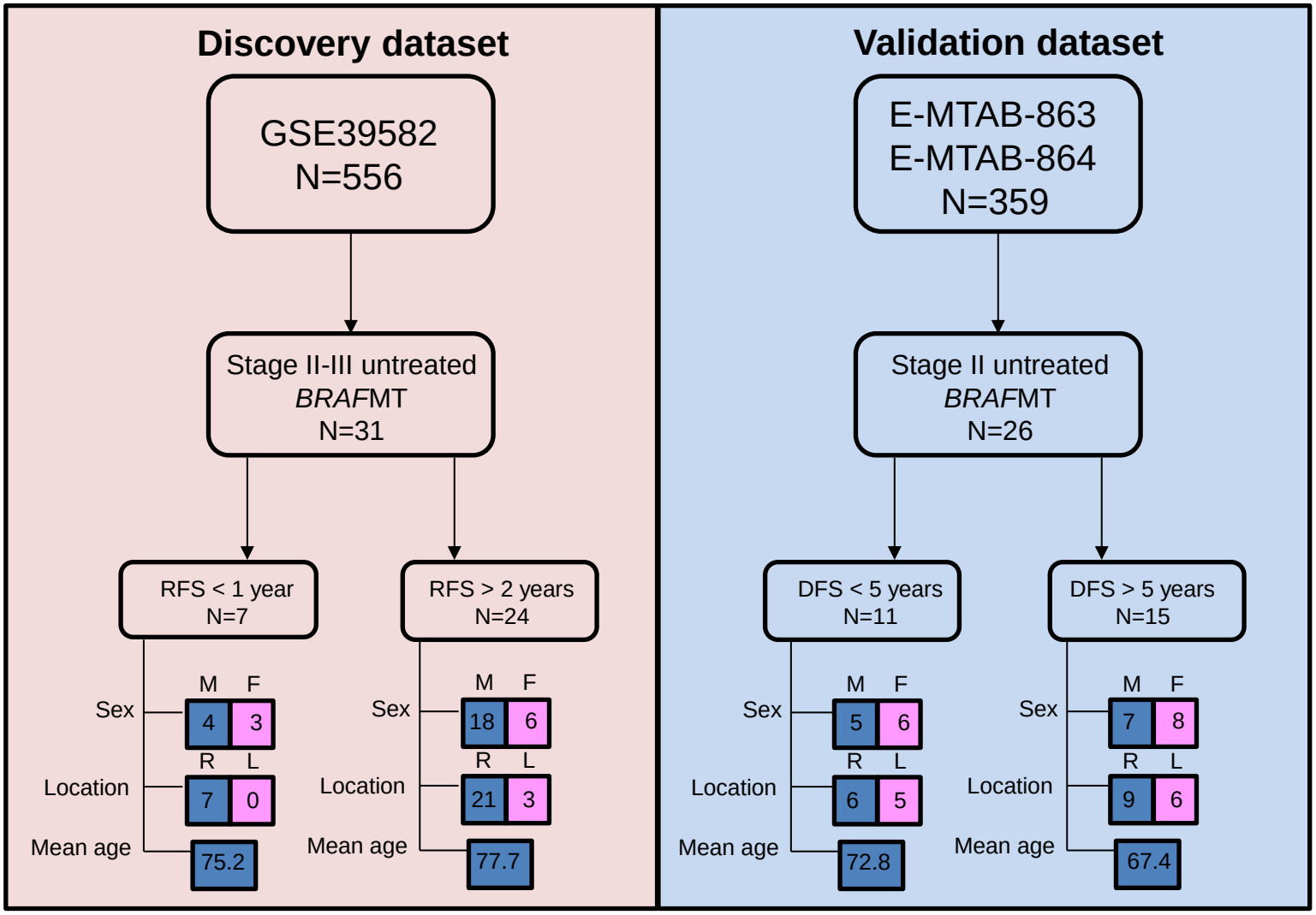
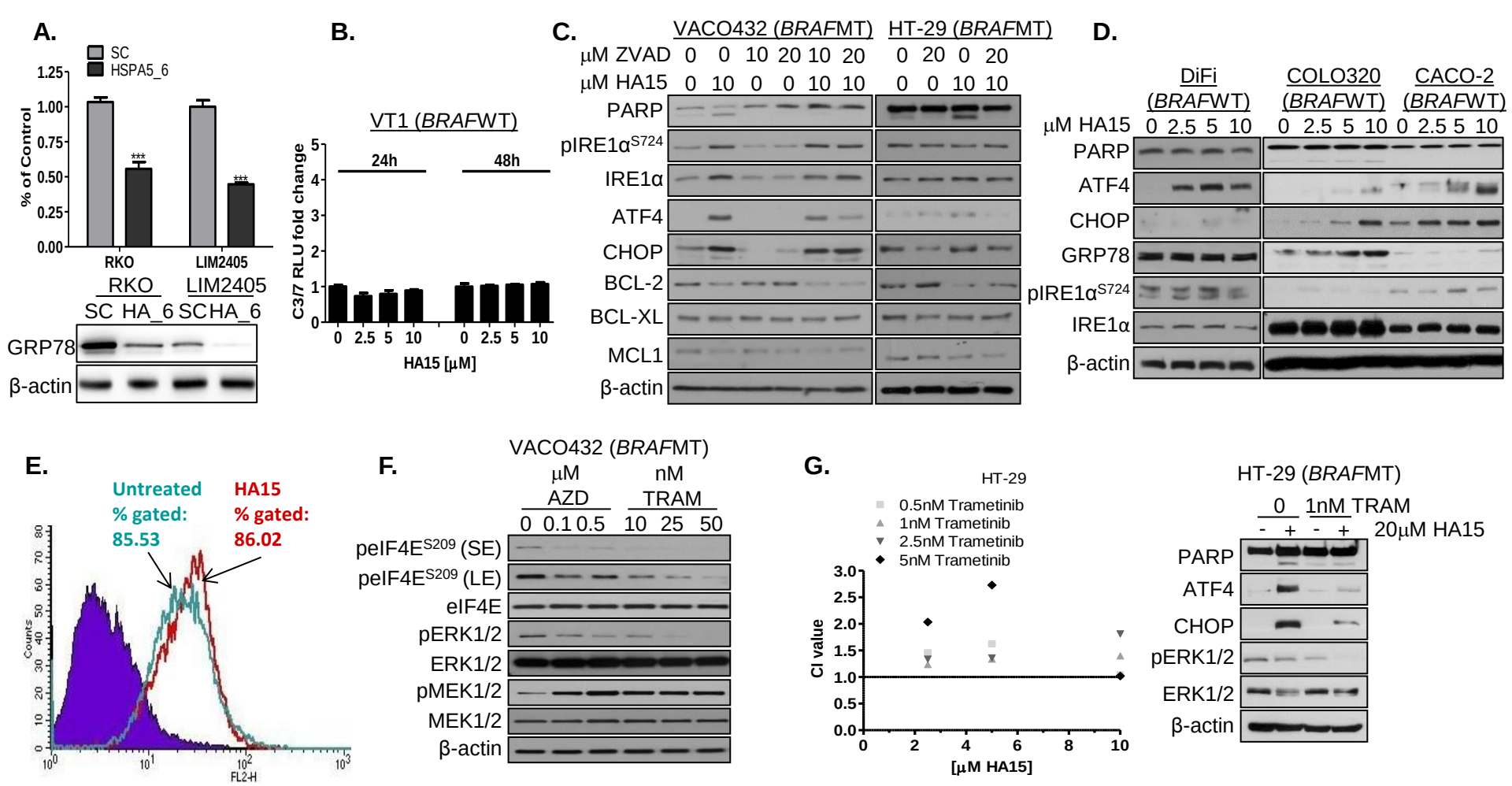
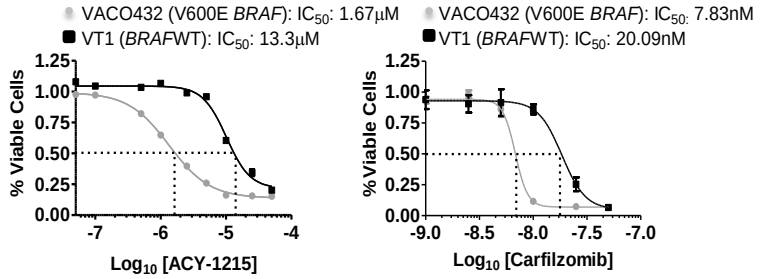


Supplementary Figure 1. Discovery and validation datasets used in the study. Consort diagram showing datasets selected for analysis of genes/pathways differentially expressed in poor and good prognostic *BRAF*MT CRC patients. Tumour location, sex and mean age are indicated for the selected good and poor prognostic *BRAF*MT patients within GSE39582 and E-MTAB-863/E-MTAB-864. RFS = relapse free survival; DFS = disease free survival. M = male; F = female; R = right; L = left.



