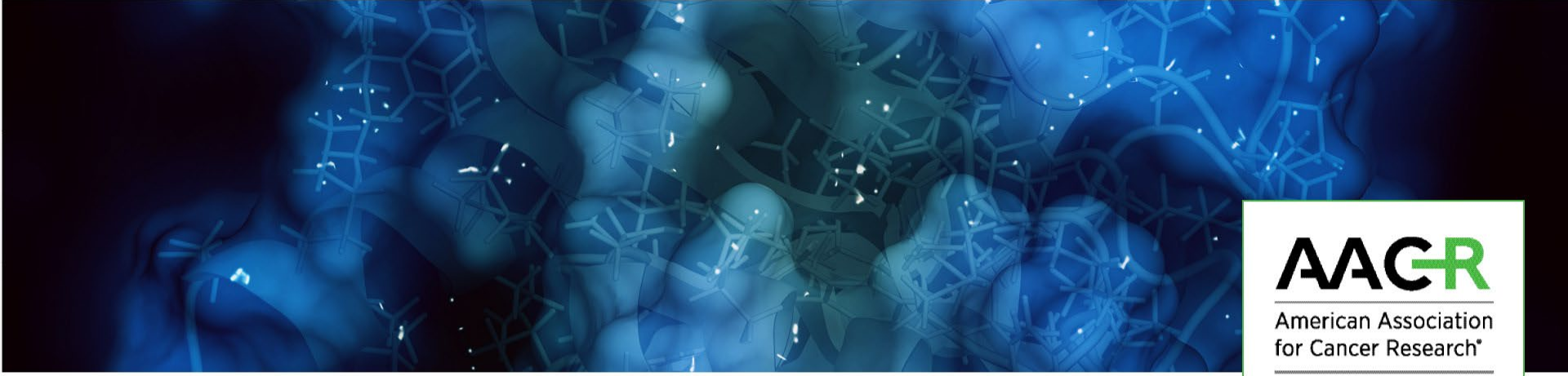

# Preclinical activity of an orally bioavailable PROTAC pan-KRAS degrader versus inhibitors in mutant KRAS models

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**RAS ONCOGENESIS AND THERAPEUTICS**
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# Disclosure Information

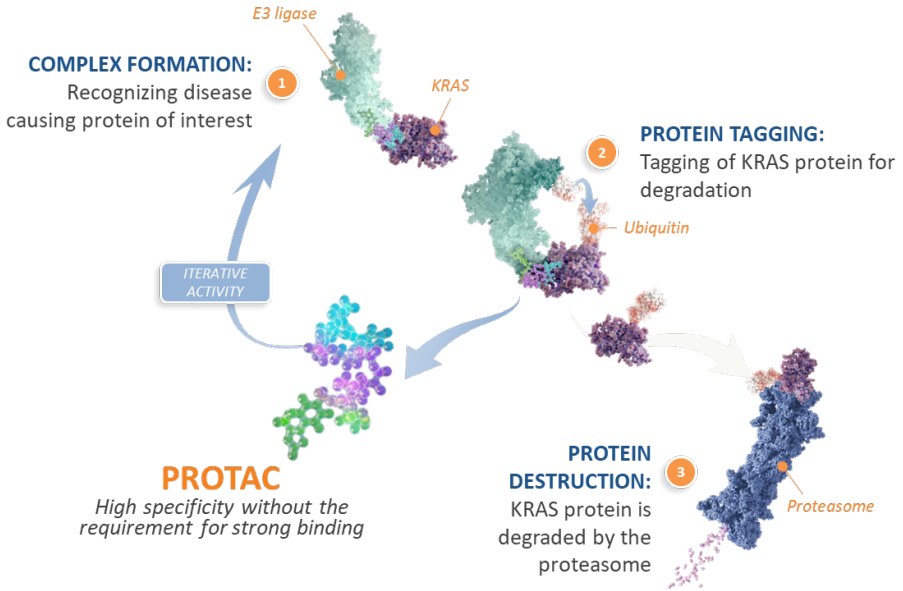

## Andrea Lopez-Arroyo, Ph.D.

I have the following relevant financial relationships to disclose:

Employee of: Arvinas Inc

Stockholder in: Arvinas Inc

# PROTAC protein degraders harness the body's natural machinery to degrade disease-causing proteins

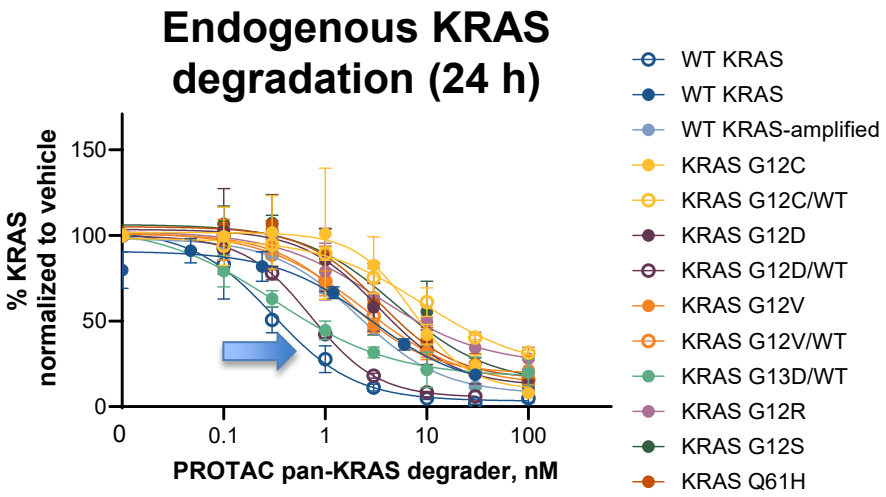


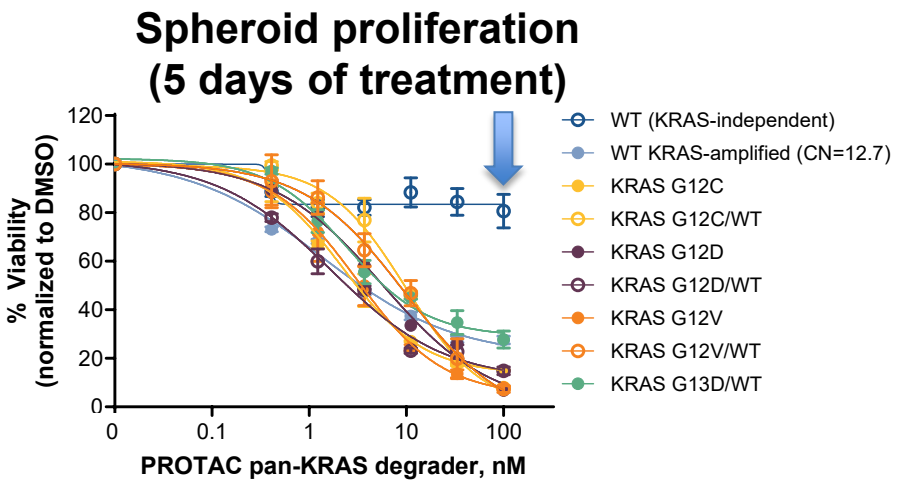

General PROTAC protein degrader is shown

- **Potential advantages of PROTAC MOA for targeting KRAS:**
  - Degradation of both the ON and OFF forms of KRAS (Poster #B004)
  - Durable pharmacodynamic activity and KRAS selectivity may allow for an improved therapeutic window while maintaining efficacy
  - Overcome KRAS upregulation commonly observed upon inhibitor treatment due to iterative activity

KRAS=Kirsten rat sarcoma viral oncogene homolog; MOA=mechanism of action; PROTAC=PROteolysis TArgeting Chimera.

# PROTAC pan-KRAS degrader targets multiple KRAS alterations including G12C/D/V/R/S, G13D, Q61H, and WT-amplified

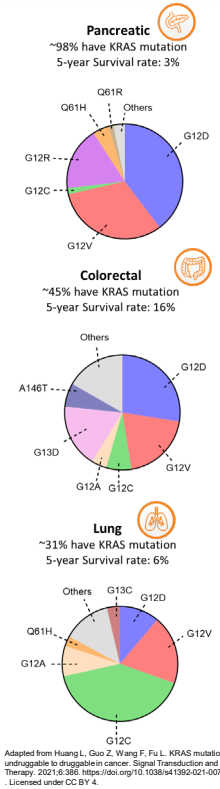



- Selective degradation of KRAS that spares HRAS and NRAS (poster #B004)
  - Degradation of KRAS G12R and Q61H
- Potent KRAS degradation ($DC_{50}$ = 0.3 – 9 nM) and antiproliferative activity ($IC_{50}$ = 2-10 nM)
- Degradation of WT-KRAS degradation but no antiproliferative activity in cells independent of KRAS

