CLAIMS

1. A kit comprising a bispecific polypeptide and one or more therapeutic agent, in which the bispecific polypeptide comprises a first binding domain, designated B1, which is capable of specifically binding to OX40, and a second binding domain, designated B2, which is capable of specifically binding to CTLA-4.

2. A composition comprising a bispecific polypeptide and one or more therapeutic agent, in which the bispecific polypeptide comprises a first binding domain, designated B1, which is capable of specifically binding to OX40, and a second binding domain, designated B2, which is capable of specifically binding to CTLA-4.

3. A bispecific polypeptide comprising a first binding domain, designated B1, which is capable of specifically binding to OX40, and a second binding domain, designated B2, which is capable of specifically binding to CTLA-4 for use as a medicament, in which the polypeptide is for use in combination with one or more additional therapeutic agents.

4. Use of a bispecific polypeptide comprising a first binding domain, designated B1, which is capable of specifically binding to OX40, and a second binding domain, designated B2, which is capable of specifically binding to CTLA-4, in the manufacture of a medicament, in which the polypeptide is for use in combination with one or more additional therapeutic agents.

5. A kit according to Claim 1, a composition according to Claim 2, a polypeptide for use according to Claim 3 or a use according to Claim 4, in which the one or more additional therapeutic agents is/are used in the treatment of cancers, such as antimetabolites, alkylating agents, anthracyclines and other cytotoxic antibiotics, vinca alkyloids, etoposide, platinum compounds, taxanes, topoisomerase I inhibitors, other cytostatic drugs, antiproliferative immunosuppressants, corticosteroids, sex hormones and hormone antagonists, and other therapeutic antibodies (such as antibodies against a tumour-associated antigen or an immune checkpoint modulator).

6. A kit according to Claim 1, a composition according to Claim 2, a polypeptide for use according to Claim 3 or a use according to Claim 4, in which the one or more additional therapeutic agents is/are an immunotherapeutic agent that binds a target selected from the group consisting of PD-1/PD-L1, CD137, CD40, GITR, LAG3, TIM3, CD27 and KIR;

optionally, in which the one or more additional therapeutic agents is/are an immunotherapeutic agent that binds PD-1 or PD-L1, such as an anti-PD-1 antibody or antigen-binding fragment thereof capable of inhibiting PD1 function (for example, Nivolumab, Pembrolizumab, Lambrolizumab, PDR-001, MEDI-0680 and AMP-224), or an anti-PD-L1 antibody or antigen-binding fragment thereof capable of inhibiting PD1 function (for example, Durvalumab, Atezolizumab, Avelumab and MDX-1105).

7. A kit according to any of Claims 1, 5 or 6, a composition according to any of Claims 2, 5 or 6, a polypeptide for use according to any of Claims 3, 5 or 6 or a use according to any of Claims 4, 5 or 6, in which the first and/or second binding domains are selected from the group consisting of: antibodies or antigen-binding fragments thereof; optionally, in which the antigen-binding fragment is selected from the group consisting of: an Fv fragment (such as a single chain Fv fragment, or a disulphide-bonded Fv fragment), a Fab-like fragment (such as a Fab fragment, a Fab' fragment or a $F(ab)_2$ fragment) and domain antibodies; and/or in which the polypeptide is a bispecific antibody; optionally, in which the bispecific antibody comprises:

(a) binding domain B1 and/or binding domain B2 is an intact IgG antibody;

(b) binding domain B1 and/or binding domain B2 is an Fv fragment;

(c) binding domain B1 and/or binding domain B2 is a Fab fragment; and/or

(d) binding domain B1 and/or binding domain B2 is a single domain antibody; further optionally, in which the bispecific polypeptide is selected from the groups consisting of:

(a) bivalent bispecific antibodies, such as IgG-scFv bispecific antibodies (for example, in which B1 is an intact IgG and B2 is an scFv attached to B1 at the N-terminus of a light chain and/or at the C-terminus of a light chain and/or at the N-terminus of a heavy chain and/or at the C-terminus of a heavy chain of the IgG, or *vice versa*);

(b) monovalent bispecific antibodies, such as a *DuoBody*® or a 'knob-in-hole' bispecific antibody (for example, an scFv-KIH, scFv-KIH^r, a BiTE-KIH or a BiTE-KIH^r;

(c) $scFv_2$-Fc bispecific antibodies (for example, *ADAPTIR*™ bispecific antibodies);

(d) BiTE/$scFv_2$ bispecific antibodies;

(e) DVD-Ig bispecific antibodies or other IgG-FAb, FAb-IgG bispecific antibodies regardless of bivalency or linkers/ connectors employed;

(f) DART-based bispecific antibodies (for example, DART-Fc, $DART_2$-Fc or DART);

(g) $DNL\text{-}Fab_3$ bispecific antibodies; and

(h) scFv-HSA-scFv bispecific antibodies.

8. A kit according to any of Claims 1 or 5 to 7, a composition according to any of Claims 2 or 5 to 7, a polypeptide for use according to any of Claims 3 or 5 to 7 or a use according to any of Claims 4 to 7, in which the polypeptide comprises a human Fc region or a variant of a the region, where the region is an IgG1, IgG2, IgG3 or IgG4 region, preferably an IgG1 or IgG4 region.

9. A kit according to any of Claims 1 or 5 to 8, a composition according to any of Claims 2 or 5 to 8, a polypeptide for use according to any of Claims 3 or 5 to 8 or a use according to any of Claims 4 to 8, in which the polypeptide is capable of inducing antibody dependent cell cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), and/or apoptosis.

10. A kit according to any of Claims 1 or 5 to 9, a composition according to any of Claims 2 or 5 to 9, a polypeptide for use according to any of Claims 3 or 5 to 9 or a use according to any of Claims 4 to 9, in which:

B1 is an antibody, or antigen binding fragment thereof, specific for OX40; and

B2 is a polypeptide binding domain specific for CTLA-4, which comprises or consists of:

(i) the amino acid sequence of SEQ ID NO: 3; or

(ii) an amino acid sequence in which at least one amino acid is changed when compared to the amino acid sequence of SEQ ID NO: 3 provided that the binding domain binds to human CTLA-4 with higher affinity than wild-type human CD86.

11. A kit according to any of Claims 1 or 5 to 10, a composition according to any of Claims 2 or 5 to 10, a polypeptide for use according to any of Claims 3 or 5 to 10 or a use according to any of Claims 4 to 10, in which the CTLA-4 specifically bound by the polypeptide is

primate or murine, preferably human, CTLA-4, and/or in which the OX40 specifically bound by the polypeptide is primate, preferably human, OX40.

12. A kit according to any of Claims 1 or 5 to 11, a composition according to any of Claims 2 or 5 to 11, a polypeptide for use according to any of Claims 3 or 5 to 11 or a use according to any of Claims 4 to 11, in which B1 comprises at least one heavy chain (H) and/or at least one light chain (L) and B2 is attached to the at least one heavy chain (H) or least one light chain (L); optionally, in which B1 comprises:

- at least one heavy chain (H) and at least one light chain (L) and B2 is attached to either the heavy chain or the light chain; or

- two identical heavy chains (H) and two identical light chains (L) and B2 is attached to both heavy chains or to both light chains.

13. A kit according to any of Claims 1 or 5 to 12, a composition according to any of Claims 2 or 5 to 12, a polypeptide for use according to any of Claims 3 or 5 to 12 or a use according to any of Claims 4 to 12, in which the polypeptide comprises or consists of a polypeptide chain arranged according to any of the following formulae, written in the direction N-C:

(A) L-(X)n-B2;

(B) B2-(X)n-L;

(C) B2-(X)n-H;

(D) H-(X)n-B2;

in which X is a linker and n is 0 or 1; optionally, in which X is a peptide with the amino acid sequence SGGGGSGGGGS (SEQ ID NO: 47), SGGGGSGGGGSAP (SEQ ID NO: 48), NFSQP (SEQ ID NO:49), KRTVA (SEQ ID NO: 50), GGGGSGGGGSGGGGS (SEQ ID NO: 144) or (SG)m, where m = 1 to 7.

