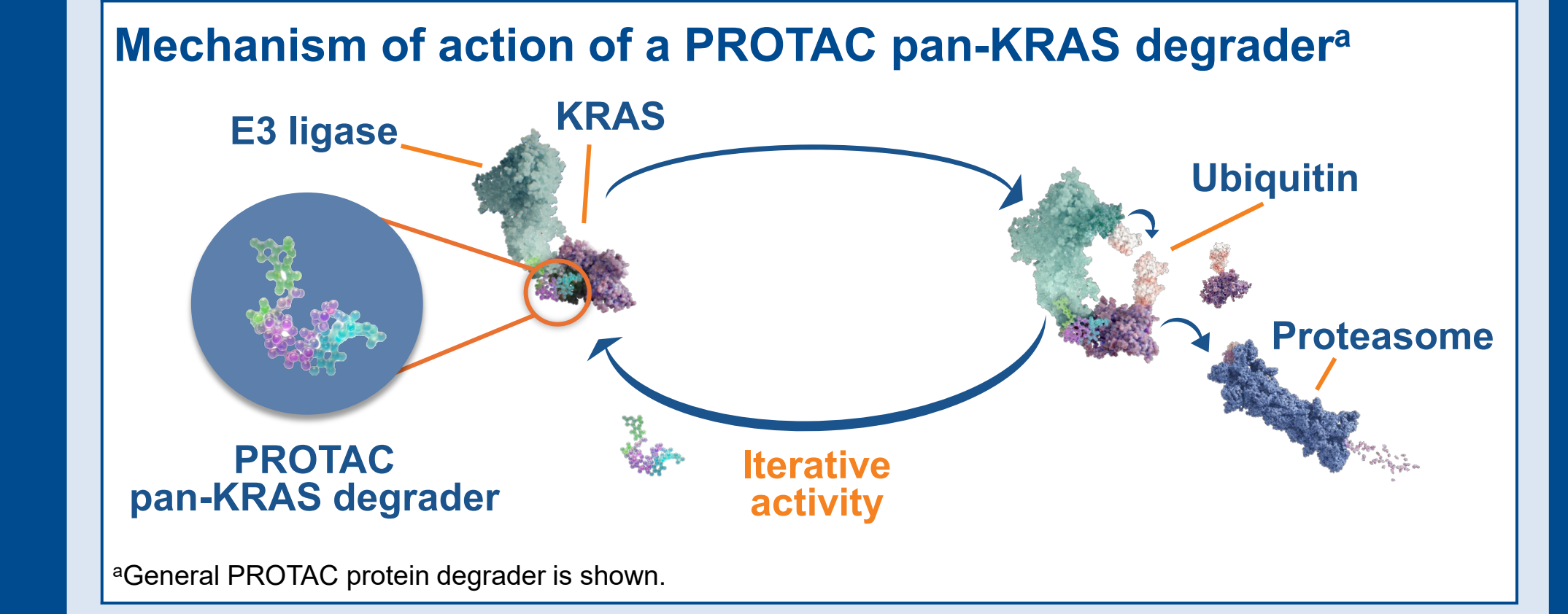


Preclinical Efficacy of a PROTAC Pan-KRAS Degradator in a KRAS G12D Syngeneic Mouse Model and Concurrent Immune TME Changes

Jason M Berk, Andrea Lopez-Arroyo, Dana M Klug, John P Caldwell, Peter Hegan, Samantha Andella, Jessica Kraus, Amanda Chapman, Jennifer Pizzano, Mark Bookbinder, Gregory Cadelina, Debbie Gordon, Kim Davenport, Wendy Wu, Madeline A Dorso, Morena Scopel, Rebecca Conrad, William L Corwin, Goutham Pattabiraman, Keith R Hornberger, Angela Cacace, Ignacio J Juncadella, Kathryn D Smith
Arvinas Operations, Inc., New Haven, CT, USA

