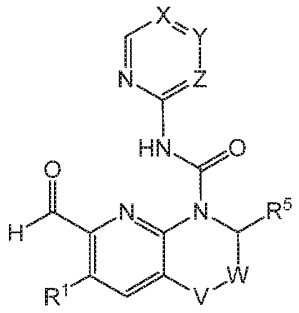
What is claimed:

1. A pharmaceutical combination comprising a selective FGFR4 inhibitor and a bile acid sequestrant.

2. A pharmaceutical combination comprising a FGFR4 inhibitor which is a compound of formula (I) in free form or in pharmaceutically acceptable salt form



(I)

wherein

V is selected from CH_2, O, CH(OH);

W is selected from CH_2, CH_2CH_2, bond;

X is $C(R^X)$ or N;

Y is $C(R^Y)$ or N;

Z is CH or N;

wherein when X is N, Y and Z are not N;

wherein when Y is N, X and Z are not N;

wherein when Z is N, X and Y are not N;

R^X is selected from hydrogen, halogen, haloC_1-C_3alkyl, cyano, C_1-C_6alkyl, hydroxyC_1-C_6alkyl;

R^Y is selected from hydrogen, halogen, C_1-C_3alkyl, C_1-C_6alkoxy, hydroxyC_1-C_3alkoxy, $NR^{Y1}R^{Y2}$, cyano, C_1-C_3alkoxyC_1-C_3alkoxy, C_1-C_3alkoxy-haloC_1-C_3alkoxy, di(C_1-C_3alkyl)aminoC_1-C_6alkoxy, O-$(CH_2)_{0\text{-}1}$-R^{Y3}, $CR^{Y6}R^{Y7}$, S-C_1-C_3alkyl, haloC_1-C_6alkoxy optionally substituted with hydroxy;

or

R^X and R^Y together with the ring to which they are attached form a bicyclic aromatic ring system optionally further comprising one or two heteroatoms selected from N, O, or S, which ring system is optionally substituted with C_1-C_3alkyl;

R^{Y1} is hydrogen and

R^{Y2} is selected from C_1-C_6alkyl; hydroxyC_1-C_6alkyl; haloC_1-C_6alkyl optionally substituted with hydroxy; C_1-C_4alkoxyC_1-C_6alkyl; haloC_1-C_3alkoxyC_1-C_6alkyl; $(CH_2)_{0-1}$-R^{Y4}; di(C_1-C_3alkyl)aminoC_1-C_6alkyl substituted with hydroxy; bicycloC_5-C_8alkyl optionally substituted with hydroxyC_1-C_3alkyl; phenyl substituted with $S(O)_2$-$CH(CH_3)_2$; C_2-C_3alkylsulfonic acid;

or

R^{Y1} and R^{Y2} together with the N atom to which they are attached form a saturated or unsaturated non-aromatic 6-membered heterocyclic ring which may contain an O atom, which ring may be substituted once or twice by R^{Y5};

R^{Y3} is selected from quinuclidinyl, a 4-, 5- or 6-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O or S, or a 5- or 6-membered aromatic heterocyclic ring, which saturated or aromatic heterocyclic ring is optionally substituted with C_1-C_3alkyl and/or oxo;

R^{Y4} is a 4-, 5- or 6-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O, or S, which ring is optionally substituted with C_1-C_3alkyl;

R^{Y5} is independently selected from C_1-C_3alkyl, hydroxy, di(C_1-C_3alkyl)aminoC_1-C_3alkyl,

or

two R^{Y5} attached at the same carbon atom form together with the carbon atom to which they are attached a 5-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O or S, which ring is substituted once or more than once with C_1-C_3alkyl;

R^{Y6} and R^{Y7} together with the carbon atom to which they are attached form a 6-membered saturated or unsaturated non-aromatic heterocyclic ring comprising one heteroatom selected from N, O or S;

R^1 is selected from hydrogen; halogen; C_1-C_3alkyl; haloC_1-C_3alkyl; hydroxyC_1-C_3alkyl; C_3-C_6cycloalkyl; $CH_2NR^2R^3$; $CH(CH_3)NR^2R^3$; C_1-C_3alkoxyC_1-C_3alkyl; CH_2CO_2H; C(O)H; C_1-C_3alkoxy; a 5- or 6-membered saturated heterocyclic or aromatic heterocyclic ring comprising at least one heteroatom selected from N, O or S, which ring is optionally substituted once or more than once with a group independently selected from C_1-C_3alkyl, haloC_1-C_3alkyl, oxetanyl or oxo;

R^2 is selected from C_1-C_3alkyl, di(C_1-C_3alkyl)aminoC_1-C_3alkyl;

R^3 is selected from C_1-C_3alkyl, C(O)C_1-C_3alkyl, C(O)-CH_2-OH, C(O)-CH_2-O-CH_3, C(O)-CH_2-$N(CH_3)_2$, $S(O)_2CH_3$;

or

R^2 and R^3 together with the N atom to which they are attached form a saturated 5- or 6-membered ring optionally comprising one additional heteroatom selected from N, N-oxide, O or S, which ring may be substituted once or more than once with R^4;

R^4 is independently selected from C_1-C_3alkyl, di(C_1-C_3alkyl)amino, $C(O)CH_3$, hydroxy;
or
two R^4 attached at the same carbon atom form together with the carbon atom to which they are attached a 4-, 5- or 6-membered non-aromatic heterocyclic ring comprising at least one heteroatom selected from N, O or S;
or
two R^4 attached at the same ring atom form an oxo group;
R^5 is selected from hydrogen or C_1-C_3alkyl.

