

## CLAIMS

1. ~~A pharmaceutical formulation comprising~~
- 5       a. ~~a binding agent comprising a first antigen binding region binding to human CD137 (4-1BB) and a second antigen binding region binding to human PD-L1 (CD274);~~
- 10       ~~— the first antigen binding region comprising a first heavy chain variable region (VH) comprising the three complementarity determining regions, CDR1, CDR2, and CDR3, present within the amino acid sequence set forth in SEQ ID NO: 15, and a first light chain variable region (VL) comprising the three complementarity determining regions, CDR1, CDR2, and CDR3, present within the amino acid sequence set forth in SEQ ID NO: 16, and~~
- 15       ~~— the second antigen binding region comprising a second heavy chain variable region (VH) comprising the three complementarity determining regions, CDR1, CDR2, and CDR3, present within the amino acid sequence set forth in SEQ ID NO: 17, and a second light chain variable region (VL) comprising the three complementarity determining regions, CDR1, CDR2, and CDR3, present within the amino acid sequence set forth in SEQ ID NO: 21;~~
- 20       b. ~~a histidine buffer,~~
- c. ~~about 100 to about 400 mM of a sugar, and~~
- d. ~~about 0.001 to about 0.1% (w/v) non-ionic surfactant;~~
- and having a pH between about 4.5 and about 6.5.
- 25       2. ~~The pharmaceutical formulation according to claim 1, said formulation comprising 1 to 100 mM histidine, such as 5 to 100 mM, 10 to 100 mM, 15 to 100 mM, 5 to 90 mM, 5 to 80 mM, 5 to 70 mM, 5 to 60 mM, 5 to 50 mM, 5 to 40 mM, 5 to 30 mM, 10 to 90 mM, 10 to 80 mM, 10 to 70 mM, 10 to 60 mM, 10 to 50 mM, 10 to 40 mM, 10 to 30 mM, 15 to 90 mM, 15 to 80 mM, 15 to 70 mM, 15 to 60 mM, 15 to 50 mM, 15 to 40 mM, 15 to 30 mM or 15 to 20 mM histidine.~~
- 30       3. ~~The pharmaceutical formulation according to any one of the preceding claims, said formulation comprising about 20 mM Histidine, such as 20 mM Histidine.~~
4. ~~The pharmaceutical formulation according to any one of the preceding claims, said pharmaceutical formulation comprising 100 to 400 mM sugar, such as 125 to 400 mM, 150 to 400 mM, 150 to 400 mM, 175 to 400 mM, 200 to 400 mM, 225 to 400 mM, 100~~

