

Rinzimetostat, an allosteric EED inhibitor, promotes and maintains a luminal, AR-dependent phenotype with mechanistic confirmation in patients with mCRPC

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Background: Polycomb repressive complex 2 (PRC2) regulates transcription through H3K27 trimethylation (H3K27me3) and plays a key role in cell growth and differentiation. Elevated PRC2 activity promotes lineage plasticity and is associated with therapeutic resistance and poor prognosis in prostate cancer. Rinzimetostat is a potent, selective, orally bioavailable allosteric inhibitor of PRC2 targeting the EED subunit, with potential best-in-class properties.

Methods: Rinzimetostat was evaluated against EZH2 and EZH1/2 inhibitors in preclinical models of acquired PRC2 inhibitor resistance. Rinzimetostat, alone or in combination with AR pathway inhibition (ARPI), was also assessed across CSPC and CRPC models. Mechanistic effects were characterized by RNA-seq and ATAC-seq. Tumor biopsies and plasma from patients with metastatic CRPC (mCRPC) treated with single-agent rinzimetostat in the Phase 1b ORIC-944-01 study (NCT05413421) were evaluated by immunohistochemistry and cell-free DNA (cfDNA) methylation profiling, respectively.

Results: Rinzimetostat has potential best-in-class drug properties, including reduced drug-drug interaction liabilities and a superior half-life relative to other clinical PRC2 inhibitors. Because targeting EED may provide an advantage in EZH(1/2) inhibitor-acquired resistance contexts, rinzimetostat was evaluated in models representing resistance scenarios to these inhibitors. In prostate cancer cells overexpressing EZH1, a potential resistance mechanism to EZH2 inhibition, the EZH2 inhibitors tazemetostat and mevrometostat lost potency, whereas rinzimetostat retained activity. Rinzimetostat also maintained H3K27me3 inhibition in cells harboring the clinically observed EZH2 Y666N resistance mutation, against which tazemetostat and mevrometostat were inactive, and in cells harboring the EED H213R resistance mutation, which conferred resistance to the EZH1/2 inhibitor valemotostat.

In combination with darolutamide, rinzimetostat demonstrated antitumor activity across in vivo models spanning castration-sensitive and -resistant, ARPI-sensitive and -resistant, and AR-mutant and -wildtype prostate cancer. In preclinical models, rinzimetostat promoted a more luminal, AR-dependent state, with increased AR signaling and enhanced luminal differentiation, and extended ARPI efficacy. Rinzimetostat also restricted chromatin accessibility at binding sites for transcription factors associated with lineage plasticity, including FOXA, HNF1A, and ONECUT2.

Consistent with these preclinical mechanistic findings, plasma cfDNA methylation profiling from patients treated with single-agent rinzimetostat demonstrated epigenetic changes suggestive of increased AR signaling after one treatment cycle in most patients. Tumor biopsies also showed increased expression of the luminal marker PSMA following rinzimetostat treatment.

Conclusions: Preclinical data demonstrate that rinzimetostat can overcome resistance to EZH(1/2) inhibitors, and support a mechanism in which PRC2 inhibition constrains lineage plasticity and promotes a luminal, AR-dependent tumor state. Clinical cfDNA methylation and tumor biopsy findings confirm modulation toward a luminal phenotype in patients treated with rinzimetostat. Together, the convergence of preclinical and clinical evidence supports a mechanism whereby rinzimetostat promotes a luminal, AR-dependent lineage state, providing rationale for the clinical development of combination rinzimetostat and

AR pathway inhibition. The Phase 3 Himalayas-1 study evaluating rinzimetostat plus darolutamide in post-abiraterone mCRPC is enrolling (NCT07723248).

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