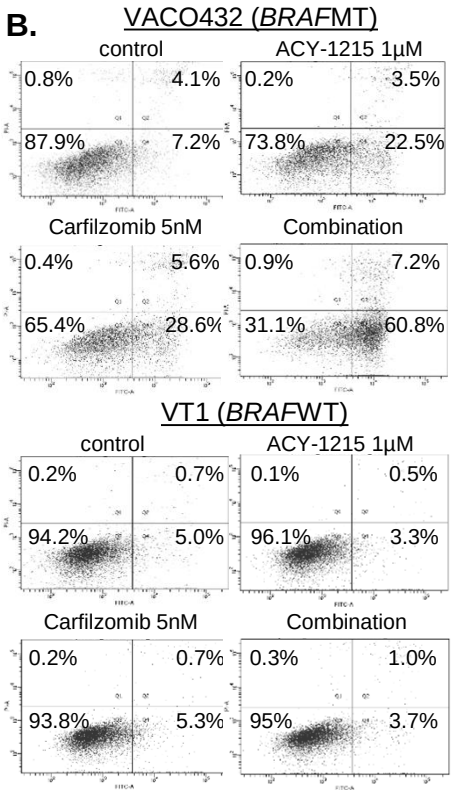
Supplementary Figure 2. Sensitivity of *BRAF*MT and WT CRC cells to acute ER stress induction. A. Top: *BRAF*MT RKO and LIM2405 cells were reverse transfected with 10nM of sequence specific siRNA against HSPA5 (sequence 6, HSPA5_6) for 72h and cell viability was measured using the Cell Titre Glo assay. **Bottom:** RKO and LIM2405 cells were reverse transfected with 10nM of sequence specific siRNA against HSPA5 (sequence 6, HA_6) for 48h and levels of GRP78 determined by Western blotting (WB). **B.** Caspase-3/7 activity levels in VT1 cells, following treatment with HA15 for the indicated time. **C.** VACO432 and HT-29 cells were incubated with the caspase inhibitor ZVAD for 24h, followed by treatment with HA15 for 24h and PARP, pIRE1α^{S724}, IRE1α, ATF4, CHOP, BCL-2, BCL-XL and MCL1 expression levels determined by WB. **D.** *BRAF/KRAS*WT DiFi, CACO-2 and COLO320 cells were treated with HA15 for 24h and PARP, ATF4, CHOP, GRP78, pIRE1α^{S724} and IRE1α levels determined by WB. **E.** VACO432 cells were treated with 10μM HA15 for 24h and DR4 cell membrane expression assessed by flow cytometry using receptor-specific phycoerythrin-conjugated mAbs. Expression was compared with a nonspecific isotype-matched control antibody. **F.** VACO432 cells were treated with MEK1/2i AZD6244 (AZD) or trametinib (TRAM) for 24h and peIF4E^{S209}, eIF4E, pERK1/2, ERK1/2, pMEK1/2, MEK1/2 and PARP levels determined by WB. **G. Left:** HT-29 cells were treated with no drug (control), Trametinib or HA15 alone or Trametinib in combination with HA15 for 72h. CI values were calculated using the method of Chou and Talalay. CI < 0.3, 0.3 < CI < 0.7, 0.7 < CI < 0.85, 0.85 < CI < 1, CI = 1, and CI > 1 denotes very strong synergism, strong synergism, moderate synergism, slight synergism, an additive interaction, and antagonism, respectively. **Right:** CHOP, ATF4 and PARP expression in cells following co-treatment with HA15 and TRAM for 24h. SE=short exposure; LE=long exposure.

