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Preclinical Efficacy of ARV-806, a PROTAC KRAS G12D Degrader, in Combination With EGFR mAbs in *KRAS* G12D–Mutated CRC Models

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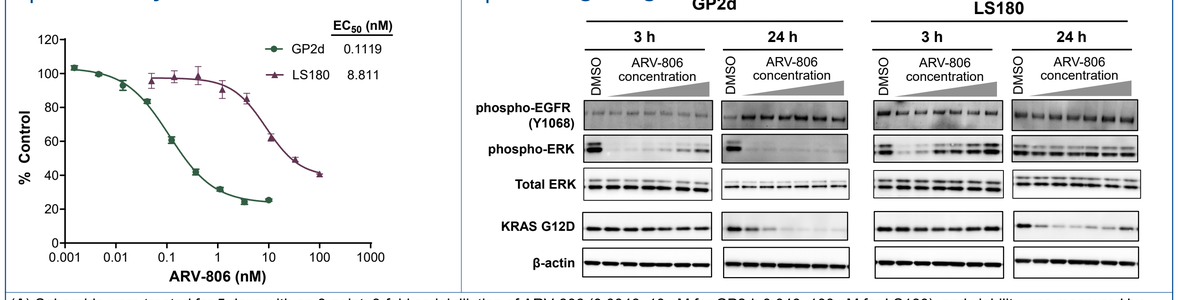
Background

- ARV-806, a potent, selective PROTAC KRAS G12D degrader, forms a ternary complex with KRAS G12D and an E3 ubiquitin ligase, which induces ubiquitination of KRAS G12D protein and its subsequent degradation by the proteasome[1]
- ARV-806 engages both the ON (active GTP-bound) and OFF (inactive GDP-bound) forms of KRAS G12D[1]
- ARV-806 exhibited >25-fold higher potency for inhibition of cell proliferation vs investigational KRAS G12D OFF and ON inhibitors or other KRAS G12D degraders in preclinical models[1]
- In patients with CRC, efficacy of KRAS mutant inhibitors is frequently limited by feedback activation of EGFR[2]
- Improved PFS compared with standard treatment when the EGFR mAb panitumumab was administered with the KRAS G12C inhibitor sotorasib in patients with *KRAS* G12C–mutated CRC has led to approval of the combination therapy[3]

Objective

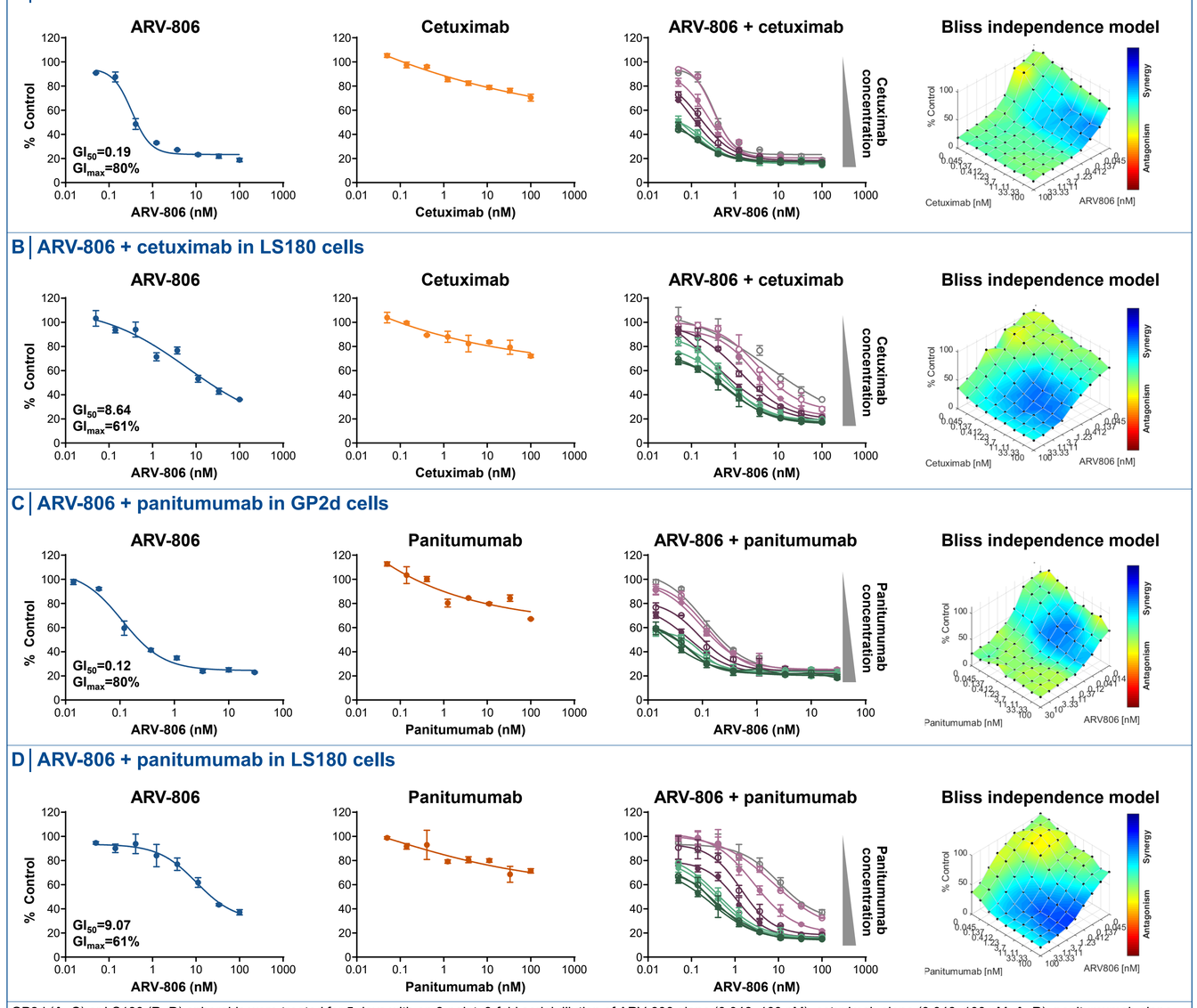
- To examine the effects of ARV-806 as a single agent and in combination with EGFR mAbs in *KRAS* G12D–mutated CRC models

