ICI182780 and AZD9496), have been used previously or are being developed in the treatment of ER-positive breast cancers.

[0006] SERMs and AIs are often used as a first-line adjuvant systemic therapy for ER-positive breast cancer. AIs suppress estrogen production in peripheral tissues by blocking the activity of aromatase, which turns androgen into estrogen in the body. However, AIs cannot stop the ovaries from making estrogen. Thus, AIs are mainly used to treat post-menopausal women. Furthermore, as AIs are more effective than the SERM tamoxifen with fewer serious side effects, AIs may also be used to treat pre-menopausal women with their ovarian function suppressed. See, e.g., Francis et al., "Adjuvant Ovarian Suppression in Premenopausal Breast Cancer," the *N. Engl. J. Med.*, 372:436-446 (2015).

[0007] Resistance to endocrine therapy is a challenging aspect in the management of patients with estrogen receptor positive (ER+) breast cancer. Recent studies have demonstrated that acquired resistance can develop after treatment with aromatase inhibitors through the emergence of mutations in the estrogen receptor 1 (ESR1) gene. While initial treatment with these agents may be successful, many patients eventually relapse with drug-resistant breast cancers. Mutations affecting the ER have emerged as one potential mechanism for the development of this resistance. See, e.g., Robinson et al., "Activating ESR1 mutations in hormone-resistant metastatic breast cancer," *Nat Genet.* 45:1446–51 (2013). Mutations in the ligand-binding domain (LBD) of ER are found in 20-40% of metastatic ER-positive breast tumor samples from patients who received at least one line of endocrine treatment. Jeselsohn, et al., "ESR1 mutations—a mechanism for acquired endocrine resistance in breast cancer," *Nat. Rev. Clin. Oncol.*, 12:573-83 (2015).

[0008] Therefore, there remains a need for more durable and effective ER-targeted therapies to overcome some of the challenges associated with current endocrine therapies and to combat the development of resistance.

SUMMARY

[0009] In one aspect, the present disclosure relates to the use of elacestrant, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for inhibiting and degrading a mutant estrogen receptor alpha positive cancer in a subject, wherein the subject was previously treated with an aromatase inhibitor, tamoxifen, and fulvestrant.

[0009a] In another aspect, the present disclosure relates to the use of elacestrant, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for

treating a drug resistant estrogen receptor alpha-positive cancer in a subject having a mutant estrogen receptor alpha,

wherein the mutant estrogen receptor alpha comprises one or more mutations selected from the group consisting of D538G, $Y537X_1$, $L536X_2$, P535H, V534E, S463P, V392I, E380Q and combinations thereof, wherein: X_1 is S, N, or C; and X_2 is R or Q, and wherein the subject was previously treated with an aromatase inhibitor, tamoxifen, and fulvestrant.

[0009c] In one example, the disclosure relates to a method of inhibiting and degrading a mutant estrogen receptor alpha positive cancer in a subject comprising administering to the subject a therapeutically effective amount of elacestrant, or a pharmaceutically acceptable salt or solvate thereof.

[0010] Examples of this example of the disclosure may include one or more of the following optional features. In some examples, the mutant estrogen receptor alpha positive cancer comprises one or more mutations selected from the group consisting of D538G, $Y537X_1$, $L536X_2$, P535H, V534E, S463P, V392I, E380Q and combinations thereof, wherein: X_1 is S, N, or C; and X_2 is R or Q. In some examples, the mutation is Y537S. In some examples, the mutation is D538G. In some examples, the mutant estrogen receptor alpha positive cancer is resistant to a drug selected from the group consisting of anti-estrogens, aromatase inhibitors, and combinations thereof. In some examples, the mutant estrogen receptor alpha positive cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, and pituitary cancer. In some examples, the mutant estrogen receptor alpha positive cancer is advanced or metastatic breast cancer. In some examples, the mutant estrogen receptor alpha positive cancer is breast cancer. In some examples, the subject is a post-menopausal woman. In some examples, the subject is a pre-menopausal woman. In some examples, the subject is a post-menopausal woman who had relapsed or progressed after previous treatment with selective estrogen receptor modulators (SERMs) and/or aromatase inhibitors (AIs). In some examples, the elacestrant is administered to the subject at a dose of from about 200 mg/day to about 500 mg/day. In some examples, the elacestrant is administered to the subject at a dose of about 200 mg/day, about 300 mg/day, about 400 mg/day, or about 500 mg/day. In some examples, the elacestrant is administered to the subject at a dose that is the maximum tolerated dose for the subject. In some examples, the method further comprises identifying the subject for treatment by measuring increased expression of one or more genes selected from ABL1, AKT1, AKT2, ALK, APC, AR, ARID1A, ASXL1, ATM, AURKA, BAP, BAP1, BCL2L11, BCR, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCND3, CCNE1, CDH1, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CEBPA, CTNNB1, DDR2, DNMT3A, E2F3, EGFR, EML4, EPHB2,

