

Efforts to target T cells to ROR2 have also been made. A ROR2/CD3 bispecific in scFv-Fc format, based on a humanized ROR2 rabbit antibody has been described, displaying T cell cytotoxicity in tumor cell lines (Goydel et al 2020, J Biol Chem 295:5995-6006).

While some progress has been made, there is still a need for the development of antibody-based cancer therapies targeting ROR2 that are efficacious and safe for human use such as for use in the treatment of cancer.

It is an object of the present invention to provide an antibody comprising at least one antigen-binding region capable of binding to human ROR2. It is a further object of the invention to provide an antibody comprising two antigen-binding regions capable of binding to human ROR2. It is a further object to provide a bispecific antibody capable of binding to human ROR2 and human CD3, such as human CD3ε (epsilon). It is a further object to provide a CD3xROR2 bispecific antibody of IgG format such as human IgG1 format. It is a further object to provide a CD3xROR2 bispecific antibody of IgG1 format where the Fc region is inert. It is a further object to provide a CD3xROR2 bispecific antibody that has a plasma half-life in the range of a regular human IgG1 antibody. It is a further object to provide a ROR2 antibody and/or a CD3xROR2 bispecific antibody that is efficacious and safe for the treatment of cancer.

SUMMARY OF INVENTION

In a main aspect, the present ~~invention~~disclosure relates to ROR2 binding antibodies and in particular to an antibody comprising at least one antigen-binding region capable of binding to human ROR2 wherein said antibody comprises a heavy chain variable (VH) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 3, 4, and 5, respectively, and a light chain variable (VL) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:7, 8 and 9, respectively.

In ~~a further aspect~~example, the antibody may in particular be a bispecific antibody comprising a first antigen binding region capable of binding human ROR2 wherein said antibody comprises a VH region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 3, 4, and 5, respectively, and a VL region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:7, 8 and 9, respectively, and comprising a second antigen binding region capable of binding to human CD3 such as human CD3ε (epsilon), such as human CD3ε (epsilon) as specified in SEQ ID NO: 21.

In ~~a further aspect~~another example, the present ~~invention~~disclosure relates to a bispecific antibody comprising a first antigen binding region capable of binding human ROR2 as described herein and a second antigen binding region capable of binding to human CD3 comprising a VH region CDR1, CDR2, and CDR3 having the

sequences as set forth in SEQ ID NOs: 23, 24, and 25, respectively, and a VL region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:27, GTN and 28, respectively.

In another [aspectexample](#), the present [inventiondisclosure](#) relates to a nucleic acid construct comprising

- 5 a) a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as defined herein, and/or
- b) a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as defined herein.

In another aspect, the present [inventiondisclosure](#) relates to an expression vector comprising

- 10 a) a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as defined herein, and/or
- b) a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as defined herein.

15 In another [aspectexample](#), the present [inventiondisclosure](#) relates to a cell comprising a nucleic acid construct or an expression vector as defined herein.

In a further aspect, the present [inventiondisclosure](#) relates to a composition comprising an antibody according to any aspect or [embodimentexample](#) herein.

20 In a further aspect, the present [inventiondisclosure](#) relates to a pharmaceutical composition comprising an antibody according to any aspect or [embodimentexample](#) herein and a pharmaceutically acceptable carrier.

In another aspect, the present [inventiondisclosure](#) relates to an antibody according to any aspect or [embodimentexample](#) herein for use as a medicament, such as for use in the treatment of a disease.

25 In a further aspect, the present [inventiondisclosure](#) relates to [the antibody as disclosed herein for use as a medicament. In one example, the present disclosure relates to](#) a method of treating a disease or disorder, the method comprising administering an antibody, a composition or pharmaceutical composition according to any aspect or [embodimentexample](#) herein, to a subject in need thereof.

[In a further aspect, the present disclosure relates to the use of the antibody as disclosed herein in the manufacture of a medicament for treating cancer.](#)

30 [In a further aspect, the present disclosure relates to a nucleic acid comprising: a. a nucleic acid sequence encoding a heavy chain variable region sequence of an antigen-binding region capable of binding to ROR2 as described herein, and/or b. a nucleic acid sequence encoding the corresponding light chain variable region sequence of said antigen-binding region capable of binding to ROR2 as described herein.](#)

35 [In a further aspect, the present disclosure relates to one or more nucleic acids comprising a. a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as set forth in SEQ ID NO:13, and/or b. a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as set forth in SEQ ID NO:19.](#)

40 [In a further aspect, the present disclosure relates to a nucleic acid, or one or more nucleic acids as described herein for use in expression in mammalian cells.](#)

In a further aspect, the present disclosure relates to an expression vector comprising a) a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as described herein, and/or b) a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as described herein.

