

CLAIMS

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

FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4 (I)

5 in which

FW1 is a framework region

CDR1 is a CDR sequence

FW2 is a framework region

HV2 is a hypervariable sequence

10 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

15 or a functional variant thereof.

2. An ROR1-specific antigen binding molecule according to Claim 1, in which the ROR1-specific antigen binding molecule

(i) does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2),

(ii) binds to both human ROR1 and murine ROR1 (mROR1),

20 (iii) binds to deglycosylated ROR1, and/or

(iv) 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)

25 QCVATNGKEVVSSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37).

3. An ROR1-specific antigen binding molecule according to Claim 1 or 2, in which

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)

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

10 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

15 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, optionally in which FW1 is selected from:

20 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

TRVDQSPSSLSASVGDRVITITCVLT (SEQ ID NO: 24) , FW2 is selected from:

25 TSWERKNPG (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),

SFTLTISSLQPEDSATYYCRA (SEQ ID NO: 30), or SFTLTISSLQPEDFATYYCKA

(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%.

4. An ROR1-specific antigen binding molecule according to Claim 1, 2 or 3, in which the ROR1-specific antigen binding molecule comprises an amino acid sequence selected from:

5 ASVNQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR
YVESVNKRAKSFSRLRIKDLTVADSATYYCKAQSGMAISTGSGHGYNWYDGAG
TVLTVN (SEQ ID NO: 39);

AKVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR
YVESVNKRAKSFSRLRIKDLTVADSATYYCKAQSGMAIDIGSGHGYNWYDGAGT
10 VLTVN (SEQ ID NO: 40);

TRVDQTPRTATKETGESLTINCVTGAKYGLAATYWYRKNPGSSNQERISISGR
YVESVNKRTMSFSRLRIKDLTVADSATYYCKAYPWAMWGQWYDGAGTVLTVN
(SEQ ID NO: 41);

TRVDQTPRTATKETGESLTINCVTGAKYGLFATYWYRKNPGSSNQERISISGR
YVESVNKRTMSFSRLRIKDLTVADSATYYCKAVFMPQHWHPAAHWYDGAGTVL
15 TVN (SEQ ID NO: 42);

TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR
YVESVNKGAKSFSRLRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTV
N (SEQ ID NO: 43);

20 ASVNQTPRTATKETGESLTINCVTGANYGLAATYWYRKNPGSSNQERISISGR
YVESVNKRTMSFSRLRIKDLTVADSATYYCKAYPWGAGAPWLQWYDGAGTV
LTVN (SEQ ID NO: 44);,

TRVDQSPSSLSASVGDRVITITCVLTGANYGLASTYWYRKNPGSSNKEQISISGRY
SESVNKGKTSFTLTISLQPEDSATYYCRAYPWGAGAPWLQWYDGAGTKVEI
25 K (SEQ ID NO: 45);

TRVDQSPSSLSASVGDRVITITCVLTGANYGLASTYWYRKNPGSSNQERISISGRY
SESVNKRRTMSFTLTISLQPEDSATYYCRAYPWGAGAPWLQWYDGAGTKVEI
K (SEQ ID NO: 46);

TRVDQSPSSLSASVGDRVITITCVLTDTSYGLYSTSWFRKNPGTTDWERM SIGGR
YVESVNKGAKSFTLTISLQPEDFATYYCKAREARHPWLRQWYDGAGTKVEIK
(SEQ ID NO: 47);

TRVDQSPSSLSASVGDRVITITCVLTDTSYGLYSTYWYRKNPGSSNKEQISISGRY
SESVNKGTKSFTLTISLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK
(SEQ ID NO: 48);

TRVDQSPSSLSASVGDRVITITCVLTDTSYGLYSTYWYRKNPGTTDWERM SIGGR
YSESVNKGAKSFTLTISLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK
(SEQ ID NO: 49); or a functional variant thereof with a sequence identity of at least
45%.

5. An ROR1-specific antigen binding molecule according to any preceding claim, in which the ROR1-specific antigen binding molecule is humanized, or in which the ROR1-specific antigen binding molecule is de-immunized.

6. An ROR1-specific antigen binding molecule according to any preceding claim, in which the ROR1-specific antigen binding molecule is conjugated to a detectable label, dye, toxin, drug, pro-drug, radionuclide or biologically active molecule.

7. An ROR1-specific antigen binding molecule according to any preceding claim, in which the 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.

