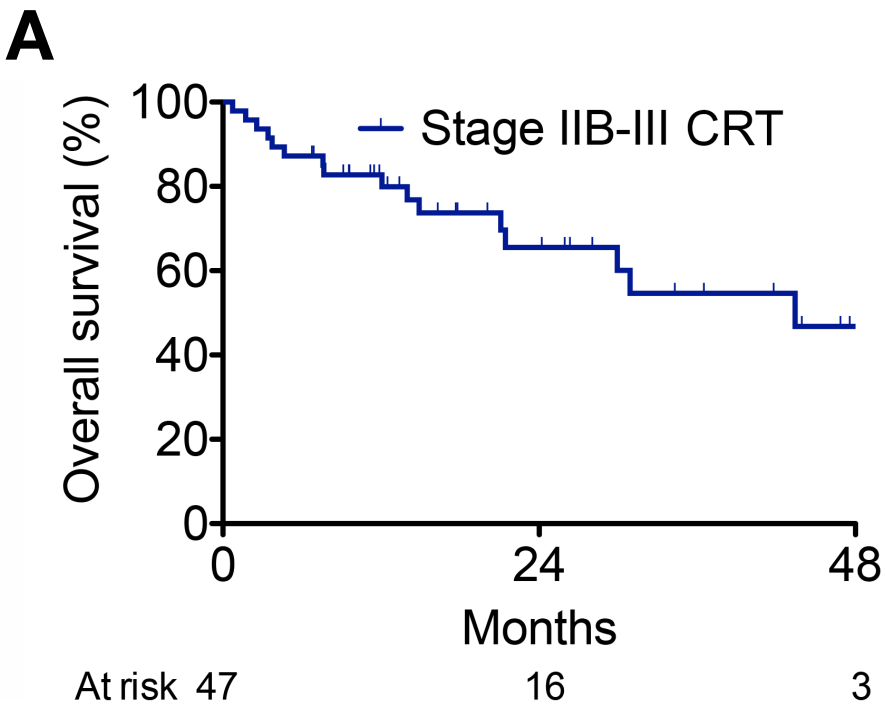
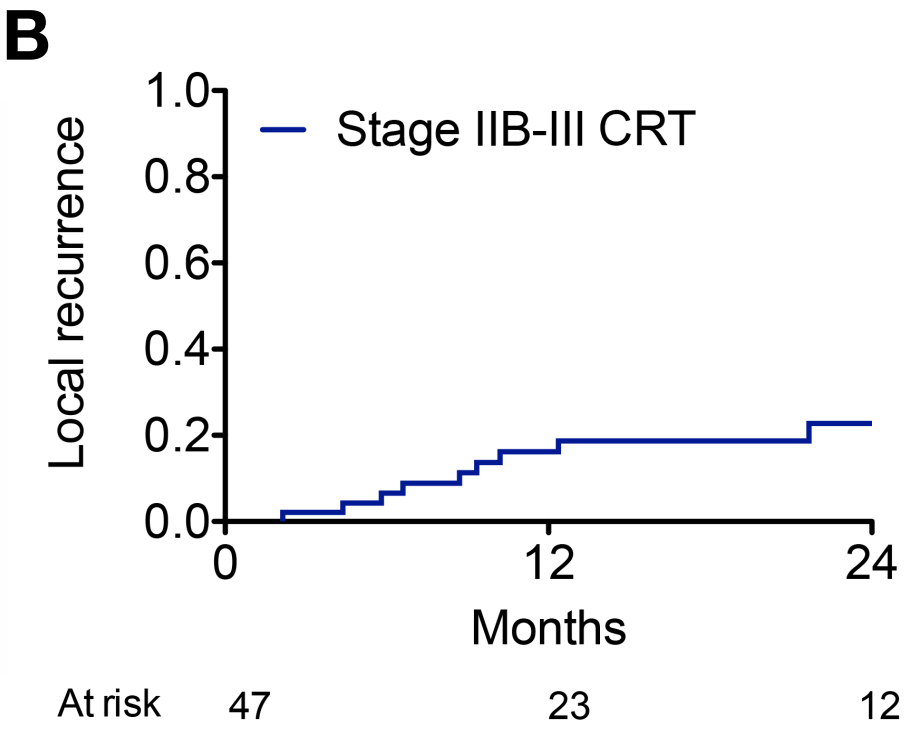
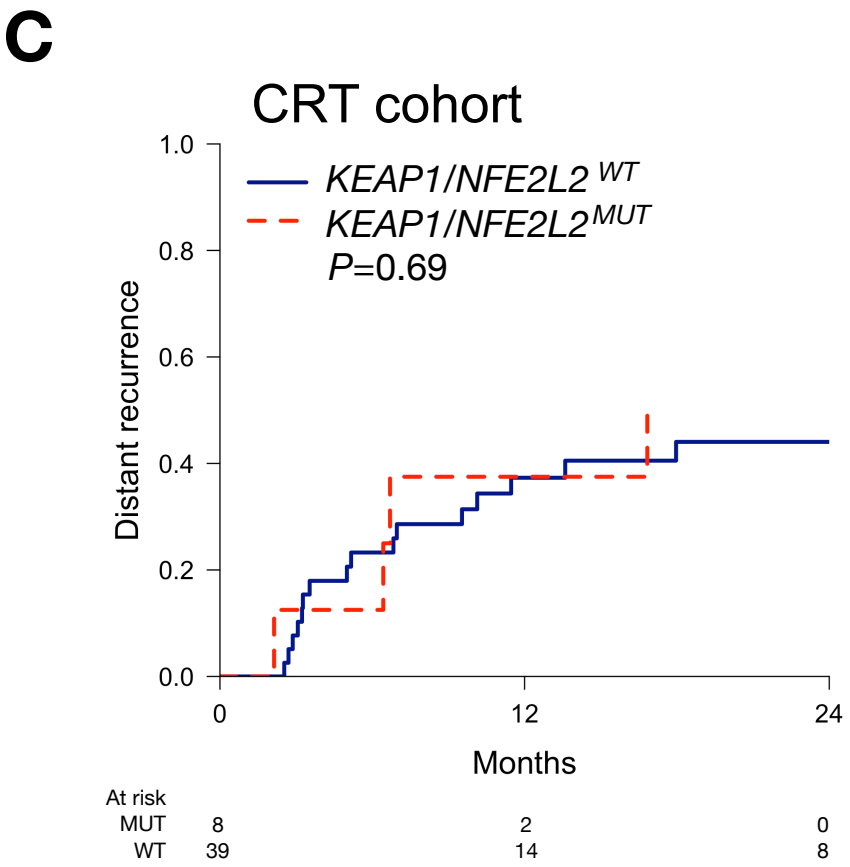
