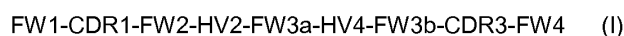


CLAIMS

1. A bi-specific antigen binding molecule comprising:
(i) a receptor tyrosine kinase-like orphan receptor 1 (ROR1) specific antigen binding molecule comprising an amino acid sequence represented by the formula (I):



wherein

FW1 is a framework region

CDR1 is a CDR sequence

FW2 is a framework region

HV2 is a hypervariable sequence

FW3a is a framework region

HV4 is a hypervariable sequence

FW3b is a framework region

CDR3 is a CDR sequence

FW4 is a framework region

;and

- (ii) an epidermal growth factor receptor (EGFR) specific antigen binding molecule;

or a functional variant thereof.

2. The bi-specific antigen binding molecule of claim 1, wherein the ROR1-specific antigen binding molecule does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2).

3. The bi-specific antigen binding molecule of either claim 1 or claim 2, wherein the ROR1-specific antigen binding molecule binds to both human ROR1 and murine ROR1 (mROR1).

4. The bi-specific antigen binding molecule any one of claims 1 to 3, wherein the ROR1-specific antigen binding molecule binds to deglycosylated ROR1.

5. The bi-specific antigen binding molecule of any one of claims 1 to 4, wherein the ROR1-specific antigen binding molecule does not bind to a linear peptide sequence selected from:

YMESLHMQGEIENQI (SEQ ID NO: 34)
 CQPWNSQYPHTHTFTALRFP (SEQ ID NO: 35)
 RSTIYGSRLRIRNLDTTDTGYFQ (SEQ ID NO: 36)
 QCVATNGKEVVSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37)

6. The bi-specific antigen binding molecule of any one of claims 1 to 5 comprising a ROR1-specific antigen binding molecule wherein

FW1 is a framework region of from 20 to 28 amino acids

CDR1 is a CDR sequence selected from DTSYGLYS (SEQ ID NO: 1), GAKYGLAA (SEQ ID NO: 2), GAKYGLFA (SEQ ID NO: 3), GANYGLAA (SEQ ID NO: 4), or GANYGLAS (SEQ ID NO: 5)

FW2 is a framework region of from 6 to 14 amino acids

HV2 is a hypervariable sequence selected from TTDWERMSIG (SEQ ID NO: 6), SSNQERISIS (SEQ ID NO: 7), or SSNKEQISIS (SEQ ID NO: 8)

FW3a is a framework region of from 6 to 10 amino acids

HV4 is a hypervariable sequence selected from NKRAK (SEQ ID NO: 9), NKRTM (SEQ ID NO: 10), NKGAK (SEQ ID NO: 11), or NKGTK (SEQ ID NO: 12)

FW3b is a framework region of from 17 to 24 amino acids

CDR3 is a CDR sequence selected from QSGMAISTGSGHGYNWY (SEQ ID NO: 13), QSGMAIDIGSGHGYNWY (SEQ ID NO: 14), YPWAMWGQWY (SEQ ID NO: 15), VFMPQHWHPAAHWY (SEQ ID NO: 16), REARHPWLRQWY (SEQ ID NO: 17), or YPWGAGAPWLVQWY (SEQ ID NO: 18)

FW4 is a framework region of from 7 to 14 amino acids

or a functional variant thereof with at least 45% sequence identity thereto.

7. The bi-specific antigen binding molecule of claim 6, wherein FW1 is selected from: ASVNQTPRPTATKETGESLTINCVL (SEQ ID NO: 19), AKVDQTPRPTATKETGESLTINCVL (SEQ ID NO: 20), or a functional variant thereof with at least 45% sequence identity thereto.

NO: 20), TRVDQTPRTATKETGESLTINCVVT (SEQ ID NO: 21), TRVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 22), ASVNQTPRTATKETGESLTINCVVT (SEQ ID NO: 23), or TRVDQSPSSLSASVGDRVITITCVLT (SEQ ID NO: 24), FW2 is selected from: TSWFRKNPG (SEQ ID NO: 25), or TYWYRKNPG (SEQ ID NO: 26); FW3a is selected from: GRYVESV (SEQ ID NO: 27), or GRYSESV (SEQ ID NO: 28), FW3b is selected from: SFSLRIKDLTVADSATYYCKA (SEQ ID NO: 29), SFTLTISLQPEDSATYYCRA (SEQ ID NO: 30), or SFTLTISLQPEDFATYYCKA (SEQ ID NO: 31), and FW4 is selected from: DGAGTVLTVN (SEQ ID NO: 32), or DGAGTKVEIK (SEQ ID NO: 33); or functional variants thereof with a sequence identity of at least 45%.

