Poster B107

Preclinical Activity of ARV-806, a PROTAC KRAS G12D Degrader

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Objectives

- To assess the in vitro and in vivo activity of the PROteolysis TArgeting Chimera (PROTAC) KRAS G12D degrader, ARV-806, including comparison with other G12D-targeting therapies with distinct mechanisms of action, and evaluation of pharmacokinetics, pharmacodynamics, and efficacy in KRAS G12D-tumor models
- To determine the activity and selectivity of tool PROTAC pan-KRAS degraders in vitro and in vivo and compare with a pan-RAS inhibitor

Key Findings

- ARV-806 potently (picomolar to low nanomolar) and selectively degraded KRAS G12D and targeted both the ON (GTP-bound) and OFF (GDP-bound) forms
- ARV-806 had >40-fold higher potency in reducing KRAS G12D levels in pancreatic cancer cells compared with another clinical-stage KRAS G12D degrader
- ARV-806 showed >25-fold higher potency in inhibition of cell proliferation compared with clinical-stage KRAS G12D ON and OFF inhibitors and a clinical-stage KRAS G12D degrader
- ARV-806 reduced KRAS G12D levels in tumors by >90% for 7 days after a single intravenous (IV) dose
- ARV-806 demonstrated significant efficacy in models of pancreatic, colorectal, and lung cancer
- Oral tool pan-KRAS degraders were KRAS-selective and potently degraded multiple KRAS mutants
- In the CT26 syngeneic mouse model, a tool pan-KRAS degrader led to complete responses in 70% of mice compared with 20% with a pan-RAS ON inhibitor

Conclusions

- Based on preclinical data, the PROTAC KRAS G12D degrader ARV-806 shows differentiated activity from clinical-stage KRAS G12D ON and OFF inhibitors and a KRAS G12D degrader, with greater potency in inhibiting cell proliferation and inducing cell death
- Durable pharmacology and robust efficacy supports intermittent ARV-806 dosing in the clinic
- ARV-806 administered IV weekly or every 2 weeks is currently being evaluated in a phase 1 clinical trial in patients with *KRAS* G12D–mutated advanced solid tumors (NCT07023731)
- Tool pan-KRAS PROTAC degraders are orally bioavailable and can lead to tumor regressions in multiple models
- Despite similar in vitro pharmacology, pan-KRAS degraders show significant differentiation from a pan-RAS ON inhibitor in an in vivo model with an intact immune system, suggesting degradation may be superior at eliciting an antitumor immune response

References

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Acknowledgments

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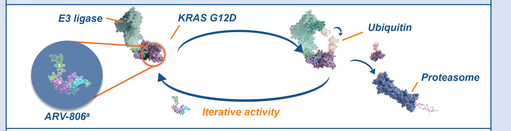
Background

- The KRAS protein is a member of the small GTPase family of enzymes that regulate key processes in the cell by cycling between an "ON" state (bound to GTP) and an "OFF" state (bound to GDP)[1]
- *KRAS* is the most frequently mutated oncogene and is altered in 20-25% of all cancers[2,3]
  - The most common *KRAS* alteration is the G12D mutation, which causes the protein to primarily exist in the "ON" state; the highest prevalence of KRAS G12D is in pancreatic ductal adenocarcinoma (PDAC), colorectal cancer (CRC), and non-small cell lung cancer (NSCLC)[3,4]
- Despite significant recent advances in targeting mutant KRAS (eg, G12C inhibitors), improvements in response rates and durability are needed to improve patient outcomes; there are currently no approved therapies targeting KRAS G12D
- ARV-806 is a PROTAC that harnesses the ubiquitin-proteasome system to induce degradation of KRAS G12D (**Figure 1**)
  - ARV-806 is a bifunctional molecule with KRAS G12D- and E3 ubiquitin ligase–binding regions that forms a trimer complex to induce ubiquitination and subsequent degradation of KRAS G12D by the proteasome
- The PROTAC mechanism of action may offer several key advantages for targeting KRAS, including potential:
  - To target both ON (GTP-bound) and OFF (GDP-bound) forms of KRAS
  - To overcome KRAS upregulation commonly observed upon inhibitor treatment due to iterative activity
  - For a mechanistically independent resistance profile vs other RAS-directed therapies
  - To increase immune antitumor response

