

1 WHAT IS CLAIMED IS

- 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, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:4.
- 1 4. The antibody of claim 1, wherein said antibody is a humanized antibody, a
2 Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.
- 1 5. The antibody of claim 1, wherein said 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. 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. The antibody of claim 14, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:6.
- 1 16. The antibody of claim 14, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:8.
- 1 17. The antibody of claim 14, wherein said antibody is a humanized antibody,
2 a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.
- 1 18. The antibody of claim 14, wherein said antibody is an IgG1 or an IgG2.

- 1 19. The antibody of claim 14, wherein said antibody is capable of binding a
2 ROR2 protein comprising the amino acid sequence of SEQ ID NO:18.
- 1 20. The antibody of claim 19, wherein said antibody is capable of binding an
2 extracellular domain of said ROR2 protein.
- 1 21. The antibody of claim 20, wherein said extracellular domain comprises the
2 amino acid sequence of SEQ ID NO:22.
- 1 22. The antibody of claim 20, wherein said extracellular domain is an Ig-like
2 domain.
- 1 23. The antibody of claim 19, wherein said ROR2 protein comprises a
2 methionine at a position corresponding to position 386 of SEQ ID NO:22.
- 1 24. The antibody of claim 19, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) from about 0.2 nM to about 5 nM.
- 1 25. The antibody of claim 19, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) of about 1.9 nM.
- 1 26. 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. The antibody of claim 26, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:10.

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

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

1 30. The antibody claim 26, wherein said antibody is an IgG1 or an IgG2.

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

1 32. The antibody of claim 31, wherein said antibody is capable of binding an
2 extracellular domain of a ROR2 protein.

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

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

1 35. The antibody of claim 31, 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. The antibody of claim 31, wherein said antibody is capable of binding said
2 ROR2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 150
3 nM.

1 37. 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:

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

1 38. The antibody of claim 37, wherein said heavy chain variable domain
2 comprises the sequence of SEQ ID NO:14.

1 39. The antibody of claim 37, wherein said light chain variable domain
2 comprises the sequence of SEQ ID NO:16.

1 40. The antibody of claim 37, wherein said antibody is a humanized antibody,
2 a Fab' fragment, a single chain antibody (scFv) or a chimeric antibody.

1 41. The antibody of claim 37, wherein said antibody is an IgG1 or an IgG2.

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

1 43. The antibody of claim 42, wherein said antibody is capable of binding an
2 extracellular domain of said ROR2 protein.

1 44. The antibody of claim 43, wherein said extracellular domain comprises the
2 amino acid sequence of SEQ ID NO:22.

1 45. The antibody of claim 41, wherein said extracellular domain is an Ig-like
2 domain.

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

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

1 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 50. The antibody of any one of claims 1, 14, 26 or 37, wherein said antibody
2 is attached to a therapeutic agent.

1 51. The antibody of any one of claims 1, 14, 26 or 37, wherein said antibody
2 is attached to a diagnostic agent.

1 52. 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 antibody of any
3 one of claims 1, 14, 26 or 37.

1 53. 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 of any one of claims 1, 14, 26 or 37.

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

1 55. 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; and
4 (ii) detecting binding of said antibody to a ROR2 protein expressed by said cell.

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

1 57. The method of claim 55, wherein said ROR2-expressing cell is in a
2 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 73. 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 74. 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 75. 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. 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. 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. 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. 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. 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 81. The chimeric antigen receptor of any one of claims 77, 78, 79 or 80,
2 further comprising an intracellular T-cell signaling domain.
- 1 82. The chimeric antigen receptor of claim 81, wherein the intracellular T-cell
2 signaling domain is a CD3 ζ intracellular T-cell signaling domain.
- 1 83. The chimeric antigen receptor of claim 81, further comprising an
2 intracellular co-stimulatory T-cell signaling domain.
- 1 84. The chimeric antigen receptor of claim 83, wherein said intracellular co-
2 stimulatory signaling domain is a CD28 intracellular co-stimulatory signaling domain, a 4-1BB
3 intracellular co-stimulatory signaling domain, a ICOS intracellular co-stimulatory signaling
4 domain, or an OX-40 intracellular co-stimulatory signaling domain.

1 85. A method of treating cancer in a subject in need thereof said method
2 comprising, administering a therapeutically effective amount of a chimeric antigen receptor of
3 any one of claims 77, 78, 79 or 80 to a subject.

1 86. The method of claim 85, 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.