8. The bi-specific antigen binding molecule of any one of claims 1 to 7, wherein the ROR1-specific antigen binding molecule comprises an amino acid sequence selected from: ASVNQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSSIGGRYVESVNKRAKSFS LRIKDLTVADSATYYCKAQSGMAISTGSGHGYNWDGAGTVLTVN (SEQ ID NO: 39); AKVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSSIGGRYVESVNKRAKSFS LRIKDLTVADSATYYCKAQSGMAIDIGSGHGYNWDGAGTVLTVN (SEQ ID NO: 40); TRVDQTPRTATKETGESLTINCVVTGAKYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL RIKDLTVADSATYYCKAYPWAMWGQWYDGAGTVLTVN (SEQ ID NO: 41); TRVDQTPRTATKETGESLTINCVVTGAKYGLFATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL RIKDLTVADSATYYCKAVFMPQHWHPAAHWYDGAGTVLTVN (SEQ ID NO: 42); TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSSIGGRYVESVNKGAKSFS LRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTVN (SEQ ID NO: 43); ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL RIKDLTVADSATYYCKAYPWGAGAPWLWQWYDGAGTVLTVN (SEQ ID NO: 44); TRVDQSPSSLSASVGDRVITITCVLTGANYGLASTYWYRKNPGSSNKEQISISGRYSESVNKGTKSFTL TISSLQPEDSATYYCRAYPWGAGAPWLWQWYDGAGTKVEIK (SEQ ID NO: 45); TRVDQSPSSLSASVGDRVITITCVLTGANYGLASTYWYRKNPGSSNQERISISGRYSESVNKRRTMSFTL TISSLQPEDSATYYCRAYPWGAGAPWLWQWYDGAGTKVEIK (SEQ ID NO: 46); TRVDQSPSSLSASVGDRVITITCVLTDTSYGLYSTSWFRKNPGTTDWERMSSIGGRYVESVNKGAKSFT LTISLQPEDFATYYCKAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 47); TRVDQSPSSLSASVGDRVITITCVLTDTSYGLYSTYWYRKNPGSSNKEQISISGRYSESVNKGTKSFTL TISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 48); TRVDQSPSSLSASVGDRVITITCVLTDTSYGLYSTYWYRKNPGTTDWERMSSIGGRYSESVNKGAKSFT LTISLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 49); or a functional variant thereof with a sequence identity of at least 45%.

9. The bi-specific antigen binding molecule of any one of claims 1 to 8, wherein the ROR1-specific antigen binding molecule is humanized.

10. The bi-specific antigen binding molecule of any one of claims 1 to 8, wherein the ROR1-specific antigen binding molecule is de-immunized.

11. The bi-specific antigen binding molecule of any one of claims 1 to 10, wherein the bi-specific antigen binding molecule is conjugated to a detectable label, dye, toxin, drug, pro-drug, radionuclide or biologically active molecule.
12. The bi-specific antigen binding molecule of any one of claims 1 to 11, wherein the ROR1-specific antigen binding molecule selectively interacts with ROR1 protein with an affinity constant of approximately 0.01 to 50 nM, preferably 0.1 to 30 nM, even more preferably 0.1 to 10 nM.
13. The bi-specific antigen binding molecule of any one of claims 1 to 12, wherein the bi-specific antigen binding molecule is capable of mediating killing of ROR1-expressing tumour cells.
14. The bi-specific antigen binding molecule of any one of claims 1 to 12, wherein the bi-specific antigen binding molecule is capable of inhibiting cancer cell proliferation.
15. The bi-specific antigen binding molecule of any one of claims 1 to 12, wherein the bi-specific antigen binding molecule is capable of being endocytosed upon binding to ROR1.
16. The bi-specific antigen binding molecule of any one of claims 1 to 12, wherein the bi-specific antigen binding molecule is capable of down regulating ROR1 or EGFR upon binding.
17. The bi-specific antigen binding molecule of any one of claims 1 to 12, wherein the bi-specific antigen binding molecule is capable of down regulating ROR1 or EGFR signalling.
18. A recombinant fusion protein comprising a bi-specific antigen binding molecule as claimed in any one of claims 1 to 17.
19. A recombinant fusion protein as claimed in claim 18, in which the bi-specific antigen binding molecule is fused to one or more biologically active proteins.
20. A recombinant fusion protein as claimed in claim 19, wherein the specific antigen binding molecule is fused to one or more biologically active proteins via one or more linker domains.
21. The recombinant fusion protein as claimed in either claim 19 or 20, wherein at least one biologically active protein is an immunoglobulin, an immunoglobulin Fc region, an immunoglobulin Fab region, a single chain Fv (scFv), a diabody, a triabody, a tetrabody, a bispecific t-cell engager (BiTE), an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, or a scaffold protein.
22. The recombinant fusion protein as claimed in claim 21, wherein at least one biologically active protein is an immunoglobulin Fc region.