Figure 1: Mechanism of action of ARV-806



ªGeneral PROTAC protein degrader is shown.
KRAS=Kirsten rat sarcoma viral oncogene homolog; PROTAC=PROteolysis TArgeting Chimera.

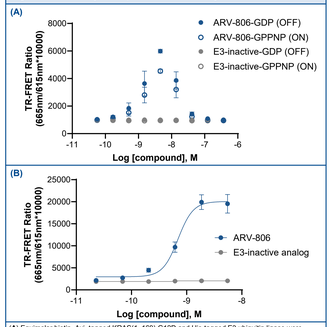
Results

ARV-806: PROTAC KRAS G12D DEGRADER

In vitro studies

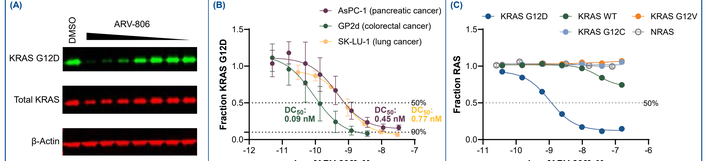
- ARV-806 formed an E3-ligase complex with both OFF (GDP-bound) and ON (GTP-bound) KRAS G12D (**Figure 2A**) and induced ubiquitination of KRAS G12D (**Figure 2B**)
- ARV-806 degraded KRAS G12D with picomolar potency in pancreatic, colorectal, and lung cancer cell lines (**Figure 3A–B**) but did not induce degradation of wild-type RAS or other mutant forms of RAS (**Figure 3C**)
  - ARV-806–mediated degradation of KRAS G12D reduced phospho-ERK1/2 levels, consistent with mitogen-activated protein kinase (MAPK) pathway suppression, and decreased cell proliferation (data not shown)
- ARV-806 was >40-fold more potent in reducing KRAS G12D levels in pancreatic cancer cells compared with another clinical-stage KRAS G12D degrader (**Figure 4A**) and induced expression of the pro-apoptotic factor Bcl-2-interacting mediator of cell death (BIM) at concentrations >10-fold lower compared with other KRAS G12D-targeting agents (**Figure 4B**)
- ARV-806 was >25-fold more potent in inhibition of proliferation of pancreatic or colorectal cancer cells compared with KRAS G12D inhibitors or another KRAS G12D degrader (**Figure 4C**) and decreased expression of the proliferation marker c-MYC (data not shown)

Figure 2: Ternary complex formation by ARV-806



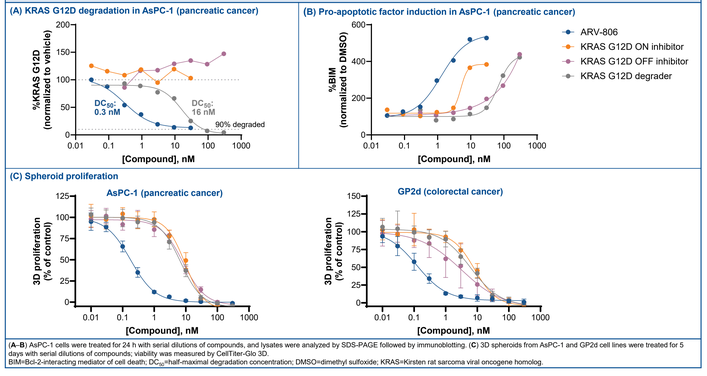
(**A**) Equimolar biotin–Avi–tagged KRAS(1–169) G12D and His-tagged E3 ubiquitin ligase were incubated with serial dilutions of ARV-806 or an E3-inactive analog in the presence of excess GDP or GPPNP (non-hydrolyzable GTP analog); ternary complex formation was measured by TR-FRET. (**B**) TR-FRET–based KRAS ubiquitination used biotin–Avi–tagged KRAS(1–169) G12D and Cy5–ubiquitin with serial titrations of compounds in the presence of excess ATP, unlabeled ubiquitin, and recombinant ubiquitination machinery.
TR-FRET=time-resolved Förster resonance energy transfer.