14. A kit according to any of Claims 1 or 5 to 13, a composition according to any of Claims 2 or 5 to 13, a polypeptide for use according to any of Claims 3 or 5 to 13 or a use according to any of Claims 4 to 13, in which the polypeptide binds to human OX40 with a Kd of less than $50x10^{-10}$M, $25x10^{-10}$M, or $20x10^{-10}$M and/or which binds to human CTLA-4 with a Kd value which is less than $60x10^{-9}$M, $25x10^{-9}$M, or $10x10^{-9}$M and/or in which B1 exhibits at least one of the following functional characteristics when present independently of B2:

I. binding to human OX40 with a KD value which is less than 10x10-10M, more preferably less than 5x10-10M;

II. does not bind to murine OX40; and

III. does not bind to other human TNFR superfamily members, for example human CD137 or CD40.

15. A kit according to any of Claims 1 or 5 to 14, a composition according to any of Claims 2 or 5 to 14, a polypeptide for use according to any of Claims 3 or 5 to 14 or a use according to any of Claims 4 to 14, in which the polypeptide induces an increase in the activity of an effector T cell, preferably a CD4+ effector T cell, optionally in which the increase is at least 1.5 fold, 4.5 fold or 7 fold higher than the increase in activity of an effector T cell induced by a combination of B1 and B2 administered to the T cell as separate molecules; optionally in which the increase in T cell activity is an increase in proliferation and/or IL-2 production by the T cell.

16. A kit according to any of Claims 1 or 5 to 15, a composition according to any of Claims 2 or 5 to 15, a polypeptide for use according to any of Claims 3 or 5 to 15 or a use according to any of Claims 4 to 15, in which the polypeptide competes for binding to OX40 with antibody 1166/1167 and/or in which the polypeptide competes for binding to CTLA-4 with CD86 mutant 1040 (SEQ ID NO: 17); and/or in which the polypeptide competes for binding to OX40 with antibody 1166/1261, and/or in which the polypeptide competes for binding to CTLA-4 with antibody 1166/1261.

17. A kit according to any of Claims 1 or 5 to 16, a composition according to any of Claims 2 or 5 to 16, a polypeptide for use according to any of Claims 3 or 5 to 16 or a use according to any of Claims 4 to 16, in which 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids in the amino acid sequence of B2 (ii) are substituted when compared to the amino acid sequence of SEQ ID NO: 3, optionally in which there are no insertions or deletions compared to the amino acid sequence of SEQ ID NO: 3; further optionally, in which at least one of the amino acid substitutions in the amino acid sequence of the first binding domain is at position 122, and optionally in which the amino acid sequence is also substituted in at least one of positions 107, 121 and 125.

18. A kit according to any of Claims 1 or 5 to 17, a composition according to any of Claims 2 or 5 to 17, a polypeptide for use according to any of Claims 3 or 5 to 17 or a use according

to any of Claims 4 to 17, in which the amino acid sequence of B2 comprises or consists of an amino acid sequence selected from any one of SEQ ID NOs 6 to 24 (as shown in Table C), or variants of the sequences which have more than 60%, or more than 70%, e.g. 75 or 80%, preferably more than 85%, e.g. more than 90 or 95% amino acid identity to the amino acid sequences of SEQ ID NOs 6 to 24.

19. A kit according to any of Claims 1 or 5 to 18, a composition according to any of Claims 2 or 5 to 18, a polypeptide for use according to any of Claims 3 or 5 to 18 or a use according to any of Claims 4 to 18, in which B1 comprises any one, two, three, four, five or all six features independently selected from the following:

(a) a heavy chain CDR1 sequence which is 8 amino acids in length and comprises the consensus sequence: “G, F, T, F, G/Y/S, G/Y/S, Y/S, Y/S/A”;

(b) a heavy chain CDR2 sequence which is 8 amino acids in length and comprises the consensus sequence: “ I, G/Y/S/T, G/S/Y, S/Y, G/S/Y, G/S/Y, G/S/Y, T”;

