SUMMARY

In one aspect, the present disclosure refers to the use of a 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 the manufacture of a medicament for treating breast cancer in a patient in need 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 or a pharmaceutically acceptable salt thereof.

In yet aspect, the present disclosure refers to a 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 for use in therapy.

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-

((*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 of 50 mg – 300 mg.

Examples may provide a method of treating breast cancer in a patient in need thereof, including administering to the patient combination of (*E*)-4-((2-(4-((E)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-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*)-4-((2-(4-((E)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof is administered in a daily dosage between 50 mg – 1000 mg. In some examples the (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof is administered in a daily dosage between 50 mg – 500 mg. In some examples the (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof is administered in a daily dosage of 50 mg – 300 mg.

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-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)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-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)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-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)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-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof is administered in a daily dosage of 50 mg – 300 mg.

In some examples the CDK 4/6 inhibitor is selected from, for example, 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (palbociclib); 7-Cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib); and *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).

In some examples the CDK 4/6 inhibitor is palbociclib. Palbociclib may be administered, for example in a dosage of 75, 100, or 125 mg/day. Typically a dosage is administered orally as a single capsule for 21 consecutive days followed by a 7 day off-treatment period.

In some examples the CDK 4/6 inhibitor is ribociclib. Ribociclib may be administered, for example, in a dosage of 200, 400, or 600 mg/day. Typically ribociclib is administered orally as 200 mg capsules or tables, for 21 consecutive days, followed by a 7 day off-treatment period.

In some examples the CDK 4/6 inhibitor is abemaciclib. Abemaciclib may be administered, for example, in a dosage of 200, 300, or 400 mg/day. Typically abemaciclib is administered twice-daily in dosages of 100, 150, or 200 mg/dose. Abemaciclib is typically administered for 21 consecutive days or 28 consecutive days, followed by a 7 day off-treatment period.

In some examples the CDK 4/6 inhibitor is G1T-38 (2'-((5-(4-isopropylpiperazin-1-yl)pyridin-2-yl)amino)-7', 8'dihydro-6'*H*-spiro[cyclohexane1,9' pyrazino[1',2':1,5] pyrrolo[2,3-d]pyrimidin]-6'-one di-hydrochloride). G1T-38 may be administered, for example, in dosages of 10 mg/kg, 50 mg/kg, 100 mg/kg, 200 mg/kg, 300 mg/kg, 500 mg/kg, or in a range from 10-500 mg/kg or 50-300 mg/kg.

In some examples the CDK 4/6 inhibitor is G1T-28 (2'-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-d]pyrimidin]-6'-one). G1T-28 may be administered, for example, in dosages of between 190 and 200 mg/m^2.

In some examples the CDK 4/6 inhibitor is AT-7519. AT-7519 may be administered, for example, in dosages of 14.4 to 32.4 mg/m^2. AT-7519 may be dosed every three weeks, with drug given on days 1, 4, 8, and 11. In one example the dose is 27 mg/m^2, given at the above frequencies.

In some examples the CDK 4/6 inhibitor is FLX-925. In some examples the CDK 4/6 inhibitor is alvocidib. Alvocidib may be administered, for example, in amounts between 8 and 122 mg/m2. Alvocidib may be administered as a 72 hour infusion. Maximum tolerated dosages of aovocidib have been reported as 40, 50, or 78 mg/m^2.

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 and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered as separate formulations. Typically the time between administration of each formulation does not exceed 12 hours. 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 and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered as a single formulation. 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 and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered sequentially with other treatments. 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 and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered simultaneously.

In some examples the form 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 that is administered is the free base form. In some examples the form 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 that is administered is a hydrochloride salt form.

Further examples may provide a pharmaceutical formulation including (*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 is a free base form. 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 is a hydrochloride salt form.

Further examples may provide use of a 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 in the treatment of breast cancer. Further examples may provide use of a 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 in the preparation of a medicament for treatment of breast cancer.

In some examples the (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N,N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered

as separate formulations. Typically the time between administration of each formulation does not exceed 12 hours. In some examples the (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered as a single formulation. In some examples the (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered sequentially with other treatments. In some examples the (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered simultaneously.

In some examples the form of (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide that is administered is the free base form. In some examples the form (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide that is administered is a hydrochloride salt form.

Further examples may provide a pharmaceutical formulation including (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-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*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide is a free base form. In some examples the (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide is a hydrochloride salt form.

Further examples may provide use of a combination of (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor in the treatment of breast cancer. Further examples may provide use of a combination of (*E*)-4-((2-(4-((*E*)-1-(1*H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)-*N*,*N*-dimethylbut-2-enamide or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor in the preparation of a medicament for treatment of breast cancer.

In some examples the (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered as separate formulations. Typically the time between administration of each

formulation does not exceed 12 hours. In some examples the (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered as a single formulation. In some examples the (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered sequentially with other treatments. In some examples the (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof are administered simultaneously.

