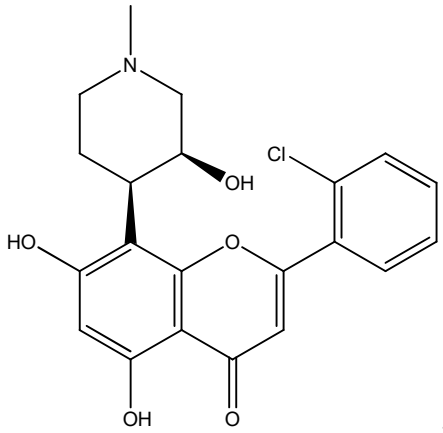


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See, for example, U.S. Patent Application Publication No. US2011189175 and US2011189175; PCT International Patent Application Publication Nos. WO 2000044362; WO 2001041747; WO 2001053293; WO 2001053294; WO 2002022133; WO 2007010946, all of which are incorporated by reference herein.

Despite advances in the treatment of HCC, there is a need to provide improved treatment for HCC. Despite advances in the treatment of IHCC, there is a need to provide improved treatment for IHCC.

SUMMARY

In one aspect, the present invention refers to a pharmaceutical formulation comprising Compound 1 or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof. In a second aspect, the present invention refers to use of N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hepatocellular carcinoma, wherein N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof is to be administered simultaneously or sequentially with a CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof to a patient in need thereof. In a third aspect, the present invention refers to use of N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of intrahepatic cholangiocarcinoma, wherein N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof is to be administered simultaneously or sequentially with a CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof to a patient in need thereof.

Examples provide a combination therapy, comprising an effective amount of Compound 1 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. In other examples the CDK 4/6 inhibitor is G1T38. In other examples the CDK 4/6 inhibitor is G1T28. Combination therapy provided herein may lead to an enhanced reduction in the viability of HCC cells and may lead to tumor growth inhibition of HCC in patients in need of treatment. Combination therapy provided

Claims

1. A pharmaceutical formulation comprising *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof and a CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical formulation of claim 1, comprising a free base form of *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide.

3. The pharmaceutical formulation of claim 1, wherein the pharmaceutically acceptable salt of *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide is a hydrochloride salt form of *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide.

4. The pharmaceutical formulation as defined in claim 1 for use in therapy.

5. Use of N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of hepatocellular carcinoma, wherein N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof is to be administered simultaneously or sequentially with a CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof to a patient in need thereof.

6. Use of N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of intrahepatic cholangiocarcinoma, wherein N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof is to be administered simultaneously or sequentially with a CDK 4/6 inhibitor or a pharmaceutically acceptable salt thereof to a patient in need thereof.

7. The use of claim 5 or claim 6, wherein the *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof is to be administered in a

daily dosage selected from the group consisting of from 50 mg to 600 mg/day, from 200 mg to 400 mg/day, from 50 mg/day to 3000 mg/day, 150 mg/day, 300 mg/day, 600 mg/day, 1000 mg/day, 1500 mg/day, and 2000 mg/day.

8. The use of any one of claims 5 to 7, wherein the *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof is to be administered as a single dosage or in multiple dosages.

9. The use of any one of claims 5 to 8, 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); G1T-38; 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.

10. The use of any one of claims 5 to 9, wherein the CDK 4/6 inhibitor is palbociclib.

11. The use of claim 10, wherein the palbociclib is to be administered in a daily dosage selected from the group consisting of 75 mg/day, 100 mg/day, and 125 mg/day.

12. The use of any one of claims 5 to 9, wherein the CDK 4/6 inhibitor is ribociclib.

13. The use of claim 12, wherein the ribociclib is to be administered in a daily dosage selecting from the group consisting of 200 mg/day, 400 mg/day, and 600 mg/day.

14. The use of any one of claims 5 to 9, 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 selected from the group consisting of 200 mg/day, 300 mg/day, and 400 mg/day.

16. The use of any one of claims 5 to 15, wherein the *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or pharmaceutically acceptable salt thereof are to be administered as separate formulations.

17. The use of any one of claims 5 to 15, wherein the *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or pharmaceutically acceptable salt thereof are to be administered as a single formulation.

18. The use of any one of claims 5 to 15, wherein the *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or pharmaceutically acceptable salt thereof are to be administered sequentially.

19. The use of any one of claims 5 to 15, wherein the *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide or a pharmaceutically acceptable salt thereof and the CDK 4/6 inhibitor or pharmaceutically acceptable salt thereof are to be administered simultaneously.

20. The use of any one of claims 5 to 19, wherein the *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide is the free base form of *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide.

21. The use of any one of claims 5 to 19, wherein the pharmaceutically acceptable salt of *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide is a hydrochloride salt form of *N*-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide.