

Claims

1. A multispecific antibody comprising a first antigen-binding region capable of binding human CD40 and a second antigen-binding region capable of binding a human V γ 9V δ 2 T cell receptor, wherein:

- the multispecific antibody binds monovalently to CD40,
- the multispecific antibody is an antagonist of human CD40,
- the multispecific antibody is able to activate human V γ 9V δ 2 T cells,
- and wherein the first antigen-binding region comprises:

○ the VH CDR1 sequence set forth in SEQ ID NO:1, the VH CDR2 sequence set forth in SEQ ID NO:2 and the VH CDR3 sequence set forth in SEQ ID NO:3, or

~~1.○~~ the VH CDR1 sequence set forth in SEQ ID NO:4, the VH CDR2 sequence set forth in SEQ ID NO:5 and the VH CDR3 sequence set forth in SEQ ID NO:6.

2. The multispecific antibody according to claim 1, wherein the multispecific antibody is a bispecific antibody.

3. The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region is a single-domain antibody.

4. The multispecific antibody according to any one of the preceding claims, wherein the second antigen-binding region is a single-domain antibody.

~~5. The multispecific antibody according to any one of the preceding claims, wherein the first antigen binding region and second antigen binding region are covalently linked via a peptide linker.~~

~~6. The multispecific antibody according to claim 5, wherein the peptide linker comprises or consists of the sequence set forth in SEQ ID NO:21.~~

~~7.5.~~ The multispecific antibody according to any one of the preceding claims,
 5 wherein the first antigen-binding region is located N-terminally of the second antigen-binding region.

~~8.6.~~ The multispecific antibody according to any one of the preceding claims,
 wherein the multispecific antibody ~~binds monovalently to CD40 and binds~~
 10 monovalently to the human V γ 9V δ 2 T cell receptor.

~~9. The multispecific antibody according to any one of the preceding claims,
 wherein the multispecific antibody is not an agonist of human CD40.~~

~~10. The multispecific antibody according to any one of the preceding claims,
 wherein the multispecific antibody is an antagonist of human CD40.~~

~~11.7.~~ The multispecific antibody according to any one of the preceding claims,
 wherein the multispecific antibody is capable of sensitizing human CD40-
 20 expressing cells to venetoclax.

~~12. The multispecific antibody according to any one of the preceding claims,
 wherein the multispecific antibody competes for binding to human CD40 with an
 antibody having the sequence set forth in SEQ ID NO:13 and/or competes for
 25 binding to human CD40 with an antibody having the sequence set forth in SEQ ID
 NO:14.~~

~~13. The multispecific antibody according to any one of the preceding claims,
 wherein the multispecific antibody binds the same epitope on human CD40 as an~~

~~antibody having the sequence set forth in SEQ ID NO:13 or binds the same epitope on human CD40 as antibody having the sequence set forth in SEQ ID NO:14.~~

5 ~~14. The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region comprises~~

- ~~• the VH CDR1 sequence set forth in SEQ ID NO:1, the VH CDR2 sequence set forth in SEQ ID NO:2 and the VH CDR3 sequence set forth in SEQ ID NO:3, or~~
- ~~• the VH CDR1 sequence set forth in SEQ ID NO:4, the VH CDR2 sequence set forth in SEQ ID NO:5 and the VH CDR3 sequence set forth in SEQ ID NO:6.~~

~~15.8. The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region is humanized.~~

15 ~~16.9. The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region comprises or consists of:~~

- ~~• the sequence set forth in SEQ ID NO:13 or the sequence set forth in SEQ ID NO:14, or~~
- ~~• a sequence having at least 90%, such as least 92%, e.g. at least 94%, such as at least 96%, e.g. at least 98% sequence identity to the sequence set forth in SEQ ID NO:13 or a sequence having at least 90%, such as least 92%, e.g. at least 94%, such as at least 96%, e.g. at least 98% sequence identity to the sequence set forth in SEQ ID NO:14.~~

25 ~~17. The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody is able to activate human V α 9V β 2 T cells.~~

~~18.10. The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody is capable of mediating killing of human CD40-~~

expressing cells from a chronic lymphocytic leukemia patient and/or from a multiple myeloma patient.

