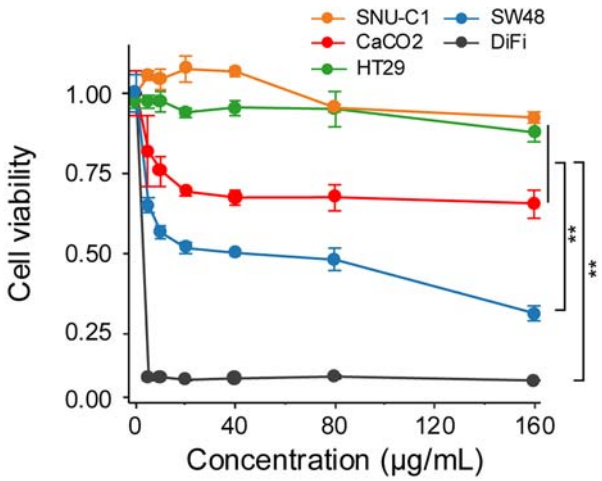
Expanded View Figures



IC_{50} (μg/mL)	CaCO2	SNU-C1	HT29	SW48	DiFi
	N/A	N/A	N/A	34.77	< 5

Figure EV1. Cell viability of five colorectal cancer cell lines measured 48 h after initial exposure to cetuximab.

GEM-R vs. SW48: $p = 0.002$, GEM-R vs. DiFi: $p = 0.001$ (two-way ANOVA). Data were representative of three independent biological replicates. Bars represent the mean, and error bars indicate SD. $^{**}p < 0.01$, N/A not available.

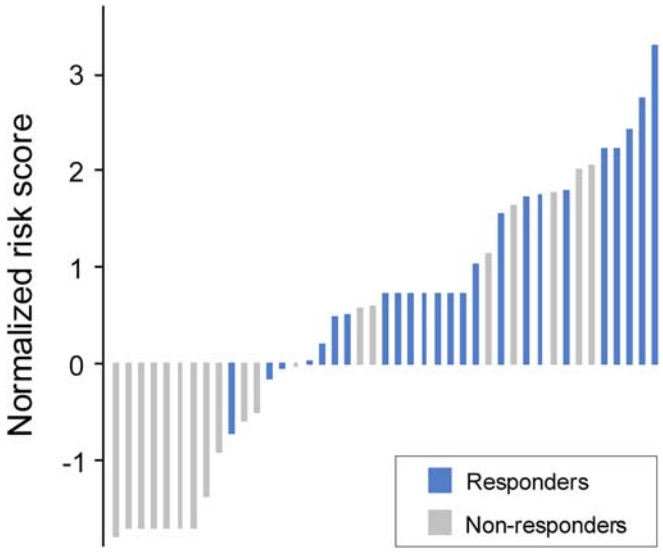


Figure EV2. The waterfall plot depicts the risk probability distribution of the normalized risk score between the responder and non-responder groups.