23. A chimeric antigen receptor (CAR), comprising at least one bi-specific antigen binding molecule as defined in any one of claims 1 to 10, fused or conjugated to at least one transmembrane region and at least one intracellular domain.
24. A cell comprising a chimeric antigen receptor according to claim 23, which cell is preferably an engineered T-cell.
25. A nucleic acid sequence comprising a polynucleotide sequence that encodes a bi-specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any one of claims 1 to 23.
26. A vector comprising a nucleic acid sequence as claimed in claim 25, optionally further comprising one or more regulatory sequences.
27. A host cell comprising a vector as claimed in claim 26.
28. A method for preparing a bi-specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor, comprising cultivating or maintaining a host cell comprising the polynucleotide of claim 25 under conditions such that said host cell produces the binding molecule, optionally further comprising isolating the binding molecule.
29. A pharmaceutical composition comprising the specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 23.
30. The bi-specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 23, for use in therapy.
31. The bi-specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 23, for use in the treatment of cancer.
32. The bi-specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of claim 31, wherein the cancer is a ROR1-positive cancer type.
33. The bi-specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of claim 31, wherein the cancer is selected from the group comprising blood cancers such as lymphomas and leukemias, chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), B-cell acute lymphoblastic leukaemia (B-ALL), marginal zone lymphoma (MZL), non-Hodgkin lymphomas (NHL), acute myeloid leukemia (AML) and solid tumours including neuroblastoma, renal cancer, lung cancer, colon cancer, ovarian cancer, pancreatic cancer, breast cancer, skin cancer, uterine cancer,

prostate cancer, thyroid cancer, Head and Neck cancer, bladder cancer, stomach cancer or liver cancer.

34. The use of a bi-specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 23 in the manufacture of a medicament for the treatment of a disease in a patient in need thereof.

35. A method of treatment of a disease in a patient in need of treatment comprising administration to said patient of a therapeutically effective dosage of a bi-specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor of any one of claims 1 to 23 or a pharmaceutical composition of claim 29.

36. The method of claim 35, wherein the disease is cancer.

37. The method of claim 36 wherein the cancer is a ROR1-positive cancer type.

38. The method of claim 36, wherein the cancer is selected from the group comprising blood cancers such as lymphomas and leukaemias, chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), B-cell acute lymphoblastic leukaemia (B-ALL), marginal zone lymphoma (MZL), non-Hodgkin lymphomas (NHL), acute myeloid leukemia (AML) and solid tumours including neuroblastoma, renal cancer, lung cancer, colon cancer, ovarian cancer, pancreatic cancer, breast cancer, skin cancer, uterine cancer, prostate cancer, thyroid cancer, Head and Neck cancer, bladder cancer, stomach cancer or liver cancer.

39. A method of assaying for the presence of a target analyte in a sample, comprising the addition of a detectably labelled bi-specific antigen binding molecule of any one of claims 1 to 17 or a recombinant fusion protein of claim 18 to 22 to the sample and detecting the binding of the molecule to the target analyte.

40. A method of imaging a site of disease in a subject, comprising administration of a detectably labelled bi-specific antigen binding molecule as claimed in any one of claims 1 to 17 or a detectably labelled recombinant fusion protein of any one of claim 18 to 22 to a subject.

41. A method of diagnosis of a disease or medical condition in a subject comprising administration of a bi-specific antigen binding molecule as claimed in any one of claims 1 to 17 or a recombinant fusion protein of claim 18 to 22.

