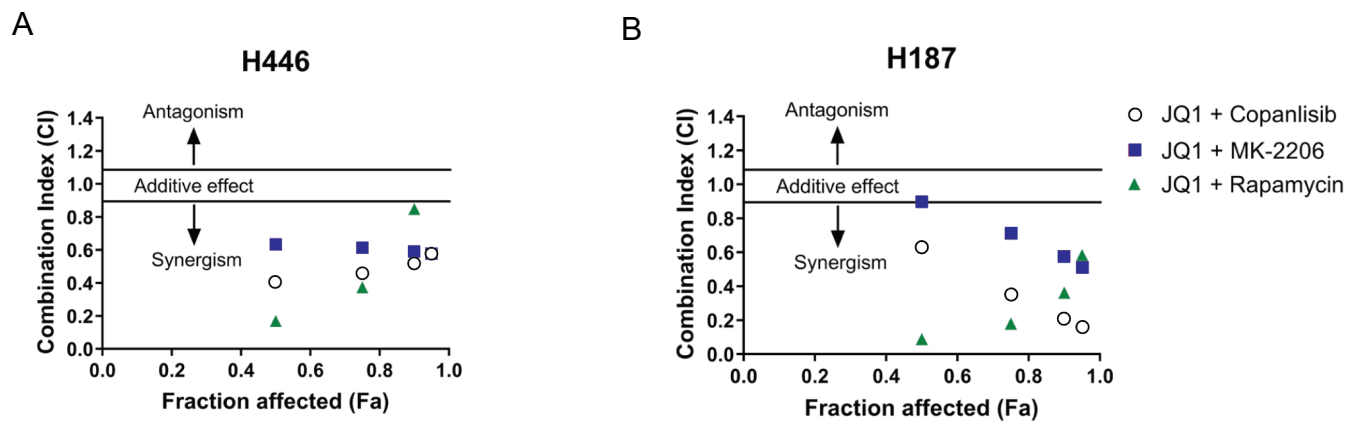
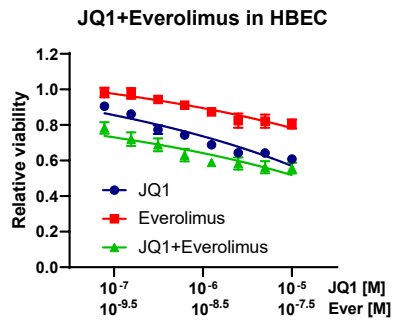


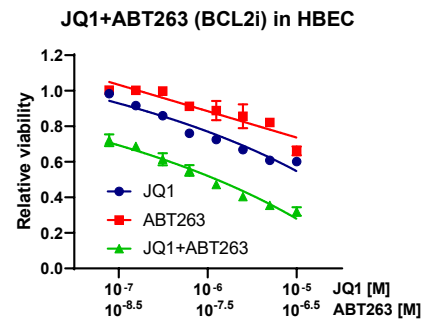


**Supplemental Figure S1. The mTORi/BETi combination resulted in a stronger synergy than the AKTi/BETi or the PI-3Ki/BETi combinations.** Synergy plots showing CIs versus affected fractions in H446 (SCLC-N subtype; A) and H187 (SCLC-A subtype; B) 72 hours after treatment with JQ1 in combination with copanlisib (PI-3Ki), MK-2206 (AKTi), or rapamycin (mTORi).