A.

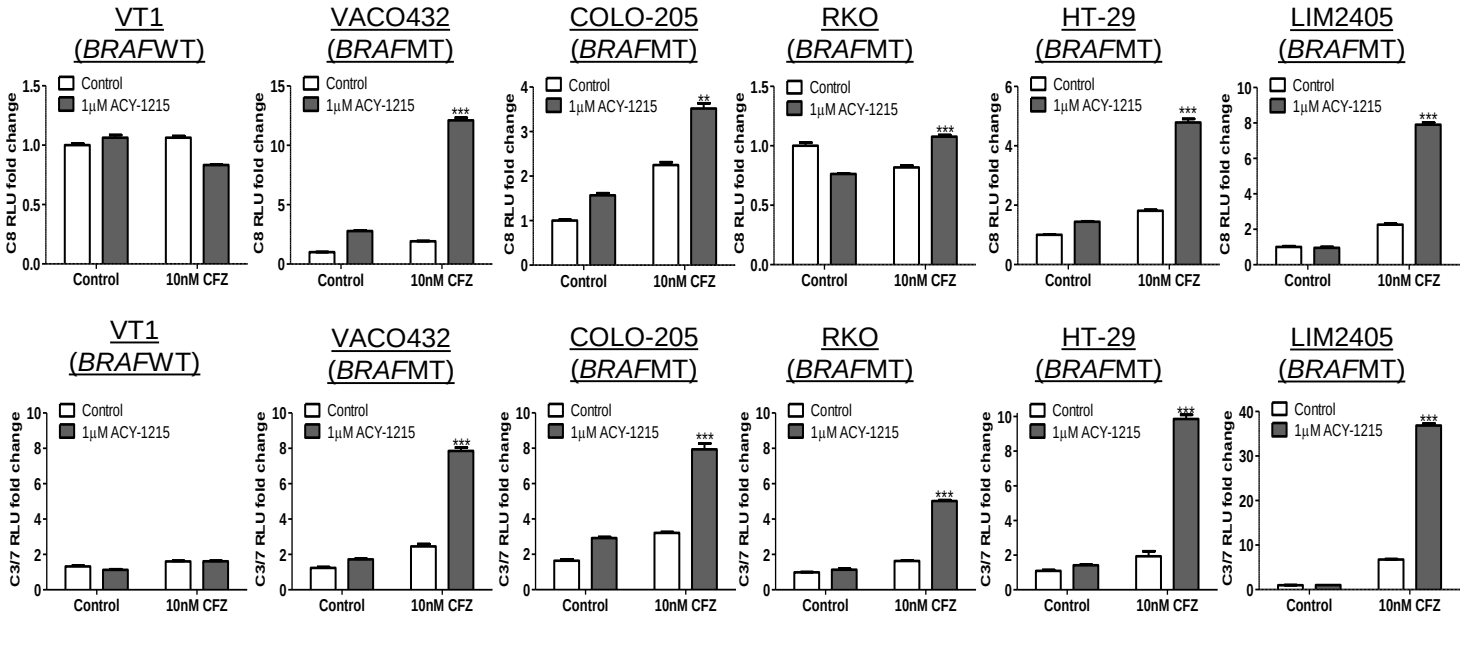


Cell line	*BRAF*	*KRAS*	Other	MSI	RF.nearest CMS	ACY-1215 IC_{50} μM	Carfilzomib IC_{50} nM
VACO432	V600E	WT	Unknown	unstable	CMS1	1.36±0.52	5.94±2.3
VT1	WT	WT	Unknown	unstable	CMS1	9.63±2.95	18.5±2.9
HT-29	V600E	WT	APC, SMAD4, TP53 (Y103 R110delYQGSYGFR)	stable	CMS1	7.65±2.08	5.39±2.22
COLO205	V600E	WT	APC, SMAD4, TP53	stable	CMS1	5.85±0.75	24.7±3.3
