TPS792

Phase 1/2 study of ARV-806, a PROTAC KRAS G12D degrader, in *KRAS* G12D–mutated advanced solid tumors, including pancreatic cancer

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Objective

- This phase 1/2, open-label, multicenter study (NCT07023731) is evaluating the safety, pharmacokinetics, and preliminary efficacy of ARV-806, a PROteolysis TArgeting Chimera (PROTAC) KRAS G12D degrader, in patients with *KRAS* G12D–mutated advanced solid tumors

References

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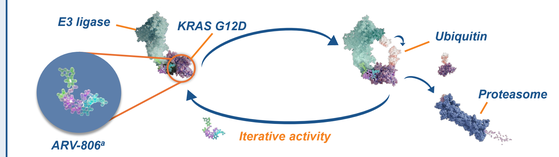
Background

- 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; *KRAS* G12D mutations are especially prevalent in pancreatic ductal adenocarcinoma (PDAC), colorectal cancer (CRC), and non-small cell lung cancer[3,4]
  - No currently approved therapies target 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
- ARV-806 binds both the active (GTP-bound) and inactive (GDP-bound) forms of KRAS G12D[5]

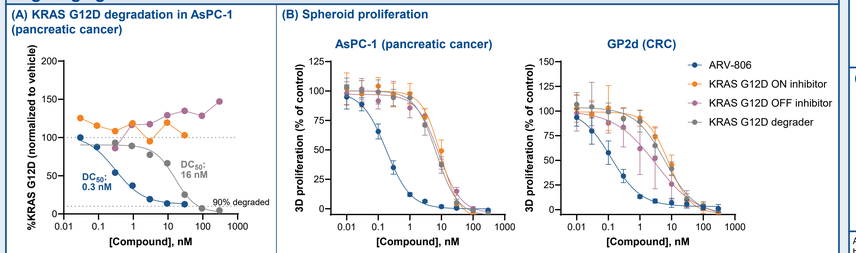
Figure 1: Mechanism of action of ARV-806



[a]General PROTAC protein degrader is shown.
KRAS=Kirsten rat sarcoma viral oncogene homolog; PROTAC=PROteolysis TArgeting Chimera.

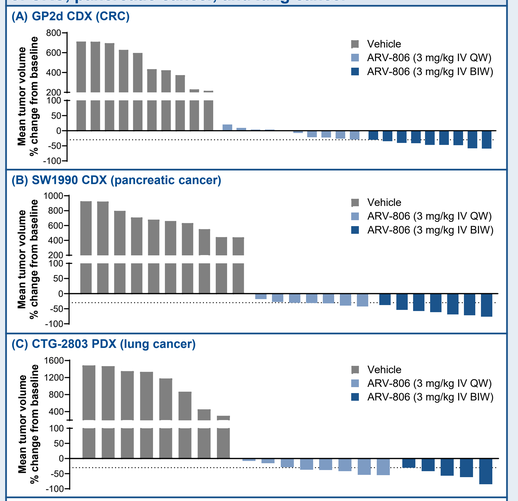
- In preclinical studies, ARV-806 demonstrated robust KRAS G12D degradation and antiproliferative activity
  - ARV-806 was >40-fold more potent than another clinical-stage KRAS G12D degrader in reducing levels of KRAS G12D in pancreatic cancer cells (**Figure 2A**)
  - ARV-806 showed >25-fold increased potency in inhibition of cell proliferation compared with clinical-stage KRAS inhibitors or another KRAS G12D degrader in pancreatic cancer and CRC cell lines (**Figure 2B**)[5]
- Low intravenous doses of ARV-806 administered once or twice weekly induced robust tumor growth inhibition (including tumor regressions) in cell line–derived xenograft models of pancreatic cancer and CRC and in a patient-derived xenograft model of lung cancer (**Figure 3**), supporting clinical investigation in these patient populations[5]
- Here, we describe a multicenter, first-in-human study that is evaluating ARV-806 in patients with *KRAS* G12D–mutated advanced solid tumors

Figure 2: KRAS G12D degradation and inhibition of proliferation with ARV-806 and KRAS G12D-targeting agents[5]



(**A**) AsPC-1 cells were treated for 24 h with serial dilutions of compounds, and lysates were analyzed by SDS-PAGE followed by immunoblotting. (B) 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.
CRC=colorectal cancer; DC_{50}=half-maximal degradation concentration; KRAS=Kirsten rat sarcoma viral oncogene homolog.