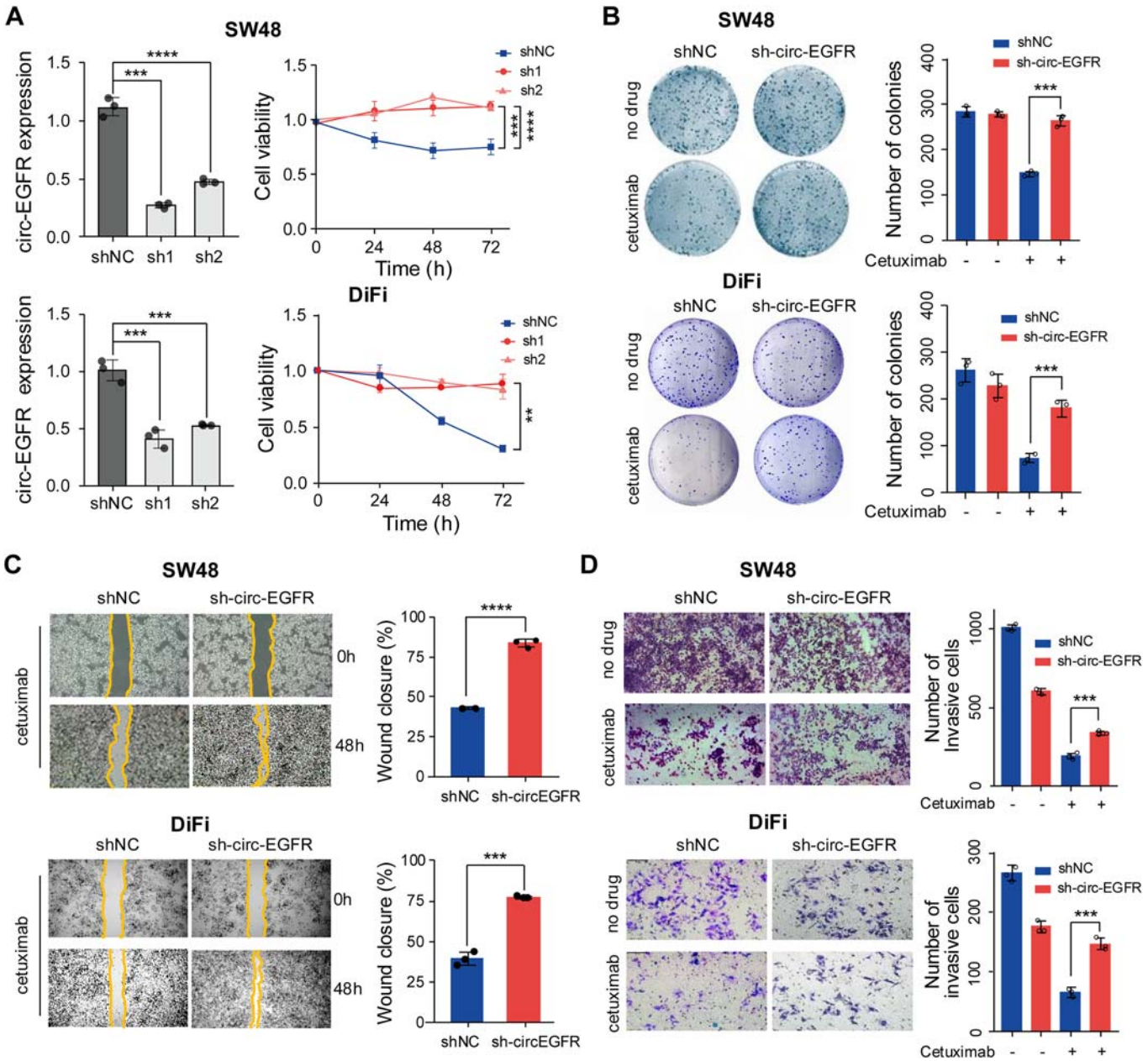


Figure EV3. Circ-EGFR depletion inhibits the response of CRC cells to cetuximab in vitro.

