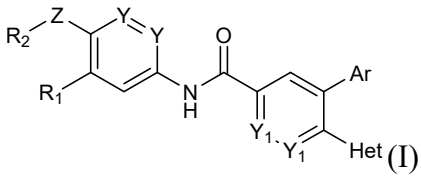
## CLAIMS

1. Use of a compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof in the manufacture of a medicament for treating chronic myeloid leukemia (CML) or acute lymphoblastic leukemia (ALL), wherein the compound of formula (I) has the following structure:



(I)

wherein:

$Y_1$ is independently selected from $CR_a$ or N;

Y is independently selected from $CR_a$ or N;

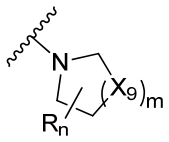
$R_1$ is selected from hydrogen, halogen, cyano, nitro, $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl, wherein the $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl is optionally substituted with an $R_{1a}$ group;

$R_2$ is selected from hydrogen, $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl, wherein the $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl is optionally substituted with an $R_{2a}$ group;

Z is a chemical bond, O, $S(O)_{0-2}$ or $NR_b$;

or, -Z-$R_2$ together represents $-SF_5$;

Ar is a six-membered heteroaryl containing at least one N atom, optionally substituted with R groups;

Het is 

;

wherein $X_9$ is selected from O, S, $NR_b$ or $C(R)_2$;

m is 0, 1 or 2;

n is 0, 1, 2, 3, 4, 5 or 6;

$R_a$ is independently selected from hydrogen, halogen, cyano, nitro, hydroxy, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy;

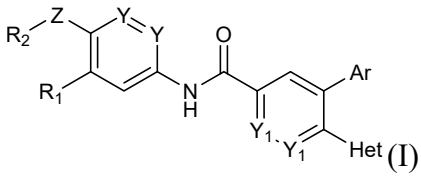
$R_b$ is independently selected from hydrogen, $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl;

$R_{1a}$, $R_{2a}$ and R are independently selected from hydrogen, halogen, hydroxy, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{3-7}$ cycloalkyl, $C_{3-7}$

heterocycloalkyl, $C_{6-10}$ aryl or $C_{5-10}$ heteroaryl;

alternatively, two R groups on the same atom or adjacent atoms may together form a $C_{3-7}$ cycloalkyl, $C_{3-7}$ heterocycloalkyl, $C_{6-10}$ aryl or $C_{5-10}$ heteroaryl.

2. A compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof, for use in therapy, optionally, for use in treating chronic myeloid leukemia (CML) or acute lymphoblastic leukemia (ALL), wherein the compound of formula (I) has the following structure:



(I)

wherein:

$Y_1$ is independently selected from $CR_a$ or N;

Y is independently selected from $CR_a$ or N;

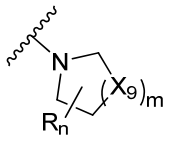
$R_1$ is selected from hydrogen, halogen, cyano, nitro, $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl, wherein the $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl is optionally substituted with an $R_{1a}$ group;

$R_2$ is selected from hydrogen, $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl, wherein the $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl is optionally substituted with an $R_{2a}$ group;

Z is a chemical bond, O, $S(O)_{0-2}$ or $NR_b$;

or, -Z-$R_2$ together represents $-SF_5$;

Ar is a six-membered heteroaryl containing at least one N atom, optionally substituted with R groups;

Het is 

;

wherein $X_9$ is selected from O, S, $NR_b$ or $C(R)_2$;

m is 0, 1 or 2;

n is 0, 1, 2, 3, 4, 5 or 6;

$R_a$ is independently selected from hydrogen, halogen, cyano, nitro, hydroxy, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl or $C_{1-6}$ alkoxy;

$R_b$ is independently selected from hydrogen, $C_{1-6}$ alkyl or $C_{1-6}$ haloalkyl;

$R_{1a}$, $R_{2a}$ and R are independently selected from hydrogen, halogen, hydroxy, $-NH_2$, $-NHC_{1-6}$ alkyl, $-N(C_{1-6}$ alkyl$)_2$, $C_{1-6}$ alkyl, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{3-7}$ cycloalkyl, $C_{3-7}$ heterocycloalkyl, $C_{6-10}$ aryl or $C_{5-10}$ heteroaryl;

alternatively, two R groups on the same atom or adjacent atoms may together form a $C_{3-7}$ cycloalkyl, $C_{3-7}$ heterocycloalkyl, $C_{6-10}$ aryl or $C_{5-10}$ heteroaryl.

