CLAIMS

1. A binding agent comprising a first antigen-binding region binding to human CD137 and a second antigen-binding region binding to human PD-L1, wherein the first antigen-binding region binding to human CD137 comprises a heavy chain variable region (VH) comprising a HCDR1, HCDR2, and HCDR3 sequence and a light chain variable region (VL) comprising a LCDR1, LCDR2, and LCDR3 sequence, wherein the HCDR1, HCDR2 and HCDR3 sequences are the sequences as set forth in: SEQ ID NO: 9, 10, 11, respectively and the LCDR1, LCDR2 and LCDR3 sequences are the sequences as set forth in: SEQ ID NO: 13, GAS, 14, respectively; and the second antigen-binding region inhibits the binding of human PD-L1 to human PD-1 and comprises a heavy chain variable region (VH) comprising a HCDR1, HCDR2, and HCDR3 sequence and a light chain variable region (VL) comprising a LCDR1, LCDR2, and LCDR3 sequence, wherein the HCDR1, HCDR2 and HCDR3 sequences are the sequences as set forth in: SEQ ID NO: 18, 19, 20 respectively and the LCDR1, LCDR2 and LCDR3 sequences are the sequences as set forth in: SEQ ID NO: 22, DDN, 23 respectively.

2. The binding agent according to claim 1, wherein said first antigen-binding region binding to human CD137 comprises a heavy chain variable region (VH), wherein the VH comprises the sequence as set forth in: SEQ ID NO: 15.

3. The binding agent according to claim 1 or 2, wherein said first antigen-binding region binding to human CD137 comprises a light chain variable region (VL), wherein the VL comprises the sequence as set forth in: SEQ ID NO: 16.

4. The binding agent according to any one of the preceding claims, wherein said first antigen-binding region binding to human CD137 comprises a heavy chain variable region (VH) and a variable region (VL), wherein the VH sequence comprises the sequence as set forth in: SEQ ID NO: 15 and the VL sequence comprises the sequence as set forth in: SEQ ID NO: 16.

5. The binding agent according to any one of the preceding claims, wherein said second antigen-binding region binding to human PD-L1 comprises a heavy chain variable region (VH), wherein the VH comprises the sequence as set forth in: SEQ ID NO: 17.

6. The binding agent according to any one of the preceding claims, wherein said second antigen-binding region binding to human PD-L1 comprises a light chain variable region (VL), wherein the VL comprises the sequence as set forth in: SEQ ID NO: 21.

7. The binding agent according to any one of the preceding claims, wherein said second antigen-binding region binding to human PD-L1 comprises a heavy chain variable region (VH) and a variable region (VL), wherein the VH comprises the sequence as set forth in: SEQ ID NO: 17 and the VL comprises the sequence as set forth in: SEQ ID NO: 21.

8. The binding agent according to any one of the preceding claims, comprising a first antigen-binding region binding to human CD137 and a second antigen-binding region binding to human PD-L1, wherein
   a. the first antigen-binding region comprises a heavy chain variable region (VH) comprising the sequence as set forth in: SEQ ID NO:15;

   and

   b. the second antigen-binding region comprises a heavy chain variable region (VH) comprising the sequence as set forth in: SEQ ID NO:17.

9. The binding agent according to any one of the preceding claims comprising a first antigen-binding region binding to human CD137 and a second antigen-binding region binding to human PD-L1, wherein
   a. the first antigen-binding region comprises a heavy chain variable region (VH) comprising the sequence as set forth in: SEQ ID NO:15 and a light chain variable region (VL) comprising the sequence as set forth in: SEQ ID NO: 16;

   and

   b. the second antigen-binding region comprises a heavy chain variable region (VH) comprising the sequence as set forth in: SEQ ID NO:17 and a light chain variable region (VL) comprising the sequence as set forth in: SEQ ID NO:21.

10. The binding agent according to any one of the preceding claims, which is an immunoglobulin molecule.

11. The binding agent according to any one of the preceding claims, wherein the binding agent is in the format of a full-length antibody.

12. The binding agent according to any one of the preceding claims, wherein said binding agent consists of two pairs of polypeptide chains: One pair of light (L) chains and one pair of heavy (H) chains, which are all four inter-connected by disulfide bonds.