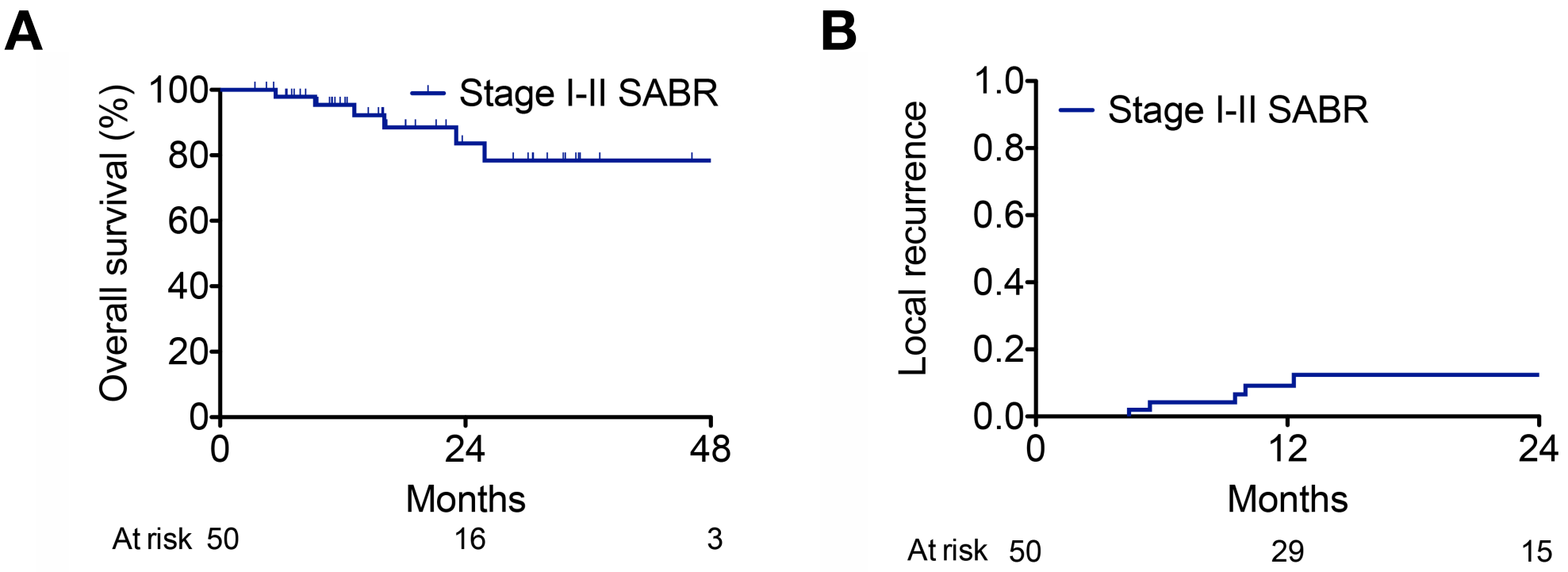
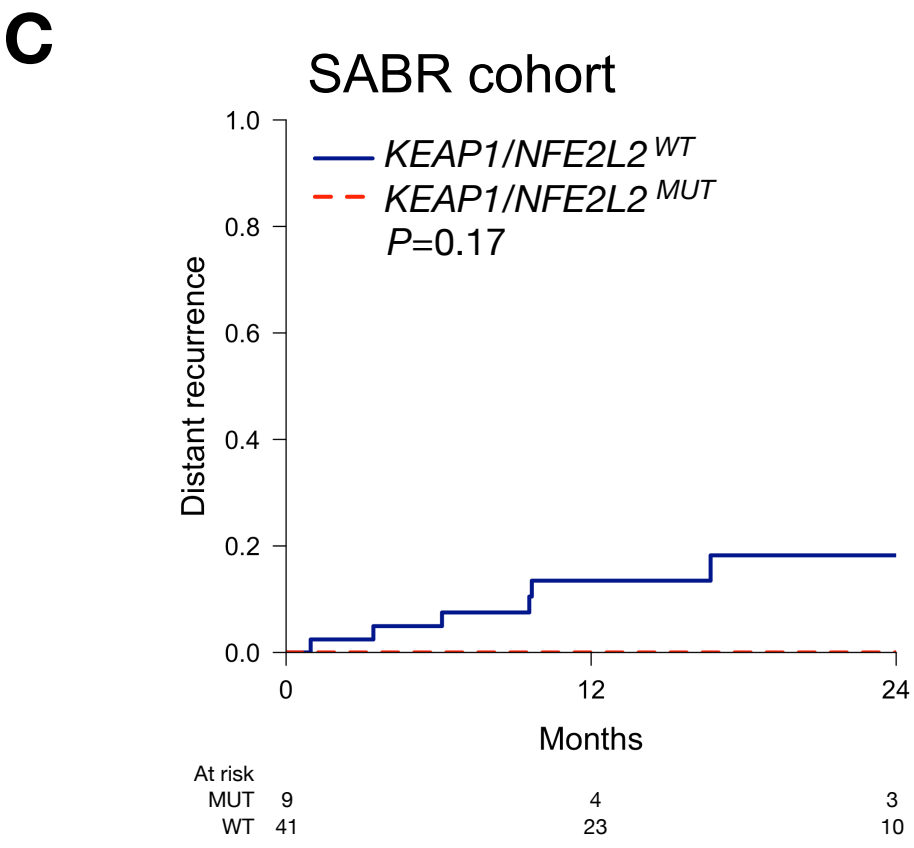




