

**CLAIMS**

1. An antibody or antigen-binding fragment thereof, which specifically binds to human OX40 and comprises:

(i) a heavy chain variable region that comprises (a) a HCDR (Heavy Chain Complementarity Determining Region) 1 of SEQ ID NO: 3, (b) a HCDR2 of SEQ ID NO:24, (c) a HCDR3 of SEQ ID NO:5 and a light chain variable region that comprises: (d) a LCDR (Light Chain Complementarity Determining Region) 1 of SEQ ID NO:25, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO:8;

(ii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:18, (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:19, and (f) a LCDR3 of SEQ ID NO: 8;

(iii) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:13, (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8; or

(iv) a heavy chain variable region that comprises (a) a HCDR1 of SEQ ID NO:3, (b) a HCDR2 of SEQ ID NO:4, (c) a HCDR3 of SEQ ID NO:5; and a light chain variable region that comprises: (d) a LCDR1 of SEQ ID NO:6, (e) a LCDR2 of SEQ ID NO:7, and (f) a LCDR3 of SEQ ID NO:8.

2. The antibody or antigen-binding fragment of claim 1, that comprises:

(i) a heavy chain variable region (VH) comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO:26, and a light chain variable region (VL) comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO: 28;

(ii) a heavy chain variable region (VH) comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO: 20, and a light chain variable region (VL) comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO: 22;

(iii) a heavy chain variable region (VH) comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO: 14, and a light chain variable region (VL) comprising an amino acid sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO: 16; or

(iv) a heavy chain variable region (VH) comprising an amino acid sequence at least 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO:9, and a light chain variable region (VL) comprising an amino acid sequence at least 91, 92, 93, 94, 95, 96, 97, 98 or 99% identical to SEQ ID NO:11.

3. The antibody or antigen-binding fragment of claim 2, wherein one, two, three, four, five, six, seven, eight, nine, or ten amino acids within SEQ ID NO:26, 28, 20, 22, 14, 16, 9, and/or 11 have been inserted, deleted or substituted.

4. The antibody or antigen-binding fragment of claim 1, that comprises:

(i) a heavy chain variable region (VH) that comprises SEQ ID NO:26, and a light chain variable region (VL) that comprises SEQ ID NO: 28;

(ii) a heavy chain variable region (VH) that comprises SEQ ID NO: 20, and a light chain variable region (VL) that comprises SEQ ID NO: 22;

(iii) a heavy chain variable region (VH) that comprises SEQ ID NO: 14, and a light chain variable region (VL) that comprises SEQ ID NO: 16; or

(iv) a heavy chain variable region (VH) that comprises SEQ ID NO:9, and a light chain variable region (VL) that comprises SEQ ID NO:11.

5. The antibody or antigen-binding fragment of any one of claims 1 to 4, which is a monoclonal antibody, a chimeric antibody, a humanized antibody, a human engineered antibody, a single chain antibody (scFv), a Fab fragment, a Fab' fragment, or a F(ab')<sub>2</sub> fragment.

6. The antibody or antigen-binding fragment of any of claims 1 to 5, which has OX40 agonist activity.

7. The antibody or antigen-binding fragment of any one of claims 1 to 6, which binds to human OX40 at an epitope comprising one or more amino acid residues selected from the group consisting of H153 to D170 of human OX40.

8. The antibody or antigen-binding fragment of any one of claims 1 to 6, which binds to human OX40 at an epitope comprising one or more amino acid residues selected from the group consisting of H153, T154, I165, E167 and D170 of human OX40.

