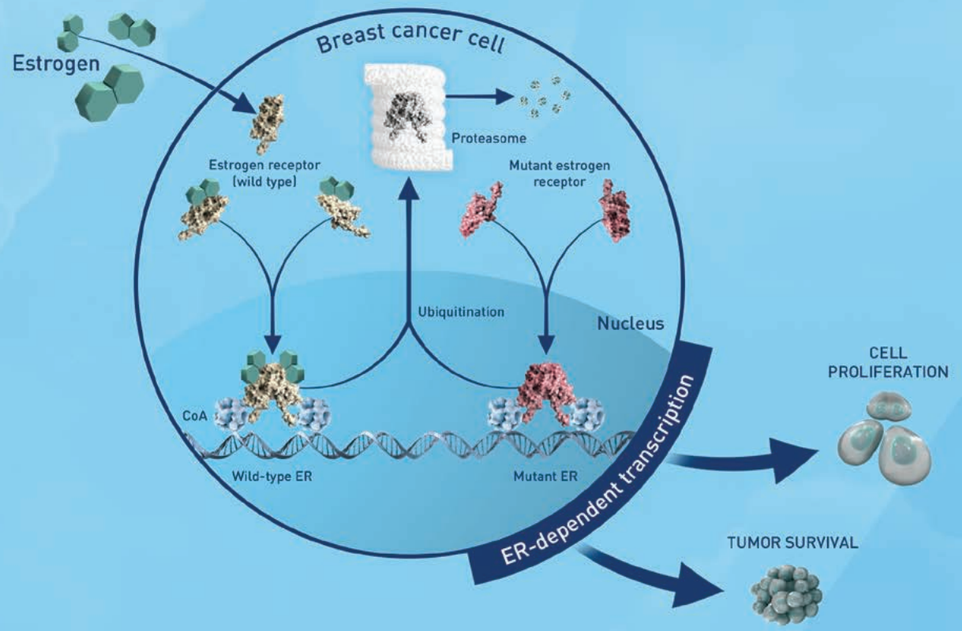
LOXO ONCOLOGY at Lilly

LY3484356

SELECTIVE ER DEGRADER



Gladden AB and Diehl JA[1]; Patel HK and Bihani T[2]; Tecalco-Cruz AC, et al[3]; Wardell SE, et al[4]

Target

Estrogen signaling plays an important role in organ development and growth. In certain cancers, abnormal estrogen signaling via the estrogen receptor is a key component of tumor growth.[5] Disruption of estrogen signaling by selective estrogen receptor degraders (SERDs) is one of the treatment options for patients with estrogen-receptor-positive (ER+) cancers.

Molecule

LY3484356 is an orally available SERD that has demonstrated the inhibition of estrogen signaling and subsequent inhibition of cell proliferation in ER-expressing tumor models.

Clinical Development

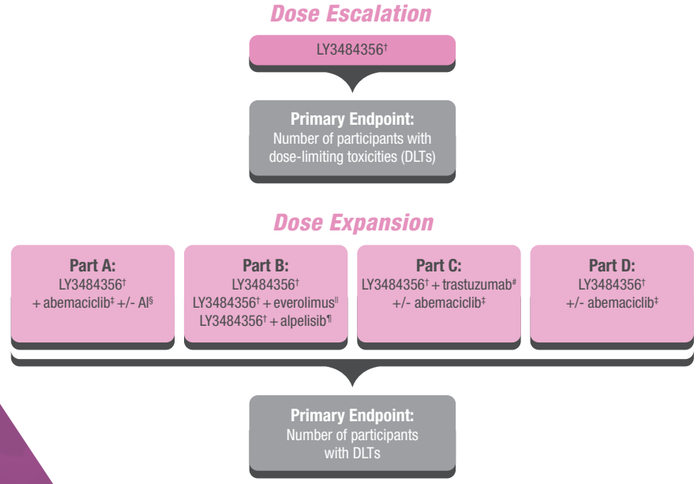
LY3484356 is being investigated in clinical trials in patients with breast cancer or endometrial cancer.

