

1 WHAT IS CLAIMED IS CLAIMS

2 1. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody
3 comprising a heavy chain variable domain and a light chain variable domain,
4 wherein said heavy chain variable domain comprises:
5 a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID
6 NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and
7 wherein said light chain variable domain comprises:
8 a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID
9 NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

1 2. The antibody of claim 1, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:2.

1 3. The antibody of claim 1 or 2, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:4.

1 4. The antibody of any one of claims 1-3, wherein said antibody is a
2 humanized antibody, a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.

1 5. The antibody of ~~claim 1~~ any one of the preceding claims, wherein said
2 antibody is an IgG1 or an IgG2.

1 ~~6. The antibody of claim 1, wherein said antibody is capable of binding a~~
2 ~~ROR2 protein.~~

1 ~~7. The antibody of claim 6, wherein said ROR2 protein comprises the amino~~
2 ~~acid sequence of SEQ ID NO:18.~~

1 ~~8. The antibody of claim 6, wherein said antibody is capable of binding the~~
2 ~~extracellular domain of said ROR2 protein.~~

1 ~~9. The antibody of claim 8, wherein said extracellular domain comprises the~~
2 ~~amino acid sequence of SEQ ID NO:22.~~

1 ~~10.~~ The antibody of claim 8, wherein said extracellular domain is a Kringle
2 domain.

1 ~~11.~~ The antibody of claim 6, wherein said ROR2 protein comprises a histidine
2 at a position corresponding to position 349 or an aspartic acid at a position corresponding to
3 position 354 of SEQ ID NO:22.

1 ~~12.~~ The antibody of claim 6, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 1 nM.

1 ~~13.~~ The antibody of claim 6, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) of about 0.06 nM.

1 ~~14~~6. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody
2 comprising a heavy chain variable domain and a light chain variable domain,
3 wherein said heavy chain variable domain comprises:
4 a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID
5 NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and
6 wherein said light chain variable domain comprises:
7 a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID NO:35, and a CDR
8 L3 as set forth in SEQ ID NO:36.

1 ~~15~~7. The antibody of claim ~~14~~6, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:6.

1 ~~16~~8. The antibody of claim ~~14~~6, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:8.

1 ~~17~~9. The antibody of claim ~~14~~6, wherein said antibody is a humanized
2 antibody, a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.

1 ~~18~~10. The antibody of claim ~~14~~6, wherein said antibody is an IgG1 or an IgG2.

1 ~~19~~11. The antibody of claim-~~14~~6, wherein said antibody is capable of binding a
2 ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

1 ~~20~~12. The antibody of claim-~~19~~11, wherein said antibody is capable of binding
2 an extracellular domain of said ROR2 protein.

1 ~~21~~13. The antibody of claim-~~20~~12, wherein said extracellular domain comprises
2 the amino acid sequence of SEQ ID NO:22.

1 ~~22~~14. The antibody of claim-~~20~~12, wherein said extracellular domain is an Ig-
2 like domain.

1 ~~23~~15. The antibody of claim-~~19~~11, wherein said ROR2 protein comprises a
2 methionine at a position corresponding to position 386 of SEQ ID NO:22.

1 ~~24~~16. The antibody of claim-~~19~~11, wherein said antibody is capable of binding
2 said ROR2 protein with an equilibrium dissociation constant (K_D) from about 0.2 nM to about 5
3 nM.

1 ~~25~~17. The antibody of claim-~~19~~11, wherein said antibody is capable of binding
2 said ROR2 protein with an equilibrium dissociation constant (K_D) of about 1.9 nM.

1 ~~26~~18. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody
2 comprising a heavy chain variable domain and a light chain variable domain,
3 wherein said heavy chain variable domain comprises:
4 a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID
5 NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and
6 wherein said light chain variable domain comprises:
7 a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID
8 NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

1 ~~27~~19. The antibody of claim-~~26~~18, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:10.

1 ~~28~~20. The antibody of claim-~~26~~ 18, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:12.

1 ~~29~~21. The antibody of claim-~~26~~ 18, wherein said antibody is a humanized
2 antibody, a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.

1 ~~30~~22. The antibody of claim-~~26~~ 18, wherein said antibody is an IgG1 or an IgG2.

