2015 AACR-NCI-EORTC Abstract #C95

ARV-330: An Androgen Receptor PROTAC Degrader for Prostate Cancer

Taavi K Neklesa, Meizhong Jin, Andrew P Crew, AnnMarie K Rossi, Ryan R Willard, Hanqing Dong, Kam Siu, Jing Wang, Deborah A Gordon, Xin Chen, Caterina Ferraro, [1]Craig M Crews, Kevin Coleman, James D Winkler

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

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Abstract

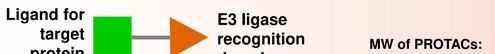
Patients with prostate cancer who progress on therapy often have enhanced Androgen Receptor (AR) signaling due to several mechanisms: increased androgen production, increased AR expression and/or specific AR mutations that render current therapies ineffective. A novel approach to block AR signaling is to specifically target AR for degradation. To do this, we have created AR PROTACs (PROtein-TArgeting Chimeras), bi-functional molecules that have an AR binding moiety on one end and an E3 ligase-recruiting element on the other end, which leads to AR ubiquitination and degradation. We have applied this technology to determine if it could address mechanisms of resistance to current therapy in prostate cancer models.

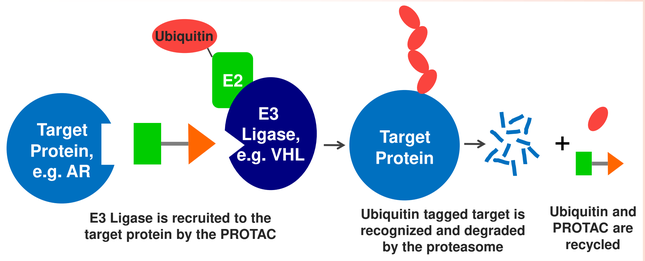
Our lead AR PROTAC, ARV-330, degrades AR in LNCaP and VCaP cells with 50% degradation concentrations (DC50s) < 1nM. AR degradation had functional consequences in cells, suppressing the AR target gene PSA, inhibiting proliferation, and potently inducing apoptosis in VCaP cells, with maximal apoptosis observed around 20 nM, versus 1 uM for enzalutamide. While both ARV-330 and enzalutamide block proliferation of VCaP cells in response to 0.1 nM of the AR agonist R1881, enzalutamide lost anti-proliferative potency with increasing R1881 concentrations, whereas ARV-330 maintained anti-proliferative effects. In cells containing the ARF876L mutation, enzalutamide was ineffective; however, ARV-330 maintained complete effectiveness. In mice, ARV-330 exhibited good pharmacokinetic properties, with t1/2 values of several hours and bioavailability of >80% after sc injection. Treatment of mice with ARV-330, at doses ranging from 0.3 to 10 mg/kg, resulted in reduction of AR protein levels and prostate involution in normal mice and, in mice implanted with VCaP tumors, reduction in plasma PSA and blockade of tumor growth.

In summary, the AR PROTAC ARV-330 removes AR from prostate cancer cells in a potent manner and produces therapeutic effects as a result. This cellular efficacy has translated into biomarker activity and efficacy in animal models, and ARV-330 is now in preclinical development. Thus, targeted degradation of AR may provide a novel mechanism for providing efficacious therapy for patients with prostate cancer for whom current therapies have failed.

PROTAC: PROteolysis TArgeting Chimera

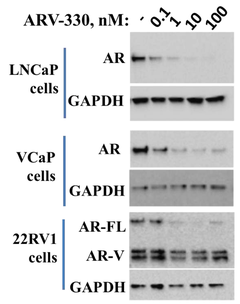
- **Technology developed by Prof. Craig Crews, Yale University**
- **Platform licensed to Arvinas in 2013**



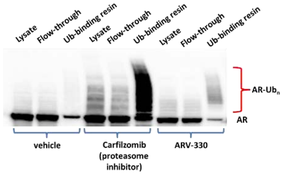


ARV-330: potent, VHL specific and selective AR degrader

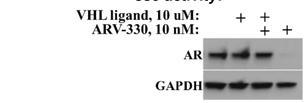
ARV-330 is a sub-nM AR degrader:



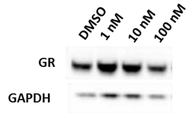
ARV-330 leads to poly-ubiquitination of AR:



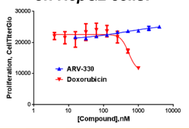
Blocking VHL binding abolishes ARV-330 activity:



ARV-330 does not degrade Glucocorticoid Receptor (GR):

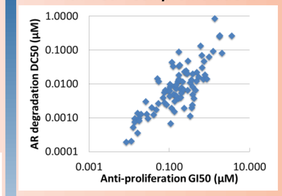


ARV-330 has no antipoliferative effect on HepG2 cells:

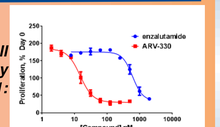


Functional characterization of ARV-330 in vitro

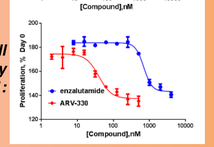
AR degradation potency correlates with VCaP cell proliferation:



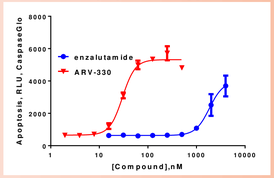
VCaP cell proliferation assay with 0.1 nM R1881:



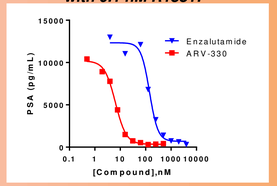
LNCaP/AR cell proliferation assay with 0.1 nM R1881:



Apoptosis in VCaP cells with 0.1 nM R1881:

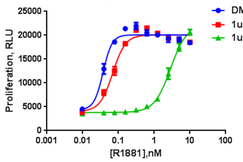


PSA synthesis VCaP cells with 0.1 nM R1881:

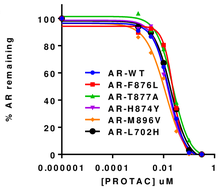


ARV-330 retains potency in high androgen milieu and across AR mutations

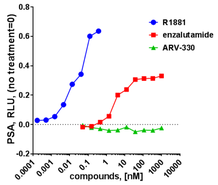
ARV-330 retains potency under high androgen conditions:



ARV-330 degrades all clinically relevant AR mutations:

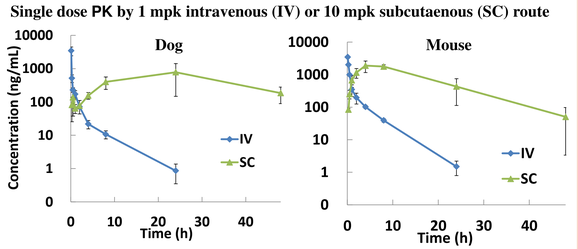


ARV-330 demonstrates no agonist properties in LNCaP/AR-F876L



AR mutation	agonist
F876L	Enzalutamide, ARN-509
T877A	Glucocorticoids, progesterone
H874Y	Glucocorticoids, progesterone
M896V	N/A
L702H	Glucocorticoids

ARV-330 exhibits favorable pharmacokinetic (PK) profile – representative curves shown

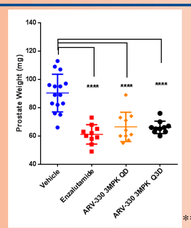


ARV-330 leads to mouse prostate involution

Ten day mouse prostate involution assay treatment arms:

- *Enzalutamide: 30 mpk, PO, QD*
- *ARV-330: 3 mpk, SC, QD*
- *ARV-330: 3 mpk, SC, Q3D*

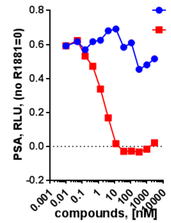
Robust efficacy observed with daily and intermittent dosing of ARV-330



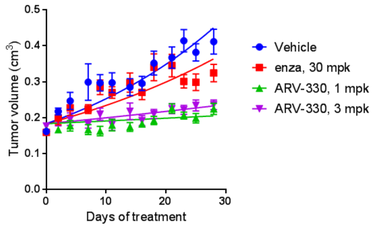
****p=0.0001

ARV-330 shows robust activity in enzalutamide resistant AR-F876L tumor model

ARV-330 suppresses PSA synthesis in LNCaP/AR-F876L: antagonist mode with 0.1 nM R1881



ARV-330 suppresses tumor growth in castrated LNCaP/AR-F876L mice:



Study part of a collaboration with Donald McDonnell lab, Duke University

ARV-330 demonstrates antitumor activity in AR-amplified prostate cancer VCaP xenograft model

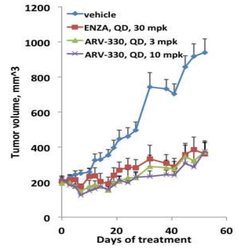
Tumor growth inhibition study:

VCaP cells implanted into CB17 *scid* mice

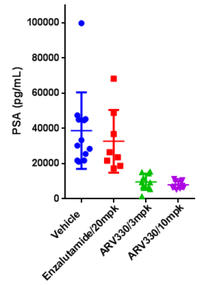
Week 4: Castrate

Week 8: Tumors start re-growing

Daily dosing with enza and PROTAC N=10 / group



Secreted PSA at Day 57:



Summary

The ARV-330 demonstrates pM 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**
- **ARV-330 targets AR irrespective of its mutational status and binding partners**
- **Since PROTACs only need to make a transient interaction with their targets, ARV-330 retains efficacy in a high androgen environment**
- **ARV-330 is currently in IND-enabling studies**
- **Phase 1 is designed to enroll enzalutamide-or abiraterone resistant patients, including patients positive for AR-V7**