angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib is reported in U.S. Patent Nos. 7,253,286; 7,612,208; and 9,006,256; all of which are incorporated by reference herein.

Despite advances in the treatment of HCC, it would be useful to provide alternative treatment of HCC, including treatment for patients whose HCC may be resistant to, poorly responsive to, or not completely responsive to current therapeutic regimens.

SUMMARY

Embodiments provide a combination therapy, comprising an amount of Compound 1 and an amount of a lenvatinib in an effective amount in a patient in need of treatment for hepatocellular carcinoma (HCC). Combination therapy provided herein may lead to a synergistic reduction in the viability of HCC cells and may lead to tumor growth inhibition of HCC in patients in need of treatment.

In one aspect, the present disclosure refers to the 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 and 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for combination therapy of hepatocellular carcinoma.

In another aspect, the present disclosure refers to 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, 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure refers to the use of in combination 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 and 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide in the manufacture of a medicament for combination therapy of hepatocellular carcinoma.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows antitumor effects of Compound 1 and lenvatinib in the Hep3B xenograft model of hepatocellular carcinoma. Both Compound 1 and lenvatinib were given orally (PO) once daily (QD) for 53 days. Data represent the mean ±SEM for Tumor Volume.

FIG. 2 shows results of a PDX xenograft in vivo study reported in Example 2.

DETAILED DESCRIPTION OF EMBODIMENTS

Provided herein are combination therapies useful in treating hepatocellular carcinoma (HCC). In some embodiments, the combination therapies include administration of Compound 1 in combination with lenvatinib.

Provided herein are combinations of therapeutic agents and methods for administration of the combination of agents to treat hepatocellular carcinoma. As used herein, a "combination of therapeutic agents" and similar terms refer to a combination of two types of therapeutic agents: (1) Compound 1 and/or pharmacologically active metabolites, salts, solvates, and racemates of Compound 1 and (2) lenvatinib and/or pharmacologically active metabolites, salts, solvates, and racemates of lenvatinib. Pharmacologically active metabolites comprise those that are inactive but converted into pharmacologically active forms in the body after administration.

Compound 1 is a selective, orally bioavailable small molecule FGFR4 inhibitor with the

We claim:

1. 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 and 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for combination therapy of hepatocellular carcinoma.

2. The use of claim 1, 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 between 50 mg to 600 mg.

3. The use of claim 2, 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 between 200 mg to 400 mg.

4. The use of claim 3, 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 of 300 mg.

5. The use of any one of claims 1-4, wherein the 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or pharmaceutically acceptable salt thereof is to be administered in a daily dosage of 8 mg.

6. The use of any one of claims 1-4, wherein the 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or pharmaceutically acceptable salt thereof is to be administered in a daily dosage of 12 mg.

7. The use of any one of claims 1-6, 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 and the 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof are to be administered as separate formulations.

8. The use of any one of claims 1-6, 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 and the 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or a pharmaceutically acceptable

salt thereof are to be administered as a single formulation.

9. The use of any one of claims 1-6, 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 and the 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof are to be administered sequentially.

10. The use of any one of claims 1-6, 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 and the 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof are to be administered simultaneously.

11. The use of any one of claims 1-6, 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 is in free base form.

12. The use of any one of claims 1-6, 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.

13. The use of any one of claims 1-6, wherein the pharmaceutically acceptable salt of 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide is a mesylate salt of 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide.

14. The use of any one of claims 1-6, 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, and wherein the pharmaceutically acceptable salt of 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide is a mesylate salt of 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide.

15. 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, 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

16. The pharmaceutical formulation of claim 15, 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.

17. The pharmaceutical formulation of claim 15, 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.

18. The pharmaceutical formulation of claim 15, wherein the pharmaceutically acceptable salt of 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide is a mesylate salt of 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide.

19. The pharmaceutical formulation of claim 15, 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, and wherein the pharmaceutically acceptable salt of 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide is a mesylate salt of 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide

20. Use of a combination 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 and 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide in the manufacture of a medicament for combination therapy of hepatocellular carcinoma.