3. The use according to claim 1, or the compound for use according to claim 2, wherein the compound of formula (I) is (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-fluoropyrrolidin-1-yl)-5-(pyrazin-2-yl)nicotinamide (Compound A) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof.

4. The use or the compound for use according to any one of claims 1-3, wherein one or more of the following definitions are met:

i) wherein the chronic myeloid leukemia is chronic myeloid leukemia in chronic phase, optionally central nervous system leukemia relapse thereof, such as brain metastasis; and/or

ii) wherein the chronic myeloid leukemia is chronic myeloid leukemia in accelerated phase, optionally central nervous system leukemia relapse thereof, such as brain metastasis; and/or

iii) wherein the chronic myeloid leukemia is chronic myeloid leukemia in blast phase, optionally central nervous system leukemia relapse thereof, such as brain metastasis; and/or

iv) wherein the chronic myeloid leukemia is Philadelphia chromosome-positive (Ph+); and/or

v) wherein the acute lymphoblastic leukemia is Philadelphia chromosome-positive (Ph+), optionally central nervous system leukemia relapse thereof, such as brain metastasis; and/or

vi) wherein the chronic myeloid leukemia is BCR-ABL1 fusion gene-positive;

optionally, the BCR-ABL1 fusion gene is wild-type;

optionally, the BCR-ABL1 fusion gene is mutant; optionally, the mutation is selected from G250E, Q252H, Y253H, E255K/V, M244V, H396P, F317L, E459K, E355G, V299L, T315I, M351T, F359V, P223S, and I502L, alternatively G250E, Q252H, Y253H, E255K/V, E459K, T315I, and M351T, alternatively T315I; and/or

vii) wherein the chronic myeloid leukemia has progressed after treatment with another therapy;

optionally, wherein the other therapy is selected from radiation therapy, drug therapy, or surgical therapy; optionally, wherein the drug therapy is chemotherapy, targeted therapy, or immunotherapy;

optionally, wherein the drug therapy is chemotherapy;

optionally, wherein the drug therapy is targeted therapy;

optionally, wherein the drug for the drug therapy is selected from one or more of imatinib, dasatinib, nilotinib, BCR-ABL tyrosine kinase inhibitors, olverembatinib, hydroxyurea, ponatinib, asciminib, interferon, cytarabine, azacitidine, interferon alfa-1b, homoharringtonine, decitabine, peginterferon alfa-2a, thalidomide, chidamide, or recombinant interferon alfa-2b; and/or

viii) wherein the chronic myeloid leukemia has progressed after treatment with a BCR-ABL tyrosine kinase inhibitor; optionally, wherein the BCR-ABL tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, olverembatinib, ponatinib or asciminib; and/or

ix) wherein the patient is an adult patient; and/or

x) wherein the patient is a pediatric patient; and/or

xi) wherein the patient has received one or more lines of treatment; optionally, wherein the patient has received two or more lines of treatment; optionally, wherein the patient has received three or more lines of treatment; optionally, the patient has received one, two, three, four, or five lines of treatment.

