SUMMARY

In one aspect, the present disclosure refers to the use of an ERα inhibitor which is (*E*)-*N,N*-dimethyl-4-((2-((5-((*Z*)-4,4,4-trifluoro-1- (3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide, or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor selected from the group consisting of 6-acetyl-8- cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (palbociclib); *N*-(5-((4-ethylpiperazin-1- yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-*1H*-benzo[d]imidazol-6- yl)pyrimidin-2-amine (abemaciclib); and 7-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for combination therapy for treating breast cancer in a patient in need thereof.

In another aspect, the present disclosure refers to a use of an ERα inhibitor which is (E)-N,N-dimethyl-4-((2-((5-((Z)-4,4,4-trifluoro-1- (3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide, or a pharmaceutically acceptable salt thereof in the manufacture of a first medicament, and use of a CDK 4/6 inhibitor selected from the group consisting of 6-acetyl-8- cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one (palbociclib); N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-amine (abemaciclib); and 7- cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib), or a pharmaceutically acceptable salt thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating breast cancer in a patient in need thereof.

In another aspect, the present disclosure refers to a use of an ERα inhibitor which is (E)-N,N-dimethyl-4-((2-((5-((Z)-4,4,4-trifluoro-1- (3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in combinatorial therapy for treating breast cancer in a patient in need thereof, wherein said medicament is to be administered in combination with a CDK 4/6 inhibitor selected from the group consisting of 6-acetyl-8- cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one (palbociclib); N-(5-((4-ethylpiperazin-1- yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6- yl)pyrimidin-2-amine (abemaciclib); and 7- cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide

(ribociclib), or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure refers to a pharmaceutical formulation comprising f (*E*)-*N,N*-dimethyl-4-((2-((5-((*Z*)-4,4,4-trifluoro-1- (3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide, or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor selected from the group consisting of 6-acetyl-8- cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (palbociclib); *N*-(5-((4-ethylpiperazin-1- yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-*1H*-benzo[d]imidazol-6- yl)pyrimidin-2-amine (abemaciclib); and 7- cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib), or a pharmaceutically acceptable salt thereof.

Examples provide a combination therapy, comprising an effective amount of Compound 1 and an effective amount of a CDK4/6 inhibitor. Further examples may provide a combination therapy comprising an effective amount of Compound 2 or Compound 3 and an effective amount of a CDK4/6 inhibitor.In certain examples the CDK 4/6 inhibitor is palbociclib. In other examples the CDK 4/6 inhibitor is ribociclib. In other examples the CDK 4/6 inhibitor is abemaciclib. Combination therapy provided herein may lead to an enhanced reduction in the viability of breast cancer cells and may lead to tumor growth inhibition of breast cancer in patients in need of treatment. In certain examples the breast cancer cells are ER-positive breast cancern cells.

Examples may provide a method of treating breast cancer in a patient in need thereof, including administering to the patient combination of (*E*)-*N,N*-dimethyl-4-((2-((5-((*Z*)-4,4,4-trifluoro-1- (3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof. In some examples the (*E*)-*N,N*-dimethyl-4-((2-((5-((*Z*)-4,4,4-trifluoro-1- (3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof is administered in a daily dosage between 50 mg – 1000 mg. In some examples the (*E*)-*N,N*-dimethyl-4-((2-((5-((*Z*)-4,4,4-trifluoro-1- (3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof is administered in a daily dosage between 50 mg – 500 mg. In some examples the (*E*)-*N,N*-dimethyl-4-((2-((5-

We claim:

1. Use of an ERα inhibitor which is (*E*)-*N,N*-dimethyl-4-((2-((5-((*Z*)-4,4,4-trifluoro-1- (3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide, or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor selected from the group consisting of 6-acetyl-8- cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (palbociclib); *N*-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-*1H*-benzo[d]imidazol-6-yl)pyrimidin-2-amine (abemaciclib); and 7- cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for combination therapy for treating breast cancer in a patient in need thereof.