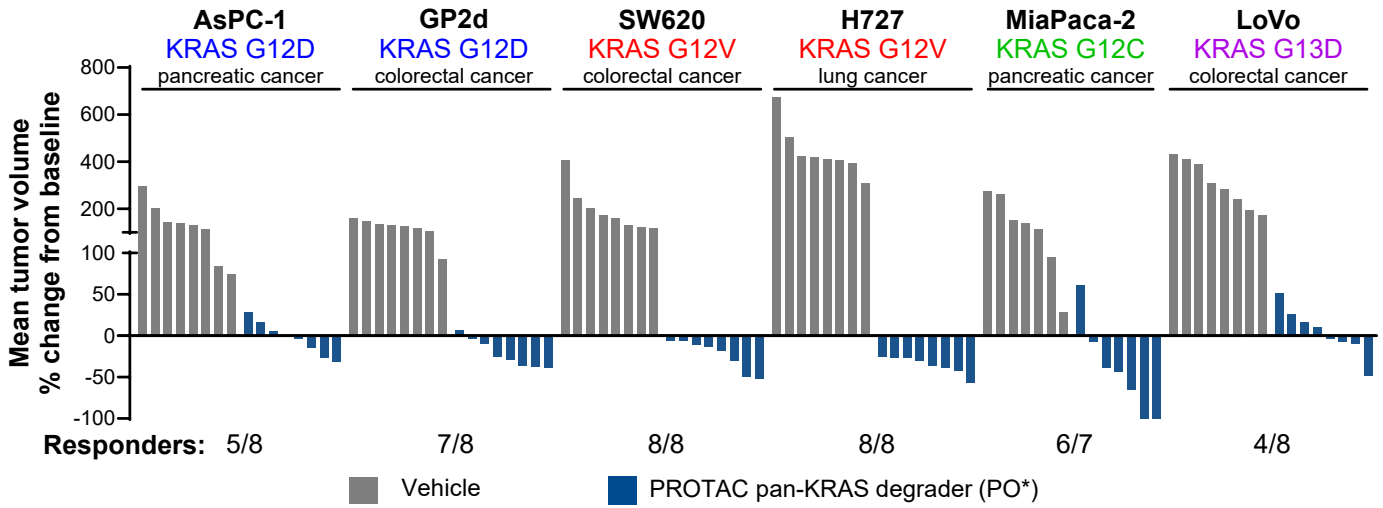
CN=copy number; HRAS=Harvey rat sarcoma viral oncogene homolog; KRAS=Kirsten rat sarcoma viral oncogene homolog; NRAS=neuroblastoma rat sarcoma viral oncogene homolog; PROTAC=PROteolysis TArgeting Chimera; WT=wild-type.

# Oral administration of PROTAC pan-KRAS degrader induced tumor regressions across multiple mutant KRAS models




Adapted from Huang L, Guo Z, Wang F, Fu L. KRAS mutation: from undruggable to druggable in cancer. Signal Transduction and Targeted Therapy. 2021;6:386. https://doi.org/10.1038/s41392-021-00780-4 . Licensed under CC BY 4.

## Change in tumor volume at end of study




- Treatment with a pan-KRAS PROTAC led to:
  - Tumor regressions in KRAS G12D/C/V and G13D CDX models
  - KRAS degradation, MAPK inhibition, increases in pro-apoptotic markers, and decreases in proliferative markers (poster #B004)

BID=twice daily; CDX=cell line–derived xenograft; KRAS=Kirsten rat sarcoma viral oncogene homolog; PO=orally; PROTAC=PROteolysis TArgeting Chimera; QD=once daily; * PROTAC dosing at 30 mpk QD to 60 mpk BID PO