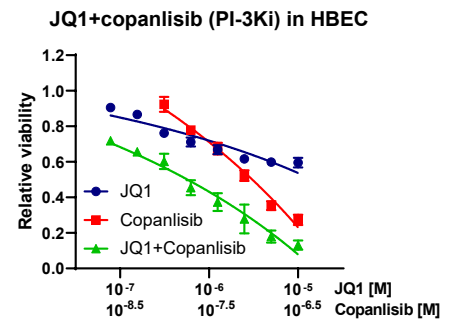
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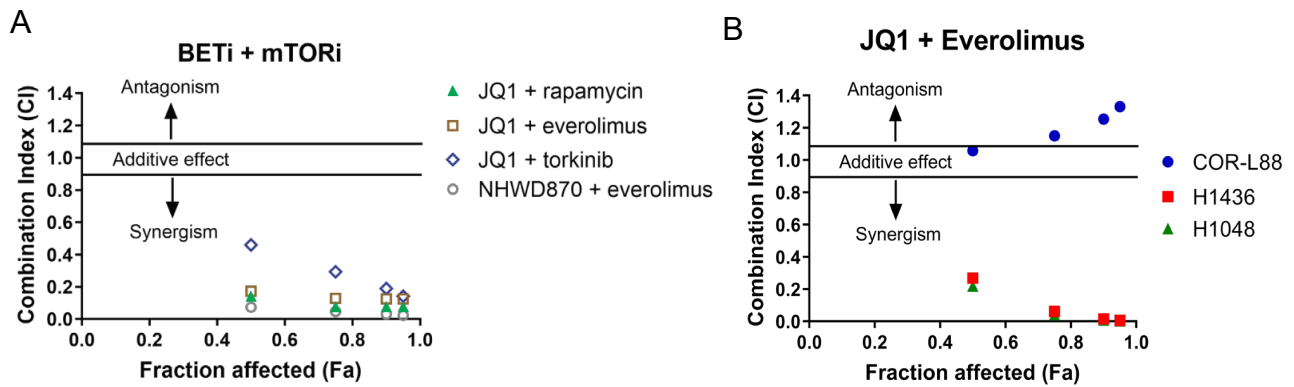
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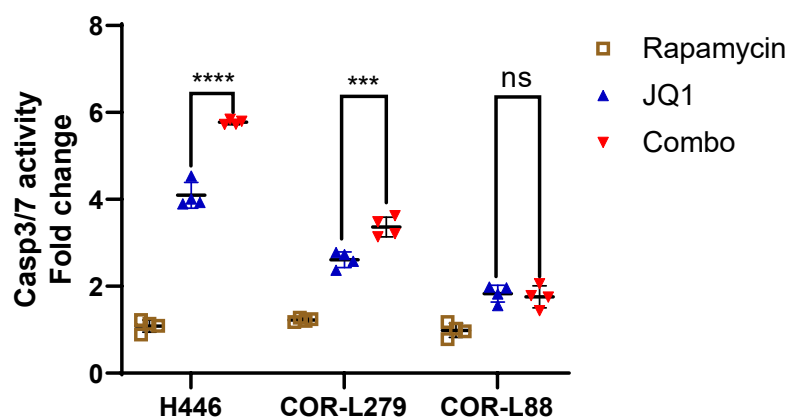
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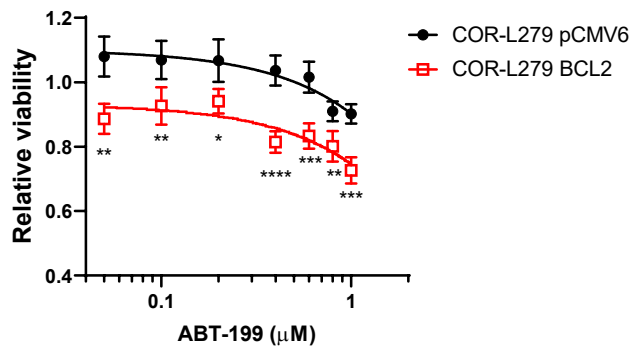
**Supplemental Figure S2. Effects of various drug combinations on the viability of immortalized human bronchial epithelial cells (HBEC).** The viability of HBEC cells following a 72-hour treatment of JQ1 in combination with everolimus (mTORi; A), ABT263 (BCL2i; B), or copanlisib (PI-3Ki; C) versus single agents.



**Supplemental Figure S3. The synergy between mTORi and BETi is not restricted to a specific drug or the BETi-sensitive SCLC. (A)** Synergy plots showing CIs versus affected fractions in COR-L279 cells following a 72-hour combinatorial treatment of various mTOR and BET inhibitors. **(B)** Synergy plot showing CIs versus affected fractions in three BETi-resistant SCLC lines (SCLC-A subtypes: COR-L88 and H1436; SCLC-Y subtype: H1048) following a 72-hour treatment with the everolimus and JQ1 combination.

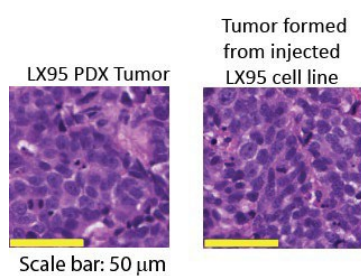


**Supplemental Figure S4. Everolimus augments the JQ1-induced apoptosis in H446 and COR-L279 but not in COR-L88 cells.** Caspase 3/7 activity was measured at the 48-hour interval in H446, COR-L279, and COR-L88 cells treated with DMSO, rapamycin (50 nmol/L), JQ1 (0.5 micromol/L), and their combination, and the results were presented as the relative changes to untreated cells. The significance of the two-group comparisons was determined using the Student's *t*-test with FDR multiple comparison corrections. ns, not significant; \*\*\*,  $p < 0.001$ ; \*\*\*\*,  $P < 0.0001$ .

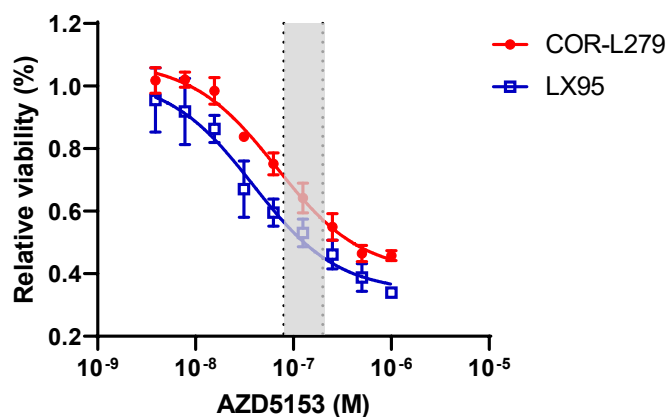


**Supplemental Figure S5. Ectopic BCL2 increases the sensitivity of COR-L279 cells to ABT-199, a BCL2 inhibitor.** The significance of the two-group comparisons was determined using the Student's *t*-test with the FDR multiple comparison corrections. Error bars represent the SD of four replicates. \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ ; \*\*\*\*,  $P < 0.0001$ .