3. The pharmaceutical combination according to claim 1 or 2, wherein the FGFR4 inhibitor is N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.

4. The pharmaceutical combination according to any of claims 1 to 3, wherein the FGFR4 inhibitor is N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form.

5. The pharmaceutical combination according to any of the preceding claims, wherein the bile acid sequestrant is selected from cholestyramine, colesevelam, colesevalam hydrochloride, colestipol or selevamer preferably wherein the bile acid sequestrant is cholestyramine.

6. A pharmaceutical combination according to any of claims 1 to 5 for use as a medicament.

7. The pharmaceutical combination according to claim 6, for use in the treatment of cancer, in particular liver cancer.

8. A pharmaceutical combination according to any of claims 1 to 5 for use in reducing or preventing side effects associated with FGFR4 inhibition therapy wherein the side effect does not include diarrhea.
9. A pharmaceutical combination according to any of claims 1 to 5 for use in reducing or preventing an increase of liver enzymes in the serum, plasma or blood of a subject taking FGFR4 inhibition therapy.
10. A pharmaceutical combination for use according to claim 8 or 9 wherein FGFR4 inhibition therapy is administration of an FGFR4 inhibitor as described in claim 2 or

administration of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, or a pharmaceutically acceptable salt thereof.

11. A bile acid sequestrant for use in reducing or preventing side effects associated with FGFR4 inhibition therapy wherein the side effect does not include diarrhea.

12. A bile acid sequestrant for use in reducing or preventing side effects associated with FGFR4 inhibition therapy, wherein the side effects comprise the increase of liver enzymes in the serum, plasma or blood of a subject taking FGFR4 inhibition therapy, optionally wherein the FGFR4 inhibition therapy is for the treatment of liver cancer.

13. A bile acid sequestrant for use according to claim 11 or 12, wherein the liver enzyme is alanine aminotransferase (ALT).

14. A bile acid sequestrant for use according to claim 11, wherein the side effects comprise the increase of miRNA122 in a subject taking FGFR4 inhibition therapy.

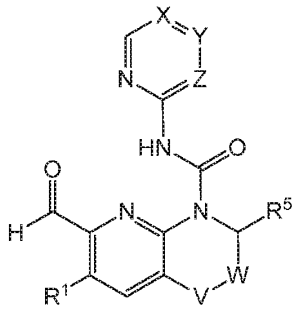
15. A bile acid sequestrant for use according to any of claims 11 to 14, which is cholestyramine.

16. A bile acid sequestrant for use in reducing or preventing an increase of liver enzymes in the serum, plasma or blood of a subject wherein the subject is administered an FGFR4 inhibitor as described in claim 2 or is administered N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, or a pharmaceutically acceptable salt thereof.

17. A method for diminishing the incidence or severity of side effects associated with FGFR4 inhibition therapy other than diarrhea comprising administering to a subject in need of FGFR4 inhibition therapy a combination comprising the simultaneous or sequential administration of a bile acid sequestrant and a selective FGFR4 inhibitor.

18. A method according to claim 17, wherein the bile acid sequestrant is cholestyramine.

19. The method according to claim 17 or 18, wherein the FGFR4 inhibitor is a compound of formula (I) in free form or in pharmaceutically acceptable salt form



(I)

wherein

V is selected from CH_2, O, CH(OH);

W is selected from CH_2, CH_2CH_2, bond;

X is $C(R^X)$ or N;

Y is $C(R^Y)$ or N;

Z is CH or N;

wherein when X is N, Y and Z are not N;

wherein when Y is N, X and Z are not N;

wherein when Z is N, X and Y are not N;

R^X is selected from hydrogen, halogen, haloC_1-C_3alkyl, cyano, C_1-C_6alkyl, hydroxyC_1-C_6alkyl;

