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 (H3K27me3) which leads to transcriptional silencing, cell growth and differentiation. Core subunits EED directly interact with H3K27me3 and is essential for the histone methylation 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 interactions (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 Biological Potency and Nanomolar Cell Potency

2. Clean CYP Profile of ORIC-944

3. ORIC-944 Induces Regressions in DLBCL

4. Single Agent Efficacy in Prostate Cancer

5. Efficacy in Enzalutamide Resistant Tumors, cont’d

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 tazetostat in DLBCL
- Dose-dependent P450 modulation of H3K27me3 across models
- Strong single agent efficacy in prostate xenografts including the enzalutamide-resistant 22Rv1 model

REFERENCE