Preclinical Efficacy of ARV-806, a PROTAC KRAS G12D Degrader, in Combination With the RAS-ON Multi-Selective Inhibitor Daraxonrasib in *KRAS* G12D–Mutated Models

Jessica Teh, Christopher Kuhlberg, Kim Davenport, Jennifer Pizzano, Arman Fathizadeh, Madeline A Dorso, Eric Masson, XiaoZhe (Janet) Wang

Arvinas Operations, Inc., New Haven, CT, USA

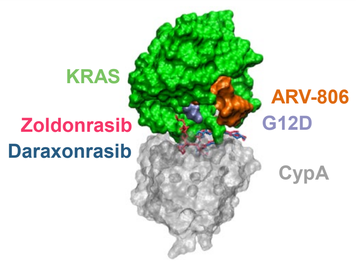
Background

- ARV-806 is a potent, selective PROTAC KRAS G12D degrader that targets both ON (active GTP-bound) and OFF (inactive GDP-bound) forms and has shown >25-fold higher potency in cell proliferation inhibition vs investigational KRAS G12D inhibitors or other KRAS G12D degraders in preclinical models[1]
- In contrast, the RAS-ON inhibitor daraxonrasib and KRAS G12D inhibitor zoldonrasib bind to RAS and KRAS G12D, respectively, and CypA to form inhibitory trimer complexes that suppress downstream RAS signaling[2]
- Concurrent targeting of mutant KRAS and pan-RAS is thought to deepen pathway inhibition in *KRAS*–mutated cells while overcoming adaptive and acquired mechanisms of resistance observed in the clinic,[3] supporting the scientific rationale for combining ARV-806 and daraxonrasib
- Combined mutant-selective and multi-selective RAS inhibition is being clinically evaluated in patients with *KRAS* G12D–mutated PDAC[4]

Objectives

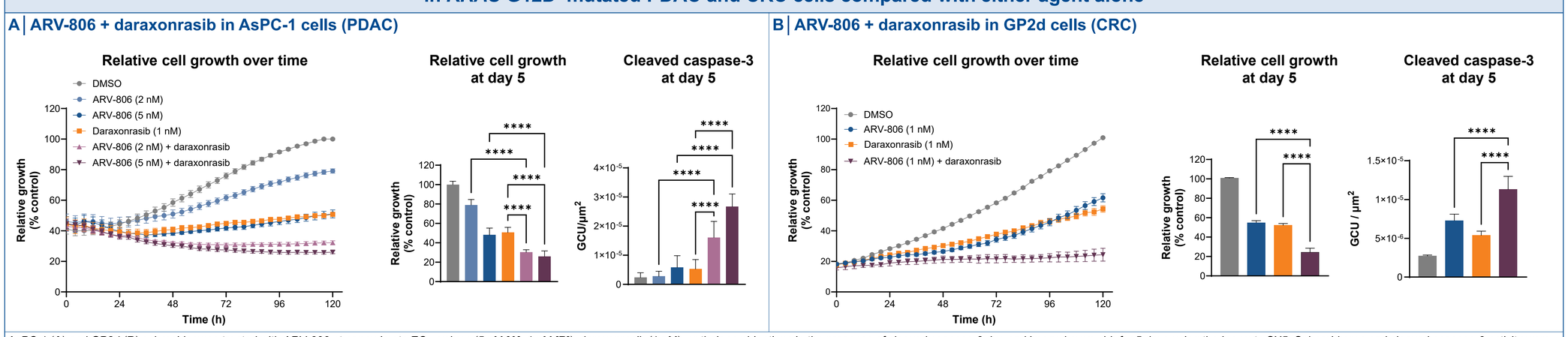
- To evaluate the activity of ARV-806 plus daraxonrasib in preclinical models of *KRAS* G12D–mutated PDAC and CRC
- To compare the combination activity and downstream pathway effects of ARV-806 plus daraxonrasib with those of zoldonrasib plus daraxonrasib

Figure 1: ARV-806 binds within the KRAS switch II pocket of both ON and OFF forms, whereas daraxonrasib and zoldonrasib bind at the CypA interface of ON forms of RAS/KRAS