2. Use of an ERα inhibitor which is (E)-N,N-dimethyl-4-((2-((5-((Z)-4,4,4-trifluoro-1- (3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide, or a pharmaceutically acceptable salt thereof in the manufacture of a first medicament, and use of a CDK 4/6 inhibitor selected from the group consisting of 6-acetyl-8- cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one (palbociclib); N-(5-((4-ethylpiperazin-1- yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6- yl)pyrimidin-2-amine (abemaciclib); and 7- cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib), or a pharmaceutically acceptable salt thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating breast cancer in a patient in need thereof.

3. Use of an ERα inhibitor which is (E)-N,N-dimethyl-4-((2-((5-((Z)-4,4,4-trifluoro-1- (3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in combinatorial therapy for treating breast cancer in a patient in need thereof, wherein said medicament is to be administered in combination with a CDK 4/6 inhibitor selected from the group consisting of 6-acetyl-8- cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one (palbociclib); N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-amine (abemaciclib); and 7- cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib), or a pharmaceutically acceptable salt thereof.

4. The use of any one of claims 1-3, wherein the ERα inhibitor or pharmaceutically acceptable salt thereof is to be administered in a daily dosage between 50 mg – 1000 mg.

5. The use of claim 4, wherein the ERα inhibitor or pharmaceutically acceptable salt thereof is to be administered in a daily dosage of 500 mg.

6. The use of any one of claims 1-3, wherein the CDK 4/6 inhibitor is palbociclib.

7. The use of claim 6, wherein the palbociclib is to be administered in a daily dosage of 75 mg.

8. The use of claim 6, wherein the palbociclib is to be administered in a daily dosage of 100 mg.

9. The use of claim 6, wherein the palbociclib is to be administered in a daily dosage of 125 mg.

10. The use of any one of claims 1-3, wherein the CDK 4/6 inhibitor is ribociclib.

11. The use of claim 10, wherein the ribociclib is to be administered in a daily dosage of 200 mg/day.

12. The use of claim 10, wherein the ribociclib is to be administered in a daily dosage of 400 mg/day.

13. The use of claim 10, wherein the ribociclib is to be administered in a daily dosage of 600 mg/day.

14. The use of any one of claims 1-3, wherein the CDK 4/6 inhibitor is abemaciclib.

15. The use of claim 14, wherein the abemaciclib is to be administered in a daily dosage of 200 mg/day.

16. The use of claim 14, wherein the abemaciclib is to be administered in a daily dosage of 300 mg/day.

17. The use of claim 14, wherein the abemaciclib is to be administered in a daily dosage of 400 mg/day.

18. The use of any one of claims 1-17, wherein the ERα inhibitor or pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or pharmaceutically acceptable salt thereof are to be administered as separate formulations.

19. The use of any one of claims 1-17, wherein the ERα inhibitor or pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or pharmaceutically acceptable salt thereof are to be administered as a single formulation.

20. The use of any one of claims 1-17, wherein the ERα inhibitor or pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or pharmaceutically acceptable salt thereof are to be administered sequentially.

21. The use of any one of claims 1-17, wherein the ERα inhibitor or pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or pharmaceutically acceptable salt thereof are to be administered simultaneously.

22. The use of any one of claims 1-17, and 21, wherein the ERα inhibitor is the free base form of the ERα inhibitor.

23. The use of any one of claims 1-17, and 21, wherein the pharmaceutically acceptable salt of the ERα inhibitor is a hydrochloride salt.

24. A pharmaceutical formulation comprising (*E*)-*N,N*-dimethyl-4-((2-((5-((*Z*)-4,4,4-trifluoro-1- (3-fluoro-1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)pyridin-2-yl)oxy)ethyl)amino)but-2-enamide, or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor selected from the group consisting of 6-acetyl-8- cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (palbociclib); *N*-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-*1H*-benzo[d]imidazol-6-yl)pyrimidin-2-amine (abemaciclib); and 7- cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib), or a pharmaceutically acceptable salt thereof.