

CLAIMS

1. An antibody or an antigen-binding fragment thereof with binding specificity for domain 2 of human CD137 in which the antibody or antigen-binding fragment is a CD137 agonist and is capable of inhibiting the binding of reference antibody '1630/1631' to human CD137.
- 5 2. An antibody or an antigen-binding fragment thereof according to Claim 1, in which the antibody or antigen-binding fragment is capable of inhibiting the binding of reference antibody '2674/2675' to human CD137.
3. An antibody or antigen-binding fragment thereof according to Claim 1 or 2 in which the antibody or antigen-binding fragment exhibits one or more of the following properties:
 - 10 (a) the ability to stimulate CD137 and activate T cells and other immune cells via a cross-linking dependent mechanism; and/or
 - (b) cross-reactivity with cyno-CD137 antibodies; and/or
 - (c) is capable of binding an Fc receptor; optionally, in which the ability of the antibody to activate T cells is dependent upon binding to both CD137 and Fc receptors;
 - 15 and/or
 - (d) is capable of inducing tumour immunity.
4. An antibody or antigen-binding fragment thereof according to any one of the preceding claims in which the antibody or antigen-binding fragment is substantially incapable of inducing the following upon binding to cells expressing CD137:
 - 20 (a) antibody-dependent cellular cytotoxicity (ADCC);
 - (b) antibody-dependent cellular phagocytosis (ADCP); and/or
 - (c) complement-dependent cytotoxicity (CDC).
5. An antibody or antigen-binding fragment thereof according to any one of the preceding claims in which the antibody or antigen-binding fragment is capable of binding to an epitope
 - 25 on the extracellular domain of CD137 which overlaps, at least in part, with the epitope on CD137 to which reference antibody 1630/1631 is capable of binding; optionally, in which the antibody or antigen-binding fragment is capable of binding to an epitope on the extracellular domain of CD137 which overlaps, at least in part, with the epitope on CD137 to which

reference antibody 2674/2675 is capable of binding; further optionally. in which the epitope is located at or within amino acids 66 to 107 of human CD137.

6. An antibody or antigen-binding fragment thereof according to any one of the preceding claims comprising or consisting of:

- 5 (a) an intact antibody, for example an IgG1, IgG2, IgG3 or IgG4 antibody; or
- (b) an antigen-binding fragment selected from the group consisting of Fv fragments (*e.g.* single chain Fv and disulphide-bonded Fv), Fab-like fragments (*e.g.* Fab fragments, Fab' fragments and F(ab)₂ fragments) and domain antibodies (*e.g.* single V_H variable domains or V_L variable domains).

10 7. An antibody or antigen-binding fragment according to any one of the preceding claims in which:

(a) the antibody or antigen-binding fragment thereof is a recombinant polypeptide; and/or

(b) the antibody or antigen-binding fragment thereof is monoclonal; and/or

15 (c) the antibody or antigen-binding fragment thereof is human or humanised.

8. An antibody or antigen-binding fragment according to any one of the preceding claims comprising:

(i)

20 (a) a heavy chain CDR1 sequence with the consensus sequence G, F, T/N, F, G, Y, S, Y; optionally in which heavy chain CDR1 comprises the sequence GFTFGYSY [SEQ ID NO: 3] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 3, for example 1, 2 or 3 mutations;

(b) a heavy chain CDR2 sequence with the consensus sequence I, G, S, G/T, S, S, Y/H, T; optionally in which heavy chain CDR2 comprises the sequence
25 IGSGSSYT [SEQ ID NO: 4] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 4, for example 1, 2 or 3 mutations; and

(c) a heavy chain CDR3 sequence with the sequence ARVYSSPGIDY; optionally in which heavy chain CDR3 comprises the sequence ARVYSSPGIDY

[SEQ ID NO: 5] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 5, for example 1, 2 or 3 mutations; and/or

(ii)

(a) a light chain CDR1 sequence with the consensus sequence Q, S, I, S/G, S, Y/T; optionally, in which light chain CDR1 comprises the sequence QSISSY [SEQ ID NO: 6] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 6, for example 1, 2 or 3 mutations;

(b) a light chain CDR2 sequence with the consensus sequence A/G, A, S; optionally in which light chain CDR2 comprises the sequence AAS [SEQ ID NO: 7] or an amino acid sequence containing up to 2 amino acid mutations compared to SEQ ID NO: 7; for example 1 or 2 mutations; and

(c) a light chain CDR3 sequence with the sequence QQYYTWVPFT; optionally in which light chain CDR2 comprises the sequence QQYYTWVPFT [SEQ ID NO: 8] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 8, for example 1, 2 or 3 mutations.

9. An antibody or antigen-binding fragment thereof according to Claim 8 comprising:

(a) a heavy chain variable region comprising the CDRs of SEQ ID NOs 3, 4 and 5; optionally, in which the antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO 1: or an amino acid sequence having at least 60% sequence identity therewith, for example at least 70%, 80%, or 90% sequence identity; and/or

(b) a light chain variable region comprising the CDRs of SEQ ID NOs: 6, 7 and 8; optionally, in which the antibody or antigen-binding fragment thereof comprises a light chain variable region having the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence having at least 60% sequence identity therewith, for example at least 70%, 80%, or 90% sequence identity; and/or

(c) the antibody or antigen-binding fragment thereof comprises the CDRs of SEQ ID NOs: 3, 4, 5, 6, 7 and 8; optionally, in which the antibody or antigen-binding fragment thereof comprises a heavy chain variable region which comprises or consists of the amino acid sequence of SEQ ID NO: 1 and a light chain variable region which comprises or consists of the amino acid sequence of SEQ ID NO: 2.

10. An antibody or antigen-binding fragment thereof according to any one of Claims 1 to 8 comprising:

(i) a heavy chain variable region comprising the following CDRs:

(a) GFNFGYSY [SEQ ID NO: 21] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 21, for example 1, 2 or 3 mutations;

(b) IGSTSSHT [SEQ ID NO: 22] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 22, for example 1, 2 or 3 mutations; and

(c) ARVYSSPGIDY [SEQ ID NO: 23] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 23, for example 1, 2 or 3 mutations; and/or

(ii) a light chain variable region comprising the following CDRs:

(a) QSIGST [SEQ ID NO: 24] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 24, for example 1, 2 or 3 mutations;

(b) GAS [SEQ ID NO: 25] or an amino acid sequence containing up to 2 amino acid mutations compared to SEQ ID NO: 25; for example 1 or 2 mutations; and

(c) QQYYTWVPFT [SEQ ID NO: 26] or an amino acid sequence containing up to 3 amino acid mutations compared to SEQ ID NO: 26, for example 1, 2 or 3 mutations.

11. An antibody or antigen-binding fragment thereof according to Claim 10 comprising:

(a) a heavy chain variable region comprising the CDRs of SEQ ID NOs 21, 22 and 23; optionally, in which the antibody or antigen-binding fragment thereof comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO 19; or an amino acid sequence having at least 60% sequence identity therewith, for example at least 70%, 80%, or 90% sequence identity; and/or

(b) a light chain variable region comprising the CDRs of SEQ ID NOs: 24, 25 and 26; optionally, in which the antibody or antigen-binding fragment thereof comprises a light chain variable region having the amino acid sequence of SEQ ID NO: 20 or an amino

acid sequence having at least 60% sequence identity therewith, for example at least 70%, 80%, or 90% sequence identity; and/or

(c) the antibody or antigen-binding fragment thereof comprises the CDRs of SEQ ID NOs: 21, 22, 23, 24, 25 and 26; optionally, in which the antibody or antigen-binding fragment thereof comprises a heavy chain variable region which comprises or consists of the amino acid sequence of SEQ ID NO: 19 and a light chain variable region which comprises or consists of the amino acid sequence of SEQ ID NO: 20.

12. An antibody or antigen-binding fragment thereof according to any one of the preceding claims comprising:

(a) a heavy chain constant region, or part thereof; optionally, in which the heavy chain constant region is of an immunoglobulin subtype selected from the group consisting of IgG1, IgG2, IgG3 and IgG4, further optionally in which the heavy chain constant region comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 13, 14 and 15; and/or

(b) a light chain constant region, or part thereof; optionally, in which the light chain constant region is of a kappa or lambda light chain; further optionally, in which the light chain constant region comprises or consists of an amino acid sequence of SEQ ID NO: 16.

13. An antibody or antigen-binding fragment thereof according to any one of the preceding claim comprising an Fc region; optionally, in which

(a) the Fc region is naturally occurring; or

(b) the Fc region is non-naturally occurring; further optionally, in which the Fc region comprises mutations to shorten the half-life of the antibody or antigen binding fragment.

14. An antibody or antigen-binding fragment thereof according to any one of the preceding claims comprising:

(i)

(a) a heavy chain comprising a variable region of SEQ ID NO: 1 together with a constant region of SEQ ID NO: 13; and

(b) a light chain comprising a variable region of SEQ ID NO: 2 together with a constant region of SEQ ID NO: 16; and/or

(ii)

(a) a heavy chain comprising a variable region of SEQ ID NO: 19 together with a constant region of SEQ ID NO: 13; and

(b) a light chain comprising a variable region of SEQ ID NO: 20 together with a constant region of SEQ ID NO: 16.