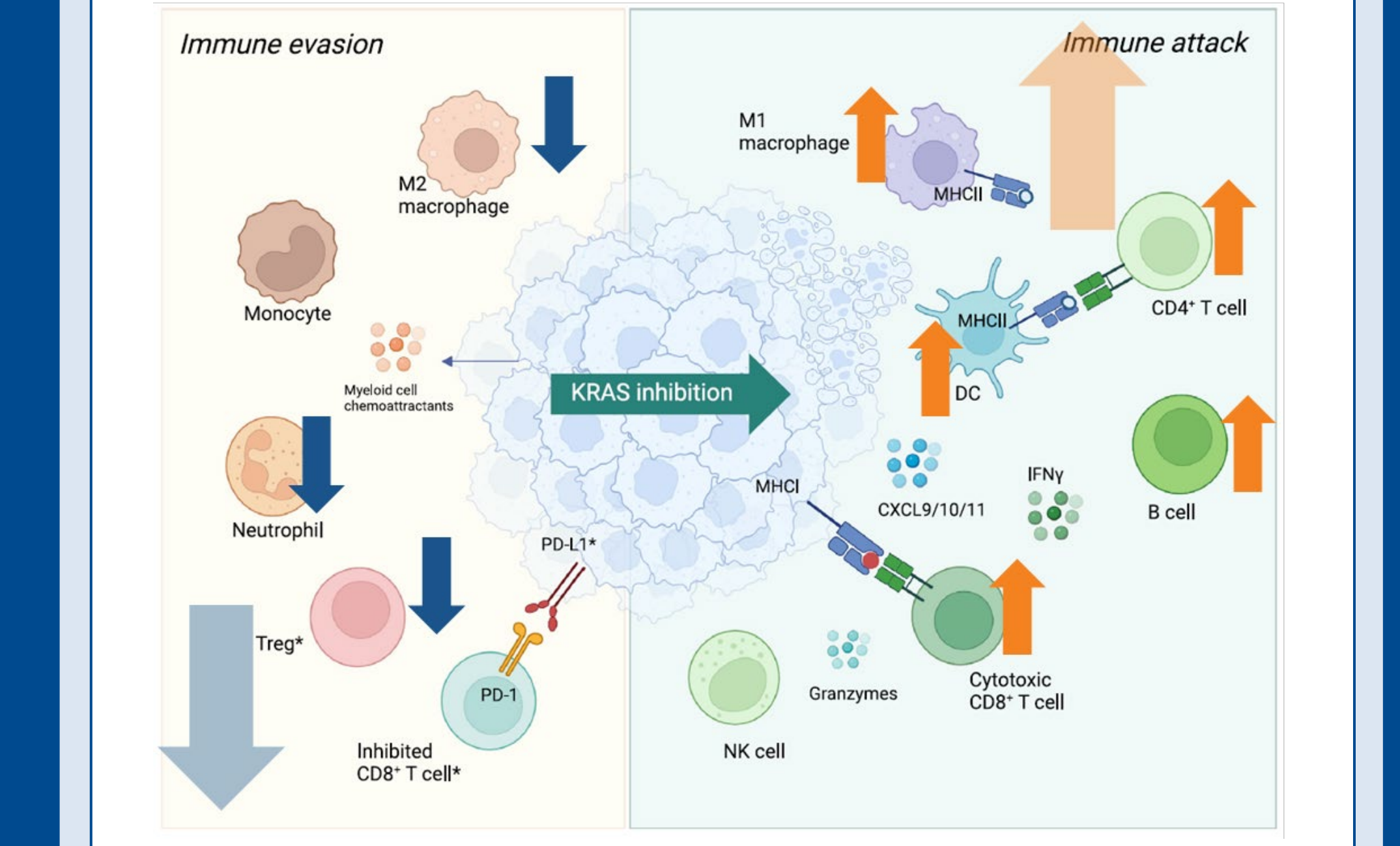
Background

- KRAS 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
- Alterations in KRAS occur in ~20% of cancers^{2,3}
- Although 2 KRAS inhibitors have been approved for patients with KRAS G12C-mutated disease, resistance commonly develops, supporting the need for combination approaches
- Moreover, no approved agents target other KRAS mutants
- We developed an oral tool PROTAC pan-KRAS degrader that induces ubiquitination and subsequent proteasomal degradation of KRAS



- The PROTAC pan-KRAS degrader had potent activity toward a broad set of KRAS alterations, degrading KRAS G12C/D/V/R/S, G13D, Q61H, and WT-amplified KRAS, while sparing HRAS and NRAS^{4,5}
- Mutant KRAS is an established intrinsic driver of an immunosuppressive TME, which can be alleviated by KRAS inhibition, suggesting potential synergy with ICI⁶

Potential synergy of KRAS inhibition and ICI



Objective

- To compare the effects of PROTAC-mediated KRAS degradation vs pan-RAS (ON) inhibition (± an anti-PD-1 antibody) on the TME and associated antitumor activity in the CT26 KRAS G12D murine colorectal cancer model