- to 375 mM, 100 to 350 mM, 100 to 325 mM, 100 to 300 mM, 125 to 375 mM, 125 to 350 mM, 125 to 325 mM, 125 to 300 mM, 125 to 275 mM, 150 to 375 mM, 150 to 350 mM, 150 to 325 mM, 150 to 300 mM, 150 to 275 mM, 175 to 375 mM, 175 to 350 mM, 175 to 325 mM, 175 to 300 mM, 175 to 275 mM, 200 to 375 mM 1, 200 to 350 mM 1, 200 to 325 mM, 200 to 300 mM, 200 to 275 mM, 225 to 375 mM, 225 to 350 mM, 225 to 325 mM, 225 to 300 mM, or such as 225 to 275 mM sugar.
5. The pharmaceutical formulation according to any one of the preceding claims, said formulation comprising about 250 mM sugar, such as 250 mM sugar.
6. The pharmaceutical formulation according to any one of the preceding claims, wherein the sugar is sucrose.
7. The pharmaceutical formulation according to any one of the preceding claims, said pharmaceutical formulation comprising 0.005 to 0.1% (w/v) non ionic surfactant, such as 0.01 to 0.1% (w/v), 0.015 to 0.1% (w/v), 0.001 to 0.09% (w/v), 0.001 to 0.08% (w/v), 0.001 to 0.07% (w/v), 0.001 to 0.06% (w/v), 0.001 to 0.05% (w/v), 0.001 to 0.04% (w/v), 0.001 to 0.02% (w/v), 0.005 to 0.1% (w/v), 0.005 to 0.09% (w/v), 0.005 to 0.08% (w/v), 0.005 to 0.07% (w/v), 0.005 to 0.06% (w/v), 0.005 to 0.05% (w/v), 0.005 to 0.04% (w/v), 0.005 to 0.03% (w/v), 0.005 to 0.02% (w/v), 0.01 to 0.09% (w/v), 0.01 to 0.08% (w/v), 0.01 to 0.07% (w/v), 0.01 to 0.06% (w/v), 0.01 to 0.05% (w/v), 0.01 to 0.04% (w/v), 0.01 to 0.03% (w/v), 0.01 to 0.02% (w/v), 0.015 to 0.09% (w/v), 0.015 to 0.08% (w/v), 0.015 to 0.07% (w/v), 0.015 to 0.06% (w/v), 0.015 to 0.05% (w/v), 0.015 to 0.04% (w/v), 0.015 to 0.03% (w/v), or such as 0.015 to 0.02% (w/v) non ionic surfactant.
8. The pharmaceutical formulation according to any one of the preceding claims, said formulation comprising about 0.02% (w/v) non ionic surfactant, such as 0.02% (w/v) non ionic surfactant.
9. The pharmaceutical formulation according to any of the preceding claims, wherein the non ionic surfactant is 2 [2 [3,4 bis(2 hydroxyethoxy)oxolan 2 yl] 2 (2 hydroxyethoxy)ethoxy]ethyl (E) octadec 9 enoate (Polyoxyethylene (20) sorbitan monooleate; Polysorbate 80) or 2 [2 [3,4 bis(2 hydroxyethoxy)oxolan 2 yl] 2 (2 hydroxyethoxy)ethoxy]ethyl dodecanoate (Polyoxyethylene (20) sorbitan monolaurate; Polysorbate 20).
10. The pharmaceutical formulation according to any one of the preceding claims, having a pH between 4.5 and 6.5, such as between 4.7 and 6.5, e.g. between 4.9 and 6.5,

~~between 5.1 and 6.5, between 5.3 and 6.5, between 4.5 and 6.3, between 4.7 and 6.1,  
between 4.7 and 5.9, between 4.7 and 5.7, between 5.1 and 6.3, between 4.7 and 6.1,  
between 4.7 and 5.9, between 4.7 and 5.7, between 4.9 and 6.3, between 4.9 and 6.1,  
between 4.9 and 5.9, between 4.9 and 5.7, between 5.1 and 6.3, between 5.1 and 6.1,  
between 5.1 and 5.9, between 5.1 and 5.7, between 5.3 and 6.3, between 5.3 and 6.1,  
between 5.3 and 5.9, such as between 5.3 and 5.7.~~

~~11. The pharmaceutical formulation according to any one of the preceding claims, having  
a pH, which is about 5.5, such as a pH of 5.5.~~

~~12. The pharmaceutical formulation according to any one of the preceding claims,  
comprising 5 to 200 mg/mL of the binding agent, such as 10 to 200 mg/mL, 20 to 200  
mg/mL, 40 to 200 mg/mL, 60 to 200 mg/mL, 80 to 200 mg/mL, 100 to 200 mg/mL,  
120 to 200 mg/mL, 150 to 200 mg/mL, 5 to 150 mg/mL, 10 to 150 mg/mL, 20 to 150  
mg/mL, 40 to 150 mg/mL, 60 to 150 mg/mL, 80 to 150 mg/mL, 100 to 150 mg/mL, 5  
to 130 mg/mL, 10 to 130 mg/mL, 20 to 130 mg/mL, 40 to 130 mg/mL, 60 to 130  
mg/mL, 80 to 130 mg/mL, 100 to 130 mg/mL, 5 to 100 mg/mL, 10 to 100 mg/mL, 15  
to 100 mg/mL, 20 to 100 mg/mL, 30 to 100 mg/mL, 40 to 100 mg/mL, 50 to 100  
mg/mL, 60 to 100 mg/mL, 5 to 80 mg/mL, 5 to 60 mg/mL, 5 to 50 mg/mL, 5 to 40  
mg/mL, 5 to 30 mg/mL, 5 to 20 mg/mL, 10 to 80 mg/mL, 10 to 60 mg/mL, 10 to 50  
mg/mL, 10 to 40 mg/mL, 10 to 30 mg/mL, 15 to 80 mg/mL, 15 to 60 mg/mL, 15 to  
40 mg/mL, or such as 15 to 25 mg/mL of the binding agent.~~

