Preclinical characterization of LY3484356, a novel, potent and orally available selective estrogen receptor degrader (SERD)

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Preclinical characterization of LY3484356, a novel, potent and orally bioavailable selective estrogen receptor degrader (SERD)

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#1236

Background

- Nearly 70% of newly diagnosed breast cancers are estrogen receptor alpha (ERα) positive, for which endocrine therapy (ET) is the mainstay of treatment.[1]
- Fulvestrant, the only approved SERD, is administered via intramuscular injection and as a result, is limited by suboptimal systemic pharmacology, as well as patient administration challenges.[2]
- Additionally, approximately 40% of patients develop resistance to ET through mutations in ERα (ESR1) that drive constitutive activation of ERα.[3]
- Novel degraders and antagonists of ERα have been developed, to deliver more ERα target coverage, more convenient dosing, and overcome ERα-mediated acquired resistance.[4]
- Here we describe the preclinical profile of LY3484356, a novel oral SERD and pure ERα antagonist, with potent activity against the wild type and mutant ERα.

Table 1. Biochemical and cellular potency of LY3484356

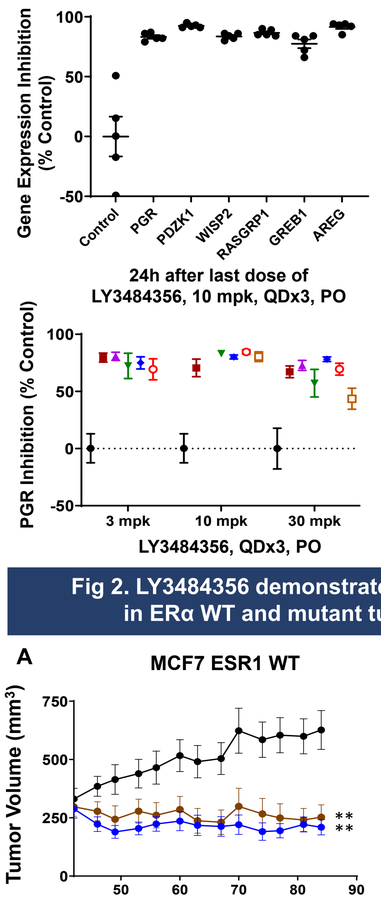
Assay	LY3484356
Wild type ERα binding, K_i, nM	0.31
Y537S ERα binding, K_i, nM	2.79
MCF7 cell ERα wild type degradation, IC_{50}, nM	3
MCF7 cell ERα Y537N degradation, IC_{50}, nM	9.6
MCF7 cell ERα wild type antagonism, IC_{50}, nM	41
MCF7 cell ERα Y537N antagonism, IC_{50}, nM	13
MCF7 cell PRα agonism, IC_{50}, nM	>2000
MCF7 cell ERα wild type proliferation, IC_{50}, nM	3
MCF7 cell ERα Y537N proliferation, IC_{50}, nM	17

IC_{50} values are averages from replicate assays

Assays

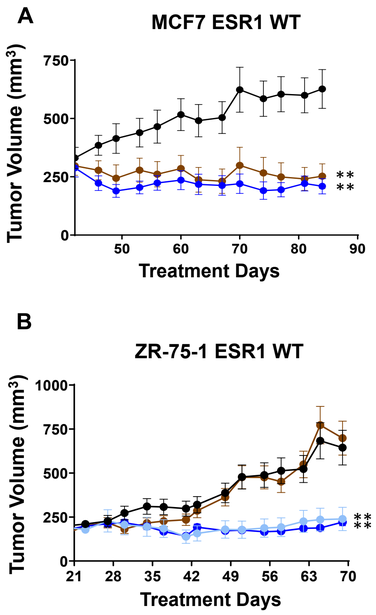
- Degradation/Antagonism: Cells were treated with various concentrations of LY3484356 or fulvestrant in phenol red free DMEM containing 10% charcoal stripped FBS and incubated for 24h.
  - ERα degradation was measured using high content imaging assay
  - The antagonistic activity was measured by measuring PRα inhibition by high content imaging assay
- Proliferation: Cells were treated with various concentrations of LY3484356 or fulvestrant in phenol red free DMEM or RPMI containing 10% FBS and incubated for 6 or 7 days. Cell number was measured using high content imaging assay.