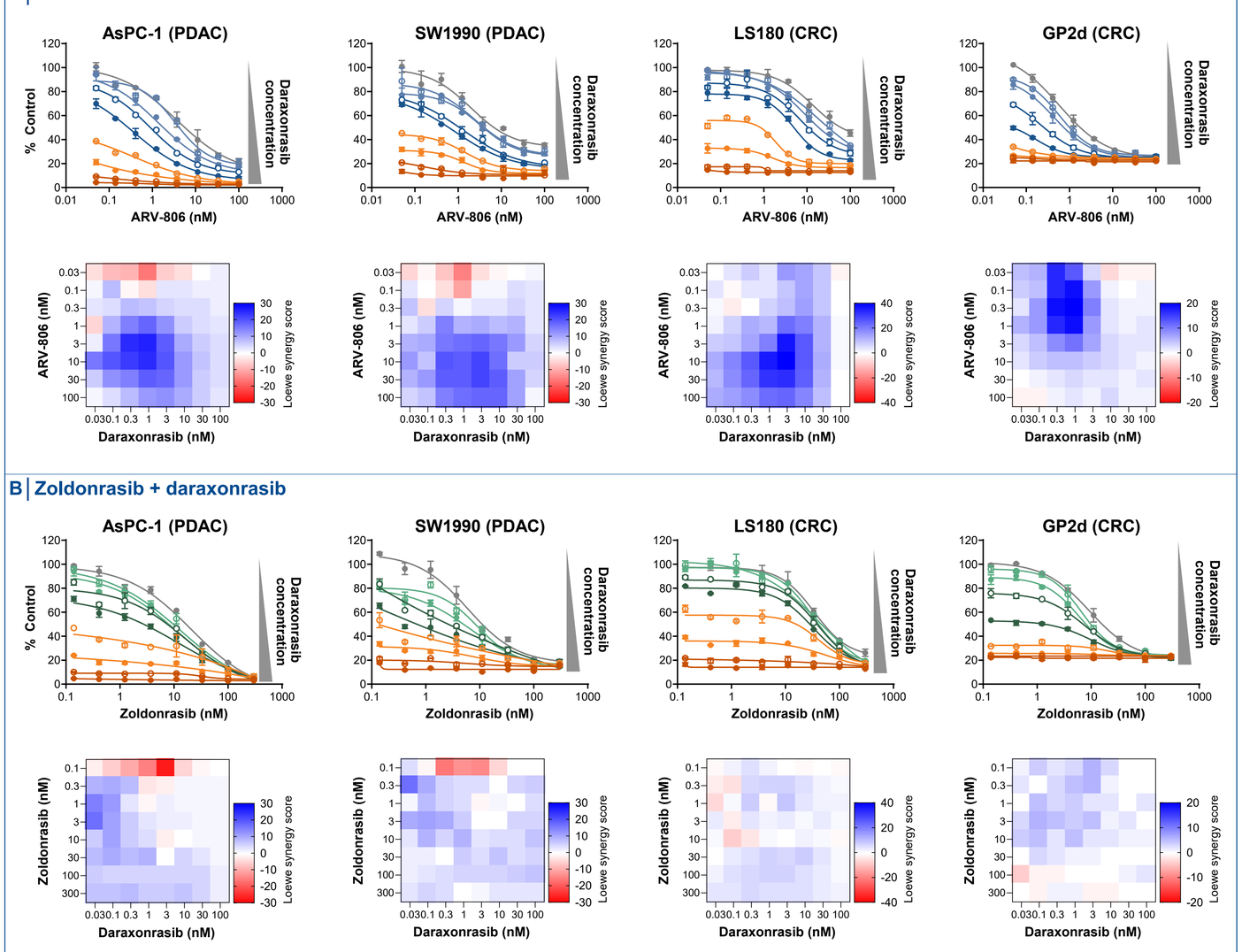
Model was generated using the available co-crystal structures for daraxonrasib (PDB 9BG6) and zoldonrasib (PDB 9CTB). The ARV-806 pose was obtained by docking.

