KRAS-Targeted PROTAC Degraders are Broadly Efficacious Against KRAS-Dependent Tumor Models

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I have the following relevant financial relationships to disclose:

- Employee of: Arvinas Operations, Inc.
- Stockholder in: Arvinas, Inc.
Arvinas’ proteolysis-targeting chimera (PROTAC®) degraders can:

- Eliminate (rather than inhibit) disease-causing proteins
- Disrupt scaffolding functions of target proteins
- Bind and degrade classically “undruggable” proteins
- Act iteratively (catalytically)
- Be delivered orally and achieve broad tissue distribution, including across the blood-brain-barrier

PROTAC® protein degraders combine the benefits of small molecules and gene-based knockdown technologies

POI = protein of interest
Why might a KRAS PROTAC degrader have advantages?

- KRAS biology (scaffolding role):
  - KRAS exists in a multi-protein complex at the membrane that may be disrupted by degradation
- Catalytic/durable pharmacodynamics (PD):
  - Slow resynthesis rate of KRAS
  - Extended exposure due to possible accumulation of PROTAC in the tumor

Focus on KRAS G12D for this talk

G12D PROTAC degraders have picomolar potency and high selectivity

- Optimized degraders exhibit $D_{50} < 1$ nM and $D_{max} > 90\%$ for G12D
- Potent pERK suppression
- Highly selective for KRAS G12D
G12D PROTAC degraders are dependent on the Ubiquitin Proteasome System (UPS)

- Inactivating either the KRAS or E3 ligase ligand prevents degradation
- Inhibiting the UPS pathway rescues degradation
- G12D PROTAC leads to direct ubiquitination of KRAS G12D

Does degradation have advantages over inhibition? Compare active PROTAC vs E3-inactive PROTAC (same physiochemical properties)
Degrader shows more potent anti-proliferative effect

- Active degrader >20-fold more potent at inhibiting proliferation in 3D
- Degrader displays GI$_{50}$ < 1 nM in multiple G12D models
- MAPK (pERK) and AKT (pS6<sup>240/244</sup>; data not shown) signaling more potently suppressed with active degrader
Single dose of G12D PROTAC suppresses KRAS levels for ≥7 days

- Single 3 mpk IV dose of PROTAC D administered
- Maximum degradation of >90% achieved at 24 hrs
- After 7 days, KRAS is still 70% degraded
- Prolonged exposure in tumor

![Graph showing Tumor PK/PD for G12D PROTAC D in GP2d tumors. The graph displays % KRAS G12D normalized to vehicle and % total PROTAC concentration over days post treatment. Maximum degradation achieved within 24 hrs, with 93% reduction observed at 7 days post treatment.](image-url)
Low, infrequent dosing of G12D PROTAC is efficacious *in vivo*

- PROTAC dosed at 1 mpk BiW or 3 mpk QW and Q2W demonstrates 93-100% TGI
  - Significantly more efficacious than E3-inactive
- No body weight effects
Summary

- KRAS G12D PROTAC degraders are potent and selective
- Degradation of KRAS G12D provides an advantage \textit{in vitro} and \textit{in vivo}
  - Potent signaling suppression, anti-proliferation and apoptosis induction (data not shown) \textit{in vitro}
  - Single, low dose of PROTAC suppresses KRAS in tumors for \textgreater{}7 days
  - Extended \textit{in vivo} PD correlates with \textasciitilde{}100\% TGI with intermittent dosing
  - Well tolerated in mice
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