8. An ROR1-specific antigen binding molecule according to any preceding claim, in which the specific antigen binding molecule is capable of

- (i) mediating killing of ROR1-expressing tumour cells,
- (ii) inhibiting cancer cell proliferation, or
- (iii) being endocytosed upon binding to ROR1.

9. A recombinant fusion protein comprising a specific antigen binding molecule according to any preceding claim.

10. A recombinant fusion protein according to Claim 9, in which the specific antigen binding molecule is fused to one or more biologically active proteins, optionally in which

- (i) the specific antigen binding molecule is fused to one or more biologically active proteins via one or more linker domains, and/or
- (ii) 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.

11. A ROR1-specific chimeric antigen receptor (CAR), comprising at least one ROR1-specific antigen binding molecule as defined in any of Claims 1 to 5 fused or conjugated to at least one transmembrane region and at least one intracellular domain.

12. A cell comprising a chimeric antigen receptor according to Claim 11, which cell is preferably an engineered T-cell.

13. A nucleic acid sequence comprising a polynucleotide sequence that encodes a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 11, a vector comprising the nucleic acid sequence and optionally further comprising one or more regulatory sequences, or a host cell comprising the vector.

14. A method for preparing a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor, comprising cultivating or maintaining a host cell comprising a polynucleotide according to Claim 13 under conditions such that the host cell produces the binding molecule, optionally further comprising isolating the binding molecule.

15. A pharmaceutical composition comprising a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 11.

16. A specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 11, for use in therapy.

17. A specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 11, for use in the treatment of cancer, optionally in which the cancer is a ROR1-positive cancer type, or 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.

18. A method of assaying for the presence of a target analyte in a sample, comprising the addition of a detectably labelled specific antigen binding molecule according to any of Claims 1 to 8 or a recombinant fusion protein according to Claim 9 or 10 to the sample and detecting the binding of the molecule to the target analyte.

19. A method of imaging a site of disease in a subject, comprising administration of a detectably labelled specific antigen binding molecule according to any of Claims 1 to 8 or a detectably labelled recombinant fusion protein according to Claim 9 or 10 to a subject.

20. A method of diagnosis of a disease or medical condition in a subject comprising administration of a detectably labelled specific antigen binding molecule according to any of Claims 1 to 8 or a recombinant fusion protein according to Claim 9 or 10 to the subject and detecting the molecule.

21. An antibody, antibody fragment or antigen-binding molecule that competes for binding to ROR1 with the ROR1-specific antigen binding molecule according to any of Claims 1 to 8.

22. 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, in which the detection means comprises a ROR1-specific antigen binding molecule as defined in any of Claims 1 to 8, a recombinant fusion protein as defined in Claim 9 or 10, a CAR as defined in Claim 11, or a nucleic acid as defined in Claim 13, each being optionally derivatized, in which presence of antigen in the sample suggests that the subject suffers from cancer, optionally in which

(i) the antigen comprises ROR1 protein, more preferably an extracellular domain thereof,

(ii) 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,

(iii) the kit comprises a positive control and/or a negative control against which the assay is compared, or

(iv) the kit further comprises a label which may be detected.

23. A specific antigen binding molecule comprising an amino acid sequence represented by the formula (II):

X-FW1-CDR1-FW2-HV2-FW3a-HV4-FW3b-CDR3-FW4-Y (II)

in which

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

X and Y are optional amino acid sequences

in which the specific antigen binding molecule is conjugated to a second moiety.

24. A specific antigen binding molecule according to Claim 23, in which 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.

25. A specific antigen binding molecule according to Claim 23 or 24, in which

(i) the conjugation is via a cysteine residue in the amino acid sequence of the specific antigen binding molecule, or 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, and/or

(ii) 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, a scaffold protein, detectable label, dye, toxin, drug, pro-drug, radionuclide or biologically active molecule, or 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 ^{227}Th or ^{225}Ac label
- liposomes comprising a toxic payload,
- protein toxins
- taxanes
- pyrrolbenzodiazepines and/or
- indolinobenzodiazepine pseudodimers and/or
- spliceosome inhibitors
- CDK11 inhibitors
- Pyridinobenzodiazepines

26. A specific antigen binding molecule according to Claim 23, 24 or 25, in which the specific antigen binding molecule is a receptor tyrosine kinase-like orphan receptor 1 (ROR1) specific antigen binding molecule, optionally in which

- (i) the ROR1-specific antigen binding molecule does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2),

