inhibiting and degrading a palbociclib resistant, ribociclib resistant, or abemaciclib 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 palbociclib resistant, ribociclib resistant, or abemaciclib 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

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 palbociclib resistant, ribociclib resistant, or abemaciclib 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.

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

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

5. The use of any one of claims 1-4, 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.

6. The use of claim 5, wherein the mutation is Y537S.

7. The use of claim 5, wherein the mutation is D538G.

8. The use of any one of claims 1-7, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is additionally resistant to, or progresses over, a drug selected from the group consisting of anti-estrogens, aromatase inhibitors, and combinations thereof.

9. The use of any one of claims 1-8, wherein the CDK4/6 inhibitor 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.

10. The use of any one of claims 1-9, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is advanced or metastatic breast cancer.

11. The use of any one of claims 1-9, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is breast cancer.

12. The use of any one of claims 1-11, wherein the subject is a post-menopausal woman.

13. The use of any one of claims 1-11, wherein the subject is a pre-menopausal woman.

14. The use of any one of claims 1-11, 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).

15. The use of any one of claims 1-14, wherein the elacestrant is to be administered to the subject at a dose of from 200 mg/day to 500 mg/day.

16. The use of any one of claims 1-15, 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.

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

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

19. The use of claim 18, wherein the one or more genes is selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1, and MTOR.

20. The use of any one of claims 1-19, 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.

21. Use of elacestrant, or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a palbociclib resistant, ribociclib resistant, or abemaciclib 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.

22. The use of claim 21, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to palbociclib.

23. The use of claim 21, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to ribociclib.

24. The use of claim 21, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is resistant to abemaciclib.

25. The use of any one of claims 21-24, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is additionally resistant to, or progresses over, a drug selected from the group consisting of anti-estrogens, aromatase inhibitors, and combinations thereof.

26. The use of claim 25, 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.

27. The use of any one of claims 21-26, wherein the CDK4/6 inhibitor 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.

28. The use of any one of claims 21-27, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is advanced or metastatic breast cancer.

29. The use of any one of claims 21-27, wherein the CDK4/6 inhibitor resistant estrogen receptor alpha positive cancer is breast cancer.

30. The use of any one of claims 21-29, wherein the subject is a post-menopausal woman.

31. The use of any one of claims 21-29, wherein the subject is a pre-menopausal woman.

32. The use of any one of claims 21-29, wherein the subject is a post-menopausal woman who had relapsed or progressed after previous treatment with SERMs and/or AIs.

33. The use of any one of claims 21-32, 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.

34. The use of claim 33, wherein the mutation includes Y537S.

35. The use of claim 33, wherein the mutation includes D538G.

36. The use of any one of claims 21-35, 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.

37. The use of claim 36, wherein the one or more genes is selected from AKT1, AKT2, BRAF, CDK4, CDK6, PIK3CA, PIK3R1, and MTOR.

38. The use of any one of claims 21-37, wherein the elacestrant is to be administered to the subject at a dose of from 200 to 500 mg/day.

39. The use of any one of claims 21-38, 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.

40. The use of any one of claims 21-39, 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.