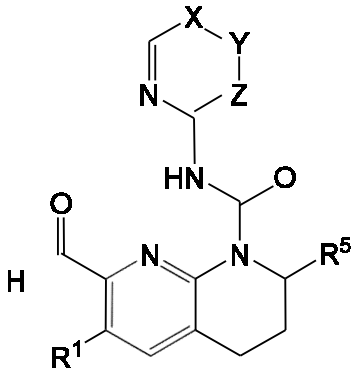
Claims

1. Use of 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

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, and 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, and 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, and 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 $S(O)_2$-$CH(CH_3)_2$; or 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 and S, and 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, and S, which ring is optionally substituted with C_1-C_3alkyl;~~
~~R^{Y5} is independently selected from C_1-C_3alkyl, hydroxy, and 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 and 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 and 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; and a 5- or 6-membered saturated heterocyclic or aromatic heterocyclic ring comprising at least one heteroatom selected from N, O and 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 and oxo;~~
~~R^2 is selected from C_1-C_3alkyl, and 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-$N(CH_3)_2$, and $S(O)_2CH_3$;~~
~~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 and 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, and 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 and S;~~

~~or~~

~~two R^4 attached at the same ring atom form an oxo group;~~

~~R^5 is selected from hydrogen and C_1-C_3alkyl; and~~

~~a bile acid sequestrant in the manufacture of a medicament for the treatment of liver cancer.~~

~~2. The use according to claim 1, 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.~~

~~3. The use according to claim 1 or claim 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 citric acid salt form.~~

~~4. The use according to any one of the preceding claims, wherein the bile acid sequestrant is selected from cholestyramine, colesevelam, colesevalam hydrochloride, colestipol and selevamer.~~

~~5. The use according to any one of claims 1 to 3, wherein the bile acid sequestrant is cholestyramine.~~

~~6.~~1. Use of a pharmaceutical combination comprising a 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 and a bile acid sequestrant in the manufacture of a medicament for reducing or preventing side effects associated with treatment of liver cancer with the FGFR4 inhibitor alone, wherein the side effect does not include diarrhea, wherein the bile acid sequestrant is cholestyramine.

~~7. The use according to claim 6, wherein the bile acid sequestrant is selected from cholestyramine, colesevelam, colesevalam hydrochloride, colestipol and selevamer.~~

~~8. The use according to claim 7, wherein the bile acid sequestrant is cholestyramine~~

~~9.~~2. Use of a pharmaceutical combination comprising a 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 and a bile acid sequestrant in the manufacture of a medicament in the manufacture of a medicament for reducing or preventing an increase of liver enzymes in the serum, plasma or blood of a subject taking FGFR4 inhibitor for the treatment of liver cancer, wherein the bile acid sequestrant is cholestyramine.

~~10. The use according to claim 9, wherein the bile acid sequestrant is selected from cholestyramine, colesevelam, colesevalam hydrochloride, colestipol and selevamer~~

~~11. The use according to claim 10, wherein the bile acid sequestrant is cholestyramine.~~

~~12.~~3. Use of cholestyramine ~~a bile acid sequestrant~~ in the manufacture of a medicament for reducing or preventing side effects associated with treatment of liver cancer with 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 wherein the side effect does not include diarrhea.

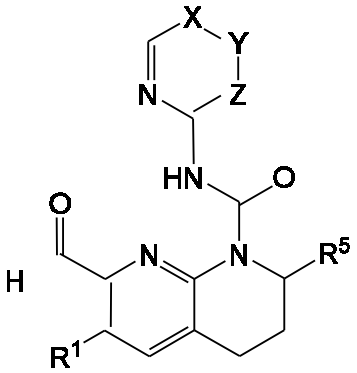
~~13.~~4. Use of cholestyramine ~~a bile acid sequestrant~~ in the manufacture of a medicament for reducing or preventing side effects associated with treatment of liver cancer with N-(5-cyano-4-((2- methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4- dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form in a subject, wherein the side effects comprise the increase of liver enzymes in the serum, plasma or blood of the subject.

~~14.~~5. The use according to claim ~~13~~4, wherein the liver enzyme is alanine aminotransferase (ALT).

~~15.~~6. The use according to claim ~~13~~4, wherein the side effects comprise the increase of miRNA122.

16. The use of the bile acid sequestrant according to any one of claims 12 to 15, when the bile extract is cholestyramine.

17. A pharmaceutical combination for use in the treatment of liver cancer comprising a FGFR4 inhibitor which is a compound of formula (I) in free form or in pharmaceutically acceptable salt form



(I)

wherein

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, and 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, and 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, and 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 $S(O)_2$-$CH(CH_3)_2$; or 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 and S, and 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, and S, which ring is optionally substituted with C_1-C_3alkyl;

R^{Y5} is independently selected from C_1-C_3alkyl, hydroxy, and 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 and 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 and 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; and a 5- or 6-membered saturated heterocyclic or aromatic heterocyclic ring comprising at least one heteroatom selected from N, O and 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 and oxo;

R^2 is selected from C_1-C_3alkyl, and 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-$N(CH_3)_2$, and $S(O)_2CH_3$;~~

~~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 and 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, and 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 and S;~~

~~or~~

~~two R^4 attached at the same ring atom form an oxo group;~~

~~R^5 is selected from hydrogen and C_1-C_3alkyl; and~~

~~a bile acid sequestrant.~~