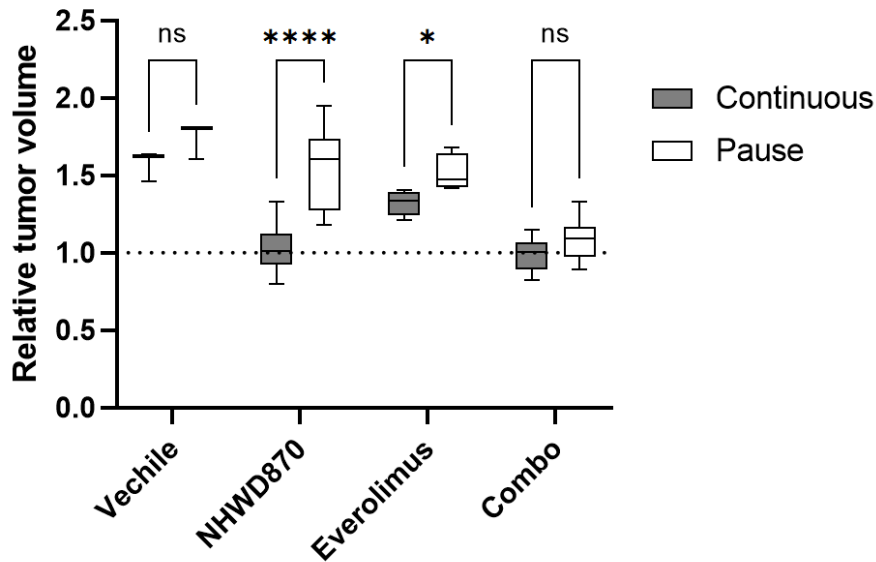
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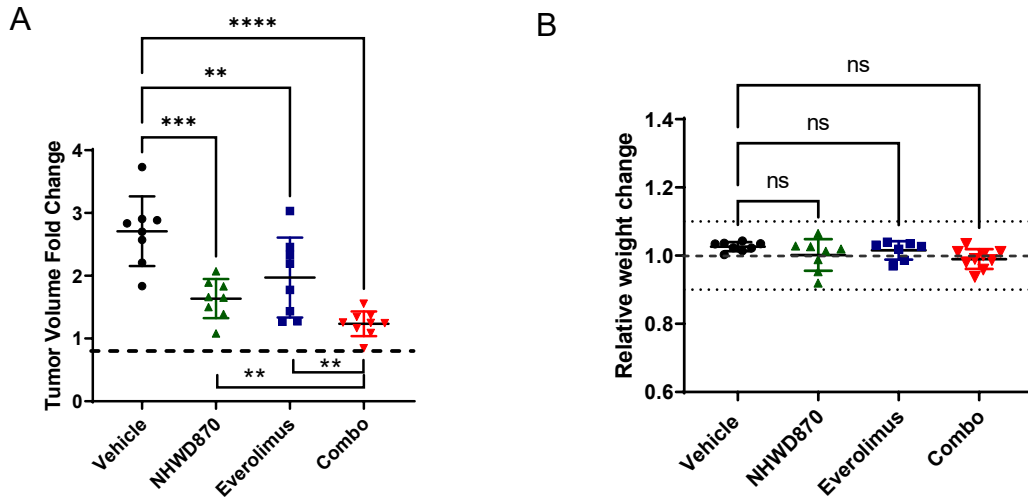
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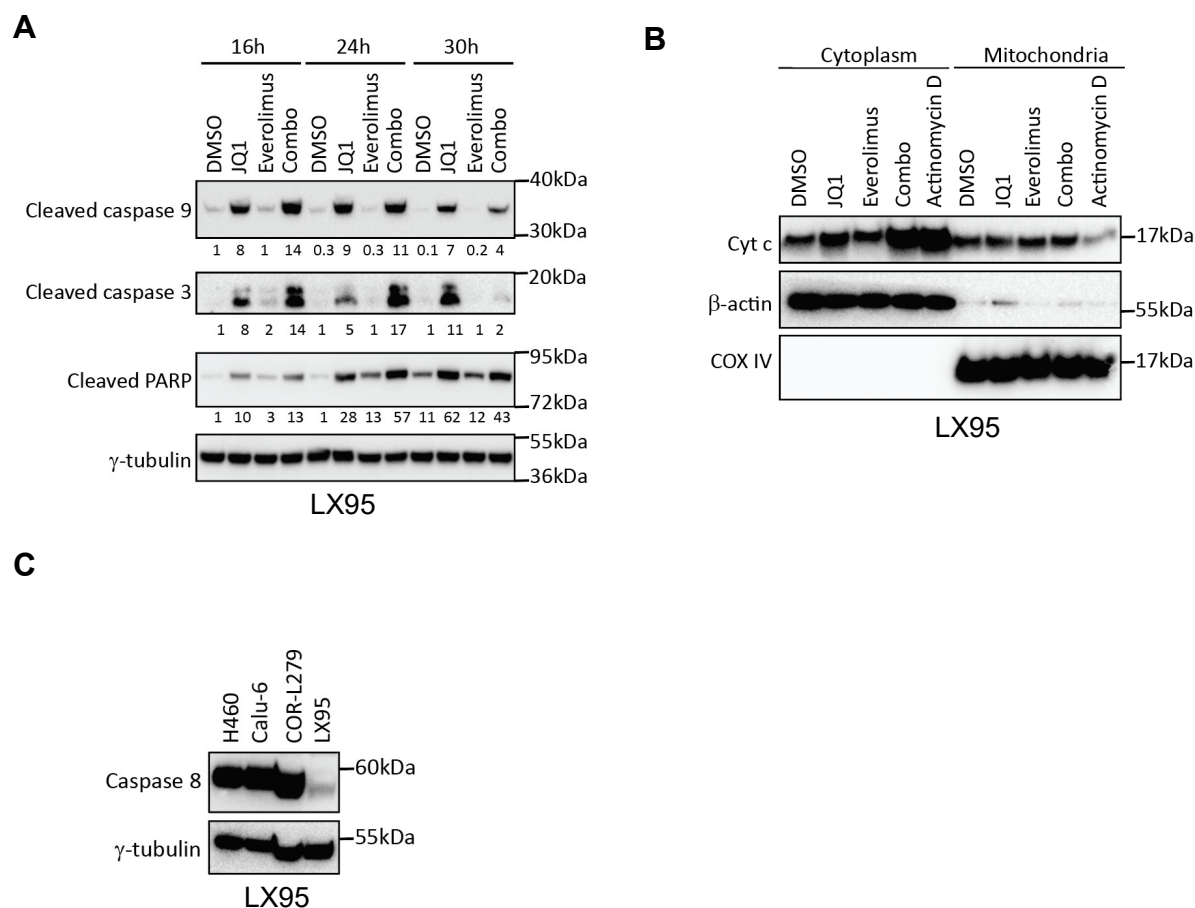
**Supplemental Figure S6. The LX95 tumor cell line, established from an SCLC-A subtype PDX, shows exquisite sensitivity to AZD5153 in vitro. (A)** A representative histological image of the xenograft tumors formed from the injected LX95 cells (right) was compared to one from LX95 PDX tumor block (left). **(B)** Relative viability of COR-L279 and LX95 cells after a 72-hour treatment of AZD5153. The gray column represents the in vitro dose ranges of AZD5153 (80-200 nmol/L) corresponding to the plasma Cmax in the patients receiving 10-40 mg daily in a phase I trial.



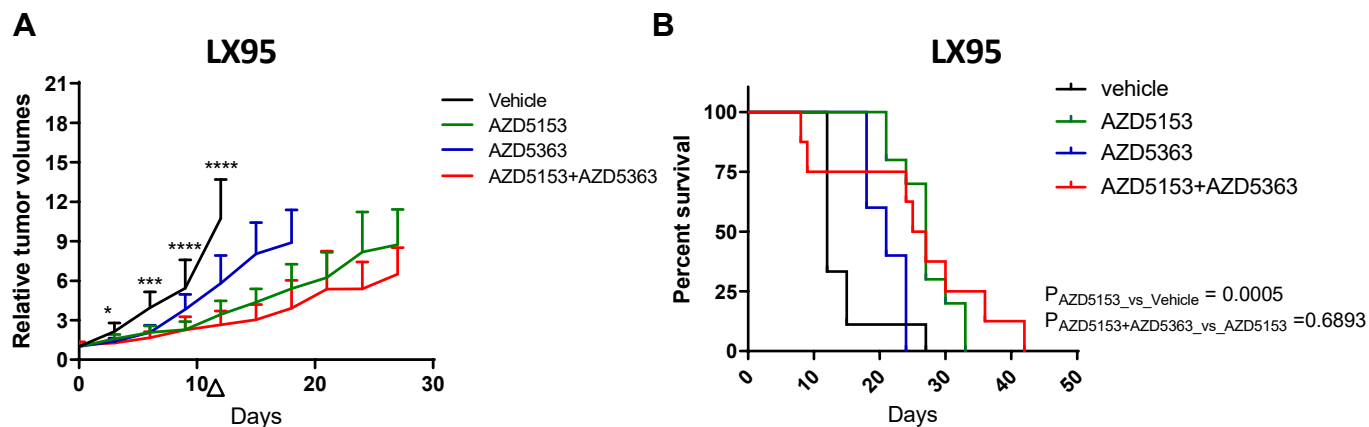
**Supplemental Figure S7. A short-term pause of the everolimus/NHWD870 combo treatment did not affect tumor volume control in the LX95 model.** Relative tumor volume changes of LX95 tumors in mice receiving continuous treatments of vehicle, everolimus (2 mg/kg daily), NHWD870 (1.5mg/kg, daily), or the combination (NHWD870 1 mg/kg and everolimus 1.5mg/kg, daily) versus those with a 3-day treatment pause. n=3-10 per group. The significance of tumor volume changes between the treatment pause groups and the continuous groups was determined using the Student's *t*-test with the FDR multiple comparison corrections. Whiskers represent minimum to maximum, and boxes show the first, median, and third quartile. The dotted line represents no tumor growth. Where indicated, \*,  $p < 0.05$ ; \*\*\*\*,  $p < 0.0001$ ; ns, not significant.



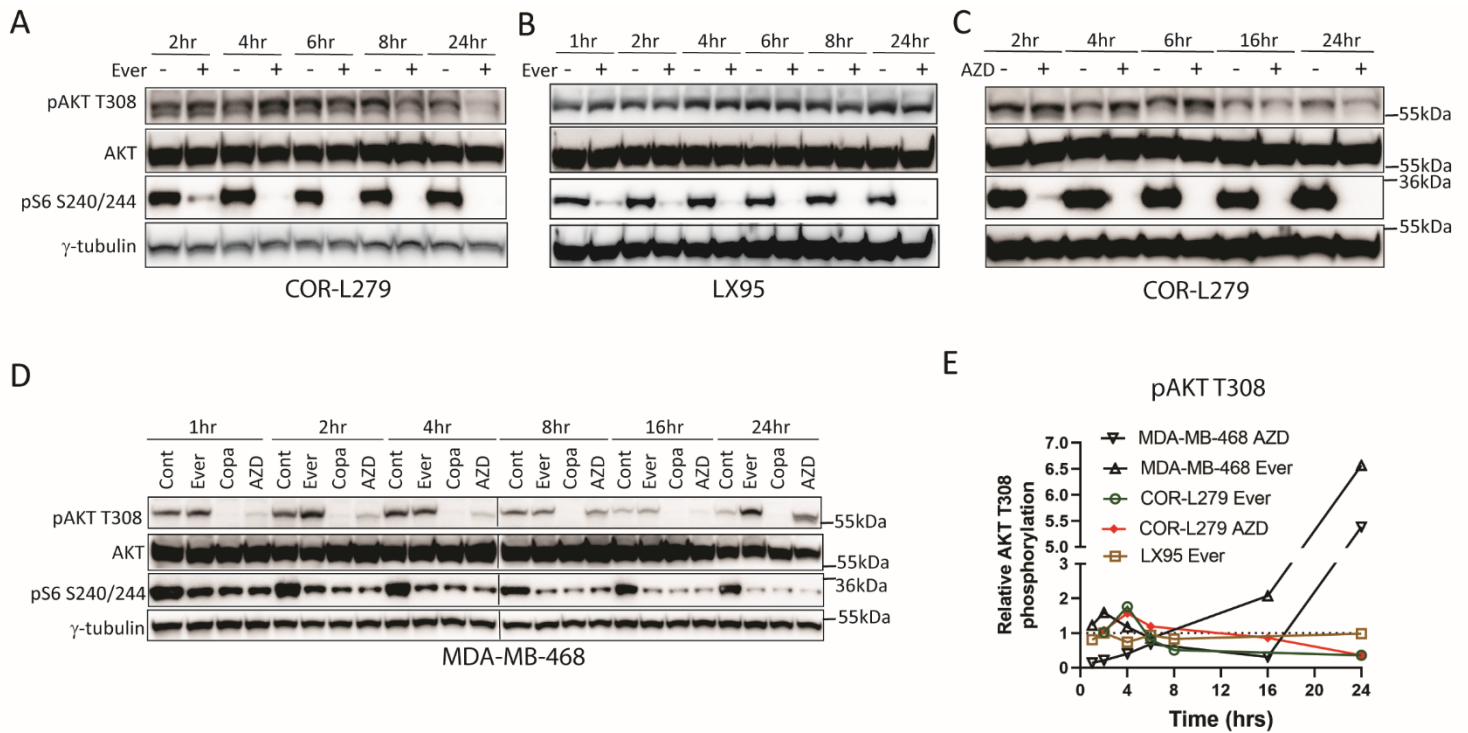
**Supplemental Figure S8. Relative tumor volume and body weight changes after one-week treatment of the everolimus/NHWD870 combination in the LX95 PDX model.** Relative tumor volume and body weight changes of LX95 PDXs after one-week treatment of vehicle, NHWD870 (1.5mg/kg, daily), everolimus (2mg/kg, daily), or their combination (everolimus 1.5mg/kg and NHWD870 1mg/kg, daily).  $n \geq 8$  per group. The significance of the two-group comparisons was determined using the ANOVA test with Dunnett's multiple test correction. Error bars represent SD. ns, not significant; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ ; \*\*\*\*,  $p < 0.0001$ .