5. The use or the compound for use according to any one of claims 1-4, wherein one or more of the following definitions are met:

i) wherein the patient has previously received treatment with ≥1 different BCR-ABL1 tyrosine kinase inhibitor(s) and subsequently experienced disease progression to accelerated phase or blast phase, with treatment evaluation results being failure, warning, or intolerance;

alternatively, wherein the patient has previously received treatment with ≥2 different BCR-ABL1 tyrosine kinase inhibitor(s) and subsequently experienced disease progression to accelerated phase or blast phase, with treatment evaluation results being failure, warning, or intolerance;

alternatively, wherein the patient has previously received treatment with ≥3 different BCR-

ABL1 tyrosine kinase inhibitor(s) and subsequently experienced disease progression to accelerated phase or blast phase, with treatment evaluation results being failure, warning, or intolerance;

alternatively, wherein the patient has previously received treatment with ≥4 different BCR-ABL1 tyrosine kinase inhibitor(s) and subsequently experienced disease progression to accelerated phase or blast phase, with treatment evaluation results being failure, warning, or intolerance;

alternatively, wherein the patient has previously received treatment with ≥1 different BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) and subsequently experienced disease progression to accelerated phase or blast phase, with treatment evaluation results being failure, warning, or intolerance;

alternatively, wherein the patient has previously received treatment with ≥2 different BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) and subsequently experienced disease progression to accelerated phase or blast phase, with treatment evaluation results being failure, warning, or intolerance;

alternatively, wherein the patient has previously received treatment with ≥3 different BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) and subsequently experienced disease progression to accelerated phase or blast phase, with treatment evaluation results being failure, warning, or intolerance;

alternatively, wherein the patient has previously received treatment with ≥4 different BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) and subsequently experienced disease progression to accelerated phase or blast phase, with treatment evaluation results being failure, warning, or intolerance; and/or

ii) wherein the patient has previously received treatment with ≥1 different BCR-ABL1 tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;

alternatively, wherein the patient has previously received treatment with ≥2 different BCR-ABL1 tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;

alternatively, wherein the patient has previously received treatment with ≥3 different BCR-ABL1 tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;

alternatively, wherein the patient has previously received treatment with ≥4 different BCR-

ABL1 tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;
alternatively, wherein the patient has previously received treatment with ≥1 different BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;
alternatively, wherein the patient has previously received treatment with ≥2 different BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;
alternatively, wherein the patient has previously received treatment with ≥3 different BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;
alternatively, wherein the patient has previously received treatment with ≥4 different BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently experienced relapse or became refractory.

6. The use or the compound for use according to claim 5, wherein any one of the following definitions is met:
i) wherein the BCR-ABL1 tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, ponatinib, olverembatinib, radotinib, bafetinib, vodobatinib, CHMFL-ABL-039, CHMFL-ABL-053, CHMFL-ABL-KIT-155, PF-114, pacritinib, rebasinib, danusertib, tozasertib, AT9283, KW-2449, XL228, asciminib or HS-10382;
alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, ponatinib, olverembatinib, radotinib or asciminib;
alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, ponatinib, olverembatinib or asciminib;
alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib or radotinib;
alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib or nilotinib;
alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is selected from ponatinib, olverembatinib, asciminib or HS-10382;

alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is selected from ponatinib or olverembatinib;

alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is selected from asciminib or HS-10382;

alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is a first-line, second-line, third-line, fourth-line, or fifth-line therapeutic agent;

alternatively, BCR-ABL1 tyrosine kinase inhibitor(s) is a first-line, second-line, or third-line therapeutic agent; or

ii) wherein BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, ponatinib, olverembatinib, radotinib, bafetinib, vodobatinib, CHMFL-ABL-039, CHMFL-ABL-053, CHMFL-ABL-KIT-155, PF-114, pacritinib, rebasinib, danusertib, tozasertib, AT9283, KW-2449 or XL228;

alternatively, BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, ponatinib, olverembatinib or radotinib;

alternatively, BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, ponatinib or olverembatinib;

alternatively, BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib or radotinib;

alternatively, BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib or nilotinib;

alternatively, BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from ponatinib or olverembatinib;

alternatively, BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is a first-line, second-line, third-line, fourth-line, or fifth-line therapeutic agent;

alternatively, BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is a first-line, second-line, or third-line therapeutic agent.

