289

Preclinical Efficacy of ARV-806, a PROTAC KRAS G12D Degrader, in Combination With Chemotherapy in *KRAS* G12D–Mutated Pancreatic Cancer Models

Jessica Teh, Christopher Kuhlberg, Greg Cadelina, Jennifer Pizzano, Madeline A Dorso, Eric Masson, XiaoZhe (Janet) Wang

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

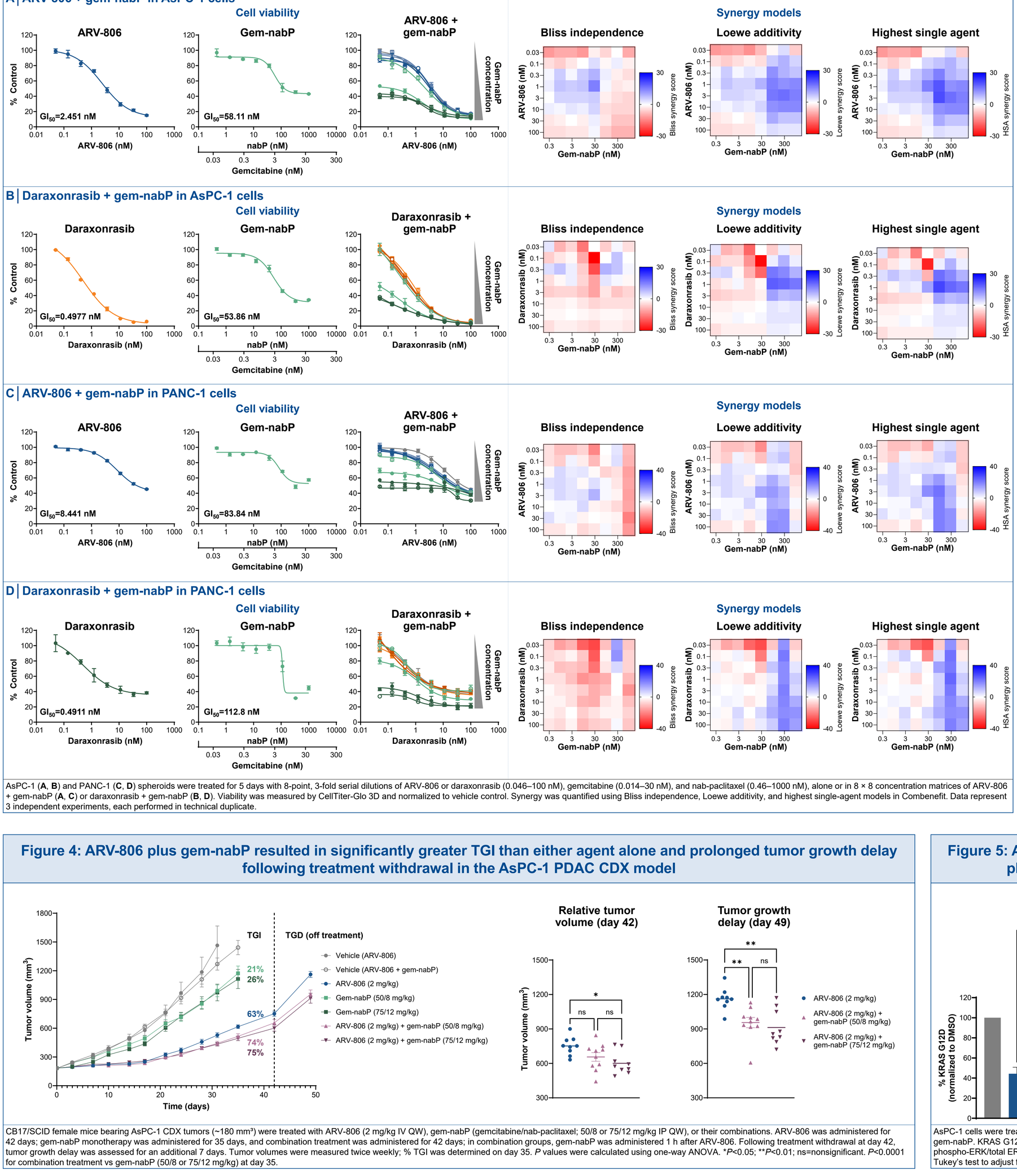
Background

- ARV-806, a potent and selective PROTAC KRAS G12D degrader, forms a ternary complex with KRAS G12D and an E3 ubiquitin ligase to induce KRAS G12D ubiquitination and subsequent proteasomal degradation[1]
- ARV-806 targets both ON (active GTP-bound) and OFF (inactive GDP-bound) forms of KRAS G12D[1]
- In preclinical models, ARV-806 showed >25-fold higher potency in cell proliferation inhibition vs investigational KRAS G12D OFF and ON inhibitors or other KRAS G12D degraders[1]
- Based on promising preclinical activity, ARV-806 administered QW or Q2W is being evaluated in the phase 1 portion of a clinical trial in patients with *KRAS* G12D–mutated advanced solid tumors (NCT07023731)