Figure 3: Effect of ARV-806 on tumor volume in murine models of CRC, pancreatic cancer, and lung cancer[5]

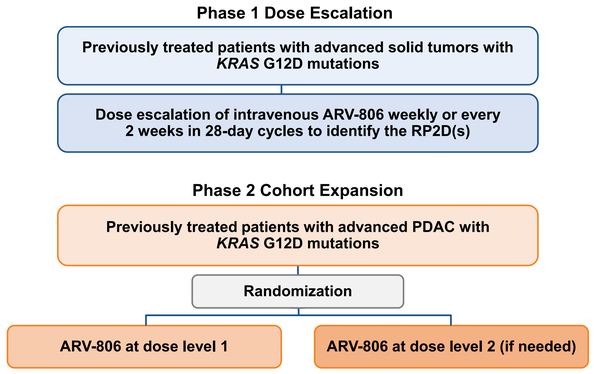


ARV-806 was administered 3 mg/kg IV QW or BIW with vehicle controls to CB17 SCID female mice (~200 mm³ at dosing) bearing (**A**) a GP2d CDX or (**B**) SW1990 CDX or (**C**) athymic nude mice (NU(Ncr)-Foxn1nu; ~200 mm³ at dosing) bearing a CTG-2803 PDX. Tumor volume was monitored and change in tumor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

Study Design

- This multicenter, open-label, phase 1/2 study (NCT07023731; **Figure 4**) is evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of ARV-806 in patients with *KRAS* G12D-mutated advanced solid tumors (**Table 1**)
- Phase 1 uses a Bayesian optimal interval design for ARV-806 dose escalation to determine the recommended phase 2 doses (RP2Ds); phase 2 evaluates 1 or more doses selected from phase 1 to support further RP2D optimization
- Key outcome measures are shown in **Table 2**

Figure 4: Trial schema



KRAS=Kirsten rat sarcoma virus; PDAC=pancreatic ductal adenocarcinoma; RP2D=recommended phase 2 dose.

Table 1: Key eligibility criteria[a]

Inclusion criteria
• Participants aged ≥18 years
• ≥1 measurable lesion
• Evidence of *KRAS* G12D mutation in tumor tissue or blood (ctDNA)
• ECOG performance status of 0 or 1
Phase 1 Dose Escalation
• Histologically or cytologically confirmed unresectable or metastatic solid tumor malignancy
• Received appropriate prior SOC therapy and has no curative option or is unlikely to benefit from further SOC therapy
Phase 2 Cohort Expansion
• Histologically or cytologically confirmed unresectable or metastatic PDAC
• ≥1 prior line of systemic therapy for PDAC
Exclusion criteria
• Active brain metastases or carcinomatous meningitis
• Prior treatment with a KRAS G12D- or a KRAS G12C-targeting therapy, including pan-KRAS inhibitors or degraders

[a]This is not the complete list of inclusion/exclusion criteria.
ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; KRAS=Kirsten rat sarcoma virus; PDAC= pancreatic ductal adenocarcinoma; SOC=standard of care.

Table 2: Outcome measures

	Phase 1	Phase 2
Primary	• DLTs • Safety and tolerability	• ORR[a]
Secondary	• Pharmacokinetic parameters of ARV-806 • ORR[a], TTR, DOR, and DCR[b]	• Safety and tolerability • Pharmacokinetic parameters of ARV-806 • TTR, DOR, and DCR[b]

[a]The proportion of participants achieving a complete response or partial response.
[b]The proportion of participants achieving a complete response, partial response, or stable disease.
DCR=disease control rate; DLT=dose-limiting toxicity; DOR=duration of response; ORR=objective response rate; TTR=time to response.

Study Status

- Enrollment is currently ongoing
- To view currently recruiting sites, please visit clinicaltrials.gov (NCT07023731)

Scan this QR code to view the clinicaltrials.gov page for this study.