~~13. The pharmaceutical formulation according to any one of the preceding claims,  
comprising about 20 mg/mL of the binding agent, such as 20 mg/mL of the binding  
agent.~~

~~14. The pharmaceutical formulation according to any one of the preceding claims, wherein  
the formulation comprises~~

~~i) about 20 mg/mL of the binding agent, such as about 40 mg/mL, about 60  
mg/mL, about 80 mg/mL, about 100 mg/mL, about 120 mg/mL, or about 140  
mg/mL, and~~

~~ii) about 20 mM Histidine, about 250 mM sugar, and about 0.02% (w/v) non ionic  
surfactant and has a pH about 5.5.~~

~~15. The pharmaceutical formulation according to any one of the preceding claims, wherein  
the formulation comprises~~

~~i) 20 mg/mL of the binding agent such as 40 mg/mL, 60 mg/mL, 80 mg/mL, 100  
mg/mL, 120 mg/mL, or 140 mg/mL, and~~

ii) ~~20 mM Histidine, 250 mM sugar, and 0.02% (w/v) non-ionic surfactant and has a pH of 5.5.~~

5 ~~16. The pharmaceutical formulation according to any one of the preceding claims, wherein the formulation is essentially free of visible particles after having been subjected to 5 freeze thaw cycles consisting of freezing for 12h at -65°C following by thawing for 12h at 25°C, as determined by visible particle count performed against a black background and against a white background at an illumination of an intensity between 2000 and 3750 lux.~~

10 ~~17. The pharmaceutical formulation according to any one of the preceding claims, wherein the binding agent is an antibody, such as a bispecific antibody.~~

~~18. The pharmaceutical formulation 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.~~

15 ~~19. The pharmaceutical formulation according to claim 18, 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.~~

20 ~~20. The pharmaceutical formulation according to any one of the preceding claims, wherein~~  
~~— the first antigen binding region comprises a first heavy chain variable region (VH) comprising the CDR1, CDR2, and CDR3 sequences set forth in: SEQ ID NO: 9, 10, 11, respectively, and a first light chain variable region (VL) comprising the CDR1, CDR2, and CDR3 sequences as set forth in: SEQ ID NO: 13, GAS, and SEQ ID NO: 14, respectively, and~~  
~~— the second antigen binding region comprises a second heavy chain variable region (VH) comprising the CDR1, CDR2, and CDR3 sequences set forth in: SEQ ID NO: 18, 19 and 20 respectively, and a second light chain variable region (VL) comprising the CDR1, CDR2, and CDR3 sequences set forth in: SEQ ID NO: 22, DDN and SEQ ID NO: 23, respectively.~~

25 ~~21. The pharmaceutical formulation according to any one of the preceding claims, wherein~~  
~~— the first antigen binding region comprises a first heavy chain variable region (VH) having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 15; and a first light chain variable region (VL) having at least 70%, at least 75%, at least 80%, at~~

~~least 85%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 16; and~~  
~~the second antigen binding region comprises a second heavy chain variable region (VH) having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 17; and a second light chain variable region (VL) having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 21.~~

22. ~~The pharmaceutical formulation according to any one of the preceding claims, wherein~~  
~~the first antigen binding region comprises a first heavy chain variable region (VH) comprising a CDR1, CDR2, and CDR3 sequence, as set forth in: SEQ ID NO: 9, 10 and 11, respectively, the first heavy chain variable region having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 15; and a first light chain variable region (VL) comprising a CDR1, CDR2, and CDR3 sequence, as set forth in: SEQ ID NO: 13, GAS, and SEQ ID NO: 14, respectively, the first light chain variable region having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 16, and~~  
~~the second antigen binding region comprises a second heavy chain variable region (VH) comprising a CDR1, CDR2, and CDR3 sequence, as set forth in: SEQ ID NO: 18, 19 and 20, respectively, the second heavy chain variable region having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 17; and a second light chain variable region (VL) comprising a CDR1, CDR2, and CDR3 sequence, as set forth in: SEQ ID NO: 22, DDN, 23, respectively, the second light chain variable region having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to the sequence set forth in SEQ ID NO: 21.~~

