ORIC-944, a potent and selective allosteric PRC2 inhibitor with best-in-class properties, demonstrates combination synergy with AR pathway inhibitors in prostate cancer models

Anneleen Daemen, Natalie Yuen, Aleksandr Pankov, Amber Wang, Livia Ulicna, Chelsea Chen, Frank L. Duong, Jason Long, Lori S. Friedman, Melissa R. Junttila

Affiliations
ORIC Pharmaceuticals, Inc., South San Francisco, California, USA

Abstract Body
Background: Polycomb repressive complex 2 (PRC2) dysregulation occurs in multiple tumor types and is associated with poor prognosis in patients with prostate cancer. In patients treated with androgen receptor pathway inhibitors (ARPI), emergence of tumor cell plasticity is associated with resistance to therapy. Dysregulation of epigenetic reprogramming factors, including PRC2, creates an environment that is permissive for such lineage plasticity. Inhibition of the PRC2 complex therefore may provide an opportunity to overcome or prevent the emergence of plasticity in prostate cancer. Notably, emerging clinical trial data has demonstrated the potential of ARPI and PRC2 inhibitor combination therapy to improve outcomes in patients with metastatic prostate cancer.
PRC2 tri-methylates histone H3 at lysine 27 (H3K27me3), leading to long-term transcriptional silencing, a key mechanism regulating cellular functions such as cell growth and differentiation. Three core subunits comprise PRC2: the catalytic subunit enhancer of zeste homolog 2 (EZH2), suppressor of zeste 12 (SUZ12) and embryonic ectoderm development (EED). EED is essential for chromatin recruitment and the histone methyltransferase activity of PRC2. First-generation PRC2 inhibitors exhibit poor drug properties and short half-life requiring twice daily dosing at high doses in patients.
Methods: We developed a second generation PRC2 inhibitor, ORIC-944, an allosteric inhibitor of PRC2 that binds the EED subunit. ORIC-944 is a potent, highly selective, orally bioavailable inhibitor of PRC2 with best-in-class properties. We explored RNA-seq, H3K27me3 ChIP-seq, and ATAC-seq data from in vitro and in vivo efficacy studies for mechanistic insight into the role of PRC2 in prostate cancer lineage plasticity and ORIC-944 + ARPI combination response.
Results: Single agent tumor growth inhibition was observed for ORIC-944 in a spectrum of in vivo prostate cancer models, including AR-positive, AR-mutant, ARv7, ARPI-responsive and ARPI-resistant models, and coincided with luminal state transition as an early event. In both in vitro and in vivo studies, PRC2 inhibitor-induced luminal fate acquisition enhanced response to ARPI treatment in the presence of hormone. At the same time, anti-tumor effects of PRC2 inhibition in prostate cancer require suppression of AR signaling. Adaptation of prostate tumors to the absence of AR signaling involves chromatin and transcriptional reprogramming events to enable reduced reliance on AR signaling and an altered cell state. ORIC-944 restores the luminal transcriptional landscape and restricts lineage-associated plasticity transcription factors, resulting in a luminal state sensitive to AR inhibition and leading to impaired tumor cell viability.
Conclusions: These results position ORIC-944 as a potential best-in-class PRC2 inhibitor for evaluation in combination with ARPIs in patients with metastatic prostate cancer. A phase 1b trial of ORIC-944 in combination with ARPI is ongoing (NCT05413421).

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Conflicts of Interest Disclosure Statement
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