- First-line treatment options for PDAC are limited, with SOC chemotherapy yielding modest clinical benefit, supporting evaluation of novel combination approaches to enhance efficacy[2]
- RAS- or KRAS-targeting agents in combination with chemotherapy have shown encouraging activity as first-line treatment in early-phase studies in patients with metastatic PDAC[3]

Objectives

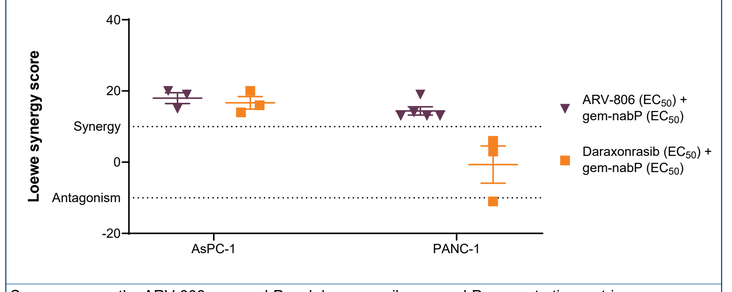
- To evaluate ARV-806 in combination with SOC chemotherapy gemcitabine plus nab-paclitaxel (gem-nabP) in preclinical models of *KRAS* G12D–mutated PDAC
- To compare the synergistic activity of ARV-806 plus gem-nabP with that of daraxonrasib plus gem-nabP

Figure 1: ARV-806 plus gem-nabP demonstrated synergistic activity in vitro across multiple synergy models in *KRAS* G12D–mutated AsPC-1 and PANC-1 PDAC cells, with similar activity observed for daraxonrasib plus gem-nabP