RKO	V600E	WT	NF1, PIK3CA (H1047R) NF1, PIK3CA (H1047R)	unstable	CMS1	5.72±0.29	8.94±1.12
LIM2405	V600E	WT	APC	unstable	CMS1	6.29±1.44	1.58±1.45
DIFI	WT	WT	TP53 (K132R)	stable	CMS2	1.83±0.18	10.24±0.49
CACO-2	WT	WT	p53	stable	CMS2	30.3±11.4	25.2±4.7
COLO320	WT	WT	TP53 (K132R)	stable	CMS2	2.39±0.37	18.4±3.6

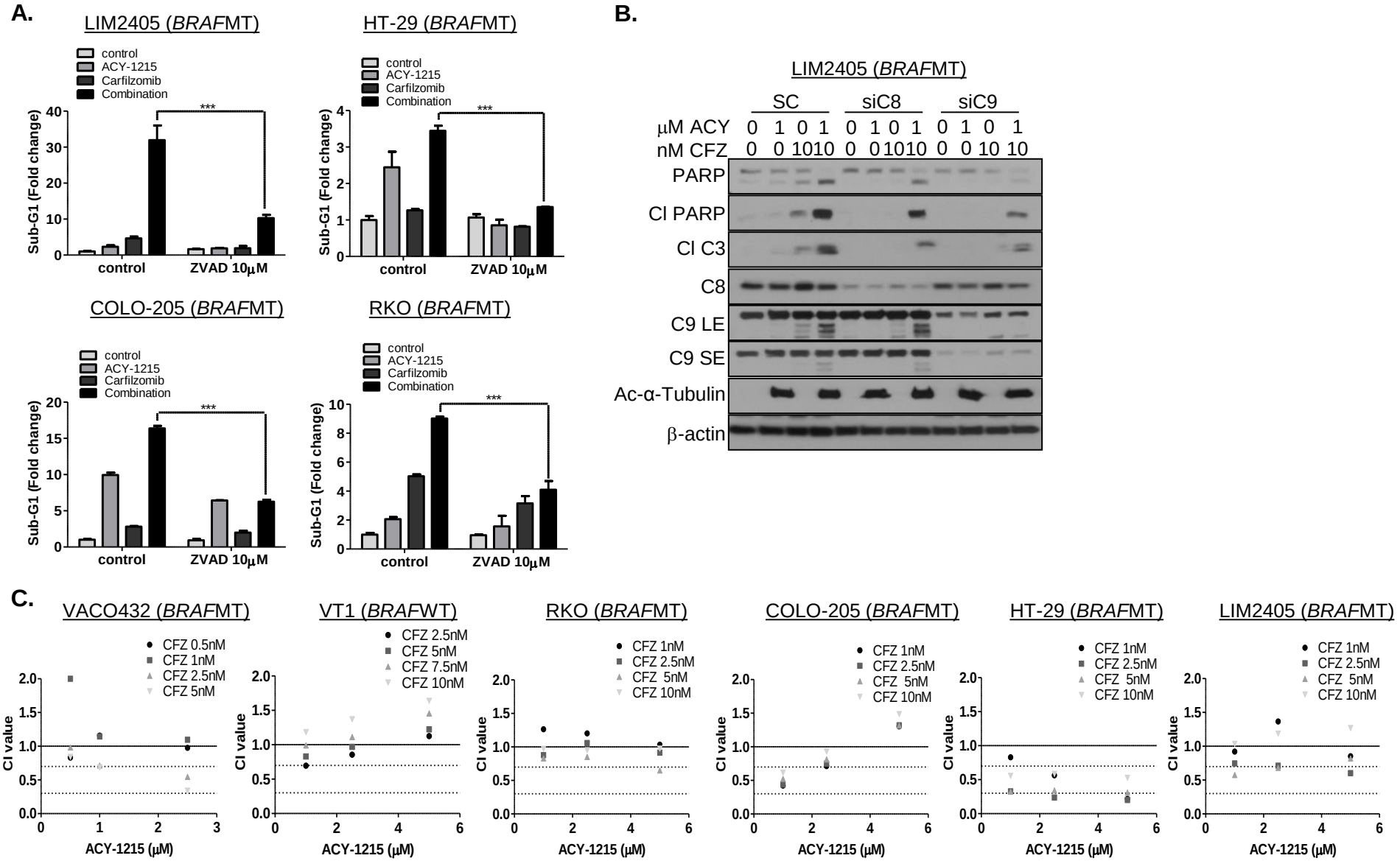
B.