(ii) the ROR1-specific antigen binding molecule binds to both human ROR1 and murine ROR1 (mROR1),

(iii) the ROR1-specific antigen binding molecule binds to deglycosylated ROR1, and/or

5 (iv) 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)

10 QCVATNGKEVVSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37)

27. A specific antigen binding molecule according to Claim 26, in which:

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
15 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

20 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), QSCMAIDIGSGHGYNWY (SEQ ID NO: 14), YPWAMWGQWY (SEQ ID NO: 15),
25 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, optionally in which

(i) FW1 is selected from ASVNQTPRTATKETGESLTINCVLT (SEQ ID NO: 19), AKVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 20),
 5 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

10 selected from GRYVESV (SEQ ID NO: 27), or GRYSESV (SEQ ID NO: 28), FW3b is
 selected from SFSRLIKDLTVADSATYYCKA (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
 15 identity of at least 45%, or

(ii) the ROR1-specific antigen binding molecule comprises an amino acid sequence
 selected from

ASVNQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR
 YVESVNKRAKSFSRLIKDLTVADSATYYCKAQSGMAISTGSGHGYNWYDGAG
 20 TVLTVN (SEQ ID NO: 39);

AKVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR
 YVESVNKRAKSFSRLIKDLTVADSATYYCKAQSGMAIDIGSGHGYNWYDGAGT
 VLTVN (SEQ ID NO: 40);

TRVDQTPRTATKETGESLTINCVVTGAKYGLAATYWYRKNPGSSNQERISISGR
 25 YVESVNKRTMSFSRLIKDLTVADSATYYCKAYPWAMWGQWYDGAGTVLTVN
 (SEQ ID NO: 41);

TRVDQTPRTATKETGESLTINCVVTGAKYGLFATYWYRKNPGSSNQERISISGR
 YVESVNKRTMSFSRLIKDLTVADSATYYCKAVFMPQHWHPAAHWYDGAGTVL
 TVN (SEQ ID NO: 42);

TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR
YVESVNKGAKSFSRLRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTV
N (SEQ ID NO: 43);

5 ASVNQTPRTATKETGESLTINCVVTGANYGLAATYWYRKNPGSSNQERISISGR
YVESVNKRTMSFSRLRIKDLTVADSATYYCKAYPWGAGAPWLVQWYDGAGTV
LTVN (SEQ ID NO: 44);,

TRVDQSPSSLSASVGDRVTITCVLTGANYGLASTYWYRKNPGSSNKEQISISGRY
SESVNKGTKSFTLTISLQPEDSATYYCRAYPWGAGAPWLVQWYDGAGTKVEI
K (SEQ ID NO: 45);

10 TRVDQSPSSLSASVGDRVTITCVLTGANYGLASTYWYRKNPGSSNQERISISGRY
SESVNKRRTMSFTLTISLQPEDSATYYCRAYPWGAGAPWLVQWYDGAGTKVEI
K (SEQ ID NO: 46);

15 TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGR
YVESVNKGAKSFTLTISLQPEDFATYYCKAREARHPWLRQWYDGAGTKVEIK
(SEQ ID NO: 47);

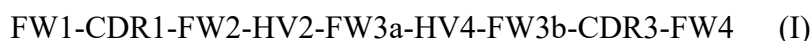
TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTYWYRKNPGSSNKEQISISGRY
SESVNKGTKSFTLTISLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK
(SEQ ID NO: 48);

20 TRVDQSPSSLSASVGDRVTITCVLTDTSYGLYSTYWYRKNPGTTDWERMSIGGR
YSESVNKGAKSFTLTISLQPEDSATYYCRAREARHPWLRQWYDGAGTKVEIK
(SEQ ID NO: 49); or a functional variant thereof with a sequence identity of at least
45%.

25 28. A specific antigen binding molecule according to Claim 26 or 27, in which the ROR1-
specific antigen binding molecule is humanized, or the ROR1-specific antigen binding
molecule is de-immunized.

