CLAIMS

1. **A SIK3 inhibitor for use in athe treatment of a proliferative disorder, which is a cancer or tumour,** in a subject, wherein the treatment involvesby inhibiting SIK3 and sensitising cells involved with the proliferative disorder to a cell-mediated immune response, the treatment comprising administering the SIK3 inhibitor to the subject.; wherein: (i) the subject has a plasma concentration of TNF greater than 2 pg/mL; and/or (ii) the proliferative disorder is a solid tumour that, in the subject, has an intratumoural concentration of TNF greater than 0.5 pg/mL.

2. The SIK3 inhibitor for use of claim 1, wherein the SIK3 inhibitor is administered in a therapeutically effective amount that is effective to reduce activity of SIK3; preferably of SIK3 in thesaid cells involved with the proliferative disorder.

3 The SIK3 inhibitor for use of claim 1 or 2, wherein the SIK3 inhibitor is administered in a therapeutically effective amount that is not effective to reduce the activity of ABL1are **characterised by** activated TNFR2- and/or SRC kinase; preferably ABL1 and/or SRC kinase in the cells involved with the proliferative disorder.

4. The SIK3 inhibitor for use of any one of claims 1 to 3, wherein the treatment comprises that the cell-mediated immune response induces killing of cells involved with the proliferative disorder.

5. The SIK3 inhibitor for use of any one of claims 1 to 4, wherein the SIK3 inhibitor is administered to the subject to sensitise cells involved with the proliferative disorder to killing induced by TNF.

6. The SIK3 inhibitor for use of any one of claims 1 to 5, wherein the treatment is mediated by inhibiting SIK3; and wherein the treatment is not mediated by inhibiting Abl and/or SRC kinase.

7. The SIK3 inhibitor for use of any one of claims 1 to 6, wherein the treatement comprises that SIK3 in the cells involved with the proliferative disorder is inhibited; preferably wherein activity of the SIK3 is reduced; and wherein the treatement comprises that ABL and/or SRC in the cells involved with the proliferative disorder is not inhibited; preferably wherein activity of the ABL1 and/or SRC is not reduced.

2. 8. The SIK3 inhibitor for use of any one of claims 1 to 7, wherein cells involved with the proliferative disorder are exposed to TNF and/or an agonist of TNFR1- signalling.

9. The SIK3 inhibitor for use of any one of claims 1 to 8, wherein: (x) the subject is distinguished by having a plasma concentration of TNF greater than about 5 pg/mL; and/or (y) the proliferative disorder is a solid tumour that, in the subject, by having an intratumoural concentration of TNF greater than about 1 pg/mL.

10.
A SIK3 inhibitor for use in athe treatment of a proliferative disorder, which is a cancer or tumour, in a subject, the treatment comprising exposing cells involved with the proliferative disorder in the subject to: (i) TNF, and/or an agonist of TNFR1-signalling; and (ii) thea SIK3 inhibitor.

11. The , wherein the SIK3 inhibitor for use of claim 10, wherein the amount of TNF exposed to cells involved with the proliferative disorder in the subject is increased.

3. 12. The SIK3 inhibitor for use of claim 10 or 11,is administered to the subject; and wherein: (i)a) the TNF or anthe agonist of TNFR1-signalling is administered to the subject; (iib) an agent that is capable of inducing or induces the exposure of the cells involved with the proliferative disorder to the TNF or anthe agonist of TNFR1-signalling, is administered to the subject; or (iiic) the exposure of the cells involved with the proliferative

disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.

~~13. The SIK3 inhibitor for use of any one of claims 10 to 12, wherein the treatment comprises that the SIK3 inhibitor is administered to the subject.~~

~~14. The SIK3 inhibitor for use of any one of claims 10 to 13, wherein the treatment comprises that the SIK3 inhibitor is administered to the subject in a therapeutically effective amount effective to inhibit SIK3, in particular SIK3 in the cells involved with the proliferative disorder.~~

~~15. The SIK3 inhibitor for use of any one of claims 10 to 14, wherein the treatment comprises that the SIK3 inhibitor is administered to the subject in a therapeutically effective amount not effective to inhibit ABL and/or SRC, in particular ABL and/or SRC in the cells involved with the proliferative disorder.~~

~~16. The SIK3 inhibitor for use of any one of claims 10 to 15, wherein the treatment comprises that TNF or the agonist of TNFR1 signalling is administered to the subject.~~

4.~~17.~~ ~~The SIK3 inhibitor for use of any one of claims 10 to 15, wherein the treatment comprises that an agent that is capable of inducing or induces the exposure of the cells involved with the proliferative disorder to TNF or an agonist of TNFR1 signalling, is administered to the subject.~~

~~18. The SIK3 inhibitor for use of any one of claims 10 to 15, wherein the exposure of the cells involved with the proliferative disorder to TNF is induced by a pharmaceutical, therapeutic or other procedure that increases the amount of TNF in the plasma of the subject and/or in the environment of such cells.~~

~~19. The SIK3 inhibitor for use of claim 18, wherein the pharmaceutical, therapeutic or other procedure comprises cancer immunotherapy and/or radiotherapy.~~

~~20. The SIK3 inhibitor for use of any one of claims 1 to 19, wherein the subject is distinguished by having cells involved in the proliferative disorder characterised by expression and/or activity of SIK3, in particular such cells express mRNA and/or protein of SIK3, and/or are positive for such SIK3 expression and/or activity.~~

~~21. The SIK3 inhibitor for use of any one of claims 1 to 20, wherein the proliferative disorder is a tumour, in particular a solid tumour.~~

~~22. The SIK3 inhibitor for use of claim 21, wherein the subject is distinguished as having been previously treated with an immunotherapy and whose tumour has progressed, in particular whose tumour relapsed, recurred or did not respond.~~

~~23. The SIK3 inhibitor for use of claim 21 or 22, wherein the subject is distinguished as having a tumour that progressed, in particular relapsed, recurred or did not respond to, prior radiotherapy.~~

~~24.~~ **A SIK3 inhibitor for use in a treatment for the reduction in risk of developing ~~a haematological proliferative disorder as a secondary disorder~~an iatrogenic immunodeficiency-associated lymphoproliferative disease** in a subject being treated with an anti-TNF agent, the treatment comprising administering the ~~SIK3~~ inhibitor of SIK3 to the subject.

5. ~~25.~~ The SIK3 inhibitor for use of claim ~~24~~4, wherein the ~~subject suffers from, and/or the subject is being treated with the~~ anti-TNF agent ~~for, an autoimmune disorder; preferably an autoimmune disorder~~ is one selected from ~~the group~~a list consisting of: ~~rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis and Crohn's Disease, most preferably rheumatoid arthritis~~infliximab, adalimumab, golimumab, humicade, etanercept, onercept and certolizumab pegol, in particular infliximab or humicade.

~~26. The SIK3 inhibitor for use of any one of claims 1 to 25, wherein the SIK3 inhibitor is a SIK3-specific inhibitor.~~

6. ~~27.~~The SIK3 inhibitor for use of any one of claims 1 to ~~26~~5, wherein the SIK3 inhibitor inhibits SIK3 more potently than it inhibits ~~ABL1 and/or SRC kinase; and~~SIK2.

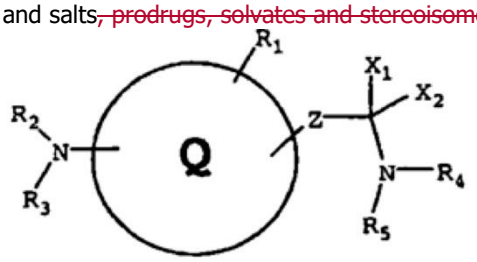
6.7. The SIK3 inhibitor for use of any one of claims 1 to 6, wherein the SIK3 inhibitor inhibits SIK3 ~~more potently than it inhibits SIK2~~preferentially to inhibiting Abl and/or Bcr-Abl.

~~28.~~

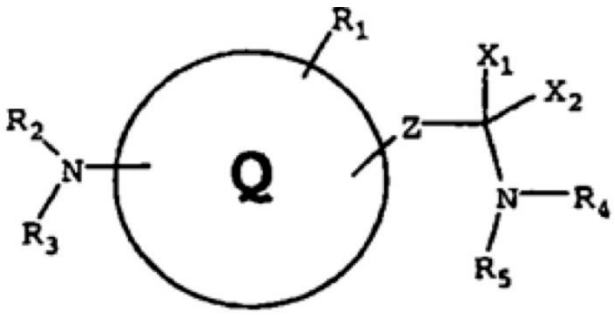
The SIK3 inhibitor for use of any one of claims 1 to ~~27, wherein the SIK3 inhibitor is an inhibitory nucleic acid.~~

~~7.~~8. ~~29. The SIK3 inhibitor for use of any one of claims 1 to 27~~7, wherein the SIK3 inhibitor is a small molecule, in particular, a small molecule ligand or a small cell-permeable molecule.

~~8.~~9. ~~30.~~ The SIK3 inhibitor for use of any one of claims 1 to ~~27~~8, wherein the SIK3 inhibitor is a cyclic compound of the following formula I~~,~~ and salts~~, prodrugs, solvates and stereoisomers~~ thereof~~:~~



~~formula I,~~



formula I

where

Q is:

(1) a 5-membered heteroaryl ring;
(2) a 6-membered heteroaryl ring; or
(3) an aryl ring;

optionally substituted with one or more groups R_1;

Z is:

(1) a single bond;
(2) $-R_{16}C=CH-$; or
(3) $-(CH_2)_m-$, where m is 1 to 2;

X_1 and X_2 are each hydrogen, or together form =O or =S;

R_1 is:

(1) hydrogen or R_6,

where R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, or heterocycloalkyl, each of which is unsubstituted or substituted with Z_1, Z_2 and one or more (preferably, one or two) groups Z_3;

(2) -OH or -OR_6;

(3) -SH or -SR_6;

(4) -$C(O)_2H$, -$C(O)_qR_6$, or -O-$C(O)_qR_6$, where q is 1 or 2;

(5) -SO_3H or -$S(O)_qR_6$;

(6) halo;

(7) cyano;

(8) nitro;

(9) -Z_4-NR_7R_8;

(10) -Z_4-$N(R_9)$-~~Z_5-$NR_{10}R_{11}$~~$Z_r$$NR_{10}R_{11}$;

~~(1)~~ (11) -Z_4-$N(R_{12})$-Z_5-R_6;

(12) -$P(O)(OR_6)_{2z}$;

R_2 and R_3 are each independently:

~~(1)~~ (1) hydrogen or R_6;

(2) -Z_4-R_6; or

(3) -Z_{13}-NR_7R_8;

R_4 and R_5:

(1) are each independently hydrogen or R_6;

(2) -Z_4-$N(R_9)$-Z_5-$NR_{10}R_{11}$;

(3) -$N(R_9)Z_4R_6$; or

(4) together with the nitrogen atom to which they are attached complete a 3- to 8-membered saturated or unsaturated heterocyclic ring which is unsubstituted or substituted with Z_1, Z_2 and Z_3, which heterocyclic ring may optionally have fused to it a benzene ring itself unsubstituted or substituted with Z_1, Z_2 and Z_3;

R_7, R_8, R_9, R_{10}, R_{11} and R_{12}:

(1) are each independently hydrogen or R_6;

(2) R_7, and R_8 may together be alkylene, alkenylene or heteroalkyl, completing a 3- to 8-membered saturated or unsaturated ring with the nitrogen atom to which they are attached, which ring is unsubstituted or ~~substituted~~substituted with Z_1~~,~~ Z_2 and Z_3; or

(3) any two of R_9, R_{10} and R_{11} may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with Z_1, Z_2 and Z_3;

R_{13} is:

(1)cyano;

(2) nitro;

(3) -NH_2;

(4) -NHOalkyl;

(5) -OH;

(6) -NHOaryl;

(7) -NHCOOalkyl;

(8) -NHCOOaryl;

(9) -$NHSO_2$alkyl;

(10) -$NHSO_2$aryl;

(11) aryl;

~~(1)~~ (12) heteroaryl;

~~(2)~~

(13) -Oalkyl; or

(14) -Oaryl;

R_{14} is:
(1) $-NO_2$;
(2) -COOalkyl; or
(3) -COOaryl;

R_{15} is:

(1) hydrogen;
(2) alkyl;
(3) aryl;
(4) arylalkyl; or
(5) cycloalkyl;

Z_1, Z_2 and Z_3 are each independently:

(1) hydrogen or Z_6, where Z_6 is (i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, alkylaryl, cycloalkylaryl, heterocyclo, or heterocycloalkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is substituted by one or more of the following groups (2) to (16) of the definition of Z_1, Z_2 and Z_3;
(2) -OH or $-OZ_6$;
(3) -SH or $-SZ_6$;
(4) $-C(O)_qH$, $-C(O)_qZ_6$, or $-O-C(O)_qZ_6$;
(5) $-SO_3H$, $-S(O)_qZ_6$; or $S(O)_qN(Z_9)Z_6$;
(6) halo;
(7) cyano;
(8) nitro;
(9) $-Z_4-NZ_7Z_8$;
(10) $-Z_4-N(Z_9)-Z_5-NZ_7Z_8$;
(11) $-Z_4-N(Z_{10})-Z_5-Z_6$;
~~(1)~~ $-Z_4-N(Z_{10})-Z_5-H$;
(12)
(13) oxo;
(14) $-O-C(O)-Z_6$;
(15) any two of Z_1, Z_2, and Z_3 may together be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached; or
(16) any two of Z_1, Z_2, and Z_3 may together be $-O-(CH_2)_r-O-$,where r is 1 to 5, completing a 4- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached;

Z_4 and Z_5 are each independently:

(1) a single bond;
(2) $-Z_{11}-S(O)_q-Z_{12}$~~-;~~
(3) $-Z_{11}-C(O)-Z_{12}$;
(4) $-Z_{11}-C(S)-Z_{12}-$;
(5) $-Z_{11}-O-Z_{12}-$;
(6) $-Z_{11}-S-Z_{12}-$;
(7) $-Z_{11}-O-C(O)-Z_{12}$; or
(8) $-Z_{11}-C(O)-O-Z_{12}-$;

Z_7, Z_8, ~~Z_9~~Z_9 and Z_{10}:

(1) are each independently hydrogen or Z_6;
(2) Z_7 and Z_8, or Z_6 and Z_{10}, may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with Z_1, Z_2 and Z_3; or

(3) Z_7 or Z_8, together with Z_9, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted ~~or substituted with Z_1, Z_2 and Z_3;~~
or substituted with Z_1, Z_2 and Z_3;

Z_{11} and Z_{12} are each independently:

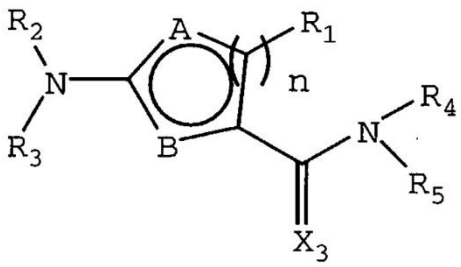
(1) a single bond;
(2) alkylene;
(3) alkenylene; or
(4) alkynylene; and

Z_{13} is:

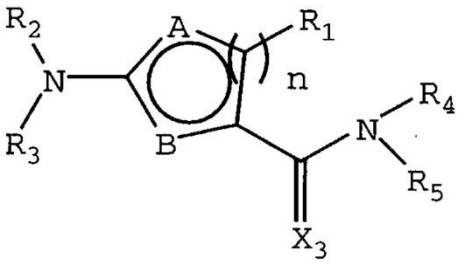
(1) a single bond;
(2) $-Z_{11}-S(O)_q-Z_{12}-$;
(3) $-Z_{11}-C(O)-Z_{12}-$;
(4) $-Z_{11}-C(S)-Z_{12}-$;
(5) $-Z_{11}-O-Z_{12}-$;
(6) $Z_{11}-S-Z_{12}-$;
(7) $-Z_{11}-O-C(O)-Z_{12}$~~-;~~
~~-Z_{11}-C~~ (8) $-Z_{11}C(O)-O-Z_{12}$~~-;~~
~~(1)~~ (9) $-C(NR_{13})-$;
~~(2) -~~
(10) $-C(CHR_{14})-$; or
(11) $-C(C(R_{14})_2)$~~-.)-~~;

wherein~~:~~

~~Q is thiazole;~~
~~Z is a single bond;~~
~~R_1 is hydrogen;~~
~~X_1 and X_2 together form =O;~~
~~R_2 is hydrogen;~~
~~R_3 is $-Z_4-R_6$, wherein Z_4 is a si~~
~~which is unsubstituted or sut~~
~~more groups Z_3; and~~
~~R_4 is hydrogen,~~



~~wherein,~~ the cyclic compound of formula I has the following formula II:



formula II~~,~~

where

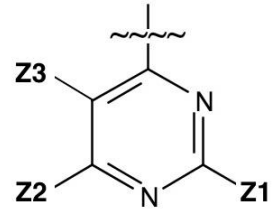
n is 1; or 2
A is selected from carbon and nitrogen;
B is selected from nitrogen, oxygen and sulphur;
X_3 is oxygen; or sulphur; and
R_1, P_2, R_3, R_4 and R_5 are as described above; and

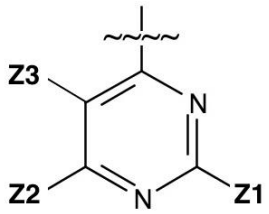
wherein the R2 of formula II is hydrogen;

~~R_2 is hydrogen;~~

~~R_4 is hydrogen;~~, and

R3 of formula II is Rx, ~~where~~wherein Rx has the following formula X:





formula X,

wherein Z1, Z2 and Z3 of formula X are as defined above.

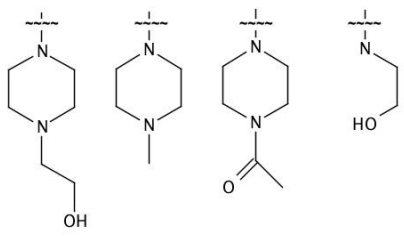
~~31.~~ The SIK3 inhibitor for use of claim ~~30~~9, wherein~~, in formula X:~~

~~Z_1 is methyl;~~

~~Z_2 is $-Z_4-NZ_7Z_8$, $-Z_4-N(Z_9)-Z_5-NZ_7Z_8$ or $-Z_4-N(Z_{10})-Z_5-H$; wherein Z_4 and Z_5 to Z_{10} are as defined herein, in particular where Z_4 is a single bond; and~~

~~Z_3 is hydrogen.~~

~~32. The SIK3 inhibitor for use of claim 30 or 31, wherein: Z_2 in formula X is a substituent selected from the group consisting of:~~



~~33. The SIK3 inhibitor for use of any one of claims 30 to 32, wherein R_4 of formula II is hydrogen and R_5 of formula II is R_6, where R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, aryl, aralkyl, heterocyclo, heteroaryl or heterocycloalkyl, each of which is unsubstituted or substituted with Z_1, Z_2 and one, two or more groups Z_3; wherein Z_1, Z_2 and Z_3 are as defined above; preferably wherein R_6 is aryl, aralkyl, heterocyclo, or~~

~~heterocycloalkyl, each of which is unsubstituted or substituted with Z_1, Z_2 and one, two or more groups Z_3; wherein Z_1, Z_2 and Z_3 are as defined above.~~

~~34. The SIK3 inhibitor for use of claim 33, wherein R_6 is aryl or heteroaryl, each of which is unsubstituted or substituted with Z_1, Z_2 and one, two or more groups Z_3; wherein Z_1, Z_2 and Z_3 are as defined above; and wherein R_6 is a monocyclic aryl or heteroaryl substituted with one, two or three Zx, with at least one Zx at an ortho-position on the monocyclic aryl or heteroaryl; wherein each Zx may be, independently: (i) Zy, where Zy is a C1, C2 or C3 alkyl, alkenyl or alkynyl; (ii) -OH or -OZy; (iii) -SH or -SZy; (iv) halo; or (v) -SO2-Zy or -SO2-N(Zy)(Zy).~~

~~35. The SIK3 inhibitor for use of claim 34, wherein R_6 is phenyl, optionally substituted with one, two or three Zx; in particular where one Zx is substituted at the ortho position of the phenyl; and/or in particular where each Zx is independently selected from the group consisting of: -Cl, -F, -Br, -Me, -OMe, -OEt and -CN (preferably, selected from -Cl, -F, -Me and -Br).~~

~~36. The SIK3 inhibitor for use of claim 34, wherein the R_6 is a monocyclic heteroaryl.~~

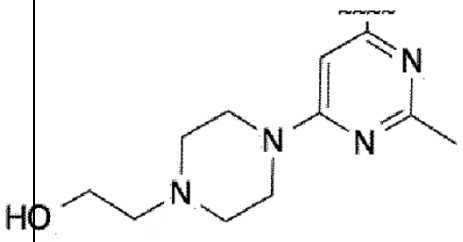
~~37. The SIK3 inhibitor for use of claim 36, wherein the monocyclic heteroaryl R_6 is a pyridinyl, preferably pyridin-2-yl, or more preferably pyridin-3-yl, where the monocyclic heteroaryl is optionally substituted with one, two or three Zx; in particular where one Zx is substituted at the ortho position of the pyridinyl; and/or in particular where each Zx is independently selected from the group consisting of: -Cl, -F, -Br, -Me, -OMe, -OEt and -CN (preferably, selected from -Cl, -F, -Me and -Br).~~