Figure 2: ARV-806 plus daraxonrasib led to enhanced reduction of cell growth and induction of apoptosis, as assessed by increased cleaved caspase-3 activity, in *KRAS* G12D–mutated PDAC and CRC cells compared with either agent alone



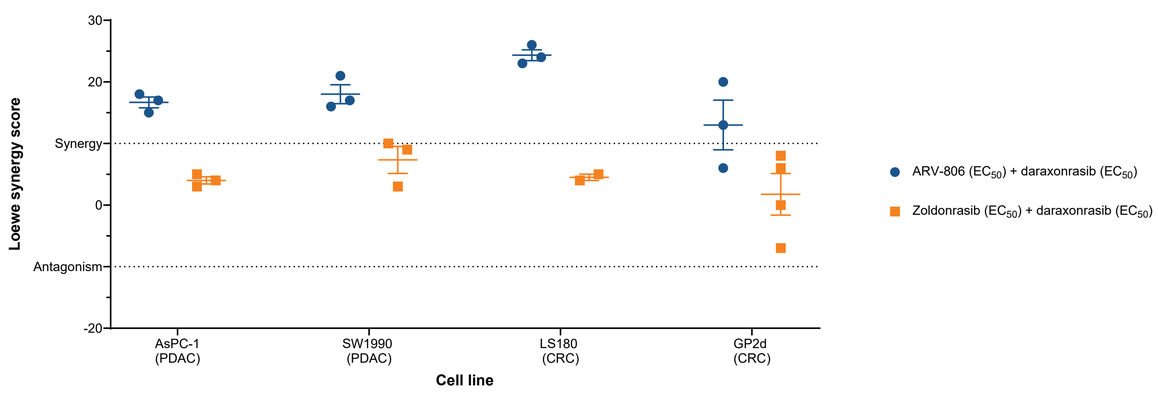
AsPC-1 (**A**) and GP2d (**B**) spheroids were treated with ARV-806 at approximate EC_{50} values (5 nM [**A**]; 1 nM [**B**]), daraxonrasib (1 nM), or their combinations in the presence of cleaved caspase-3 dye and imaged every 4 h for 5 days using the Incucyte SX5. Spheroid area and cleaved caspase-3 activity were normalized to vehicle control at 120 h. Data represent 3 independent experiments. *P* values were calculated using one-way ANOVA. ****$P<0.0001$.

Figure 3: ARV-806 plus daraxonrasib demonstrated robust synergy across *KRAS* G12D–mutated PDAC and CRC cell lines, whereas zoldonrasib plus daraxonrasib demonstrated additive to modestly synergistic activity



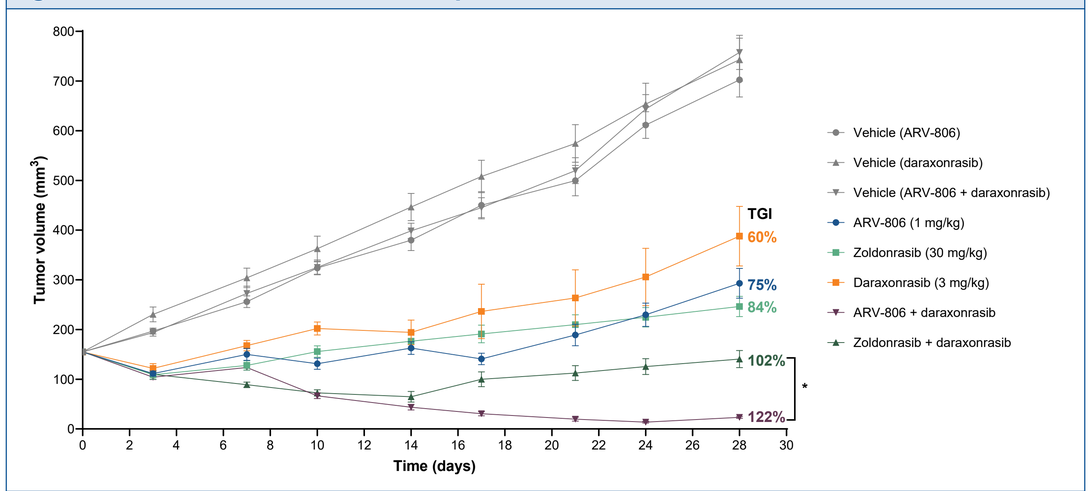
AsPC-1, SW1990, LS180, and GP2d spheroids were treated for 5 days with 8-point, 3-fold serial dilutions of ARV-806 (0.046–100 nM; **A**), zoldonrasib (0.14–300 nM; **B**), or daraxonrasib (0.046–100 nM), alone or in 8 × 8 concentration matrices of ARV-806 + daraxonrasib or zoldonrasib + daraxonrasib. Viability was measured by CellTiter-Glo 3D and normalized to vehicle control. Synergy was quantified using the Loewe additivity model in Combenefit. Data represent 3 independent experiments, each performed in technical duplicate. Consistent synergy results were observed using the Bliss independence and highest single-agent models (data not shown).