Figure 3: KRAS G12D degradation in cancer cell lines treated with ARV-806



Cells were treated for 24 h with serial dilutions of ARV-806, and lysates were analyzed by SDS-PAGE or capillary electrophoresis followed by immunoblotting. (**A**) GP2d cells (KRAS G12D/WT) treated with 3 pM to 3 nM concentrations. (**B**) Quantified data from immunoblot of endogenous KRAS G12D levels from cancer cell lines. (**C**) Data from luminescence readout of RAS protein levels from cell lines bearing HiBit-tagged variants of KRAS and NRAS.
DC_{50}=half-maximal degradation concentration; KRAS=Kirsten rat sarcoma viral oncogene homolog; NRAS=neuroblastoma rat sarcoma viral oncogene homolog; SDS-PAGE=sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

Figure 4: KRAS G12D degradation, apoptosis, and inhibition of proliferation with ARV-806 and KRAS G12D-targeting agents

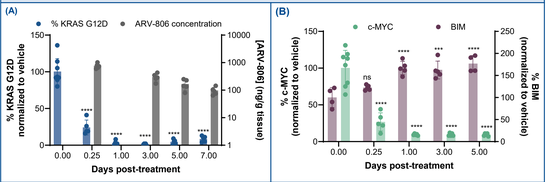


(**A–B**) AsPC-1 cells were treated for 24 h with serial dilutions of compounds, and lysates were analyzed by SDS-PAGE followed by immunoblotting. (**C**) 3D spheroids from AsPC-1 and GP2d cell lines were treated for 5 days with serial dilutions of compounds; viability was measured by CellTiter-Glo 3D.
BIM=Bcl-2-interacting mediator of cell death; DC_{50}=half-maximal degradation concentration; DMSO=dimethyl sulfoxide; KRAS=Kirsten rat sarcoma viral oncogene homolog.

In vivo studies

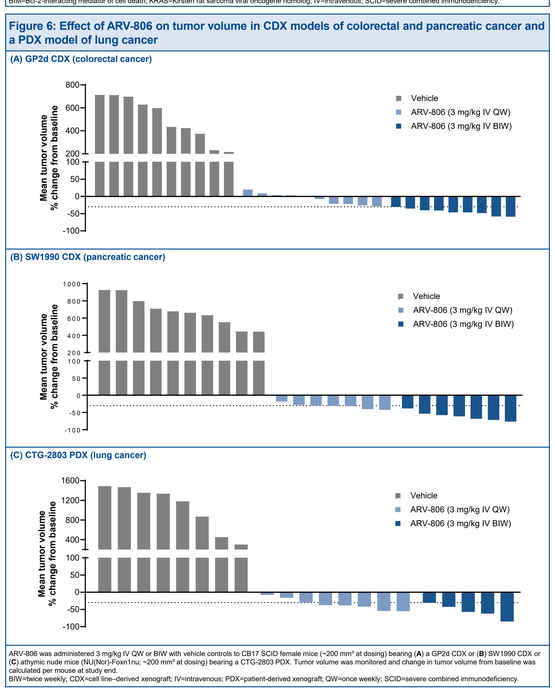
- After a single IV dose of ARV-806 in a cell line–derived xenograft (CDX) model of colorectal cancer, KRAS G12D was degraded >90% for 7 days (**Figure 5A**) with c-MYC suppressed and BIM induced for ≥5 days (**Figure 5B**)
- Weekly or biweekly IV dosing of ARV-806 resulted in tumor growth inhibition, including robust regressions (≥30% reduction from baseline in all tumors treated 3 mg/kg biweekly) in CDX models of pancreatic and colorectal cancer and in a patient-derived xenograft (PDX) model of lung cancer (**Figure 6**)