7. The use or the compound for use according to any one of claims 1-6, wherein one or more of the following definitions are met:

i) wherein the patient has previously received treatment with ≥1 different first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine

kinase inhibitors and subsequently developed resistance or intolerance;

alternatively, the patient has previously received treatment with ≥2 different first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently developed resistance or intolerance;

alternatively, the patient has previously received treatment with ≥3 different first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently developed resistance or intolerance;

alternatively, the patient has previously received treatment with ≥4 different first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently developed resistance or intolerance; and/or

ii) wherein the resistance arises from BCR-ABL1 kinase domain point mutation(s);

optionally, the BCR-ABL1 kinase domain point mutation(s) is selected from one or more of T315I/A, Y253F/H, E255V/K, M351T, G250E, F359V/I/C, H396P/R, M244V, E355G, F317L/V/I/C, F311L, M237I, Q252H/R, D276G, L248V, V379I, L384M, L387M, E279K, F486S, E459K, P223S, I502L or V299L;

optionally, the BCR-ABL1 kinase domain point mutation(s) is selected from one or more of T315I, Y253H, E255V/K, M351T, G250E, F359V/, H396P, M244V, E355G, F317L, Q252H, E459K, P223S, I502L or V299L; and/or

iii) wherein the patient has previously received treatment with ≥1 different first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;

alternatively, the patient has previously received treatment with ≥2 different first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;

alternatively, the patient has previously received treatment with ≥3 different first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently experienced relapse or became refractory;

alternatively, the patient has previously received treatment with ≥4 different first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitors and subsequently experienced relapse or became refractory; and/or

iv) wherein the first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib or radotinib;

alternatively, the first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib or nilotinib;

alternatively, the first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, radotinib, ponatinib or olverembatinib;

alternatively, the first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is selected from imatinib, dasatinib, nilotinib, flumatinib or, ponatinib or olverembatinib;

alternatively, the first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is a first-line, second-line, third-line, fourth-line, or fifth-line therapeutic agent;

alternatively, the first-generation and/or second-generation and/or third-generation BCR-ABL1 ATP-competitive tyrosine kinase inhibitor(s) is first-line or second-line therapeutic agent; and/or

v) wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 20 mg/day to about 400 mg/day;

alternatively, the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 20 mg/day to about 240 mg/day;

alternatively, the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 20 mg/day, about 40 mg/day, about 60 mg/day, about 80 mg/day, about 100 mg/day, about 120 mg/day, about 160 mg/day, or about 240 mg/day;

alternatively, the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 20 mg/day, about

40 mg/day, about 80 mg/day, about 160 mg/day, or about 240 mg/day; and/or

vi) wherein the compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is administered orally or intranasally; alternatively, administered orally; alternatively, administered orally under fasting conditions; and/or

vii) wherein the compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively Compound A) is administered once daily (QD), twice daily (BID), or three times daily (TID); and/or

viii) wherein the compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively Compound A) is administered at about 10 mg BID, about 20 mg BID, about 40 mg QD, about 40 mg BID, about 80 mg QD, about 80 mg BID, about 160 mg QD, or about 240 mg QD; and/or

ix) wherein the compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively Compound A) is administered until disease progression, intolerable toxicity, or death.

8. A pharmaceutical combination comprising:

(a) the compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and

(b) an ATP-competitive BCR-ABL1 inhibitor, or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof.

9. The pharmaceutical combination according to claim 8, wherein the pharmaceutical combination has one or more of the following definitions:

i) wherein the compound of formula (I) is (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-fluoropyrrolidin-1-yl)-5-(pyrazin-2-yl)nicotinamide (Compound A), or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and/or

ii) wherein the ATP-competitive BCR-ABL1 inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, ponatinib, olverembatinib, radotinib, bafetinib, vodobatinib, CHMFL-ABL-039, CHMFL-ABL-053, CHMFL-ABL-KIT-155, PF-114, pacritinib, rebasinib,

danusertib, tozasertib, AT9283, KW-2449 or XL228;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, ponatinib, olverembatinib or PF-114;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from imatinib, nilotinib, radotinib, flumatinib, ponatinib, bafetinib, CHMFL-ABL-039, CHMFL-ABL-053, CHMFL-ABL-KIT-155, vodobatinib, PF-114, olverembatinib or rebastinib;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from ponatinib, PF-114, olverembatinib or rebastinib;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from ponatinib, olverembatinib or PF-114;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from ponatinib or olverembatinib;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from ponatinib; and/or

