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

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Background: The Androgen Receptor (AR) remains the principal driver of castration-resistant prostate cancer during the transition from a localized to metastatic disease. 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 locus, either in the form of amplifications or point mutations in the AR gene. Given these mechanisms of resistance, our goal is to eliminate the AR protein using the PROteolysis TArgeting Chimera (PROTAC™) technology.

Methods: Here we report 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 (DC_{50}) of ~1 nM. ARV-110 treatment leads to highly selective AR degradation, as demonstrated by proteomic 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 at 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 1Q2019.

Conflict of Interest All authors hold equity in Arvinas

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