Fig 1. LY3484356 shows potent and sustained ERα signaling modulation *in vivo*



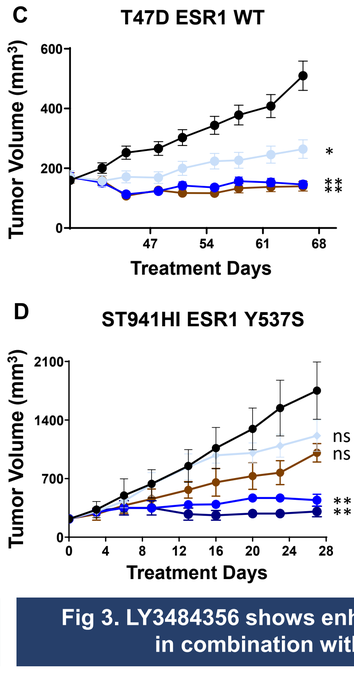
MCF7 xenografts were treated with LY3484356, and plasma and tumor were harvested at indicated timepoints. Inhibition of gene expression was measured by qPCR. GAPDH was used as the control. Data are mean ± SEM.

Fig 2. LY3484356 demonstrates *in vivo* efficacy in ERα WT and mutant tumor models



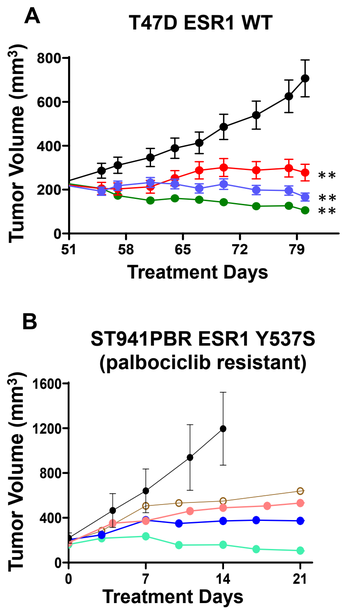
MCF7 and ZR-75-1 ESR1 WT cells were implanted in NOD SCID mice with estrogen pellets or estradiol valerate injections. All treatments were tolerated. Data are mean ± SEM. **p<0.001, treatment vs vehicle control.

Fig 2 (cont). LY3484356 demonstrates *in vivo* efficacy in ERα WT and mutant tumor models



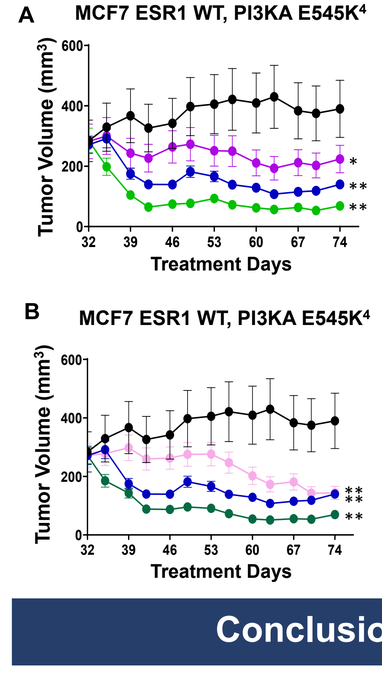
T47D ESR1 WT cells were implanted in NSG mice with estrogen pellets and ST941HI ESR1 Y537S mutant PDX tumor fragments were implanted in athymic nude mice with no estrogen pellets. All treatments were tolerated. Data are mean ± SEM. *p<0.01, **p<0.001, ns – not significant, treatment vs vehicle control.

Fig 3. LY3484356 shows enhanced *in vivo* efficacy in combination with abemaciclib



T47D ESR1 WT cells were implanted in NSG mice with estrogen pellets. ST941PBR ESR1 Y537S PDX tumor fragments were implanted in athymic nude mice. ST941PBR ESR1 Y537S is a palbociclib resistant PDX model rederived in mice. All treatments were tolerated. Data are mean ± SEM, except where n=1. **p<0.001, treatment vs vehicle control.

Fig 4. LY3484356 shows enhanced *in vivo* efficacy in combination with alpelisib or with everolimus



MCF7 ESR1 WT cells were implanted in NOD SCID with estrogen pellets. All treatments were tolerated. Data are mean ± SEM. *p<0.01, **p<0.001, treatment vs vehicle control.

Conclusions

- LY3484356, an oral SERD and a potent degrader of WT and mutant ERα, is a pure antagonist of ERα with no tissue-specific agonism in the uterus. LY3484356:
  - Inhibits ERα-mediated gene transcription as shown by sustained inhibition of a set of ERα-dependent genes
  - Demonstrates *in vivo* efficacy in ESR1 WT and mutant models
  - Demonstrates enhanced *in vivo* efficacy in combination with abemaciclib, alpelisib and everolimus in xenograft models
- The first-in-human Phase 1/2 clinical trial of LY3484356 (EMBER, NCT04188548) is ongoing. A window-of-opportunity clinical trial (EMBER-2, NCT04647487) evaluating the pharmacodynamic effects of LY3484356 in early-stage breast cancer patients will begin in the first half of 2021.

References

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