

CLAIMS

What is claimed is:

1. ~~—A method for treating or preventing hepatocellular carcinoma (HCC) characterized by hepatitis B virus (HBV) infection in a patient, comprising administering an effective amount of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((trans)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof to the patient having HCC characterized by HBV infection.~~

2. ~~—A method for treating or preventing HCC characterized by HBV infection in a patient, comprising screening the patient's HCC for HBV infection, and administering an effective amount of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((trans)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof to the patient having HCC characterized by HBV infection.~~

3. ~~—A method for selecting a patient having HCC for treatment with 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((trans)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof, comprising a) obtaining a biological test sample from the patient; b) analyzing the sample for HBV infection; c) selecting the patient having HCC for treatment with 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((trans)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof if HBV infection is determined in the sample.~~

4.1. A method for predicting response to treatment with 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((trans)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof in a patient having hepatocellular carcinoma (HCC), the method comprising: a) ~~obtaining a biological test sample from the patient;~~ ba) analyzing the a biological test -sample from the patient for HBV infection; ~~eb) predicting an increased likelihood of response to treatment with 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((trans)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-~~

b]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof in the patient having HCC if HBV infection is determined in the sample.

5.2. A method for predicting therapeutic efficacy of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof in a patient having HCC, the method comprising: a) ~~obtaining a biological test sample from the patient;~~ b) analyzing a biological test sample from the patient for HBV infection; ~~c) predicting an increased likelihood of therapeutic efficacy of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof in the patient having HCC if HBV infection is determined in the sample.~~

6. ~~The method of any one of claims 3-5, further comprising a step d) administering an effective amount of 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof to the patient having HCC.~~

7. ~~A compound for use in a method for treating or preventing hepatocellular carcinoma (HCC) characterized by hepatitis B virus (HBV) infection in a patient, wherein the compound is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof and wherein the method comprises administering an effective amount of the compound to the patient having HCC characterized by HBV infection.~~

8. ~~A compound for use in a method for treating or preventing HCC characterized by HBV infection in a patient, wherein the compound is 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof and wherein the method comprises screening the patient's HCC for HBV infection, and administering an effective amount of the compound to the patient having HCC characterized by HBV infection.~~

9. ~~A compound for use in method of any one of claims 3-5, wherein the method further comprises a step d) administering an effective amount of 7-(6-(2-hydroxypropan-2-~~

yl)pyridin-3-yl)-1-((*trans*-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof to the patient having HCC.

~~10.3.~~ The method of ~~any one of claims 1-6~~ claim 1 or 2, or the compound for use of ~~any one of claims 7-9,~~ wherein HBV infection is determined by at least one of the variables selected from the group consisting of: patient history of HBV, prior or current treatment for HBV, cirrhosis attributed to HBV, the presence of HBV proteins or antigens, the presence of antibodies to HBV proteins or antigens, the use of HBV medications, the HBV viral load, and the presence of HBV DNA and the presence of HBV mRNA.

~~11.4.~~ The method of claim ~~103~~ or the compound for use of claim 10, wherein HBV infection is determined by patient history of HBV; or

~~12.~~ The method of claim 10 or the compound for use of claim 10, wherein HBV infection is determined by prior treatment for HBV; or

~~13.~~ The method of claim 10 or the compound for use of claim 10, wherein HBV infection is determined by current treatment for HBV; or

~~14.~~ The method of claim 10 or the compound for use of claim 10, wherein HBV infection is determined by cirrhosis attributed to HBV; or

~~15.~~ The method of claim 10 or the compound for use of claim 10, wherein HBV infection is determined by the presence of HBV proteins or antigens; or

~~16.~~ The method of claim 10 or the compound for use of claim 10, wherein HBV infection is determined by the presence of antibodies to HBV proteins or antigens; or wherein the HBV infection is determined by the use of HBV medications; or

~~17.~~ The method of claim 10 or the compound for use of claim 10, wherein HBV infection is determined by HBV viral load; or

~~18.~~ The method of claim 10 or the compound for use of claim 10, wherein HBV infection is determined by the presence of HBV DNA; or wherein the HBV infection is determined by the presence of HBV mRNA.