(**A**) The expression of circ-EGFR in stable circ-EGFR-silenced (sh1 and sh2) or negative control (shNC) from DiFi and SW48 cell lines (left). Assessment of cell proliferation capacity by MTT assay in circ-EGFR knockdown (sh1 and sh2) or shNC group from DiFi and SW48 cell lines after 48 h treatment with cetuximab (right). circ-EGFR expression of shNC vs. sh1 in SW48: $p < 0.0001$, shNC vs. sh2 in SW48: $p = 0.0002$, shNC vs. sh1 in DiFi: $p = 0.001$, shNC vs. sh2 in DiFi: $p = 0.0007$ (student's t-test). Cell viability of shNC vs. sh1 in SW48: $p = 0.0004$, shNC vs. sh2 in SW48: $p < 0.0001$, shNC vs. sh1 in DiFi: $p = 0.0004$, shNC vs. sh2 in DiFi: $p = 0.0004$ (two-way ANOVA). (**B**) Proliferation in stable circ-EGFR knockdown (sh-circ-EGFR) or shNC from DiFi and SW48 cells as determined by colony formation assay. SW48 $p = 0.0001$, DiFi $p = 0.0007$ (student's t-test). (**C**) Wound healing assay of sh-circ-EGFR or shNC in DiFi and SW48 cell lines after 48 h treatment with cetuximab. Scale bar = 50 μm. SW48 $p < 0.0001$, DiFi $p < 0.0001$ (Student's *t*-test). (**D**) Invasion assay of sh-circ-EGFR or shNC in DiFi and SW48 cell lines with or without cetuximab treatment. Scale bar = 100 μm. The number of invading cells was counted in randomly selected three fields. SW48 $p = 0.0002$, DiFi $p = 0.0007$ (student's *t*-test). Data were representative of at least three independent biological replicates. Bars represent the mean, and error bars indicate SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, **** $p < 0.0001$, ns not significant.

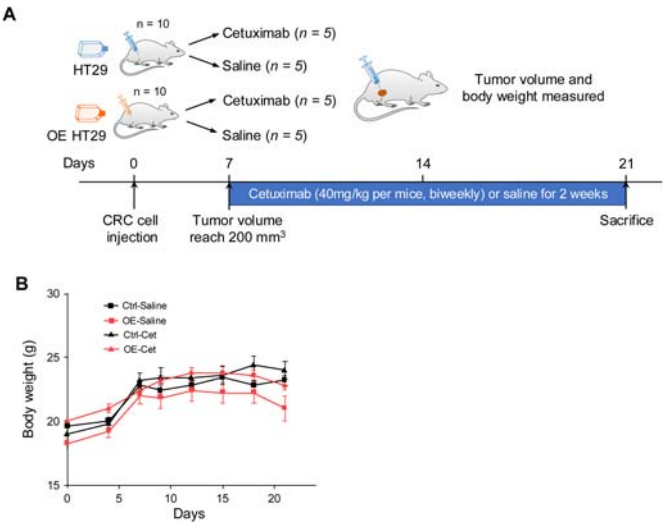


Figure EV4. Circ-EGFR enhances the efficacy of cetuximab in vivo.

(**A**) Schematic diagram of the HT29 cell (transfected with circ-EGFR and mock plasmids)-derived xenograft model in 20 nude mice and the treatment schedule of cetuximab. (**B**) The body weight of nude mice injected with circ-EGFR and mock plasmids in each treatment group was measured at different time points after inoculation. Ctrl Cet: mice inoculated with the HT29 cell line transfected with vector control and treated with cetuximab, Ctrl Saline: mice inoculated with the HT29 cell line transfected with vector control and treated with saline, OE Cet: mice inoculated with circ-EGFR overexpressing HT29 cells and treated with cetuximab, OE Saline: mice inoculated with circ-EGFR overexpressing HT29 cells and treated with saline. Data were representative of five biological replicates. Bars represent the mean, and error bars indicate SD.

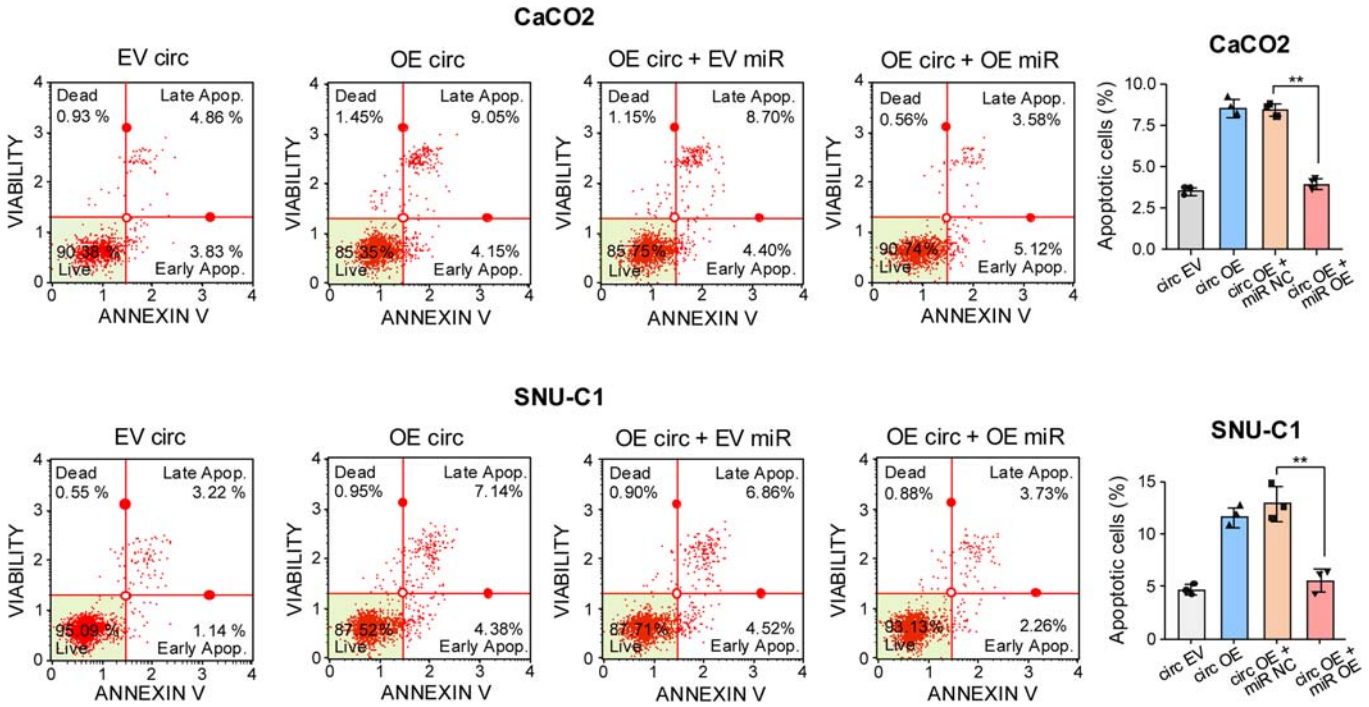
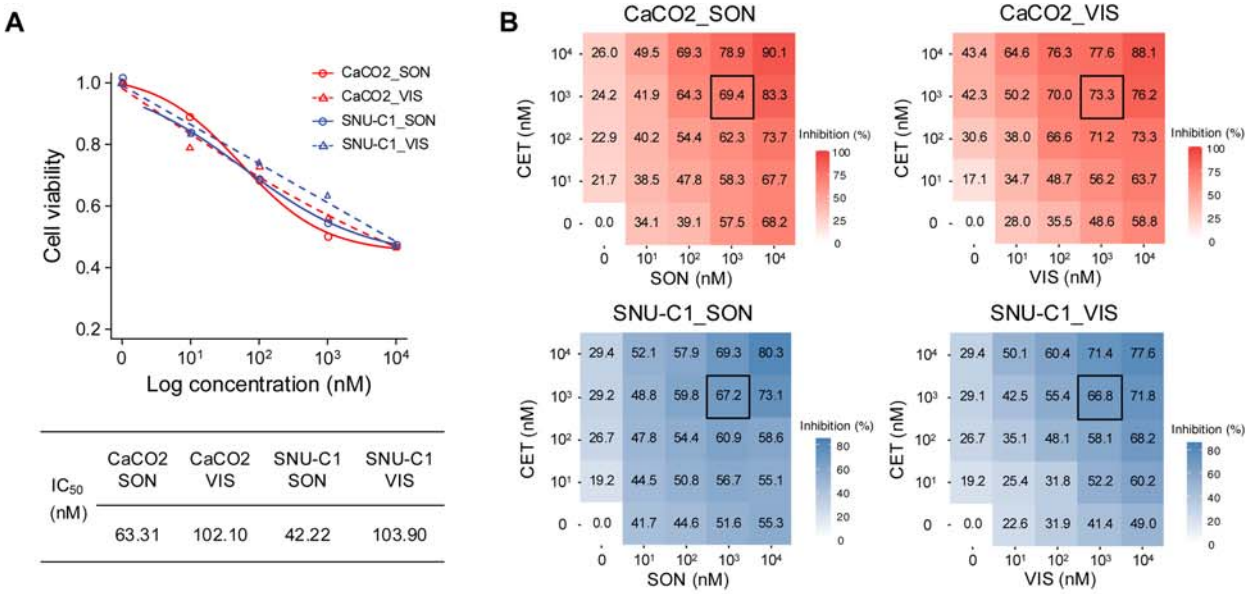