42. An antibody, antibody fragment or antigen-binding molecule that competes for binding to ROR1 with the ROR1-specific antigen binding molecule of any one of claims 1 to 17; or a ROR1 and EGFR bi-specific antibody, ROR1 and EGFR bi-specific antibody fragment or ROR1 and EGFR bi-

specific antigen-binding molecule that competes for binding to ROR1 and/or EGFR with the bi-specific antigen binding molecule of any one of claims 1 to 17

43. A kit for diagnosing a subject suffering from cancer, or a pre-disposition thereto, or for providing a prognosis of the subject's condition, the kit comprising detection means for detecting the concentration of antigen present in a sample from a test subject, wherein the detection means comprises a bi-specific antigen binding molecule as defined in any one of claims 1 to 17, a recombinant fusion protein as defined in any one of claims 18 to 22, a CAR as defined in claim 23, or a nucleic acid as defined in claim 25, each being optionally derivatized, wherein presence of antigen in the sample suggests that the subject suffers from cancer.

44. The kit according to claim 43, wherein the antigen comprises ROR1 protein, more preferably an extracellular domain thereof.

45. The kit according to claim 43, wherein the kit is used to identify the presence or absence of ROR1-positive cells in the sample, or determine the concentration thereof in the sample.

46. The kit according to claim 43, wherein the kit comprises a positive control and/or a negative control against which the assay is compared.

47. The kit according to claim 43, wherein the kit further comprises a label which may be detected.

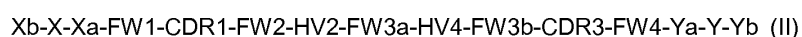
48. A method for diagnosing a subject suffering from cancer, or a pre-disposition thereto, or for providing a prognosis of the subject's condition, the method comprising detecting the concentration of antigen present in a sample obtained from a subject, wherein the detection is achieved using a bi-specific antigen binding molecule as defined in any one of claims 1 to 17, a recombinant fusion protein as defined in any one of claims 18 to 22, a CAR as defined in claim 23, or a nucleic acid sequence as defined in claim 25, each being optionally derivatized, and wherein presence of antigen in the sample suggests that the subject suffers from cancer.

49. A method of killing or inhibiting the growth of a cell expressing ROR1 in vitro or in a patient, which method comprises administering to the cell a pharmaceutically effective amount or dose of (i) bi-specific antigen binding molecule as defined in any one of claims 1 to 17, a recombinant fusion protein as defined in any one of claims 18 to 22, a nucleic acid as defined in claim 25, or the CAR or cell according to claim 23 or 25, or (ii) of a pharmaceutical composition according to claim 29.

50. The method of claim 49, wherein the cell expressing ROR1 is a cancer cell.

51. The method according to either claim 49 or 50, wherein the ROR1 is human ROR1.

52. A method of killing or inhibiting the growth of a cell expressing EGFR in vitro or in a patient, which method comprises administering to the cell a pharmaceutically effective amount or dose of (i) bi-specific antigen binding molecule as defined in any one of claims 1 to 17, a recombinant fusion protein as defined in any one of claims 18 to 22, a nucleic acid as defined in claim 25, or the CAR or cell according to claim 23 or 25, or (ii) of a pharmaceutical composition according to claim 29.
53. The method of claim 52, wherein the cell expressing EGFR is a cancer cell.
54. A method of killing or inhibiting the growth of a cell expressing ROR1 and EGFR in vitro or in a patient, which method comprises administering to the cell a pharmaceutically effective amount or dose of (i) bi-specific antigen binding molecule as defined in any one of claims 1 to 17, a recombinant fusion protein as defined in any one of claims 18 to 22, a nucleic acid as defined in claim 25, or the CAR or cell according to claim 23 or 25, or (ii) of a pharmaceutical composition according to claim 29.
55. The method of claim 54, wherein the cell expressing ROR1 and EGFR is a cancer cell.
56. A bi-specific antigen binding molecule comprising an amino acid sequence represented by the formula (II):



wherein

FW1 is a framework region

CDR1 is a CDR sequence

FW2 is a framework region

HV2 is a hypervariable sequence

FW3a is a framework region

HV4 is a hypervariable sequence

FW3b is a framework region

CDR3 is a CDR sequence

FW4 is a framework region

wherein Xa, Xb, Ya and Yb are either absent or an EGFR-specific binding molecule,
wherein at least one of Xa, Xb, Ya and Yb is an EGFR-specific binding molecule,
X and Y are optional amino acid sequences,
wherein the bi-specific antigen binding molecule is conjugated to a second moiety.

57. The bi-specific antigen binding molecule of claim 56, wherein X or Y are individually either absent or selected from the group comprising an immunoglobulin, an immunoglobulin Fc region, an immunoglobulin Fab region, a single chain Fv (scFv), a diabody, a triabody, a tetrabody, a bispecific t-cell engager (BiTE), an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, or a scaffold protein.