10. ~~38. The SIK3 inhibitor for use of any one of claims 30 to 35, wherein when, in general formula II, n is 1,~~ A is nitrogen~~,~~; B is sulphur~~,~~; n is 1; X3 is oxygen~~, R_1 is hydrogen, R_2 is hydrogen, R_4 is hydrogen, R_5 is R_6 and R_6 is: ~~; R_1, R_2 and R_4 are hydrogen; and R_5 is selected from aryl groups or heteroaryl groups which are substituted with Z1, Z2 and one or more groups Z3, preferably substituted with one or two groups Z3, and R3 is selected from -Z4-R_6 or -Z13-NR_7R_5.

- ~~a phenyl substituted at an ortho position with a -Cl, then either (x) the other ortho position is hydrogen, or a Zx that is not methyl, in particular a Zx that is -Cl, -F, -Br, -OMe, -OEt, or -CN, and at least one of the meta or the para positions is substituted with Zx as defined above; or (y) the other ortho position is methyl and at least two of the meta or para positions are substituted with Zx; or (z) R_3 is not formula Y; or~~
- ~~a phenyl substituted at an ortho position with a methyl, then either (x) the other ortho position is hydrogen, or a Zx that is not -Cl, in particular a Zx that is -F, -Br, -Me, -OMe, -OEt or -CN, and at least one of the meta or the para positions is substituted with Zx as defined above; or (y) the other ortho position is -Cl and at least two of the meta or para positions are substituted with Zx; or (z) R3 is not formula Y.~~

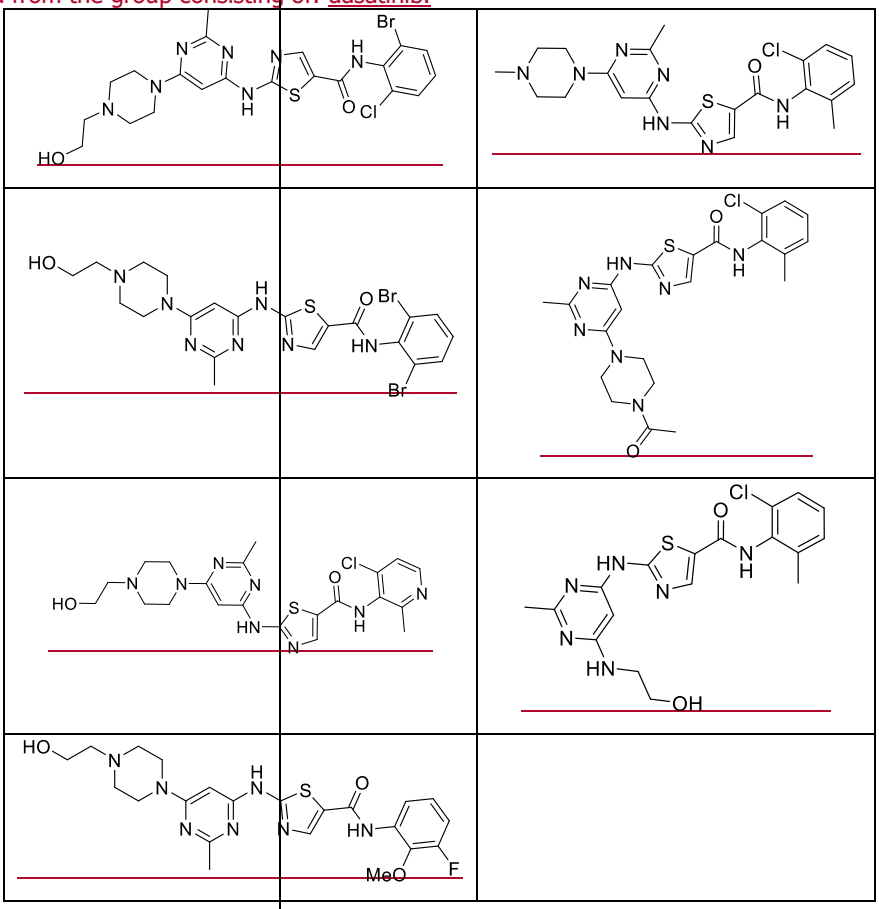
11. ~~39.~~ The SIK3 inhibitor for use of claim 9 or 10, wherein R_2 is a hydrogen and R_3 has the following formula

Y:

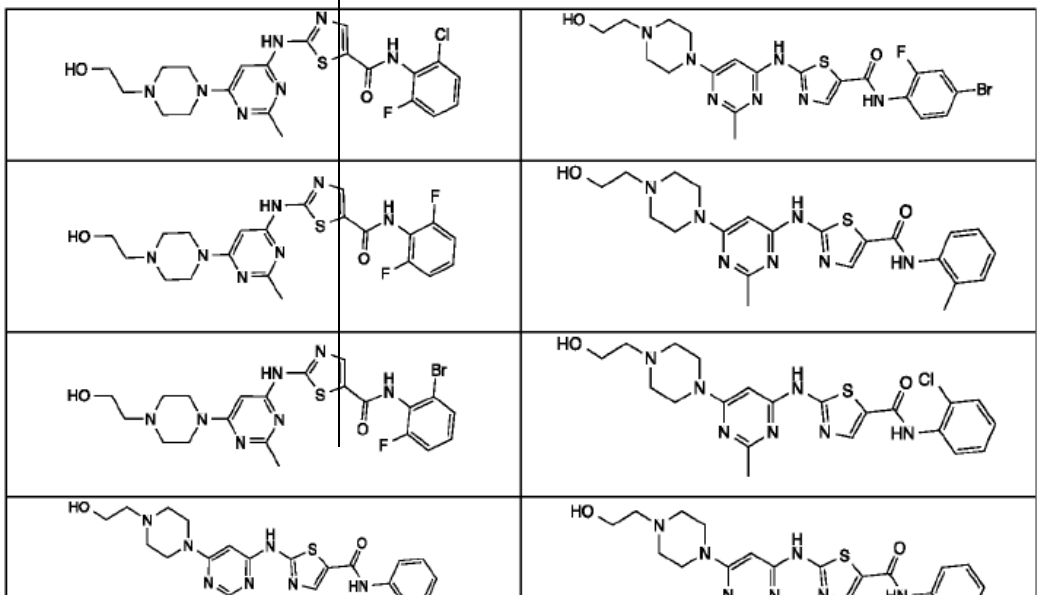


formula Y.

12. The SIK3 inhibitor for use of any one of claims 1 to ~~27~~11, wherein the SIK3 inhibitor is ~~a cyclic compound selected from the group consisting of:~~ dasatinib.



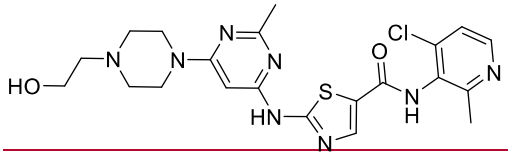
13. The SI K3 inhibitor for use of any one of claims 1 to 11, wherein the SIK3 inhibitor is selected from the group consisting of:



and solvates, salts, complexes~~, stereoisomers~~, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, isotopically labelled forms, ~~prodrugs,~~ and combinations thereof.

~~40.~~

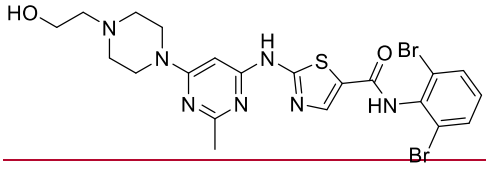
~~13.~~14. The SIK3 inhibitor for use of any one of claims 1 to ~~27~~7, wherein the SIK3 inhibitor is ~~the cyclic compound:~~ an inhibitory nucleic acid.



~~**B3,**~~

~~and solvates, salts, stereoisomers, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, isotopically labelled forms, prodrugs, and combinations thereof.~~

~~14.~~15. ~~41.~~ The SIK3 inhibitor for use of any one of claims 1 to ~~27~~3, or 6 to 14 when not referring to claim 4 or 5, wherein ~~the SIK3 inhibitor is the cyclic compound:~~ cells involved in the proliferative disorder are resistant against a cell-mediated immune response.

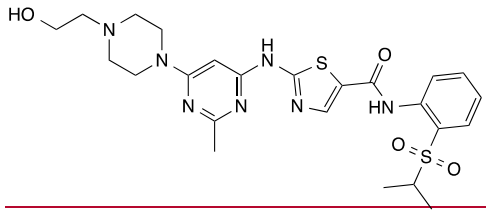


~~**B2,**~~

~~and solvates, salts, stereoisomers, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, isotopically labelled forms, prodrugs, and combinations thereof.~~

~~42.~~

~~15.~~16. The SIK3 inhibitor for use of any one of claims 1 to ~~27~~3, or 6 to 15 when not referring to claim 4 or 5, wherein ~~the SIK3 inhibitor is the cyclic compound;~~ cells involved in the proliferative disorder have been subjected to prior immunotherapy, in particular the subject has had prior immunotherapy by administration with an immune checkpoint molecule.

17. 

~~A6,~~

~~and solvates, salts, stereoisomers, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, isotopically labelled forms, prodrugs, and combinations thereof; preferably wherein such SIK3 inhibitor inhibits SIK2 more potently than SIK3 and inhibits SIK3 more potently than SIK1.~~

~~43. **A cyclic compound** as set forth in claim 36, and solvates, salts, stereoisomers, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, isotopically labelled forms, prodrugs, and combinations thereof.~~

~~44. **A cyclic compound** as set forth in claim 42, and solvates, salts, stereoisomers, complexes, polymorphs, crystalline forms, racemic mixtures, diastereomers, enantiomers, tautomers, isotopically labelled forms, prodrugs, and combinations thereof.~~

~~45. **A**~~The SIK3 inhibitor for use of any one of claims 1 to 3, 15 or 16, or 6 to 14 when not referring to claim 4 or 5, wherein cells involved in the proliferative disorder are **characterised by** expression and/or activity of SIK3, in particular such cells express mRNA and/or protein of SIK3, and/or are positive for such SIK3 expression and/or activity.