Figure 1: In *KRAS* G12D–mutated CRC cell lines GP2d and LS180, single-agent ARV-806 led to induction of phospho-EGFR and rapid reactivation of phospho-ERK, respectively



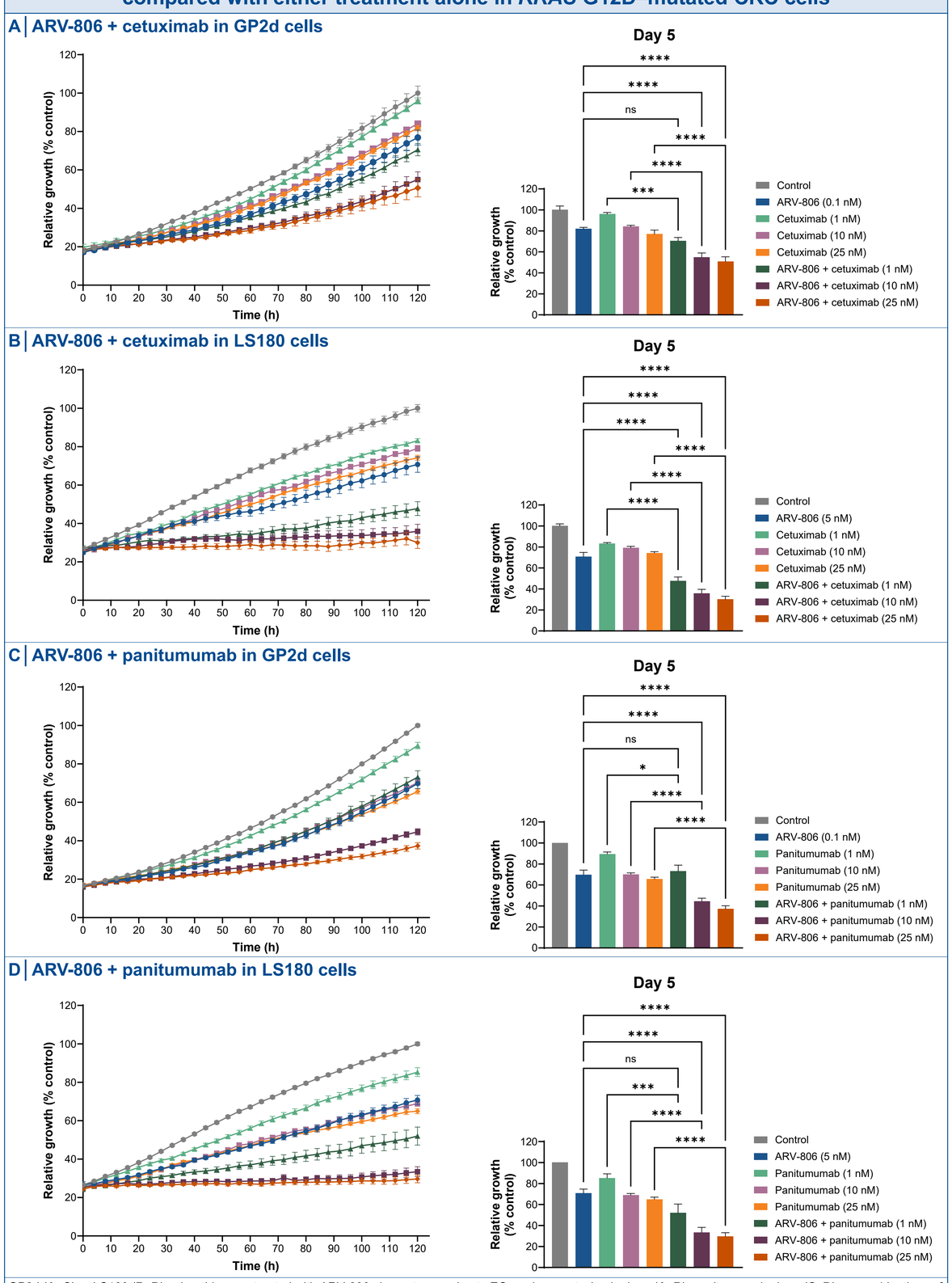
(**A**) Spheroids were treated for 5 days with an 8-point, 3-fold serial dilution of ARV-806 (0.0046–10 nM for GP2d; 0.046–100 nM for LS180), and viability was measured by CellTiter-Glo 3D and normalized to vehicle control to determine EC_{50}. (**B**) GP2d cells and LS180 cells were treated with ARV-806 (1.23–300 nM) for 3 or 24 h and analyzed by Western blot. CRC cell lines were selected based on baseline drug sensitivity to monotherapy and response profiles relative to the benchmark compound.

