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. Another mechanism associated with de novo and acquired resistance is the adaptive upregulation of parallel growth-factor signaling pathways as well as crosstalk between these pathways, including those that promote expression of cyclin D1 and activation of Cyclin Dependent Kinase 4 (CDK4) and CDK6 (CDK4/6). 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 CDK4/6 resistance.

## SUMMARY

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

inhibiting and degrading a CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer in a subject.

**[0009a]** In another aspect, the present disclosure relates to use of elacestrant, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a CDK4/6 inhibitor resistant estrogen receptor alpha-positive cancer in a subject having a wild-type estrogen receptor alpha and/or 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.

**[0009b]** In one example, the disclosure relates to a method of inhibiting and degrading a CDK4/6 inhibitor resistant 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 CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib, ribociclib, abemaciclib, or a combination thereof. In some examples, the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib. In some examples, the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to ribociclib. In some examples, the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to abemaciclib. In some examples, the CDK4/6 inhibitor resistant 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 CDK4/6 inhibitor resistant 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 CDK4/6 inhibitor resistant 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 CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is advanced or metastatic breast cancer. In some examples, the CDK4/6 inhibitor resistant 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, 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. In some examples, the one or more genes is selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1, and MTOR. In some examples, 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.

**[0011]** In another example, the disclosure relates to a method of treating a CDK4/6 inhibitor resistant estrogen receptor alpha-positive cancer in a subject having a wild-type estrogen receptor alpha and/or a mutant estrogen receptor alpha, the method comprising administering to the subject a therapeutically effective amount of elacestrant, or a pharmaceutically acceptable salt or solvate thereof, 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.

**[0012]** Examples of this example of the disclosure may include one or more of the following optional features. In some examples, the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib, ribociclib, abemaciclib, or a combination thereof. In some examples, the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib. In some examples, the CDK4/6 inhibitor

resistant estrogen receptor alpha positive cancer is resistant to ribociclib. In some examples, the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to abemaciclib. In some examples, the cancer is resistant to a drug selected from the group consisting of anti-estrogens, aromatase inhibitors, and combinations thereof. In some examples, 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. In some examples, the CDK4/6 inhibitor resistant 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 cancer is advanced or metastatic breast cancer. In some examples, the 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 SERMs and/or AIs. In some examples, the 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. In some examples, the mutation includes Y537S. In some examples, the mutation includes D538G. 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, 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. In some examples, the one or more genes is selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1, and MTOR. In some examples, the elacestrant is administered to the subject at a dose of from about 200 to about 500 mg/day. In some examples, the elacestrant is administered to the subject at a dose of about 200 mg, about 300 mg, about 400 mg, or about 500 mg. In some examples, the elacestrant is administered to the subject at a dose of about 300 mg/day. In some examples, 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.

**[0013]** Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

**[0014]** Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

## BRIEF DESCRIPTION OF FIGURES

**[0015]** The following figures are provided by way of example and are not intended to limit the scope of the claimed invention.

**[0016]** FIG. 1A. The generation of resistance to palbociclib in the ESR1:wild-type LTED cell lines is plotted for the palbociclib sensitive ($palbo^S$) and palbociclib resistant ($palbo^R$) cell lines.

**[0017]** FIG. 1B. The percent growth inhibition (normalized to control as 100%) with respect to the Log[Palbociclib(μM)] is plotted for the $palbo^S$ and $palbo^R$ ESR1:wild-type cell lines.

**[0018]** FIG. 1C. Colony formation assay pictures of the $palbo^S$ and $palbo^R$ ESR1:wild-type cell lines are provided for the control and after treatment with palbociclib (500 nM).

**[0019]** FIG. 1D. A Western blot illustrating the LTED, LTED + palbo, LTED- $palbo^R$, and LTED- $palbo^R$ + palbo models having an ESR1:wild-type gene.

**[0020]** FIG. 2A. The generation of resistance to palbociclib in the ESR1:D538G LTED cell lines plotted for the palbociclib sensitive ($palbo^S$) and palbociclib resistant ($palbo^R$) cell lines.

**[0021]** FIG. 2B. The percent growth inhibition (normalized to control as 100%) with respect to the Log[Palbociclib(μM)] are plotted for the $palbo^S$ and $palbo^R$ ESR1:D538G cell lines.