In a further aspect, the present disclosure relates to a cell comprising a nucleic acid, or comprising one or more nucleic acids, as described herein or an expression vector as described herein, optionally wherein said cell is of human origin, such as a human embryonic kidney (HEK) cell, or is of rodent origin, such as a Chinese hamster ovary cell (CHO cell).

In a further aspect, the present disclosure relates to a method for producing an antibody capable of binding to both ROR2 and CD3 as described herein, comprising the steps of: a. providing an antibody capable of binding to ROR2, said antibody comprising an antigen-binding region capable of binding to ROR2 as described herein; b. providing an antibody capable of binding to CD3, said antibody comprising an antigen-binding region capable of binding to CD3 as described herein; c. incubating said antibody capable of binding to ROR2 together with said antibody capable of binding to CD3 under reducing conditions sufficient to allow cysteines in the hinge region to undergo disulfide-bond isomerization, and d. obtaining said antibody capable of binding to ROR2 and CD3. In one aspectexample, the inventiondisclosure relates to a method of producing an antibody according to any aspect or embodimentexample herein, comprising cultivating a recombinant host cell in a culture medium and under conditions suitable for producing the antibody.

In another aspect, the present inventiondisclosure relates to a kit-of-parts, such as a kit for use as a companion diagnostic/for identifying within a population of patients those patients which have a propensity to respond to treatment with an antibody as described herein, comprising an antibody as described herein; and instructions for use of said kit. In another example, the present disclosure relates to a kit-of-parts comprising an antibody as defined herein; and instructions for use of said kit.

These and other aspects and embodimentexamples of the inventiondisclosure are described in more detail below.

Claims

1. An antibody comprising at least one antigen-binding region capable of binding to human ROR2 wherein said antibody comprises a heavy chain variable (VH) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 3, 4, and 5, respectively, and a light chain variable (VL) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:7, 8 and 9, respectively.

~~2. The antibody of claim 1 wherein said antibody comprises two antigen-binding regions capable of binding to human ROR2 wherein said antibody comprises the heavy chain variable (VH) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 3, 4, and 5, respectively, and the light chain variable (VL) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO:7, 8 and 9 respectively.~~

~~3.2.~~ The antibody of ~~any one of claims 1 or 2~~ wherein said antibody is humanized from an antibody which comprises a VH region having the sequence set forth in SEQ ID NO: 2 and/or a VL region having the sequence set forth in SEQ ID NO: 6.

~~4.3.~~ The antibody of any one of the above claims wherein said antibody comprises a VH region having a sequence selected from the group comprising:

- a. a VH region as set forth in SEQ ID NO:10 (HC1);
- b. a VH region as set forth in SEQ ID NO:11(HC2);
- c. a VH region as set forth in SEQ ID NO:12(HC3);
- d. a VH region as set forth in SEQ ID NO:13 (HC4);
- e. a VH region as set forth in SEQ ID NO:14(HC5);
- f. a VH region as set forth in SEQ ID NO:15(HC6);
- g. a VH region as set forth in SEQ ID NO:16(HC7) or
- h. a VH region having at least 90% sequence identity to any one of the sequences of SEQ IDNOs 10, 11, 12, 13, 14, 15 or 16

~~5. The antibody of any one of the above claims wherein said antibody comprises a VH region having the sequence set forth in SEQ ID NO:13.~~

~~6.4.~~ The antibody of any one of the preceding claims wherein said antibody comprises a VL region having a sequence selected from the group comprising:

- a. a VL region as set forth in SEQ ID NO:17(LC1);
- b. a VL region as set forth in SEQ ID NO:18 (LC2);
- c. a VL region as set forth in SEQ ID NO:19 (LC3);
- d. a VL region as set forth in SEQ ID NO:20 (LC4) or
- e. a VL region having at least 90% sequence identity to any one of the sequences of SEQ IDNOs 17, 18, 19 or 20.

~~7. The antibody of any one of the preceding claims wherein said antibody comprises a VL region having the sequence set forth in SEQ ID NO:19.~~

8-5. The antibody of any one of the preceding claims wherein said antibody comprises the VH and VL regions having the sequences selected from the group comprising:

- a. The VH region having the sequence of SEQ ID NO. 10 and the VL region having the sequence of SEQ ID NO. 17;
- b. The VH region having the sequence of SEQ ID NO. 10 and the VL region having the sequence of SEQ ID NO. 18;
- c. The VH region having the sequence of SEQ ID NO. 10 and the VL region having the sequence of SEQ ID NO. 19;
- d. The VH region having the sequence of SEQ ID NO. 10 and the VL region having the sequence of SEQ ID NO. 20;
- e. The VH region having the sequence of SEQ ID NO. 11 and the VL region having the sequence of SEQ ID NO. 17;
- f. The VH region having the sequence of SEQ ID NO. 11 and the VL region having the sequence of SEQ ID NO. 18;
- g. The VH region having the sequence of SEQ ID NO. 11 and the VL region having the sequence of SEQ ID NO. 19;
- h. The VH region having the sequence of SEQ ID NO. 11 and the VL region having the sequence of SEQ ID NO. 20;
- i. The VH region having the sequence of SEQ ID NO. 12 and the VL region having the sequence of SEQ ID NO. 17;
- j. The VH region having the sequence of SEQ ID NO. 12 and the VL region having the sequence of SEQ ID NO. 18;
- k. The VH region having the sequence of SEQ ID NO. 12 and the VL region having the

sequence of SEQ ID NO. 19;

- l. The VH region having the sequence of SEQ ID NO. 12 and the VL region having the sequence of SEQ ID NO. 20;
- m. The VH region having the sequence of SEQ ID NO. 13 and the VL region having the sequence of SEQ ID NO. 17;
- n. The VH region having the sequence of SEQ ID NO. 13 and the VL region having the sequence of SEQ ID NO. 18;
- o. The VH region having the sequence of SEQ ID NO. 13 and the VL region having the sequence of SEQ ID NO. 19;
- p. The VH region having the sequence of SEQ ID NO. 13 and the VL region having the sequence of SEQ ID NO. 20;
- q. The VH region having the sequence of SEQ ID NO. 14 and the VL region having the sequence of SEQ ID NO. 17;
- r. The VH region having the sequence of SEQ ID NO. 14 and the VL region having the sequence of SEQ ID NO. 18;
- s. The VH region having the sequence of SEQ ID NO. 14 and the VL region having the sequence of SEQ ID NO. 19;
- t. The VH region having the sequence of SEQ ID NO. 14 and the VL region having the sequence of SEQ ID NO. 20;
- u. The VH region having the sequence of SEQ ID NO. 15 and the VL region having the sequence of SEQ ID NO. 17;
- v. The VH region having the sequence of SEQ ID NO. 15 and the VL region having the sequence of SEQ ID NO. 18;
- w. The VH region having the sequence of SEQ ID NO. 15 and the VL region having the sequence of SEQ ID NO. 19;
- x. The VH region having the sequence of SEQ ID NO. 15 and the VL region having the sequence of SEQ ID NO. 20;
- y. The VH region having the sequence of SEQ ID NO. 16 and the VL region having the sequence of SEQ ID NO. 17;
- z. The VH region having the sequence of SEQ ID NO. 16 and the VL region having the

sequence of SEQ ID NO. 18;

aa. The VH region having the sequence of SEQ ID NO. 16 and the VL region having the sequence of SEQ ID NO. 19; and

bb. The VH region having the sequence of SEQ ID NO. 16 and the VL region having the sequence of SEQ ID NO. 20.

~~9-6.~~ The antibody according to any one of the preceding claims wherein said antibody comprises the VH and VL regions having the sequences of SEQ ID Nos 13 and 19.

~~10.~~ The antibody according to any one of the preceding claims wherein the VH and VL regions are humanized.

~~11-7.~~ The antibody according to any one of the preceding claims wherein the heavy chain constant region is human IgG1.

~~12-8.~~ The antibody according to any one of the preceding claims wherein the light chain constant region is human kappa.

~~13-9.~~ The antibody according to any of the preceding claims, wherein the antibody is a full-length antibody, such as a full length IgG1 antibody.

~~14.~~ The antibody according to any one of the preceding claims, which is a monovalent antibody.

~~15.~~ The antibody according to any one of the preceding claims, which is a bivalent antibody.

~~16.~~ The antibody according to any one of the preceding claims, which is a monospecific antibody.

~~17.~~ The antibody according to any one of the preceding claims, which is a bispecific antibody.

~~18-10.~~ The antibody according to any one of the preceding claims, wherein said human ROR2 is human ROR2 of SEQ ID NO. 1.

~~19-11.~~ The antibody according to any one of the preceding claims wherein the antibody is able to bind to the Kringle domain of human ROR2.

~~20-12.~~ The antibody according to any one of the preceding claims, wherein said antibody binds to an epitope or antibody binding region on human ROR2 that involves the amino acid residue at position 322 of human ROR2, the numbering referring to its position in SEQ ID NO: 1.