13. The binding agent according to claim 12, wherein each heavy chain comprises a heavy chain variable region (VH) and a heavy chain constant region (CH) and each light chain comprises a light chain variable region (VL) and a light chain constant region (CL).

14. The binding agent according to claim 13, wherein each heavy chain constant region comprises of three domains, CH1, CH2, and CH3, the CH1 and CH2 domains being separated by a hinge region; and each light chain comprises one domain (CL).

15. The binding agent according to any one of the preceding claims, wherein each variable region comprises three complementarity determining regions (CDR1, CDR2, and CDR3) and four framework regions (FR1, FR2, FR3, and FR4).

16. The binding agent according to claim 15, wherein said complementarity determining regions and said framework regions are arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

17. The binding agent according to any one of the preceding claims, which comprises (i) a polypeptide comprising said first heavy chain variable region (VH) and further comprising a first heavy chain constant region (CH) and (ii) a polypeptide comprising said second heavy chain variable region (VH) and further comprising a second heavy chain constant region (CH).

18. The binding agent according to any one of the preceding claims, which comprises (i) a polypeptide comprising said first light chain variable region (VL) and further comprising a first light chain constant region (CL) and (ii) a polypeptide comprising said second light chain variable region (VL) and further comprising a second light chain constant region (CL).

19. The binding agent according to claims 17 to 18, which is an antibody comprising a first binding arm and a second binding arm, wherein

    a. the first binding arm comprises i) a polypeptide comprising said first heavy chain variable region (VH) and said first heavy chain constant region (CH) and ii) a polypeptide comprising said first light chain variable region (VL) and said first light chain constant region (CL) and;
    b. the second binding arm comprises iii) a polypeptide comprising said second heavy chain variable region (VH) and said second heavy chain constant region (CH) and iv) a polypeptide comprising said second light chain variable region (VL) and said second light chain constant region (CL).

20. The binding agent according to any one of claims 17 to 19, wherein each of the first and second heavy chain constant region (CH) comprises one or more of a constant domain 1 region (CH1 region), a hinge region, a CH2 region and a CH3 region, preferably at least a hinge region, a CH2 region and a CH3 region.

21. The binding agent according to any one of the preceding claims, wherein the binding agent is of an isotype selected from the group consisting of IgG1, IgG2, IgG3, and IgG4.

22. The binding agent according to any one of the preceding claims, wherein the binding agent is a full-length IgG1 antibody.

23. The binding agent according to any one of the preceding claims, wherein
    a. the first antigen-binding region binding to human CD137 is derived from a human antibody, and/or
    b. the second antigen-binding region binding to human PD-L1 is derived from a human antibody.

24. The binding agent according to any one of the preceding claims, wherein in said first heavy chain constant region (CH) at least one of the amino acids in a position corresponding to a position selected from the group consisting of T366, L368, K370, D399, F405, Y407, and K409 in a human IgG1 heavy chain according to EU numbering has been substituted, and in said second heavy chain constant region (CH) at least one of the amino acids in a position corresponding to a position selected from the group consisting of T366, L368, K370, D399, F405, Y407, and K409 in a human IgG1 heavy chain according to EU numbering has been

substituted, and wherein said first and said second heavy chains are not substituted in the same positions.

25. The binding agent according to claim 24, wherein (i) the amino acid in the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering is L in said first heavy chain constant region (CH), and the amino acid in the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering is R in said second heavy chain constant region (CH), or (ii) the amino acid in the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering is R in said first heavy chain, and the amino acid in the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering is L in said second heavy chain.

26. The binding agent according to any one of the preceding claims, wherein in at least one of said first and second heavy chain constant region (CH) one or more amino acids in the positions corresponding to positions L234, L235, D265, N297, and P331 in a human IgG1 heavy chain according to EU numbering, are not L, L, D, N, and P, respectively.

27. The binding agent according to claim 26, wherein the positions corresponding to positions L234 and L235 in a human IgG1 heavy chain according to EU numbering are F and E, respectively, in said first and second heavy chains.