15. An antibody or antigen-binding fragment thereof according to any one of the preceding claims in which

(a) the antibody is an intact IgG4 molecule comprising or consisting of two heavy chains having an amino acid sequence of SEQ ID NO: 17 and two light chains having an amino acid sequence of SEQ ID NO: 18; and/or

(b) the antibody is an intact IgG4 molecule comprising or consisting of two heavy chains having an amino acid sequence of SEQ ID NO: 29 and two light chains having an amino acid sequence of SEQ ID NO: 30.

16. An antibody or antigen-binding fragment thereof according to any one of the preceding claims further comprising:

(i) a cytotoxic moiety;

optionally, in which the cytotoxic moiety comprises or consists of:

(a) a radioisotope; or

(b) a cytotoxic drug; and/or

(ii) a detectable moiety;

optionally, in which the detectable moiety comprises or consists of a radioisotope, and in which optionally the cytotoxic moiety and/or detectable moiety is joined to the antibody or antigen-binding fragment thereof indirectly, via a linking moiety; optionally in which the linking moiety is a chelator; further optionally, in which the chelator is selected from the group consisting of derivatives of 1,4,7,10-tetraazacyclododecane-1,4,7,10, tetraacetic acid (DOTA), deferoxamine (DFO), derivatives of diethylenetriaminepentaacetic acid (DTPA), derivatives of S-2-(4-

Isothiocyanatobenzyl)-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) and derivatives of 1,4,8,11-tetraazacyclododecan-1,4,8,11-tetraacetic acid (TETA).

17. An isolated nucleic acid molecule encoding an antibody or antigen-binding fragment thereof according to any one of the preceding claims or a component polypeptide chain thereof.

18. A nucleic acid molecule according to Claim 17 encoding an antibody heavy chain or variable region thereof; optionally, in which the nucleic acid molecule encoding an antibody heavy chain or variable region thereof comprises or consists of a nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence of SEQ ID NO: 27; and/or the nucleic acid molecule encodes an antibody light chain or variable region thereof; optionally in which the nucleic acid molecule encoding an antibody light chain or variable region thereof comprises or consists of a nucleotide sequence of SEQ ID NO: 10 or a nucleotide sequence of SEQ ID NO: 28.

19. A vector comprising a nucleic acid molecule according to Claim 17 or 18; optionally in which the vector is an expression vector.

20. A recombinant host cell comprising a nucleic acid molecule according to Claim 17 or 18 or a vector according to Claim 19; optionally in which the host cell is a bacterial cell or a mammalian cell; optionally, in which the mammalian cell is a human cell.

21. A method for producing an antibody or antigen-binding fragment according to any one of the Claims 1 to 16, the method comprising culturing a host cell as defined in Claim 20 under conditions which permit expression of the encoded antibody or antigen-binding fragment thereof.

22. A pharmaceutical composition comprising an effective amount of an antibody or antigen-binding fragment thereof according to any one of Claims 1 to 16 and a pharmaceutically-acceptable diluent, carrier or excipient.

23. An antibody or antigen-binding fragment thereof according to any one of Claims 1 to 16 for use in the treatment of cancer, in which the cancer is preferably selected from the group consisting of: prostate cancer, breast cancer; colorectal cancer; kidney cancer; pancreatic cancer; ovarian cancer; lung cancer; cervical cancer; rhabdomyosarcoma; neuroblastoma; bone cancer; multiple myeloma; leukemia (such as acute lymphoblastic leukemia [ALL] and

acute myeloid leukemia [AML]), skin cancer (e.g. melanoma), bladder cancer and glioblastoma.

24. Use of an antibody or antigen-binding fragment according to any one of Claims 1 to 16 in the manufacture of a medicament for the treatment of cancer.

5 25. Use of an antibody or antigen-binding fragment according to Claim 24 in which the cancer is selected from the group consisting of: prostate cancer; breast cancer; colorectal cancer; kidney cancer; pancreatic cancer; ovarian cancer; lung cancer; cervical cancer; rhabdomyosarcoma; neuroblastoma; bone cancer; multiple myeloma; leukemia (such as acute lymphoblastic leukemia [ALL] and acute myeloid leukemia [AML]), skin cancer (e.g.
10 melanoma), bladder cancer and glioblastoma; optionally in which the medicament is for treating a patient who has been pre-screened and identified as having a tumour with cells expressing CD137 and FcγR.

26. A method of identifying a patient susceptible to treatment with an antibody of any of Claims 1 to 16 comprising screening a patient to identify if they have a tumour with cells
15 expressing CD137 and FcγR.

27. A combination therapy comprising an antibody or antigen-binding fragment thereof according to any one of Claims 1 to 16 and one or more further therapeutic agents; optionally in which the one or more further therapeutic agents are cancer therapies.