ORIC-944, a Potent and Selective Allosteric PRC2 Inhibitor, Demonstrates Robust In Vivo Activity in Prostate Cancer Models

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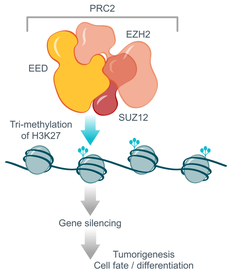
BACKGROUND

The polycomb repressive complex 2 (PRC2) is responsible for the methylation of histone 3 at lysine 27 (H3K27) which leads to long-term transcriptional silencing with implications for cellular functions such as cell growth and differentiation. Core subunit EED directly interacts with H3K27me3 and is essential for the histone methyltransferase activity of PRC2.

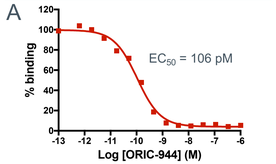


PRC2 dysregulation occurs in multiple solid tumors and hematological malignancies and has been linked to poor prognosis in patients with metastatic prostate cancer.

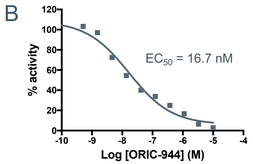
First-generation PRC2 inhibitors which target EZH2 have demonstrated clinical activity in several cancers, yet their pharmacological and ADME properties require high doses that only achieve partial target inhibition in the clinic, and they exhibit drug-drug interaction (DDI) due to CYP liabilities. ORIC-944 is a potent and highly selective allosteric inhibitor of PRC2 via binding the EED subunit with improved drug properties compared to first generation PRC2 inhibitors.

1. ORIC-944 has Picomolar Biochemical Potency and Nanomolar Cell Potency

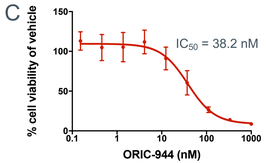
ORIC-944 prevents binding of EED to the H3K27me3 peptide



ORIC-944 inhibits the methyltransferase activity of the PRC2 complex



ORIC-944 inhibits the viability of EZH2 mutant KARPAS-422 DLBCL cells



ORIC-944 inhibits PRC2 activity of EZH2 mutant Pfeiffer DLBCL cells

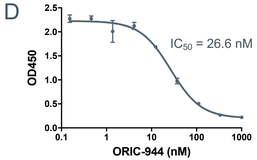


Figure 1. A. 14-point binding curve of ORIC-944 in the RBC EED binding assay; measures inhibition of recombinant EED to bind biotinylated H3K27me3 peptide. **B.** 10-point binding curve of ORIC-944 in the RBC EZH2 complex hotspot methyltransferase assay; monitors transfer of tritiated methyl groups from SAM to core histone proteins. **C.** Activity of ORIC-944 in a 7-day KARPAS-422 Cell Titer-Glo (Promega) viability assay; average cell viability as % of vehicle ± SD. **D.** PD inhibition by ORIC-944 in a 4-day cell-based PRC2 methyltransferase assay (PathScan Trimethyl H3 (Lys27) sandwich ELISA); average H3K27me3 levels by OD450 ± SD.

2. Clean CYP Profile of ORIC-944

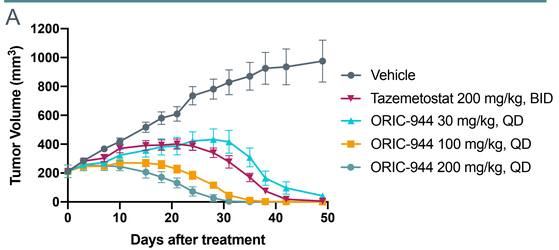
ORIC-944 exhibits clean CYP profile in inhibition and induction studies

CYP Inhibition	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4	IC_{50} >10 µM
CYP Induction	CYP1A2, CYP2B6, CYP3A4 (1 µM)	<2X of vehicle control; <20% of positive control

3. ORIC-944 Induces Regressions in DLBCL

Once daily oral dosing of ORIC-944 significantly induced tumor regressions at all dose levels tested in a diffuse large B-cell lymphoma (DLBCL) model. In vivo efficacy was superior compared to tazemetostat at a clinically relevant dose. ORIC-944 was well tolerated at all dose levels assessed.

ORIC-944 demonstrates dose-dependent and superior efficacy in KARPAS-422 DLBCL xenograft model



ORIC-944 pharmacokinetic/pharmacodynamic study: modulation of H3K27me3 in G401 rhabdoid xenograft tumors is dose- and concentration-dependent

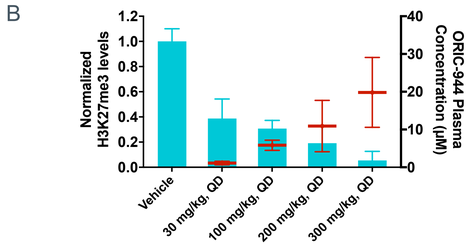


Figure 3. A. KARPAS-422 xenografts carry EZH2 Y641N activating mutation; average tumor volume ± SEM, n=6-8/group; significant difference in all treatment groups vs vehicle, two-tailed t-test. **B.** Samples collected 4 hrs post final dose on day 7. Left axis: average H3K27me3 protein levels by western blot / densitometry ± SD in tumor lysates. Right axis: average ORIC-944 plasma concentration ± SD, n=3/group.

4. Single Agent Efficacy in Prostate Cancer

ORIC-944 shows strong single agent efficacy with oral dosing in C4-2 prostate cancer xenografts, with consistent anti-tumor activity for QD vs. BID dosing

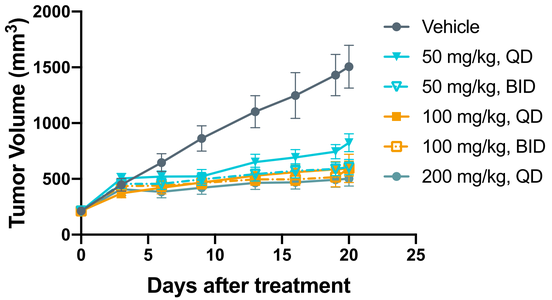


Figure 4. C4-2 model: Average tumor volume ± SEM, with n=7-9/group; mice were castrated when C4-2 tumors reached 200mm^3; significant difference in all treatment groups vs vehicle.

5. Efficacy in Enzalutamide Resistant Tumors

ORIC-944 demonstrates strong single agent activity in enzalutamide-resistant, AR-v7+ prostate cancer xenograft model, 22Rv1

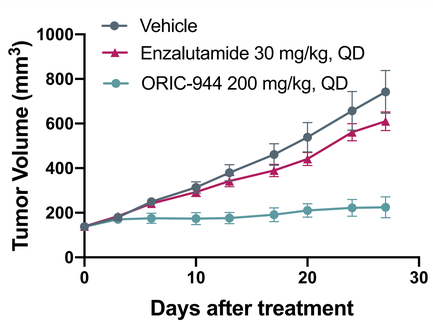
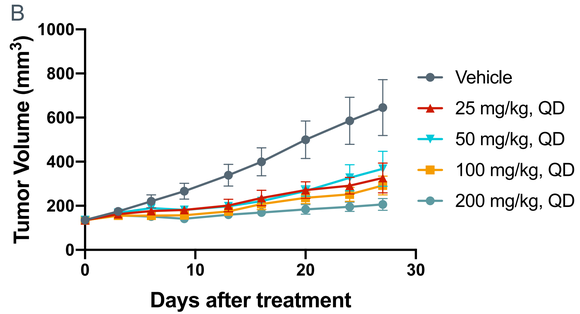


Figure 5. A. 22Rv1 model: Once daily oral administration of enzalutamide or ORIC-944 in 22Rv1 tumor-bearing castrated mice; average tumor volume ± SEM, with n=8-10/group; significant difference in ORIC-944 treatment group vs vehicle.

5. Efficacy in Enzalutamide Resistant Tumors, cont'd

Strong single agent activity with ORIC-944 in 22Rv1 was achieved across once daily doses from 25 to 200 mg/kg



ORIC-944 depletes H3K27me3 in 22Rv1 tumors in a dose-dependent manner

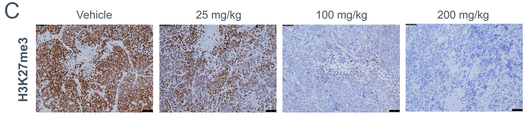


Figure 5. B. Once daily oral administration of ORIC-944 in 22Rv1 tumor-bearing castrated mice; average tumor volume ± SEM, with n=10/group; significant difference in all treatment groups vs vehicle. **C.** Representative IHC images of 22Rv1 tumors treated QDx28 days 4 hrs post final dose of study, H3K27me3 antibody.

CONCLUSIONS

- ORIC-944 is a potent, highly selective, and orally bioavailable allosteric PRC2 inhibitor targeting the EED subunit, with potential best-in-class properties
  - Picomolar biochemical potency and nanomolar cell potency
  - Clean CYP profile eliminating CYP-mediated DDI risk
  - Single agent efficacy superior to tazemetostat in DLBCL
  - Dose-dependent PD modulation of H3K27me3 across models
  - Strong single agent efficacy in prostate xenografts including the enzalutamide-resistant 22Rv1 model

ORIC-944 is being developed for the treatment of prostate cancer with IND filing anticipated in the second half of 2021

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