iii) wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 1-500 mg;

alternatively, wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 1-250 mg;

alternatively, wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg or 250 mg;

alternatively, wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 80 mg, 160 mg or 240 mg;

alternatively, wherein the compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is administered once daily

or twice daily; and/or

iv) wherein the dose of the ATP-competitive BCR-ABL1 inhibitor is about 0.1-200 mg, alternatively about 0.1-60 mg; and/or

v) wherein the ATP-competitive BCR-ABL1 inhibitor is ponatinib at a dose of about 0.1-200 mg, alternatively about 0.1-60 mg;

alternatively, the dose of ponatinib is 0.1 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 20.5 mg, 21 mg, 21.5 mg, 22 mg, 22.5 mg, 23 mg, 23.5 mg, 24 mg, 24.5 mg, 25 mg, 25.5 mg, 26 mg, 26.5 mg, 27 mg, 27.5 mg, 28 mg, 28.5 mg, 29 mg, 29.5 mg, 30 mg, 30.5 mg, 31 mg, 31.5 mg, 32 mg, 32.5 mg, 33 mg, 33.5 mg, 34 mg, 34.5 mg, 35 mg, 35.5 mg, 36 mg, 36.5 mg, 37 mg, 37.5 mg, 38 mg, 38.5 mg, 39 mg, 39.5 mg, 40 mg, 40.5 mg, 41 mg, 41.5 mg, 42 mg, 42.5 mg, 43 mg, 43.5 mg, 44 mg, 44.5 mg, 45 mg, 45.5 mg, 46 mg, 46.5 mg, 47 mg, 47.5 mg, 48 mg, 48.5 mg, 49 mg, 49.5 mg, 50 mg, 50.5 mg, 51 mg, 51.5 mg, 52 mg, 52.5 mg, 53 mg, 53.5 mg, 54 mg, 54.5 mg, 55 mg, 55.5 mg, 56 mg, 56.5 mg, 57 mg, 57.5 mg, 58 mg, 58.5 mg, 59 mg, 59.5 mg or 60 mg;

alternatively, the dose of ponatinib is 2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 45 mg or 60 mg;

alternatively, ponatinib is administered once daily or twice daily; or

vi) wherein the ATP-competitive BCR-ABL1 inhibitor is olverembatinib at a dose of about 0.1-200 mg, alternatively about 0.1-60 mg;

alternatively, the dose of olverembatinib is 0.1 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 20.5 mg, 21 mg, 21.5 mg, 22 mg, 22.5 mg, 23 mg, 23.5 mg, 24 mg, 24.5 mg, 25 mg, 25.5 mg, 26 mg, 26.5 mg, 27 mg, 27.5 mg, 28 mg, 28.5 mg, 29 mg, 29.5 mg, 30 mg, 30.5 mg, 31 mg, 31.5 mg, 32 mg, 32.5 mg, 33 mg, 33.5 mg, 34 mg, 34.5 mg, 35 mg, 35.5 mg, 36 mg, 36.5 mg, 37 mg, 37.5 mg, 38 mg, 38.5 mg, 39 mg, 39.5 mg, 40 mg, 40.5 mg, 41 mg, 41.5 mg, 42 mg, 42.5 mg, 43 mg, 43.5 mg, 44 mg, 44.5 mg, 45 mg, 45.5 mg, 46 mg, 46.5 mg, 47 mg, 47.5 mg, 48 mg,

48.5 mg, 49 mg, 49.5 mg, 50 mg, 50.5 mg, 51 mg, 51.5 mg, 52 mg, 52.5 mg, 53 mg, 53.5 mg, 54 mg, 54.5 mg, 55 mg, 55.5 mg, 56 mg, 56.5 mg, 57 mg, 57.5 mg, 58 mg, 58.5 mg, 59 mg, 59.5 mg or 60 mg;

alternatively, the dose of olverembatinib is 1 mg, 2 mg, 4 mg, 8 mg, 12 mg, 20 mg, 30 mg, 40 mg, 45 mg, 50 mg or 60 mg;

alternatively, olverembatinib is administered once daily or twice daily; and/or

vii) wherein the (a) compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and (b) ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof are present in the same dosage form; or

viii) wherein the (a) compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and (b) ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof are present in different dosage forms.