(c) a heavy chain CDR3 sequence which is 9 to 17 amino acids in length and which comprises the consensus sequence of : “A, R, G/Y/S/H, G/Y/F/V/D, G/Y/P/F, -/H/S, -/N/D/H, -/Y/G, -/Y, -/Y, -/W/A/V, -/A/Y, -/D/A/Y/G/H/N, Y/S/W/A/T, L/M/I/F, D, Y”

(d) a light chain CDR1 sequence which consists of the sequence: “Q, S, I, S, S, Y”;

(e) a light chain CDR2 sequence which consists of the sequence: “A, A, S”;

(f) a light chain CDR3 sequence which is 8 to 10 amino acids in length and comprises the consensus sequence: “Q,Q, S/Y/G, -/Y/H/G, -/S/Y/G/D/W, S/Y/G/D , S/Y/G/T, P/L, Y/S/H/L/F, T”;

in which the heavy chain CDR3 sequence of (c) is preferably a sequence of 10 amino acids in length which comprises the consensus sequence “A, R, Y/H, D, Y, A/Y/G, S/W/A, M/L, D, Y”; and

the light chain CDR3 sequence of (f) preferably consists of the sequence “Q, Q, Y, Y, W, Y, G, L, S, T”;

optionally, in which B1 comprises all three heavy chain CDR sequences of a VH sequence as shown in Table A(1) and/or all three light chain CDR sequences of a VL sequence as shown in Table A(2) or in which B1 comprises a heavy chain VH sequence and/or a light chain VL sequence as shown in Table B; and/or in which B1 comprises a

heavy chain CDR3 sequence of 11 amino acids in length which comprises the consensus sequence “A, R, Y/H, D, Y, A/Y/G, S/W/A, M/L, D, Y” and the light chain VL sequence of SEQ ID NO: 89 (1167 as shown in Table B), further optionally in which the light chain VL sequence of SEQ ID NO: 89 is present as part of the longer sequence of SEQ ID NO: 125 (1261 as shown in Table D) and/or in which binding domain B1 comprises the light chain VL sequence of SEQ ID NO: 89 (1167 as shown in Table B), and the heavy chain VH sequence of SEQ ID NO: 91 (1166 as shown in Table B), or variants of the sequences which have more than 60%, or more than 70%, e.g. 75 or 80%, preferably more than 85%, e.g. more than 90 or 95% amino acid identity to SEQ ID NO: 89 and/or SEQ ID NO: 91.

20. A kit according to any of Claims 1 or 5 to 19, a composition according to any of Claims 2 or 5 to 19, a polypeptide for use according to any of Claims 3 or 5 to 19 or a use according to any of Claims 4 to 19, in which the polypeptide comprises or consists of the amino acid sequence of any one of SEQ ID NOs 125 to 134, optionally in which the polypeptide is a provided as a component part of an antibody, or variants of the sequences which have more than 60%, or more than 70%, e.g. 75 or 80%, preferably more than 85%, e.g. more than 90 or 95% amino acid identity to the amino acid sequences of SEQ ID NOs 125 to 134.

21. A kit according to any of Claims 1 or 5 to 20, or a composition according to any of Claims 2 or 5 to 20 for use as a medicament.

22. Use of a kit according to any of Claims 1 or 5 to 20, or use of a composition according to any of Claims 2 or 5 to 20 in the manufacture of a medicament.

23. A kit for use according to Claim 21, a composition for use according to Claim 21, a use according to Claim 22, a polypeptide for use according to any of Claims 3 or 5 to 20 or a use according to any of Claims 4 to 20, in which the medicament is for the treatment of cancer and optionally in which the individual is a human; further optionally in which the cancer is prostate cancer, breast cancer, colorectal cancer, pancreatic cancer, ovarian cancer, lung cancer, cervical cancer, rhabdomyosarcoma, neuroblastoma, multiple myeloma, leukemia, acute lymphoblastic leukemia, melanoma, bladder cancer, gastric cancer, head and neck cancer, liver cancer, skin cancer, lymphoma or glioblastoma.