EZH2 inhibition as an effective treatment for metastatic castration-resistant prostate cancer

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Introduction

- EZH2 is the catalytic subunit of the PRC2 complex, and interacts with histone H3 on lysine 27, resulting in repression of gene transcription
- EZH2 mutations and increased expression are often observed in cancer, leading to repression of genes associated with suppression and differentiation (1)
- Recent advances in EZH2 catalytic activity have led to the development of EZH2 and PRC2 inhibitors (2, 3), and a growing interest in EZH2 as a potential therapeutic target for prostate cancer
- While accounting for a small percentage of the overall disease incidence (5), mCRPC is often selected for androgen receptor (AR) inhibitors, such as abiraterone and enzalutamide, and exhibits resistance to ARS inhibitors

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- Given this unmet need, and the link between EZH2 and advanced prostate cancer, we hypothesized that EZH2 inhibition may provide a novel treatment option for mCRPC

EZH2 expression is high and polycomb repression signature low in mCRPC

Specificity of CPI-1205 mediated cell growth inhibition

- CPI-1205 combines with ARS inhibitors resulting in synergistic or additive cell growth inhibition

EZH2 inhibition in prostate cancer xenograft models, and combines with enzalutamide for enhanced efficacy in LNCaP model

Conclusions

- CPI-1205 is a potent, reversible, SAM-competitive small molecule inhibitor of EZH2, which can be combined with ARS inhibitor therapies to enhance their efficacy
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EZH2 inhibition remains effective in cell lines with enhanced AR signaling

Transcriptomic analysis reveals CPI-1205 restricts PC growth in manner distinct from enzalutamide, yet enhances enzalactamide effect when combined with abiraterone

Semi-empirical modeling

- Combination of RNA expression from TCGA vs. mCRPC datasets
- Comparison of RNA expression from TCGA vs. mCRPC datasets

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