Figure 1: In vitro activity and in vivo degradation and pathway suppression with PROTAC pan-KRAS degrader vs pan-RAS (ON) inhibitor

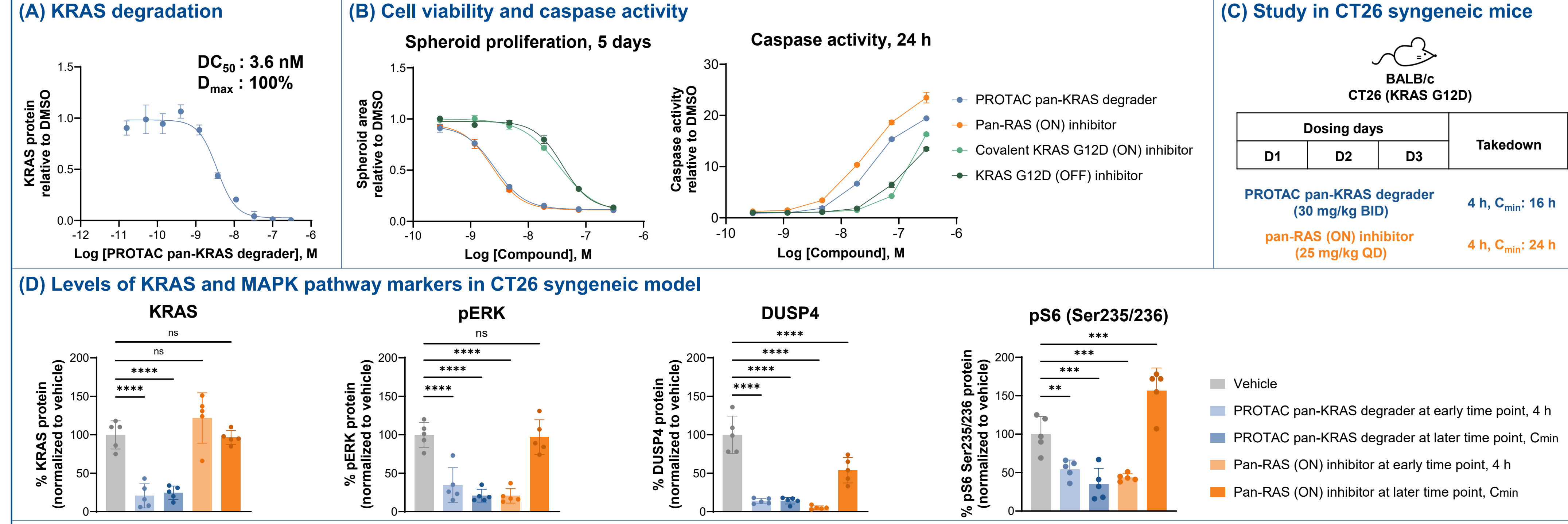


Figure 2: Antitumor activity and changes in immune cell populations in TME with PROTAC pan-KRAS degrader vs pan-RAS (ON) inhibitor ± anti-PD-1 antibody