28. The binding agent according to claim 26, wherein the positions corresponding to positions L234, L235, and D265 in a human IgG1 heavy chain according to EU numbering are F, E, and A, respectively, in said first and second heavy chain constant regions (HCs).

29. The binding agent according to claim 28, wherein the positions corresponding to positions L234, L235, and D265 in a human IgG1 heavy chain according to EU numbering of both the first and second heavy chain constant regions are F, E, and A, respectively, and wherein (i) the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering of the first heavy chain constant region is L, and the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering of the second heavy chain constant region is R, or (ii) the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering of the first heavy chain is R, and the position corresponding to F405 in

a human IgG1 heavy chain according to EU numbering of the second heavy chain is L.

30. The binding agent according to claim 27, wherein the positions corresponding to positions L234 and L235 in a human IgG1 heavy chain according to EU numbering of both the first and second heavy chain constant regions are F and E, respectively, and wherein (i) the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering of the first heavy chain constant region is L, and the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering of the second heavy chain is R, or (ii) the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering of the first heavy chain constant region is R, and the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering of the second heavy chain is L.

31. The binding agent according to any one of the preceding claims, wherein the binding agent is a multispecific antibody such as a bispecific antibody.

32. A nucleic acid encoding a binding agent according to any one of claims 1 to 31.

33. An expression vector comprising a nucleic acid according to claim 32.

34. A cell comprising a nucleic acid according to claim 32 or an expression vector according to claim 33.

35. The cell according to claim 34, wherein said cell is a mammalian cell, such as a Chinese hamster ovary cell.

36. A composition comprising a binding agent according to any one of claims 1 to 31, a nucleic acid according to claim 32, an expression vector according to claim 33, or a cell according to claim 34 or 35.

37. The composition according to claim 36, which is a pharmaceutical composition.

38. The composition according to claim 37, further comprising a pharmaceutically acceptable carrier and/or excipient.

39. A binding agent according to any one of claims 1 to 31, a nucleic acid according to claim 32, an expression vector according to claim 33, or a composition according to any one of claims 36 to 38 for use as a medicament, wherein the binding agent is a bispecific antibody and wherein the binding agent is an IgG1 antibody.

40. The binding agent, nucleic acid, expression vector, or composition according to claim 39 for use in the treatment of cancer.

41. The binding agent, nucleic acid, expression vector, or composition for use according to claim 40, wherein the cancer is characterized by the presence of solid tumors or is selected from the group consisting of: melanoma, ovarian cancer, lung cancer, colon cancer and head and neck cancer.

42. The binding agent, nucleic acid, expression vector, or composition for use according to claim 41, wherein the cancer is non-small cell lung cancer (NSCLC).

43. Use of a binding agent according to any one of claims 1 to 31, a nucleic acid according to claim 32, an expression vector according to claim 33, or a composition according to any one of claims 36 to 38 for the manufacture of a medicament for the treatment of cancer, wherein the binding agent is a bispecific antibody and wherein the binding agent is an IgG1 antibody.

44. The use according to claim 43, wherein the cancer is a cancer characterized by the presence of solid tumors or a cancer selected from the group consisting of: melanoma, ovarian cancer, lung cancer, colon cancer and head and neck cancer.

45. The use according to claim 44, wherein the lung cancer is non-small cell lung cancer (NSCLC).

46. The use according to any one of claims 43 to 45, wherein the medicament is to be used in combination with one or more further therapeutic agents.

47. The use according to claim 46, wherein one or more further therapeutic agents is a chemotherapeutic agent.

48. A method for producing a bispecific antibody according to claim 31, comprising the steps of:
    a. culturing a host cell producing a first antibody comprising an antigen-binding region binding to human CD137 as defined in any one of claims 1 to 4, 8 and 9, and optionally purifying said first antibody from the culture;
    b. culturing a host cell producing a second antibody comprising an antigen-binding region binding to human PD-L1 as defined in any one of claims 1, and 5-9 and optionally purifying said second antibody from the culture;
    c. incubating said first antibody together with said second antibody under reducing conditions sufficient to allow the cysteines in the hinge region to undergo disulfide-bond isomerization, and
    d. obtaining said CD137xPD-L1 bispecific antibody.