Supplementary

Table S1 Correlation of IC_{50} values to lurbinectedin and RPPA values across all cell lines

RPPA target	Correlation	P value
mTOR	0.685	<0.001
p-p90RSK (T359)	0.664	0.001
SLFN11	-0.618	0.003
P53	0.562	0.008
B7.H4	-0.517	0.016
RecQ4	-0.475	0.029
p-ERK1/2 (S217/221)	0.474	0.030
CHK1	-0.455	0.038
WRN	0.448	0.041
cKIT	-0.434	0.049
PI3K	0.434	0.049

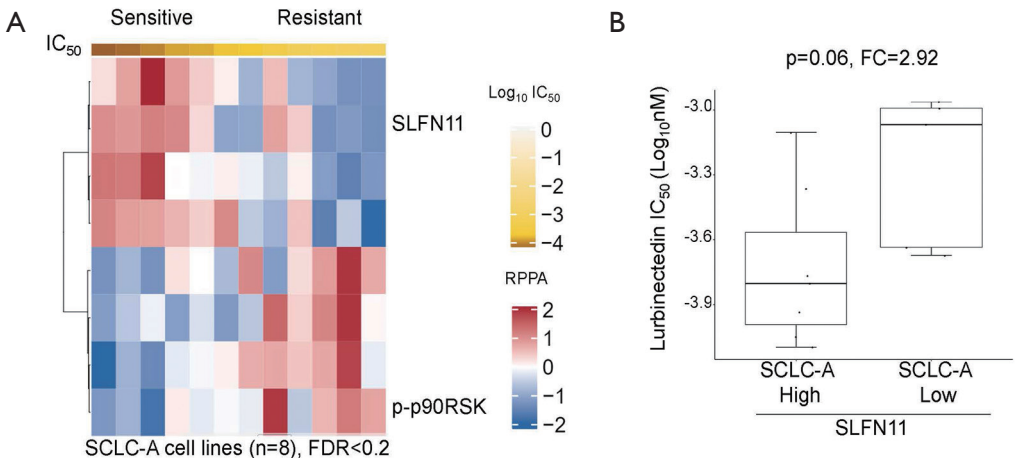

Figure S1 SLFN11 predicts sensitivity to lurbinectedin in SCLC-A cell lines. (A) Spearman correlation of RPPA protein markers and IC_{50} values in panel of 12 SCLC-A cell lines (FDR <0.2). (B) Comparison of lurbinectedin IC_{50} values between SCLC-A cell lines with high and low SLFN11 expression by RPPA (bi-modal separation, mean ± SEM, P value by student's *t*-test).

Table S2 Correlation of IC_{50} values to lurbinectedin and RPPA values in SCLC-A cell lines

RPPA target	Correlation	P value
p-cJUN (S73)	-0.867	<0.001
SLFN11	-0.825	0.001
p-STING (S366)	-0.825	0.001
B7.H4	-0.804	0.002
mTOR	0.762	0.004
p-p90RSK (T359)	0.755	0.005
P53	0.748	0.005
ZEB1	0.727	0.007