18. **An in-vitro method for determining** whether a subject has, or is at risk of~~,~~ developing~~,~~ a proliferative disorder, such as a tumour, that is associated with cellular resistance against a cell-mediated immune response, the method comprising the step of:

(a)~~-~~ detecting an applicable biomarker in a biological sample from said subject; and

~~wherein~~ (b) determining the ~~detection~~presence or amount of ~~the applicable biomarker~~TNF in ~~the~~a biological sample ~~indicates the proliferative disorder, or a risk of developing the proliferative disorder, in the~~from said subject; and

wherein the applicable biomarker is~~-one or more selected from the group consisting of:~~:

- SIK3, in particular the presence (or an amount) of or expression and/or activity of SIK3, preferably of phosphorylated SIK3~~;~~ protein; and
- ~~HDAC4, in particular the presence (or an amount) of or expression and/or activity of phosphorylated HDAC4, preferably in the cytoplasm in cells comprised in the sample;~~
- ~~TNFR1, in particular the presence (or an amount) of or expression and/or activity of TNFR1; and~~
- ~~LKB1, in particular the presence (or an amount) of or expression and/or activity of LKB1, preferably of phosphorylated LKB1.~~

~~46. The method according to claim 45,~~ wherein: (x) the detection of the applicable biomarker ~~comprises determining the presence or an amount of phosphorylated HDAC4, or activity thereof, in the sample, in particular in the cytoplasm in cells comprised in the sample.~~

~~47. The method according to claim 45 or 46, further comprising a step of determining the presence or amount of TNF in the sample, wherein~~ in the sample; and (y) the presence of or an amount of TNF in the sample indicates ~~the~~a proliferative disorder or a risk of developing ~~the~~a proliferative disorder that is

associated with cellular resistance against the cell-mediated immune response~~, and/or associated with expression or activity of SIK3,~~ in the subject~~; and wherein: (i) a plasma concentration of TNF greater than about 5 pg/mL in a plasma sample from the subject; and/or (ii) an intratumoural concentration of TNF greater than about 1 pg/mL plasma from a tissue sample from the subject, indicates the proliferative disorder or a risk of developing the proliferative disorder that is associated with cellular resistance against the cell-mediated immune response in the subject.~~

19.~~48. **A**~~ The method ~~**for determining** whether~~ according to claim 18, wherein (i) the sample is a ~~subject has, or has a risk~~plasma sample and the plasma concentration of ~~developing,~~ TNF greater than 2 pg/mL; and/or (ii) the sample is a sample of a solid tumour and the intratumoural concentration of TNF greater than 0.5 pg/mL.

20. ~~disease, disorder~~The method according to claim 18 or ~~condition that is associated with cellular resistance against a cell-mediated immune response and that is associated with~~ 19, wherein the applicable biomarker further includes: (i) TNFR1 or TNFR2, in particular the presence of, or an amount of, or expression and/or activity of ~~SIK3, the method comprising the steps of:~~ TNFR1 or TNFR2, in each case preferably TNFR1; and/or (ii) LKB1, preferably the presence of, or an amount of, or expression and/or activity of LKB1, preferably increased activity of LKB1 or pLKB1.

21. The method according to any one of claims 18 to 20, wherein the applicable biomarker further includes: (i) one or more class II or I la HDACs, or HDAC4, in particular the presence of, or an amount of, or expression and/or activity of such HDAC, preferably increased amount or activity of such HDAC or pHDAC, especially in the cytoplasm of cells of the tumour; and/or (ii) NF-kappa-B, in particular the presence of, or an amount of, or expression and/or activity of NF-kappa-B, preferably increased amount or activity of NF-kappa-B or acetylated NF-kappa-B, especially in the nucleus of cells of the tumour.

~~22. (a) contacting cells of the subject suspected to be involved with the disease, disorder or condition with a SIK3 inhibitor in the presence of a cell-mediated immune response being: (i) immune cells selected from the group consisting of: lymphocytes, T-cells, CTLs and TILs; or (ii) a pro-inflammatory cytokine in particular TNF; and~~

~~(b) determining the cell-mediated immune response against such cells of the subject,~~

~~wherein an enhancement of the cell-mediated immune response against such cells of the subject indicates that the subject has or has a risk of developing such disease, disorder or condition.~~

~~49. **A use of an antigen binding protein** (ABP) capable of binding specifically to SIK3 or HDAC4 in an in-vitro diagnosis of a proliferative disease, disorder or condition in a subject; wherein the proliferative disease, disorder or condition is associated with cellular resistance against a cell-mediated immune response, and that is associated with expression or activity of SIK3.~~

~~50. The use according to claim 49, wherein the ABP is capable of binding specifically to phosphorylated SIK3.~~

~~51. The use according to claim 49, wherein the ABP is capable of binding specifically to phosphorylated HDAC4.~~

~~52. **A use of a kit** in an in-vitro diagnosis of a proliferative disease, disorder or condition in a subject, wherein the proliferative disease, disorder or condition is associated with cellular resistance against a cell-mediated immune response and that is associated with expression or activity of SIK3, wherein the kit comprises: (a) either (x) a nucleic acid capable of binding specifically to SIK3 or HDAC4, or (y) an ABP binding specifically to SIK3 or HDAC4; and (b) optionally (i) instructions describing how to use the ABP or a nucleic acid or kit for detecting SIK3 activity in a sample obtained from a subject; and/or (ii) one or more other item, component, reagent or other means useful for the use of the kit or the detection of SIK3 activity in the sample.~~

~~53. **A kit for use in a diagnostic method** for determining whether a subject has, or has a risk of developing, a disease, disorder or condition that is associated with cellular resistance against a cell-mediated immune response and that is associated with expression or activity of SIK3;~~