~~19.5. The method of any one of claims 1-6 or the compound for use of any one of claims 7-9 of claim 1 or 2, wherein HBV infection is determined by at least one of the variables selected from the group consisting of: the presence of HBV surface antigen (HBsAg), the presence of HBV core antigen (HBcAg), the presence of HBV envelope antigen (HBeAg), the presence of HBV x antigen (HBxAg), the presence of HBV core-related antigen (HBcrAg), the presence of antibody to HBV surface antigen (anti-HBsAg), the presence of antibody to HBV core antigen (anti-HBcAg), the presence of antibody to HBV envelope antigen (anti-HBeAg), the presence of antibody to HBV x antigen (anti-HBxAg), and the presence of antibody to HBV core-related antigen (anti-HBcrAg), the use of HBV medications, HBV viral load, the presence of HBV DNA, the presence of HBV mRNA, and the presence of HBV protein.~~

~~20.6. The method of claim 19 or the compound for use of claim 19 claim 5, wherein HBV infection is determined by the presence of HBsAg; or~~

~~21. The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of HBcAg; or~~

~~22. The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of HBeAg; or~~

~~23. The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of HBxAg; or~~

~~24. The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of HBcrAg; or~~

~~25. The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of anti-HBsAg; or~~

~~26. The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of anti-HBcAg; or~~

~~27. The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of anti-HBeAg; or~~

28.—~~The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of anti-HBxAg; or~~

29. ~~The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of anti-HBcrAg.~~

30.—~~The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the use of HBV medications.~~

31.—~~The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by HBV viral load.~~

32.—~~The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of HBV DNA.~~

33.—~~The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of HBV mRNA.~~

34.—~~The method of claim 19 or the compound for use of claim 19, wherein HBV infection is determined by the presence of HBV protein.~~

35.—~~The method of any one of claims 1-6 or 10-34 or the compound for use of any one of claims 7-34, wherein 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof is administered in combination with a second therapeutic agent to the HCC patient characterized by HBV infection.~~

36.—~~The method of claim 35 or the compound for use of claim 35, wherein the second therapeutic agent is sorafenib.~~

37.—~~The method of claim 35 or the compound for use of claim 35, wherein the second therapeutic agent is 3-(5-amino-2-methyl-4-oxo-4H-quinazolin-3-yl)-piperidine-2,6-dione (Compound 2).~~

38. — ~~The method of claim 35 or the compound for use of claim 35, wherein the second therapeutic agent is an immune check point inhibitor.~~

39. — ~~The method of any one of claims 1-6 or 10-34 or the compound for use of any one of claims 7-34, wherein 7-(6-(2-hydroxypropan-2-yl)pyridin-3-yl)-1-((*trans*)-4-methoxycyclohexyl)-3,4-dihydropyrazino[2,3-*b*]pyrazin-2(1*H*)-one or a pharmaceutically acceptable salt or tautomer thereof is administered in combination with a second and a third therapeutic agents to the HCC patient characterized by HBV infection.~~

40. — ~~The method of claim 39 or the compound for use of claim 39, wherein the second and the third therapeutic agents are selected from the group consisting of sorafenib, Compound 2, and an immune check point inhibitor.~~

41. — ~~The method of claim 40 or the compound for use of claim 40, wherein the immune check point inhibitor is nivolumab.~~

42. — ~~7. The method of any one of claims 1-6 or 10-41 claims 1 to 6, or the compound for use of any one of claims 7-41, wherein the HCC is unresectable HCC; or~~

43. — ~~The method of any one of claims 1-6 or 10-42 or the compound for use of any one of claims 7-42, wherein the HCC is previously untreated HCC; or~~

44. — ~~The method of any one of claims 1-6 or 10-42 or the compound for use of any one of claims 7-42, wherein the HCC is previously treated HCC, wherein the previous treatment comprises sorafenib; or~~

45. ~~The method of any one of claims 1-6 or 10-42 or the compound for use of any one of claims 7-42, wherein the HCC is previously treated HCC, wherein the previous treatment comprises chemotherapy.~~