1 ~~34~~23. The antibody of claim-~~26~~ 18, wherein said antibody is capable of binding a
2 ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

1 ~~32~~24. The antibody of claim-~~34~~ 23, wherein said antibody is capable of binding
2 an extracellular domain of a ROR2 protein.

1 ~~33~~25. The antibody of claim-~~32~~ 24, wherein said extracellular domain comprises
2 the amino acid sequence of SEQ ID NO:22.

1 ~~34~~26. The antibody of claim-~~32~~ 24, wherein said wherein said extracellular
2 domain is a Kringle domain.

1 ~~35~~27. The antibody of claim-~~34~~ 23, wherein said ROR2 protein comprises a
2 histidine at a position corresponding to position 349, an aspartic acid at a position corresponding
3 to position 354, or a methionine at a position corresponding to position 386 of SEQ ID NO:22.

1 ~~36~~28. The antibody of claim-~~34~~ 23, wherein said antibody is capable of binding
2 said ROR2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about
3 150 nM.

1 ~~37~~29. An anti-tyrosine kinase-like orphan receptor 2 (ROR2) antibody
2 comprising a heavy chain variable domain and a light chain variable domain,
3 wherein said heavy chain variable domain comprises:
4 a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID
5 NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and
6 wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

~~38~~30. The antibody of claim-~~37~~ 29, wherein said heavy chain variable domain comprises the sequence of SEQ ID NO:14.

~~39~~31. The antibody of claim-~~37~~ 29, wherein said light chain variable domain comprises the sequence of SEQ ID NO:16.

~~40~~32. The antibody of claim-~~37~~ 29, wherein said antibody is a humanized antibody, a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.

~~41~~33. The antibody of claim-~~37~~ 29, wherein said antibody is an IgG1 or an IgG2.

~~42~~34. The antibody of claim-~~37~~ 29, wherein said antibody is capable of binding a ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.

~~43~~35. The antibody of claim-~~42~~ 34, wherein said antibody is capable of binding an extracellular domain of said ROR2 protein.

~~44~~36. The antibody of claim-~~43~~ 35, wherein said extracellular domain comprises the amino acid sequence of SEQ ID NO:22.

~~45~~37. The antibody of claim-~~41~~ 33, wherein said extracellular domain is an Ig-like domain.

~~46~~38. The antibody of claim-~~42~~ 34, wherein said antibody is capable of binding said ROR2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 150 nM.

~~47. The antibody of any one of claims 6, 19, 31 or 42, wherein said ROR2 protein is expressed on a cell.~~

~~48. The antibody of claim 47, wherein said cell is a cancer cell.~~

1 49. ~~The antibody of claim 48, wherein said cancer cell is a breast cancer cell,~~
2 ~~ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer~~
3 ~~cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.~~

1 5039. The antibody of any one of claims 1, 146, 26-18 or 37 29, wherein said
2 antibody is attached to a therapeutic agent.

1 5140. The antibody of any one of claims 1, 146, 26-18 or 37 29, wherein said
2 antibody is attached to a diagnostic agent.

1 5241. ~~A method of treating cancer in a subject in need thereof, said method~~
2 ~~comprising administering to a subject a therapeutically effective amount of an~~ Use of the
3 antibody of any one of claims 1, 146, 26-18 or 37 29 in the manufacture of a medicament for the
4 treatment of cancer in a subject in need thereof.

1 5342. ~~A method of inhibiting metastasis of a ROR2-expressing cancer in a~~
2 ~~subject in need thereof, said method comprising administering to a subject a therapeutically~~
3 ~~effective amount~~ Use of the antibody of any one of claims 1, 146, 26-18 or 37 29 in the
4 manufacture of a medicament for inhibiting metastasis of a ROR2-expressing cancer in a subject
5 in need thereof.

1 5443. The ~~method~~ use of claim ~~52 41 or 42~~, wherein said cancer is breast cancer,
2 ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck
3 cancer, bone cancer, skin cancer or prostate cancer.

1 5544. A method of detecting a ROR2-expressing cell, said method comprising
2 (i) contacting a ROR2-expressing cell with an antibody of any one of claims 1,
3 14, 26 or 37-40; and
4 (ii) detecting binding of said antibody to a ROR2 protein expressed by said cell.