References: 1. Gladden AB, Diehl JA. *J Cell Biochem*. 2005;96(5):906-913. **2.** Patel HK, Bihani T. *Pharmacol Ther*. 2018;186:1-24. **3.** Tecalco-Cruz AC, et al. *Cell Signal*. 2017;34:121-132. **4.** Wardell SE, et al. *Clin Cancer Res*. 2015;21(22):5121-5130. **5.** Lee HR, et al. *Int J Mol Med*. 2012;29:883-890.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

ember CLINICAL TRIAL

A Phase 1a/1b Study of LY3484356 Administered as Monotherapy and in Combination With Anticancer Therapies for Patients With ER+, Locally Advanced or Metastatic Breast Cancer and Other Select Non-breast Cancers*



* This clinical trial is being conducted globally.
† LY3484356 is administered PO QD.
‡ Abemaciclib is administered PO BID.
§ Aromatase inhibitor (AI) is administered PO.
‖ Everolimus is administered PO QD.
¶ Alpelisib is administered PO QD.
# Trastuzumab is administered intravenously Q21D.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

Key Inclusion Criteria

- All study parts:
  - Willing to provide adequate archival tissue sample
  - Willing to use highly effective birth control
  - Adequate organ function
  - Able to swallow capsules
- Participants must have one of the following (dose escalation):
  - Parts A and B: Estrogen-receptor-positive (ER+), HER2-negative breast cancer with evidence of locally advanced, unresectable or metastatic disease and have had the following:
    - Part A: Up to one prior regimen of any kind in the advanced/metastatic setting and no prior CDK4 & 6 inhibitor therapy
    - Part B: Up to two prior regimens; no more than one of which may be endocrine therapy in the advanced/metastatic setting, and must have received a prior CDK4 & 6 inhibitor
    - Cohort E4: No prior everolimus
    - Cohort E5: No prior alpelisib and must have a phosphatidylinositol 3-kinase catalytic α (PIK3Cα) mutation as determined by local testing
  - Part C: ER+, HER2-positive breast cancer with evidence of locally advanced, unresectable or metastatic disease and have had at least two HER2-directed therapies for advanced disease and prior trastuzumab, pertuzumab, and TDM-1 required in any setting
  - Part D: ER+, EEC that has progressed after platinum-containing chemotherapy and no prior fulvestrant or AI therapy
- Participants with ER+, HER2-negative breast cancer enrolled in this study must have had evidence of clinical benefit while on endocrine therapy for at least 24 months in the adjuvant setting or at least 6 months in the advanced/metastatic setting, or have untreated de novo metastatic breast cancer

Key Exclusion Criteria

- Uncontrolled infections such as hepatitis, tuberculosis, or HIV
- Another serious medical condition
- Unstable cancer of the central nervous system
- Pregnant or breastfeeding

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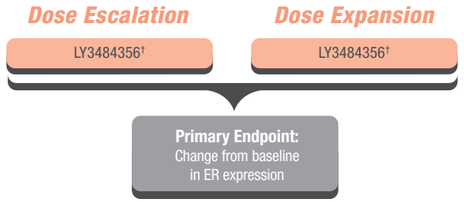
Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT04188548].

ember-2 CLINICAL TRIAL

A Phase 1, Open-Label, Preoperative Window Study Evaluating the Biological Effects of LY3484356 in Postmenopausal Women With Stage I-III, Estrogen-Receptor-Positive, HER2-Negative Breast Cancer*



The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

* This clinical trial is being conducted globally.
† LY3484356 is administered PO.

Key Inclusion Criteria

- Invasive estrogen-receptor-positive (ER+), HER2-negative breast cancer
- Willing and able to provide pre- and on-treatment tumor samples
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Able to swallow capsules

Key Exclusion Criteria

- Bilateral invasive or metastatic breast cancer
- Plan to receive concurrent neoadjuvant therapy with any other nonprotocol anticancer therapy
- Prior therapy (of any kind) for an invasive or noninvasive breast cancer
- Prior radiotherapy to the ipsilateral chest wall for any malignancy
- Prior antiestrogen therapy with raloxifene, tamoxifen, aromatase inhibitor, or other selective estrogen receptor modulator (SERM), either for osteoporosis or prevention of breast cancer
- Prior hormone-replacement therapy within 4 weeks of the start of study treatment
- Major surgery within 28 days prior to randomization to allow for postoperative healing of the surgical wound and site(s)
- Pregnant or breastfeeding
- Certain infections such as hepatitis, tuberculosis, or HIV that are not well controlled
- Another serious medical condition

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Please visit **www.clinicaltrials.gov** for more information on this clinical trial [NCT04647487].

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Pipeline information is current through April 27, 2021.

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