Background: The Androgen Receptor (AR) remains the principal driver of castration-resistant prostate cancer during the metastatic disease process and is a major therapeutic target. Most patients initially respond to inhibitors of the AR pathway, but the response is often relatively short-lived. The majority of patients progressing on enzalutamide or abiraterone exhibit genetic alterations in the AR isoform, either in the form of amplifications or point mutations in the AR gene. These mechanisms of resistance, in our goal is to eliminate the AR protein using the PROTAC himera (PROTAC™) 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 (DC50) of ~1 nM. ARV-110 treatment leads to highly selective AR degradation, as demonstrated by proteomic studies. In VCaP cells, PROTAC-induced AR degradation suppresses the expression of the AR target gene PSA, inhibits AR-dependant cell proliferation, and induces apoptosis in low nanomolar concentrations. Further, ARV-110 degrades clinically relevant mutant AR proteins and retains activity in a high androgen environment. In mouse xenograft studies, greater than 90% AR degradation is observed at a 1 mg/kg PO QD 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, castrate, 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: PROTAC® Technology

Targeted degradation technology developed by Prof. Craig Crews, Yale University

• Arvinas LLC, New Haven, CT, USA; Arvinas Inc., New Haven, CT, USA

Selected publications on PROTAC technology:
1. PNAS. 2020 Jun 22;117(24):12124-9

ARV-110: an oral androgen receptor PROTAC degrader for prostate cancer

ARV-110 is active in an enzalutamide resistant setting

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

• ARV-110 is active in an enzalutamide resistant setting

• In an enzalutamide resistant model, ARV-110 robustly degrades AR and blocks the expression of AR target gene GS

In vitro Characterization of ARV-110

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.

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