**[0022]** FIG. 2C. Colony formation assay pictures of the $palbo^S$ and $palbo^R$ ESR1:D538G cell lines are provided for the control and after treatment with palbociclib (500 nM).

**[0023]** FIG. 2D. A Western blot illustrating the LTED, LTED + palbo, LTED- palbo$^{R}$, and LTED- palbo$^{R}$ + palbo models having an ESR1:D538G mutation.

**[0024]** FIG. 3A. The generation of resistance to palbociclib in the ESR1:Y537S LTED cell lines is plotted for the palbociclib sensitive (palbo$^{S}$) and palbociclib resistant (palbo$^{R}$) cell lines.

**[0025]** FIG. 3B. The percent growth inhibition (normalized to control as 100%) with respect to the Log[Palbociclib(μM)] is plotted for the palbo$^{S}$ and palbo$^{R}$ ESR1:Y537S cell lines.

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 CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer in a subject.

2. The use of claim 1, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib, ribociclib, abemaciclib, or a combination thereof.

3. The use of claim 1, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib.

4. The use of claim 1, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to ribociclib.

5. The use of claim 1, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to abemaciclib.

6. The use of any one of claims 1-5, wherein the CDK4/6 inhibitor resistant 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.

7. The use of claim 6, wherein the mutation is Y537S.

8. The use of claim 6, wherein the mutation is D538G.

9. The use of any one of claims 1-8, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is additionally resistant to a drug selected from the group consisting of anti-estrogens, aromatase inhibitors, and combinations thereof.

10. The use of any one of claims 1-9, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, and pituitary cancer.

11. The use of any one of claims 1-10, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is advanced or metastatic breast cancer.

12. The use of any one of claims 1-10, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is breast cancer.

13. The use of any one of claims 1-12, wherein the subject is a post-menopausal woman.

14. The use of any one of claims 1-12, wherein the subject is a pre-menopausal woman.

15. The use of any one of claims 1-12, 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).

16. The use of any one of claims 1-15, wherein the elacestrant is to be administered to the subject at a dose of from about 200 mg/day to about 500 mg/day.

17. The use of any one of claims 1-16, 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.

18. The use of any one of claims 1-15, wherein the elacestrant is to be administered to the subject at a dose that is the maximum tolerated dose for the subject.

19. The use of any one of claims 1-18, the use further comprising:

identification of 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, 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.

20. The use according to claim 19, wherein the one or more genes is selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1, and MTOR.

21. The use of any one of claims 1-20, 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.

22. Use of elacestrant, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a CDK4/6 inhibitor resistant estrogen receptor

alpha-positive cancer in a subject having a wild-type estrogen receptor alpha and/or 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.

23. The use of claim 22, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib, ribociclib, abemaciclib, or a combination thereof.

24. The use of claim 22, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib.

25. The use of claim 22, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to ribociclib.

26. The use of claim 22, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to abemaciclib.

27. The use of any one of claims 22-26, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is additionally resistant to a drug selected from the group consisting of anti-estrogens, aromatase inhibitors, and combinations thereof.

28. The use of claim 27, 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.

29. The use of any one of claims 22-28, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha-positive cancer is selected from the group consisting of breast cancer, uterine cancer, ovarian cancer, and pituitary cancer.

30. The use of any one of claims 22-29, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is advanced or metastatic breast cancer.

31. The use of any one of claims 22-29, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is breast cancer.

32. The use of any one of claims 22-31, wherein the subject is a post-menopausal woman.

33. The use of any one of claims 22-31, wherein the subject is a pre-menopausal woman.

34. The use of any one of claims 22-31, wherein the subject is a post-menopausal woman who had relapsed or progressed after previous treatment with SERMs and/or AIs.

35. The use of any one of claims 22-34, 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.

36. The use of claim 35, wherein the mutation includes Y537S.

37. The use of claim 35, wherein the mutation includes D538G.

38. The use of any one of claims 22-37, the use further comprising:

identification of 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, 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.

39. The use according to claim 38, wherein the one or more genes is selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1, and MTOR.

40. The use of any one of claims 22-39, wherein the elacestrant is to be administered to the subject at a dose of from about 200 to about 500 mg/day.

41. The use of any one of claims 22-40, 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.

42. The use of any one of claims 22-41, 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.