Background

Polycomb repressive complex 2 (PRC2) tri-methylates histone H3 at lysine 27 (H3K27me3) leading to transcriptionally silenced genes.

ORIC-944 is a potent, orally selective allosteric PR2 inhibitor. 22Rv1 prostate cancer xenografts (Baemen et al, AACR Annual Meeting 2021).

Here, to devise and implement a biomarker strategy to inform ORIC-944 dose selection in the ongoing phase I study (NCT05413421), we undertook predilection pharmacology studies and assay development.

1. ORIC-944 Induced Dose-dependent H3K27me3 Reduction in Murine Skin Punch Biopsies In Vivo

2. ORIC-944 Reduced H3K27me3 in Murine Peripheral Blood Monocytes In Vivo

3. ORIC-944 Induced a Time- and Dose-dependent H3K27me3 Reduction in Cell Free Nucleosomes In Vivo

4. H3K27me3 Modulation in c-nucleosomes was Tumor Specific In Vivo

5. Putative PRC2 Target Genes Revealed with Time-dependent Transcriptional Profiling of Xenografts Dosed with ORIC-944

6. Biomarker Plan for the Ongoing Phase 1 Study

Conclusions

This comprehensive biomarker strategy enables the assessment of target engagement and captures exposure-pharmacodynamics in the ongoing phase I study evaluating ORIC-944 as a potential best-in-class PRC2 inhibitor for the treatment of patients with advanced prostate cancer (NCT05413421).