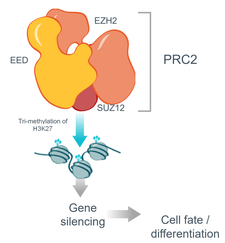
PRC2 Inhibition Enhances KRAS Inhibitor Response to Delay Treatment Relapse in KRAS-mutant Preclinical Lung and Colorectal Cancer Models

Stephanie W Ni, Natalie Yuen, Livia Ulicna, Denise F Reyes, Eunice Lopez-Fuentes, Michal Pawlak, Frank L Duong, Jason E Long, Aleksandr Pankov, Lori S Friedman, Anneleen Daemen, Melissa R Junttila
ORIC Pharmaceuticals, Inc., South San Francisco, CA 94080

Abstract A048

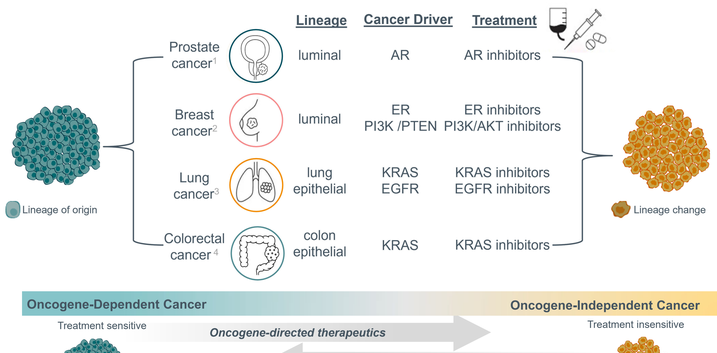
BACKGROUND

- **PRC2:** Polycomb repressive complex 2 (PRC2) silences transcription by tri-methylating histone H3 at lysine 27, thereby regulating cell growth and differentiation. Elevated PRC2 activity promotes lineage plasticity and therapeutic resistance and has been associated with poor prognosis in several types of cancer.
- **ORIC-944:** ORIC-944 is a next-generation, potent, highly selective, orally bioavailable small molecule inhibitor of PRC2 that allosterically targets the EED subunit, with potential best-in-class drug properties including limited CYP interactions and superior pharmacokinetics (PK) and half-life.
- **Mechanistic Rationale:** Cancer cells evade therapies by cellular reprogramming to an oncogene-independent state. PRC2 inhibition can reverse this process, potentially restoring driving oncogene-dependence, similarly to what has been demonstrated in prostate cancer.



1. Background: PRC2 Activity Enables Lineage Change Underlying Therapeutic Resistance

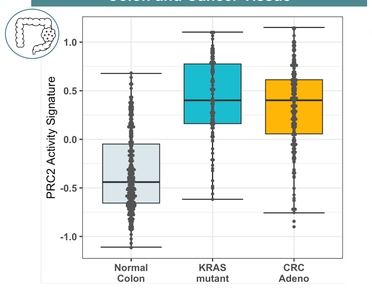
PRC2 Inhibition May Maximize Antitumor Benefit When Combined With Oncogene Inhibitors



Source: [1] Yu et al. Cancer Res. (2007), Dardenne et al. Cancer Cell (2016), Mu et al. Science (2017), Davies et al. Nat Cell Biol (2021), Nouruzi et al. Nat Commun (2022), Goel et al. Semin Cancer Bio (2022); [2] Yu et al. Cancer Res. (2007), Yomtoubian et al. Cell Reports (2020), Schade et al., Nature (2024), Liang et al., Nat Cancer (2025), Jones et al., Scientific Reports (2025); [3] Quintanal-Villalonga A et al., Nat Cli n Can Rev (2020), Araujo HA et al., Cancer Discovery 2024; [4] Loi et al., Cancer Disc (2024)

2. PRC2 Activity Is Increased in NSCLC and CRC Patient Tumors

PRC2 Activity Signature in Normal Human Colon and Cancer Tissue



PRC2 Activity Signature in Normal Human Lung and Cancer Tissue

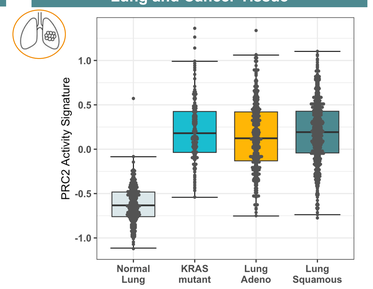
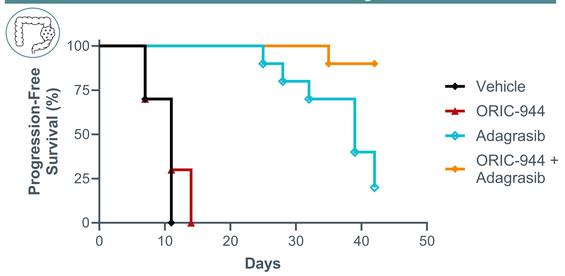