~~19.11.~~ The multispecific antibody according to any one of the preceding claims,
5 wherein the multispecific antibody is capable of mediating killing of human CD40-
expressing cells from a chronic lymphocytic leukemia patient that have been
stimulated with CD40L.

~~20.12.~~ The multispecific antibody according to any one of the preceding claims,
10 wherein the multispecific antibody is capable of binding to human V δ 2.

~~21.13.~~ The multispecific antibody according to any one of the preceding claims,
wherein the multispecific antibody competes for binding to human V δ 2 with an
antibody having the sequence set forth in SEQ ID NO: 17 or competes for binding
15 to human V δ 2 with an antibody having the sequence set forth in SEQ ID NO: 18.

~~22.14.~~ The multispecific antibody according to any one of the preceding claims,
wherein the multispecific antibody binds the same epitope on human V δ 2 as an
antibody having the sequence set forth in SEQ ID NO: 17 or binds the same
20 epitope on human V δ 2 as an antibody having the sequence set forth in SEQ ID
NO: 18.

~~23.15.~~ The multispecific antibody according to any one of the preceding claims,
wherein the second antigen-binding region comprises the VH CDR1 sequence set
25 forth in SEQ ID NO:7, the VH CDR2 sequence set forth in SEQ ID NO:8 and the
VH CDR3 sequence set forth in SEQ ID NO:9 or comprises the VH CDR1 sequence
set forth in SEQ ID NO:10, the VH CDR2 sequence set forth in SEQ ID NO:11 and
the VH CDR3 sequence set forth in SEQ ID NO:12.

~~24.16.~~ The multispecific antibody according to any one of the preceding claims, wherein the second antigen-binding region is humanized.

~~25.17.~~ The multispecific antibody according to any one of the preceding claims, wherein the second antigen-binding region comprises or consists of

- the sequence set forth in SEQ ID NO:17, or
- a sequence having at least 90%, such as least 92%, e.g. at least 94%, such as at least 96%, e.g. at least 98% sequence identity to the sequence set forth in SEQ ID NO:17, or
- a sequence selected from the group consisting of SEQ ID NO: 25, 26, 27, 28, 29, 30, 31, 32, 33 and 34.

18. The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody comprises an inert Fc region.

19. The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody comprises a Leu to Phe mutation at position 234 and a Leu to Glu mutation at position 235.

~~26. The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region comprises~~

- ~~• the VH CDR1 sequence set forth in SEQ ID NO:1, the VH CDR2 sequence set forth in SEQ ID NO:2 and the VH CDR3 sequence set forth in SEQ ID NO:3, or~~
 - ~~• the VH CDR1 sequence set forth in SEQ ID NO:4, the VH CDR2 sequence set forth in SEQ ID NO:5 and the VH CDR3 sequence set forth in SEQ ID NO:6,~~
- ~~and wherein the second antigen-binding region comprises the VH CDR1 sequence set forth in SEQ ID NO:7, the VH CDR2 sequence set forth in SEQ ID NO:8 and the VH CDR3 sequence set forth in SEQ ID NO:9.~~

~~27. An antibody comprising a first antigen-binding region capable of binding human CD40, wherein the antibody competes for binding to human CD40 with an antibody having the sequence set forth in SEQ ID NO:13 and/or competes for binding to human CD40 with an antibody having the sequence set forth in SEQ ID NO:14.~~

~~28. The antibody according to claim 27, wherein the antibody binds the same epitope on human CD40 as an antibody having the sequence set forth in SEQ ID NO:13 or binds the same epitope on human CD40 as antibody having the sequence set forth in SEQ ID NO:14.~~