Figure 4: ARV-806 plus daraxonrasib at EC_{50} values showed greater synergy than zoldonrasib plus daraxonrasib in *KRAS* G12D–mutated PDAC and CRC cell lines



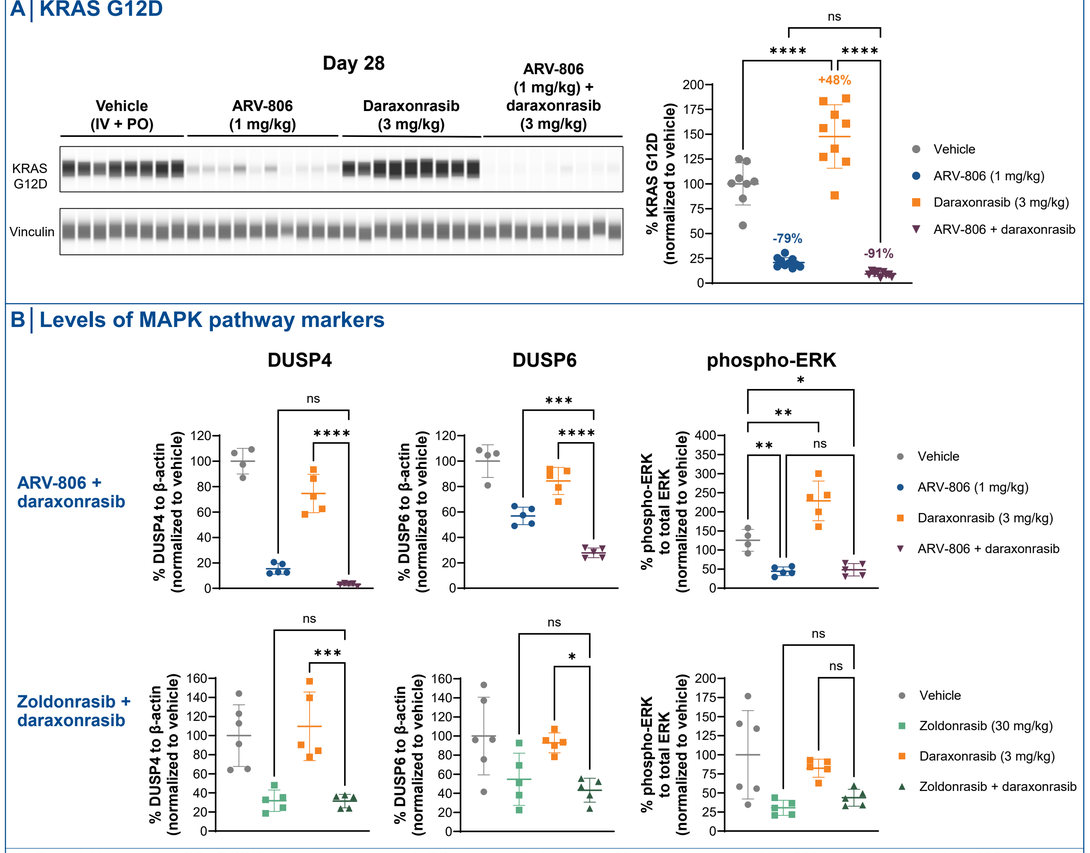
Synergy across the ARV-806–daraxonrasib concentration matrix was quantified using the Loewe additivity model in Combenefit. Plotted data represent the synergy scores at the intersection of daraxonrasib EC_{50} value for each cell line (0.3, 3, 3, and 1 nM, for AsPC-1, SW1990, LS180, and GP2d, respectively) with the EC_{50} of ARV-806 (0.1, 1, 10, and 0.1 nM, respectively) or zoldonrasib (3, 10, 30, and 3 nM, respectively) in the combination matrix, as reported by Combenefit; scores ≥10 indicate synergy.

