**PCF Poster**

# ARV-330: PROTAC Androgen Receptor 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, New Haven, CT, USA; [1]Yale University, New Haven, CT, USA; contact: taavi.neklesa@arvinas.com

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## Abstract

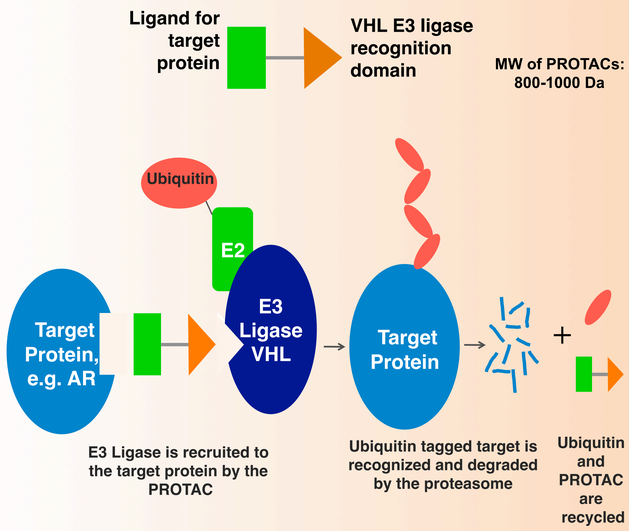
Patients with prostate cancer who progress on therapy often have enhanced Androgen Receptor (AR) signaling due to several mechanisms: increased androgen production, increased AR expression and/or specific AR mutations that render current therapies ineffective. A novel approach to block AR signaling is 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. Treatment of cell with AR PROTACs 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 AR-F876L 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.

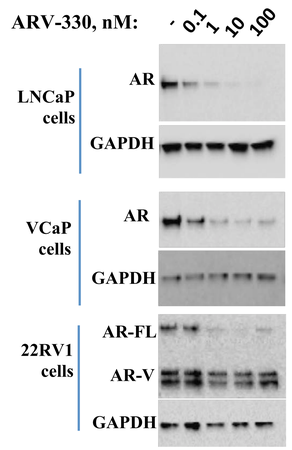
In summary, the AR PROTAC ARV-330 removes AR from prostate cancer cells in a potent manner and produces therapeutic effects as a result. This cellular efficacy has translated into biomarker activity and efficacy in animal models, and ARV-330 is now in preclinical development. Thus, targeted degradation 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**
- **Platform licensed to Arvinas**

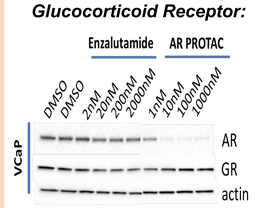



## ARV-330 potently degrades AR in prostate cancer cell lines

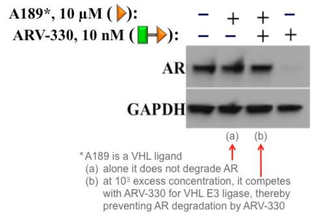



## ARV-330 is a selective AR degrader

*AR PROTAC does not degrade Glucocorticoid Receptor:*



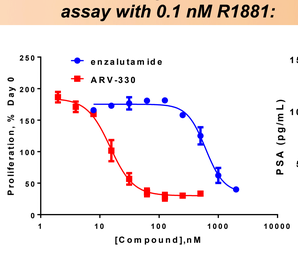

*Blocking VHL binding abolishes AR PROTAC activity:*



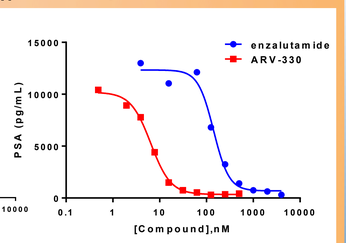

*A189 is a VHL ligand
(a) alone it does not degrade AR
(b) at $10^3$ excess concentration, it competes with ARV-330 for VHL E3 ligase, thereby preventing AR degradation by ARV-330

## Functional characterization of ARV-330 *in vitro*

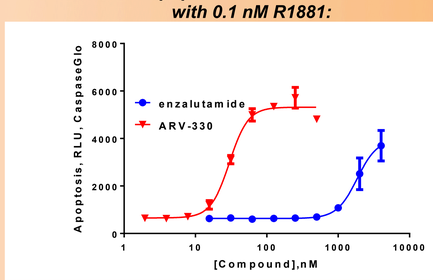
*VCaP cell proliferation assay with 0.1 nM R1881:*




*VCaP PSA synthesis assay with 0.1 nM R1881:*

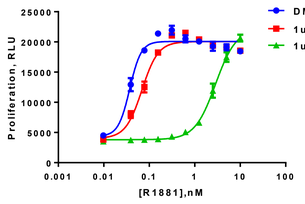



*Apoptosis in VCaP cells with 0.1 nM R1881:*

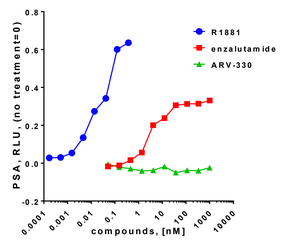



## ARV-330 retains potency in high androgen milieu and across AR mutations

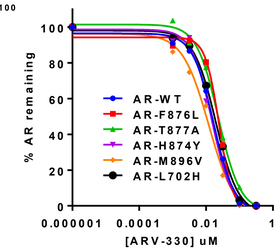
*VCaP cell proliferation with increasing R1881:*