1 5645. The method of claim ~~55 44~~, wherein said antibody is attached to a
2 detectable moiety.

1 5746. The method of claim ~~55~~ 44 or 45, wherein said ROR2-expressing cell is in
2 a subject.

1 58. ~~The method of claim 57, wherein said subject is a subject having cancer.~~

1 59. ~~The method of claim 58, wherein said cancer is cancer is breast cancer,~~
2 ~~ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck~~
3 ~~cancer, bone cancer, skin cancer or prostate cancer.~~

1 60. ~~The method of claim 55, wherein said contacting occurs *in vitro*.~~

1 61. ~~A method of delivering a therapeutic agent to a ROR2-expressing cell,~~
2 ~~said method comprising contacting a ROR2-expressing cell with an antibody of any one of~~
3 ~~claims 1, 14, 26 or 37, wherein said antibody is attached to a therapeutic agent.~~

1 62. ~~The method of claim 61, wherein said therapeutic agent is an anti-cancer~~
2 ~~agent.~~

1 63. ~~The method of claim 61, wherein said ROR2-expressing cell is in a~~
2 ~~subject.~~

1 64. ~~The method of claim 63, wherein said subject is a subject having cancer.~~

1 65. ~~The method of claim 64, wherein said cancer is cancer is breast cancer,~~
2 ~~ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck~~
3 ~~cancer, bone cancer, skin cancer or prostate cancer.~~

4 66. ~~The method of claim 62, wherein said contacting occurs *in vitro*.~~

1 67. ~~A method of inhibiting migration of a ROR2-expressing cell, said method~~
2 ~~comprising contacting a ROR2-expressing cell with an antibody of any one of claims 1, 14, 26 or~~
3 ~~37.~~

1 68. ~~The method of claim 67, wherein said ROR2-expressing cell is in a~~
2 ~~subject having cancer.~~

1 69. ~~The method of claim 68, wherein said cancer is cancer is breast cancer,~~
2 ~~ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and neck~~
3 ~~cancer, bone cancer, skin cancer or prostate cancer.~~

1 70. ~~The method of claim 67, wherein said contacting occurs in vitro.~~

1 71. ~~The method of claim 67, wherein said ROR2-expressing cell is a cancer~~
2 ~~cell.~~

1 72. ~~The method of claim 71, wherein said cancer cell is a breast cancer cell,~~
2 ~~ovarian cancer cell, pancreatic cancer cell, cervical cancer cell, gastric cancer cell, renal cancer~~
3 ~~cell, head and neck cancer cell, bone cancer cell, skin cancer cell or prostate cancer cell.~~

1 7347. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same
2 epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising:
3 a CDR H1 as set forth in SEQ ID NO:25, a CDR H2 as set forth in SEQ ID
4 NO:26 and a CDR H3 as set forth in SEQ ID NO:27; and
5 a light chain variable domain comprising:
6 a CDR L1 as set forth in SEQ ID NO:28, a CDR L2 as set forth in SEQ ID
7 NO:29, and a CDR L3 as set forth in SEQ ID NO:30.

1 7448. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same
2 epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising:
3 a CDR H1 as set forth in SEQ ID NO:31, a CDR H2 as set forth in SEQ ID
4 NO:32 and a CDR H3 as set forth in SEQ ID NO:33; and
5 a light chain variable domain comprising:
6 a CDR L1 as set forth in SEQ ID NO:34, a CDR L2 as set forth in SEQ ID
7 NO:35, and a CDR L3 as set forth in SEQ ID NO:36.

1 7549. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same
2 epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising:
3 a CDR H1 as set forth in SEQ ID NO:37, a CDR H2 as set forth in SEQ ID
4 NO:38 and a CDR H3 as set forth in SEQ ID NO:39; and

5 a light chain variable domain comprising:
6 a CDR L1 as set forth in SEQ ID NO:40, a CDR L2 as set forth in SEQ ID
7 NO:41, and a CDR L3 as set forth in SEQ ID NO:42.