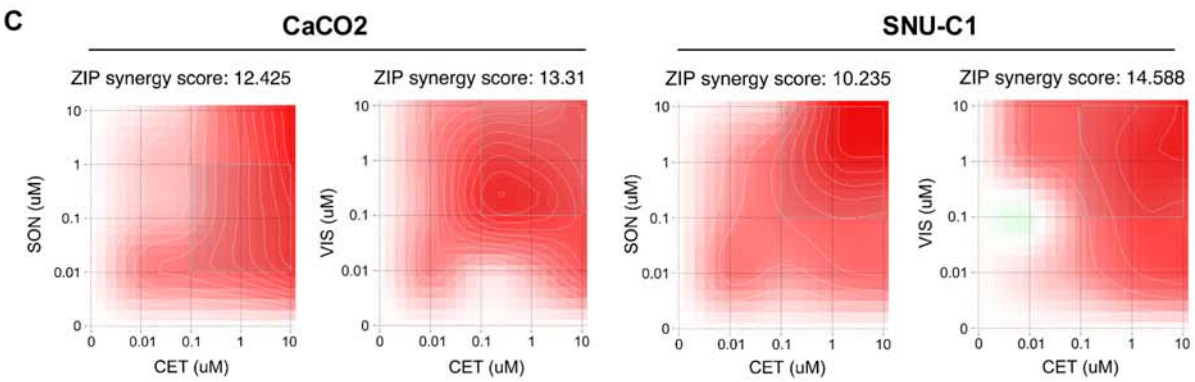