~~29. The antibody according to claim 27 or 28, wherein the first antigen-binding region comprises~~

- ~~• the VH CDR1 sequence set forth in SEQ ID NO:1, the VH CDR2 sequence set forth in SEQ ID NO:2 and the VH CDR3 sequence set forth in SEQ ID NO:3, or~~
- ~~• the VH CDR1 sequence set forth in SEQ ID NO:4, the VH CDR2 sequence set forth in SEQ ID NO:5 and the VH CDR3 sequence set forth in SEQ ID NO:6.~~

~~30. The antibody according to any one of claims 27 to 29, wherein the first antigen-binding region comprises or consists of:~~

- ~~• the sequence set forth in SEQ ID NO:13 or the sequence set forth in SEQ ID NO:14, or~~
- ~~• a sequence having at least 90%, such as least 92%, e.g. at least 94%, such as at least 96%, e.g. at least 98% sequence identity to the sequence set forth in SEQ ID NO:13 or a sequence having at least 90%, such as least 92%, e.g. at least 94%, such as at least 96%, e.g. at least 98% sequence identity to the sequence set forth in SEQ ID NO:14.~~

~~31. The antibody according to any one of claims 27 to 30, wherein the first~~

~~antigen-binding region is a single domain antibody.~~

~~32. The antibody according to any one of claims 27 to 31, wherein the antibody is a monospecific antibody, e.g. a monovalent antibody.~~

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~~33. The antibody according to any one of claims 27 to 31, wherein the antibody comprises a second antigen-binding region which binds an antigen which is not human CD40 or V β 2.~~

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~~34. The antibody according to any one of claims 27 to 33, having one or more of the properties defined in claims 9 to 11.~~

~~35.20. A pharmaceutical composition comprising a multispecific antibody according to any one of claims 1 to 26-19 or an antibody according to any one of claims 27 to 34 and a pharmaceutically-acceptable excipient.~~

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~~36.21. The multispecific antibody according to any one of claims 1 to 26-19 or the antibody according to any one of claims 27 to 34 for use as a medicament.~~

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~~37.22. The multispecific antibody according to any one of claims 1 to 26-19 or the antibody according to any one of claims 27 to 34 for use in the treatment of cancer.~~

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~~38.23. The multispecific antibody according to any one of claims 1 to 26-19 or the antibody according to any one of claims 27 to 34 for use in the treatment of chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, follicular lymphoma, head and neck cancer, pancreatic cancer, ovarian cancer, lung cancer, breast cancer, colon cancer, prostate cancer, B-cell lymphoma/leukemia, Burkitt lymphoma or B acute lymphoblastic leukemia.~~

~~39-24.~~ The multispecific antibody according to any one of claims 1 to ~~26-19~~ for use in the treatment of chronic lymphocytic leukemia or multiple myeloma.

5 ~~40-25.~~ The multispecific antibody according to any one of claims 1 to ~~26-19~~ or the antibody according to any one of claims ~~27 to 34~~ for use according to any one of claims ~~36-21~~ to ~~39~~24, wherein the use is in combination with a Bcl-2 blocker, such as venetoclax.

10 ~~41.~~ A method of treating a disease comprising administration of a multispecific antibody according to any one of claims 1 to ~~26~~ or an antibody according to any one of claims ~~27 to 34~~ to a human subject in need thereof.

~~42.~~ The method according to claim ~~41~~, wherein the disease is cancer.

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~~43-26.~~ A nucleic acid construct encoding the multispecific antibody according to any one of claims 1 to ~~26~~ or the antibody according to any one of claims ~~27 to 34~~19.

20 ~~44-27.~~ An expression vector comprising a nucleic acid construct according to claim ~~43~~26.

~~45-28.~~ A host cell comprising a nucleic acid construct according to claim ~~43-26~~ or an expression vector according to claim ~~44~~27.

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