10. A pharmaceutical composition comprising the pharmaceutical combination of any one of claims 8-9.

11. Use of (a) the compound of formula (I) of claim 1 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof and (b) an ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof in the manufacture of a medicament for treating a disease regulated by wild-type or mutant BCR-ABL1 kinase.

12. Use of (a) the compound of formula (I) of claim 1 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof in the manufacture of a medicament for use in combination with (b) an ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof for treating a disease regulated by wild-type or mutant BCR-ABL1 kinase.

13. Use of (b) an ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt,

crystal form, solvate, or hydrate thereof in the manufacture of a medicament for use in combination with (a) the compound of formula (I) of claim 1 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof for treating a disease regulated by wild-type or mutant BCR-ABL1 kinase.

14. A pharmaceutical combination of (a) the compound of formula (I) of claim 1 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof and (b) an ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof, for use in therapy, optionally, for use in treating a disease regulated by wild-type or mutant BCR-ABL1 kinase.

15. (a) The compound of formula (I) of claim 1 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof, for use in combination with (b) an ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof, for use in therapy, optionally, for use in treating a disease regulated by wild-type or mutant BCR-ABL1 kinase.

16. (b) An ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof, for use in combination with (a) the compound of formula (I) of claim 1 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof, for use in therapy, optionally, for use in treating a disease regulated by wild-type or mutant BCR-ABL1 kinase.

17. The use according to any one of claims 11-13, or the compound and/or inhibitor for use according to any one of claims 14-16, wherein one or more of the following definitions are met:
i) wherein the disease regulated by the wild-type and/or mutant BCR-ABL1 kinase is a hematological malignancy or central nervous system leukemia relapse thereof, such as brain metastasis;
alternatively, the disease regulated by the wild-type and/or mutant BCR-ABL1 kinase is leukemia, neurodegenerative disease, neurofibroma, melanoma, breast cancer, colon cancer,

lung cancer, prostate cancer, Kaposi's sarcoma, gastrointestinal stromal tumor, mesothelioma, systemic mastocytosis, hypereosinophilic syndrome, liver fibrosis, renal fibrosis, rheumatoid arthritis, polyarthritis, scleroderma, lupus erythematosus, graft-versus-host disease, pulmonary arterial hypertension, seminoma, dysgerminoma, and psoriasis;

alternatively, the leukemia is acute lymphoblastic leukemia, acute myeloid leukemia, acute promyelocytic leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, chronic neutrophilic leukemia, acute undifferentiated leukemia, prolymphocytic leukemia, juvenile myelomonocytic leukemia, adult T-cell leukemia, acute myeloid leukemia with trilineage myelodysplasia, and mixed lineage leukemia;

alternatively, the leukemia is chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia;

alternatively, the neurodegenerative disease is Parkinson's disease, Alzheimer's disease, Down syndrome, memory and cognitive impairment, dementia, amyloid neuropathy, or cerebral inflammation;

alternatively, the disease regulated by wild-type and/or mutant BCR-ABL1 kinase is chronic myeloid leukemia, Philadelphia chromosome-positive acute lymphoblastic leukemia, Parkinson's disease, Alzheimer's disease, neurofibromatosis, gastrointestinal stromal tumor, systemic mastocytosis, hypereosinophilic syndrome, liver fibrosis, renal fibrosis, or scleroderma; and/or

ii) wherein the mutation of the mutant BCR-ABL1 kinase is one or more of T315I, T315M, F317L, E355G, V299L, M244V, G250E, Q252H, Y253H, E255K, E255V, H396P, H396R, H396A, A397P, P223S, K294E, M351T, F359V, E459K, P465S, V468F, I502L, A337V or A424T;

alternatively, the mutation of the mutant BCR-ABL1 kinase is one or more of T315I, T315M, Y253H/T315I, E255V/T315I, Q252H/T315I, F317L/T315I, F359V/T315I, Y253H/E255K, Y253H/F359V;