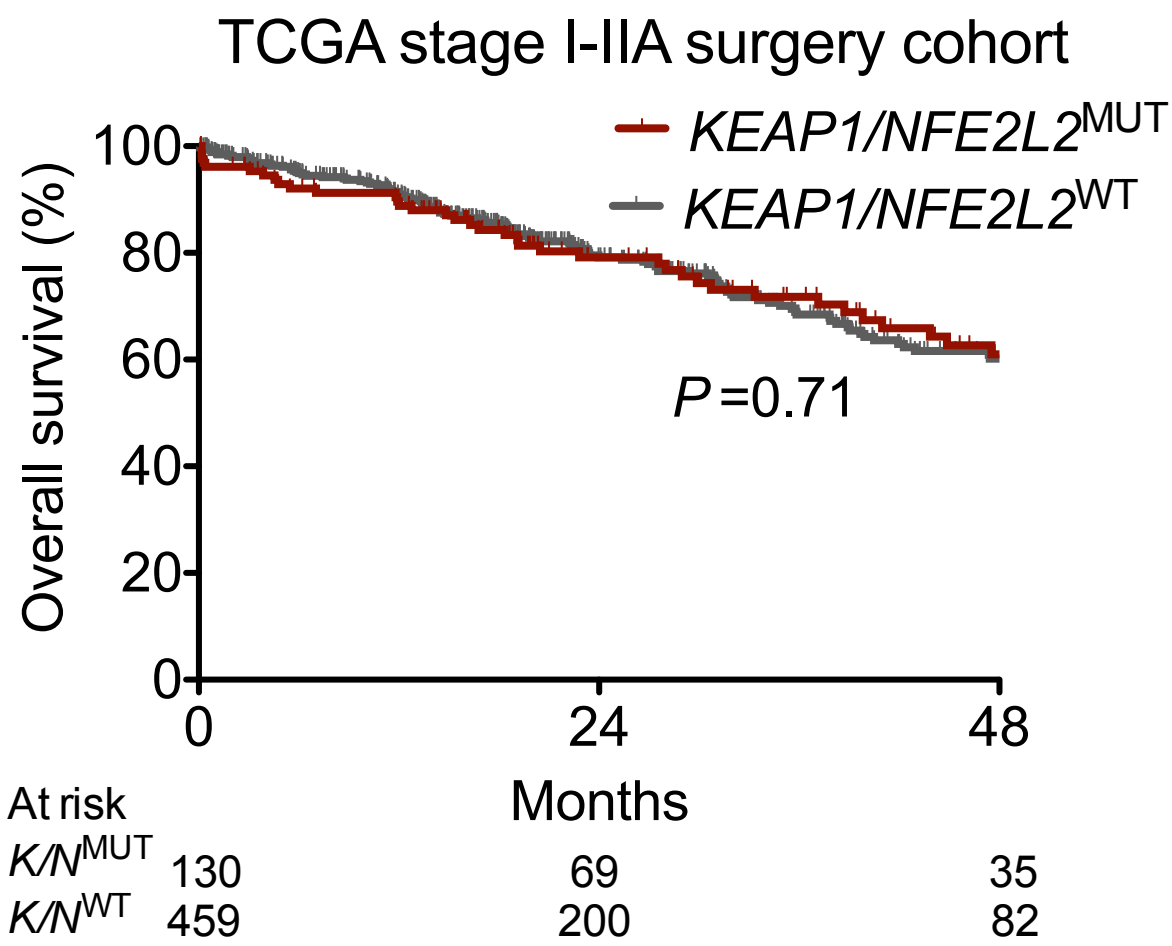


Supplementary Figure 1. OS (panel A) and LR (panel B) for patients receiving CRT. Panel C shows the cumulative incidence plot adjusted for the competing risk of death and demonstrates no significant increased risk of distant recurrence as first recurrence by Gray's test for patients who received CRT stratified by *KEAP1/NFE2L2* mutation status.





Supplementary Figure 2. OS (panel A) and LR (panel B) for patients receiving SABR. Panel C shows the cumulative incidence plot adjusted for the competing risk of death and demonstrates no significant increased risk of distant recurrence as first recurrence by Gray's test for patients who received SABR stratified by *KEAP1/NFE2L2* mutation status.



Supplementary Figure 3. Kaplan-Meier curves demonstrate OS for patients with stage I-IIA NSCLC identified from the TCGA (reference 24) who underwent surgical resection without neoadjuvant or adjuvant treatments stratified by *KEAP1/NFE2L2* mutation status.

A

KEAP1 Exon 2

sgRNAPAMMutation

Parental 5'- GGCCGCCCAGTTCATGGCCCACAAGGTGG --- 82 bp --- GGTGTCCATTGAGGGTATCCACCCCA AGG - 3'

KEAP1^{NULL} 5'- GGCCGCCCAGTTCATGGCCCA ----------(107 bp deletion)----------TCCACCCCA AGG - 3'