23. ~~The pharmaceutical formulation according to any one of the preceding claims, wherein:~~  
 a. ~~said first antigen binding region binding to human CD137 comprises~~

5       ~~— a first heavy chain variable region comprising the sequence set forth in SEQ ID NO: 15 or a sequence wherein up to 20 amino acid residues, such as up to 19, up to 18, up to 17, up to 16, up to 15, up to 14, up to 13, up to 12, up to 11, up to 10, up to 9, up to 8, up to 7, up to 6, up to 5, up to 4, up to 3, up to 2, up to 1 amino acid residues is/are modified as compared to the sequence set forth in SEQ ID NO: 15, the first heavy chain variable region (VH) comprising a CDR1, CDR2, and CDR3 sequence, as set forth in: SEQ ID NO: 9, 10 and 11, respectively; and~~

10       ~~— a first light chain variable region comprising the sequence set forth in SEQ ID NO: 16 or a sequence wherein up to 20 amino acid residues, such as up to 19, up to 18, up to 17, up to 16, up to 15, up to 14, up to 13, up to 12, up to 11, up to 10, up to 9, up to 8, up to 7, up to 6, up to 5, up to 4, up to 3, up to 2, up to 1 amino acid residues is/are modified as compared to the sequence set forth in SEQ ID NO: 16 the first light chain variable region (VL) comprising a CDR1, CDR2, and CDR3 sequence, as set forth in: SEQ ID NO: 13, GAS and SEQ ID NO: 14, respectively; and~~

15       ~~b. said second antigen-binding region binding to human PD-L1 comprises~~

20       ~~— a second heavy chain variable region comprising the sequence set forth in SEQ ID NO: 17 or a sequence wherein up to 20 amino acid residues, such as up to 19, up to 18, up to 17, up to 16, up to 15, up to 14, up to 13, up to 12, up to 11, up to 10, up to 9, up to 8, up to 7, up to 6, up to 5, up to 4, up to 3, up to 2, up to 1 amino acid residues is/are modified as compared to the sequence set forth in SEQ ID NO: 17, the second heavy chain variable region (VH) comprising a CDR1, CDR2, and CDR3 sequence, as set forth in: SEQ ID NO: 18, 19 and 20, respectively; and~~

25       ~~— a second light chain variable region comprising the sequence set forth in SEQ ID NO: 21 or a sequence wherein up to 20 amino acid residues, such as up to 19, up to 18, up to 17, up to 16, up to 15, up to 14, up to 13, up to 12, up to 11, up to 10, up to 9, up to 8, up to 7, up to 6, up to 5, up to 4, up to 3, up to 2, up to 1 amino acid residues is/are modified as compared to the sequence set forth in SEQ ID NO: 21, the second light chain variable region (VH) comprising a CDR1, CDR2, and CDR3 sequence, as set forth in: SEQ ID NO: 22, DDN and SEQ ID NO: 23, respectively.~~

35       ~~24. The pharmaceutical formulation according to any one of the preceding claims, wherein said binding agent 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).~~

5      ~~25. The pharmaceutical composition 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).~~

10      ~~26. The pharmaceutical formulation according to any one of the preceding claims, which is an antibody comprising a first binding arm and a second binding arm, wherein~~

10              ~~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;~~

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

20      ~~27. The pharmaceutical formulation according to any one of the preceding claims, wherein the first antigen binding region binds to human CD137 as set forth in SEQ ID NO: 30, or a mature polypeptide thereof.~~

25      ~~28. The pharmaceutical formulation according to any one of the preceding claims, wherein the first antigen binding region binds to cynomolgus monkey (*Macaca fascicularis*) CD137, as set forth in SEQ ID NO: 31, or a mature polypeptide thereof.~~

25      ~~29. The pharmaceutical formulation according to any one of the preceding claims, wherein the first antigen binding region binds to human PD-L1 as set forth in SEQ ID NO: 28, or a mature polypeptide thereof.~~

30      ~~30. The pharmaceutical formulation according to any one of the preceding claims, wherein the second antigen binding region binds to cynomolgus monkey (*Macaca fascicularis*) PD-L1 as set forth in SEQ ID NO: 29, or a mature polypeptide thereof.~~

30      ~~31. The pharmaceutical formulation according to any one of the preceding claims, wherein the second antigen binding region inhibits the binding of human PD-L1 to human PD-1.~~