*ARV-330 has no agonist activity in LNCaP/AR-F876L:*

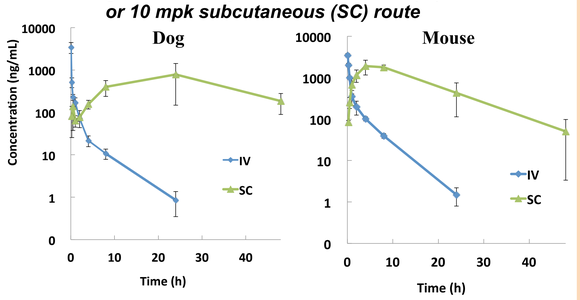



*ARV-330 degrades all clinically relevant AR mutations:*



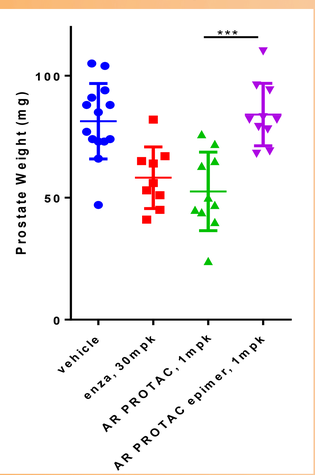

## *ARV-330 has favorable PK profile*

*Single dose PK by 1 mpk intravenous (IV) or 10 mpk subcutaneous (SC) route*




## *Stereoselective anti-androgen activity of ARV-330 in vivo*

*Ten day mouse prostate involution assay:*




*Plasma PK shows equal exposures for ARV-330 and its epimer:*

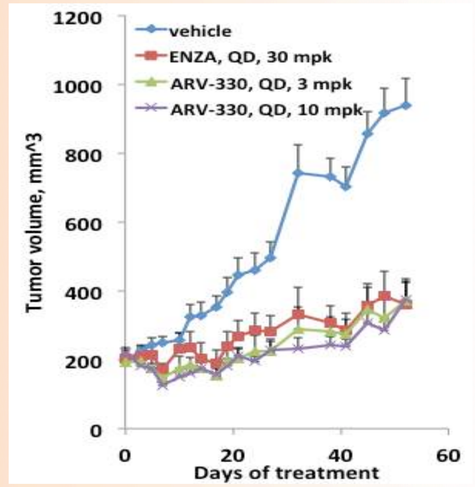
| Drug | Dose | Plasma Conc (nM) 4 hr Post Dose |
|---|---|---|
| Enza | 30 mg/kg PO | 59900 |
| ARV-330 | 1 mg/kg IP | 280 |
| ARV-330 Epimer | 1 mg/kg IP | 290 |

***ARV-330 and its epimer are cis/trans analogues with respect to the hydroxyl residue in the VHL binding moiety. The epimer does not bind VHL, does not degrade AR and does not show in vivo efficacy.***

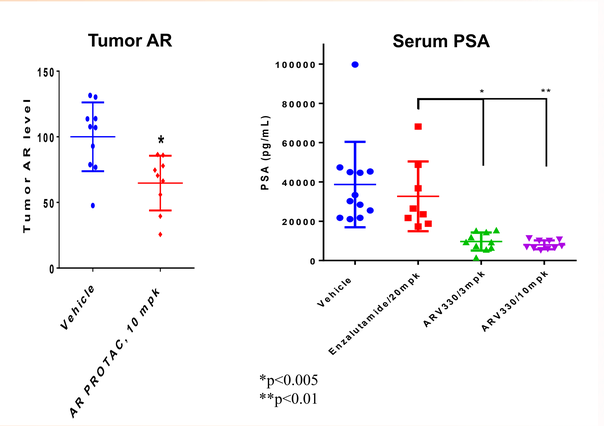
## ARV-330 demonstrates antitumor activity in prostate cancer xenograft model

**VCaP xenograft in castrated mice.**
**ARV-330 was delivered SC QD.**

VCaP cells implanted into CB17 *scid* mice → Week 4: Castrate → Week 8: Tumors start re-growing → Dosing with enza and PROTACs N=10 / group




**Tumor AR degradation and serum PSA in VCaP xenograft 8 hrs post last dose:**




*p<0.005
**p<0.01

## Summary

ARV-330 is a Androgen Receptor PROteolysis TArgeting Chimera (AR PROTAC)

In prostate cancer cells, ARV-330 degrades AR potently, extensively, and selectively

Degradation of AR leads to inhibition of AR transcription, cell proliferation and apoptosis

ARV-330 addresses mechanisms of enzalutamide resistance

ARV-330 has acceptable PK, and demonstrates efficacy and on-target PD in animal models

Targeted degradation of AR may provide efficacious therapy for patients with prostate cancer for whom current therapies have failed

ARV-330 is in IND-enabling studies