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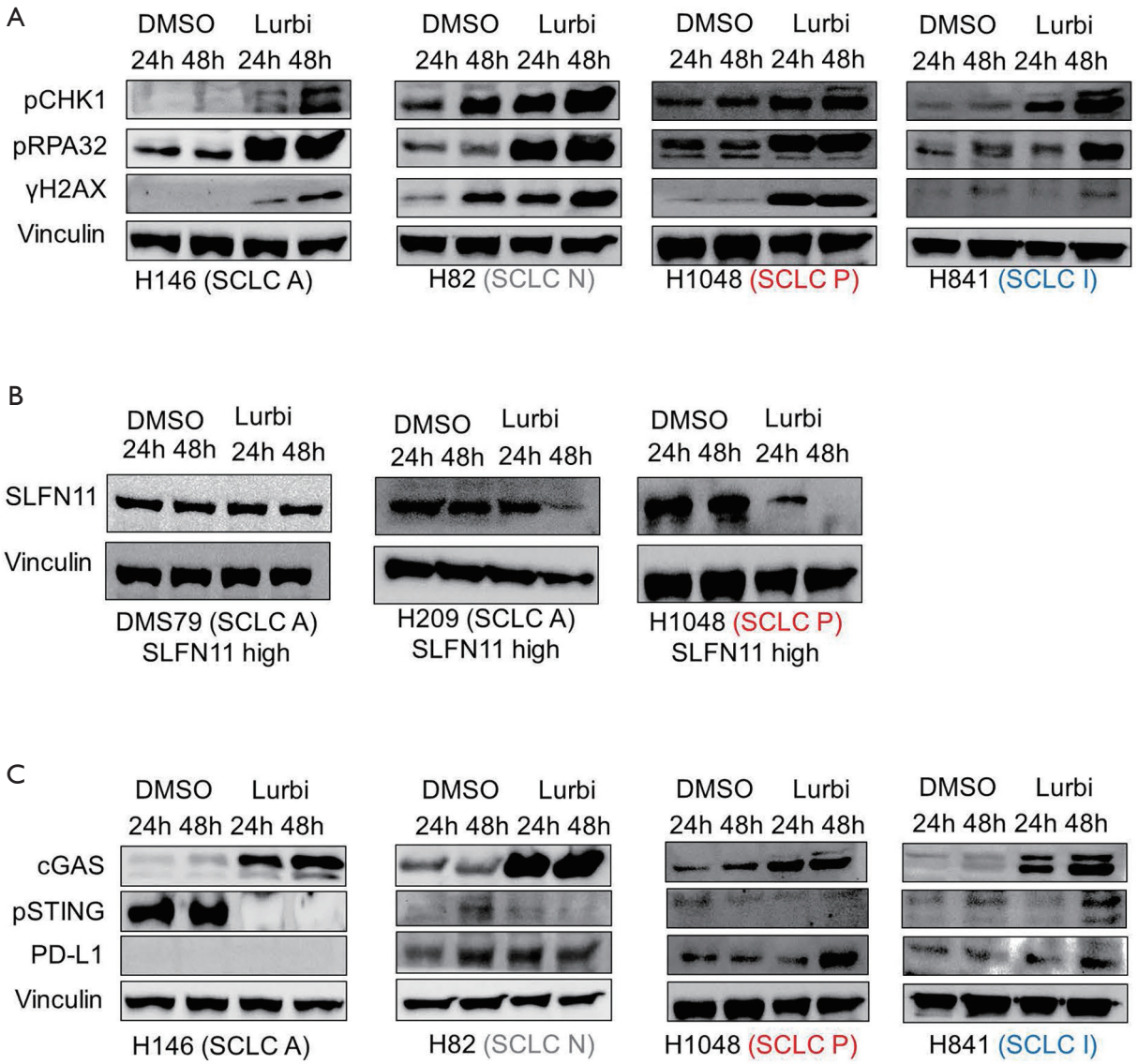

Figure S2 (A) Western- blot showing changes in replication stress markers (pCHK1 and pRPA32) and DNA damage (γH2Ax) in SCLC cell lines following 24- and 48-hour treatment with DMSO or lurbinectedin (Lurbi, 0.9 nM). (B) Western blots showing changes in SLFN11 expression following lurbinectedin treatment. (C) Treatment with lurbinectedin activates cGAS, phosphorylates STING and increases PD-L1 expression in SCLC-P and SCLC-I cell lines.

