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

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Abstract

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.

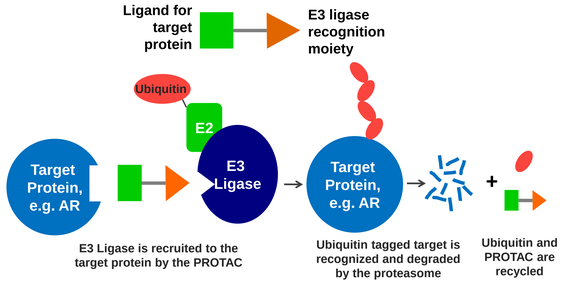
Methods: Here we report an orally bioavailable small molecule AR PROTAC degrader, ARV-110, that promotes ubiquitination and degradation of AR. This molecule has been characterized in *in vitro* degradation and functional assays, and DMPK, toxicology and preclinical efficacy studies.

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.

PROTAC: PROteolysis TArgeting Chimera

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

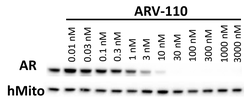


Selected publications on PROTAC technology:

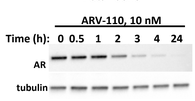
1. PNAS. 2016 Jun 28;113(26):7124-9
2. Nature Chem Biology. 2015 Aug;11(8):611-7
3. Nature Reviews Drug Discov. 2017 Feb;16(2):101-114

In vitro Characterization of ARV-110

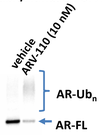
Dose response of ARV-110 in cells in LNCaP cells



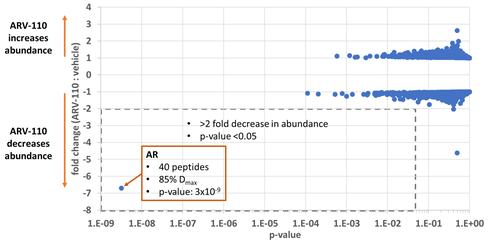
Time course of AR degradation in VCaP cells



ARV-110 leads to poly-ubiquitination of AR

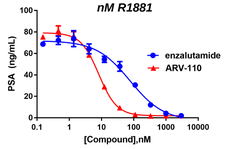


ARV-110 selectively degrades AR in VCaP cells (10 nM; 8 hrs)

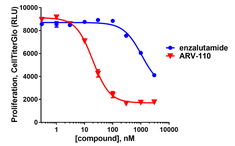


- ARV-110 blocks PSA synthesis, inhibits AR-dependent cell proliferation and causes apoptosis

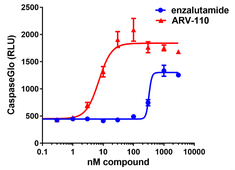
Inhibition of PSA synthesis in LNCaP/AR cells stimulated with 0.1 nM R1881



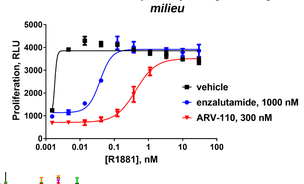
Inhibition of cell proliferation in VCaP cells stimulated with 0.1 nM R1881



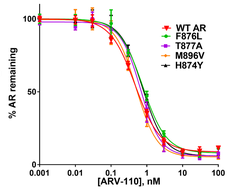
Apoptosis in VCaP cells stimulated with 0.1 nM R1881:



ARV-110 retains potency in high androgen milieu

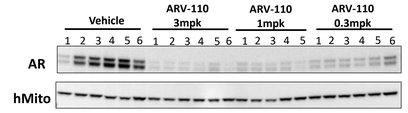


- AR point mutations are amenable to ARV-110 mediated degradation



In vivo Characterization of ARV-110

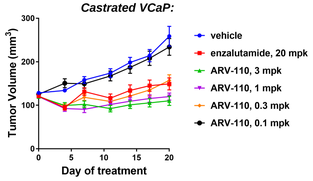
- Orally administered ARV-110 degrades >90% of AR in castrated VCaP tumors



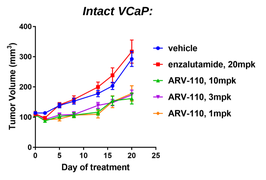
Castrated male mice harboring VCaP tumors were treated with ARV-110 PO QDx3. The tumors were harvested 16 hrs post last dose.

- ARV-110 demonstrates tumor growth inhibition in castrated and intact VCaP models

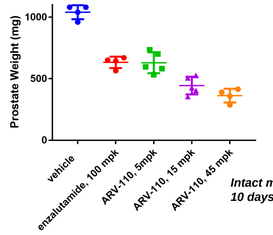
Castrated VCaP:



Intact VCaP:



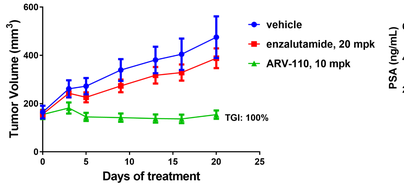
- ARV-110 demonstrates involution of the rat prostate

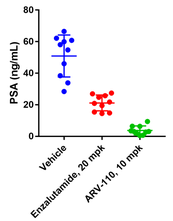


	p-value
Enza v. ARV-110 (15 mpk)	0.0027
Enza v. ARV-110 (45 mpk)	0.0003

Intact male adult rats were treated daily PO for 10 days. Prostates were isolated and weighed.

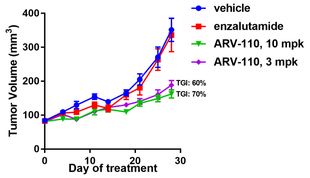
- ARV-110 demonstrates tumor growth inhibition and PSA reductions in an AR-expressing prostate patient derived xenograft (PDX) model TM00298 (Jackson Labs)



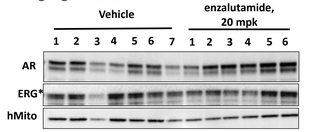


ARV-110 is active in an enzalutamide resistant setting

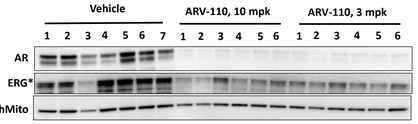
- AR amplified, TMPRSS2-ERG translocation positive VCaP tumors were passaged in castrated, enzalutamide treated (20 mpk) mice for 3 years
- In this enzalutamide resistant model, ARV-110 retains efficacy



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



*VCaP cells harbor TMPRSS2-Erg fusion, putting Erg under transcriptional control of AR



The tumors were harvested at the end of an efficacy study, 16 hrs post last dose.

Summary

Orally bioavailable ARV-110 demonstrates robust AR degradation 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 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 10-15% 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 1Q2019

Acknowledgements

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