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ARV-471, an oral estrogen receptor PROTAC™ protein degrader for breast cancer

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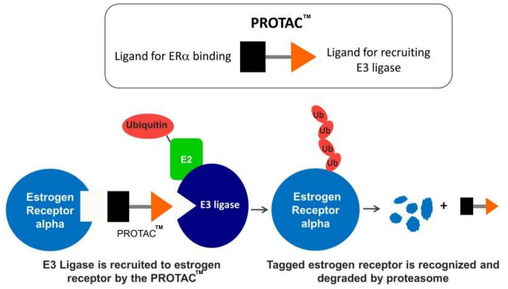
ARVINAS

Abstract

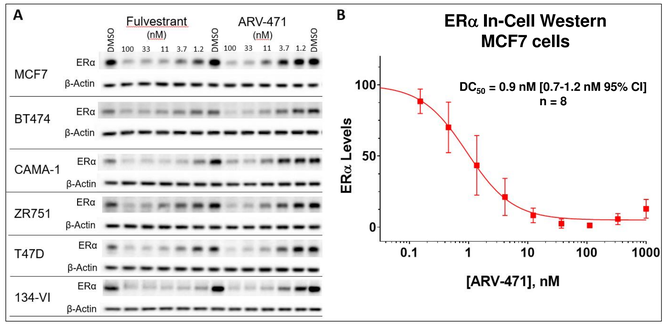
ARV-471, an estrogen receptor (ER) alpha PROTAC™ protein degrader, is a hetero-bifunctional molecule that facilitates the interactions between estrogen receptor alpha and an intracellular E3 ligase complex, leading to the ubiquitylation and subsequent degradation of estrogen receptors via the proteasome. ARV-471 robustly degrades ER in ER-positive breast cancer cell lines with a half-maximal degradation concentration (DC_{50}) of ~ 1 nM. PROTAC-mediated ER degradation decreases the expression of classically-regulated ER-target genes and inhibits cell proliferation of ER-dependent cell lines (MCF7, T47D). Additionally, ARV-471 degrades clinically-relevant ESR1 variants (Y537S and D538G) and inhibits growth of cell lines expressing those variants. In an immature rat uterotrophic model, ARV-471 degrades rat uterine ER and demonstrates no agonist activity. Daily, oral-administration of single agent ARV-471 (3, 10, and 30 mpk) leads to significant anti-tumor activity of estradiol-dependent MCF7 xenografts and concomitant tumor ER protein reductions of >90% at study termination. Moreover, when a CDK4/6 inhibitor is combined with ARV-471 in the MCF7 model, even more pronounced tumor growth inhibition is observed (131% TGI), accompanied by significant reductions in ER protein levels. In an ESR1 Y537S, hormone-independent patient-derived xenograft model, ARV-471 at 10 mpk completely inhibited growth and also significantly reduced mutant ER protein levels. Taken together, the preclinical data of ARV-471 supports its continued development as a best-in-class oral ER PROTAC™ protein degrader.

PROTAC™: PROteolysis TArgeting Chimera

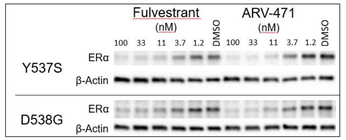


ARV-471 is a potent ERα degrader

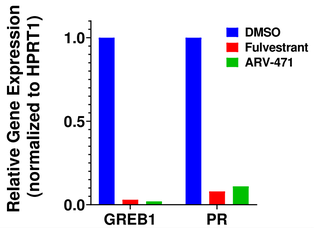
ARV-471 degrades ERα across multiple ER+ cell lines