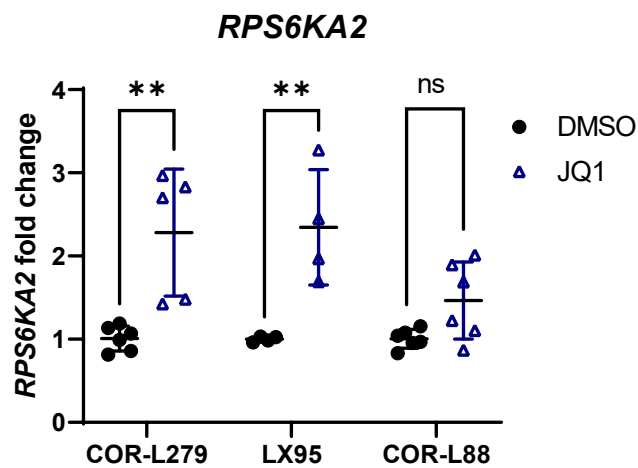
**Supplemental Figure S9. Everolimus augments the JQ1-induced apoptosis via the intrinsic apoptotic cascade in LX95 cells.** (A) Western blots show cleavage of caspase 9, caspase 3, or PARP at the 16-hour, 24-hour, and 30-hour intervals in LX95 cells treated with JQ1 (156 nmol/L), everolimus (6.25 nmol/L), or the combination. (B) Western blots show cytochrome c (Cyt c) abundance in the mitochondrial and cytoplasmic fractions of LX95 cells following a 16-hour treatment of JQ1 (1 micromol/L), everolimus (6.25 nmol/L), or their combination. Actinomycin D (1 microgram/ml, 16 hours) was used as a positive control. (C) Western blots showing expression of caspase 8 in two non-small cell lung cancer lines (H460 and Calu-6) and two SCLC lines (SCLC-N: COR-L279 and SCLC-A: LX95).



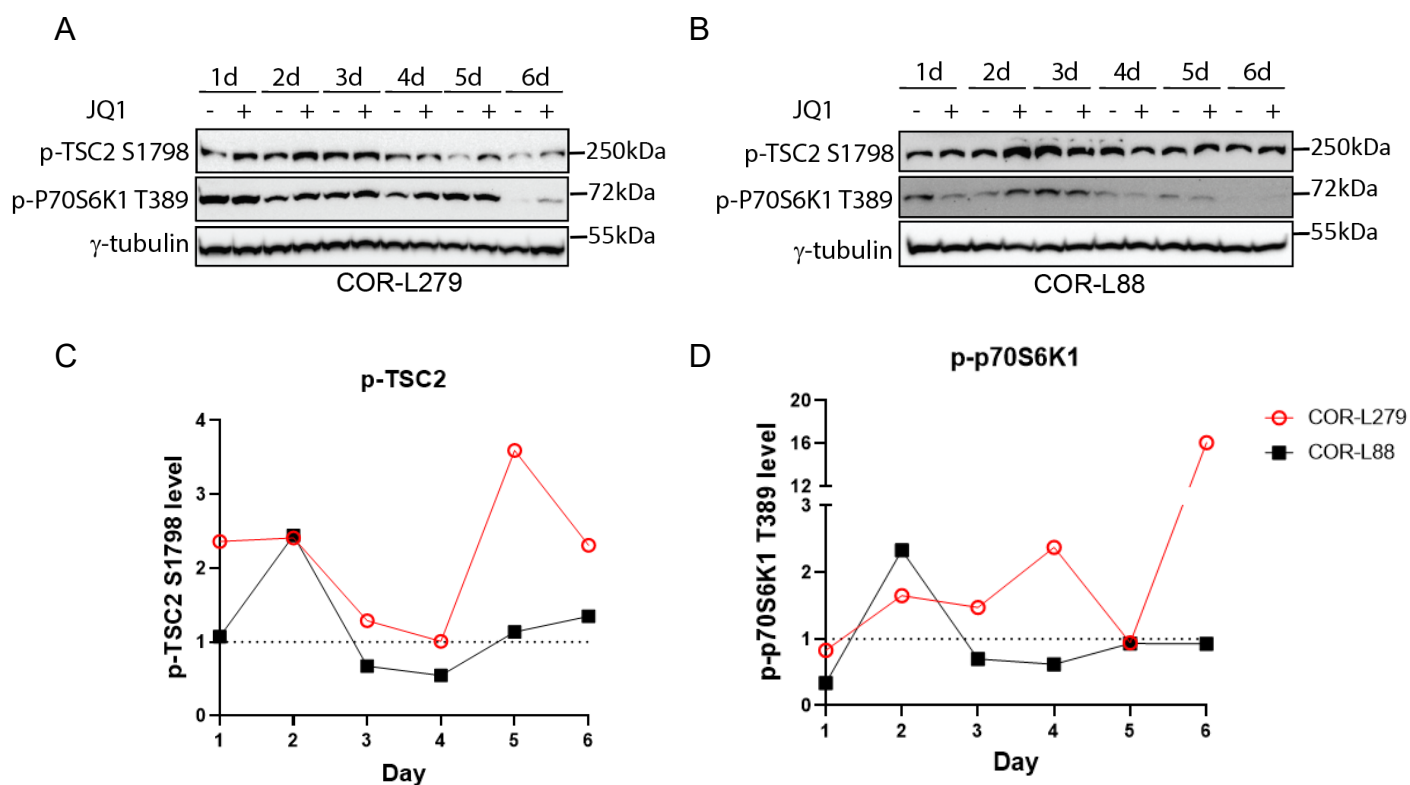
**Supplemental Figure S10. The combination of AZD5363 (AKTi) and AZD5153 (BETi) failed to improve tumor control or extend survival in the LX95 PDX model. (A)** Relative tumor volume changes within 29 days of drug administration. LX95 PDX mice were initially treated with single-agent AZD5153 (1.5 mg/kg, daily), single-agent AZD5363 (50 mg/kg, daily), or the combination (AZD5153 1 mg/kg and AZD5363 50 mg/kg, daily). Due to premature deaths in the combo group, the dose of AZD5363 in the combination group was reduced to 30mg/kg two weeks after the first dose (triangle). Black asterisks indicate a statistically significant change in tumor volume in the AZD5153 single-agent group compared to Vehicle, as determined by the Student's *t*-test with the FDR multi-comparison corrections. Error bars represent SD. \*,  $p < 0.05$ ; \*\*\*,  $p < 0.001$ ; \*\*\*\*,  $p < 0.0001$ . **(B)** Kaplan-Meier survival curves of (A). The significance of the two-group comparisons in (B) was determined by the Log-rank test.



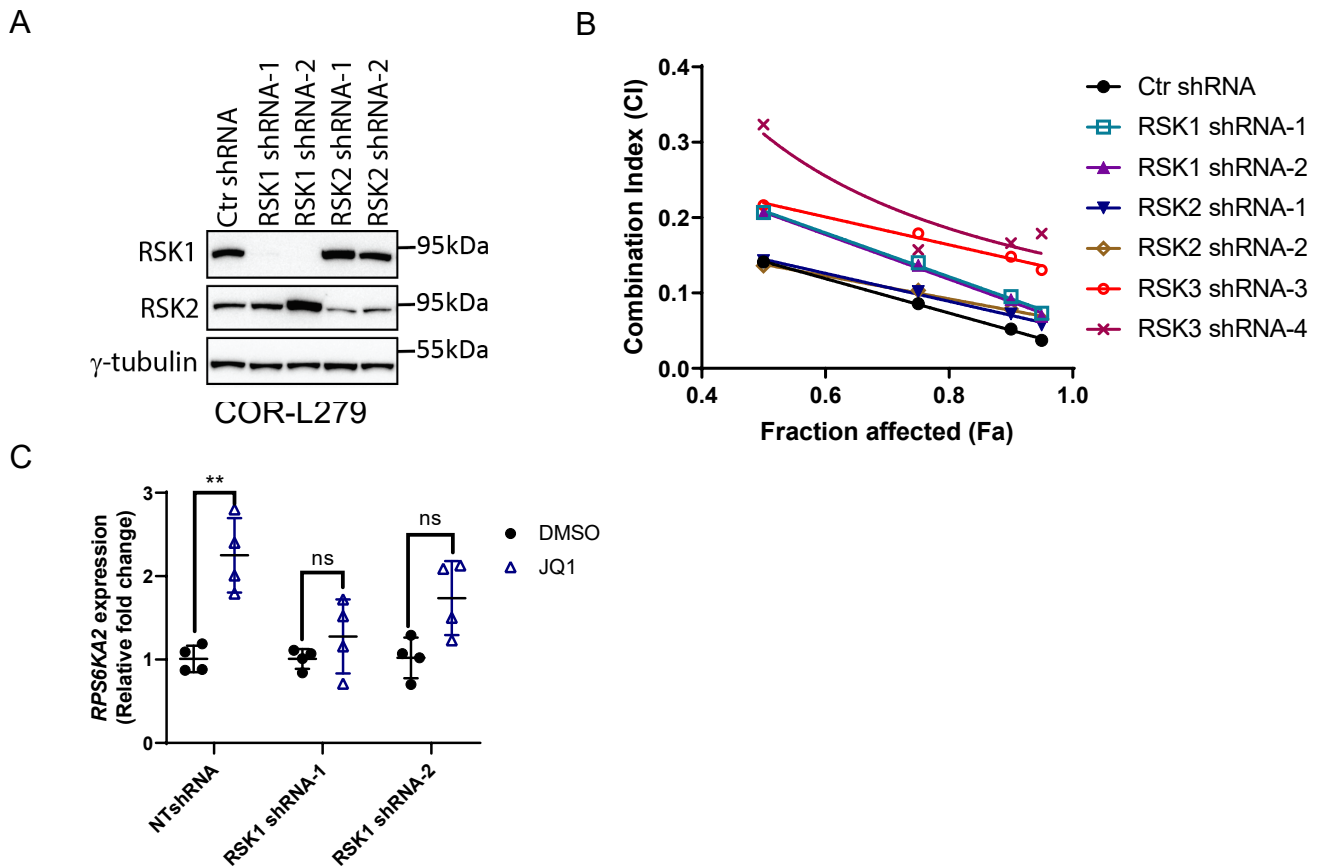
**Supplemental Figure S11. mTOR inhibition does not activate the RTK feedback loop in SCLC.** (A-C) Western blots show the changes of AKT T308 phosphorylation after treatment of everolimus (5 nmol/L) in COR-L279 (A) and LX95 cells (B), or after treatment of AZD8055 (a mTORi; 500 nmol/L) in COR-L279 cells (C). Phosphorylation of S6 S240/244 was assessed to ensure mTOR inhibition after drug treatment. (D) Western blots show the dynamic changes of AKT T308 phosphorylation in MDA-MB-468 cells after treatment with everolimus (5 nmol/L) or AZD8055 (500 nmol/L). Copanlisib (1 micromol/L) was used as a positive control. (E) Densitometry of phos-AKT T308 from (A-D). AZD, AZD8055.