32. ~~The pharmaceutical formulation according to any one of the preceding claims, wherein the binding agent is in the format of a full length antibody or an antibody fragment.~~
33. ~~The pharmaceutical formulation 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.~~
34. ~~The pharmaceutical formulation according to any one of the preceding claims, wherein the binding agent is a full length IgG1 antibody.~~
35. ~~The pharmaceutical formulation according to any one of the preceding claims, wherein~~  
a. ~~the first antigen binding region binding to CD137 is derived from a chimeric antibody, and/or~~  
b. ~~the second antigen binding region binding to human PD-L1 is derived from a chimeric antibody.~~
36. ~~The pharmaceutical formulation according to any one of the preceding claims, wherein~~  
a. ~~the first antigen binding region binding to CD137 is derived from a humanized antibody, and/or~~  
b. ~~the second antigen binding region binding to human PD-L1 is derived from a humanized antibody.~~
37. ~~The pharmaceutical formulation 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.~~
38. ~~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 humanized antibody, and/or~~  
b. ~~the second antigen binding region binding to human PD-L1 is derived from a human antibody.~~
39. ~~The pharmaceutical formulation according to any one of claims 26 to 38, wherein each of the first and second heavy chain constant regions (CH) comprises one or more of a constant region 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.~~

40. ~~The pharmaceutical formulation according to claim 39, wherein each of the first and second heavy chain constant regions (CHs) comprises a CH3 region and wherein the two CH3 regions comprise asymmetrical mutations.~~
- 5 41. ~~The pharmaceutical formulation according to any one of claims 25 to 40, 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~~
- 10 ~~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.~~
- 15 42. ~~The pharmaceutical formulation according to claim 41, 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~~
- 20 ~~corresponding to F405 in a human IgG1 heavy chain according to EU numbering is L in said second heavy chain.~~
- 25 43. ~~The pharmaceutical formulation according to any of the preceding claims, wherein said antibody induces Fc mediated effector function to a lesser extent compared to another antibody comprising the same first and second antigen binding regions and two heavy chain constant regions (CHs) comprising human IgG1 hinge, CH2 and CH3 regions.~~
- 30 44. ~~The pharmaceutical formulation according to claim 43, wherein said first and second heavy chain constant regions (CHs) are modified so that the antibody induces Fc mediated effector function to a lesser extent compared to an antibody which is identical except for comprising non modified first and second heavy chain constant regions (CHs).~~
45. ~~The pharmaceutical formulation according to any one of claims 43 to 44, wherein said Fc-mediated effector function is measured by binding to Fcγ receptors, binding to C1q, or induction of Fc mediated cross linking of Fcγ receptors.~~

46. ~~The pharmaceutical formulation according to claim 45, wherein said Fc-mediated effector function is measured by binding to C1q.~~
- 5 47. ~~The pharmaceutical formulation according to any one of claims 43-46, wherein said first and second heavy chain constant regions have been modified so that binding of C1q to said antibody is reduced compared to a wild-type antibody, preferably reduced by at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or 100%, wherein C1q binding is preferably determined by ELISA.~~
- 10 48. ~~The pharmaceutical formulation 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.~~
- 15 49. ~~The pharmaceutical formulation according to claim 48, 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.~~
50. ~~The pharmaceutical formulation according to claim 48, 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).~~
- 20 51. ~~The pharmaceutical formulation according to claim 48, 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.~~
- 25 52. ~~The pharmaceutical formulation according to claim 48, 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~~
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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.

53. The pharmaceutical formulation according to any one of claims 26 to 52, wherein the first binding arm comprises a kappa ( $\kappa$ ) light chain, such as a kappa light chain comprising the amino acid sequence set forth in SEQ ID NO: 26 and said second binding arm comprises a lambda ( $\lambda$ ) light chain, such as a lambda light chain comprising the amino acid sequence set forth in SEQ ID NO: 27.

54. The pharmaceutical formulation according to any one of claims 26 to 52, wherein the first binding arm comprises a lambda ( $\lambda$ ) light chain, such as a lambda light chain comprising the amino acid sequence set forth in SEQ ID NO: 27 and said second binding arm comprises a kappa ( $\kappa$ ) light chain, such as a kappa light chain comprising the amino acid sequence set forth in SEQ ID NO: 26.