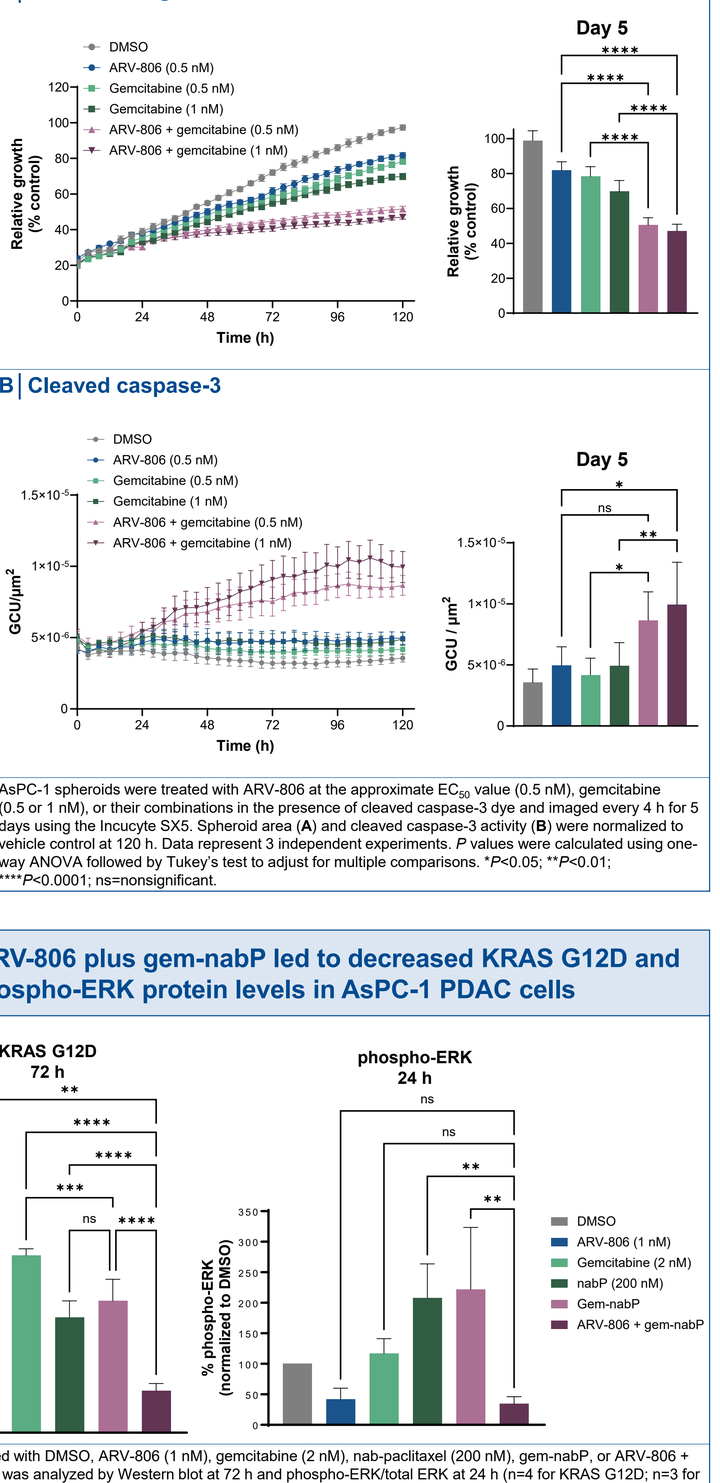
AsPC-1 (**A**, **B**) and PANC-1 (**C**, **D**) spheroids were treated for 5 days with 8-point, 3-fold serial dilutions of ARV-806 or daraxonrasib (0.046–100 nM), gemcitabine (0.014–30 nM), and nab-paclitaxel (0.46–1000 nM), alone or in 8 × 8 concentration matrices of ARV-806 + gem-nabP (**A**, **C**) or daraxonrasib + gem-nabP (**B**, **D**). Viability was measured by CellTiter-Glo 3D and normalized to vehicle control. Synergy was quantified using Bliss independence, Loewe additivity, and highest single-agent models in Combenefit. Data represent 3 independent experiments, each performed in technical duplicate.

Figure 2: ARV-806 plus gem-nabP demonstrated synergy at EC_{50} concentrations in AsPC-1 and PANC-1 PDAC cells



Synergy across the ARV-806–gem-nabP and daraxonrasib–gem-nabP concentration matrices was quantified using the Loewe additivity model in Combenefit. Plotted data represent synergy scores at the intersection of the gem-nabP EC_{50} (100 nM) and the ARV-806 (1 and 10 nM) or daraxonrasib (0.3 and 1 nM) EC_{50} in AsPC-1 and PANC-1 cells, respectively.

Figure 3: ARV-806 plus gemcitabine led to enhanced reduction of cell growth and induction of apoptosis, as assessed by increased cleaved caspase-3 activity, in AsPC-1 PDAC cells compared with either agent alone



AsPC-1 spheroids were treated with ARV-806 at the approximate EC_{50} value (0.5 nM), gemcitabine (0.5 or 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 (**A**) and cleaved caspase-3 activity (**B**) were normalized to vehicle control at 120 h. Data represent 3 independent experiments. *P* values were calculated using one-way ANOVA followed by Tukey's test to adjust for multiple comparisons. **P*<0.05; ***P*<0.01; *****P*<0.0001; ns=nonsignificant.