ERBB2, ERBB3, ESR1, EWSR1, FBXW7, FGF4, FGFR1, FGFR2, FGFR3, FLT3, FRS2, HIF1A, HRAS, IDH1, IDH2, IGF1R, JAK2, KDM6A, KDR, KIF5B, KIT, KRAS, LRP1B,

What is claimed is:

1. Use of elacestrant, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for inhibiting and degrading a mutant estrogen receptor alpha positive cancer in a subject, wherein the subject was previously treated with an aromatase inhibitor, tamoxifen, and fulvestrant.

2. The use of claim 1, wherein the mutant estrogen receptor alpha positive cancer comprises one or more mutations selected from the group consisting of D538G, $Y537X_1$, $L536X_2$, P535H, V534E, S463P, V392I, E380Q and combinations thereof, wherein: X_1 is S, N, or C; and X_2 is R or Q.

3. The use of claim 2, wherein the mutation is Y537S.

4. The use of claim 2, wherein the mutation is D538G.

5. The use of any one of claims 1-4, wherein the mutant estrogen receptor alpha positive cancer is resistant to, or progresses over, a drug selected from the group consisting of anti-estrogens, aromatase inhibitors, and combinations thereof.

6. The use of any one of claims 1-5, wherein the mutant estrogen receptor alpha positive cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, breast cancer brain metastasis, and pituitary cancer.

7. The use of any one of claims 1-6, wherein the mutant estrogen receptor alpha positive cancer is ~~advanced or metastatic~~ breast cancer.

8. The use of any one of claims 1-7, wherein the mutant estrogen receptor alpha positive cancer is advanced or metastatic breast cancer.

9. The use of any one of claims 1-8, wherein the subject is a post-menopausal woman.

10. The use of any one of claims 1-8, wherein the subject is a pre-menopausal woman.

11. The use of any one of claims 1-8, wherein the subject is a post-menopausal woman who had relapsed or progressed after previous treatment with selective estrogen receptor modulators (SERMs) and/or aromatase inhibitors (AIs).

12. The use of any one of claims 1-11, wherein the elacestrant is to be administered to the subject at a dose of from about 200 mg/day to about 500 mg/day.

13. The use of any one of claims 1-12, wherein the elacestrant is to be administered to the subject at a dose of about 200 mg/day, about 300 mg/day, about 400 mg/day, or about 500 mg/day.

14. The use of any one of claims 1-11, wherein the elacestrant is to be administered to the subject at a dose that is the maximum tolerated dose for the subject.

15. The use of any one of claims 1-14, ~~the method further comprising:~~ ~~identifying the subject~~ wherein the subject is to be identified for treatment by measuring increased expression of one or more genes selected from ABL1, AKT1, AKT2, ALK, APC, AR, ARID1A, ASXL1, ATM, AURKA, BAP, BAP1, BCL2L11, BCR, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCND3, CCNE1, CDH1, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CEBPA, CTNNB1, DDR2, DNMT3A, E2F3, EGFR, EML4, EPHB2, ERBB2, ERBB3, ESR1, EWSR1, FBXW7, FGF4, FGFR1, FGFR2, FGFR3, FLT3, FRS2, HIF1A, HRAS, IDH1, IDH2, IGF1R, JAK2, KDM6A, KDR, KIF5B, KIT, KRAS, LRP1B, MAP2K1, MAP2K4, MCL1, MDM2, MDM4, MET, MGMT, MLL, MPL, MSH6, MTOR, MYC, NF1, NF2, NKX2-1, NOTCH1, NPM, NRAS, PDGFRA, PIK3CA, PIK3R1, PML, PTEN, PTPRD, RARA, RB1, RET, RICTOR, ROS1, RPTOR, RUNX1, SMAD4, SMARCA4, SOX2, STK11, TET2, TP53, TSC1, TSC2, and VHL.

