**Identification of Oral Estrogen Receptor PROTAC Degraders for Breast Cancer**

**John J. Flanagan, Yimin Qian, Sheryl M. Gough, Monica Andreoli, Mark Bookbinder, John Bradley, Emma Rousseau, Ryan Willard, Craig M. Andrews, Andrew P. Crew, Ian Taylor, and John Houston**

**Abstract**

ER-positive breast cancers comprise approximately 70-80% of all newly diagnosed cases. Downregulation or degradation of ER is a treatment approach currently used in the clinic to target estrogen receptor signaling. Faslodex, the only clinically-approved ER-downregulator, is administered as a monthly intramuscular injection with limiting pharmaceutical properties. Reasoning that an orally-available estrogen receptor degrader would be beneficial to patients, we have leveraged our experience in targeted protein degradation to generate and characterize novel proteolysis targeting chimeras (PROTACs) against estrogen receptor alpha. PROTACs are heterobifunctional molecules that facilitate the formation of a ternary complex comprised of the PROTAC, a pathogenic target protein of interest and an E3 ligase, which catalyzes the ubiquitylation and subsequent degradation of the target protein via the proteasome.

To identify novel ER degraders (ER PROTACs), we have used several in vitro assays to characterize the extent of target engagement and receptor degradation. Potent ER PROTACs with excellent oral exposure in multiple pre-clinical species were further evaluated in a breast cancer xenograft model. Orally-administered ER PROTACs achieved >80% degradation of estrogen receptor alpha and demonstrated single agent tumor growth inhibition in this disease model. Further, ER PROTAC combination with a CDK4/6 inhibitor resulted in robust anti-tumor activity.

**In vitro characterization of ERα PROTAC**

**PK summary of ERα PROTAC**

**In vivo efficacy with ERα PROTAC**

**ERα PROTAC activity against ERα mutants**

**Summary**

- Orally-bioavailable ER PROTACs demonstrate nanomolar ERα degradation potency and growth inhibition in a variety of wild-type ERα expressing cell lines
- ER PROTACs degrade and inhibit growth of cells expressing clinically-relevant ERα variants, suggesting that ER PROTACs will be active in that resistance setting
- Oral administration of ER PROTAC provided more robust tumor growth inhibition and ERα degradation compared to fulvestrant in an orthotopic MCF7/E2 xenograft model
- Combination of ER PROTAC and CDK4/6 inhibitor demonstrated superior tumor growth inhibition when compared to fulvestrant and CDK4/6 inhibitor combination
- Data supports the clinical development of ER PROTACs for advanced breast cancer

---

**This presentation is the intellectual property of the author/presenter. Contact John.Flanagan@arvinas.com for permission to print and/or distribute.**