# PROTAC pan-KRAS degrader had stronger antiproliferative effects and greater caspase activity vs inhibitors

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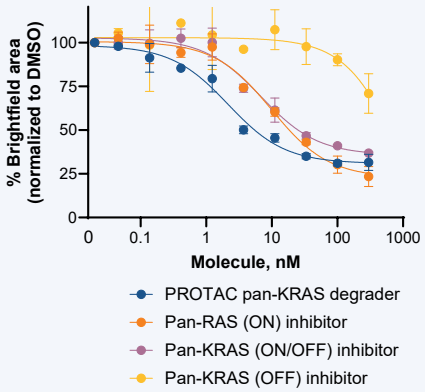
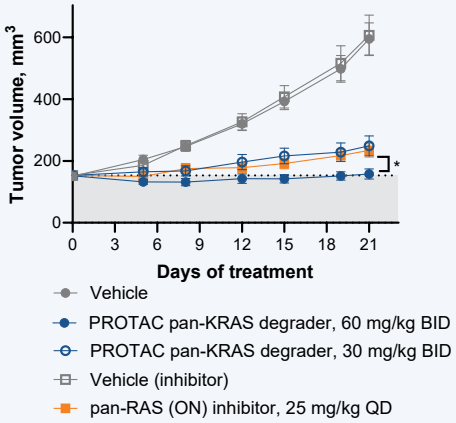
## KRAS G13D model (LoVo CDX)

### Spheroid proliferation (5 days)




### Tumor volume

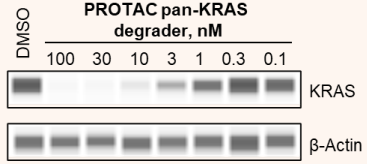



- The pan-KRAS PROTAC demonstrated:
  - Greater antiproliferative effects than pan-RAS (ON) or pan-KRAS inhibitors
  - Greater TGI than a pan-RAS (ON) inhibitor

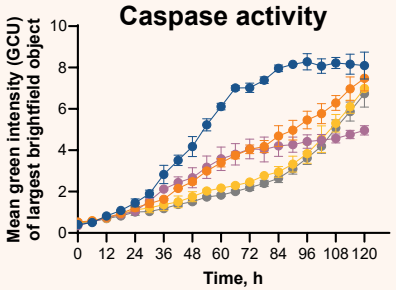
## KRAS WT-amplified model (MKN1)

MKN1 cells express ~30-fold more KRAS than a non-amplified line (H520)

### KRAS degradation




### Caspase activity



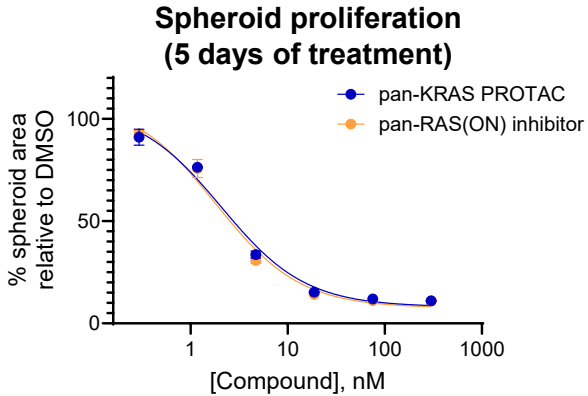

DMSO
PROTAC pan-KRAS degrader
pan-RAS (ON) inhibitor
pan-KRAS (ON/OFF) inhibitor
pan-KRAS (OFF) inhibitor

*All molecules at equivalent concentration

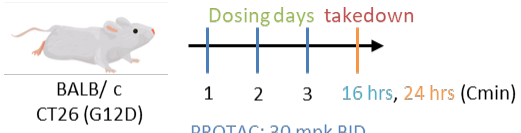
- The pan-KRAS PROTAC can lead to:
  - Elimination of amplified KRAS in MKN1 cells
  - Greater apoptosis and antiproliferative activity than pan-RAS (ON) or pan-KRAS inhibitors (data not shown)