Figure 2: ARV-806 in combination with cetuximab or panitumumab led to robust synergy in *KRAS* G12D–mutated CRC cells



GP2d (**A**, **C**) or LS180 (**B**, **D**) spheroids were treated for 5 days with an 8-point, 3-fold serial dilution of ARV-806 alone (0.046–100 nM), cetuximab alone (0.046–100 nM; **A**, **B**), panitumumab alone (0.046–100 nM; **C**, **D**), or with an 8 × 8 concentration matrix of ARV-806 and cetuximab or panitumumab (0.046–100 nM each). Viability was measured by CellTiter-Glo 3D and normalized to vehicle control. Synergy across the ARV-806–cetuximab/panitumumab concentration matrix was quantified using the Bliss independence model in Combenefit. Data represent 3 independent experiments, each performed in technical duplicate. Consistent synergy results were observed using the Loewe additivity and highest single-agent models (data not shown).

Figure 3: ARV-806 in combination with cetuximab or panitumumab reduced cell growth in vitro compared with either treatment alone in *KRAS* G12D–mutated CRC cells

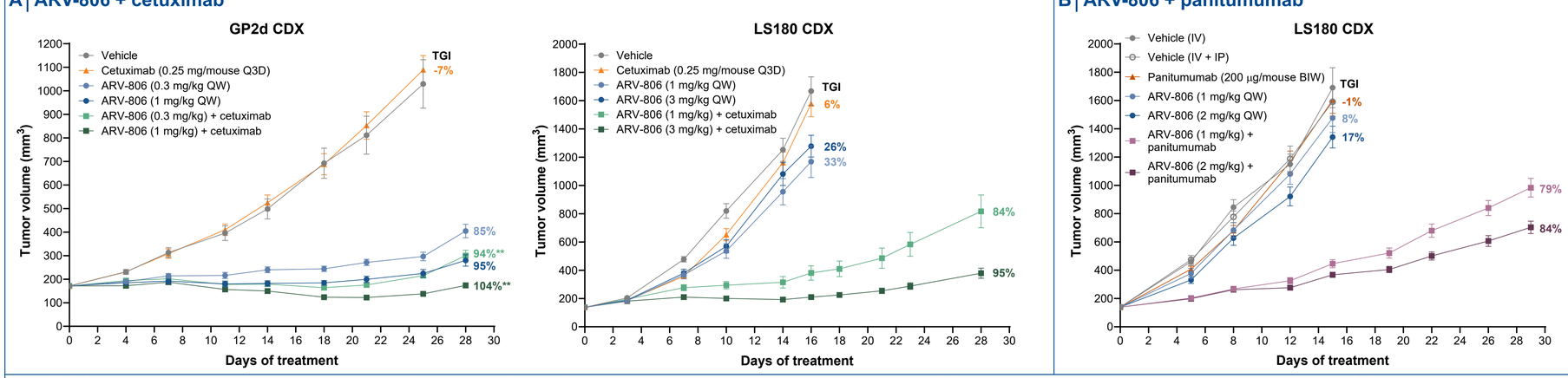


GP2d (**A**, **C**) or LS180 (**B**, **D**) spheroids were treated with ARV-806 alone at approximate EC_{50} values, cetuximab alone (**A**, **B**), panitumumab alone (**C**, **D**), or combinations of ARV-806 and cetuximab or panitumumab at the concentrations indicated. Spheroids were imaged every 4 h for 5 days using the Incucyte SX5; spheroid area was normalized to the vehicle-control area at 120 h. Data represent 4 (**A**), 8 (**B**), 8 (**C**), and 6 (**D**) independent experiments. *P* values were calculated using one-way ANOVA. **P*<0.05; ****P*<0.001; *****P*<0.0001; ns=nonsignificant.

Figure 4: ARV-806 in combination with cetuximab or panitumumab overcame feedback activation of EGFR and led to sustained inhibition of phospho-ERK, decrease in KRAS G12D protein levels, and induction of apoptosis, as indicated by cleaved PARP, in *KRAS* G12D–mutated CRC cells

GP2d (**A**) and LS180 (**B**) cells were treated with DMSO, ARV-806, cetuximab, panitumumab, or ARV-806 plus either EGFR mAb for 24 or 72 h followed by Western blot analysis of KRAS G12D, phospho-EGFR, total EGFR, phospho-ERK, total ERK, cleaved PARP, and β-actin (n=3–5). Western blot band intensities were quantified by densitometry and normalized to β-actin and DMSO control. *P* values were calculated using one-way ANOVA. **P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001; ns=nonsignificant.