B

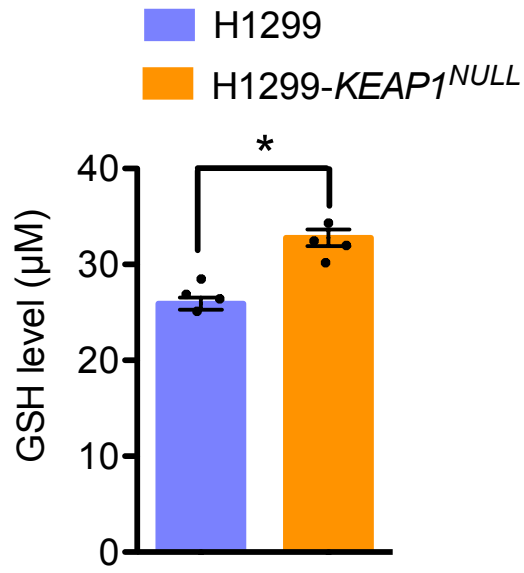
NFE2L2 Exon 4

sgRNAPAMMutation

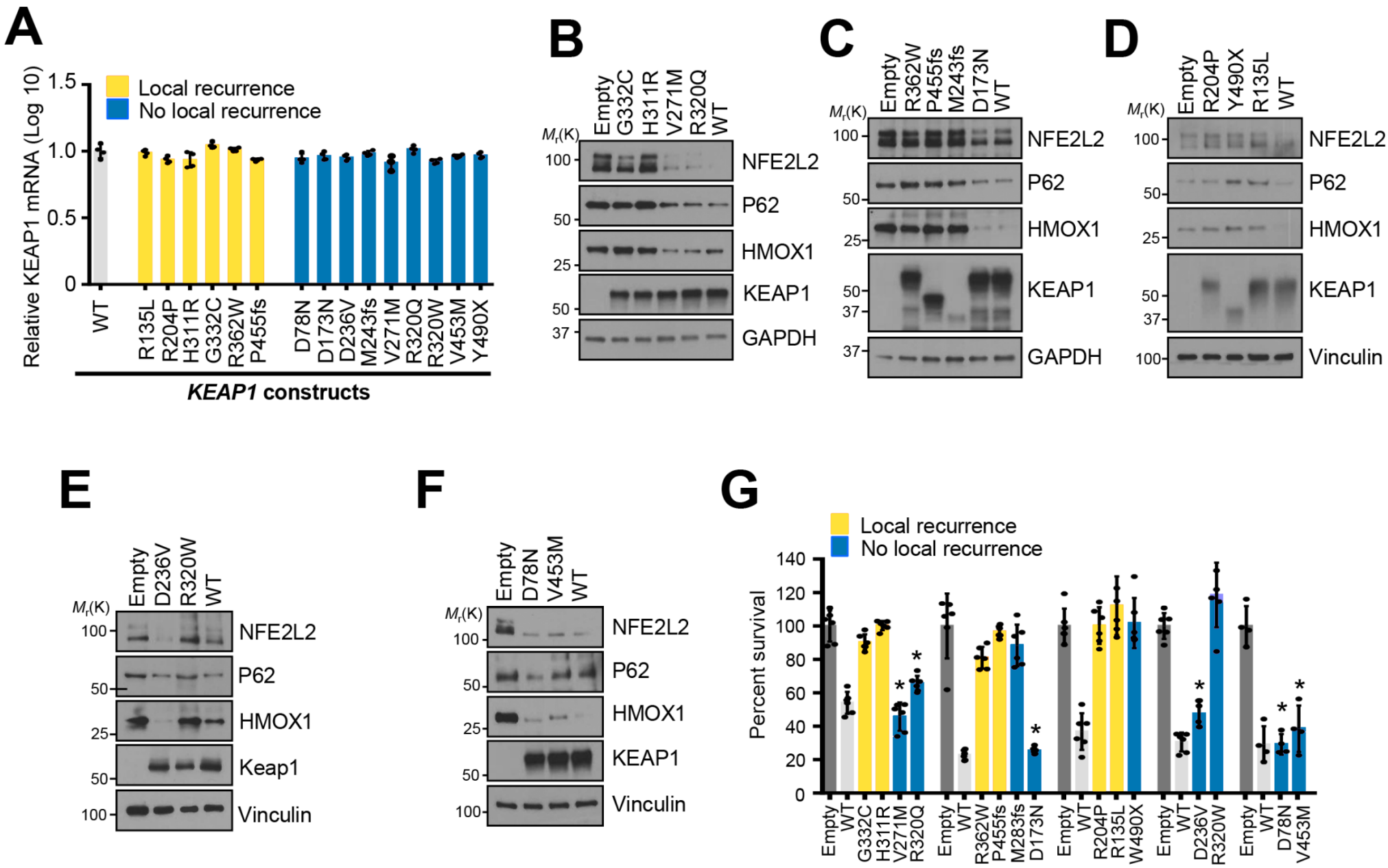
Parental 5'- GAGAAGTATTTGACTTCAGTCAGCGACGG --- 135 bp --- GCCCAGCACATCCAGTCAGAAACCAGTGG - 3'

NFE2L2^{NULL} 5'- GAGAAGTATTTGACTTCAGTCAGC----------(164 deletion)----------AGTGG - 3'