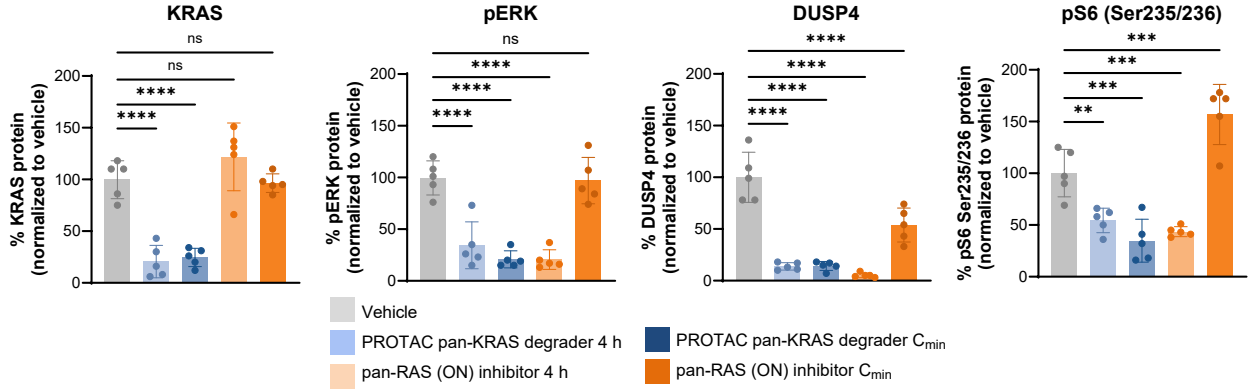
BID=twice daily; DMSO=dimethyl sulfoxide; GCU=generic caspase units; KRAS=Kirsten rat sarcoma viral oncogene homolog; PO=orally; PROTAC=PROteolysis TArgeting Chimera; QD=once daily; TGI=tumor growth inhibition; WT=wild-type.

# PROTAC pan-KRAS degrader led to more durable MAPK pathway inhibition vs a pan-RAS (ON) inhibitor




Kathryn Smith et al., AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC) Poster B107. Presented October 24, 2025




- PROTAC pan-KRAS degrader and pan-RAS (ON) inhibitor had similar activity in CT26 spheroids
- Signaling suppression was more durable with the PROTAC pan-KRAS degrader compared with a pan-RAS (ON) inhibitor in the CT26 syngeneic model

BID=twice daily; $C_{min}$=minimum plasma concentration; DMSO=dimethyl sulfoxide; DUSP4/6=dual specificity phosphatase 4/6; KRAS=Kirsten rat sarcoma viral oncogene homolog; MAPK=mitogen-activated protein kinase; pERK=phosphorylated extracellular signal-regulated kinase; PROTAC=PROteolysis TArgeting Chimera; pS6 (Ser235/236)=ribosomal protein S6 phosphorylated at serine 235 and 236.

# PROTAC pan-KRAS degrader had enhanced combinatorial efficacy with immune checkpoint blockade vs pan-RAS (ON) inhibitor

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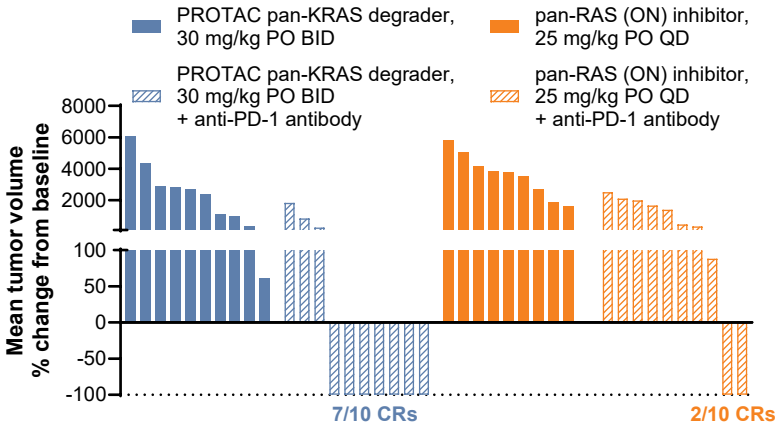
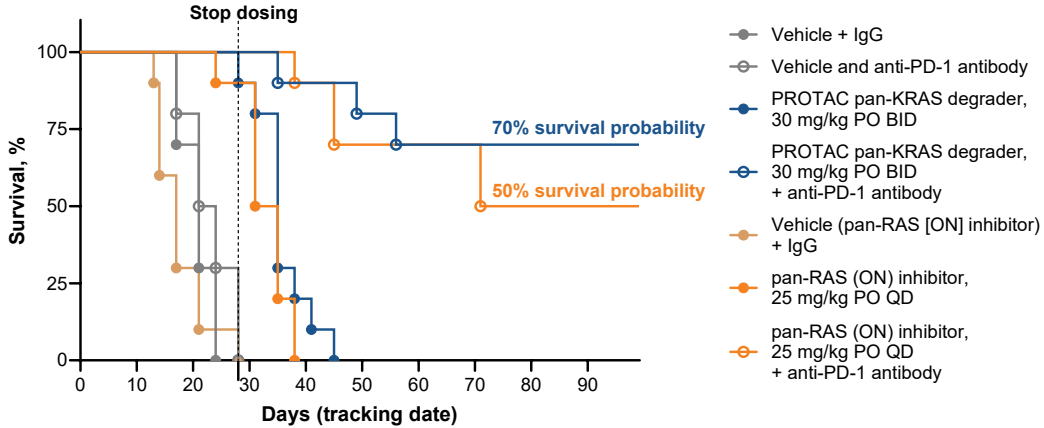
## Change in tumor volume



