An oral androgen receptor PROTAC degrader for prostate cancer

Taavi Neklesa, Lawrence B Snyder, Ryan R Willard, Nicholas Vitale, Kanak Raina, Jennifer Pizzano, Deborah A Gordon, Craig M Crews1, John Houston, Andrew P Crew, Ian Taylor

Arvinas LLC, New Haven, CT, USA; 1Yale University, New Haven, CT, USA; contact: taavi.neklesa@arvinas.com

Background: The Androgen Receptor (AR) remains the principal driver of castration-resistant prostate cancer in the transition from a localized to metastatic disease. Most patients initially respond to inhibitors of the AR pathway, but the response is often 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. Given these mechanisms of resistance, our goal is to eliminate the AR protein using the PROTAC technology.

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

Results: ARV-110 robustly degrades AR in all cell lines tested, with an observed 50% degradation concentration (C50) 1 nM. PROTAC-mediated AR degradation suppresses the expression of the AR-target gene PSA, inhibits AR-dependent cell proliferation, and induces potent apoptosis in VCaP cells. 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 1 mg/kg PO QD dose. Significant inhibition of tumor growth and AR signaling can be achieved in an intact and castrate resistant prostate cancer model.

Conclusions: In summary, we report preclinical data on an orally bioavailable AR PROTAC degrader ARV-110 that demonstrates efficacy in enzalutamide-resistant prostate cancer.

**PROTAC: PROteolysis Targenting Chimeras**

- Technology developed by Prof. Craig Crews, Yale University
- Arvinas founded in 2013

*ARV-110 is active in an enzalutamide resistant setting*

- AR amplified, TMPRSS2-ERG translocation positive VCP tumors were passages in castrated, enzalutamide treated (10X) mouse for 3 years.
- In this enzalutamide resistant model, ARV-110 retains efficacy.

**Summary**

Orally bioavailable ARV-110 demonstrates robust AR degragation potency 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 resistance of current prostate cancer treatment regimens. Robust degradation of AR is achieved with ARV-110 in models representing different stages of disease progression. In an androgen sensitive model, ARV-110 robustly degrades AR and blocks the expression of AR target gene EXO5.

This work was partly funded by NIH SBIR grant (8R44CA203199-01)

---

**Abstract**

**Background:** The Androgen Receptor (AR) remains the principal driver of castration-resistant prostate cancer in the transition from a localized to metastatic disease. Most patients initially respond to inhibitors of the AR pathway, but the response is often 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. Given these mechanisms of resistance, our goal is to eliminate the AR protein using the PROTAC technology.

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

**Results:** ARV-110 robustly degrades AR in all cell lines tested, with an observed 50% degradation concentration (C50) 1 nM. PROTAC-mediated AR degradation suppresses the expression of the AR-target gene PSA, inhibits AR-dependent cell proliferation, and induces potent apoptosis in VCaP cells. 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 1 mg/kg PO QD dose. Significant inhibition of tumor growth and AR signaling can be achieved in an intact and castrate resistant prostate cancer model.

**Conclusions:** In summary, we report preclinical data on an orally bioavailable AR PROTAC degrader ARV-110 that demonstrates efficacy in enzalutamide-resistant prostate cancer.

---

**In vitro Characterization of ARV-110**

**In vivo Characterization of ARV-110**

- **Dose response of ARV-110 in cells**
- **Time course of AR levels by ARV-110**

**Selected publications on PROTAC technology:**

1. PMID: 29566136

**Target Validation**

- Ligand for target protein
- E3 ligase for target protein
- Ubiquitin tagged target in high androgen environment
- ARV-110 robustly degrades AR and blocks the expression of AR target gene EXO5.

**Efficacy Study**

- ARV-110 demonstrates efficacy in a high androgen environment
- *ARV-110* demonstrates efficacy in the intact mouse VCaP model, unlike enzalutamide.