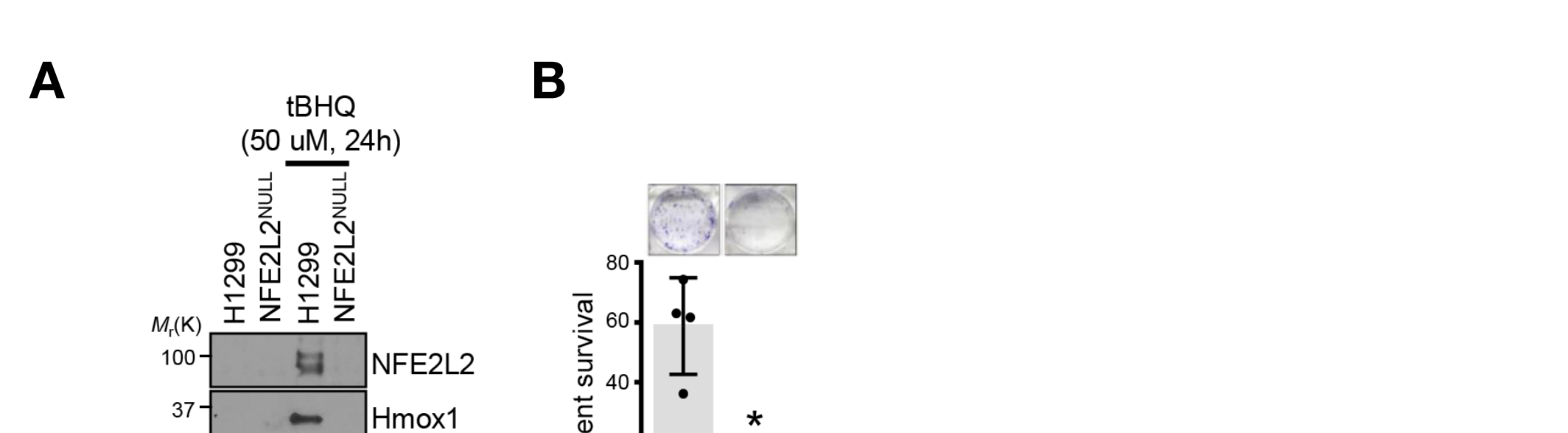
C



Supplementary Figure 4. Genomic DNA sequences by Sanger sequencing for the *KEAP1*^{NULL} (panel A) and *NFE2L2*^{NULL} (panel B) isogenic cell lines generated using CRISPR-Cas9 mediated gene editing by directly introducing the sgRNA-Cas9 complex. (C) Glutathione (GSH) levels in parental and *KEAP1*^{NULL} H1299 cells (n=4; *P< 0.05 by Student's t-test).

