; PDX, patient-derived xenograft; BIW, bi-weekly; IV, intravenously.

Supplementary Figure S5. Animals treated with TAK-243 or vehicle control maintained or recovered their baseline body weights across 3 PDX models.
A-C. Relative body weight changes from baseline over time for animals engrafted with (A) JHU-LX33 CN, (B) SCRX-Lu149 CN or (C) SCRX-Lu149 CR SCLC PDX models. Tumour bearing mice were treated with either the vehicle control (10% HP-β-CD[2-hydroxypropyl-β-cyclodextrin] diluted in sterile water) or TAK-243 (20mg/kg) BIW for three weeks). Animals did not lose >20% of their body weight and weight recovery was observed, suggesting no excessive toxicity from this therapeutic approach. Weight of control animals is indicated by the black and grey dotted lines, while TAK-243 treated mice are specified by the purple and blue shaded solid lines. SCLC, small cell lung cancer; PDX, patient-derived xenograft; BIW, bi-weekly; IV, intravenously.

Supplementary Figure S6. TAK-243 synergizes with cisplatin and etoposide chemotherapy by the Bliss Independence model.
SCLC cell-line specific dose response matrices employed to evaluate TAK-243 synergy with cisplatin and etoposide chemotherapy. Relative Bliss synergy scores are color-coded where red indicates a synergy, white indicates lack of synergy and green indicates antagonism based on respective synergy scoring. MSAS was calculated using the values outline in grey boxes. SCLC, small cell lung cancer; MSAS, most synergistic area score.

Supplementary Figure S7. TAK-243 synergizes with olaparib by the Bliss Independence model.
SCLC cell-line specific dose response matrices employed to evaluate TAK-243 synergy with olaparib. Relative Bliss synergy scores are color-coded where red indicates a synergy, white indicates lack of synergy and green indicates antagonism based on respective synergy scoring. MSAS was calculated using the values outline in grey boxes. SCLC, small cell lung cancer; MSAS, most synergistic area score.

Supplementary Figure S8. Dose response curves of SCLC cell-lines treated with increasing concentrations of 1:1 C/E chemotherapy and a fixed dose of TAK-243.
The alamarBlue cell viability assay was performed to evaluate cell survival after 6 days of treatment. Individual points on the plots indicate the mean of 3 technical replicates. Outliers were excluded from analysis. The four-parameter log-logistic dose response model was used to generate dose response curves normalized to the control cells. Dose response was then reanalyzed by calculating cell survival relative to the survival of wells treated only with the single agent of C/E alone, to account for additive drug interactions. SCLC, small cell lung cancer; C/E, cisplatin and etoposide.

Supplementary Figure S9. Dose response curves of SCLC cell-lines treated with increasing concentrations of olaparib and a fixed dose of TAK-243.
The alamarBlue cell viability assay was performed to evaluate cell survival after 6 days of treatment. Individual points on the plots indicate the mean of 3 technical replicates. Outliers were excluded from analysis. The four-parameter log-logistic dose response model was used to generate dose response curves normalized to the control cells. Dose response was then reanalyzed by calculating cell survival relative to the survival of wells treated only with the single agent of olaparib, to account for additive drug interactions. SCLC, small cell lung cancer.

Supplementary Figure S10. Dose response curves of SCLC cell-lines treated with increasing concentrations of TAK-243 and a fixed dose of 1:1 C/E chemotherapy.
The alamarBlue cell viability assay was performed to evaluate cell survival after 6 days of treatment. Individual points on the plots indicate the mean of 3 technical replicates. Outliers were excluded from analysis. The four-parameter log-logistic dose response model was used to generate dose response curves normalized to the control cells. Dose response was then reanalyzed by calculating cell survival relative to the survival of wells treated only with the single agent of TAK-243 alone, to account for additive drug interactions. SCLC, small cell lung cancer; C/E, cisplatin and etoposide.

