4. SUMMARY OF THE INVENTION

[0006] We engineered ERα expression constructs to express four ESR1 mutations in the ligand binding domain (LBD) of the ERα protein, Y537S, Y537N, Y537C, and D538G, and introduced these expression constructs into cells in culture. These mutations are found in ER^+ metastatic breast cancer patients who have been treated with endocrine therapy. See Jeselsohn *et al.*, *Nature Reviews Clinical Oncology* 12(10): 573-583 (2015); Jeselsohn *et al.*, *Clinical Cancer Research* 20(7): 1757-1767 (2014); Robinson *et al.*, *Nature Genetics* 45(12): 1446-1451(2013); Thomas and Gustafsson, *Trends in Endocrinology and Metabolism* 26(9): 467-476 (2015); and Toy *et al.*, *Nature Genetics* 45(12): 1439-1445 (2013).

[0007] Using an estrogen receptor-responsive reporter construct, we confirmed in an ovarian cell line and in a breast cancer cell line that all mutants are constitutively active as compared to wild type ERα. We then treated the cells with lasofoxifene, a selective ER modulator (SERM), and found that lasofoxifene effectively inhibited the transcriptional activity of the ERα LBD mutants in a dose-response manner, at concentrations that are clinically achievable.

[0008] In a second series of experiments, we confirmed that lasofoxifene is able to reduce viability of the breast cancer cell line MCF7 stably transfected with either the Y537S or D538G ESR1 mutant receptor, at clinically achievable concentrations.

[0009] Accordingly, in a first aspect, a method of treating locally advanced or metastatic breast cancer in women is presented. The method comprises selecting for treatment a patient who has been diagnosed with estrogen receptor positive (ER^+) locally advanced or metastatic breast cancer, and administering to the selected patient an effective amount of lasofoxifene, a pharmaceutically acceptable salt thereof, or a prodrug thereof.

[0009a] In another aspect, the present invention provides a use of lasofoxifene or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for reducing the progression of estrogen receptor positive (ER^+) locally advanced or metastatic breast cancer in a patient, wherein the cancer has at least one gain of function missense mutation within the ligand binding domain (LBD) of the Estrogen Receptor 1 (*ESR1*) gene, and wherein the medicament is to be administered to the patient.

[0010] In various embodiments, the selected patient has previously been treated with one or more lines of endocrine therapy. In certain embodiments, the patient has previously been treated with a plurality of lines of endocrine therapy.

[0011] In some embodiments, the endocrine therapy that the patient has previously been treated with is a selective ER modulator (SERM). In certain embodiments, the SERM is tamoxifen, raloxifene, bazedoxifene, toremifene, or ospemifene.

[0012] In some embodiments, the endocrine therapy that the patient has previously been treated with is a selective ER degrader (SERD). In certain embodiments, the SERD is fulvestrant, RAD1901, ARN-810 (GDC-0810), or AZD9496.

CLAIMS

1. Use of lasofoxifene or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for reducing the progression of estrogen receptor positive (ER^+) locally advanced or metastatic breast cancer in a patient, wherein the cancer has at least one gain of function missense mutation within the ligand binding domain (LBD) of the Estrogen Receptor 1 (*ESR1*) gene, and wherein the medicament is to be administered to the patient.

2. The use of claim 1, wherein the cancer has previously been determined to have at least one gain of function missense mutation within the ligand binding domain (LBD) of the Estrogen Receptor 1 (*ESR1*) gene.

3. The use of claim 1, further comprising the earlier step of: determining that the cancer has at least one gain of function missense mutation within the ligand binding domain (LBD) of the Estrogen Receptor 1 (*ESR1*) gene.

4. The use of claim 1, wherein the at least one of gain of function missense mutation is in any one of amino acids D538, Y537, L536, P535, V534, S463, V392, and E380 of the ERα protein.

5. The use of claim 4, wherein the at least one of gain of function missense mutation is D538G, Y537S, Y537N, Y537C, Y537Q, L536R, L536Q, P535H, V534E, S463P, V392I, or E380Q.

6. The use of claim 4, wherein the at least one of gain of function missense mutation is in amino acid D538 or Y537 of the ERα protein.

7. The use of claim 6, wherein the at least one of gain of function missense mutation is D538G, Y537S, Y537N, Y537C, or Y537Q.

8. The use of claim 1, wherein the patient has previously been treated with one or more lines of endocrine therapy.

9. The use of claim 8, wherein the endocrine therapy that the patient has previously been treated with is a selective ER modulator (SERM), a selective ER degrader (SERD), or an aromatase inhibitor (AI).

10. The use of claim 9, wherein the endocrine therapy that the patient has previously been treated with is an aromatase inhibitor.

11. The use of claim 10, wherein the aromatase inhibitor is exemestane, letrozole, or anastrozole.

12. The use of claim 8, wherein the patient has had disease progression after endocrine therapy.

13. The use of claim 1, wherein the patient is postmenopausal.

14. The use of claim 1, wherein lasofoxifene is to be administered as lasofoxifene tartrate.

15. The use of claim 1, wherein lasofoxifene is to be administered by oral administration.

16. The use of claim 15, wherein lasofoxifene is to be administered at 5 mg/day per os.

17. The use of claim 1, wherein the medicament is to be further administered with an effective amount of cyclin-dependent kinase 4/6 (CDK4/6) inhibitor.