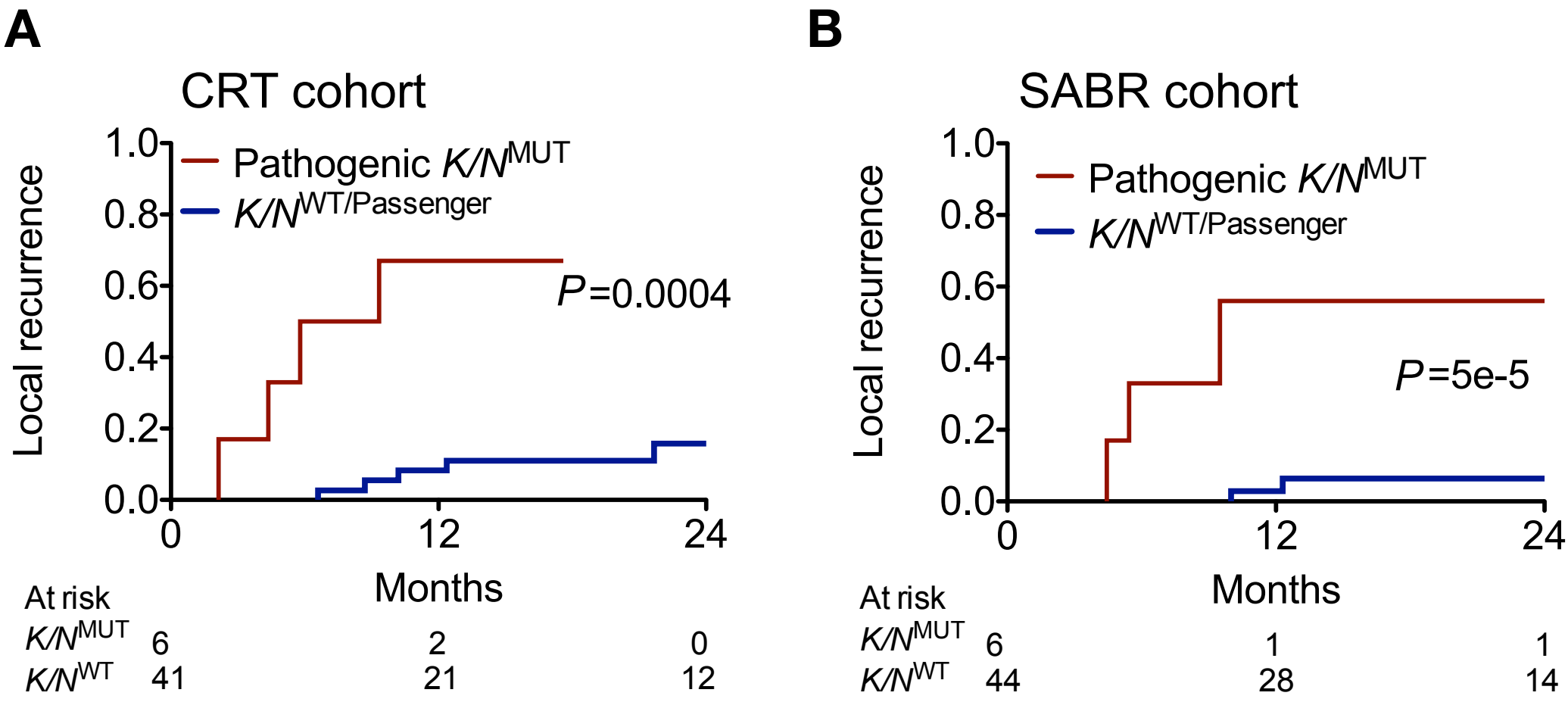


Supplementary Figure 5. (A) qRT-PCR analysis confirms the expression level of wild type and mutant *KEAP1* constructs were similar (n=4). (B-F) Protein expression of NFE2L2 downstream targets for each of the patient-derived KEAP1 mutations in the *KEAP1*^{NULL} cell line. *KEAP1*^{NULL} were transfected by plasmids harboring wild type or KEAP1 mutant alleles, and the abundance of NFE2L2, P62 and HMOX1 proteins were analyzed by Western blot to determine NFE2L2 activation. (G) Percent survival as quantified by CellTiter-glo for H1299-*KEAP1*^{NULL} cells transiently transfected with *KEAP1* mutant plasmids following exposure to hydrogen peroxide (150 mM, n=5, **P* <0.01 by Student's t-test).



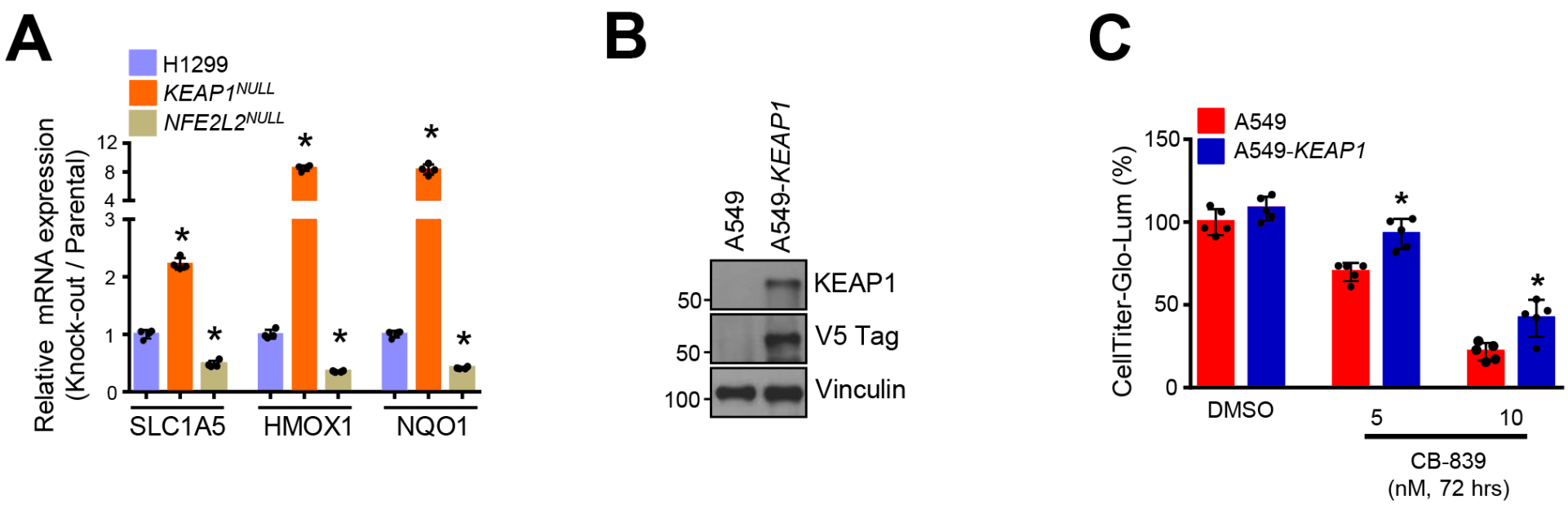
Supplementary Figure 6. (A) Western blot analysis for NFE2L2 and NFE2L2 target proteins in parental H1299 and *NFE2L2*^{NULL} cells with and without tBHQ treatment (50 uM for 24 hrs). (B) Clonogenic survival of parental and *NFE2L2*^{NULL} H1299 cells exposed to 5 Gy of ionizing radiation (n=4, *P<0.01 by Student's t-test). (C) qRT-PCR analysis confirms the expression level of wild type and mutant each *NFE2L2* were similar (n=4). (D) Protein expression of NFE2L2 downstream targets for each of the patient-derived *NFE2L2* mutations in the *NFE2L2*^{NULL} cell line. *NFE2L2*^{NULL} cells were transfected by plasmids harboring wild type or *NFE2L2* mutant alleles, and the abundance of NFE2L2, GCLm and HMOX1 proteins were analyzed by Western blot to determine NFE2L2 activation (n=4). (E) Percent survival as quantified by CellTiter-glo for H1299-*NFE2L2*^{NULL} cells transiently transfected with patient derived *NFE2L2* mutant ORF plasmids or wildtype. After 48 hrs, the cells were treated with hydrogen peroxide (150 mM) for 24 hrs. (n=6, *P<0.001 by Student's t-test).