58. The bi-specific antigen binding molecule of either claim 56 or claim 57, wherein the conjugation is via a cysteine residue in the amino acid sequence of the specific antigen binding molecule.

59. The bi-specific antigen binding molecule of either claim 56 or claim 57, wherein the conjugation is via a thiol, aminoxy or hydrazinyl moiety incorporated at the N-terminus or C-terminus of the amino acid sequence of the specific antigen binding molecule.

60. The bi-specific antigen binding molecule of any one of claims 56 to 59, wherein the second moiety is selected from the group comprising an immunoglobulin, an immunoglobulin Fc region, an immunoglobulin Fab region, a single chain Fv (scFv), a diabody, a triabody, a tetrabody, a bispecific t-cell engager (BiTE), an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, or a scaffold protein.

61. The bi-specific antigen binding molecule of any one of claims 56 to 59, wherein the second moiety is selected from the group comprising detectable label, dye, toxin, drug, pro-drug, radionuclide or biologically active molecule.

62. The bi-specific antigen binding molecule according to any one of claims 56 to 59 or 61, wherein the second moiety is at least one toxin selected from the group comprising:

- maytansinoids,
- auristatins,
- anthracyclins, preferably PNU-derived anthracyclins
- amanitin derivatives, preferably α -amanitin derivatives
- calicheamicins,
- tubulysins
- duocarmycins

- radioisotopes - such as an alpha-emitting radionuclide, such as ²²⁷Th and ²²⁵Ac label
- liposomes comprising a toxic payload,
- protein toxins
- taxanes
- pyrrolbenzodiazepines and/or
- indolinobenzodiazepine pseudodimers and/or
- spliceosome inhibitors
- CDK11 inhibitors
- Pyridinobenzodiazepines

63. The bi-specific antigen binding molecule according to any one of claims 56 to 62, wherein the specific antigen binding molecule is a receptor tyrosine kinase-like orphan receptor 1 (ROR1) specific antigen binding molecule.

64. The bi-specific antigen binding molecule according to claim 63, wherein the ROR1-specific antigen binding molecule does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2).

65. The bi-specific antigen binding molecule according to either claim 63 or 64, wherein the ROR1-specific antigen binding molecule binds to both human ROR1 and murine ROR1 (mROR1).

66. The bi-specific antigen binding molecule according to any one of claims 63 to 65, wherein the ROR1-specific antigen binding molecule binds to deglycosylated ROR1.

67. The bi-specific antigen binding molecule according to any one of claims 63 to 66, wherein the ROR1-specific antigen binding molecule does not bind to a linear peptide sequence selected from:

YMESLHMQGEIENQI (SEQ ID NO: 34)
 CQPWNSQYPHTHTFTALRFP (SEQ ID NO: 35)
 RSTIYGSRLRIRNLDTTDTGYFQ (SEQ ID NO: 36)
 QCVATNGKEVVSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37)

68. The bi-specific antigen binding molecule according to any one of claims 63 to 67, wherein:

FW1 is a framework region of from 20 to 28 amino acids

CDR1 is a CDR sequence selected from DTSYGLYS (SEQ ID NO: 1), GAKYGLAA (SEQ ID NO: 2), GAKYGLFA (SEQ ID NO: 3), GANYGLAA (SEQ ID NO: 4), or GANYGLAS (SEQ ID NO: 5)

FW2 is a framework region of from 6 to 14 amino acids

HV2 is a hypervariable sequence selected from TTDWERMSIG (SEQ ID NO: 6), SSNQERISIS (SEQ ID NO: 7), or SSNKEQISIS (SEQ ID NO: 8)

FW3a is a framework region of from 6 to 10 amino acids

HV4 is a hypervariable sequence selected from NKRAK (SEQ ID NO: 9), NKRTM (SEQ ID NO: 10), NKGAK (SEQ ID NO: 11), or NKGTK (SEQ ID NO: 12)

FW3b is a framework region of from 17 to 24 amino acids

CDR3 is a CDR sequence selected from QSGMAISTGSGHGYNWY (SEQ ID NO: 13), QSGMAIDIGSGHGYNWY (SEQ ID NO: 14), YPWAMWGQWY (SEQ ID NO: 15), VFMPQHWHPAAHWY (SEQ ID NO: 16), REARHPWLRQWY (SEQ ID NO: 17), or YPWGAGAPWLVQWY (SEQ ID NO: 18)