Figure 5: KRAS G12D degradation and signaling suppression following ARV-806 treatment in a CDX model of colorectal cancer



GP2d cells were implanted subcutaneously in CB17 SCID female mice and grown to ~200 mm³ before dosing. ARV-806 was administered once by IV bolus at 3 mg/kg (vehicle-controlled). Tumors were collected at indicated post-dose timepoints for (**A**) immunoblotting of KRAS G12D and tumor drug-concentration analysis (ARV-806 concentrations were not collected day 1 post-treatment) and (**B**) immunoblotting of c-MYC and BIM. ***P≤0.0001; ****P<0.0001.
BIM=Bcl-2-interacting mediator of cell death; KRAS=Kirsten rat sarcoma viral oncogene homolog; IV=intravenous; SCID=severe combined immunodeficiency.

Figure 6: Effect of ARV-806 on tumor volume in CDX models of colorectal and pancreatic cancer and a PDX model of lung cancer

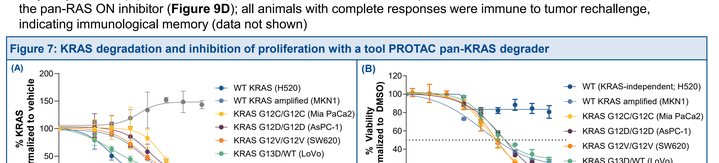


ARV-806 was administered 3 mg/kg IV QW or BIW with vehicle controls to CB17 SCID female mice (~200 mm³ at dosing) bearing (**A**) a GP2d CDX or (**B**) SW1990 CDX or (**C**) athymic nude mice (NU(Ncr)-Foxn1nu; ~200 mm³ at dosing) bearing a CTG-2803 PDX. Tumor volume was monitored and change in tumor volume from baseline was calculated per mouse at study end.
BIW=twice weekly; CDX=cell line–derived xenograft; IV=intravenous; PDX=patient-derived xenograft; QW=once weekly; SCID=severe combined immunodeficiency.

ORAL TOOL PROTAC PAN-KRAS DEGRADERS

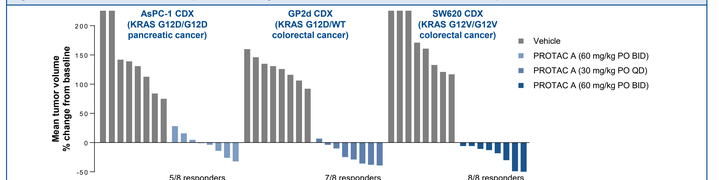
- A PROTAC pan-KRAS degrader induced selective degradation of multiple KRAS mutants in a dose-dependent manner (half-maximal degradation concentration [DC_{50}]: <10 nM; **Figure 7A**) and inhibited proliferation of multiple KRAS-dependent cell lines (**Figure 7B**)
- Once or twice daily oral dosing of a PROTAC pan-KRAS degrader induced robust regressions in CDX models of pancreatic and colorectal cancer (**Figure 8**)
- In the mutant KRAS CT26 syngeneic model, similar in vitro pharmacology was observed between the PROTAC pan-KRAS degrader and a pan-RAS ON inhibitor (**Figure 9A–B**)
- Oral dosing of the PROTAC led to ~90% degradation of KRAS G12D in CT26 tumors (**Figure 9C**), resulting in robust single-agent activity (data not shown) and superior combination efficacy with immune checkpoint blockade compared with the pan-RAS ON inhibitor (**Figure 9D**); all animals with complete responses were immune to tumor rechallenge, indicating immunological memory (data not shown)