Figure 4: ARV-806 plus gem-nabP resulted in significantly greater TGI than either agent alone and prolonged tumor growth delay following treatment withdrawal in the AsPC-1 PDAC CDX model

CB17/SCID female mice bearing AsPC-1 CDX tumors (~180 mm³) were treated with ARV-806 (2 mg/kg IV QW), gem-nabP (gemcitabine/nab-paclitaxel; 50/8 or 75/12 mg/kg IP QW), or their combinations. ARV-806 was administered for 42 days; gem-nabP monotherapy was administered for 35 days, and combination treatment was administered for 42 days; in combination groups, gem-nabP was administered 1 h after ARV-806. Following treatment withdrawal at day 42, tumor growth delay was assessed for an additional 7 days. Tumor volumes were measured twice weekly; % TGI was determined on day 35. *P* values were calculated using one-way ANOVA. **P*<0.05; ***P*<0.01; ns=nonsignificant. *P*<0.0001 for combination treatment vs gem-nabP (50/8 or 75/12 mg/kg) at day 35.

Figure 5: ARV-806 plus gem-nabP led to decreased KRAS G12D and phospho-ERK protein levels in AsPC-1 PDAC cells

AsPC-1 cells were treated with DMSO, ARV-806 (1 nM), gemcitabine (2 nM), nab-paclitaxel (200 nM), gem-nabP, or ARV-806 + gem-nabP. KRAS G12D was analyzed by Western blot at 72 h and phospho-ERK/total ERK at 24 h (n=4 for KRAS G12D; n=3 for phospho-ERK/total ERK). Data were normalized to DMSO control. *P* values were calculated using one-way ANOVA followed by Tukey's test to adjust for multiple comparisons. ***P*<0.01; ****P*<0.001; *****P*<0.0001; ns=nonsignificant.

Conclusions

- ARV-806 plus gem-nabP demonstrated synergistic activity across multiple synergy models in *KRAS* G12D–mutated PDAC cells, with synergy similar to or greater than that observed with daraxonrasib plus gem-nabP
- ARV-806 combined with gemcitabine led to enhanced reduction in cell growth and induction of apoptosis in AsPC-1 PDAC cells
- In the AsPC-1 PDAC CDX model, ARV-806 plus gem-nabP resulted in greater TGI than either agent alone and prolonged tumor growth delay compared with ARV-806 alone following treatment withdrawal
- ARV-806 plus gem-nabP decreased KRAS G12D and phospho-ERK protein levels in AsPC-1 PDAC cells
- These data demonstrate the preclinical benefit of combining ARV-806 with gem-nabP and support evaluation of this combination regimen as first-line treatment for patients with *KRAS* G12D–mutated PDAC

References

1. Smith K, et al. AACR-NCI-EORTC Int Conf on Mol Targets & Cancer Ther. 2025;Poster B107.
2. Nichetti F, et al. JAMA Netw Open. 2024;7:e2350756.
3. Wolpin B, et al. Ann Oncol. 2026;37:S122-S123.

Abbreviations

ANOVA=analysis of variance; CDX=cell line-derived xenograft; DMSO=dimethyl sulfoxide; EC_{50}=half-maximal effective concentration; ERK=extracellular signal-regulated kinase; gem-nabP=gemcitabine plus nab-paclitaxel; GI_{50}=concentration resulting in 50% growth inhibition; HSA=highest single agent; IP=intraperitoneal; IV=intravenous; KRAS=Kirsten rat sarcoma viral oncogene homolog; PDAC=pancreatic ductal adenocarcinoma; PROTAC=PROteolysis TArgeting Chimera; Q2W=every 2 weeks; QW=once weekly; SCID=severe combined immunodeficiency; SOC=standard of care; TGD=tumor growth delay; TGI=tumor growth inhibition

Acknowledgments

This research was funded by Arvinas, Inc. Medical writing support was provided by Joanna Bloom of Arvinas Operations, Inc.

Contact
Jessica Teh:
jessica.teh@arvinas.com

Scan to view a copy of this poster