Figure 5: ARV-806 combined with cetuximab or panitumumab resulted in greater TGI than either agent alone in CDX models of *KRAS* G12D–mutated CRC



CB17-SCID female mice were subcutaneously implanted in the right flank with 5×10^6 GP2d or LS180 cells, and tumor-bearing mice were administered vehicle, ARV-806 alone, cetuximab alone, panitumumab alone, or combinations of ARV-806 and cetuximab or panitumumab at the doses indicated during 28-day cetuximab studies or a 29-day panitumumab study (n=8–10 mice per arm). TGI was calculated on day 25 in the GP2d model and on days 16 and 15, respectively, in the LS180 cetuximab and panitumumab studies. *P* values were calculated using one-way ANOVA. ***P*<0.01 vs ARV-806 alone at same concentration.

Conclusions

- ARV-806 combined with cetuximab or panitumumab demonstrated synergistic activity, enhanced reduction of cell growth, and sustained inhibition of phospho-ERK, with induction of apoptosis in *KRAS* G12D–mutated CRC cells
- In *KRAS* G12D–mutated CRC CDX models, ARV-806 in combination with cetuximab or panitumumab resulted in greater TGI than either agent alone
- These findings support future investigation of ARV-806 in combination with EGFR mAbs in patients with *KRAS* G12D–mutated CRC

References

1. Smith K, et al. AACR-NCI-EORTC Int Conf on Mol Targets & Cancer Ther. 2025;Poster B107.
2. Amodio V, et al. Cancer Discov. 2020;10:1129-1139.
3. Fakih M, et al. N Engl J Med. 2023;389:2125–2139.

Abbreviations

ANOVA=analysis of variance; BIW=twice weekly; CDX=cell line-derived xenograft; CRC=colorectal cancer; DMSO=dimethyl sulfoxide; EC_{50}=half-maximal effective concentration; EGFR=epidermal growth factor receptor; ERK=extracellular signal-regulated kinase; GI_{50}=concentration resulting in 50% growth inhibition; GI_{max}=maximum growth inhibition; IP=intraperitoneal; IV=intravenous; mAb=monoclonal antibody; PARP=poly(ADP-ribose) polymerase; PFS=progression-free survival; PROTAC=PROteolysis TArgeting Chimera; Q3D=once every 3 days; QW=once weekly; SCID=severe combined immunodeficiency; TGI=tumor growth inhibition.

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