alternatively, the mutation of the mutant BCR-ABL1 kinase is T315I, T315M, Y253H/T315I, E255V/T315I or Q252H/T315I;

alternatively, the mutation of the mutant BCR-ABL1 kinase is T315M, Y253H/T315I, E255V/T315I or Q252H/T315I; and/or

iii) wherein the compound of formula (I) is (R)-N-(4-(chlorodifluoromethoxy)phenyl)-6-(3-fluoropyrrolidin-1-yl)-5-(pyrazin-2-yl)nicotinamide (Compound A) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and/or

iv) wherein the ATP-competitive BCR-ABL1 inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, ponatinib, olverembatinib, radotinib, bafetinib, vodobatinib, CHMFL-ABL-039, CHMFL-ABL-053, CHMFL-ABL-KIT-155, PF-114, pacritinib, rebasinib, danusertib, tozasertib, AT9283, KW-2449 or XL228;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from imatinib, dasatinib, nilotinib, bosutinib, flumatinib, ponatinib, olverembatinib or PF-114;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from imatinib, nilotinib, radotinib, flumatinib, ponatinib, bafetinib, CHMFL-ABL-039, CHMFL-ABL-053, CHMFL-ABL-KIT-155, vodobatinib, PF-114, olverembatinib or rebastinib;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from ponatinib, PF-114, olverembatinib or rebastinib;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from ponatinib, olverembatinib or PF-114;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from ponatinib or olverembatinib;

alternatively, the ATP-competitive BCR-ABL1 inhibitor(s) is selected from ponatinib; and/or

v) wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 1-500 mg;

alternatively, wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 1-250 mg;

alternatively, wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg or 250 mg;

alternatively, wherein the dose of the compound of formula (I) or pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 80 mg, 160 mg or 240 mg;

alternatively, wherein the compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof (alternatively compound A) is administered once daily or twice daily; and/or

vi) wherein the dose of the ATP-competitive BCR-ABL1 inhibitor is about 0.1-200 mg, alternatively about 0.1-60 mg; and/or

vii) wherein the ATP-competitive BCR-ABL1 inhibitor is ponatinib at a dose of about 0.1-200 mg, alternatively about 0.1-60 mg;

alternatively, the dose of ponatinib is 0.1 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 20.5 mg, 21 mg, 21.5 mg, 22 mg, 22.5 mg, 23 mg, 23.5 mg, 24 mg, 24.5 mg, 25 mg, 25.5 mg, 26 mg, 26.5 mg, 27 mg, 27.5 mg, 28 mg, 28.5 mg, 29 mg, 29.5 mg, 30 mg, 30.5 mg, 31 mg, 31.5 mg, 32 mg, 32.5 mg, 33 mg, 33.5 mg, 34 mg, 34.5 mg, 35 mg, 35.5 mg, 36 mg, 36.5 mg, 37 mg, 37.5 mg, 38 mg, 38.5 mg, 39 mg, 39.5 mg, 40 mg, 40.5 mg, 41 mg, 41.5 mg, 42 mg, 42.5 mg, 43 mg, 43.5 mg, 44 mg, 44.5 mg, 45 mg, 45.5 mg, 46 mg, 46.5 mg, 47 mg, 47.5 mg, 48 mg, 48.5 mg, 49 mg, 49.5 mg, 50 mg, 50.5 mg, 51 mg, 51.5 mg, 52 mg, 52.5 mg, 53 mg, 53.5 mg, 54 mg, 54.5 mg, 55 mg, 55.5 mg, 56 mg, 56.5 mg, 57 mg, 57.5 mg, 58 mg, 58.5 mg, 59 mg, 59.5 mg or 60 mg;

alternatively, the dose of ponatinib is 2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 45 mg or 60 mg;

alternatively, ponatinib is administered once daily or twice daily; or

viii) wherein the ATP-competitive BCR-ABL1 inhibitor is olverembatinib at a dose of about 0.1-200 mg, alternatively about 0.1-60 mg;

alternatively, the dose of olverembatinib is 0.1 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg,