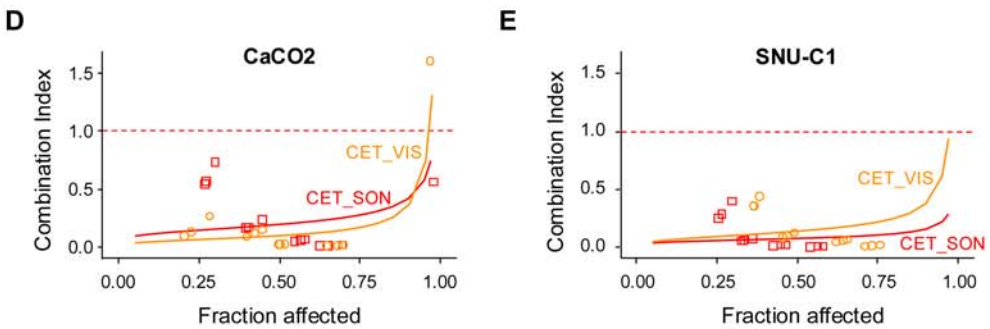
Figure EV5. Representative images of cells undergoing apoptosis that stained for the annexin V assay in CaCO2 and SNU-C1 transfected with circ-EGFR and/or miR-942-3p plasmids.

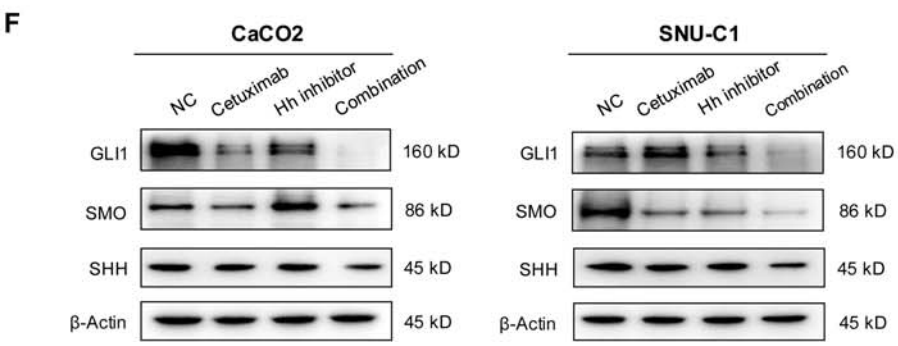
DiFi $p = 0.006$, SW48 $p = 0.005$ (student's *t*-test). Data were representative of three independent biological replicates. Bars represent the mean, and error bars indicate SD. $^{**}p < 0.01$.



IC_{50} (nM)	CaCO2 SON	CaCO2 VIS	SNU-C1 SON	SNU-C1 VIS
	63.31	102.10	42.22	103.90







◀ **Figure EV6. Synergistic effects of cetuximab and hedgehog inhibitor combinations in CRC cells.**

(**A**) Dose-response curves for Sonidegib or Vismodegib in CaCO2 and SNU-C1 cells. (**B**) Dose-response matrix (inhibition) for Cetuximab and Sonidegib, or Cetuximab and Vismodegib in CaCO2 and SNU-C1 cells. (**C**) Synergy distribution and scores for different drug combinations in CaCO2 and SNU-C1 cells were assessed using SynergyFinder with the ZIP model. (**D**, **E**) Combination index (CI-Fa) plots for CaCO2 and SNU-C1 cells treated with combinations of Cetuximab and Sonidegib or Cetuximab and Vismodegib. (**F**) Western blot analysis of Hh signaling pathway components in CaCO2 and SNU-C1 following Cetuximab, Sonidegib or Vismodegib, and the combination therapy. β-Actin served as an internal control.

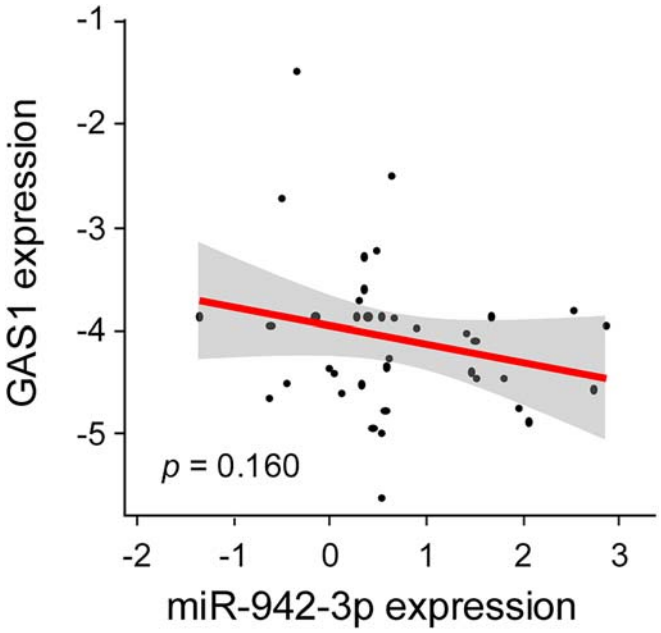


Figure EV7. The correlation between miR-942-3p expression and GAS1 expression in the clinical trial cohort.

$p = 0.160$ (Pearson correlation analysis).