55. The pharmaceutical formulation according to any one of claims 26 to 52, wherein both the first binding arm and the second binding arm comprises a lambda ( $\lambda$ ) light chain, such as a lambda light chain comprising the amino acid sequence set forth in SEQ ID NO: 27.

56. The pharmaceutical formulation according to any one of claims 26 to 52, wherein both the first binding arm and the second binding arm comprises a kappa ( $\kappa$ ) light chain, such as a kappa light chain comprising the amino acid sequence set forth in SEQ ID NO: 26.

57. The pharmaceutical formulation according to claim any one of claims 26 to 56, wherein the first binding arm comprises the amino acid sequences set forth in SEQ ID NO: 24 and the second binding arm comprises the amino acid sequence set forth in SEQ ID NO: 25.

58. The pharmaceutical formulation according to claim any one of claims 26 to 56, wherein the first binding arm comprises the amino acid sequences set forth in SEQ ID NO: 25 and the second binding arm comprises the amino acid sequence set forth in SEQ ID NO: 24.

59. The pharmaceutical formulation according to any one of the preceding claims, wherein the binding agent induces and/or enhances proliferation of T cells.

- 5 60. ~~The pharmaceutical formulation according to claim 59, wherein said T cells are CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells.~~
61. ~~The pharmaceutical formulation according to any one of the preceding claims, wherein the binding agent activates CD137 signaling only when the second antigen binding region binds to PD-L1.~~
62. ~~The pharmaceutical formulation according to claims 59 to 61, wherein proliferation of T cells is measured by co-culturing T cells expressing a specific T cell receptor (TCR) with dendritic cells (DCs) presenting the corresponding antigen on the major histocompatibility complex, which is recognized by the TCR.~~
- 10 63. ~~The pharmaceutical formulation according to any one of the preceding claims, the formulation being an aqueous formulation.~~
64. ~~A pharmaceutical formulation as defined in any one of the preceding claims for use as a medicament.~~
- 15 65. ~~A pharmaceutical formulation as defined in any one of claims 1 to 64 for use in the treatment of cancer.~~
66. ~~A method of treatment of a disease comprising administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to 64 to a subject in need thereof.~~
67. ~~The method according to claim 66, wherein the disease is cancer.~~
- 20 68. ~~A method for producing a pharmaceutical formulation as defined in any one of claims 1 to 64, the method comprising providing a binding agent as defined in any one of claims 1 to 65 and combining it with:~~
  - ~~a. a histidine buffer,~~
  - ~~b. about 100 to about 400 mM of a sugar, and~~
  - ~~c. about 0.001 to about 0.1% (w/v) non-ionic surfactant;~~

25 ~~at a pH between about 4.5 and about 6.5.~~

69. ~~A method of inducing cell death, or inhibiting growth and/or proliferation of a tumor cell expressing PD-L1 comprising administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to 64 to a subject in need thereof and/or bearing said tumor cell.~~

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70. ~~The pharmaceutical formulation for use according to claim 65, or the method according to claim 67, 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.~~
- 5 71. ~~The pharmaceutical formulation for use according to claim 65, or the method according to claim 67 or 68, wherein the cancer is non-small cell lung cancer (NSCLC).~~
72. ~~Use of a pharmaceutical formulation according to any one of claims 1 to 64, for the manufacture of a medicament, such as a medicament for the treatment of cancer, e.g. a cancer characterized by the presence of solid tumors or a cancer selected from the~~  
10 ~~group consisting of: melanoma, ovarian cancer, lung cancer, colon cancer and head and neck cancer.~~
73. ~~The use according to claim 72, wherein the lung cancer is non-small cell lung cancer (NSCLC).~~
74. ~~The pharmaceutical formulation for use according to claim 64 or 65, the use according to any one of claims 72 to 73 or the method according to any one of claims 66, 67, 69, wherein the pharmaceutical formulation is administered intravenously.~~
- 15 75. ~~The pharmaceutical formulation for use according to claim 64 or 65, the use according to any one of claims 72 to 73 or the method according to any one of claims 66, 67, 69, wherein the use or method comprises combination with one or more further therapeutic~~  
20 ~~agents, such as a chemotherapeutic agent.~~

1. An invention not claimed in any divisional application.