R^Y is selected from hydrogen, halogen, C_1-C_3alkyl, C_1-C_6alkoxy, hydroxyC_1-C_3alkoxy, $NR^{Y1}R^{Y2}$, cyano, C_1-C_3alkoxyC_1-C_3alkoxy, C_1-C_3alkoxy-haloC_1-C_3alkoxy, di(C_1-C_3alkyl)aminoC_1-C_6alkoxy, O-$(CH_2)_{0-1}$-R^{Y3}, $CR^{Y6}R^{Y7}$, S-C_1-C_3alkyl, haloC_1-C_6alkoxy optionally substituted with hydroxy;

or

R^X and R^Y together with the ring to which they are attached form a bicyclic aromatic ring system optionally further comprising one or two heteroatoms selected from N, O, or S, which ring system is optionally substituted with C_1-C_3alkyl;

R^{Y1} is hydrogen and

R^{Y2} is selected from C_1-C_6alkyl; hydroxyC_1-C_6alkyl; haloC_1-C_6alkyl optionally substituted with hydroxy; C_1-C_4alkoxyC_1-C_6alkyl; haloC_1-C_3alkoxyC_1-C_6alkyl; $(CH_2)_{0-1}$-R^{Y4}; di(C_1-C_3alkyl)aminoC_1-C_6alkyl substituted with hydroxy; bicycloC_5-C_8alkyl optionally substituted with hydroxyC_1-C_3alkyl; phenyl substituted with $S(O)_2$-$CH(CH_3)_2$; C_2-C_3alkylsulfonic acid;

or

R^{Y1} and R^{Y2} together with the N atom to which they are attached form a saturated or unsaturated non-aromatic 6-membered heterocyclic ring which may contain an O atom, which ring may be substituted once or twice by R^{Y5};

R^{Y3} is selected from quinuclidinyl, a 4-, 5- or 6-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O or S, or a 5- or 6-membered aromatic heterocyclic ring, which saturated or aromatic heterocyclic ring is optionally substituted with C_1-C_3alkyl and/or oxo;

R^{Y4} is a 4-, 5- or 6-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O, or S, which ring is optionally substituted with C_1-C_3alkyl;

R^{Y5} is independently selected from C_1-C_3alkyl, hydroxy, di(C_1-C_3alkyl)aminoC_1-C_3alkyl,

or

two R^{Y5} attached at the same carbon atom form together with the carbon atom to which they are attached a 5-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O or S, which ring is substituted once or more than once with C_1-C_3alkyl;

R^{Y6} and R^{Y7} together with the carbon atom to which they are attached form a 6-membered saturated or unsaturated non-aromatic heterocyclic ring comprising one heteroatom selected from N, O or S;

R^1 is selected from hydrogen; halogen; C_1-C_3alkyl; haloC_1-C_3alkyl; hydroxyC_1-C_3alkyl; C_3-C_6cycloalkyl; $CH_2NR^2R^3$; $CH(CH_3)NR^2R^3$; C_1-C_3alkoxyC_1-C_3alkyl; CH_2CO_2H; C(O)H; C_1-C_3alkoxy; a 5- or 6-membered saturated heterocyclic or aromatic heterocyclic ring comprising at least one heteroatom selected from N, O or S, which ring is optionally substituted once or more than once with a group independently selected from C_1-C_3alkyl, haloC_1-C_3alkyl, oxetanyl or oxo;

R^2 is selected from C_1-C_3alkyl, di(C_1-C_3alkyl)aminoC_1-C_3alkyl;

R^3 is selected from C_1-C_3alkyl, C(O)C_1-C_3alkyl, C(O)-CH_2-OH, C(O)-CH_2-O-CH_3, C(O)-CH_2-N(CH_3)$_2$, S(O)$_2$$CH_3$;

or

R^2 and R^3 together with the N atom to which they are attached form a saturated 5- or 6-membered ring optionally comprising one additional heteroatom selected from N, N-oxide, O or S, which ring may be substituted once or more than once with R^4;

R^4 is independently selected from C_1-C_3alkyl, di(C_1-C_3alkyl)amino, C(O)CH_3, hydroxy;

or

two R^4 attached at the same carbon atom form together with the carbon atom to which they are attached a 4-, 5- or 6-membered non-aromatic heterocyclic ring comprising at least one heteroatom selected from N, O or S;

or

two R^4 attached at the same ring atom form an oxo group;
R^5 is selected from hydrogen or C_1-C_3alkyl.

20. The method according to claim 19, wherein the FGFR4 inhibitor is N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.

21. The method according to any of claims 17 to 20, wherein the side effect is elevated liver enzymes, in particular elevated ALT.

22. The method according to any of claims 17 to 20, wherein the side effect is elevated miRNA122.

23. The method according to any of claims 17 to 22, wherein the FGFR4 inhibition therapy is for the treatment of cancer.

24. The method according to claim 23, wherein the FGFR4 inhibition therapy is for the treatment of liver cancer.

25. A therapeutic regimen comprising the simultaneous or sequential administration of an FGFR4 inhibitor and a bile acid sequestrant.

26. A therapeutic regimen comprising the simultaneous or sequential administration of cholestyramine and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.

27. A therapeutic regimen according to any of claims 25 to 26 for the treatment of liver cancer, including HCC.