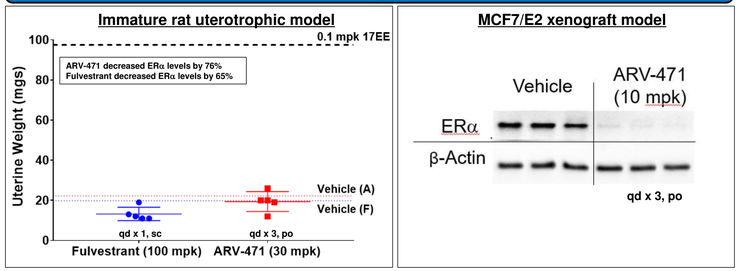
ARV-471 degrades ERα mutants



ARV-471 decreases classic ERα genes

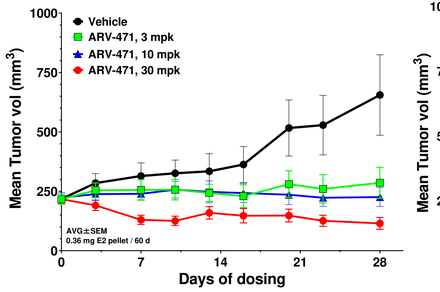


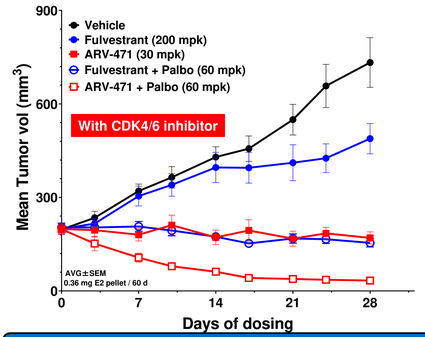
In vivo activity of ARV-471



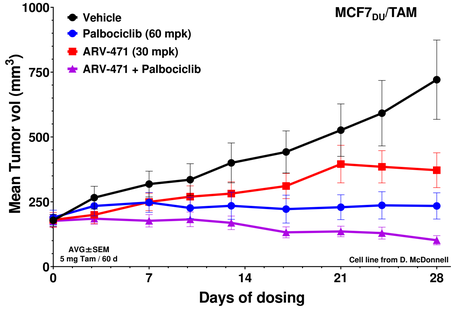
In vivo efficacy with ARV-471 in various ERα-dependent models

MCF7 / estradiol

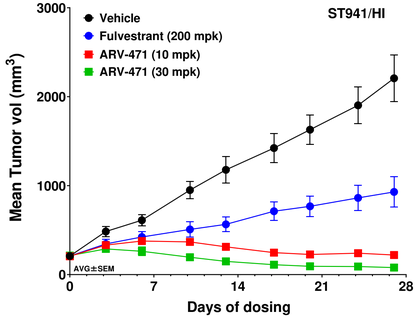




Tamoxifen-resistant MCF7



ESR1 (Y537S) PDX



Fulvestrant dosed weekly via sc ARV-471 dosed daily via po	MCF7 / estradiol		Tamoxifen-Resistant MCF7		ESR1 (Y537S) PDX	
	% TGI	%ERα ↓	% TGI	%ERα ↓	% TGI	%ERα ↓
3 mpk ARV-471	85	95	nd	nd	nd	nd
10 mpk ARV-471	94	97	nd	nd	99	79
30 mpk ARV-471	105 - 124	94	65	73	106	88
200 mpk Fulv	46	None	nd	nd	62	63
With 60 mpk Palbociclib (qd; po)						
30 mpk ARV-471	131	89	113	72	nd	nd
200 mpk Fulv	108	None	nd	nd	nd	nd

Summary

- Orally-bioavailable ARV-471 demonstrates single-digit nanomolar ERα degradation potency in wild-type and variant ERα–expressing cell lines
- ARV-471 displays no agonist activity in rodent uterine tissue
- Oral administration of ARV-471 provides more robust tumor growth inhibition and ERα degradation compared to fulvestrant in an orthotopic MCF7/estradiol xenograft model
- Combination of ARV-471 and CDK4/6 inhibitor palbociclib results in significant tumor regressions and overall superior anti-tumor activity when compared to fulvestrant and palbociclib combination
- ARV-471 inhibits growth of tamoxifen-resistant and ESR1 (Y537S) tumors while also reducing tumor ERα levels
- ARV-471 is currently being developed as a best-in-class, orally-bioavailable ERα degrader