Supplementary Figure S11. Dose response curves of SCLC cell-lines treated with increasing concentrations of TAK-243 and a fixed dose of olaparib.
The alamarBlue cell viability assay was performed to evaluate cell survival after 6 days of treatment. Individual points on the plots indicate the mean of 3 technical replicates. Outliers were excluded from analysis. The four-parameter log-logistic dose response model was used to generate dose response curves normalized to the control cells. Dose response was then reanalyzed by calculating cell survival relative to the survival of wells treated only with the single agent of TAK-243 alone, to account for additive drug interactions. SCLC, small cell lung cancer.

Supplementary Figure S12. Body weight changes in SCRX-Lu149 CN tumour-bearing animals treated with either vehicle control, TAK-243, olaparib or a combination of TAK-243 and olaparib.
SCRX-Lu149 CN tumour bearing mice were treated with either the vehicle control (10% HP-β-CD[2-hydroxypropyl-β-cyclodextrin] diluted in sterile water; BIW, IV, 5 weeks) or TAK-243 (20mg/kg, BIW, IV, 5 weeks) Olaparib (50 mg/kg, orally, until endpoint; 5x per week) or both TAK-243 and olaparib as previously described. Changes in body weight of less than 10% were observed following treatment for all treated groups. Body weights recovered starting 10 days after treatment initiation for most animals. SCLC, small cell lung cancer; PDX, patient-derived xenograft; BIW, bi-weekly; IV, intravenously.

Supplementary Figure S13. TAK-243 and olaparib combination therapy is effective in the JHU-LX33 CN PDX model.
Kaplan-Meier survival of JHU-LX33 CN at a 400mm^3 volumetric endpoint. Animals were treated with either the vehicle control (10% HP-β-CD[2-hydroxypropyl-β-cyclodextrin] diluted in sterile water; BIW, IV, 5 weeks) or TAK-243 (20mg/kg, BIW, IV, 5 weeks),

Olaparib (50 mg/kg, orally, until endpoint; 5x per week) or both TAK-243 and olaparib. Freedom from volumetric endpoint was determined. Shaded areas represent the 95% confidence intervals around each curve, and the dotted line represents the median freedom from volumetric endpoint. The Log Rank test was used to evaluate statistical significance, with adjusted *p*-values to account for multiple tests. SCLC, small cell lung cancer; PDX, patient-derived xenograft; BIW, bi-weekly; IV, intravenously.

Supplementary Figure S14. Body weight changes in JHU-LX33 CN tumour-bearing animals treated with either vehicle control, TAK-243, olaparib or a combination of TAK-243 and olaparib.
JHU-LX33 CN tumour bearing mice were treated with either the vehicle control (10% HP-β-CD[2-hydroxypropyl-β-cyclodextrin] diluted in sterile water; BIW, IV, 5 weeks) or TAK-243 (20mg/kg, BIW, IV, 5 weeks), Olaparib (50 mg/kg, orally, until endpoint; 5x per week) or both TAK-243 and olaparib as previously described. Changes in body weight of less than 10% were observed following treatment for all treated groups. Body weights recovered starting 10 days after treatment initiation for most animals. SCLC, small cell lung cancer; PDX, patient-derived xenograft; BIW, bi-weekly; IV, intravenously.

Supplementary Figure S15. Body weight changes in SCRX-Lu149 CN tumour-bearing animals treated with either vehicle control, TAK-243, RT or a combination of TAK-243 and RT.
SCRX-Lu149 CN tumour bearing mice were treated with either the vehicle control (10% HP-β-CD[2-hydroxypropyl-β-cyclodextrin] diluted in sterile water; BIW, IV, 3 weeks) or TAK-243 (20mg/kg, BIW, IV, 3 weeks), radiation (2Gy x 4, days 0-3) or both TAK-243 and RT as previously described. Changes in body weight of up to 17% were observed immediately following radiation treatment for both the combination and radiation monotherapy treated groups. Body weights recovered starting 10 days after treatment initiation for most animals. SCLC, small cell lung cancer; PDX, patient-derived xenograft; RT, radiation; BIW, bi-weekly; IV, intravenously.