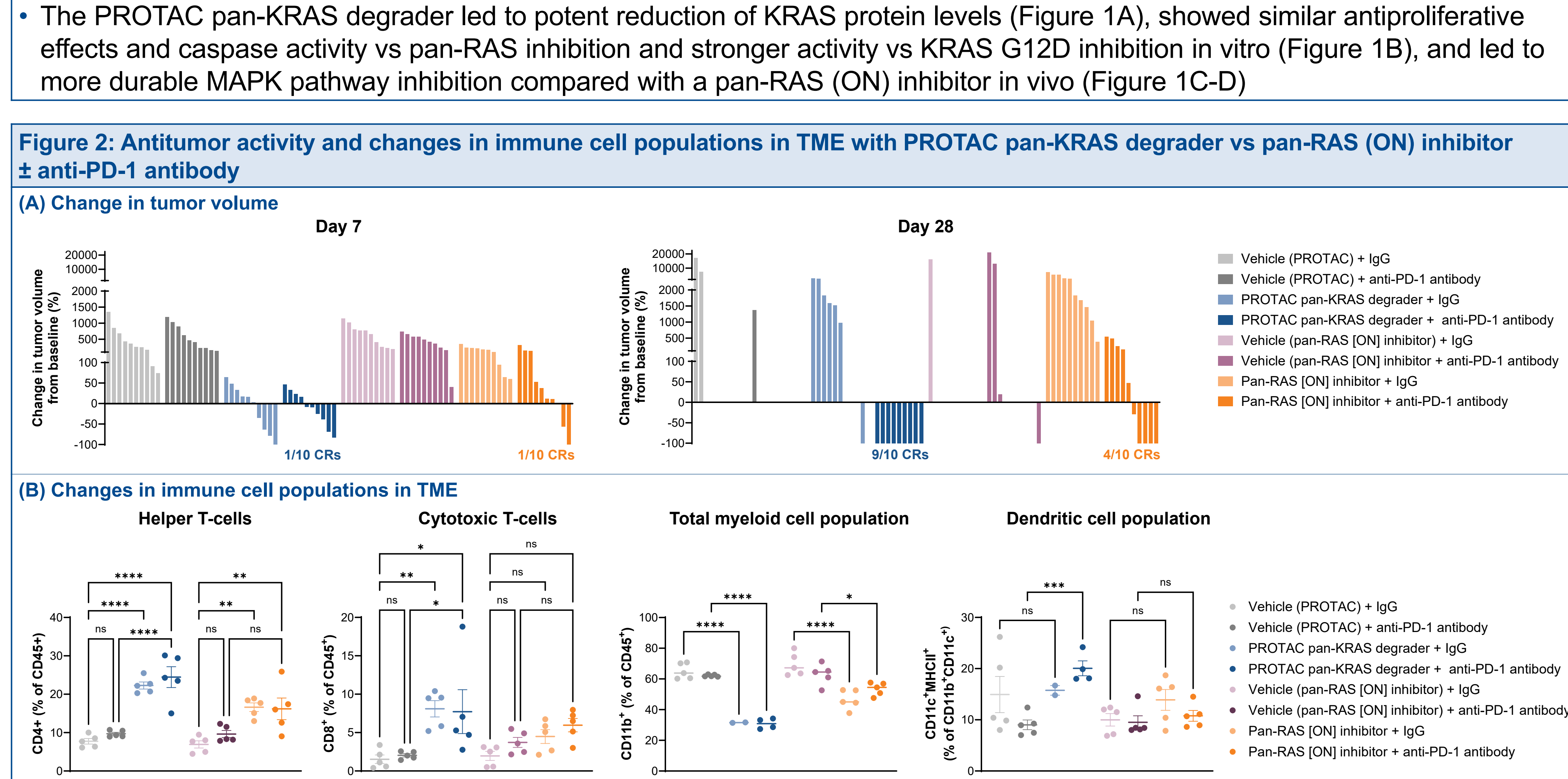


Figure 3: RAS pathway activity and TME-suppressive cytokine and chemokine expression with PROTAC pan-KRAS degrader vs pan-RAS (ON) inhibitor ± anti-PD-1 antibody