~~wherein:~~

- ~~the diagnostic method comprises a step of surgically obtaining a sample from the subject; and~~
- ~~the kit comprises: (a) either (x) a nucleic acid capable of binding specifically to SIK3 or HDAC4, or (y) an ABP binding specifically to SIK3 or HDAC4; and (b) optionally (i) instructions describing how to use the ABP or a nucleic acid or kit for detecting SIK3 activity in the sample; and/or (ii) one or more other item, component, reagent or other means useful for the use of the kit or the detection of SIK3 activity in the sample.~~

~~54. The method of any one of claims 45 to 48, the~~ The SIK3 inhibitor for use of any one of claims ~~49 to 52, or the kit of claim 53, wherein the disease, disorder or condition is, and/or is determined to be, one, or the subject is distinguished as one, suitable for treatment with a SIK3 inhibitor.~~

~~55. The~~ 1 to 17, or the method of any one of claims ~~45 to 48 or 54, the use of any one of claims 49 to 52 or 54, or the kit of claim 53 or 54, wherein the subject is distinguished as having been previously treated with an immunotherapy and whose tumour has progressed, in particular whose tumour relapsed, recurred or did not respond~~18 to 21, wherein the subject is a human subject.

23. ~~56. The method of any one of claims 45 to 48, 54 or 55, the use of any one of claims 49 to 52, 54 or 55, or the kit for use of any one of claims 53 to 55, wherein the subject is distinguished as having been previously treated with radiotherapy and whose tumour has progressed, in particular whose tumour relapsed, recurred or did not respond.~~

~~57. A~~ **An in-vitro method for identifying and/or characterising** a compound suitable for ~~a~~the treatment of a disease, disorder or condition that is **characterised by** cellular resistance against a cell-mediated immune response ~~and that is characterised by expression or activity of SIK3,~~ the method comprising the steps of:

(a) bringing into contact a first cell expressing SIK3 and ~~(i)~~ the candidate compound~~, or (ii) the candidate compound and a cell-mediated immune response; and~~ ; and

(b) determining (i) the expression, activity, function and/or stability of ~~the (eg protein or mRNA of)~~ SIK3~~(~~, in particular, of phosphorylated ~~SIK3),~~SI K3, in the first cell; and~~/or~~ (ii) the cytotoxicity of ~~the~~a cell-mediated immune response against the first cell,

wherein: (~~i~~x) a reduced expression, activity function and/or stability of the SIK3, in said first cell contacted with the candidate compound compared to said first cell not contacted with said candidate compound; and~~/or (ii~~ (y) an enhanced cytotoxicity of the cell-mediated immune response against the first cell contacted with the candidate compound compared to the cytotoxicity of the cell-mediated immune response against the first cell not contacted with the candidate compound; ~~indicates~~indicate that the candidate compound is a compound suitable for the treatment of the disease, disorder or condition that is **characterised by** cellular resistance against a cell-mediated immune response; and ~~that~~wherein the cell-mediated immune response is ~~characterised by expression or activity of SIK3~~TNF.

24. ~~58. **A method for identifying and/or characterising** a compound suitable for a treatment of a disease, disorder or condition that is characterised by cellular resistance against a cell-mediated immune response, the method comprising the steps of:~~

~~(a) bringing into contact a first cell expressing SIK3 and~~The method of claim 23, wherein the candidate compound~~;~~ ~~and~~

~~(b) determining:~~

~~(i) the expression, activity, function and/or stability of protein or mRNA of SIK3~~ is a SIK3 inhibitor, in particular~~,~~ ~~of phosphorylated~~ a SIK3~~,~~ inhibitor as defined in ~~the first cell; and~~

~~(ii) the cytotoxicity of a cell-mediated immune response against the first cell,~~

~~wherein:~~

(i) a reduced expression, activity function and/or stability of the SIK3, in said first cell contacted with the candidate compound comparedany one of claims 9 to said first cell not contacted with said candidate compound; and 13.

(ii) an enhanced cytotoxicity of the cell-mediated immune response against the first cell contacted with the candidate compound compared to the cytotoxicity of the cell-mediated immune response against the first cell not contacted with the candidate compound;

indicates that the candidate compound is a compound suitable for the treatment of the disease, disorder or condition that is characterised by cellular resistance against a cell-mediated immune response and/or one that is characterised by expression or activity of SIK3; and

wherein, the cell-mediated immune response is: (x) a pro-inflammatory cytokine, in particular TNF; or (y) a second cell which is a cytotoxic immune cell immunologically recognising the first cell, in particular a CTL.

59. The method according to claim 58, wherein the cell-mediated immune response is a pro-inflammatory cytokine, in particular TNF.

60.

25. The method ~~according to~~of claim ~~58~~23 or ~~59~~24, wherein the ~~first cell~~disease, disorder or condition is a ~~cell involved with a~~proliferative disorder.

~~25.~~26. The method of any one of claims 18 to 21 or 25, wherein the proliferative disorder~~, in particular~~ is a cancer or tumour.

27. The SIK3 inhibitor for use of any one of claims 1 to 3, or 6 to 17 and 22, when not referring to claim 4 or 5, or the method of claim 26, wherein the proliferative disorder is a solid tumour.

28. The SIK3 inhibitor for use of any one of claims 1 to 3, 6 to 14, 17, or 22, when not referring to claim 4 or 5, or the method of claim 26, wherein the proliferative disorder is a haematological malignancy.