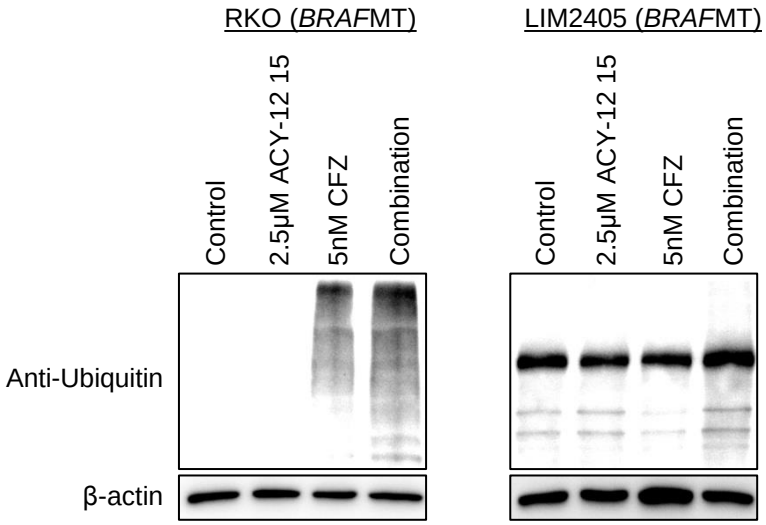
C.



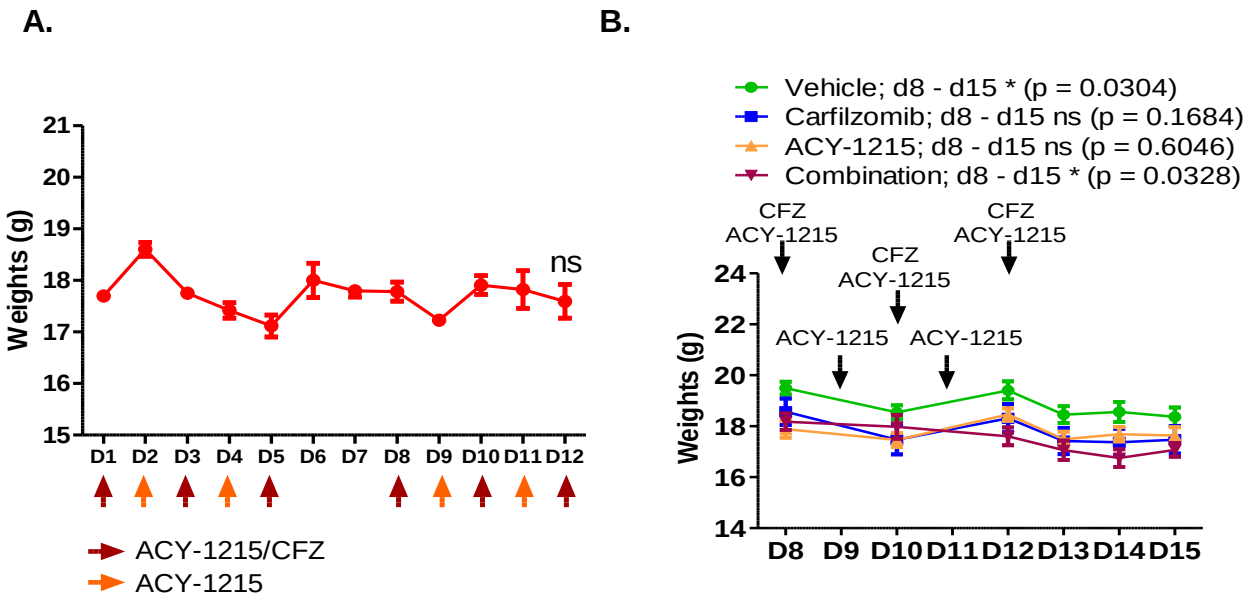
Supplementary Figure 3. Sensitivity of *BRAF*MT and WT CRC cells to ACY-1215 and Carfilzomib. A. Left and right: *BRAF*MT and *BRAF*WT CRC cells were treated with increasing concentrations of ACY-1215 or Carfilzomib for 72h and cell viability was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide assay (MTT). IC_{50} was calculated using Prism software package. Mean of 3 independent experiments with Standard Deviation is presented in the table (CMS = Consensus Molecular Classification). **B**. Annexin V/PI flow cytometry of ACY-1215 and Carfilzomib in VACO432 and VT1 CRC cells. **C.** Caspase 8 and 3/7 activity levels were measured in *BRAF*MT COLO205, RKO, HT-29, VACO432, LIM2405 and *BRAF*WT VT1 cells following 24h treatment with ACY-1215, CFZ or combined ACY-1215/CFZ treatment.



Supplementary Figure 4. Effect of combined ACY-1215 and Carfilzomib on survival of *BRAF*MT and WT CRC cells. A. *BRAF*MT cells were pre-incubated with 10 μM of the pan-caspase inhibitor, z-VAD-fmk, for 24h following treatment with 1μM ACY-1215, 10nM CFZ or combined ACY-1215/CFZ treatment for 24h and apoptosis assessed by PI flow cytometric analysis. **B.** *BRAF*MT cells were transfected with 10nM C8 or C9 siRNA for 24h and thereafter treated with ACY-1215 (ACY) and CFZ for 24h and apoptosis was assessed by WB for cleaved C3 and PARP. **C.