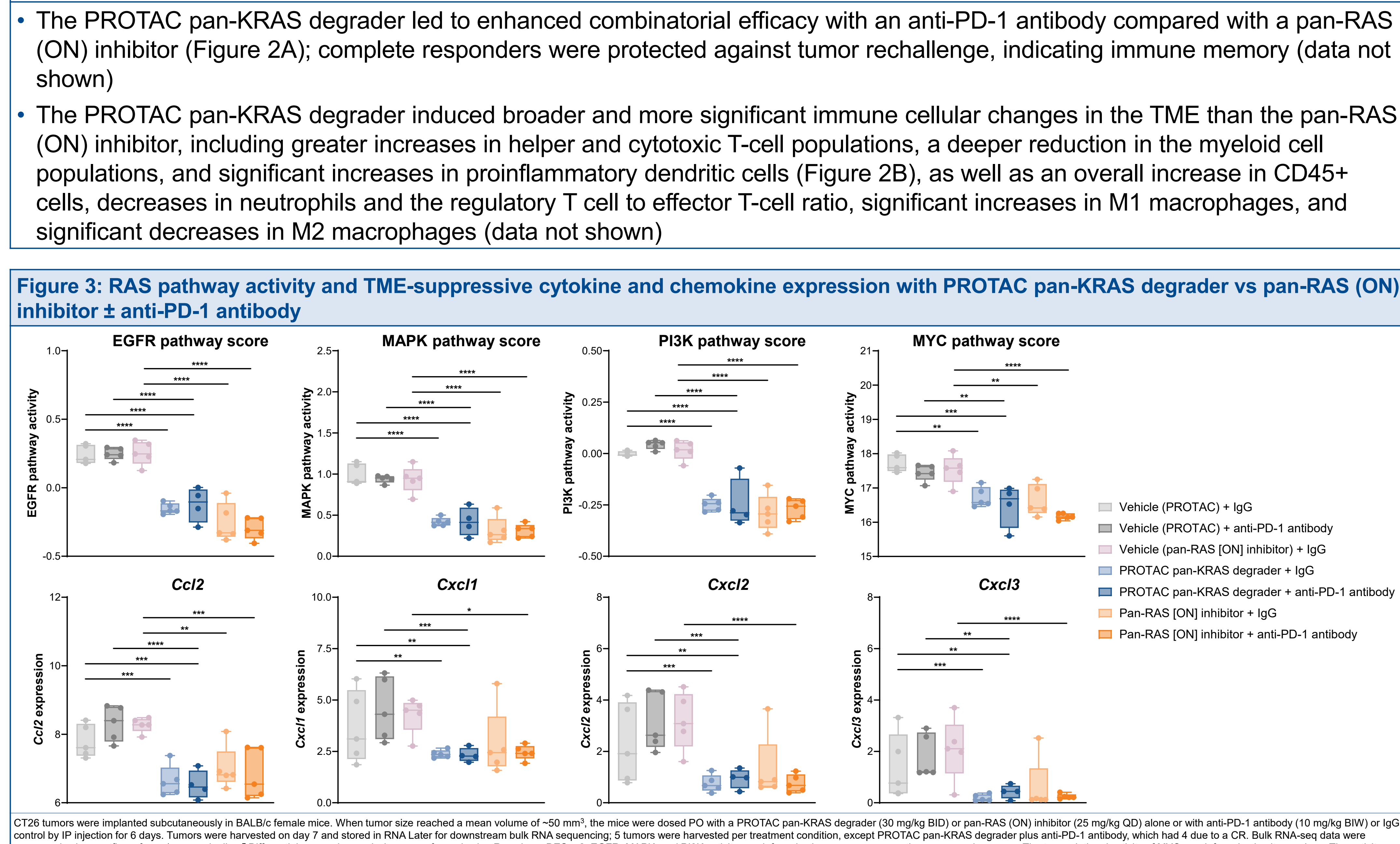


Figure 4: Differential pathway enrichment in TME with PROTAC pan-KRAS degrader vs pan-RAS (ON) inhibitor



Figure 5: Evaluation of predictive ICI response signature using GSEA with PROTAC pan-KRAS degrader vs pan-RAS (ON) inhibitor ± anti-PD-1 antibody

