**An oral androgen receptor PROTAC degrader for prostate cancer**

Taavi K Neklesa, Lawrence B Snyder, Martha Altieri, Mark Bookbinder, Xin Chen, Andrew P Crew, Craig M Crews,1 Haqing Dong, Deborah A Gordon, Jennifer Macaluso, Kanak Raina, AnnMarie K Rossi, Ian Taylor, Nicholas Vitale, Gan Wang, Jing Wang, Ryan R Willard, Kurt Zimmermann

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

### Abstract

**Background:** The Androgen Receptor (AR) remains the principal driver of metastatic prostate cancer. Most patients initially respond to androgen deprivation therapy, but the resistance to these treatments is a major clinical challenge. Current treatments are not effective in reducing cell numbers in the bone microenvironment.

**Methods:** We describe the development of ARCC-34, an oral androgen receptor PROTAC (PROteolysis Targeting Chimera) that degrades AR in a stable, high androgen environment.

**Results:** ARCC-34 induces a robust reduction in AR protein in a stable, high androgen environment.

**Conclusions:** ARCC-34 is a potential therapeutic candidate to treat AR-mediated prostate cancer.

### Characterization of ARCC-34 - a potent AR PROTAC degrader

- **ARCC-34** induces a robust reduction in AR protein in a stable, high androgen environment.
- **ARCC-34** demonstrates a potent and selective degradation of AR in a stable, high androgen environment.
- **ARCC-34** shows a good correlation between AR degradation and consistent antiproliferative activity.

### Functional characterization of ARCC-34

- **ARCC-34** shows a potent and selective degradation of AR in a stable, high androgen environment.
- **ARCC-34** demonstrates a potent and selective degradation of AR in a stable, high androgen environment.
- **ARCC-34** shows a good correlation between AR degradation and consistent antiproliferative activity.

### Orally bioavailable AR PROTACs ARCC-34 and ARCC-44

- **ARCC-34** and **ARCC-44** possess robust oral bioavailability.
- **ARCC-34** and **ARCC-44** demonstrate a robust reduction in AR protein in a stable, high androgen environment.

### Summary

Orally bioavailable AR PROTACs demonstrate their ability to reduce AR protein levels and inhibit disease progression in a stable, high androgen environment. Complete degradation of AR provides a novel mechanism to address mCRC. Degradation is typically suited for all-arylmediated PROTACs.


### Acknowledgements

This work was partly funded by NIH/GRANT 1R01CA203159-01.