CLAIMS

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



5 in which

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

CDR1 is DTSYGLYS (SEQ ID NO: 1)

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

HV2 is TTDWERMSIG (SEQ ID NO: 6)

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

HV4 is NKGAK (SEQ ID NO: 11)

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

CDR3 is REARHPWLRQWY (SEQ ID NO: 17)

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

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

2. An ROR1-specific antigen binding molecule according to Claim 1, in which the ROR1-specific antigen binding molecule

(i) does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2),

(ii) binds to both human ROR1 and murine ROR1 (mROR1),

20 (iii) binds to deglycosylated ROR1, and/or

(iv) 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)

25 QCVATNGKEVVSSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37).

3. An ROR1-specific antigen binding molecule according to Claim 1 or 2, in which

FW1 is TRVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 22), FW2 is TSWFRKNPG (SEQ ID NO: 25), FW3a is GRYVESV (SEQ ID NO: 27), FW3b is SFSRLRIKDLTVADSATYYCKA (SEQ ID NO: 29) and FW4 is DGAGTVLTVN (SEQ ID NO: 32), or functional variants thereof with a sequence identity of at least 45%.

- 5 4. An ROR1-specific antigen binding molecule according to Claim 1, 2 or 3, in which the ROR1-specific antigen binding molecule comprises the amino acid sequence TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSIGGRYVES VNKGAKSFSRLRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTVN (SEQ ID NO: 43); or a functional variant thereof with a sequence identity of at least 45%.
- 10 5. An ROR1-specific antigen binding molecule according to any preceding claim, in which the ROR1-specific antigen binding molecule is humanized, or in which the ROR1-specific antigen binding molecule is de-immunized.
6. An ROR1-specific antigen binding molecule according to any preceding claim, in which the ROR1-specific antigen binding molecule is conjugated to a detectable label, dye, toxin,
 - 15 drug, pro-drug, radionuclide or biologically active molecule.
7. An ROR1-specific antigen binding molecule according to any preceding claim, in which the specific antigen binding molecule selectively interacts with ROR1 protein with an affinity constant of 0.01 to 50 nM, preferably 0.1 to 30 nM, even more preferably 0.1 to 10 nM.
8. An ROR1-specific antigen binding molecule according to any preceding claim, in which
 - 20 the specific antigen binding molecule is capable of
 - (i) mediating killing of ROR1-expressing tumour cells,
 - (ii) inhibiting cancer cell proliferation, or
 - (iii) being endocytosed upon binding to ROR1.
9. A recombinant fusion protein comprising a specific antigen binding molecule according
 - 25 to any preceding claim.
10. A recombinant fusion protein according to Claim 9, in which the specific antigen binding molecule is fused to one or more biologically active proteins, optionally in which
 - (i) the specific antigen binding molecule is fused to one or more biologically active proteins via one or more linker domains, and/or

(ii) 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.

- 5 11. A ROR1-specific chimeric antigen receptor (CAR), comprising at least one ROR1-specific antigen binding molecule as defined in any of Claims 1 to 5, fused or conjugated to at least one transmembrane region and at least one intracellular domain.
12. A cell comprising a chimeric antigen receptor according to Claim 11, which cell is preferably an engineered T-cell.
- 10 13. A nucleic acid sequence comprising a polynucleotide sequence that encodes a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 11, a vector comprising the nucleic acid sequence and optionally further comprising one or more regulatory sequences, or a host cell comprising the vector.
14. A method for preparing a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor, comprising cultivating or maintaining a host cell comprising a polynucleotide according to Claim 13 under conditions such that the host cell produces the binding molecule, optionally further comprising isolating the binding molecule.
- 15 15. A pharmaceutical composition comprising a specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 11.
- 20 16. A specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 11, for use in therapy.
17. A specific antigen binding molecule, recombinant fusion protein or chimeric antigen receptor according to any of Claims 1 to 11, for use in the treatment of cancer, optionally in which the cancer is a ROR1-positive cancer type, or the cancer is selected from the group
- 25 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,
- 30 thyroid cancer, Head and Neck cancer, bladder cancer, stomach cancer or liver cancer.

18. A method of assaying for the presence of a target analyte in a sample, comprising the addition of a detectably labelled specific antigen binding molecule according to any of Claims 1 to 8 or a recombinant fusion protein according to Claim 9 or 10 to the sample and detecting the binding of the molecule to the target analyte.

5 19. A method of imaging a site of disease in a subject, comprising administration of a detectably labelled specific antigen binding molecule according to any of Claims 1 to 8 or a detectably labelled recombinant fusion protein according to Claim 9 or 10 to a subject.

20. A method of diagnosis of a disease or medical condition in a subject comprising administration of a detectably labelled specific antigen binding molecule according to any of
10 Claims 1 to 8 or a recombinant fusion protein according to Claim 9 or 10 to the subject and detecting the molecule.