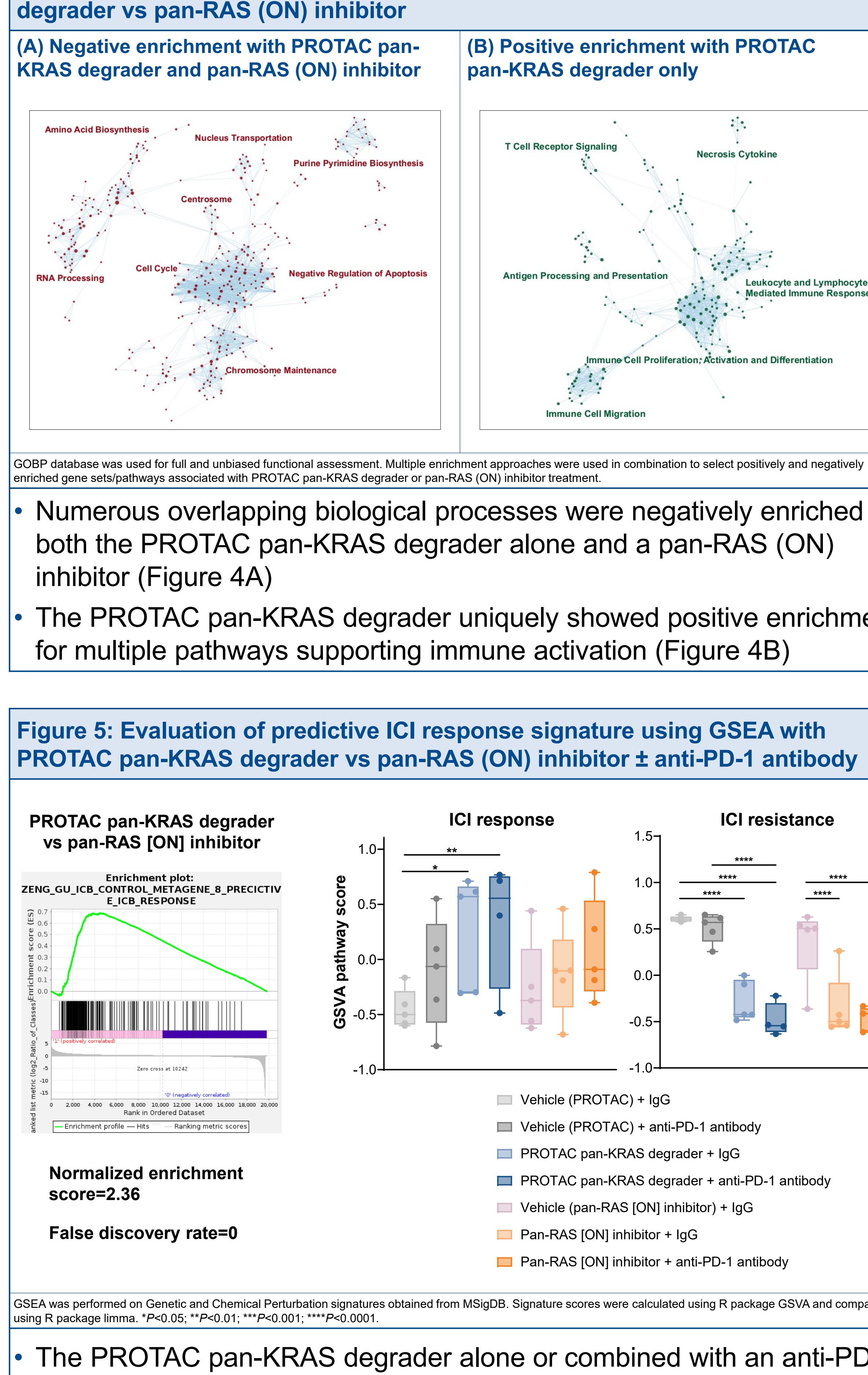
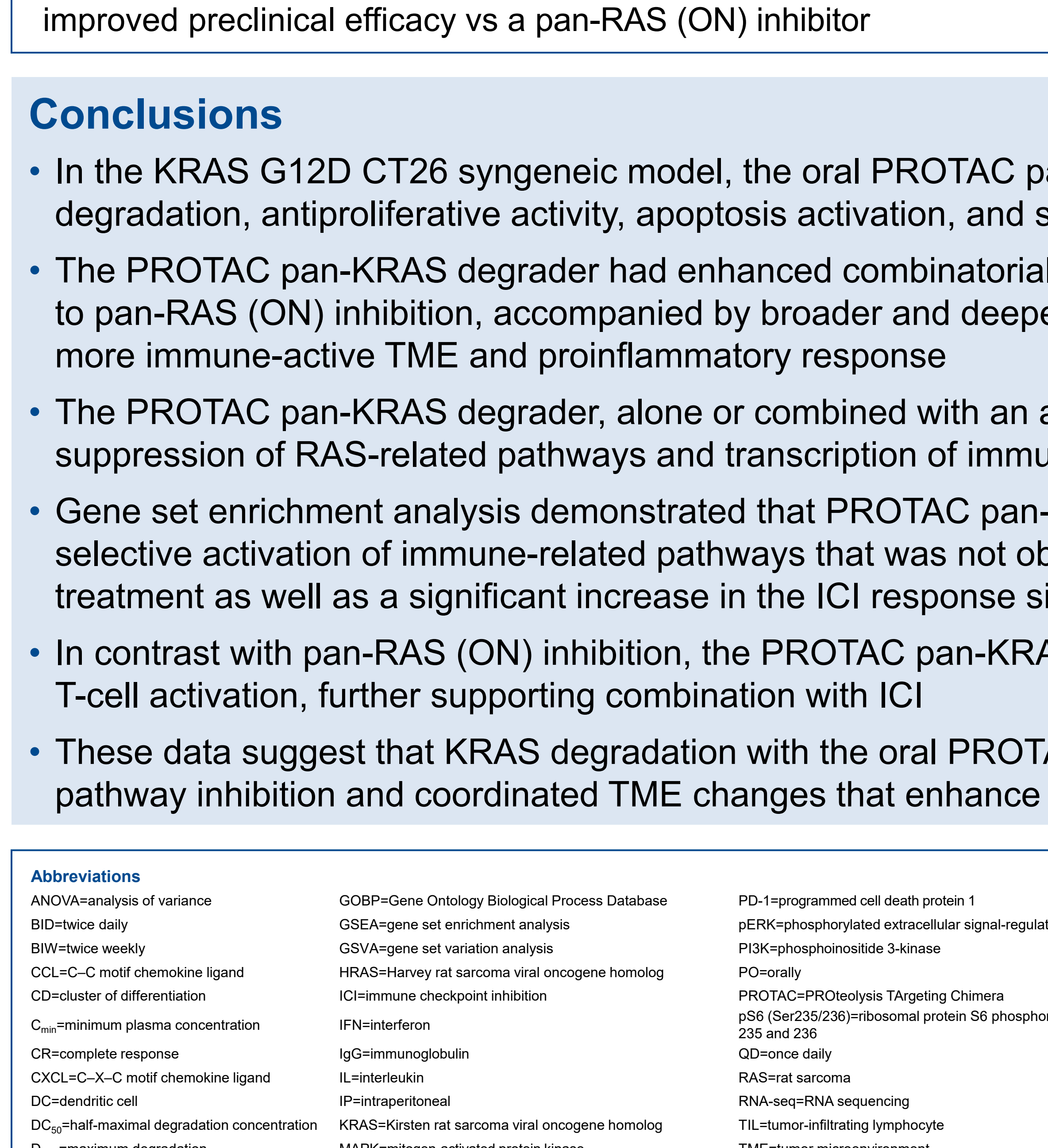


