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

*Presented at:* AACR Annual Meeting 2021  
*Date:* April 10, 2021
Preclinical characterization of LY3484356, a novel, potent and orally bioavailable selective estrogen receptor degrader (SERD)

Shripad V. Bhagwat1, Baohui Zhao1, Weihua Shen1, Cecilia Mur2, Robert Barr2, Lisa J. Kindler2, Almudena Rubio3, Jolie A. Bastian4, Jeffrey D. Cohen5, Brian E. Mattioni5, Eunice Yuen5, Thomas K. Baker5, Mark A. Castaneras6, Dongling Fei6, Jason R. Manro7, Maria Jose Lallena8, Sheng-Bin Peng9, Alfonso De Dios9

1Lux Oncology at Lilly; 2Eli Lilly and Company, Indianapolis, IN

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 are mean ± SEM.

• Novel degraders and antagonists of ERα have been developed, to deliver more ERα target coverage, more convenient dosing, and overcome ERα-mediated acquired resistance.3

• 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 ERαs.

Table 1. Biochemical and cellular potency of LY3484356

<table>
<thead>
<tr>
<th>Assay</th>
<th>LY3484356</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type ERα binding, Kd, nM</td>
<td>0.31</td>
</tr>
<tr>
<td>Y537S ERα binding, Kd, nM</td>
<td>2.79</td>
</tr>
<tr>
<td>MCF7 cell ERα wild type degradation, IC50, nM</td>
<td>0.3</td>
</tr>
<tr>
<td>MCF7 cell ERα Y537N degradation, IC50, nM</td>
<td>9.6</td>
</tr>
<tr>
<td>MCF7 cell ERα wild type antagonism, IC50, nM</td>
<td>41</td>
</tr>
<tr>
<td>MCF7 cell ERα Y537N antagonism, IC50, nM</td>
<td>13</td>
</tr>
<tr>
<td>MCF7 cell PRα agonism, IC50, nM</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>MCF7 cell ERα wild type proliferation, IC50, nM</td>
<td>3</td>
</tr>
<tr>
<td>MCF7 cell ERα Y537N proliferation, IC50, nM</td>
<td>17</td>
</tr>
</tbody>
</table>

IC50 values are averages from replicate assays.

Assays

• Degradation/Agonist: Cells were treated with various concentrations of LY3484356 or fulvestrant in phenol red free DMEM containing 10% FBS and incubated for 6 or 7 days. Cell number was measured using 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 24h.

• ERα degradation was measured using high content imaging assay.

• The antagonist activity was measured by measuring PRα inhibition by high content imaging assay.

• The first-in-human Phase 1/2 clinical trial of LY3484356 (EMBER, NCT01885548) is ongoing, A placebo-controlled, 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.

Conclusions

References

2. van Kruiningen M et al Cancer Discov 2015; 7:72–81