15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 20.5 mg, 21 mg, 21.5 mg, 22 mg, 22.5 mg, 23 mg, 23.5 mg, 24 mg, 24.5 mg, 25 mg, 25.5 mg, 26 mg, 26.5 mg, 27 mg, 27.5 mg, 28 mg, 28.5 mg, 29 mg, 29.5 mg, 30 mg, 30.5 mg, 31 mg, 31.5 mg, 32 mg, 32.5 mg, 33 mg, 33.5 mg, 34 mg, 34.5 mg, 35 mg, 35.5 mg, 36 mg, 36.5 mg, 37 mg, 37.5 mg, 38 mg, 38.5 mg, 39 mg, 39.5 mg, 40 mg, 40.5 mg, 41 mg, 41.5 mg, 42 mg, 42.5 mg, 43 mg, 43.5 mg, 44 mg, 44.5 mg, 45 mg, 45.5 mg, 46 mg, 46.5 mg, 47 mg, 47.5 mg, 48 mg, 48.5 mg, 49 mg, 49.5 mg, 50 mg, 50.5 mg, 51 mg, 51.5 mg, 52 mg, 52.5 mg, 53 mg, 53.5 mg, 54 mg, 54.5 mg, 55 mg, 55.5 mg, 56 mg, 56.5 mg, 57 mg, 57.5 mg, 58 mg, 58.5 mg, 59 mg, 59.5 mg or 60 mg;

alternatively, the dose of olverembatinib is 1 mg, 2 mg, 4 mg, 8 mg, 12 mg, 20 mg, 30 mg, 40 mg, 45 mg, 50 mg or 60 mg;

alternatively, olverembatinib is administered once daily or twice daily; and/or

ix) wherein the (a) compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and (b) ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof are present in the same dosage form; or

x) wherein the (a) compound of formula (I) or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and (b) ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof are present in different dosage forms.

18. (a) a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and

(b) an ATP-competitive BCR-ABL1 inhibitor, or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof, for use in therapy; optionally for use in inhibiting a mutant BCR-ABL1 kinase;

optionally, wherein the mutant BCR-ABL1 kinase is selected from one or more of T315I, T315M, F317L, E355G, V299L, M244V, G250E, Q252H, Y253H, E255K, E255V, H396P, H396R, H396A, A397P, P223S, K294E, M351T, F359V, E459K, P465S, V468F, I502L, A337V or A424T;

alternatively, the mutant BCR-ABL1 kinase is T315I, T315M, Y253H/T315I, E255V/T315I, Q252H/T315I, F317L/T315I, F359V/T315I, Y253H/E255K or Y253H/F359V;

alternatively, the mutant BCR-ABL1 kinase is T315I, T315M, Y253H/T315I, E255V/T315I or Q252H/T315I;

alternatively, the mutant BCR-ABL1 kinase is T315M, Y253H/T315I, E255V/T315I or Q252H/T315I.

19. A commercial package, comprising any one of the following definitions:

i) (a) Compound A of claim 3 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and

(b) an ATP-competitive BCR-ABL1 inhibitor or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof;

wherein (a) and (b) are present in a single unit dosage form or in two separate unit dosage forms; or

ii) (a) Compound A of claim 3 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and

(b) Ponatinib or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof;

wherein (a) and (b) are present in a single unit dosage form or in two separate unit dosage forms; or

iii) (a) Compound A of claim 3 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and

(b) Olverembatinib or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof;

wherein (a) and (b) are present in a single unit dosage form or in two separate unit dosage forms; or

iv) (a) Compound A of claim 3 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof; and

(b) PF-114 or a pharmaceutically acceptable salt, crystal form, solvate, or hydrate thereof;

wherein (a) and (b) are present in a single unit dosage form or in two separate unit dosage forms;

optionally, wherein one or more of the following definitions are met:

i) wherein the unit dosage form is a fixed combination; and/or

ii) for use in therapy, optionally, for use in treating a disease regulated by wild-type or mutant BCR-ABL1 kinase.