** MTT assays were performed in *BRAF*MT and WT CRC cells. Cells were treated with no drug (control), ACY-1215, Carfilzomib, or ACY-1215 in combination with Carfilzomib for 72h. CI values were calculated using the method of Chou and Talalay, where CI < 0.3, 0.3 < CI < 0.7, 0.7 < CI < 0.85, 0.85 < CI < 1, CI = 1, and CI > 1 denotes very strong synergism, strong synergism, moderate synergism, slight synergism, an additive interaction, and antagonism, respectively. Representative results of at least three experiments. SE=short exposure; LE=long exposure.



Supplementary Figure 5. Effect of combined ACY-1215 and Carfilzomib on accumulation of ubiquitinated proteins. Total levels of ubiquitinated proteins in *BRAF*MT CRC cells following treatment with ACY-1215 and Carfilzomib (CFZ) for 12 hours (LIM2405) and 24 hours (RKO) respectively.



Supplementary Figure 6. Tolerability of combined ACY-1215/Carfilzomib treatment in BALB/c Nude mice. A. Weights of non-tumour-bearing BALB/c Nude mice following 2 weeks treatment of ACY-1215 (30mg/kg/day 5/7 days IP) with/without Carfilzomib (6mg/kg 3x week IP) n = 3. **B.** Body weights of mice with VACO432 tumours treated with vehicle, ACY-1215 (30mg/kg), CFZ (6mg/kg) or in combination (n = 7 in each group). Differences in body weight were determined using Student's t-test.