In some examples the form of (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide that is administered is the free base form. In some examples the form of (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide that is administered is a hydrochloride salt form.

Further examples may provide a pharmaceutical formulation including (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)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-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide is a free base form. In some examples the (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide is a hydrochloride salt form.

Further examples may provide use of a combination of (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor in the treatment of breast cancer. Further examples may provide use of a combination of (*E*)-*N*,*N*-dimethyl-4-((2-(4-((*E*)-4,4,4-trifluoro-1-(3-fluoro-*1H*-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor in the preparation of a medicament for treatment of breast cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows viability of MCF7.6 cells treated for 144 hours with different doses of

Compound 1 and palbociclib. Compound 1 and palbociclib synergistically inhibit growth of MCF7.6 cells *in vitro*. Inhibition of cell viability was measured using CellTiter-Glo, and Chalice software was used to calculate excess inhibition over Loewe additivity for each Compound 1 and palbociclib dose combination.

FIG. 2 shows viability of MCF7.7 cells treated for 144 hours with different doses of Compound 1 and palbociclib. Compound 1 and palbociclib synergistically inhibit growth of MCF7.7 cells *in vitro*. Inhibition of cell viability was measured using CellTiter-Glo, and Chalice

We claim:

1. Use of a 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 the manufacture of a medicament for treating breast cancer in a patient in need thereof.

2. The use of claim 1, wherein the ERα inhibitor or pharmaceutically acceptable salt thereof is to be administered in a daily dosage between 50 mg – 1000 mg.

3. The use of claim 2, wherein the ERα inhibitor or pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt thereof is to be administered in a daily dosage of 300 mg.

4. The use of any one of claims 1, 2, and 3, wherein the CDK 4/6 inhibitor is 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) and pharmaceutically acceptable salts thereof; *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 pharmaceutically acceptable salts thereof; and 7-cyclopentyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid dimethylamide (ribociclib); 2'-((5-(4-isopropylpiperazin-1-yl)pyridin-2-yl)amino)-7', 8'dihydro-6'*H*-spiro[cyclohexane1,9' pyrazino[1',2':1,5] pyrrolo[2,3-d]pyrimidin]-6'-one di-hydrochloride; 2'-((5-(4-methylpiperazin-1-yl)pyridin-2-yl)amino)-7',8'-dihydro-6'H-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-d]pyrimidin]-6'-one (G1T-28); N-(4-piperidinyl)-4-(2,6-dichlorobenzoylamino)-1*H*-pyrazole-3 carboxamide (AT-7519); 2-Hydroxy-1-[2-[[9-(trans-4-methylcyclohexyl)-9*H*-pyrido[4',3':4,5]pyrrolo[2,3-d]pyrimidin-2-yl]amino]-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl]ethanone (FLX-925); 2-(2-chlorophenyl)-5,7-dihydroxy-8-((3*S*,4*R*)-3-hydroxy-1-methylpiperidin-4-yl)-4*H*-chromen-4-one (alvocidib) and pharmaceutically acceptable salts thereof.

5. The use of claim 4, wherein the CDK 4/6 inhibitor is palbociclib.

6. The use of claim 5, wherein the palbociclib is to be administered in a daily dosage of 75 mg.

7. The use of claim 5, wherein the palbociclib is to be administered in a daily dosage of 100 mg.

8. The use of claim 5, wherein the palbociclib is to be administered in a daily dosage

of 125 mg.

9. The use of claim 4, wherein the CDK 4/6 inhibitor is ribociclib.

10. The use of claim 9, wherein the ribociclib is to be administered in a daily dosage of 200 mg/day.

11. The use of claim 9, wherein the ribociclib is to be administered in a daily dosage of 400 mg/day.

12. The use of claim 9, wherein the ribociclib is to be administered in a daily dosage of 600 mg/day.

13. Theuse of claim 4, wherein the CDK 4/6 inhibitor is abemaciclib.

14. The use of claim 13, wherein the abemaciclib is to be administered in a daily dosage of 200 mg/day.

15. The use of claim 13, wherein the abemaciclib is to be administered in a daily dosage of 300 mg/day.

16. The use of claim 13, wherein the abemaciclib is to be administered in a daily dosage of 400 mg/day.

17. The use of any one of claims 1 and 2-16, 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.

18. The use of any one of claims 1 and 2-16, 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.

19. The use of any one of claims 1 and 2-16, 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.

20. The use of any one of claims 1 and 2-16, 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.

21. The use of any one of claims 1, 2-16, and 20, wherein the ERα inhibitor is the free base form of the ERα inhibitor.

22. The use of any one of claims 1, 2-16, and 20, wherein the pharmaceutically acceptable salt of the ERα inhibitor is a hydrochloride salt.

23. 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 or a pharmaceutically acceptable salt thereof.

24. A 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 for use in therapy.