16. The use according to claim 15, wherein the one or more genes is selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1, and MTOR.

17. The use of any one of claims 1-16, wherein the ratio of the concentration of elacestrant or a salt or solvate thereof in the tumor to the concentration of elacestrant or a salt or solvate thereof in plasma (T/P) following administration is at least about 15.

18. Use of elacestrant, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a drug resistant estrogen receptor alpha-positive cancer in a subject having a mutant estrogen receptor alpha, wherein the mutant estrogen receptor alpha comprises one or more mutations selected from the group consisting of D538G, $Y537X_1$, $L536X_2$, P535H, V534E, S463P, V392I, E380Q and combinations thereof, wherein: X_1 is S, N,

or C; and X_2 is R or Q, and wherein the subject was previously treated with an aromatase inhibitor, tamoxifen, and fulvestrant.

19. The use of claim 18, wherein the cancer is resistant to, or progresses over, a drug selected from the group consisting of anti-estrogens, aromatase inhibitors, and combinations thereof.

20. The use of claim 19, wherein the anti-estrogens are selected from the group consisting of tamoxifen, toremifene and fulvestrant and the aromatase inhibitors are selected from the group consisting of exemestane, letrozole and anastrozole.

21. The use of any one of claims 18-20, wherein the drug resistant estrogen receptor alpha-positive cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, breast cancer brain metastasis, and pituitary cancer.

22. The use of any one of claims 18-21, wherein the cancer is advanced or metastatic breast cancer.

23. The use of any one of claims 18-21, wherein the cancer is breast cancer.

24. The use of any one of claims 18-23, wherein the subject is a post-menopausal woman.

25. The use of any one of claims 18-23, wherein the subject is a pre-menopausal woman.

26. The use of any one of claims 18-23, wherein the subject is a post-menopausal woman who had relapsed or progressed after previous treatment with SERMs and/or AIs.

27. The use of any one of claims 18-26, wherein said subject expresses at least one mutant estrogen receptor alpha selected from the group consisting of D538G, Y537S, Y537N, Y537C, E380Q, S463P, L536R, L536Q, P535H, V392I and V534E.

28. The use of any one of claims 18-27, wherein the mutation includes Y537S.

29. The use of any one of claims 18-28, wherein the mutation includes D538G.

30. The use of any one of claims 18-29, ~~the method further comprising:~~ ~~identifying the subject~~ wherein the subject is to be identified for treatment by measuring increased expression of one or more genes selected from ABL1, AKT1, AKT2, ALK, APC, AR, ARID1A, ASXL1, ATM, AURKA, BAP, BAP1, BCL2L11, BCR, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCND3, CCNE1, CDH1, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CEBPA, CTNNB1, DDR2, DNMT3A, E2F3, EGFR, EML4, EPHB2,

ERBB2, ERBB3, ESR1, EWSR1, FBXW7, FGF4, FGFR1, FGFR2, FGFR3, FLT3, FRS2, HIF1A, HRAS, IDH1, IDH2, IGF1R, JAK2, KDM6A, KDR, KIF5B, KIT, KRAS, LRP1B, MAP2K1, MAP2K4, MCL1, MDM2, MDM4, MET, MGMT, MLL, MPL, MSH6, MTOR, MYC, NF1, NF2, NKX2-1, NOTCH1, NPM, NRAS, PDGFRA, PIK3CA, PIK3R1, PML, PTEN, PTPRD, RARA, RB1, RET, RICTOR, ROS1, RPTOR, RUNX1, SMAD4, SMARCA4, SOX2, STK11, TET2, TP53, TSC1, TSC2, and VHL.

31. The use according to claim 30, wherein the one or more genes is selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1, and MTOR.

32. The use of any one of claims 18-31, wherein the elacestrant is to be administered to the subject at a dose of from about 200 to about 500 mg/day.

33. The use of any one of claims 18-32, wherein the elacestrant is to be administered to the subject at a dose of about 200 mg, about 300 mg, about 400 mg, or about 500 mg.

34. The use of any one of claims 18-33, wherein the elacestrant is to be administered to the subject at a dose of about 300 mg/day.

35. The use of any one of claims 18-34, wherein the ratio of the concentration of elacestrant or a salt or solvate thereof in the tumor to the concentration of elacestrant or a salt or solvate thereof in plasma (T/P) following administration is at least about 15.