Background: The Androgen Receptor (AR) remains the principal driver of castration-resistant prostate cancer (CRPC) resulting in the majority of metastatic disease. Most patients initially respond to inhibitors of the AR pathways, but the response is often relatively short-lived. The majority of patients progressing on enzalutamide or abiraterone exhibit genetic alterations in the AR locus, either in the form of amplifications or point mutations in the AR gene. Given these mechanisms of resistance, we aim to utilize the AR protein for the PROTAC (PROtein Targeting Chimeric) technology.

Methods: Here we report on an orally bioavailable small molecule AR PROTAC degrader, ARV-110, that promotes ubiquitination and degradation of AR. This molecule has been characterized in in vitro degradation and functional assays, and DMPK, toxicology and preclinical efficacy studies.

Results: ARV-110 robustly degrades AR in all cell lines tested, with an observed half-maximal degradation concentration (IC50) of ≤1 nM. ARV-110 treatment leads to highly selective AR degradation, as demonstrated by proteomics studies. In VCaP cells, PROTAC-mediated AR degradation suppresses the expression of the AR target gene PSA, inhibits AR-dependent cell proliferation, and induces apoptosis in androgen resistant conditions. Further ARV-110 degrades clinically relevant AR-proteins and retains activity in a high androgen environment. In mouse castrated models, greater than 80% AR degradation is observed at 1 mg/L PO dose. Significant inhibition of tumor growth and AR signaling has been achieved in LNCaP, VCaP and prostate cancer patient derived xenograft (PDX) models. Notably, ARV-110 demonstrates in vivo efficacy and reduction of AR target gene expression in a long term, castrated, enzalutamide-resistant VCaP tumor model.

Conclusions: In summary, we report preclinical data on an orally bioavailable AR PROTAC degrader, ARV-110, that demonstrates efficacy in multiple prostate cancer models. ARV-110 has completed IND-enabling studies and FIH studies are planned for 2019.

PROTAC: PROteolysis Targeting Chimera

Technology developed by Prof. Craig Crews, Yale University

- Arvinas founded in 2013
- Arvinas LLC, New Haven, CT, USA;
- Yale University, New Haven, CT, USA; contact: taavi.nekleasa@arvinas.com

ARV-110 is active in an enzalutamide resistant setting

- ARV-110 robustly degrades AR and blocks the expression of AR target gene ESR1

Summary

Oral administration of ARV-110 demonstrates robust AR degradation and consistent functional activity in various in vitro and in vivo systems thought to represent the shortcomings of current prostate cancer treatment regimens. Complete degradation of AR provides a novel mechanism to address mCRPC.

- Degradation is ideally suited for AR amplified mCRPC (observed in 60-85% of patients progressing on current AR axis targeted therapies).
- PROTACs target AR irrespective of its mutational status and binding partners mCRPC (observed in 10-33% of patients progressing on current AR axis targeted therapies).
- Since PROTACs only need to make a transient interaction with their targets, ARV-110 retains efficacy in a high androgen environment.

ARV-110 has completed IND-enabling studies and FIH studies are planned for 2019.

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