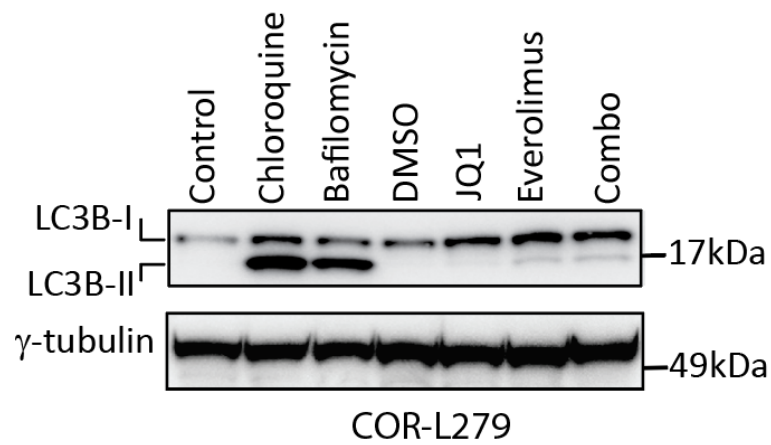
**Supplemental Figure S12. JQ1 induces *RPS6KA2* expression in COR-L279 and LX95 but not in COR-L88 cells.** COR-L279 and COR-L88 cells were treated with JQ1 (100 nmol/L) for 7 days, while LX95 cells were treated with JQ1 (250 nmol/L) for 24 hours. The significance of the two-group comparisons was determined using the Student's *t*-test with the FDR multiple comparison corrections. Where indicated, \*\*,  $p < 0.01$ ; ns, not significant.



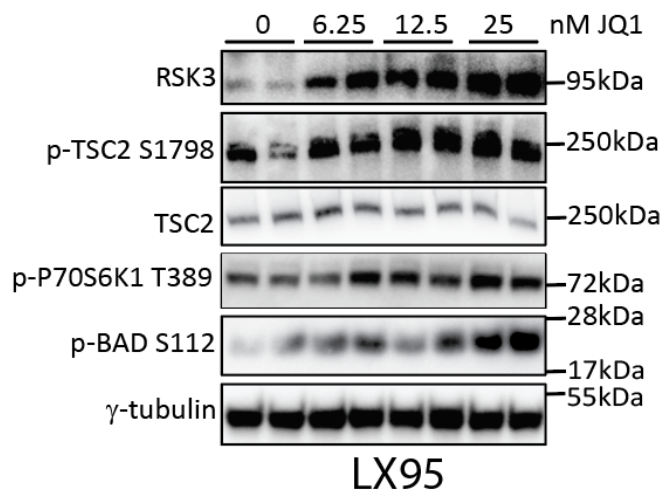
**Supplemental Figure S13. The temporal changes of phos-TSC2 S1798 and phos-p70S6K1 T389 in COR-L279 and COR-L88 cells during a 6-day course of JQ1 treatment.** COR-L279 (A) and COR-L88 (B) cells were treated with JQ1 (100 nmol/L) or DMSO for six days, and fresh media with the drugs were replenished every 2 days. (C) Densitometry of phos-TSC2 S1798 in (A-B). (D) Densitometry of phos-p70S6K1 T389 in (A-B).



**Supplemental Figure S14. RSK1 impacts the synergy of mTORi and BETi in part by regulating the BETi-induced *RPS6K42* expression.** (A) Western blots showing knockdown of RSK1 and RSK2 in COR-L279 cells by shRNAs. (B) A synergy plot comparing the combination index of the JQ1 and rapamycin combo in the COR-L279 stably expressing shRNA targeting RSK1, RSK2, or RSK3. (C) Effect of RSK1 knockdown on the *RPS6K42* induction by JQ1 (0.5 micromol/L, 24 hours) in COR-L279 cells. The significance of the two-group comparisons was determined using the Student's *t*-test with the FDR multiple comparison correction. \*\*,  $p < 0.01$ ; ns, not significant.



**Figure S15. JQ1 does not affect the everolimus-induced autophagy in COR-L279 cells.** COR-L279 cells were treated with JQ1 (1 micromol/L), everolimus (6.25 nmol/L), or the combination for 24 hours before measurement of the LC3B-I and LC3B-II levels. Chloroquine (200 micromol/L, 24 hours) and bafilomycin (150 nmol/L, 24 hours) were used as positive controls.



**Supplemental Figure S16. JQ1 induces phos-BAD S112 by activating the RSK3-TSC2-p70S6K1 cascade in LX95 cells.** Western blots show the alterations in RSK3, phos-TSC2 S1798, phos-P70S6K1 T389, and phos-BAD S112 expression in LX95 cells following one-week treatment of JQ1 at the specified doses. Fresh media and JQ1 were replenished every three days. Two experimental replicates were used.