21. 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, in which the
15 detection means comprises a ROR1-specific antigen binding molecule as defined in any of Claims 1 to 8, a recombinant fusion protein as defined in Claim 9 or 10, a CAR as defined in Claim 11, or a nucleic acid as defined in Claim 13, each being optionally derivatized, in which presence of antigen in the sample suggests that the subject suffers from cancer, optionally in which

20 (i) the antigen comprises ROR1 protein, more preferably an extracellular domain thereof,

(ii) 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,

(iii) the kit comprises a positive control and/or a negative control against which the
25 assay is compared, or

(iv) the kit further comprises a label which may be detected.

22. A specific antigen binding molecule comprising an amino acid sequence represented by the formula (II):



in which

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

CDR1 is DTSYGLYS (SEQ ID NO: 1)

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

5 HV2 is TTDWERMSIG (SEQ ID NO: 6)

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

HV4 is NKGAK (SEQ ID NO: 11)

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

CDR3 is REARHPWLRQWY (SEQ ID NO: 17)

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

X and Y are optional amino acid sequences

in which the specific antigen binding molecule is conjugated to a second moiety, or a functional variant thereof with at least 45% sequence identity thereto.

23. A specific antigen binding molecule according to Claim 22, in which X or Y are
15 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.

24. A specific antigen binding molecule according to Claim 22 or 23, in which

20 (i) the conjugation is via a cysteine residue in the amino acid sequence of the specific antigen binding molecule, or 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, and/or

(ii) the second moiety is selected from the group comprising an immunoglobulin, an
25 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, a scaffold protein, detectable

label, dye, toxin, drug, pro-drug, radionuclide, biologically active molecule, or at least one toxin selected from the group comprising:

- maytansinoids,
- auristatins,
- 5 • anthracyclins, preferably PNU-derived anthracyclins
- amanitin derivatives, preferably α -amanitin derivatives
- calicheamicins,
- tubulysins
- duocarmycins
- 10 • radioisotopes - such as an alpha-emitting radionuclide, such as ^{227}Th or ^{225}Ac label
- liposomes comprising a toxic payload,
- protein toxins
- taxanes
- 15 • pyrrolbenzodiazepines and/or
- indolinobenzodiazepine pseudodimers and/or
- spliceosome inhibitors
- CDK11 inhibitors
- Pyridinobenzodiazepines
- 20 25. A specific antigen binding molecule according to Claim 22, 23 or 24, in which the specific antigen binding molecule is a receptor tyrosine kinase-like orphan receptor 1 (ROR1) specific antigen binding molecule, optionally in which
 - (i) the ROR1-specific antigen binding molecule does not bind to receptor tyrosine kinase-like orphan receptor 2 (ROR2),
 - 25 (ii) the ROR1-specific antigen binding molecule binds to both human ROR1 and murine ROR1 (mROR1),

(iii) the ROR1-specific antigen binding molecule binds to deglycosylated ROR1, and/or

(iv) the ROR1-specific antigen binding molecule does not bind to a linear peptide sequence selected from:

- 5 YMESLHMQGEIENQI (SEQ ID NO: 34)
- CQPWNSQYPHTHTFTALRFP (SEQ ID NO: 35)
- RSTIYGSRLRIRNLDTTDTGYFQ (SEQ ID NO: 36)
- QCVATNGKEVVSSSTGVLFVKFGPPPTASPGYSDEYE (SEQ ID NO: 37)

26. A specific antigen binding molecule according to Claim 25, in which:

- 10 (i) FW1 is TRVDQTPRTATKETGESLTINCVLT (SEQ ID NO: 22), FW2 is TSWFRKNPG (SEQ ID NO: 25), FW3a is GRYVESV (SEQ ID NO: 27), FW3b is SFSLRIKDLTVADSATYYCKA (SEQ ID NO: 29), and FW4 is DGAGTVLTVN (SEQ ID NO: 32), or functional variants thereof with a sequence identity of at least 45%, or

- 15 (ii) the ROR1-specific antigen binding molecule comprises the amino acid sequence TRVDQTPRTATKETGESLTINCVLTDTSYGLYSTSWFRKNPGTTDWERMSSIGGR YVESVNKGAKSFSLRIKDLTVADSATYYCKAREARHPWLRQWYDGAGTVLTV N (SEQ ID NO: 43); or a functional variant thereof with a sequence identity of at least 45%.

- 20 27. A specific antigen binding molecule according to Claim 25 or 26, in which the ROR1-specific antigen binding molecule is humanized, or the ROR1-specific antigen binding molecule is de-immunized.