Supplementary Figure 7.

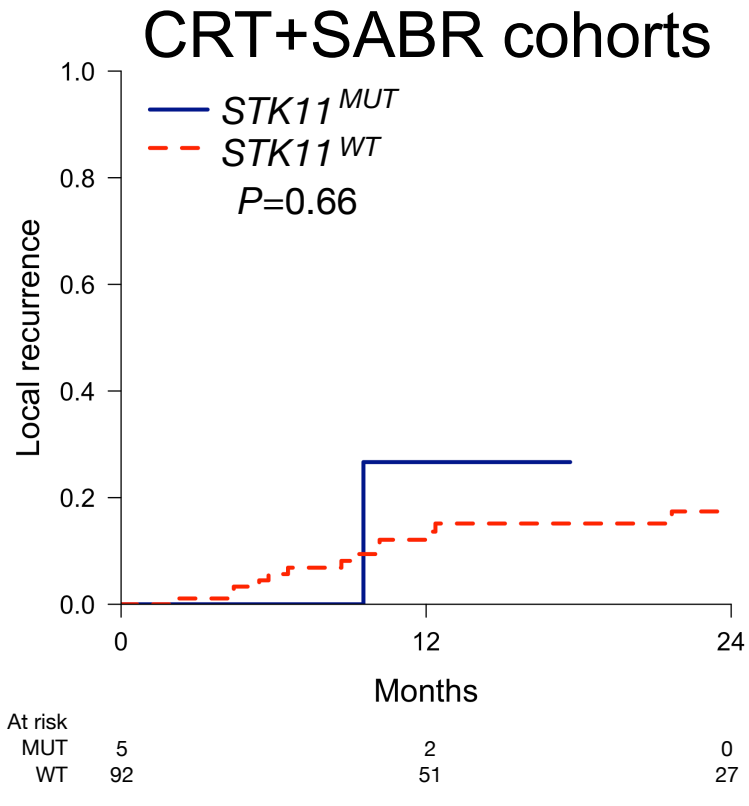


Supplementary Figure 7. Estimate of local recurrence stratified by pathogenic *KEAP1/NFE2L2* mutation status for patients who received either CRT (panel A) or SABR (panel B, comparison using Gray's test).

Supplementary Figure 8



Supplementary Figure 8. (A) qRT-PCR analysis shows increased expression of SLC1A5, HMOX1, and NQO1 in *KEAP1*^{NULL} but decreased expression in *NFE2L2*^{NULL} cell lines (n=4, **P* <0.01 by Student's t-test). (B) Western blot analysis shows expression of KEAP1 in the A549-KEAP1 over expression cell lines cells. (C) *KEAP1*^{NULL} A549 cell lines had preferentially lower cell survival compared to the A549-KEAP1 overexpressing cells after exposure to CB-839 (5 or 10 nM) for 72 hours as determined by CellTiter-glo assay (n=4, **P*<0.01 by Student's t-test).



Supplementary Figure 9. Cumulative incidences adjusted for the competing risk of death and demonstrates no significant increased risk of LR for patients with *STK11* mutant versus *STK11* wildtype tumors (comparison using Gray's test).