9. The antibody or antigen-binding fragment of any one of claims 1 to 6, which binds to human OX40 at an epitope comprising one or more amino acid residues selected from the group consisting of H153, I165 and E167 of human OX40.
10. The antibody or antigen-binding fragment of any one of claims 1 to 6, which binds to human OX40 at or within SEQ ID NO.30.
11. The antibody or antigen-binding fragment of any one of claims 1 to 6, wherein the antibody or antigen-binding fragment thereof has antibody dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC).
12. The antibody or antigen-binding fragment of any one of claims 1 to 6, wherein the antibody or antigen-binding fragment thereof has reduced glycosylation or no glycosylation or is hypofucosylated.
13. The antibody or antigen-binding fragment of any one of claims 1 to 6, wherein the antibody or antigen-binding fragment thereof comprises increased bisecting GlcNac structures.
14. The antibody or antigen-binding fragment of any one of claims 1 to 6, wherein the Fc domain is of an IgG1.
15. The antibody or antigen-binding fragment of any one of claims 1 to 6, wherein the Fc domain is of an IgG4.
16. The antibody or antigen-binding fragment of claim 15, wherein the IgG4 has an S228P substitution (according to EU numbering system).
17. The antibody or antigen-binding fragment of claim 16, wherein the IgG4 has S228P and R409K substitutions (according to EU numbering system).
18. The antibody or antigen-binding fragment of any one of the claims 1-17, which has one or more of the following properties:
- (i) capable of cross-reacting with cyno OX40;
  - (ii) does not interfere with OX40-OX40L interaction;
  - (iii) capable of co-stimulating T cells to produce IL-2

- (iv) capable of co-activating CD4<sup>+</sup> T-cells, particularly as measured in a mixed lymphocyte reaction (MLR) assay;
- (v) capable of mediating ADCC, particularly as measured in a lactate dehydrogenase (LDH) release-based ADCC assay;
- (vi) capable of depleting CD4<sup>+</sup> Tregs;
- (vii) capable of increasing the CD8<sup>+</sup> T<sub>eff</sub>/T<sub>reg</sub> ratio; or
- (viii) capable of mediating partial regression of tumors in an animal tumor model.

19. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, of any one of claims 1 to 18 further comprising a pharmaceutically acceptable carrier.

20. A method of treating cancer comprising administering to a patient in need an effective amount of the antibody or antigen-binding fragment of any one of claims 1 to 18.

21. The method of claim 20, wherein the cancer is breast cancer, head and neck cancer, gastric cancer, kidney cancer, liver cancer, small cell lung cancer, non-small cell lung cancer, ovarian cancer, skin cancer, mesothelioma, lymphoma, leukemia, myeloma and sarcoma.

22. The method of claim 21, wherein the antibody or antigen-binding fragment is administered in combination with another therapeutic agent.

23. The method of claim 22, wherein the therapeutic agent is paclitaxel or a paclitaxel agent, docetaxel, carboplatin, topotecan, cisplatin, irinotecan, doxorubicin, lenalidomide or 5-azacytidine.

24. The method of claim 23, wherein the therapeutic agent is a paclitaxel agent, lenalidomide or 5-azacytidine.

25. An isolated nucleic acid that encodes the antibody or antigen-binding fragment of any one of claims 1 to 18.

26. A vector comprising the nucleic acid of claim 25.

27. A host cell comprising the nucleic acid of claim 25 or the vector of claim 26.

28. A process for producing an antibody or antigen-binding fragment thereof comprising cultivating the host cell of claim 27 and recovering the antibody or antigen-binding fragment from the culture.

29. The antibody or antigen-binding fragment thereof of any one of claims 1 to 18, for use in the treatment or reducing the likelihood of: breast cancer, head and neck cancer, gastric cancer, kidney cancer, liver cancer, small cell lung cancer, non-small cell lung cancer, ovarian cancer, skin cancer, mesothelioma, lymphoma, leukemia, myeloma and sarcoma.

30. A diagnostic reagent comprising the antibody or antigen-binding fragment thereof of any one of claims 1 to 18 which is labeled.

31. The diagnostic reagent of claim 30, wherein the label is selected from the group consisting of a radiolabel, a fluorophore, a chromophore, an imaging agent, and a metal ion.