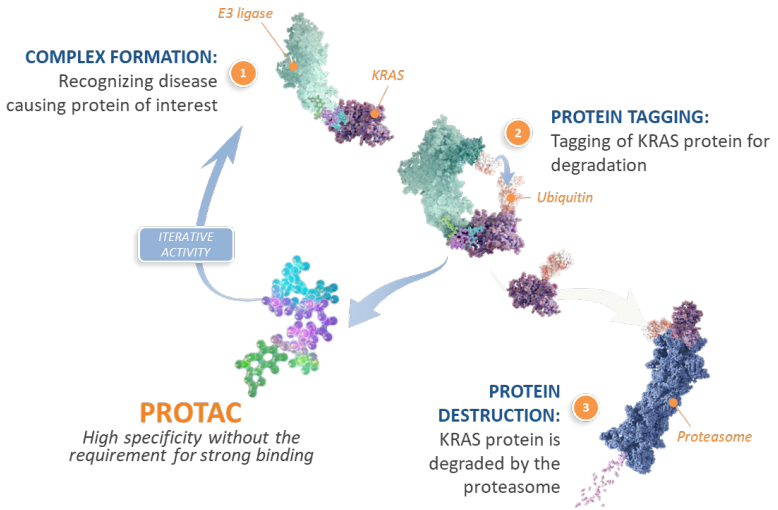

## Survival




- Combining a PROTAC pan-KRAS degrader with anti-PD-1 immune checkpoint blockade yielded greater efficacy than a pan-RAS (ON) inhibitor combined with an anti-PD-1 antibody

BID=twice daily; CR=complete response; DMSO=dimethyl sulfoxide; DUSP4/6=dual specificity phosphatase 4/6; IgG=immunoglobulin; KRAS=Kirsten rat sarcoma viral oncogene homolog; MAPK=mitogen-activated protein kinase; PD-1=programmed cell death protein 1; PO=orally; PROTAC=PROteolysis TArgeting Chimera; QD=once daily.

# Summary




- The PROTAC pan-KRAS degrader demonstrated:
  - Selective degradation of multiple KRAS mutants
  - Robust efficacy in CDX models of pancreatic, colorectal, and lung cancer
  - Greater tumor growth inhibition than a pan-RAS (ON) inhibitor in a KRAS G13D model
  - Enhanced combination efficacy with immune checkpoint blockade compared with a pan-RAS (ON) inhibitor in a KRAS G12D syngeneic model

CDX=cell line–derived xenograft; KRAS=Kirsten rat sarcoma viral oncogene homolog; PROTAC=PROteolysis TArgeting Chimera; QD=once daily.

Poster #B004

# Thank you!

Jason M Berk, Dana M Klug, John P Caldwell, Peter Hegan, Samantha Andella, Jessica Kraus, Amanda Chapman, Jennifer Pizzano, Mark Bookbinder, Debbie Gordon, Kim Davenport, Gregory Cadelina, Madeline A Dorso, Emma Rousseau, Christopher Kuhlberg, Morena Scopel, Rebecca Conrad, William L Corwin, Goutham Pattabiraman, Wendy Wu, Rashaun Wilson, Christine Jones, John Corradi, Keith R Hornberger, Angela M Cacace, Ignacio J Juncadella, Kathryn D Smith