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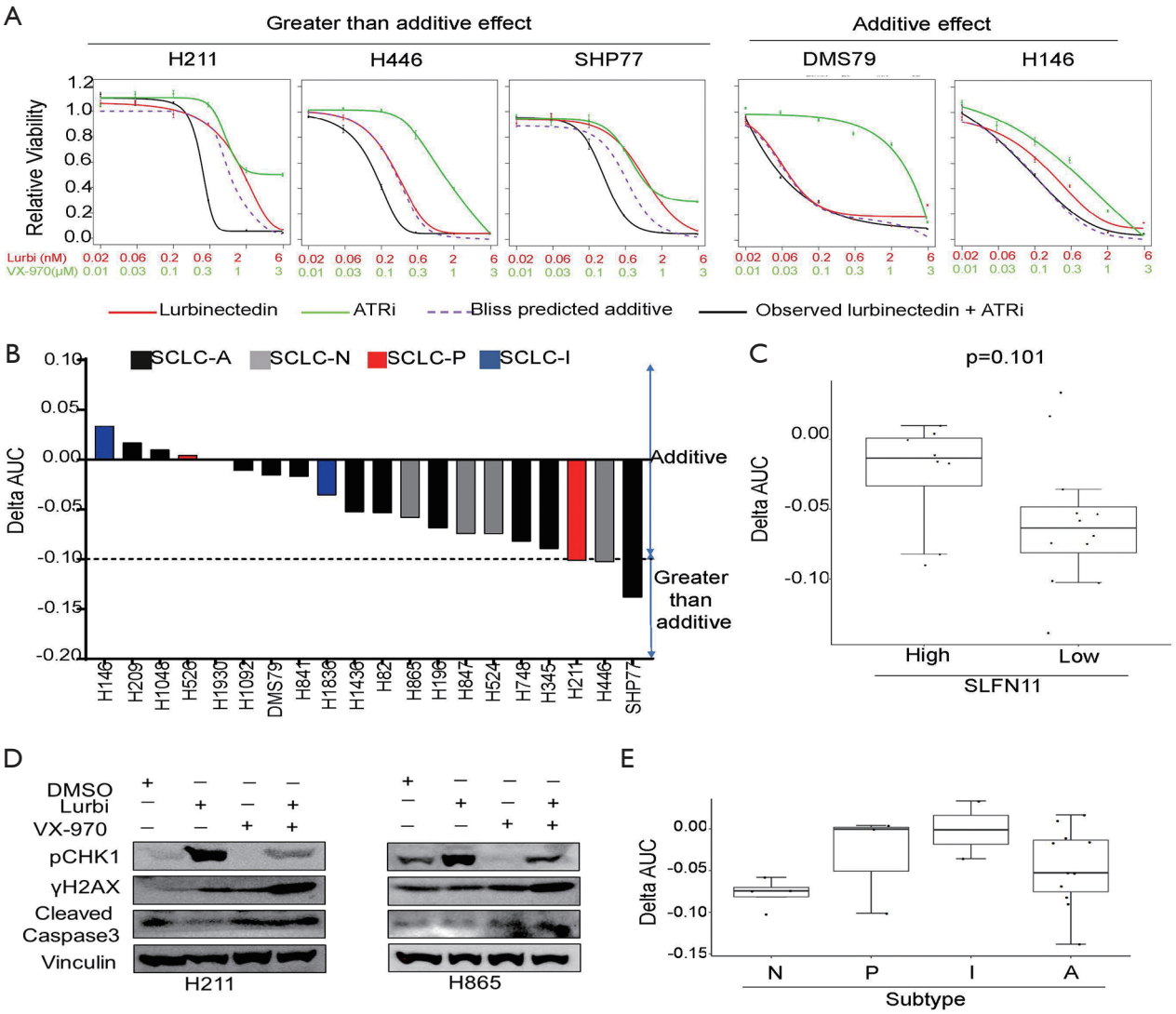

Figure S3 (A) Relative proliferation of cell lines representing greater than additive, and additive responses following 96h treatment with lurbinectedin (Lurbi), VX-970 and their combination at indicated concentrations (mean ± SEM). (B) Bar-graph representing ΔAUC for all SCLC cell lines tested, color coded by SCLC subtype. (C) Comparison of ΔAUC values between cell lines with high and low SLFN11 expression by RPPA (bi-modal separation, mean ± SEM, P values by *t*-test). (D) Western blot showing changes in pCHK1, pγH2Ax and cleaved caspase3 in H211 and H865 cell lines treated with 0.6 nM of lurbinectedin, 0.3 μM of VX-970 and their combination. (E) Comparison of delta AUC values for the combination of lurbinectedin and cerelasertib between cell lines from the four SCLC subtypes SCLC-A, -N, -P and -I (P values by student's *t*-test).

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