FW4 is a framework region of from 7 to 14 amino acids

or a functional variant thereof with at least 45% sequence identity thereto,

69. The bi-specific antigen binding molecule according to any one of claims 63 to 68, wherein FW1 is selected from ASVNQTPRTATKETGESLTINCVLT (SEQ ID NO: 19), AKVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 20), TRVDQTPRTATKETGESLTINCVVT (SEQ ID NO: 21), TRVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 22), ASVNQTPRTATKETGESLTINCVVT (SEQ ID NO: 23), or TRVDQSPSSLSASVGDRVTITCVLT (SEQ ID NO: 24), FW2 is selected from TSWFRKNPG (SEQ ID NO: 25), or TYWYRKNPG (SEQ ID NO: 26), FW3a is selected from GRYVESV (SEQ ID NO: 27), or GRYSESV (SEQ ID NO: 28), FW3b is selected from SFSRLRIKDLTVADSATYYCKA (SEQ ID NO: 29), SFTLTISLQPEDSATYYCRA (SEQ ID NO: 30), or SFTLTISLQPEDFATYYCKA (SEQ ID NO: 31), and FW4 is selected from DGAGTVLTVN (SEQ ID NO: 32), or DGAGTKVEIK (SEQ ID NO: 33), or functional variants thereof with a sequence identity of at least 45%.

70. The bi-specific antigen binding molecule according to any one of claims 63 to 68, wherein the ROR1-specific antigen binding molecule comprises an amino acid sequence selected from ASVNQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMISIGGRYVESVNKRAKSFS LRIKDLTVADSATYYCKAQSGMAISTGSGHGYNWYDGAGTVLTVN (SEQ ID NO: 39); AKVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMISIGGRYVESVNKRAKSFS LRIKDLTVADSATYYCKAQSGMAIDIGSGHGYNWYDGAGTVLTVN (SEQ ID NO: 40); TRVDQTPRTATKETGESLTINCVVTGAKYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL RIKDLTVADSATYYCKAYPWAMWGQWYDGAGTVLTVN (SEQ ID NO: 41); TRVDQTPRTATKETGESLTINCVVTGAKYGLFATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL RIKDLTVADSATYYCKAVFMPQHWHPAAHWYDGAGTVLTVN (SEQ ID NO: 42); TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMISIGGRYVESVNKGAKSFS

LRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTVN (SEQ ID NO: 43);
 ASVNQTPRTATKETGESLTINC VVTGANYGLAATYWYRKNPGSSNQERISISGRYVESVNKRTMSFSL
 RIKDLTVADSATYYCKAYPWGAGAPWL VQWYDGAGTVLTVN (SEQ ID NO: 44);,
 TRVDQSPSSLSASVGDRVTITCVLTGANYGLASTYWYRKNPGSSNKEQISISGRYSESVNKGTKSFTL
 TISSLQPEDSATYYCRAYPWGAGAPWL VQWYDGAGTKVEIK (SEQ ID NO: 45);
 TRVDQSPSSLSASVGDRVTITCVLTGANYGLASTYWYRKNPGSSNQERISISGRYSESVNKR TMSFTL
 TISSLQPEDSATYYCRAYPWGAGAPWL VQWYDGAGTKVEIK (SEQ ID NO: 46);
 TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGRYVESVNKGAKSFT
 LTISSLQPEDFATYYCKAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 47);
 TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTYWYRKNPGSSNKEQISISGRYSESVNKGTKSFTL
 TISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 48);
 TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTYWYRKNPGTTDWERMSIGGRYSESVNKGAKSFT
 LTISSLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK (SEQ ID NO: 49); or a functional variant
 thereof with a sequence identity of at least 45%.

71. The bi-specific antigen binding molecule according to any one of claims 63 to 70, wherein the ROR1-specific antigen binding molecule is humanized.

72. The bi-specific antigen binding molecule according to any one of claims 63 to 70, wherein the ROR1-specific antigen binding molecule is de-immunized.

73. The bi-specific antigen binding molecule according to any one of claims 56 to 71, wherein the EGFR-specific antigen binding molecule is selected from the group comprising an immunoglobulin, an immunoglobulin Fab region, a single chain Fv (scFv), a diabody, a triabody, a tetrabody, a bispecific t-cell engager (BiTE), an intein, a VNAR domain, a single domain antibody (sdAb), a VH domain, or a scaffold protein.