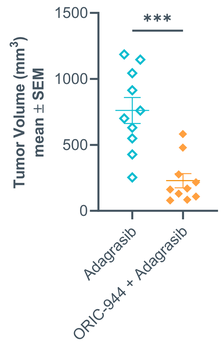
Figure 2. PRC2 activity gene signature is increased in KRAS-mutant CRC and NSCLC. PRC2 activity gene signature [Yu et al., Cancer Research (2007)]; TCGA/GTEX data sets; KRAS mutant includes: G12X, G13X and Q61X; Cohort sizes: Normal Colon (n=304), KRAS mutant colorectal cancer (CRC) adenocarcinoma (n=110), KRAS wildtype CRC adenocarcinoma (n=178), Normal Lung (286), KRAS mutant NSCLC (n=146), KRAS wildtype NSCLC adenocarcinoma (n=371), KRAS wildtype NSCLC squamous (n=494).

3. ORIC-944 Improves Adagrasib Durability In Vivo in KRAS G12C CRC Xenografts

ORIC-944 Combined with Adagrasib Prevents Relapse in KRAS G12C SW1463 CRC Xenograft Model



Combination Treatment Significantly Reduced Tumor Volume

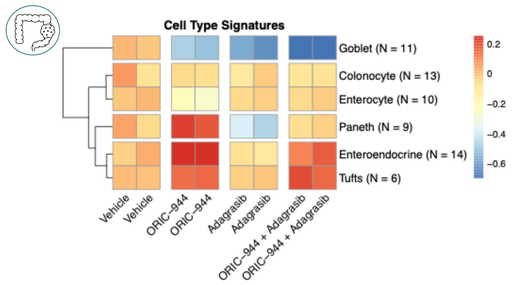


	Vehicle	ORIC-944	Adagrasib	Combination
Median PFS (days)	11	11	39	Not reached

Figure 3. Adagrasib in combination with ORIC-944 prevents tumor relapse observed with single agent adagrasib. Subcutaneously implanted SW1463 was treated once daily (QD) by oral gavage (PO) (n=10 per treatment cohort) with vehicle, ORIC-944 100 mg/kg, adagrasib 30 mg/kg or the combination for up to 43 days. Tumors were measured by caliper and mice weighed twice weekly. No PK drug-drug interaction (DDI) or significant body weight loss was observed; Progression-free survival (PFS) is based on tumor volume exceeding 500mm^3 or morbidity. **Right:** End of study tumor volumes assessed at day 42, unpaired t-test ***p=0.0002.

4. PRC2 Inhibition Drives Cell Differentiation in CRC Xenografts

Secretory Lineage Gene Expression Pathways Are Upregulated in ORIC-944-treated KRAS G12C CRC Xenograft Tumors



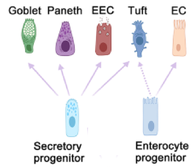
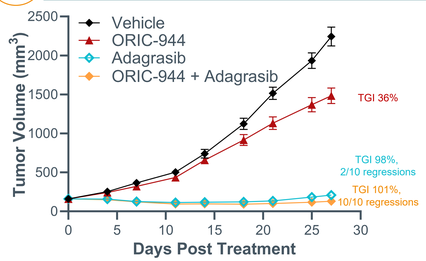


Figure 4. RNA sequencing of SW1463 tumors demonstrates lineage conversion of CRC tumors. Cell type signatures [Haber et al., Nature (2017), Parikh et al., Nature (2019), Gu et al., Genes and Dev (2022)] from SW1463 xenograft tumors treated as indicated. Signature score is the average of vehicle-centered expression. Mechanism of combination was confirmed to be consistent with the literature report Loi et al., Cancer Discovery (2024). EC, enterocyte; EEC, enteroendocrine

5. ORIC-944 Combination with KRAS G12C Inhibitor Induces 100% of Tumors to Regress in Two NSCLC Xenograft Models

ORIC-944 Combined With Adagrasib in Squamous NSCLC Model (Calu-1)



ORIC-944 Combined With Adagrasib in Adenocarcinoma NSCLC Model (NCI-H2030)

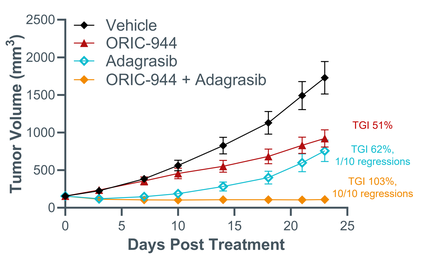
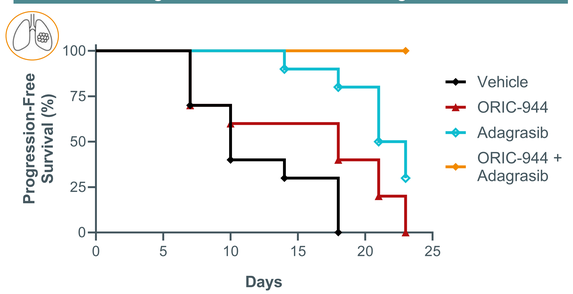


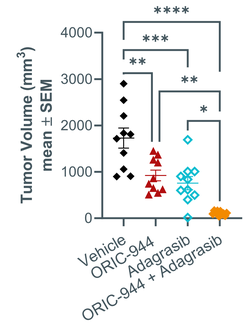
Figure 5. Combined ORIC-944 and adagrasib regress 100% of NSCLC tumors in vivo. Subcutaneously implanted Calu-1 or NCI-H2030 were treated once daily (QD) by oral gavage (PO) for indicated days (n=10 per treatment cohort) with vehicle, ORIC-944 100 mg/kg, adagrasib 30 mg/kg or the combination. Tumors were measured by caliper and mice weighed twice weekly. No PK drug-drug interaction (DDI) or significant body weight loss was observed. Calu-1 line contains a KRAS^{G12C} mutation and TP53 homozygous deletion; NCI-H2030 line contains KRAS^{G12C}, TP53^{G262V} and STK11 mutations. Shown is mean tumor volume ± SEM. Percent tumor growth inhibition (TGI) calculated as: $[1-(TV_{tx,\ Day\ last} - TV_{tx,\ Day\ 0})/(TV_{veh,\ Day\ last} - TV_{veh,\ Day\ 0})] \times 100\%$; Regression defined as $TV_{Day\ last} \leq TV_{Day\ 0}$.

6. ORIC-944 Prevents Adagrasib Tumor Relapse in KRAS G12C Adenocarcinoma NSCLC Xenograft Model

ORIC-944 Combined with Adagrasib Prevents Acquired Resistance to Adagrasib in NCI-H2030 NSCLC Xenograft Model



Combination Treatment Regressed All Tumors

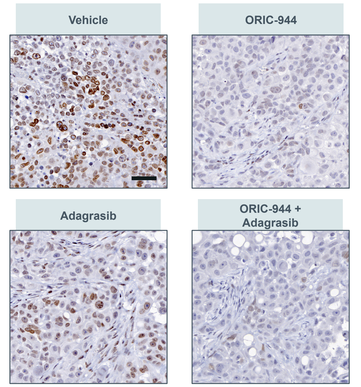


	Vehicle	ORIC-944	Adagrasib	Combination
Median PFS (days)	10	18	22	Not reached

Figure 6. ORIC-944 increases the durability of adagrasib response in KRAS G12C mutant NSCLC. Progression-free survival (PFS) of NCI-H2030 xenograft mice treated orally with vehicle, ORIC-944 100 mg/kg, adagrasib 30 mg/kg or the combination QD for 24 days. PFS is based on tumor volume exceeding 500mm^3 or morbidity; Tumor volume plot on day 23 of study; One-way ANOVA *p=0.013, **p≤0.0015, ***p=0.0001, ****p<0.0001.

7. ORIC-944 Strongly Inhibits H3K27me3 and the Combination with Adagrasib Impacts Cell Proliferation Genes in NSCLC Xenograft

ORIC-944 Potently Reduces H3K27me3



ORIC-944 Enhances Cell Cycle Gene Suppression in Combination With Adagrasib

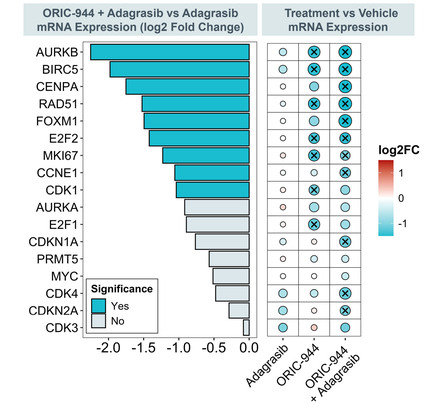


Figure 7. ORIC-944 potently inhibits H3K27me3 and combined with KRAS inhibition impacts cell proliferation genes. (left) Representative images of immunohistochemistry of H3K27me3 from NCI-H2030 xenograft tumors treated tumors following 24 days of treatment with vehicle, ORIC-944 100 mg/kg, adagrasib 30 mg/kg or the combination. Scale bar is 40 μm. (right) Representative cell cycle genes from H2030 tumors treated as indicated for 24 days. The size of each dot is proportional to its –log10(p-value) and an "X" indicates if that comparison is significant (p-value < 0.001 & log2(FC) > 2 & log2(TPM+1) > 2).

CONCLUSIONS

- Combining ORIC-944 PRC2 inhibitor with KRAS inhibition significantly improved efficacy and progression-free survival in KRAS G12C mutant NSCLC and CRC models
  - PRC2 inhibition deepened KRAS inhibitor responses to prevent or delay resistance to KRAS inhibition
  - ORIC-944 led to lineage change in KRAS-mutant CRC xenografts, increased differentiation and thus sensitivity to KRAS inhibition
  - Further mechanistic exploration in KRAS-mutant NSCLC is underway

ORIC-944 is under clinical evaluation in a global prostate cancer Phase 1b trial (NCT05413421)