Figure 6: Human T-cell effector cytokine production with PROTAC pan-KRAS degrader vs pan-RAS (ON) inhibitor



Abbreviations

ANOVA=analysis of variance
 BID=twice daily
 BIW=twice weekly
 CCL=C-C motif chemokine ligand
 CR=complete response
 CXCL=C-X-C motif chemokine ligand
 DC=dendritic cell
 DC50=half-maximal degradation concentration
 Dmax=maximum degradation
 DMSO=dimethyl sulfoxide
 DUSP=dual specificity phosphatase 4
 EGFR=epidermal growth factor receptor
 FOXP3=forkhead box P3

GOBP=Gene Ontology Biological Process Database
 GSEA=Gene Set Enrichment Analysis
 GSV=Gene Set Variation Analysis
 HRAS=Harvey rat sarcoma viral oncogene homolog
 ICI=immune checkpoint inhibition
 IFN=interferon
 IgG=immunoglobulin
 IL=interleukin
 IP=intraperitoneal
 KRAS=Kirsten rat sarcoma viral oncogene homolog
 MAPK=mitogen-activated protein kinase
 MHC=major histocompatibility complex
 NK=natural killer
 NRAS=neuroblastoma rat sarcoma viral oncogene homolog
 PBMC=peripheral blood mononuclear cell

PD-1=programmed cell death protein 1
 pERK=phosphorylated extracellular signal-regulated kinase
 PI3K=phosphatidylinositol 3-kinase
 PO=orally
 PROTAC=PROTACylation Targeting Chimera
 pS6(Ser235/236)=ribosomal protein S6 phosphorylated at serine 235 and 236
 QD=once daily
 RAS=rat sarcoma
 RNA-seq=RNA sequencing
 TIL=tumor-infiltrating lymphocyte
 TME=tumor microenvironment
 TNF=tumor necrosis factor
 Treg=regulatory T cell
 WT=wild-type

References

1. Yin G, et al. Signal Transduct Target Ther. 2023;8:212.
2. Prior IA, et al. *Cancer Res*. 2020;80:2998-2974.
3. Lee K, et al. *Nat Rev Clin Oncol*. 2022;6:91.
4. Smith K, et al. AACR-NCI-EORTC Int Conf on Mol Targets & Cancer Ther. 2025;Poster B107.
5. Lopez-Arroyo A, et al. AACR Special Conference in Cancer Research: RAS Oncogenesis and Therapeutics 2026:B004.
6. Molina-Arcas M and Downward J. *Cancer Cell*. 2024;11:338-357.
7. Ewels PA, et al. *Nat Biotechnol*. 2020;38:276-278.

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

Contact
Jason Berk: jason.berk@arvinas.com