1 ~~76~~50. An anti-ROR2 antibody, wherein said anti-ROR2 antibody binds the same
2 epitope as an anti-ROR2 antibody comprising a heavy chain variable domain comprising:
3 a CDR H1 as set forth in SEQ ID NO:43, a CDR H2 as set forth in SEQ ID
4 NO:44 and a CDR H3 as set forth in SEQ ID NO:45; and
5 a light chain variable domain comprising:
6 a CDR L1 as set forth in SEQ ID NO:46, a CDR L2 as set forth in SEQ ID
7 NO:47, and a CDR L3 as set forth in SEQ ID NO:48.

1 ~~77~~51. A chimeric antigen receptor comprising:
2 (i) an antibody region comprising:
3 (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID
4 NO: 28, a CDR L2 as set forth in SEQ ID NO:29 and a CDR L3 as set forth in SEQ ID NO:30;
5 and
6 (b) a heavy chain variable region domain comprising a CDR H1 as set forth in
7 SEQ ID NO:25, a CDR H2 as set forth in SEQ ID NO:26, and a CDR H3 as set forth in SEQ ID
8 NO:27; and
9 (ii) a transmembrane domain.

10 ~~78~~52. A chimeric antigen receptor comprising:
11 (i) an antibody region comprising:
12 (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID
13 NO:34, a CDR L2 as set forth in SEQ ID NO:35 and a CDR L3 as set forth in SEQ ID NO:36;
14 and
15 (b) a heavy chain variable region domain comprising a CDR H1 as set forth in
16 SEQ ID NO:31, a CDR H2 as set forth in SEQ ID NO:32, and a CDR H3 as set forth in SEQ ID
17 NO:33; and
18 (ii) a transmembrane domain.

19 ~~79~~53. A chimeric antigen receptor comprising:

20 (i) an antibody region comprising:
21 (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID
22 NO:40, a CDR L2 as set forth in SEQ ID NO:41 and a CDR L3 as set forth in SEQ ID NO:42;
23 and
24 (b) a heavy chain variable region domain comprising a CDR H1 as set forth in
25 SEQ ID NO:37, a CDR H2 as set forth in SEQ ID NO:38, and a CDR H3 as set forth in SEQ ID
26 NO:39; and
27 (ii) a transmembrane domain.

1 ~~80~~54. A chimeric antigen receptor comprising:

2 (i) an antibody region comprising:

3 (a) a light chain variable domain comprising a CDR L1 as set forth in SEQ ID
4 NO:46, a CDR L2 as set forth in SEQ ID NO:47 and a CDR L3 as set forth in SEQ ID NO:48;
5 and

6 (b) a heavy chain variable region domain comprising a CDR H1 as set forth in
7 SEQ ID NO:43, a CDR H2 as set forth in SEQ ID NO:44, and a CDR H3 as set forth in SEQ ID
8 NO:45; and

9 (i) (ii) a transmembrane domain.

1 ~~80~~55. The chimeric antigen receptor of any one of claims ~~77~~51, ~~78~~52, ~~79~~53 or
2 ~~80~~54, further comprising an intracellular T-cell signaling domain.

1 ~~82~~56. The chimeric antigen receptor of claim ~~81~~55, wherein the intracellular T-
2 cell signaling domain is a CD3 ζ intracellular T-cell signaling domain.

1 ~~83~~57. The chimeric antigen receptor of claim ~~81~~55, further comprising an
2 intracellular co-stimulatory T-cell signaling domain.

1 ~~84~~58. The chimeric antigen receptor of claim ~~83~~57, wherein said intracellular
2 co-stimulatory signaling domain is a CD28 intracellular co-stimulatory signaling domain, a 4-
3 1BB intracellular co-stimulatory signaling domain, a ICOS intracellular co-stimulatory signaling
4 domain, or an OX-40 intracellular co-stimulatory signaling domain.

1 ~~8559. A method of treating cancer in a subject in need thereof said method~~
2 ~~comprising administering a therapeutically effective amount of a~~ Use of the chimeric antigen
3 receptor of any one of claims ~~77, 78, 79 or 80~~ 51-58 in the manufacture of a medicament for the
4 treatment of cancer in a subject in need thereof ~~to a subject.~~

1 ~~8660. The method use of claim 85 59, wherein said cancer is~~ ~~cancer is~~ breast
2 cancer, ovarian cancer, pancreatic cancer, cervical cancer, gastric cancer, renal cancer, head and
3 neck cancer, bone cancer, skin cancer or prostate cancer.