~~21-13.~~ The antibody according to any one of the preceding claims, said antibody being able to bind human ROR2 extra cellular domain with a binding affinity that corresponds to a KD value of 100nM or less, such as 50 nM or less, 10nM or less, 6 nM or less or such as 3nM or less such as with a binding affinity corresponding to a KD value which is within the range of 100nM to

0.1 nM, such as within the range of 100nM to 1nM, such as 50 nM to 1 nM, such as less than about 2.5 nM or less than about 2.0 nM or less than about 1.5 nM such as about 1.1 nM, optionally,

~~22. The antibody according to claim 21,~~ wherein the binding affinity is determined by biolayer interferometry, optionally as set forth in Example 6 herein.

~~23. The antibody according to any one of claims 21 and 22, wherein the binding affinity is determined using a biolayer interferometry comprising the steps of:~~

~~a. Immobilizing the antibody at an amount of 1 µg/mL for 600 seconds on an anti-human IgG Fc Capture biosensor;~~

~~b. Determining association over a time period of 1,500 seconds and dissociation over a time period of 1,500 seconds of ROR2ECDHis using 2-fold dilution series ranging from 100 nM to 1.56 nM.~~

~~c. Referencing the data to a buffer control (0 nM).~~

~~24. The antibody according to any one of claims 21 to 23, wherein the binding affinity is determined using an antibody as defined in any one of the preceding claims, which is a monospecific, bivalent antibody, such as an antibody which is a full length IgG1.~~

~~25-14.~~ An antibody comprising a first antigen binding region capable of binding human ROR2 according to any one of the preceding claims and comprising a second antigen binding region capable of binding to a different target, optionally wherein the antibody is a bispecific antibody.

~~26-15.~~ The antibody of claim ~~25-14~~ wherein the second antigen binding region is capable of binding to human CD3 such as human CD3ε (epsilon), such as human CD3ε (epsilon) as specified in SEQ ID NO: 21.

~~27. The antibody according to claim 25 or 26, which is a bispecific antibody.~~

~~28-16.~~ The antibody according to claim ~~26 or 27~~15, wherein the antigen-binding region that binds to CD3 comprises

a heavy chain variable region (VH) comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NOs.: 23, 24 and 25, respectively;

and, optionally

a light chain variable region (VL) comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO: 27, GTN and 28, respectively.

[29-17.](#) The antibody according to any one of claims [26 to 28](#)[15 and 16](#), wherein the antigen binding region that binds to CD3 comprises

- a. a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 22, or a sequence having at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% amino acid sequence identity to the sequence of SEQ ID NO: 22;
- b. and a light chain variable region (VL) comprising the sequence of SEQ ID NO: 26 or a sequence having at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% amino acid sequence identity to the sequence of SEQ ID NO: 26.

[30-18.](#) The antibody according to any one of claims [26 to 29](#)[15 to 17](#), wherein the antigen binding region that binds to CD3 comprises

- a. a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 29, or a sequence having at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% amino acid sequence identity to the sequence of SEQ ID NO: 29;
- b. and, optionally a light chain variable region (VL) comprising the sequence of SEQ ID NO: 30 or a sequence having at least 80%, at least 90%, at least 95%, at least 97%, or at least 99% amino acid sequence identity to the sequence of SEQ ID NO: 30.

[31-19.](#) The antibody according to any one of claims [26-15](#) to [30](#)[18](#), wherein the antigen binding region that binds to CD3 comprises

- a. a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 29, and
- b. a light chain variable region (VL) comprising the sequence of SEQ ID NO: 30.

[32-20.](#) The antibody according to any one of claims [25-15](#) to [30](#)[18](#), wherein said antibody has a lower human CD3 ϵ binding affinity than an antibody having an antigen-binding region comprising a VH sequence as set forth in SEQ ID NO: 29, and a VL sequence as set forth in SEQ ID NO: 30, preferably wherein said affinity is at least 5-fold lower, such as at least 10-fold lower, e.g. at least 20-fold lower, at least 30 fold lower, at least 40 fold lower, at least 45 fold lower or such as at least 50-fold lower, such as at least 54-fold lower.

[33-21.](#) The antibody according to any one of claims [26-15](#) to [32](#)[19](#), wherein said antigen binding region that binds to CD3 binds with an equilibrium dissociation constant K_D within the range of 200 – 1000 nM, such as within the range of 300 – 1000 nM, within the range of 400 – 1000 nM, within the range of 500 – 1000 nM, within the range of 300 – 900 nM within the range of 400 – 900 nM, within the range of 400 – 700 nM, within the range of 500 – 900 nM, within the range of 500 – 800 nM, within the range of 500 – 700 nM, within the range of 600 – 1000

nM, within the range of 600 – 900 nM, within the range of 600 – 800 nM, or such as within the range of 600 – 700 nM.

~~34-22.~~ The antibody according to any one of claims ~~26-15~~ to ~~3119~~, wherein said antigen binding region that binds to CD3 binds with an equilibrium dissociation constant K_D within the range of 1 – 100 nM, such as within the range of 5 – 100 nM, within the range of 10 – 100 nM, within the range of 1 – 80 nM, within the range of 1 – 60 nM within the range of 1 – 40 nM, within the range of 1 – 20 nM, within the range of 5 – 80 nM, within the range of 5 – 60 nM, within the range of 5 – 40 nM, within the range of 5 – 20 nM, within the range of 10 – 80 nM, within the range of 10 – 60 nM, within the range of 10 – 40 nM, or such as within the range of 10 – 20 nM.

~~35-23.~~ The antibody according to any one of claims ~~26-15~~ to ~~3422~~, wherein

the antigen binding region that binds to CD3 comprises a heavy chain variable (VH) region comprising a CDR1 sequence, a CDR2 sequence and a CDR3 sequence,

the heavy chain variable (VH) region, when compared to a heavy chain variable (VH) region comprising the sequence set forth in SEQ ID NO: 29, has an amino acid substitution in one of the CDR sequences, the substitution being at a position selected from the group consisting of: T31, N57, H101, G105, S110 and Y114, the positions being numbered according to the sequence of SEQ ID NO: 29; and

the wild type light chain variable (VL) region comprises the CDR1, CDR2 and CDR3 sequences set forth in SEQ ID NO: 27, GTN and SEQ ID NO: 28, respectively.

~~36-24.~~ The antibody according to any one of claims ~~26-15~~ to ~~35-23~~ wherein the CDR1, CDR2 and CDR3 of the heavy chain variable (VH) region of the antigen binding region that binds to CD3 comprises, in total, at the most 1, 2, 3, 4 or 5 amino acid substitutions, when compared to the CDR1, CDR2 and CDR3 of the sequence set forth in SEQ ID NO: 29.

~~37-25.~~ The antibody according to any one of claims ~~2615~~ to ~~3524~~, wherein the antigen binding region that binds to CD3 comprises a mutation in the VH region selected from the group consisting of: T31M, T31P, N57E, H101G, H101N, G105P, S110A, S110G, Y114M, Y114R, Y114V.

~~38-26.~~ The antibody according to any one of claims ~~125~~ to ~~3624~~, wherein the antigen-binding region capable of binding to CD3 comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 23, 24, and 31, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having

the sequences as set forth in SEQ ID NO: 27, the sequence GTN, and the sequence as set forth in SEQ ID NO: 28, respectively, ~~respectively~~.

~~39-27.~~ The antibody according to any one of claims ~~2615~~, ~~2716~~, ~~29-18~~ to ~~3826~~, wherein the antigen-binding region capable of binding to CD3 comprises a heavy chain variable region (VH) comprising the sequence set forth in SEQ ID NO: 32 and a light chain variable region (VL) comprising the sequence set forth in SEQ ID NO: 30.

~~40-28.~~ The antibody according to any of the preceding claims which is a bispecific antibody comprising a first antigen binding region capable of binding to human ROR2 and a second binding region capable of binding to human CD3, wherein said first antigen binding region comprises:

a heavy chain variable (VH) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 3, 4, and 5, respectively, and a light chain variable (VL) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO: 7, 8 and 9, respectively;

and said second antigen binding region comprises:

a heavy chain variable (VH) region CDR1 having the sequence as set forth in SEQ ID NO.: 23, a heavy chain variable (VH) region CDR2 having the sequence as set forth in SEQ ID NO.: 24, and a heavy chain variable (VH) region CDR3 having the sequence as set forth in any one of SEQ ID NOs.: CDR2, and CDR3 having the sequences as set forth in NOs.: 23, 24 and 25 or 31, respectively; ~~[anti-CD3 (SP34/humanized SP34, WO2015001085 (Genmab)) — VH CDR sequences]~~, and a light chain variable region (VL) comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO: 27, GTN and 28, respectively.

~~41. The antibody according to any of the preceding claims which is a bispecific antibody comprising a first antigen binding region capable of binding to human ROR2 and a second binding region capable of binding to human CD3, wherein said first antigen binding region comprises:~~

~~a heavy chain variable (VH) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 3, 4, and 5, respectively, and a light chain variable (VL) region CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO: 7, 8 and 9, respectively;~~

~~and said second antigen binding region comprises:~~

~~a heavy chain variable (VH) region comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NOs: 23, 24, and 31, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 having the sequences as set forth in SEQ ID NO: 27, the sequence GTN, and the sequence as set forth in SEQ ID NO: 28, respectively.~~

~~42-29.~~ The antibody according to any one of the preceding claims wherein said antibody comprises a first antigen binding region capable of binding to human ROR2 and a second antigen binding region capable of binding to human CD3, wherein said first antigen binding region comprises a VH region comprising the sequence as set forth in SEQ ID NO: 13, and a VL region comprising the sequence as set forth in SEQ ID NO: 19, and said second antigen binding region comprises a VH region comprising the sequence as set forth in SEQ ID NO: 29, and a VL region comprising the sequence as set forth in SEQ ID NO: 30.

~~43-30.~~ The antibody according to any one of claims 1 to ~~3018, 3220, 3321, and 35-23~~ to ~~39-28 and 41~~, wherein said antibody comprises a first antigen binding region capable of binding to human ROR2 and a second antigen binding region capable of binding to human CD3, wherein said first antigen binding region comprises a VH region comprising the sequence as set forth in SEQ ID NO: 13, and a VL region comprising the sequence as set forth in SEQ ID NO: 19, and said second antigen binding region comprises a VH region comprising the sequence as set forth in SEQ ID NO: 32, and a VL region comprising the sequence as set forth in SEQ ID NO: 30.

~~44. The antibody according to any one of the preceding claims, wherein~~

- ~~a) the antigen-binding region(s) capable of binding to ROR2 is/are humanized, and/or~~
- ~~b) the antigen-binding region capable of binding to CD3, if present, is humanized.~~

~~45. The antibody according to any one of the preceding claims, wherein said antibody comprises a first and a second heavy chain constant region, each of said first and second heavy chain constant regions comprises at least a hinge region, a CH2 and CH3 region, wherein in said first heavy chain constant region at least one of the amino acids in the positions corresponding to positions selected from the group consisting of T366, L368, K370, D399, F405, Y407 and K409 in a human IgG1 heavy chain has been substituted, and in said second heavy chain constant region at least one of the amino acids in the positions corresponding to a position selected from the group consisting of T366, L368, K370, D399, F405, Y407, and K409 in a human IgG1 heavy chain has been substituted, wherein said substitutions of said first and said second heavy chains are not in the same positions, and wherein the amino acid positions in the~~

~~constant regions are numbered according to Eu numbering.~~

31. The antibody according to any one of the preceding claims, wherein the amino acid in the position corresponding to K409 in a human IgG1 heavy chain is R in said first heavy chain, and the amino acid in the position corresponding to F405 in a human IgG1 heavy chain is L in said second heavy chain, or *vice versa* and wherein the amino acid positions in the constant regions are numbered according to Eu numbering.

~~46.~~ -

47-32. The antibody according to any one of the preceding claims, wherein said antibody comprises a first and a second heavy chain and wherein the first and second heavy chains are modified so that the antibody induces Fc-mediated effector function to a lesser extent relative to an identical non-modified antibody.

~~48. The antibody according to any one of the preceding claims, wherein the antibody comprises a first and a second heavy chain, and wherein in both the first and the second heavy chain constant region, the amino acid residues at the positions corresponding to positions L234 and L235 in a human IgG1 heavy chain according to Eu numbering are F and E, respectively.~~

~~49. The antibody according to any one of the preceding claims wherein the antibody comprises a first and a second heavy chain, and wherein in both the first and the second heavy chain constant region, the amino acid residue at the position corresponding to position D265 in a human IgG1 heavy chain according to Eu numbering is A.~~

50-33. The antibody according to any one of the preceding claims wherein the antibody comprises a first and a second heavy chain, and wherein in both the first and the second heavy chain constant regions, the amino acid residue at the position corresponding to positions L234, L235 and D265 in a human IgG1 heavy chain according to Eu numbering are F, E and A respectively.

51-34. The antibody according to any one of the preceding claims wherein the antibody comprises a first and a second heavy chain, and wherein in both the first and the second heavy chain constant regions, the amino acid residue at the position corresponding to positions L234, L235 and D265 in a human IgG1 heavy chain according to Eu numbering are F, E and A respectively and wherein the first heavy chain constant region further comprises a K409R substitution and the second heavy chain constant region further comprises an F405L substitution, such as.

~~52. The antibody according to any one of the preceding claims~~ wherein the antibody

comprises a first and a second heavy chain constant region having the sequences as set forth in SEQ ID Nos 34 and 35, respectively, or a first and a second heavy chain constant region having the sequences as set forth in SEQ ID Nos 35 and 34, respectfully.

~~53-35.~~ The antibody of any one of the preceding claims wherein the antibody is a bispecific antibody capable of binding to human ROR2 and human CD3 epsilon wherein

- a. the first binding arm binding to ROR2 comprises:
 - i. The VH region having the amino acid sequence of SEQ ID NO: 13
 - ii. The VL region having the amino acid sequence of SEQ ID NO: 19
 - iii. A heavy chain constant region having the amino acid sequence of SEQ ID NO: 34 ~~(FEAR)~~ and
 - iv. A human kappa light chain constant region; and
- b. the second binding arm binding to CD3 epsilon comprises:
 - i. The VH region having the amino acid sequence of SEQ ID NO: 29 or 32
 - ii. The VL region having the amino acid sequence of SEQ ID NO: 30
 - iii. A heavy chain constant region having the amino acid sequence of SEQ ID NO: 35 ~~(FEAL)~~ and
 - iv. A human lambda light chain constant region.

~~54. The antibody of any one of the preceding claims wherein the antibody is a bispecific antibody capable of binding to human ROR2 and human CD3 epsilon wherein~~

- ~~a. the first binding arm binding to ROR2 comprises:~~
 - ~~i. The VH region having the amino acid sequence of SEQ ID NO: 13~~
 - ~~ii. The VL region having the amino acid sequence of SEQ ID NO: 19~~
 - ~~iii. A heavy chain constant region having the amino acid sequence of SEQ ID NO: 34 (FEAR) and~~
 - ~~iv. A human kappa light chain constant region; and~~
- ~~b. the second binding arm binding to CD3 epsilon comprises:~~
 - ~~i. The VH region having the amino acid sequence of SEQ ID NO: 32~~
 - ~~ii. The VL region having the amino acid sequence of SEQ ID NO: 30~~

iii. ~~A heavy chain constant region having the amino acid sequence of SEQ ID NO: 35 (FEAL) and~~

iv. ~~A human lambda light chain constant region.~~

~~55. The antibody according to any one of the preceding claims, wherein said antibody comprises a lambda (λ) light chain.~~

~~56-36.~~ The antibody according to any one of the preceding claims, wherein when said antibody:

- a. Is capable of binding to ROR2 expressing human tumor cells such as HeLa, LCLC103-H, NCI-H1650, 786-), NCI-H23 or ZR-75-1 cells such as described in Example 6 and 10 herein
- b. is capable of mediating concentration-dependent cytotoxicity of HeLa cells, when using purified PBMCs or T cells as effector cells e.g. when assayed as described in Example 11 or 12 herein,
- c. is capable of mediating concentration-dependent cytotoxicity of 786-O, LCLC-103H, NCI-H23, NCH-H1650 or ZR-75-1 cells, when using purified PBMCs or T cells as effector cells e.g. when assayed as described in Example 12 herein,
- d. is capable of activating T cells in vitro in the presence of HeLa, 786-O, LCLC-103H, NCI-H23, NCH-H1650 tumor cells; e.g. when assayed as described in Example 14 herein, and/or
- e. is capable of inducing T cell cytokine production when using tumor cells such as HeLa and 786-O cells as target cells e.g. when assayed as described in Example 13 herein.

~~57-37.~~ A composition comprising an antibody as defined in any one of claims 1 to ~~56-36~~.

~~58-38.~~ A pharmaceutical composition comprising an antibody as defined in any one of claims 1 to ~~56-36~~ and a pharmaceutically acceptable carrier.

~~59-39.~~ The antibody as defined in any of claims 1 to ~~56-36~~ for use as a medicament.

~~60. The antibody for use as a medicament according to claim 59 for use in the treatment of a disease.~~

~~61-40.~~ Use of ~~the antibody for use as a medicament~~ according to ~~any one of claims 601 to 36~~ in the manufacture of a medicament for treating, ~~wherein the disease is~~ cancer.

~~62-41.~~ The ~~antibody for use as a medicament~~ according to claim ~~61-40~~, wherein the cancer is

characterized by expression of ROR2 on the surface of the cancer cells, optionally wherein the cancer is a solid tumor.

~~63. The antibody for use as a medicament for use according to claim 62, wherein said expression of ROR2 is determined in cancer cells obtained from a patient.~~

~~64. The antibody for use as a medicament according to any one of claims 61 to 63 wherein the cancer is a solid tumor.~~

~~65-42.~~ The antibody for use according to ~~any one of claims 61-41 to 64~~, wherein the cancer is selected from the group comprising sarcomas, fibrosarcoma, gastro-intestinal stromal tumors, leiomyosarcoma, rhabdomyosarcoma, liposarcoma, uterine cancer, lung cancer, pancreatic cancer, renal cancer, colorectal cancer, cervical cancer and breast cancer.

~~66. A method of treating a disease, the method comprising administering an antibody as defined in any one of claims 1 to 56, the composition as defined in claim 57, or the pharmaceutical composition defined in claim 58, to a subject in need thereof.~~

~~67. The method according to claim 66, said method being for treatment of a cancer.~~

~~68. The method according to claim 67, wherein the cancer is selected from the group comprising sarcomas, fibrosarcoma, gastro-intestinal stromal tumors, leiomyosarcoma, rhabdomyosarcoma, liposarcoma, uterine cancer, lung cancer, pancreatic cancer, renal cancer, colorectal cancer, cervical cancer and breast cancer.~~

~~69-43.~~ A nucleic acid comprising:

- a. a nucleic acid sequence encoding a heavy chain variable region sequence of an antigen-binding region capable of binding to ROR2 as defined in any one of claims 1 to 3, 5 and 6, 8 and 9, and/or
- b. a nucleic acid sequence encoding the corresponding light chain variable region sequence of said antigen-binding region capable of binding to ROR2 as defined in any one of claims 1, 2 and 4 to ~~3 and 6 to 9~~.

~~70. One or more nucleic acids comprising~~

- ~~a. a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as defined in claim 9,~~
- ~~b. a nucleic acid sequence encoding the corresponding light chain sequence of an antibody comprising said antigen-binding region capable of binding to ROR2 as defined in claim 9.~~

~~71.44.~~ One or more nucleic acids comprising

- a. a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as set forth in SEQ ID NO:13, and/or
- b. a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as set forth in SEQ ID NO:19.

~~72.45.~~ A nucleic acid, or one or more nucleic acids, according to any one of claims ~~69-43 to 72~~ ~~71~~ ~~and 44~~, wherein said nucleic acid is RNA or DNA.

~~73.46.~~ A nucleic acid, or one or more nucleic acids, according to any one of claims ~~69-43 to 72~~ ~~45~~ for use in expression in mammalian cells.

~~74.47.~~ An expression vector comprising

- a) a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as defined in any one of claims ~~69-43 to 73~~ ~~46~~, and/or
- b) a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to ROR2 as defined in any one of claims ~~69-43 to 73~~ ~~46~~.

~~75.48.~~ The expression vector according to claim ~~74~~ ~~47~~, further comprising

- a. a nucleic acid sequence encoding a heavy chain sequence of an antibody comprising an antigen-binding region capable of binding to CD3 as defined in any one of claims ~~28-16 to 31-20~~ and ~~35-23 to 39~~ ~~27~~; and/or
- b. a nucleic acid sequence encoding a light chain sequence of an antibody comprising an antigen-binding region capable of binding to CD3 as defined in any one of claims ~~28~~ ~~16 to 31-20~~ and ~~35-23 to 39~~ ~~27~~.

~~76.~~ A cell comprising a nucleic acid, or comprising one or more nucleic acids, as defined in any one of claims ~~69-43 to 73~~ ~~46~~ or an expression vector as defined in claims ~~74-47~~ or ~~75~~ ~~48~~, optionally

~~77.49.~~ ~~The cell according to claim 76,~~ wherein said cell is of human origin, such as a human embryonic kidney (HEK) cell, or is of rodent origin, such as a Chinese hamster ovary cell (CHO cell).

~~78.50.~~ A method for producing an antibody capable of binding to both ROR2 and CD3 in

accordance with any one of claims ~~1-15~~ to ~~5636~~, comprising the steps of:

- a. providing an antibody capable of binding to ROR2, said antibody comprising an antigen-binding region capable of binding to ROR2 as defined in any one of claims 1 to ~~5636~~;
- b. providing an antibody capable of binding to CD3, said antibody comprising an antigen-binding region capable of binding to CD3 as defined in any one of claims ~~26-15~~ to ~~5636~~;
- c. incubating said antibody capable of binding to ROR2 together with said antibody capable of binding to CD3 under reducing conditions sufficient to allow cysteines in the hinge region to undergo disulfide-bond isomerization, and
- d. obtaining said antibody capable of binding to ROR2 and CD3.

~~79. The method for producing an antibody capable of binding to both ROR2 and CD3, in accordance with claim 78, wherein the steps a) and/or b) comprise:~~

~~providing cells containing expression vectors for producing said antibody or said antibodies; and~~

~~allowing the cells to produce said antibody or said antibodies and subsequently,~~

~~obtaining said antibody or said antibodies, thereby providing said antibody or said antibodies.~~

~~80-51.~~ A kit-of-parts, such as a kit for use as a companion diagnostic/for identifying within a population of patients those patients which have a propensity to respond to treatment with an antibody as defined in any one of claims 1 to ~~5636~~, comprising an antibody as defined in any one of claims 1 to ~~5636~~; and instructions for use of said kit.

~~81. An anti-idiotypic antibody, which binds to the antigen-binding region capable of binding to ROR2 as defined in any one of claims 1 to 56.~~