Figure 7: KRAS degradation and inhibition of proliferation with a tool PROTAC pan-KRAS degrader



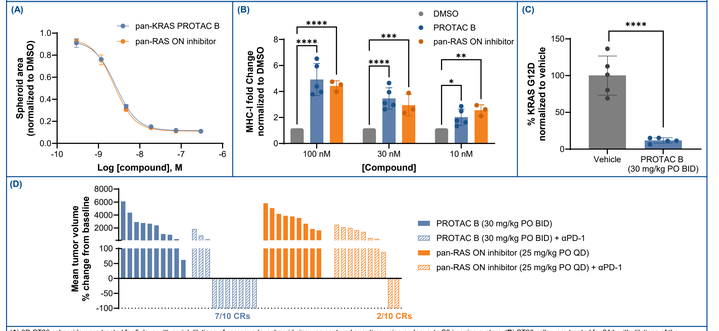
(**A**) Cells were treated for 24 h with serial dilutions of a PROTAC pan-KRAS degrader, and lysates were analyzed by capillary electrophoresis followed by immunoblotting. (**B**) 3D spheroids from cell lines were treated for 5 days with serial dilutions of a PROTAC pan-KRAS degrader; viability was measured by CellTiter-Glo 3D.
DMSO=dimethyl sulfoxide; HRAS=Harvey rat sarcoma; KRAS=Kirsten rat sarcoma viral oncogene homolog; PROTAC=PROteolysis TArgeting Chimera; WT=wild-type.

Figure 8: Effect of a tool PROTAC pan-KRAS degrader on tumor volume in CDX models of pancreatic and colorectal cancer



A PROTAC pan-KRAS degrader was administered orally 30 mg/kg QD or 60 mg/kg BID with vehicle controls to CB17 SCID female mice (~200 mm³ at dosing) bearing a AsPC1 CDX, a GP2d CDX, or a SW620 CDX; Tumor volume was monitored and change from baseline was calculated per mouse at study end.
BID=twice daily; CDX=cell line–derived xenograft; KRAS=Kirsten rat sarcoma viral oncogene homolog; PO=orally; PROTAC=PROteolysis TArgeting Chimera; QD=once daily; SCID=severe combined immunodeficiency; WT=wild-type.

Figure 9: Tool PROTAC pan-KRAS degrader activity in mutant KRAS CT26 syngeneic mouse model



(**A**) 3D CT26 spheroids were treated for 5 days with serial dilutions of compounds; spheroid size was captured over time using an Incucyte S3 imaging system. (**B**) CT26 cells were treated for 24 h with dilutions of the compounds and lysates were analyzed by SDS-PAGE followed by immunoblotting (*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001). (**C**) CT26 cells were implanted subcutaneously in BALB/c female mice and grown to >200 mm³ before dosing; pan-KRAS PROTAC B was administered orally BID at 30 mg/kg (vehicle-controlled) for 3 days. Tumors were collected 16 h post-dose and KRAS G12D levels were assessed by immunoblotting. (**D**) CT26 tumors were implanted subcutaneously in BALB/c female mice and efficacy studies were initiated when the tumor size reached a mean volume of ~20 mm³. pan-KRAS PROTAC B (30 mg/kg BID) and pan-RAS ON inhibitor (25 mg/kg QD) were dosed orally alone or with anti–PD-1 antibody (10 mg/kg BIW) or IgG control by IP injection.
BID=twice daily; BIW=twice weekly; IgG=immunoglobulin G; IP=intraperitoneal; KRAS=Kirsten rat sarcoma viral oncogene homolog; PD-1=programmed cell death protein 1; PO=orally; PROTAC=PROteolysis TArgeting Chimera; QD=once daily; SDS-PAGE=sodium dodecyl sulfate–polyacrylamide gel electrophoresis.