Figure 5: ARV-806 plus a subtherapeutic dose of daraxonrasib induced greater tumor growth inhibition than zoldonrasib plus daraxonrasib in an AsPC-1 PDAC CDX model



CB/17 SCID female mice bearing AsPC-1 xenografts (~150 mm³; n=10/group) were treated with vehicle, ARV-806 (1 mg/kg IV QW), daraxonrasib (3 mg/kg PO QD), zoldonrasib (30 mg/kg PO QD), or the indicated combinations. For combination groups, daraxonrasib was administered 30 min after ARV-806 or zoldonrasib. Tumor volumes were measured twice weekly; TGI was determined on day 28. *P* values were calculated using one-way ANOVA with Sidak's multiple comparison test; *$P=0.02$.

Figure 6: ARV-806 plus daraxonrasib led to further decrease in KRAS G12D protein levels despite its upregulation with daraxonrasib monotherapy and further decreased MAPK pathway markers compared with the single agents



(**A**) Endpoint tumors from CB/17 SCID female mice bearing AsPC-1 xenografts treated for 28 days with vehicle, ARV-806, daraxonrasib, or ARV-806 + daraxonrasib were analyzed by Western blot for KRAS G12D and vinculin. KRAS G12D levels were quantified by densitometry and normalized to vinculin and vehicle control. (**B**) Endpoint tumors from mice treated for 28 days with vehicle, ARV-806, daraxonrasib, zoldonrasib, or the corresponding combinations were analyzed by Western blot for DUSP4, DUSP6, phospho-ERK, total ERK, and β-actin. DUSP4 and DUSP6 levels were quantified by densitometry and normalized to β-actin and vehicle control; phospho-ERK levels were normalized to total ERK and vehicle control. *P* values were calculated using one-way ANOVA. *$P<0.05$; **$P<0.01$; ***$P<0.001$; ****$P<0.0001$; ns=nonsignificant.

Conclusions

- ARV-806 combined with daraxonrasib led to enhanced reduction of cell growth and increased apoptosis in *KRAS* G12D–mutated PDAC and CRC cells
- ARV-806 plus daraxonrasib demonstrated robust synergy and greater activity than zoldonrasib plus daraxonrasib in vitro across *KRAS* G12D–mutated PDAC and CRC cell lines
- In a PDAC CDX model, ARV-806 plus daraxonrasib demonstrated greater antitumor activity than zoldonrasib plus daraxonrasib
  - The addition of ARV-806 to daraxonrasib was able to overcome upregulation of KRAS G12D leading to further decrease in KRAS G12D protein levels and MAPK pathway markers
- These preclinical findings support investigation of ARV-806 plus daraxonrasib in patients with *KRAS* G12D–mutated PDAC

References

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Abbreviations

ANOVA=analysis of variance; CDX=cell line-derived xenograft; CRC=colorectal cancer; CypA=cyclophilin A; DUSP=dual-specificity phosphatase; EC_{50}=half-maximal effective concentration; ERK=extracellular signal-regulated kinase; IV=intravenous; KRAS=Kirsten rat sarcoma viral oncogene homolog; MAPK=mitogen-activated protein kinase; PDAC=pancreatic ductal adenocarcinoma; PO=oral; PROTAC=PROteolysis TArgeting Chimera; QD=once daily; QW=once weekly; RAS=rat sarcoma; SCID=severe combined immunodeficiency; TGI=tumor growth inhibition

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Contact

Jessica Teh: jessica.teh@arvinas.com

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